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Dear Colleagues and Friends, members of the Federation of the African Societies of Immunology (FAIS), it is a pleasure to welcome you at the FAIS Congress in Tunis on behalf of the International Union of Immunological Societies (IUIS). IUIS is an umbrella organization with over 70,000 fellow immunologists worldwide associated to it via national societies and federations such as FAIS. The mission of IUIS is to foster "Immunology without borders", across continents and political divides. We articulate our vision through Committees and promoting Immunology in Africa has been one of our priorities. The choice of Cape Town as a site of the 2022 IUIS International Congress of Immunology illustrates how strategic we feel is fostering Immunology in this continent. We, as a community, are proud of the impact we have had on the progress of science and health care and are confident that we have the intellectual strength to address challenges ahead of us in a global science and health perspective. I am confident that the FAIS meeting will provide a forum for fruitful scientific and personal interactions.

I look forward to meeting you at the Congress.

Alberto MANTOVANI
President
International Union of Immunological Societies

Dear Colleagues and Friends,

It is with great pleasure that we welcome you on behalf of the Federation of African Immunological Societies (FAIS) and the Tunisian Society of Immunology (STI) to10th African Congress of Immunology jointly organized with the 14thAnnual Meeting of the STI, in Hammamet, Tunisia from December 3 to 7, 2017.

It is now widely accepted that reducing the risks of major diseases transmission in Africa and worldwide heavily relies on the acquisition of skills and the proper understanding of relevant cutting-edge technologies. Immunology remains in the heart of basic and applied medical research and its achievements are of particular relevance for the African continent and that's why we have chosen "Immunology for a healthy Africa" as main theme of the conference.
It is only when nations are empowered with scientific expertise that they become better prepared to control diseases. In this context, the FAIS is playing a major role in promoting Immunology within the African continent through knowledge dissemination and training of the young scientific community. Key achievements of the FAIS during the last three years are highlighted following this address. It was for me a great honor and pleasure to chair the FAIS council since December 2014.

The Scientific Committee chaired by Prof. Ridha Barbouche did tremendous efforts to generate a highly stimulating program. With 45 conferences given by outstanding immunologists from all over the world, more than 300 short talks, oral and e-poster presentations, almost all immunology main topics will be covered during this four-day congress: innate and adaptive immunity, infection and immunity, vaccinology, allergy, autoimmunity, primary immune-deficiencies, cancer immunity. In addition, a satellite meeting dealing with gender equality in immunology and a workshop organized by the IUIS Education Committee will enrich the 10th FAIS Conference.

The conference will be a unique occasion for African immunologists to present and discuss their work together but also with eminent international field experts. Emphasis has been placed on the contribution and participation of students, post-docs and young researchers with reduced registration fees and up to 100 travel grants awarded. At this point, we cordially thank the 20 reviewers for their invaluable contribution by critically evaluating all submitted abstracts.

This African Congress of Immunology is organized under the umbrella and with full support of the International Union of Immunological Societies (IUIS) which will hold its Executive and annual Council Meetings during the 3 days preceding the congress. Proud to host all IUIS Council members, we extend a special hand of welcome to the IUIS President Prof. Alberto Mantovani and Past-President Prof. Jorge Kalil who have been great supporters of FAIS and the development of Immunology in Africa.

In addition to the IUIS, we express our deep gratitude to our 2 main sponsors, the Bill and Melinda Gates Foundation and the Medical Research Council (MRC). The meeting would not be possible without the generous financial contribution of various other organizations and institutions including the American Association of Immunologists (AAI), the UK WellcomeTrust, the European Federation of Immunological Societies (EFIS), the Tunisian Society of Immunology (STI), the Japanese Society of Immunology (JSI), the Pasteur Institute of Tunis, Tunis Air, the "Institut Français de Tunisie", the European Academy of Allergy and Clinical Immunology (EAACI) and the Society for Leucocyte Biology (SLB). We also thank all the exhibitors for their invaluable commitment and support.

We will do our best to make the 10th African Congress of Immunology a most memorable scientific, social and cultural event for all of you.

I would like to wish all participants an inspiring and interesting conference and hope that you will also keep good memories of your stay in Tunisia.

Hatem MASMOUDI
Congress President

FAIS key Achievements (2015-2017)

New societies: Mali, Tanzania and Malawi
Membership in progress: Algeria and Ivory Coast
Courses and Trainings:

- The first IUIS/FAIS regional Immunology Course held in Cape Town, 20-24 October 2015 on "Biomarkers and correlates of immune control of HIV, TB, Malaria and implications for vaccine developments".
- The second IUIS/FAIS Regional Immunology Course held in Hammamet, Tunisia, 4-8 April 2016 on "Tolerance and auto-immunity".
- The third IUIS/FAIS Regional Immunology Course held in Kilifi, Kenya, 19- 24 September 2016 on "Advances in the immunobiology of parasites, pathogens and pathogenesis".
- The fourth IUIS/FAIS Regional Immunology Course held in Banjul, Gambia, 19-26 November 2016 on "Immunology of infectious diseases".
- The fifth IUIS-FAIS Regional Immunology Course held in Gondar, Ethiopia, 26-February to 5 March 2017 on "New Developments in the Immunology, diagnosis and treatment of cutaneous and visceral Leishmaniosis, Schistosomiasis and Helminth infections in an area of high Tuberculosis prevalence".

Communication:
Improvement of the FAIS website **www.faisafrica.com** to a dynamic website, which in addition to keep the history of the federation, is able to manage its Conferences and courses (online registrations, abstract submissions…)
Elaboration of a 2 thousand contacts mail list obtained by merging mailing lists of participants to the current and previous FAIS conferences/courses with mailing lists of African Immunology Societies; this African global mailing list can be used to disseminate FAIS announcements by HTML via the dedicated server of our website.
Involvement in the activities of the IUIS:
Four members of the current FAIS board are active members of the IUIS Education Committee and two FAIS members (Lucy Ochola, Kenya, and RidhaBarbouche, Tunisia) were elected as members of the new IUIS Council.
The FAIS Secretary General, **Faith Osier (Kenya)**, was elected as **Vice President of the IUIS**.
Cape Town, South Africa (Clive Gray), was chosen to host the **ICI 2022**.

Hatem MASMOUDI
FAIS President

Dear Colleagues and Friends,

On behalf of the scientific committee members I welcome all participants to the 10th FAIS Congress.

The committee made every effort to develop a comprehensive program including cutting edge science and meaningful regional challenges in the field of immunology and immune-mediated diseases.

We are grateful to the International Union of Immunological Societies and to all other National Scientific Societies and Continental Federations for their support and significant contribution to the scientific content of the Congress.

The committee did encourage attendance of African students and young investigators working in the continent and did secure a substantial support by providing a large number of scholarships.

The 10th FAIS Congress promises to bring together the very best perspectives on both basic and clinical immunology research. It will offer an excellent opportunity for interaction between newcomers and longstanding workers in the field.

In order to improve visibility of high quality research conducted in African settings, distinguished work presented during the Congress sessions will be selected for manuscript submission and publication in a special issue of a renowned immunology journal.

Enjoy your stay in Hammamet!

Ridha BARBOUCHE
Chairman, Scientific Committee

COMMITTEES

Organizing Committee **:**

- **Chair :** Hatem Masmoudi (*Tunisia, FAIS President*)
- Yousr Gorgi-Lakhoua (*Tunisia, STI President*)
- Tom Kariuki (*Kenya, AESA Director, FAIS Past President*)
- Pa Tamba Ngom (*Gambia, FAIS Treasurer*)
- Ezzeddine Ghazouani (*Tunisia, STI Treasurer*)
- Sondes Makni-Zouari (*Tunisia, STI Past President*)
- Sawsen Fki-Ghorbel (*Tunisia, STI member*)

Scientific Committee **:**

- **Chair :** Ridha Barbouche (*Tunisia, IUIS Council and FAIS Board member, STI Vice-President*)
- Faith Osier (*Kenya, IUIS Vice President, FAIS Secretary General*)
- Henry Mwandumba (*Malawi, FAIS Vice-President, ISM President*)
- Clive Gray (*South Africa, FAIS Board member, SAIS President*)
- Boubacar Maiga (*Mali, FAIS Board member*)
- Amel Elgaaied-Benammar (*Tunisia, STI Secretary General*)
- Imen Sfar (*Tunisia, STI Deputy General Secretary*)
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- Dhafer Laouini (*Tunisia, STI member*)
- Lilia Laadhar-Kharrat (*Tunisia, STI member*)
- Melika Ben Ahmed-Haddad (*Tunisia, STI member*)
- Asma Gati (*Tunisia, STI member*)
- Imen Ben Mustapha (*Tunisia, STI member*)

Sponsors & Exhibitors acknowledgment

THE 10TH CONFERENCE OF THE FEDERATION OF AFRICAN IMMUNOLOGICAL SOCIETIES

3-7 DECEMBER 2017, HAMMAMET-TUNISIA

WE WOULD LIKE OF THANK THE FOLLOWING PARTNERS AND SPONSORS FOR THEIR GENEROUS CONTRIBUTION TO THE SUCCESS OF THE CONFERENCE

★★★★★★★★★★

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★★★★★★★★★★

The 10th African Congress of Immunology is managed by:

Travel Grant Recipients

Thanks to the generous support of our donors, Travel Grants (Air Ticket/Accommodation) have been awarded to 99 students/young investigators to help them attend the FAIS 2017 congress:

Fullname	Country	Full Name	Country	Fullname	Country
Nada Abdel Aziz	South Africa	Rym Ouni	Tunisia	Nobelle Sakwe	Cameroon
Dawn Maranga	Kenya	Amira Gabsi	Tunisia	Nesrine Zaabat	Algeria
Andrew Mwale	Malawi	Mariem Ben Jmaa	Tunisia	Visopo Harawa	Malawi
Anthony Afum-Adjei Awuah	Ghana	AymenTlili	Tunisia	Kouadio Ayebe Edwige AKA	Côte d'Ivoire
Ian Oyaro	Kenya	Olfa Maghrebi	Tunisia	Kheir Eddine Kerboua	Algeria
David Koffi	Côte d'Ivoire	Sonia Amri	Tunisia	Sara El Fakihi	Morocco
Paul Ogongo	South Africa	Asma Chikhaoui	Tunisia	Aicha El Allam	Morocco
Christopher Kintu	Uganda	Emna Dabbeche-Bouricha	Tunisia	Elvis Kidzeru	South Africa
Hassan Filali	Morocco	Imen Zamali	Tunisia	Najla Mekki	Tunisia
Vicky Gent	Kenya	Imen Namouchi	Tunisia	Nadia Sassi	Tunisia
Khanyisile Kgoadi	South Africa	Afef Rais	Tunisia	Marwa Ben Elhaj	Tunisia
Sanaa Sabour Alaoui	Morocco	Amal Gorrab	Tunisia	Sawssen Ben Elhadj	Tunisia
Eyasu Ejeta Duken	Ethiopia	Manel Khemiri	Tunisia	Khouloud Gara	Tunisia
Fatima Zahra Jadid	Morocco	Mariem Dhieb	Tunisia	Ines Maoudoud	Tunisia
FatimataThiombiano	Burkina Faso	Zied Azaiz	Tunisia	HendJlajla	Tunisia
Sukrat `Sinha	India	Youssra Haouami	Tunisia	Chourouk Ben Mahfoudh	Tunisia
Benjamin Amoani	Ghana	Ichrak Bannour	Tunisia	ImenAyadi	Tunisia
Raphael Kamng'ona	Malawi	Ferjeni Zouidi	Tunisia	Lamia Benkari	Algeria
Nora Kariche	Algeria	Hana Khenine El Hamrouni	Tunisia	Meriem Abbadi	Algeria
Imane El Mouraghi	Morocco	Raja Rekik	Tunisia	Insaf Meriem Boutemine	Algeria
Abdennour Bouattoura	Algeria	Ismail Hachicha	Tunisia	Soraya Sedfi	Algeria
Ayoub Lahmadi	Morocco	Nesrine Elloumi	Tunisia	Ahmad Waqas	Pakistan
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Ramatoulaye Ndiaye	Senegal	Achraf Ben Youssef	Tunisia	Khadidiatou Nniane	Senegal

Lilya Meriem Berkani	Algeria	Amal Abouda	Tunisia	Hasnaa Maksouri	Morocco
Aïssé Florence Judith Trebissou	Côte d'Ivoire	Améni Jerbi	Tunisia	Ahmed Abidi	France
Naffesa Al Sheikh	Sudan	Asma Boumiza	Tunisia	Hana Ben Hassine	Tunisia
Tamazouzt Hadjout	Algeria	Chiraz Atri	Tunisia	Ines Sassi	Tunisia
Salma Saadi	Morocco	Sabrina Mejdoub	Tunisia	Mourad Elghali	Tunisia
Khawla Otmani	Algeria	Selim Bouzguenda	Tunisia	Maha Changuel	Tunisia
Meryem Aarab	Morocco	Zeineb Ben Lamine	Tunisia	Hajer Lamari	Tunisia
Khalissa Saidani	Algeria	Aymen Bali	Tunisia	Fatma Dhaffouli	Tunisia
Mohamed El-Hadi Seninet	Algeria	Fatma Dehman	Tunisia	Hajer Abroud	Tunisia

Travel Grant Donors

Scientific Program

SUNDAY, DECEMBER 03, 2017

17:30 - 20:00 **Conference Room Nefertiti**

Opening Ceremony

17:30 Welcome address

H. Masmoudi (Tunisia)

17:50 FAIS, the past, the present and where from here

E. Sibanda (Zimbabwe)

18:10 Keynote Lecture: Innate immunity, inflammation and cancer

A. Mantovani (Italy)

19:00 Welcome reception and musical time-out

MONDAY, DECEMBER 04, 2017

08:30 - 10:30 **Conference Room Nefertiti**

PLENARY SESSION: INNATE IMMUNITY

Chairs: C. Blish – PT. Ngom

08:30 Next Generation Immunotherapy: Targeting innate lymphoid cells

E. Vivier (France)

08:55 Innate lymphoid cells in helminth infection

S. Koyasu (Japan)

09:20 Regulation of gut homeostasis by epithelial barriers

K. Takeda (Japan)

09:45 Human gut microbiota and health: from structure to functions

HM. Blottière (France)

10:10 Oral Communications

Interleukin-22 binding protein (IL-22BP) regulates IL-22 functions

A. Abidi (Tunisia)

ITE, a non toxic AhR ligand, activates Th22 subsets and enhances *de novo* generation of regulatory T cells in humans

I. Zamali (Tunisia)

10:30 - 11:00

Coffee Break & Poster Viewing

11:00 - 12:30 **Conference Room Nefertiti**

PLENARY SESSION: INNATE IMMUNITY

Chairs: H. Ayadi – E. Vivier

11:00 Defining protective natural killer cell subsets

C. Blish (USA)

11:25 NK cell-mediated immunosurveillance against drug-treated senescent tumor cells

A. Santoni (Italy)

11:50 Peptide-specific recognition by adaptive Natural Killer cells

C. Romagnani (Germany)

12:15 Short talk

Gene Conversion diversifies antigen-activated murine and human B lymphocytes

J. Jacob (USA)

12:30 - 14:00

Lunch break

14:00 - 15:40 **Conference Room Nefertiti**

PLENARY SESSION: INFECTION AND IMMUNITY

Chairs: A. Dieye – H. Makni

14:00 Neonatal and infant immunity in children born to HIV infected mothers

C. Gray (South Africa)

14:25 HIV-associated disruption of lung immunity favours growth and survival of *Mycobacterium tuberculosis* in human alveolar macrophages

H. Mwandumba (Malawi)

14:50 The pathogenesis of progressive HIV associated tuberculosis

R. Wilkinson (South Africa)

15:15 Challenges associated with Buruli ulcer treatment

D. Yeboah-Manu (Ghana)

15:40 - 16:00

Coffee Break & Poster Viewing

16:00 - 16:55 **Conference Room Nefertiti**

PARALLEL SESSION I: SHORT TALK AND ORAL COMMUNICATIONS: INFECTION AND IMMUNITY

Chairs: H. Mwandumba – R. Wilkinson

16:00 Short talk: Protein Kinase C-Delta (PKCδ): a regulator of tuberculosis-driven inflammation

S. Parihar (South Africa)

16:15 RV0140-Specific granzyme B as an alternative biomarker to discriminate different phases of *Mycobacterium tuberculosis* infection

R. Ouni (Tunisia)

16:25 Towards the development of a field-friendly point-of-care screening test for the diagnosis of TB disease in resource constrained settings

N. Chegou (South Africa)

16:35 HIV co-infection affects expression and function of human lung tissue resident T-cells during TB disease

P. Ogongo (South Africa)

16:45 Alternative quantiferon cytokines for diagnosis of children with active tuberculosis and HIV co-infection in Ghana

A. Afum-Adjei Awuah (Ghana)

16:00 - 16:45 **Conference Room Cesar**

PARALLEL SESSION II: SHORT TALK AND ORAL COMMUNICATIONS: INFECTION AND IMMUNITY

Chairs: B. Maiga - F. Brombacher

16:00 Short talk: Cutaneous leishmaniasis is exacerbated in the absence of IL-4 receptor alpha (IL-4Rα)-responsive T regulatory cells in mice

R. Hurdayal (South Africa)

16:15 Visceral leishmaniasis patients display altered composition and maturity of neutrophils as well as impaired neutrophil effector functions

E. Yizengaw (Ethiopia)

16:25 Histological and immunological differences between zoonotic cutaneous Leishmaniasis due to *Leishmania major* and sporadic cutaneous Leishmaniasis due to *Leishmania infantum*

T. Boussoffara (Tunisia)

16:35 ***Phlebotomus papatasi*** **yellow-related and apyrase salivary proteins are candidates for vaccination against human cutaneous leishmaniasis**

A. Tlili (Tunisia)

16:00 - 16:55 **Conference Room Luxor**

PARALLEL SESSION III: ORAL COMMUNICATIONS:

INFECTION AND IMMUNITY

Chairs: C. Gray - E. Ghazouani

16:00 **Short talk: HIV-Associated disruption of alveolar immune cell homeostasis in Malawian adults**

A. Mwale (Malawi)

16:15 **Evaluating the role of early HIV-1 specific T and B cell phenotypes and function in determining the subsequent production of functionally relevant HIV specific antibodies**

I. Oyaro (Kenya)

16:25 **Frequency of broadly neutralizing antibodies in HIV-1 chronically infected individuals in Ugandan clades A and D**

C. Kintu (Uganda)

16:35 **Filaria specific antibody response profiling in plasma from anti-retroviral naïve Loa loa microfilaraemic HIV-1 infected people**

G. Nchinda (Cameroon)

16:45 **Fluorescent isothiocyanate dextran evaluates the permeability of blood-brain barrier in Rabies infected mice model**

A. Waqas (China/Pakistan)

17:00 - 17:50 **Conference Room Nefertiti**

PLENARY SESSION: VACCINOLOGY

Chairs: S. Makni – JE. Uzonna

17:00 **Developing and testing a tetravalent attenuated dengue vaccine**

J. Kalil (Brazil)

17:25 **The beneficial and deleterious non-specific effects of vaccines: A challenge to immunology**

P. Aaby (Denmark)

TUESDAY, DECEMBER 05, 2017

08:30 - 10:30 **Conference Room Nefertiti**

PLENARY SESSION: ADAPTIVE IMMUNITY

Chairs: Y. Takahama - A. Badou

08:30 Posttranscriptional regulation of immune responses by RNA binding proteins

O. Takeuchi (Japan)

08:55 Blood and beyond: Properties of human tissue-resident T cells

R. van Lier (Netherlands)

09:20 B cell TRAF3: A regulator of B cell survival, activation, and tumorigenesis

G. Bishop (USA)

09:45 B cell selection in gut associated lymphoid tissues

MJ. Ratcliffe (Canada)

10:10 Oral Communications

Cytokines and B cells responses during Behçet disease

H. Belguendouz (Algeria)

Interleukin-37 expression is decreased in Behçet disease and is associated with inflammation

E. Bouali (Tunisia)

10:30 - 11:00

Coffee Break & Poster Viewing

11:00 - 12:30 **Conference Room Nefertiti**

PLENARY SESSION: ALLERGY AND AUTOIMMUNITY

Chairs: E. Sibanda - S. Yalaoui

11:00 Genetic restriction of antigen-presentation dictates allergic sensitization and disease in humanized mice

W. Pickl (Austria)

11:25 Shift of autoimmunity in NOD mice deficient in the ICOS costimulation pathway

O. Boyer (France)

11:50 IL-17 secreting T cells and their targeting in new immunotherapeutic approaches for autoimmune diseases

K. Mills (Ireland)

12:15 Oral Communication

Phenotypic analysis of lymphocytes and macrophages in bronchoalveolar lavage from patients with pulmonary sarcoidosis

S. El Fakihi (Morocco)

12:30 - 14:00

Lunch break

12:30 - 13:30 **Conference Room Nefertiti**

BECKMAN COULTER SYMPOSIUM

Immuno-monitoring of Cancer: From pre-clinical phases to Clinical Trial

E. Limagne (France)

14:00 - 15:40 **Conference Room Nefertiti**

PLENARY SESSION: INFECTION AND IMMUNITY

Chairs: J. Kalil – P. McDonald

14:00 IL-4–producing B cells regulate T helper cell dichotomy in type 1- and type 2-controlled diseases

F. Brombacher (South Africa)

14:25 Immunity and protection against leishmaniasis: standing up to the challenges

H. Louzir (Tunisia)

14:50 Towards a pan leishmaniasis vaccine: Are we almost there?

JE. Uzonna (Nigeria/Canada)

15:15 Correlates of protection from Controlled Human Malaria Infections (CHMI) in semi-immune Kenyan adults

F. Osier (Kenya)

15:40 - 16:00

Coffee Break & Poster Viewing

16:00 - 17:10 **Conference Room Luxor**

PARALLEL SESSION I: ORAL COMMUNICATIONS:
INFECTION AND IMMUNITY

Chairs: F. Osier – D. Yeboah-Manu

16:00 Implication of FcεRI-IgE polynuclear neutrophils in the pathogenesis of malaria: possible association with the severity of disease and with cerebral forms of malaria

B. Mbengue (Senegal)

16:10 Immunity profiling as a biomarker of integrated malaria control measures in Ivorian communities using a magnetic bead-based multiplex assay

D. Koffi (Ivory Coast)

16:20 Host Immunity to Malaria infection: Effects of malnutrition and anemia amongst under-ten children, North region of Cameroon

N. Sakwe (Cameroon)

16:30 CSF Neopterin and CXCL13 are potential biomarkers for test of cure in the non-human primate model of human African trypanosomiasis

D. Maranga (Kenya)

16:40 An investigation into the role of *Schistosoma mansoni* infection on human papillomavirus (HPV) vaccine induced protective responses

V. Gent (Kenya)

16:50 Suppression of granulocyte functions in lymphatic filariasis: role of IgG4 antibodies

F. Prodjinotho (Germany)

17:00 Foxp3+ regulatory T cells require IL-4Rα signalling to control tissue inflammation and immunopathology during helminth infections

N. Abdel Aziz (South Africa)

16:00 - 17:10 **Conference Room Cesar**

PARALLEL SESSION II: ORAL COMMUNICATIONS:

AUTOIMMUNE DISEASES

Chairs: O. Boyer - K. Djenouhat

16:00 The involvement of Notch signaling in the pathological behavior of cultured human rheumatoid arthritis fibroblast like synoviocytes

N. Sassi (Tunisia)

16:10 Circulating fibrocytes in Rheumatoid Arthritis: Is there a role for WNT5A pathway?

D. Elhaj Mahmoud (Tunisia)

16:20 FCγR2A and FCγR3B polymorphisms and biotherapy outcomes in patients with chronic inflammatory rheumatisms

C. Ben Mahfoudh (Tunisia)

16:30 CXCL4 in Tunisian patients with Systemic Sclerosis

I. Namouchi (Tunisia)

16:40 Diagnostic value of anti-phospholipase A2 receptor (APLA2R) and anti-thrombospondine type 1 domain containing 7A (ATHSD7A) in membranous nephropathy: A Tunisian cohort

A. Rais (Tunisia)

16:50 The impaired role of monocytes and regulatory T cells in the pathogenesis of Hashimoto's thyroiditis

S. Amri (Tunisia)

17:00 Expression of T helper cells master regulators in Tunisian Pemphigus Foliaceus

M. Ben Jmaa (Tunisia)

17:20 - 17:45 **Conference Room Nefertiti**

PLENARY SESSION: INFECTION AND IMMUNITY

Chairs: R. Josien

17:10 Immunoglobulin superfamily members encoded by herpesviruses and their roles in immune evasion

P. Engel (Spain)

WEDNESDAY, DECEMBER 06, 2017

08:30 - 10:30 **Conference Room Nefertiti**

PLENARY SESSION: ALLERGY AND PRIMARY IMMUNODEFICIENCY

Chairs: W. Pickl - M. Kallel Sellami

08:30 Towards prophylactic vaccination of allergy: When, how and whom

R. Valenta (Austria)

08:55 Inborn errors of immunity: susceptibility to infections and beyond

MR. Barbouche (Tunisia)

09:20 Applications and advances in next-generation sequencing for the diagnosis of PIDs

J. Chou (USA)

09:45 Next generation TREC analysis to detect abnormal T-cell proliferation in patients with PIDs

MC. van Zelm (Australia)

10:10 Short Talk

Novel insights into molecular basis of Autoimmune Lymphoproliferative Syndrome due to FAS defect revealed by the study of consanguineous patients

I. Ben-Mustapha (Tunisia)

10:30 - 11:00

Coffee Break & Poster Viewing

11:00 - 12:30 **Conference Room Nefertiti**

PLENARY SESSION: INNATE IMMUNITY

Chairs: MJ. Ratcliffe – HM. Blottière

11:00 Tight control of IL-22 actions on epithelial cells by IL-22BP during inflammation and steady state

R. Josien (France)

11:25 Identifying molecular targets in human neutrophils: The song remains the same

P. McDonald (Canada)

11:50 Complement in pathophysiology and therapeutics of human diseases

K. Djenouhat (Algeria)

12:15 Short talk

Complement deficiencies: Specific aspects for Tunisian patients

M. Kallel Sellami (Tunisia)

11:00 - 12:30 **Conference Room Cesar**

PARALLEL SESSION: WORKSHOP EDUCATION COMMITTEE

Chairs: M. Letarte – D. Kabelitz

12:30 - 14:00

Lunch break

14:00 - 15:40 **Conference Room Nefertiti**

"TUNISIAN SOCIETY OF IMMUNOLOGY" SESSION

Chairs: Y. Gorgi - R. Kemp

14:00 Thymic epithelial cells that govern T cell production and selection

Y. Takahama (Japan)

14:25 Neuroendocrine regulation of immunity

S. Ugolini (France)

14:50 Improving anti-tumor reactivity of human gamma/delta T-cells

D. Kabelitz (Germany)

15:15 A tale on the immunobiology of aging

A. Larbi (Singapore)

15:40 - 16:00

Coffee Break & Poster Viewing

16:00 - 16:50 **Conference Room Cesar**

PARALLEL SESSION: SHORT TALKS AND ORAL COMMUNICATIONS

AUTOIMMUNE DISEASES

Chairs: I. Ghedira - S. Ugolini

16:00 Short talk: Celiac disease: A Tunisian perspective

L. Laadhar (Tunisia)

16:15 Short talk: The intathecal polyspecific antiviral immune response (MRZ reaction): A potential cerebrospinal fluid (CSF) marker for multiple sclerosis diagnosis

S. Feki (Tunisia)

16:30 Ectoenzyme implication in neurological inflammatory disorders compared to autoimmune diseases

M. Belghith (Tunisia)

16:40 Circulating IL-10 producing B cells and T CD4 cells in CSF and blood of neuroimmunological disorders patients

O. Maghrebi (Tunisia)

16:00 - 17:00 **Conference Room Luxor**

PARALLEL SESSION: GENDER EQUALITY IN IMMUNOLOGY

Chairs: OJ. Finn - N. Mehra

Invited speaker: O. Ben Hassine (Tunisia)

17:00 - 18:00 **Conference Room Nefertiti**

FAIS GENERAL ASSEMBLY

20 :00

GALA DINER

THURSDAY, DECEMBER 07, 2017

08:30 - 10:35 **Conference Room Nefertiti**

PLENARY SESSION: CANCER IMMUNITY

Chairs: F. Fennira - D. Kabelitz

08:30 Infiltrating immune cells that predict patient outcome in colorectal cancer

R. Kemp (New Zealand)

08:55 Role of micro-RNAs in immunity, inflammation and cross-talk between tumor and host immune system

A. Benammar-Elgaaïed (Tunisia)

09:20 Vista as a potential promising new target in colorectal cancer

A. Badou (Morocco)

09:45 Immunotherapy of cancers: Where are we now and major challenges

S. Chouaib (France)

10:10 Vaccines for prevention of non-viral cancers

OJ. Finn (USA)

10:35 - 11:00

Coffee Break & Poster Viewing

11:00 - 11:45 **Conference Room Nefertiti**

PARALLEL SESSION I: SHORT TALKS AND ORAL COMMUNICATIONS
CANCER IMMUNITY

Chair: S. Chouaib

11:00 Short talk: Leptin decreases susceptibility of breast cancer cells to NK-lysis via PGC-1a pathway: Linking tumor progression with obesity

A. Gati (Tunisia)

11:15 Clinical significance of NOS2 expression in four types of tumor in Tunisian patients: melanoma, nasopharyngeal, colorectal and breast tumors

E. Dabbeche-Bouricha (Tunisia)

11:25 Targeting Hsp27/eIF4E interaction with phenazine compound: a promising alternative for castration-resistant prostate cancer treatment

H. Ziouziou (France/Tunisia)

11:35 Investigation of inflammatory biomarkers in systemic and in cutaneous melanoma microenvironment: Xeroderma Pigmentosum as a model

A. Chikhaoui (Tunisia)

11:00 - 11:40 **Conference Room Cesar**

PARALLEL SESSION II: SHORT TALKS AND ORAL COMMUNICATIONS:

PRIMARY IMMUNODEFICIENCIES

Chair: M. Letarte

11:00 Short talk: Homozygous *TCF3* mutation is associated with severe hypogammaglobulinemia and acute lymphoblastic leukemia

M. Ben Ali (Tunisia)

11:15 Short talk: Immunodeficiency disease related scores and leucocytes explorations for the diagnosis of primary immunodeficiency diseases

F. Seghrouchni (Morocco)

11:30 Primary immunodeficiency patients are a reservoir for potentially neurovirulent vaccine-derived polioviruses strains in post-eradication era

N. Mekki (Tunisia)

11:00 - 12:00 **Conference Room Luxor**

PARALLEL SESSION III: SHORT TALKS AND ORAL COMMUNICATIONS:

HEMATOLOGICAL MALIGNANCIES/TRANSPLANTATION

Chair: R. Bardi - A. Larbi

11:00 Short talk: Abnormal repression of SHP-1, SHP-2 and SOCS-1 transcription sustains the activation of the JAK/STAT3 pathway and the progression of the disease in multiple myeloma

M. Ben-Ahmed (Tunisia)

11:15 State of effectiveness of protein quality control by the proteasome complex in dependence on the clinical status of Moroccan patients with blood cancer

H. Filali (Morocco)

11:25 Cytokines associated with Burkitt's lymphoma in Western Kenya

I. Ndede (Kenya)

11:35 Short talk: Urinary mRNA analysis as a biomarker of epithelial mesenchymal transition in renal allograft

I. Sfar (Tunisia)

11:50 The role of IL-23/Th17 pathway in renal allograft rejection

Y. Haouami (Tunisia)

12:00 - 12:30 **Conference Room Nefertiti**

CLOSING CEREMONY

Chairs: R. Barbouche – F. Osier

12:00 See you at the 11th Fais Congress, Blantyre, Malawi, 2020

H. Mwandumba (Malawi)

12:15 Ithemba le Africa, 18th International Congress of Immunology, Cape Town, South Africa, 2022

C. Gray (South Africa)

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Innate Immunity & Inflammation

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Moses O. Akiibinu[1], AA. Adesiyan[2], SO. Akiibinu[3]

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P2. SIGNALING AND FUNCTION OF PKCδ IN PLATELET FUNCTION

Khadija Ridaoui[1,2], Y. Limami[2], M. Kabine[1], Y. Zaid[2]

[1]Biochemistry and Immunology Laboratory, Faculty of Sciences, Hassan II University, Casablanca, Morocco. [2]Laboratory of Thrombosis and Hemostasis, Faculty of Medicine, Mohamed VI University of Health Sciences, Casablanca, Morocco

P3. IL-8 AND MCP-1 CHEMOKINES CIRCULATING LEVELS IN SICKLE CELL YOUNG PATIENTS

Liliane Siransy, H. Adou, P. Kouacou, K. Nguessan, R. Yeboah, S. Hien, S. Dasse

UFR Sciences Médicales, Université Félix Houphouet Boigny, Abidjan, Côte d'Ivoire

P4. IL-17 CIRCULATING LEVELS IN SICKLE CELL PATIENTS IN COTE D'IVOIRE

Liliane Siransy, H. Adou, P. Kouacou , K. Nguessan, R. Yeboah, S. Hien, S. Dasse

UFR Sciences Médicales, Université Félix Houphouet Boigny, Abidjan, Côte d'Ivoire

P5. PREVALENCE OF NEW SEROLOGICAL MARKERS IN TUNISIAN ULCERATIVE COLITIS AND CROHN'S DISEASE

Mariem Dhieb[1], S. Feki[1], A. Jerbi[1], L. Chtourou[2], H. Hachicha[1], S. Boukthir[1], A. Amouri[2], N. Tahri[2], H. Masmoudi[1]

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P6. ABERRANT EXPRESSION OF MUC1-C SUBUNIT IN INFLAMMATORY BOWEL DISEASE

Manel Khemiri[1], R. Doghri[2], K. Mrad[2], K. Friedrich[3], R. Oueslati[1]

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P7. EVALUATION OF THE INVOLVEMENT OF VASP AND PRDX2 PROTEINS IN PLATELET FUNCTION CAUSED BY CROHN'S DISEASE

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Imane Elmouraghi[1], A. Ouarour[1], C. Kekik[2], B. Polat[2], F. Oguz[2], I. Ghozlani[3], A. El Maghraoui[3]

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Meriem Chamtouri[1], K. Sakly[1], S. Hammami [2], H. Trimeche[3], R. Ben Nejma[3], N. Sakly[1,3]

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Imen Bendaya[1], A. Riahi[2], M. Kharat[2], I. Sfar[3], W. Sdiri[4], R. Oueslati[1]

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Imen Habibi[1,2], I. Sfar[1], F. Kort [2], R. Bouraoui[2], A. Chebil[2], T. Ben Abdallah[1], L. EL Matri[2], Y. Gorgi[1]

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Mourad Belkhelfa[1], N. Beder[1], R. Belhadj[2], C. Touil-Boukoffa[1]

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Amina Sifi, S. Adi-Bessalem, F. Laraba-Djebari

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Soumaya Marzouki[1], I. Bini Dhouib[2,3], C. Ben Abdessalem[1], R. Rekik[1], R. Doghri[4], A. Maroueni[5], Z. Bellasfar[5], S. Fazaa[3], J. Bettaieb[1,6], MR. Barbouche[1.6], M. Ben Ahmed[1,6]

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Infection and immunity

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Anicet Christel Maloupazoa Siawaya[1], A. Mveang-Nzoghe[1], O. Ndjidji[1], M. Lebouenie, CN. Mnani Mpega, A. Mintsa Ndong, P. Essone Ndong, JF. Djoba Siawaya[1,2]

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Elvis Kidzeru[1,7,8], HB. Jaspan[1,3,5], N. Lejarcegui[2], E. Havyarimana[1], S. Dross[2,3], G. Itaya[2], K. Urdahl[2], S. Gantt[4], H. Horton[2,3,6], A. Gervassi[2]

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Hajer Abroud[1], S. Kacem[1,2], H. Romdane[3], I. Fodha[1,2], O. Kallala[1,2], N. Boujaffar[1], S. Yaacoub [3], A. Trabelsi[1,2]

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Moses Akiibinu[1], J. Maduabuchi[1], D. Ukpeibo[1], D. Etah[1], T. Oyewumi[2]

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P39. IMMUNE REGULATION OF LANGERHANS CELLS IN HUMAN FORESKIN

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P40. PARADOXICAL IMMUNOVIROLOGICAL RESPONSE IN PEOPLE LIVING WITH HIV STILL ANTIRETROVIRAL TREATMENT IN BURKINA FASO

A. Bagbila[1], C. Kyelem[1], Y. Marceline[1], A. PODA[1], MS. Ouédraogo[1], YJ. Drabo[2]

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P41. PROFILES OF PERIPHERAL CD4+T CELLS COUNT DURING ANTIRETROVIRALTREATMENT IN SENEGALESE ADULTS INFECTED BY HUMAN IMMUNODEFICIENCY VIRUS

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P42. SEOPREVALENCE AND RISK FACTORS OF HUMAN IMMUNE DEFICIENCY VIRUS (HIV) AND HEPATITIS C VIRUS INFECTIONS AMONG PREGNANT WOMEN ATTENDING ANTENATAL CARE CLINIC IN WESTERN ETHIOPIA

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P43. IMMUNOLOGICAL PROFILE IN HIV AND TB COINFECTED PATIENTS, IN MOZAMBIQUE

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P44. ABERRANT PLASMA IL-7 AND SOLUBLE IL-7 RECEPTOR A LEVELS INDICATE IMPAIRED T-CELL RESPONSE TO IL-7 IN HUMAN TUBERCULOSIS

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P45. KINETICS OF ALVEOLAR REGULATORY T CELLS DURING TREATMENT OF PULMONARY TUBERCULOSIS IN MALAWIAN ADULTS

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P46. THE ROLE OF DENDRITIC CELLS IN CNS-TB FOLLOWING BCG INTRACEREBRAL INFECTION

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P47. MICA-STR AND HLA-CLASS II GENES DIVERSITY IN PATIENTS WITH TUBERCULOSIS IN SOUTH TUNISIA

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P48. ASSOCIATION OF TNF MICROSATELLITE ALLELES WITH TUBERCULOSIS IN SOUTH TUNISIA

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P49. FIRST ANALYTIC EVALUATION OF THE LATEST QUANTIFERON GENERATION QFT GOLD-PLUS

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P50. CLINICAL, BIOLOGICAL AND THERAPEUTIC CHARECTERISTICS OF PATIENTS WITH AN 'UNDETERMINED' RESULT FOR THE QUANTIFERON TEST

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P51. PREDICTIVE VALUE OF TUBERCULINE SKIN TEST, QUANTIFERON AND INFG+874 SNP IN THE PROGRESSION TO TUBERCULOSIS DISEASE IN INFLAMMATORY BOWEL DISEASES PATIENTS

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P52. EVALUATION OF THE EFFECT OF TUBERCULIN SKIN TEST ON SUBSEQUENT INTERFERON GAMMA RELEASING ASSAY RESULTS (QUANTIFERON TB)

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P53. RELEVANCE OF THE USE OF TUBERCULIN SKIN TEST (TST) AND QUANTIFERON BEFORE THEPRESCRIPTION OF BIOLOGICAL AGENTS IN CHRONIC INFLAMMATORY DISEASES

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P54. EXPLORATION AND VALIDATION OF THE ROLE OF *LEISHMANIA*GENES PUTATIVELY ASSOCIATED TO PARASITE VIRULENCE

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P55. INTEGRATIVE ANALYSIS OF THE MACROPHAGE MICRO RNA-MRNA RESPONSE TO *LEISHMANIA MAJOR* INFECTION

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P56. IMMUNE RESPONSES SPECIFIC TO PHOSPHOENOLPYRUVATE CARBOXYKINASE DURING INFECTION WITH *LEISHMANIA INFANTUM*

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P57. IMMUNE CYTOKINE PROFILE OF LESIONS FROM CUTANEOUS LEISHMANIASIS PATIENTS USING A NEW NON-INVASIVE TECHNIQUE AT THE UNIVERSITY OF GONDAR HOSPITAL NORTH WEST ETHIOPIA

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P58. GENE EXPRESSION PROFILES OF INDUCIBLE NITRIC OXIDE SYNTHASE (iNOS), IL-1β, AND IL-12 CYTOKINES DURING *IN VIVO* INFECTION OF MICE BY AUTOCHTHONOUS DERMOTROPIC STRAINS OF *LEISHMANIA* SPECIES.

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P59. ROLE OF TREG CELLS IN PATHOGENESIS OF POST KALA AZAR DERMAL LEISHMANIASIS

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P60. AUTOCLAVED LEISHMANA MAJOR AND CAFFEIC ACID INDUCE HIGH LEVELS OF IGG2 AND RESTORE CUTANEOUS LESIONS IN INFECTED BALB/C MICE

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P61. DYSFUNCTION OF BLOOD NEUTROPHILS AND MONOCYTES IN CLINICAL VISCERAL LEISHMANIASIS

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P62. SKEWING OF SAG MEDIATED THERAPY FOR A PREDOMINANT TH1 DURING VISCERAL LEISHMANIASIS ON TRIGGERING CD2 EPITOPE

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P63. IMMUNOLOGICAL STATUS TO HEPATITIS B VIRUS OF PREGNANT WOMEN IN DAKAR, SENEGAL.

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P64. QUANTIFICATION OF HVB-DNA AND HVC-RNA VIRAL LOADS : A COMPARATIVE STUDY OF TWO COMMERCIAL KITS

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P65. TOLL-LIKE RECEPTOR 9 POLYMORPHISMS AND HEPATITIS B VIRUS CLEARANCE IN MOROCCAN PATIENTS

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P66. IMPACT OF TOLL-LIKE RECEPTORS 2 (TLR2) POLYMORPHISM IN HEPATITIS B

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P67. IL28B RS12979860 POLYMORPHISM IN HEALTHY AND CHRONIC HEPATITS C TUNISIAN PATIENTS: PREVALENCE AND THERAPEUTIC VALUES.

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P68. PREVALENCE OF ANTI-THYPEROXIDASE ANTIBODIES AND THYROID FUNCTION IN CHRONIC VIRAL HEPATITIS C RETROSPECTIVE STUDY OF 102 PATIENTS

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P69. ANTIBODIES ASSESSMENT DURING MALARIA SUBSEQUENT EPISODES IN CHILDREN AND ADULTS LIVING IN MALARIA HYPERENDEMIC AREA OF BURKINA FASO

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P70. IMPACT OF PLACENTAL PLASMODIUM FALCIPARUM MALARIA INFECTION ON THE CAMEROONIAN MATERNAL AND NEONATE'S PLASMA LEVELS OF SOME CYTOKINES KNOWN TO REGULATE T CELL DIFFERENTIATION AND FUNCTION

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P71. INCREASED LEVELS OF PROINFLAMMATORY AND NTINFLAMMATORY CYTOKINES ARE ASSOCIATED WITH BRAIN SWELLING IN MALAWIAN CHILDREN WITH CEREBRAL MALARIA

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P72. CEREBRAL MALARIA BRAIN SWELLING IS INFLAMMATION INDEPENDENT IN MALAWIAN CHILDREN

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P73. EFFECT OF HOOKWORM INFECTION AND ANTHELMINTIC TREATMENT ON *PLASMODIUM FALCIPARUM*-SPECIFIC ANTIBODY RESPONSES

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P74. DIFFERENCES IN IMMUNOLOGICAL PROFILE IN TWO WEST AFRICAN SETTINGS AS FUNCTION ENVIRONMENTAL CHANGES

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P75. PD-1+ T CELLS REFLECT ACTIVATED T CELL SUBSETS ASSOCIATED WITH LOWER REGULATORY PROFILE IN HIGH BURDEN OF HUMAN SCHISTOSOMIASIS.

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P76. INTERLEUKIN (IL-6 AND IL-10) ARE UP REGULATED IN LATE STAGE *Trypanosoma bruceirhodesiense* SLEEPING SICKNESS

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P77. PREVALENCE OF DENGUE AND CHIKUNGUNYA VIRUS INFECTIONS IN NORTH-EASTERN TANZANIA: A CROSS SECTIONAL STUDY AMONG PARTICIPANTS PRESENTING WITH MALARIA-LIKE SYMPTOMS

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P78.TREATMENT WITH RECOMBINANT IL-12 PROTECTS AGAINST SECONDARY CYSTIC ECHINOCOCCOSIS

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P79. IMPAIRMENT OF MACROPHAGES PRESENTING ABILITY AND VIABILITY BY *ECHINOCOCCUS GRANULOSUS* ANTIGENS : OTHER FACETS OF THE IMMUNOSUPPRESSION

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P80. A NOVEL HOMOZYGOUS CARD9 MUTATION IN A TUNISIAN PATIENT WITH DEEP DERMATOPHYTOSIS

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P81. TEMPORAL LINKS BETWEEN CYTOKINE PROFILE AND CANDIDA INFECTION IN TUNISIAN SEPSIS PATIENTS

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P82. ADD TO PROCALCITONIN, ANTI-CARDIOLIPIN ANTIBODIES ARE THEY NEW BIOMARKERS OF SEPSIS?

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P83. ANTI-INFLAMMATORY EFFECTS OF THE POTASSIUM CHANNEL (Kv1.3) BLOCKER KALIOTOXIN IN EXPERIMENTAL MODEL OF SEPSIS : TOXINS TO THERAPEUTIC AGENTS

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P84. CROSS-PROTECTION STUDIES IN MICE IMMUNIZED WITH IRON-REGULATED PASTEURELLA MULTOCIDA SEROTYPE B: 3,4 VA

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P85. PREVALENCE OF INFECTIOUS AGENTS IN PATIENTS WITH AUTOIMMUNE DISEASES: A CASE-CONTROL STUDY ON *HELICOBACTER PYLORI, RICKETTSIA CONORII* AND *TOXOPLASMA GONDII*

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Allergy

P86. THE IMPACT OF THE ENVIRONMENT IN THE DEVELOPMENT OF ALLERGIC DISEASES IN THE CASE OF THE CITY OF BENI MELLAL MOROCCO

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P87. THE EFFECT OF CD14, TLR2 AND TLR4 GENE POLYMORPHISMS ON TUNISIAN ASTHMA

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P88. ASSOCIATION BETWEEN VITAMIN D METABOLISM GENE POLYMORPHISMS AND RISK OT TUNISIAN ADULTS' ASTHMA

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P89. NOD2 GENE VARIANT IN TUNISIAN CHILDHOOD ASTHMA

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P90. ASSOCIATION OF STIP1 VARIANTS WITH ASTHMA SUSCEPTIBILITYAND TREATMENT RESPONSE TO INHALED CORTICOSTEROIDS IN TUNISIAN WOMEN.

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P91. SYSTEMIC PRODUCTION OF NITRICOXIDE DURING ALLERGIC RHINITIS, AND ALLERGIC ASTHMA: IMMONUMODULATION BY THE HELMINTH *ECHINOCOCCUS GRANULOSUS*

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P92. COMPONENT-RESOLVED DIAGNOSTICS IN PEDIATRIC FOOD ALLERGY : BOS D8 AND GALD1 COMPONENTS ARE ASSOCIATED WITH SEVERITY AND/OR PERSISTENCE IN COW'S MILK AND HEN'S EGG ALLERGY

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P93. COW MILK ALLERGY (CMA) IGE MEDIATED : ABOUT 30 CASES

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P94. INTERLEUKIN 4, INTERLEUKIN 13 AND GAMMA INTERFERON IN PATIENTS WITH FOOD ALLERGY

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P95. FATAL CASE OF TOXIC EPIDERMAL NECROLYSIS CAUSED BY PRISTINAMYCINE

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P96. SELECTIVE ALLERGY TO CEFAZOLIN CONFIRMED BY CUTANEOUS SKIN TESTING

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P97.CLOZAPINE-INDUCED MYOCARDITIS COMPLICATED WITH DILATED CARDIOMYOPATHY AND HEART FAILURE

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P98. IGE SENSITIZATION IN AUTISM CHILDREN

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Primary immunodeficiencies

P99. REFERENCE VALUES OF LEUCOCYTES EXPLORATIONS FOR THE DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES IN MOROCCAN POPULATION

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P100. MONOCLONAL GAMMOPATHY IN SCID PATIENTS PRIOR TO HEMATOPOIETIC STEM CELL TRANSPLANTATION: A REPORT OF 3 TUNISIAN PATIENTS

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P101. CHORIORETINAL DISEASES IN HUMAN IMMUNODEFICIENCY

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P102. THROMBOTIC THROMBOCYTOPENIC PURPURA REVELING PRIMARY COMBINED IMMUNODEFICIENCY

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P103. HIGH PREVALENCE OF SEVERE COMPLICATIONS IN LATE-ONSET COMBINED IMMUNE DEFICIENCY: ABOUT THREE OBSERVATIONS

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104. OUTCOME OF ECZEMA IN A PATIENT WITH WISKOTT-ALDRICH SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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P105. SEVERE DEFECT OF MEMORY B CELLS: REPORT OF 2 CASES OF PRIMARY ANTIBODY DEFICIENCIES (X-LINKED HYPER IGM SYNDROME AND CVID)

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P106. A FOUNDER MUTATION UNDERLIES A SEVERE FORM OF PHOSPHOGLUTAMASE 3 (PGM3) DEFICIENCY IN TUNISIAN PATIENTS

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P107. BONE MORROW FLOW CYTOMETRY ANALYSIS IN PATIENT WITH CONGENITAL AGAMMAGLOBULINEMIA : A CASE REPORT

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P108. A NOVEL MUTATION IN THE BRUTON'S TYROSINE KINASE GENE CAUSING X-LINKED AGAMMAGLOBULINEMIA

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P109. CGD DIAGNOSOS BY DHR TEST (PHAGOBURST): ABOUT A SERIES OF 6 PATIENTS

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P110. IS THE OEDEMA BRADYKINIC BY DEFICIT IN C1 INH, A RARE IMMUNODEFICIENCY ? THE EXPERIMENT OF BLIDA

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P111. MOLECULAR BASIS OF COMPLEMENT FACTOR H DEFICIENCY IN ATYPICAL HEMOLYTIC AND UREMIC SYNDROME PEDIATRIC TUNISIAN PATIENTS

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P112. TYPE I COMPLEMENT FACTOR I MUTATIONS IN TUNISIAN ATYPICAL HEMOLYTIC AND UREMIC SYNDROME

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P113. WEIGHTED GENE CO-EXPRESSION NETWORK ANALYSIS IDENTIFIES SPECIFIC MODULES AND HUB GENES RELATED TO ATYPICAL HEMOLYTIC HREMIC SYNDROME

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P114. CFHR1/CFHR3 DELETION IN TUNISIAN AHUS PATIENTS WITH ANTI-FACTOR H ANTIBODIES

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P115. IDENTIFICATION OF HETEROZYGOUS INTRACELLULAR FAS MUTATIONS IN TWO TUNISIAN PATIENTS WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

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Autoimmunity

P116. ANTI-NUCLEAR AUTOANTIBODY (AAN) PROFILE IN ALGERIAN LUPUS PATIENTS: ABOUT 106 CASES

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P117. IMMUNOLOGICAL PROFILE OF SLE IN NIGERIAN PATIENTS

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P118. AUTOANTIBODIES PROFIL IN LUPUS NEPHRITIS

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P119. ANTI- PHOSPHOLIPASE A2 RECEPTOR ANTIBODIES IN MEMBRANOUS NEPHROPATHY

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P120. ANTI-PCNA ANTIBODIES: PREVALENCE AND DIAGNOSTIC VALUE

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P121. ANTI-NUCLEOSOME ANTIBODIES: A NEW MARKER FOR SYSTEMIC LUPUS ERYTHEMATOSUS.

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P122. IMPLICATION OF ANNEXIN A1 IN SYSTEMIC LUPUS ERYTHEMATOSUS

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P123. USEFULNESS OF DETECTION OF DENSE FINE SPECKLED-70ANTIBODIES IN SOUTH TUNISIAN PATIENTS

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P124. RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND INCREASED SERUM IL-21 IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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P125. UP-REGULATED EXPRESSION OF TOLL-LIKE-RECEPTOR 4 IN RENAL AND SKIN LESIONS IN LUPUS ERYTHEMATOSUS

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P126. ANNEXIN A1 IMPLICATION IN CUTANEOUS LUPUS

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P127. EVALUATION OF X CHROMOSOME INACTIVATION IN PEMPHIGUS FOLIACEUS AND SYSTEMIC LUPUS ERYTHEMATOSUS

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P128. POLYMORPHISMS OF HLA MICROSATELLITE MARKERS IN TUNISIAN LUPUS ERYTHEMATOSUS

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P129. FREQUENCY OF CLASS II HLA ALLELES IN ALGERIAN LUPUS PATIENTS: ABOUT 58 CASES FOLLOWED AT BLIDA UNIVERSITY HOSPITAL

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P130. INTERLEUKIN-1-RECEPTOR-ASSOCIATED KINASE (*IRAK1*) GENE POLYMORPHISM IN SYSTEMIC LUPUS ERYTHEMATOSUS

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P131. ASSOCIATION STUDY BETWEEN *TNFAIP3* POLYMORPHISM (RS2230926) AND SYSTEMIC LUPUS ERYTHEMATOSUS IN TUNISIAN POPULATION

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P132. POLYMORPHISMS OF TOLL-LIKE RECEPTOR 4 AND CD14 GENES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

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P133. CYP27B1-1260 PROMOTER POLYMORPHISM AND VITAMIN D STATUS IN TUNISIAN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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P134. EXPRESSION OF IRF5 SNPS IS AT HIGH RISK OF DEVELOPING SLE AND RA IN ALGERIAN PATIENTS

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P135. SHARED GENETIC EFFECTS IN AUTOIMMUNE DISEASES

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P136. RHUMATOID POLYARTHRITIS, AUTOIMMUNE HEPATITIS TYPE ONE AND AUTO IMMUNE THYROIDITIS ASSOCIATION; CASE STUDY

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P137. ANTINUCLEAR ANTIBODIES IN RHEUMATOID ARTHRITIS, QUANTITATIVE AND QUALITATIVE ASPECTS

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P138. COMPARAISON OF TWO DIFFERENT KITS FOR ANTI-CCP ANTIBODIES ASSAY BY ELISA TECHNIQUE

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P139. ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND CRP/ACPA POSITIVITY IN ALGERIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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P140. IS MATRIX METALLOPROTEINASE-3 (MMP-3) A GOOD BIOMARKER IN RHEUMATOID ARTHRITIS DISEASE ACTIVITY ASSESSMENT?

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P141. CLINICAL, BIOLOGICAL AND RADIOLOGIC FACTORS ASSOCIATED WITH FAILURE OF CONVENTIONAL TREATMENTS AND THE RECOURSE TO BIOTHERAPY IN RHEUMATOID ARTHRITIS

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P142. THE INFLUENCE OF METHOTREXATE ON THE KINETICS OF BIOLOGICAL MARKERS IN RHEUMATOID ARTHRITIS AND THEIR CORRELATION WITH DISEASE ACTIVITY

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P143. TOLL-LIKE RECEPTOR 2 (–196 to 174) DEL POLYMORPHISM IS ASSOCIATED WITH RHEUMATOID ARTHRITIS IN TUNISIANS

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P144. INVOLVEMENT OF -3771C/T AND -1659C/T INOS GENE POLYMORPHISMS IN SUSCEPTIBILITY TO RHEUMATOID ARTHRITIS IN AN ALGERIAN COHORT

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P145. IRAK1 IS NOT ASSOCIATED WITH RHEUMATOID ARTHRITIS IN THE TUNISIAN POPULATION

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P146. ASSOCIATION OF MIR-146A WITH RHEUMATOID ARTHRITIS IN THE TUNISIAN POPULATION

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P147. VASCULAR ENDOTHELIAL GROWTH FACTOR GENE POLYMORPHISMS AND SUSCEPTIBILITY TO RHEUMATOID ARTHRITIS IN ALGERIAN POPULATION

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P148. IL-17A, IL-17RC POLYMORPHISMS AND IL-17 SERUM LEVELS IN TUNISIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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P149. A1298C AND C677T GENE POLYMORPHISMS OF THE METHYLENE TETRAHYDROFOLATE REDUCTASE IN RHEUMATOID ARTHRITIS IN ALGERIA

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P150. HAPLOTYPE STUDY: DETECTION OF A SUSCEPTIBILITY REGION WITHIN HLA-CLASS I FOR PRIMARY SJOGREN SYNDROME

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P151. ALL TRANS RETINOIC ACID IMMUNOMODULATES NITRIC OXIDE PRODUCTION DURING PRIMARY SJOGREN'S SYNDROME

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P152. SCREENING FOR IGG4-RELATED SYSTEMIC DISEASE IN PATIENTS WITH SICCA SYNDROME

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P153 AUTOANTIBODIES IN SYSTEMIC SCLEROSIS AND THEIR CLINICAL CORRELATION

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P154. A RARE ASSOCIATION BETWEEN ANTI-CENP A AND B, ANTI-NOR 90 AND ANTI-PM-SCL IN A PATIENT WITH LIMITED SYSTEMIC SCLEROSIS.

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P155. ANTINUCLEOLAR ANTIBODIES IN PATIENTS LACKING CLINICAL FEATURES RELATED TO SYSTEMIC SCLEROSIS

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P156. CD146 AND CD146s: ACTORS AND TARGETS OF SCLERODERMA

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P157. PTPN22 GENE POLYMORPHISM IN ALGERIAN SYSTEMIC SCLEROSIS PATIENTS

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P158. AUTOANTIBODIES IN PATIENTS WITH INFLAMMATORY MYOSITIS : ABOUT 108 CASES

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P159. BIOLOGICAL CHARACTERITICS OF ANTI-TIF1 AUTO-ANTIBODIES IN DERMATOMYOSITIS : TOWARD A NEW PROGNOSIS BIOMARKER

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P160. A RARE ASSOCIATION BETWEEN AN Mi-2, PL-7 and PL-12 ANTIBODIES IN A PATIENT WITH DERMATOMYOSITIS

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P161. AUTOANTIBODY PROFILE OF CONNECTIVE TISSUE DISEASE WITH CUTANEOUS MANIFESTATIONS

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P162. USEFULNESS OF ANTI-DESMOGLEIN 1 AND 3 ENZYME-LINKED IMMUNSORBENT ASSAY IN PEMPHIGUS VULGARIS AND FOLIACEUS IN SOUTH TUNISIA

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P163. AHR TRANSCRIPTION IS DECREASED IN SKIN OF VITILIGO PATIENTS

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P164. ASSOCIATION OF ANTI-PHOSPHATIDYLSERINE AUTO-ANTIBODIES WITH THE RISK OF THROMBOSIS IN WOMEN WITH ANTI-PHOSPHOLIPID: OBSTETRIC SYNDROME

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P165. IMMUNOLOGICAL STUDY AND CLINICAL PRESENTATION OF ANCA VASCULITIS

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P166. PR3 AND MPO-ANCA AUTOANTIBODY IN PATIENTS WITH SUSPICION OF VASCULITIS

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P167. TARGET ANTIGENS FOR ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES IN TUNISIAN PATIENTS

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P168. THE FREQUENCY OF THYROID AUTO-ANTIBODIES DURING BIERMER'S DISEASE

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P169. POLYMORPHISM -308 OF THE TNF-A GENE IN ALGERIAN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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P170. INTEREST IN THE RESEARCH OF ANTITHYROID ANTIBODIES DURING THE DIAGNOSIS OF A CETOSIC ACIDIC DIABETES

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P171. ANTI-PANCREATIC ANTIBODY PROFILE DURING THE DIAGNOSIS OF TYPE 1 DIABETES

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P172. AUTOANTIBODIES DIABETES AND MICRONUTRIENTS IN TYPE 1 DIABETICS AND SIBLINGS OF ABIDJAN DISTRICT, CÔTE D'IVOIRE.

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P173. CORRELATION BETWEEN DIABETES AUTOANTIBODIES AND ENVIRONMENTAL PARAMETERS IN TYPE 1 DIABETICS AND THEIR SIBLINGS IN ABIDJAN DISTRICT, CÔTE D'IVOIRE.

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P174. IMMUNOGLOBULIN GENES AND THE RISK OF TYPE 1 DIABETES: STUDY OF 59 FAMILIES

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P175. LACK OF ASSOCIATION BETWEEN ACE I/D GENE POLYMORPHISM AND TYPE 1 DIABETIC NEPHROPATHY IN THE TUNISIAN POPULATION

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P176. GENETIC POLYMORPHISM IN INTERFERON GAMMA (IFN-γ) IN ALGERIAN TYPE 1 DIABETES PATIENTS

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P177. INCREASED PREVALENCE OF COELIAC DISEASE IN DIABETES

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P178. CELIAC DISEASE SCREENING IN AN ALGERIAN COHORT OF CHILDREN WITH TYPE 1 DIABETES

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P179 PREVALENCE OF AUTOIMMUNE ENDOCRINOPATHIES IN CELIAC DISEASE (CD): ABOUT A RETROSPECTIVE SERIES

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P180. PREVALENCE OF INFRAMMATORY BOWEL DISEASES (IBD) DURING CELIAC DISEASE (CD)

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P181. PREVALENCE OF VIRAL HEPATITIS C (VHC) IN CELIAC DISEASE (CD): ABOUT A RETROSPECTIVE SERIES

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P182. DIAGNOSTIC VALUE OF ANTI-F-ACTIN ANTIBODIES

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P183. PREDICTIVE VALUE OF ANTI-MITOCHONDRIA ANTIBODIES TYPE 2 IN PATIENTS WITHOUT PRIMARY BILIARY CIRRHOSIS

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P184. AUTOANTIBODIES BY LINE IMMUNOASSAY IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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P185. CLINICAL AND IMMUNOLOGICAL PROFILE OF PATIENTS WITH NuMA ANTIBODIES : ABOUT 14 CASES.

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P186. AUTOIMMUNE LIMBIC ENCEPHALITIS: IMMUNOLOGICAL DIAGNOSIS

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P187. PERFORMANCE OF ANTI-AQUAPORINE 4 (AQP4- IgG) IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS DIAGNOSIS

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P188. A STUDY OF CORRELATION BETWEEN ACETYLCHOLINE RECEPTOR NITRIC OXIDE IN A SMALL COHORT OF ALGERIAN MYASTHENIA GRAVIS PATIENTS

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P189. PREVALENCE AND CLINICAL SIGNIFICANCE OF ANTI-NUCLEAR ANTIBODIES IN MULTIPLE SCLEROSIS

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P190. TUNISIAN FEMALE PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS HAVE SEVERE DEFICIENCY OF 25-HYDROXYVITAMIN D3

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P191. USE OF HEVYLITE™ ANTIBODIES IN CSF DIAGNOSIS

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P192. ASSOCIATION BETWEEN TUMOR NECROSIS FACTOR ALPHA-308 G/A POLYMORPHISM AND MULTIPLE SCLEROSIS IN ALGERIAN POPULATION

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P193. CRYOGLOBULINEMIA IN TUNISIAN PATIENTS

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P194. ANTI-DRUG ANTIBODIES AND ANTI TNF ALPHA TROUGH LEVELS: IS THERE A CLINICAL RELEVANCE FOR PATIENTS WITH CHRONIC INFLAMMATORY DISEASES?

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P195. ANTI-ERYTHROPOIETIN ANTIBODIES: PREVALENCE AND CLINICAL IMPACT IN HEMODIALYZED PATIENTS

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P196. CIRCULATING TNFα, IL-6 and IL-10 AS A POTENTIAL PROGNOSTIC MARKERS: A PROSPECTIVE STUDY IN 60 BREAST CANCER PATIENTS.

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P197. PLASMA HOMOCYSTEINE, FOLATE, VITAMIN B12 AND RISK OF BREAST CANCER IN WOMEN

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P198. PREDICTIVE VALUE OF SOLUBLE INTERLEUKIN-2 RECEPTOR α (IL2-Rα) DURING CHEMOTHERAPY IN BREAST CANCER PATIENTS

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P199. PREDICTIVE VALUE OF SOLUBLE GALECTIN-3 DURING CHEMOTHERAPY IN SENEGALESE WOMEN WITH BREAST CANCER

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P200. SMAD3 ASSOCIATION TO HIGH-GRADE TUMORS AND A HIGH PROLIFERATION INDEX IN (ERα+ERβ+) and PR+ BREAST CANCER

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P201. CYTOKINES BIOMARKERS ASSOCIATED TO GYNECOLOGICAL CANCERS

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P202. PENETRANCE OF THE MUTATIONS OF *D-LOOP* AND *CYTOCHROME B* IN THE OCCURRENCE OF OVARIAN CARCINOMES IN SENEGALESE WOMEN

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P203. HUMAN PAPILLOMAVIRUS 16 SEROPREVALENCE AMONG TUNISIAN WOMEN WITH NORMAL CYTOLOGY AND SQUAMOUS INTRAEPITHELIAL LESIONS

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P204. THE PROFILE OF IL-6 ACTIVATION MEDIATED BY STAT3 and AKT SIGNALING PATHWAYS IN HUMAN PROSTATE PATHOLOGIES

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P205. THE IL-17A/IL-10 BALANCE AND PSMA/PSA DUALITY IN PROSTATE CANCER PATIENTS

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P206. INTERPLAY BETWEEN SOLUBLE IL-6, TNF-α AND PSA LEVELS AND ITS RELEVANCE IN PROSTATE CARCINOMAS

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P207. THE EFFECT OF LEPTIN ON THE MIGRATION OF PROSTATE CANCER CELLS

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P208. EXPRESSION OF HUMAN SERUM HSP27 IN PROSTATE CANCER IS CORRELATED WITH THE GLEASON SCORE

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P209. TARGETING MENIN AS A NEW THERAPEUTIC STRATEGY IN CASTRATION-RESISTANT PROSTATE CANCER

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P210. POLY(I:C) POTENTIATES BACILLUS CALMETTE-GUÉRIN IMMUNOTHERAPY FOR BLADDER CANCER

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P211. CYTOKERATIN-21-FRAGMENT (CYFRA 21-1) AND β2-MICROGLOBILIN (β2M) MARKERS IN NASOPHARYNGEAL CANCER: A CASE-CONTROL STUDY

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P212. NITRIC OXIDE LEVELS IN PLASMA OF PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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P213. CYTOKINES PATTERN OF UNTREATED PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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P214. IL-10 AND TLR2,3 AS BIOMARKERS FOR HEAD AND NECK CANCERS

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P215. PROGNOSTIC VALUE OF TUMOR-INFILTRATING LEUKOCYTES IN NASOPHARYNGEAL CARCINOMA

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P216. EXPRESSIONS OF TOLL-LIKE RECEPTOR 9 IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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P217. NOS2 IS A KEY FACTOR OF EPITHELIAL-MESENCHYMAL TRANSITION AND MMP-9 ACTIVITY IN LARYNGEAL CARCINOMA

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P218. INVOLVEMENT OF THE FONCTIONAL DELETION (rs111200466) OF THE *TLR2* GENE IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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P219. ANTI-SOX1 ANTIBODY: AN ONCONEURONAL ANTIBODY FREQUENTLY ASSOCIATED WITH LUNG CANCERS.

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P220. JAK 2 GENE POLYMORPHISM IN LUNG CANCER

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P221. PROTEASOME: A NEW BIOMARKER OF MELANOMA IN DMBA-INDUCED SKIN CARCINOGENESIS

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P222. CIRCULATING AND SUB-CELLULAR PROTEASOME LEVELS: POTENTIAL BIOMARKERS OF MELANOMA IN DMBA-INDUCED SKIN CARCINOGENESIS

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P223. IMMUNOHISTOCHEMICAL EXPRESSION OF P53 AND VEGF PROTEINS IN A MOROCCAN SAMPLE OF GLIOBLASTOMA PATIENTS

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P224. IMMUNOHISTOCHEMICAL EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR VEGF AND p53 IN HUMAN NEUROBLASTIC TUMORS: MOROCCAN EXPERIENCE

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P225. INCREASED OXIDATIVE STRESS MARKERS AND PURINE CATABOLISM IN ALGERIANS WITH GALL BLADDER CANCER

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P226. POMEGRANATE PEELS DECREASES ABERRANT CRYPT FOCI DEVELOPMENT AND ASSOCIATED OXIDATIVE STRESS IN DISTAL COLON OF 1, 2-DIMETHYHYDRAZINE- INITIATED MICE

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P227. GENETIC VARIATION OF PD-1 IS ASSOCIATED WITH THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION

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P228. MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE: A CONTRAINDICATION FOR LIVING KIDNEY DONATION?

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P231. UTILITY OF SERUM FREE LIGHT CHAIN MEASUREMENT IN THE DIAGNOSIS AND FOLLOW-UP OF RANDALL'S DISEASE (ABOUT 03 CASES REPORTS)

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P232. CYTOKINE PROFIL IN TUNISIAN MULTIPLE MYELOMA PATIENTS

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Soumaya Chadi[1], H. Baccouche[2], T. Dhaoudi[1], I. Sfar[1], L. Mouelhi[3], T. Ben Abdallah[1], N. Ben Rhomdhane[2], Y.Gorgi[1]

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Transplantation

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P243. MICA AND RENAL TRANSPLANTATION: ANTIBODIES AND MICA-TM GENOTYPING IN A COHORT OF SOUTH TUNISIAN PATIENTS

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P247. RECOMBINANTION IN HUMAN LEUKOCYTE ANTIGEN REGION IN TUNISIAN BONE MARROW RECEIVERS AND RELATED DONORS

Manel Guirat[1], S. Mejdoub[1], A. Charfi[1], A. Kamoun[1], L. Gaddour[1], F. Hakim[1], L. Maalej[1], B. Mallek[1], I. Kammoun[1], I. Dammak[1], H. Bellaj [2], M. Mdhafer[2], S. Hdiji[2], M. Elloumi[2], H. Makni[1], N. Mahfoudh[1]

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P248. THE CONTRIBUTION OF NON-CLASSICAL METHODS IN THE LEARNING OF MEDICAL IMMUNOLOGY: PRELIMINARY STUDY AT THE FACULTY OF MEDICINE OF ORAN

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P250. *MARCKS* PROTEIN OVEREXPRESSION IN INFLAMMATORY BREAST CANCER

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Abstracts

Conferences

Innate Immunity, inflammation and cancer

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Macrophages are key orchestrators of chronic inflammation. They respond to microenvironmental signals with polarized genetic and functional programmes. M1 and M2 cells represent simplified extremes in a universe of functional states. Polarization of phagocytes sets these cells in a tissue remodeling and repair mode and orchestrate the smouldering and polarized chronic inflammation associated to established neoplasia. Intrinsic metabolic features and orchestration of metabolism are key components of macrophage polarization and function. Recent studies have begun to address the central issue of the relationship between genetic events causing cancer and activation of protumor, smouldering, non-resolving tumour-promoting inflammation. New vistas have emerged on molecules associated with M2 or M2-like polarization and its orchestration in cancer. Recently, proof-of-principle has been obtained that targeting TAM can be beneficial in human cancer. Moreover, complement and the tumoral fluid phase pattern recognition molecule PTX3 have emerged as a key component of tumor-promoting inflammation. IL-1 and members of the IL-1/IL-1 receptor family are important components of cancer related inflammation. Recent evidence on the regulatory role of components of the IL-1 system in cancer will be discussed.

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Innate lymphoid cells in helminth infection

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Innate lymphoid cells (ILCs) are classified into three groups, group 1 ILC (ILC1), group 2 ILC (ILC2) and group 3 ILC (ILC3) based on their ability to produce distinct sets of cytokines, which correspond to those produced by Th1, Th2 and Th17, respectively. In 2010, we reported a previously unidentified lymphocyte population producing large amounts of type 2 cytokines, which we named Natural helper (NH) cells. We identified NH cells in lymphoid clusters in adipose tissues, which we termed fat-associated lymphoid cluster (FALC). NH cells produce type 2 cytokines constitutively without any stimulation, and support the self-renewal of B1 cells and IgA production by B cells. Stimulation by IL-33 or helminth infection activates NH cells to produce large amounts of IL-5 and IL-13, which induce eosinophilia and goblet cell hyperplasia, both of which play an important role in anti-helminth immunity and pathophysiology of allergic diseases. NH cells are now considered to be a member of ILC2 that are tissue-resident lymphoid cells present in various tissues including skin, lung, intstines and adipose tissues. I will present our work on the role of ILC2 in helminth infection and regulatory mechanisms of ILC2 function after helminth infection.

Regulation of gut homeostasis by epithelial barriers

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Intestine is a unique tissue, where many commensal bacteria, called microbiota, inhabit. Therefore, intestinal mucosa is protected from microbiota as well as pathogenic bacteria by several types of barriers. One of these barriers is constructed by mucus layers, composed of inner and outer mucus layers in the colon. Microbiota is present in the outer mucus layer, whereas there is no microbiota in the inner mucus layer. Separation of microbiota from the intestinal epithelial cells contributes to prevention of intestinal inflammation. Indeed, invasion of bacteria into the colonic epithelial surface was shown in several mouse models of intestinal inflammation. However, the precise mechanisms by which the inner mucus layer is free of microbiota in the colon remain unknown.
Ly6/PLAUR domain-containing protein 8 (Lypd8), which was selectively expressed on the uppermost layer of colonic glands, was a highly glycosylated GPI-anchored protein and secreted into the colonic lumen, particularly the inner mucus layer. In mice lacking Lypd8, bacterial free space in the inner mucus layer disappeared and they were highly susceptible to intestinal inflammation. On the intestinal epithelial cell layer of the colon of the mutant mice, flagellated bacteria such as Escherichia, Helicobacter and Proteus were present. Depletion of these bacteria by antibiotics restored the bacterial free space in the inner mucus layer and ameliorated the intestinal inflammation of the mutant mice. Lypd8 bound to bacterial flagella and suppressed motile activity of flagellated bacteria. Thus, Lypd8 mediates segregation of microbiota from the intestinal epithelial layer in the colon, and thereby contributes to the prevention of intestinal inflammation.

Human Gut microbiota and Health: from structure to functions

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Ignored for long, the importance of the intestinal microbiota has been revealed over the last years. Although of great complexity, the metagenomic approach allowed key advance in the characterization of the genetic and genomic diversity of our microbiota. Exhaustive shotgun sequencing of healthy individuals as well as cohorts of patients suffering from various diseases including inflammatory bowel diseases, obesity and diabetes, liver diseases,… highlighted the importance of the symbiosis between the intestinal microbiota and its host (1). The first step was the establishment of a reference catalogue of 9. 9 millions non-redundant genes potentially present in the human gut microbiome (2). Then, the clustering of genes, using a method based on binning of co-abundant genes from 396 metagenomic samples, enabled comprehensive description of new microorganisms, in what was further referred as metagenomic species (MGS) and of smaller co-abundance gene groups representing viruses, phages, plasmids and other genetic entities (3). Mapping the metagenome of hundreds of individuals on the integrated catalogue of genes revealed genes, functions, MGS and species that were signatures of pathological situations termed dysbiosis (4). The richness of our microbiome was recognised a key feature of healthy people (5). Finally, to go further in the functionality of gut microbiome, an innovative functional metagenomic approach has been implemented allowing the identification of bacterial genes and molecules / metabolites involved in the cross talk between the gut microbiota and its host (1). The cutting-edge characterization of our other genome, our microbiome, remains a crucial step in the full understanding of human physiology (6).

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Defining protective natural killer cell subsets

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Natural killer (NK) cells are a critical component of innate immunity and an early line of defense against viruses. NK cell activation is tightly regulated by multiple germline-encoded inhibitory and activating receptors, allowing them to distinguish infected and malignant cells. Assortment of these receptors on the surface creates a vast diversity of NK cell subsets. Using a systems biology approach, our goal is to dissect how specific subsets respond to different infectious threats, and how viruses seek to subvert such responses.

The pathogenesis of progressive HIV associated tuberculosis

Robert Wilkinson
University of Cape Town, South Africa.

Understanding the events in early tuberculosis disease will facilitate the development of novel tests to predict disease progression and interventions to prevent it. Blood-based transcriptomic approaches consistently identify several pathways relevant to clinical disease. Here we show in asymptomatic people with HIV infection and early subclinical tuberculosis defined by combined positron emission and computed tomographic imaging, that transcripts relating to the classical complement pathway and Fc gamma-receptor remain enriched, accompanied by rising levels of circulating antibody/antigen immune complexes. Transcripts relating to these pathways also rise in the 12 months prior to disease presentation in HIV-uninfected people. This supports observations that antigen may be present in early disease despite being paucibacillary, and demonstrates that modulation of the immune response could occur via immune complex formation.

Challenges Associated with Buruli ulcer Treatment

Dorothy Yeboah-Manu
University of Ghana, Accra, Ghana.

Buruli ulcer (BU), caused by Mycobacterium ulcerans is a chronic necrotizing skin disease. It usually starts with a subcutaneous nodule or plaque containing large clusters of extracellular acid-fast bacilli. Surrounding tissue is destroyed by the cytotoxic macrolide toxin mycolactone produced by microcolonies of M. ulcerans. Late stage of the disease is the formation of large ulcers that progress, if untreated, over months and years. My talk will be on some challenges associated with case management as we have experienced from some health facilities in Ghana.

The beneficial and deleterious non-specific effects of vaccines: A challenge to immunology

Peter Aaby
Bandim Health Project, Bissau, Guinea-Bissau.

Vaccinology lives in a disease-specific paradigm with eradication of diseases as the ultimate goal. Hence, the assessment of vaccines has been based on measuring disease-specific outcomes. It is assumed that the overall effect on morbidity and mortality is always beneficial.

However, studies of the introduction of vaccines in high-mortality areas have questioned the disease-specific approach. Live vaccines like measles vaccines and BCG have been associated with much larger reductions in overall mortality than can be explained by specific prevention. Though preventing the targeted infections, some non-live vaccines are associated with increased overall mortality. The Strategic Advisory Group of Experts on Immunization (SAGE) of WHO has recently recommended further research into the potential non-specific effects (NSEs) of vaccines.

Observational studies and randomised trials have supported the existence of NSEs of vaccines. Live vaccines, including measles vaccine, oral polio vaccine (OPV), BCG and vaccinia, have beneficial NSEs whereas non-live vaccines, including DTP, Hepatitis B vaccine, inactivated polio vaccine (IPV), pentavalent vaccine and RTS,S malaria vaccine have deleterious NSEs. Similar effects have also been found with respect to morbidity in high-income countries. The NSEs of vaccines are frequently sex-differential, e.g. DTP has a stronger negative effect for girls, and vaccines often interact with other immune-modulating interventions like vitamin A.

These observations, not least the opposing effects of live and inactivated vaccines, contradict the current paradigm in vaccinology. The NSEs can only be understood as a result of beneficial or deleterious immune training. A new paradigm should be able to explain contradictions in the previous disease-specific understanding; for example, though protective against measles infection, the WHO-recommended high-titre measles vaccine (live) was associated with two-fold increased female mortality in several trials in Africa and WHO had to withdraw the vaccine in 1992. The increase in mortality was due to DTP being administered after measles vaccine. A new paradigm will raise questions which have not been considered before; for example, if a live vaccine has beneficial effects, we might do harm by stopping vaccinations once the targeted disease is eradicated. This probably happened when smallpox was eradicated and vaccinia was stopped. It may also happen once we have eradicated polio and measles and stop OPV and measles vaccinations. The data for vaccinia and OPV suggest that pursuing eradication goals and stopping live vaccinations are likely to be disastrous. Taking the non-specific effects of vaccines into consideration in the planning of vaccination programmes could lead to major improvements in child survival in low-income countries and to major reductions in health care cost in high-income countries.

Posttranscriptional regulation of immune responses by RNA binding proteins

Osamu Takeuchi
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Immune cell activation is initiated by the recognition of microbial components via Toll-like receptors (TLRs) in innate immune cells as well as by the ligation of antigen receptors in acquired immune cells. The signaling leads to the drastic changes in gene expression controlled at both transcriptional and posttranscriptional levels to regulate immune reactions. Posttranscriptional control of immune-related mRNAs is critical for preventing excess and persistent production of cytokines by degrading them via a set of RNA binding proteins (RBPs) recognizing cis-elements present in the mRNA 3'-untranslated region. Among RBPs, Roquin recognizes stem-loop structures present in mRNAs encoding inflammatory proteins and degrades them by recruiting a CCR4-NOT deadenylase complex to its target mRNAs. Roquin-mutant mice spontaneously develop autoimmunity by elevated expression of ICOS on T cells and enhanced production of TNF in innate immune cells. On the other hand, we identified Regnase-1 as an endonuclease essential for degradation of inflammation-related mRNAs such as Il6 induced by TLR stimuli in innate immune cells. Regnase-1 is also critical for suppressing activation of T cells and maintenance of immune and iron homeostasis in mice. We found that Regnase-1 and Roquin regulate an overlapping set of mRNAs via a common stem-loop structure. However, Regnase-1 and Roquin function in distinct subcellular locations: ribosome/endoplasmic reticulum and processing-body/stress granules, respectively. Moreover, Regnase-1 specifically degrades translationally active mRNAs depending on UPF1, a helicase essential for the nonsense-mediated mRNA decay. Regnase-1 and Roquin control early and late phase of inflammation, respectively. Interestingly, Regnase-1 recognizes inflammatory mRNAs undergoing pioneer rounds of translation, which is triggered by the phosphorylation of UPF1 by a kinase SMG1. Taken together, our findings reveal that differential regulation of immune-related mRNAs by two RNA binding proteins, Regnase-1 and Roquin, depends on their translation status and enables elaborate control of inflammation.

Blood and beyond: Properties of human tissue-resident T cells

René van Lier
Department of Hematopoiesis, Sanquin Research and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

Protection against respiratory infections in the lung is mediated by tissue-resident memory T-cells (TRM). We characterized memory T-cells from human lungs through transcriptome and functional analyses and revealed the existence of two distinct, but related memory T-cell populations in lung tissue. We discovered two transcriptional pathways that play essential roles the maintenance of TRM in tissue: one under the influence of NOTCH signaling1 and a second one controlled by the homologous transcriptional repressor BLIMP-1 and HOBIT2. Further, consistent with a requirement for prompt responsiveness to prevent microbial colonization of the respiratory barrier tissue, lung TRM constitutively transcribe deployment ready mRNAs encoding effector molecules and produce effector proteins with accelerated kinetics in response to TCR activation.

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B cell TRAF3: A regulator of B cell survival, activation, and tumorigenesis

Gail Bishop
University of Iowa, USA

The talk will focus upon how the adapter protein TRAF3 impacts B cell survival and activation through multiple molecular pathways, and how this explains the association of TRAF3 deficiency and mutations with human B cell malignancies.

Genetic restriction of antigen-presentation dictates allergic sensitization and disease in humanized mice

Winfried Pickl
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More than 25% of the population suffers from IgE-associated allergies. The manifestations of IgE-associated allergies include besides allergic rhinitis, conjunctivitis and dermatitis also severe organ-specific forms such as asthma, food allergy and life-threatening anaphylaxis. One major question is why certain individuals develop an allergic sensitization towards certain allergens. In a novel, humanized animal model, which uses human TCRs and HLA molecules, we identified genetic restriction of antigen-presentation as primary factor dictating allergic sensitization and disease against the major pollen allergen from the weed mugwort, which frequently causes sensitization and disease in humans. Furthermore, we confirm the importance of the balance between allergen-specific T effector and T regulatory cells for modulating initial but also already established allergic immune responses.

Shift of autoimmunity in NOD mice deficient in the ICOS costimulation pathway

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NOD mice are autoimmune-prone animals that represent an invaluable model of autoimmune type 1 diabetes (T1D). Inducible T cell co-stimulator (ICOS) has been implicated in the induction and regulation of Th1, Th2, and Th17 immunity, induction of thymus-dependent antibody responses and the germinal center reaction. We studied the consequences of ICOS gene invalidation on the autoimmune manifestations in the NOD background.

Neither Icos-/- nor Icosl-/- NOD mice developed T1D. In contrast, myositis occurred in both of them, as attested by significantly decreased muscle grip strength and locomotor disability (impaired cadence and print area). Pathological analysis revealed the presence of necrotic myofibers and important inflammatory infiltrates (CD4+T cells, macrophages). Muscle lesions were objectifiable using small animal MRI, correlated with histopathology and regressed under steroid therapy. CD4+T cells were Th1 biased. Myositis developed in CD8- but not CD4-deficient mice. Disease was conferred to NOD.scid recipients by Icosl-/- CD4+ T cell adoptive transfer. Promoting in vivo activated CD4+ effector T cells, administration of IL 2/anti-IL-2 complexes exacerbated myopathy. Serum proteomic analysis revealed five potential autoantibody targets, among two were over-expressed in diseased muscle. Searching for corresponding auto-antibodies in patients, we developed a ALBIA (Luminex™ immunoassay) using human ortholog proteins. One of them revealed positivity in a minority of individuals from a ~700 patient cohort.

These results show that the ICOS pathway is indispensable for the development of T1D in NOD mice. ICOS/ICOSL deficiency shits autoimmunity from endocrine pancreas to muscle. Myositides are severe diseases characterized by muscle weakness, leading to bedridden state and possibly death. Pathophysiological studies and therapeutic advances have been hampered by the lack of appropriate mouse models. This work establishes therefore Icos-/- and Icosl-/- NOD mice as a unique paradigm of spontaneous myositis, not requiring immunization with autoantigen.

IL-17 secreting T cells and their targeting in new immunotherapeutic approaches for autoimmune diseases

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In the field of autoimmunity, much of the focus in drug discovery has been on IL-17A production by CD4+ Th17 cells and their induction by IL-23. Stimulation of dendritic cells by pathogen-derived molecules promotes maturation and the production of T-cell differentiating cytokines. We have shown that TLR and NLR agonists induce innate IL-1 and IL-18 which synergize with IL-23 to activate memory Th17 cells, but also IL-17 production by γδ T cells. While CD4+ T cells, are considered to be the key pathogenic lymphocytes in many T cell-mediated autoimmune diseases, such as multiple sclerosis (MS) and the mouse model experimental autoimmune encephalomyelitis (EAE), innate-like lymphocytes, including γδ T cells, NK cells, NKT cells and innate lymphoid cells (ILC) can also secrete IL-17 and related cytokines. γδ T cells are found in the brains of MS patients and in the EAE model, a high frequency of γδ T cells infiltrating the CNS are IL-17-secreting.
Although γδ T cells can respond to antigens through their T cell receptor (TCR), our findings suggest that IL-17-seceting γδ T cells that are pathogenic in EAE function as innate immune cells activated by the cytokines IL-1, IL-18 and IL-23 independent of TCR engagement. We have recently identified a novel Vγ4 T cell subset, which, together with conventional γδ T cells, play a critical role in the pathogenesis of EAE by promoting the activation of Th17 cells to secrete IL-17A, IL-17F and GM-CSF and migrate into the CNS to mediate inflammation and autoimmunity. NK cells on the other hand are a key source of IFN-γ in EAE. We have shown that early IFN-γ from NK cells plays a role in the induction phase of EAE by promoting VLA-4 expression on CD4 T cells, thus conferring encephalitogenic activity on the Th17 cells.
The induction and function of Th1 and Th17 cells is regulated by cytokines secreted by the other major subtypes of T cells, especially IL-10 and TGF-β production by Treg cells but also by regulatory cells of the innate immune system. The induction of adaptive Treg cells is stimulated by retinoic acid, TGF-β and IL-10 in response to certain virulence factors from pathogens, such as helminth parasites that have evolved sophisticated mechanisms to subvert host protective immunity. Pathogens and pathogen-derived molecules can also promote activation of alternatively activated M2 macrophages, ILC2 and tolerogenic dendritic cells that can suppress Th1 or Th17 cells, either directly or through the induction of Treg cells. We have identified approaches for activation of anti-inflammatory cytokines, regulatory innate immune cells and Treg cells, without Th1 or Th17 cells. These approaches have been effective in attenuating inflammatory disease in pre-clinical models of autoimmunity.

IL-4–producing B cells regulate T helper cell dichotomy in type 1- and type 2-controlled diseases

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Interleukin-4 (IL-4)–induced T helper (Th) 2 cells promote susceptibility to the protozoan parasite Leishmania major, while conferring immunity to the intestinal trematode Schistosoma mansoni.

Here, we report that abrogation of IL-4 receptor alpha (IL-4Rα) signaling on B cells in BALB/c mice (mb1creIL-4Rα–/lox) transformed non-healer BALB/c to a healer phenotype with an early type 1 and dramatically reduced type 2 immune response and an absence of ulceration and necrosis during cutaneous leishmaniasis. From adoptive reconstitution and mixed bone-marrow chimera studies in B cell-deficient (μMT) mice, we reveal a central role for B cell-derived IL-4 and IL-4Rα in the optimal induction of the susceptible type 2 phenotype to L. major infection. We further demonstrate that the absence of IL-4Rα signaling on B cells exacerbated Schistosoma mansoni-induced mortality and pathology in BALB/c mice due to a diminished type 2 immune response. In both disease models, IL-4Rα–responsive B cells displayed increased IL-4 production as early as day 1 after infection. Together, these results demonstrate that IL-4–producing and IL-4Rα–responsive B cells are critical in regulating and assisting early T helper dichotomy toward Th2 responses, which are detrimental in cutaneous leishmaniasis but beneficial in acute schistosomiasis.

Immunity and protection against leishmaniasis: standing up to the challenges

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In terms of global disease burden, leishmaniasis are one of the most important parasitic diseases with an estimated incidence of 2 million cases annually and 2.1 million disability adjusted life years. That the majority of individuals, living in an area of Leishmania (L.) transmission, who have previously developed active cutaneous leishmaniases or asymptomatic infection are resistant to a subsequent clinical infection provides the rationale for vaccine development. During my presentation I will share with you three questions that are challenging for vaccine development:

1. The limits of the experimental models of leishmaniasis for vaccine development: these models are more predictive for the validation of vaccines when the effector mechanism requires an antibody response. For those that need a cellular (or mixed) response, things are much more complicated.
2. The identification of human immune correlates for protection and the role of Leishmania-specific CD4 and CD8 T cells responses.
3. The nature of vaccine candidate: we believe that should be composed of several parasite proteins (3-6) that could generate different peptides to be presented by MHC class II and I of diverse genetic background of the human population. The combination of, at least, one protein from the vector saliva should be considered as additional component.

Towards A Pan Leishmaniasis Vaccine: Are We Almost There?

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Parasitic diseases are among one of the major causes of mortality and morbidity around the world, particularly in developing countries. Human leishmaniasis are a complex spectrum of diseases affecting over 12 million people with an estimated 350 million people at risk of becoming infected globally. Manifestations of the disease range from small self-healing skin ulcers and lesions to large disfiguring scars or even death, depending on the species of Leishmania involved. Despite this significant health and societal burden, there is currently no effective vaccine against the disease. Worse still, the existing treatments either cause major side effects or are only effective in specific circumstances. The lack of effective vaccine is mostly attributed to lack of understanding of factors that regulate the development, maintenance and loss of secondary immunity. Interestingly, humans and animals that recover from infection remain immune for life, suggesting that memory cells able to protect against secondary infection develop following recovery from primary infection. Using reverse immunology and proteomics techniques, we identified a highly conserved protein that provides striking protection in vaccinated mice. With the help of collaborators around the globe, we demonstrated this protein also induces strong immune response in human patients. These studies subsequently led to the development of first Leishmania-specific reagent called tetramers, which is capable of identifying Leishmania-specific T cells at single cell level over an entire course of infection. It also helped to show that majority of the immune response is directed towards this protein. This unique reagent helped us to generate transgenic mice whose T cells all express receptor for this particular protein. We are now poised to use these animals to address fundamental questions regarding the factors that regulate antigen-specific memory response in leishmaniasis. Understanding these factors is critical for developing effective vaccine and vaccination strategies against leishmaniasis.

Correlates of protection from Controlled Human Malaria Infections (CHMI) in semi-immune Kenyan adults

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The need for a highly effective malaria vaccine remains urgent but the correlates of protection in humans are still poorly defined. Controlled human malaria infections (CHMI) provide a rapid means to compare immune responses between vaccinees with variable parasite growth post-challenge. This strategy may enable the identification of antigens that could be prioritized for vaccine development. We aim to use the CHMI platform as a new tool for the identification of correlates of protection against malaria. To achieve this we are screening 2000 volunteers to identify 200 participants with a range of antibody responses to malaria antigens. These 200 volunteers will undergo CHMI by direct venous inoculation (DVI) with aseptic, purified, cryopreserved *Plasmodium falciparum* (Pf) sporozoites (Sanaria® PfSPZ Challenge), and then admitted to a facility to be closely monitored clinically and for emergence of blood stage parasitaemia by PCR. Pre-CHMI antibodies will be screened using a newly developed custom protein microarray (KILChip v1.0) containing ~120 Pf merozoite antigens to investigate how they affect the outcome of CHMI. To date 129 Kenyan adults have undergone CHMI. Parasite growth rates have varied from the log-linear pattern seen previously in malaria naïve volunteers, through negative growth rates following emergence from the liver, to undetectable parasitaemia throughout monitoring. Pre-CHMI antibody levels against total parasite schizont extract and multiple merozoite antigens have varied from low or undetectable through intermediate to high. Analyses of these data are ongoing and preliminary outcomes with regards to the antibody correlates of protection will be presented.

Immunoglobulin superfamily members encoded by herpesviruses and their roles in immune evasion

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Viruses have developed a variety of strategies to manipulate host immune defenses in order to guarantee their survival. During millions of years of co-evolution with their respective hosts, large DNA viruses have extensively captured cellular genes, by horizontal gene transfer, to equip themselves with proteins that down modulate both innate and adaptive immune responses, which determine their ability to establish life-long latency. These captured genes include members of the immunoglobulin superfamily, whose products constitute the most diverse group of proteins of vertebrate genomes. The flexible structural nature of the immunoglobulin domains, which partake in a variety of functions mediated by ligand-binding interactions, makes them attractive targets for viral capture due to their capacity to generate high functional diversity. Here, we discuss the distinct structural characteristics, binding properties, and functions of herpes virus proteins that belong to the immunoglobulin superfamily, including homologs of CD200, Fc receptors, carcinoembryonic antigen-related cell adhesion molecules (CEACAMs), and signaling lymphocyte activation molecules (SLAMs). An understanding of the properties and modes of action of these viral proteins may guide the development of novel immune-modulatory therapeutic tools.

Inborn errors of immunity: susceptibility to infections and beyond

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Monogenic inborn errors of immunity in humans underlie a large spectrum of diseases which have in common a severe dysfunction of the immune system. The most common clinical features of these hereditary immune-deficiencies are extreme susceptibility to infections. During last decades, their study did help dissect pathways involved in a variety of immune responses to pathogens. More recently, these diseases are being studied as a model to decipher immune mechanisms involved in emergence of other associated clinical manifestations including allergy, auto-immunity and malignant lymphoproliferation. The tremendous progress made in the study of the genetic basis of these inborn errors of immunity is shaping our understanding of their multiple faces.

Applications and advances in next-generation sequencing for the diagnosis of primary immunodeficiencies

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This talk will focus on the uses of next-generation sequencing (NGS) technologies for the diagnosis of primary immunodeficiencies. New developments in NGS and data analysis will be discussed in relation to the practice of clinical immunology as well as for translational research focused on the discovery of novel diseases.

Next generation TREC analysis to detect abnormal T-cell proliferation in patients with primary immunodeficiencies

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T-cell receptor excision circles (TRECs) are formed during T-cell development and have proven invaluable to evaluate thymus function and to screen for T-cell deficits in neonates. However, the lack of a stable coding joint precludes analysis of in vivo replication history, because the δREC-ψJα rearrangement that forms TRECs is removed from the genome by subsequent Vα–Jα gene rearrangements. We here aimed to overcome this limitation by developing a multiplex TRG assay to quantify Vγ-Jγ rearrangements as a genomic marker for T cells, and establishing a cell line control with a stable genomic insertion of the TREC construct.
The TRG assay detected a rearrangement in 80-90% of purified αβT cells, similar to the 85% of developing αβT cells forming δREC-ψJα rearrangements. Using the HSB-2 cell line containing TRG rearrangements and stably transduced with a TREC construct, naive CD4 and CD8 T cells were shown to have undergone 5-6 cell divisions, whereas in memory subsets this was up to 12. Using DNA from full blood of 61 patients with antibody deficiency, we found a significantly increased median T-cell replication history (8 cycles vs 5 in controls). Finally, reduced numbers of TRECs were detected in dried blood spots of neonates with Down syndrome (n=84). However, as TRG numbers were reduced as well, the median T-cell replication history (2 cycles) was not different from controls (n=104).
In conclusion, we here optimised the TREC assay to quantify T-cell replication history. This approach can be applied to study human T-cell function in more detail, and especially to determine if low TRECs originate from enhanced proliferation or low circulating T-cell numbers. Hence, it could advance identification of T-cell defects in antibody deficiencies and it could serve as first follow-up test when low/absent TRECs are found during newborn screening for primary immunodeficiencies.

Identifying molecular targets in human neutrophils: The song remains the same

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In addition to being professional phagocytes, neutrophils produce a wide spectrum of inflammatory cytokines, which shape both the innate and adaptive immune responses. We and others have deciphered many of the signaling intermediates that control this response. More recently, neutrophils were shown to extrude decondensed chromatin, thus forming NETs (neutrophil extracellular traps). These structures immobilize pathogens, thus preventing their spreading, and also feature antimicrobial molecules. NETs were additionally shown to participate in the pathogenesis of autoimmune and inflammatory disorders. Despite the importance of NETs, the molecular mechanisms underlying their formation, as well as the upstream signaling pathways involved, are only partially understood. Likewise, current methodological approaches to quantify NETs suffer from significant drawbacks.

We developed a quantification method based on novel, fluorescent polymers that only bind extruded NETs. This new approach allows for a reliable, standardized quantification of NETosis, and was applied to study the signaling pathways controlling the phenomenon. We also revisited the issue of whether NET generation is ROS-dependent, and examined the involvement of citrullinating enzymes such as PAD4. Our data unveils new molecular targets that can be exploited for therapeutic intervention in pathologies known to feature neutrophils or their products.

Complement in pathophysiology and Therapeutics of human diseases

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The complement system is part of both innate and adaptative immune systems. It consists of over than 35 solubles and membranous proteins. This system is mainly activated by three different pathways, classical, alternative and lectin ones even if it's recognized more.
In this report, we will review the diversity and the involvement of complement activation and/or dysregulation in the pathophysiology of many human diseases which include both acute and chronic diseases and affect a wide range of organs.
We'll highlight on the selected examples of complement related diseades as atypical hemolytic uremic syndrome (aHUS), wet-type age-related macular degeneration (AMD), Antineutrophil Cytoplasmic Autoantibody Associated Pauci-Immune Vasculitis and others. We'll highlight the current perception of complement-targeted drugs and provides a brief overview of recent strategies and emerging trends.
At the end, we'll briefly discuss about diagnosis approaches and treatment of 03 complement-related diseases in Algeria.

Neuroendocrine regulation of immunity

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An important role of neuroendocrine-immune interactions in regulating immunity is emerging. Glucocorticoids (GCs), are steroid hormones released into the circulation upon activation of the hypothalamic-pituitary-adrenal (HPA) axis, in conditions of inflammation and stress. This pathway is known to dampen immune responses and down-regulate inflammation. However, the conditional deletion of the GC-receptor (GR) in NKp46+ innate lymphoid cells (ILCs) revealed an unexpected role of endogenous GCs on the enhancement of group 1 ILC functions in a model of viral infection. Upon murine cytomegalovirus (MCMV) infection, we found that the regulation of gene expression in group 1 ILC by GCs is both subset-dependent and organ-specific. Moreover, GR signalling in NKp46+ ILCs is required for an early recruitment of innate immune cells in the liver. Finally, we found that this novel HPA-dependent regulatory pathway is essential to prevent liver pathology, to promote virus clearance in this organ, and to ensure host resistance to infection.

Improving anti-tumor reactivity of human gamma/delta T-cells

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γδ T-cells comprise a numerically small subset of CD3+ T-cells in peripheral blood but occur at increased frequency in mucosal tissues. The major subset of human blood □□ T-cells expresses a Vγ9Vδ2-encoded T-cell receptor (TCR) which specifically recognizes pyrophosphate intermediates of the cholesterol synthesis pathway from microbes and tumor cells. Recognition of such pyrophosphates is not dependent on HLA presentation but requires the butyrophilin member BTN3A1 (also termed CD277). Due to their HLA-independent killing of many different tumor cells, γδ T-cells have recently raised great interest as potential effector cells for cell-based immunotherapy. In my presentation I will discuss various strategies to improve the efficacy of tumor cell killing by human γδ T-cells. This includes targeting of inhibitory mechanisms such as prostaglandin E2 and certain galectins but also developing bispecific antibody constructs which allow to specifically target γδ T-cells to tumor-associated cell surface antigens such as Her-2/neu. Furthermore, the sensitivity of some tumor cells towards γδ T-cell mediated cytotoxicity can be improved by epigenetic modifiers such as histone deacetylase inhibitor valproic acid. The overall goal is to improve cytotoxic effector activity of γδ T-cells (and therefore to pave the way to clinical application) by enhancing cytotoxic mechanisms and inhibiting suppressive mechanisms.

Recent review: Chitadze, Oberg, Wesch & Kabelitz, Trends Immunol 38:668-678, 2017.

A tale on the immunobiology of aging

Anis Larbi
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Early studies have shown that T cells from elderly individuals produce less IL-2 following stimulation. From there, started the concept of immunosenescence that still prevails nowadays. However, much information on the immune system has been generated especially for T cell biology. In this talk, I will cover the sequences of T cell differentiation and relate this to lifespan, which is an extended period of time with various and often repeated antigenic stimulations. I will also present novel data showing a subset of T cell that is resistant to the expected differentiation and senescence program. The implications on health and diseases will be discussed.

My unusual course of researcher woman in the context of founding fathers feminism of modern Tunisia

Oum Kalthoum Ben Hassine

Born in a conservative society in southern Tunisia where girl schooling was badly seen, my personal and professional careers has something unusual. Thus, I have already experienced the injustice done to women since childhood because at the age of 12, my family wanted to remove me out of school to get married. From there, begins for me an itinerary marked by difficulties, an obstacle course. However, beyond these difficulties, there is a fate trame that illustrates Tunisia's will to ensure, from the moment of independence, equal opportunities with the entrance on stage of political actors, including the Prime Minister at the time of Tunisia who intervened so that I could continue my studies. That is how the baccalauréat in pocket, I went to study at Tunis University and then at the Montpellier University (France) where I prepared and obtained all the university degrees until the last one (Doctoral d'Etat ès sciences). I was then the first girl in my city to go through the door of a high school and the first student of the Tunisian South to integrate an academic institution. That is how began the journey that has made me an activist for knowledge, Science, culture and the great causes of humanity. Moreover, it was from the injustice that I have known since childhood that my feminism was born and that my struggle for the cause of women and equality of opportunities and my ardent desire to address challenges.

After spending a few years as an associate professor at the University of Sciences and Technics in Montpellier (France), I returned to Tunis University (Faculty of Sciences) where I set up a Laboratory in a traditionally male domain, that of the marine sciences, created and led numerous training pathways for students and actively participated in the reform and improvement of higher education.

In my laboratory, dedicated to marine biology, ecology and parasitology, I developed research axes of scientific and socio-economic interest and carried out numerous research studies widely recognized by the scientific community (more than 250 publications and more than 300 scientific communications). I also assured the training of dozens of researchers in a Mediterranean region where highly qualified researchers are valuable and I established many fruitful scientific collaborations with other laboratories and research institutions of Mediterranean and European countries on issues of great importance for the protection of Mediterranean ecosystems and bioresources. This allowed me to obtain, in 2016, the Medal Rammal 2015 awarded by EuroScience to a distinguished scientist for his work in a Mediterranean country.

In addition, I did not cease to work for the encouragement of women in science and technology. For this, I co-founded and chaired in 1998 the Tunisian Association "Women and Sciences", which aims women empowering, equal opportunities in science, encouraging young women to integrate science and technology and building of scientific knowledge with women.

Infiltrating immune cells that predict patient outcome in colorectal cancer

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The immune response to cancer is complex and involves a network of cells and molecules exquisitely sensitive to change. Our research uses new technologies to study the immune system as a whole and to monitor changes in the immune response within the tumour itself, and over time, in the blood. We have developed tools to both analyse and visualise changes in the cells and molecules in the immune response in people with colorectal cancer. We have identifed new subsets of immune cells that may play a vital role in tumour progression or rejection. We have validated the prognosstic effect of these cells by measuring frequency and location of cells in tumour sections with associated clinical outcome data. Our approach allows both discovery and clinical relevance to be studied together, without compromising the complexity of immunology.

Role of micro-RNAs in immunity, inflammation and cross-talk between tumor and host immune system

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Micro RNA are small noncoding RNA that regulate genes expression, mostly at post-transcription stage targeting mRNA and inducing their degradation or inhibition of their translation into proteins. Most of the biological mechanisms are regulated by micro-RNAs, including immunity. Indeed, different developmental stages and effector sub-populations are not only characterized by cell surfaces molecules, transcriptions factors, transcriptomic and proteomic profiles, it is now admitted that micro-RNA profiles do characterize immune cells as well, being associated to their differentiation steps and to their function. It was revealed dynamic changes defining a specific micro-RNAs signature of each stage of differentiation, including the naïve, effector and memory T cells. Particularly, miR-155 is a critical player in both innate and adaptive immune responses. It can influence CD4+ T cell lineage choice. Results of transfection of pre-miR-155 into purified CD4+ T cells showed that miR-155 positively regulated both Treg and Th17 cell differentiation.
Moreover, some micro-RNAs are associated with inflammation. Indeed, several inflammatory stimuli are capable of regulating the expression of miRNAs. In the context of the inflammation, TLR, antigens or cytokine ligands may affect the expression of miRNAs through the regulation of specific transcriptional factors. For example, the ligand of TLR4, the lipopolysaccharide (LPS), induces different miRNAs such as miR - 155, miR-146a and miR-132. Our results on miR-146a SNP showed its association with some inflammatory diseases.
It is also admitted that micro-RNAs usually regulate genes expression in autologous cells but they can be excreted by cells within exosomes. Hence, they are present in plasma and biological fluids, playing a role, locally and at a distance, since they can enter other cells and modify the profile of their gene expression. For example, Treg produce excreted micro-RNAs that are involved in their suppressive function. It is reported that miR-146a, one of the miRNAs prevalently expressed in Treg cells, is critical for their suppressor function. The deficiency of miR-146a in Treg cells resulted in a breakdown of immunological tolerance manifested in fatal IFNγ-dependent immune-mediated lesions in a variety of organs.
Micro- RNAs could also be secreted by tumor cells. For example, an increased secretion of miR-214 was observed in various types of human cancers and mouse tumor models. Tumor-secreted miR-214 delivered into recipient T cells by microvesicles (MVs) efficiently downregulated phosphatase and tensin homolog (PTEN), promoting Treg expansion and resulting in tumor evasion and growth.
However, other secreted miRs are involved in crosstalk between tumors and host immune system. Indeed, through bioinformatics and expression studies, we were able to show that several miRs playing a role in immunity/inflammation are also either over-expressed as OncomiRs (such as miR-21) or under-expressed as tumor suppressor genes (such as miR-34) by tumors cells. In a model, we suggest that secreted miRs in a context of chronic inflammation could promote a tumor, which could in turn, induce Treg expansion, leading to

tumor growth. Mir secretion constitutes as a novel mechanism through which cancer cells and immune response actively interact.

Vista as a potential promising new target in colorectal cancer

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The targeting of immune checkpoint molecules through cancer immunotherapy has produced promising clinical results in recent years. The V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA) is a novel checkpoint candidate, which suppresses T-cell response. It has been reported that VISTA and PD-1 regulate T-cell response in a nonredundant manner, providing the rational to concurrently target VISTA and PD-1 in cancer. We will first review data from the literature indicating how VISTA blockade can enhance antitumor immune response. We will then present our data related to the expression and role of VISTA in patients presenting with colorectal cancer. Cancer samples were surgically removed along with healthy control regions. Subsequently, the level of VISTAs expression was measured using real-time RT-PCR. Our study revealed a significant expression of VISTA in tumor tissues compared to controls. Interesting preliminary observations were made when VISTA expression was correlated to various patient parameters such as tumor stage, tumor localization and metastasis. Finally, we will discuss how VISTA could be considered as a new interesting immune checkpoint target in colorectal cancer.

Immunotherapy of cancers: Where are we now and major challenges

Salem Chouaib
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Immunomodulators, cancer vaccines and checkpoint inhibitors have been used to harness patient immune response in cancer patients. Although the advent of new immunotherapy approaches based on the use of immune checkpoint inhibitors has improved the survival of many patients with advanced malignancies, the high prevalence of non-responders, also provides a strong reminder that we possess only a partial understanding of the events underlying the immune escape and resistance of tumors. At present, the major challenge in cancer immunotherapy is the harsh immunosuppressive tumor microenvironment. We will discuss how it impairs anti-tumor cytotoxic response through induction of tumor resistance and plasticity and by shaping stroma reactivity.

Vaccines for prevention of non-viral cancers

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Discovery almost three decades ago of the first few human tumor antigens, targets of human antibodies and T cells, started a new field of therapeutic cancer vaccines. Hundreds of molecules that were found to be differentially expressed on tumors versus normal cells were incorporated in various forms into vaccines to be administered to patients in hope of boosting preexisting immunity or eliciting new immune responses to control tumor growth. One such antigen was the epithelial mucin MUC1 that is overexpressed and hypoglycosylated on tumor cells compared to normal tissues and recognized as such by human antibodies and T cells. Because this tumor form of MUC1 is expressed on all human adenocarcinomas, preclinical and clinical studies of MUC1 vaccines were performed in breast, pancreatic, colon, ovarian and lung cancer among others. While immune responses could be documented post vaccination, they were usually of low titter (antibodies) and low frequency (T cells). Clinical responses were rare.
Many reasons for the failure of MUC1 vaccines were elucidated in these experiments, including the more general immunosuppressive mechanisms of the tumor microenvironment as well as immunosuppressive and tumor promoting functions of MUC1 on the tumor. The newest immunotherapy approaches directed to releasing tumor-induced immunosuppression, such as the checkpoint inhibitors, have had impressive successes in some patients and in some cancers that have been refractory to all other therapies. Therapeutic vaccines given in combination with checkpoint inhibitors might be more effective than when given alone, however the cost of that combined therapy is high. Our approach has been to test the cancer vaccines in the premalignant setting, where the immunosuppressive microenvironment should not exist and where the vaccines could induce strong immunity to prevent premalignant lesions from progressing to cancer.
We have been testing the MUC1 vaccine composed of 100aa from the MUC1 tandem repeat region, the immunogenic portion of the molecule, in combination with a TLR-3 agonist Poly-ICLC as adjuvant, in individuals at high risk for developing colon cancer. Our results show that the vaccine is much more immunogenic as a preventative than as a therapeutic vaccine. Strong antibody responses are generated as well as strong immune memory. New results will be shown from an ongoing placebo controlled efficacy trial in colon cancer prevention.

Short talks

Gene conversion is the dominant mechanism of somatic hypermutation in mice and humans.

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Affinity maturation – the progressive increase in antibody affinities – is a hallmark of humoral immunity. Somatic hypermutation generates a plethora of antibody mutants in antigen-specific B cells, including those with mutations in immunoglobulin frameworks. Survival of mutants is dependent on the functional preservation of the immunoglobulin framework as well as the increasingly fine specificity of the complementarity determining regions (CDRs) to antigen during selection. Here we show that murine somatic mutations are introduced via gene conversion from other immunoglobulin gene segments from either the cis or trans allele. Similarly, analysis of two recent human immunoglobulin data sets reveals that a majority of mutations are traceable to other immunoglobulin gene segments. This suggests that diversity generated in a humoral response is templated and genetically restricted. Further, this suggests that gene conversion allows B lymphocytes to maintain the integrity of the framework while simultaneously allowing selection for rare CDR mutants with increased affinity.

Protein Kinase C-Delta (PKCδ): a regulator of tuberculosis-driven inflammation.

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Background: We demonstrated previously that Protein Kinase C-delta (PKC-δ) is critical for host immunity against *Listeria monocytogenes*, *Leishmania major* and *Candida albicans* infection in mice. However, the functional relevance of PKCδ during *Mycobacterium tuberculosis* (*Mtb*) infection is unknown.

Methods: We used transcriptome signature of PKCδ in whole bloodof individuals 800 days prior to the diagnosis of TB and patients on anti-tubercular therapy. Expression of PKCδ was then validated in the whole blood and macrophages using quantitative RT-PCR. Furthermore, proteomics was used to determine the abundance of PKCδ in the granulomas of patients with multi-drug resistant tuberculosis. Survival and mechanistic studies were then performed in a murine model of tuberculosis using PKCδ knockout mice. Moreover, we performed metabolome in the sera of Mtb-infected mice to determine the modulation of fatty acids during the course of infection. Isolated macrophages from PKCδ knockout mice were infected with *Mtb* to determine the bacterial growth, effect of exogenous fatty acids and killing effector molecules. Western Blot analysis was performed in total macrophage lysates to determine the status of phagosome maturation and induction of host-protective autophagy.

Results: PKCδ was significantly upregulated in whole blood of patients with active TB disease. Lung proteomics further revealed that PKCδ was highly abundant in the necrotic and cavitory regions of TB granulomas in multi-drug resistant human participants. In murine *Mtb* infection studies, PKCδ$^{-/-}$ mice were highly susceptible to tuberculosis with increased mortality, weight loss, exacerbated lung pathology, uncontrolled pro-inflammatory cytokine responses (IFN-γ, TNF, IL-6 and IL-1β) and increased mycobacterial burdens. Moreover, these mice displayed a significant reduction in alveolar macrophages, dendritic cells and decreased accumulation of lipid bodies (lungs and macrophages) and serum fatty acids. Further, a peptide inhibitor of PKCδ in wild-type mice mirrored lung inflammation identical to infected PKCδ$^{-/-}$ mice. Mechanistically, increased bacterial growth in macrophages from PKCδ$^{-/-}$ mice was associated with a decline in killing effector functions independent of phagosome maturation and autophagy.

Conclusion: These data suggest that PKCδ is a marker of inflammation during active TB disease in humans and required for optimal macrophage killing effector functions and host protection during *Mtb* infection in mice.

Cutaneous leishmaniasis is exacerbated in the absence of IL-4 receptor alpha (IL-4Ra)-responsive T regulatory cells in mice.

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Introduction: Immunity to the protozoan parasite *Leishmania major* is dependent on the successful generation of a T helper (Th) 1 response whilst interleukin 4-receptor alpha (IL-4Rα)-driven Th2 immunity renders susceptibility to this parasite in BALB/c mice. B cells have also been implicated in disease progression but it is unclear if IL-4Rα-responsive B cells play a significant role.

Methods : To investigate this further, a novel BALB/c mouse lacking IL-4Rα expression specifically on B cells (mb1creIL-4Rα-/lox) was infected with *L. major* LV39 parasites and using a range of immunological techniques; ELISA, Flow cytometry, qRT-PCR, adoptive-transfer studies and mixed bone-marrow chimeras; host immune parameters were analysed at 8 weeks post-infection.

Results : Following infection with *L. major*, mb1creIL-4Rα-/lox BALB/c mice efficiently controlled cutaneous disease as shown by significantly reduced footpad swelling and absence of footpad necrosis, as well as attenuated parasite burdens. Control of infection was associated with an increase in dendritic cell-derived IL-12p40 production, which in turn led to enhanced IFN-γ production, and significantly reduced secretion of IL-4, IL-13 and IL-10 cytokines by CD4+ Th cells. A downregulation in Th2-mediated responses correlated with augmented type 1 antibody responses and upregulated iNOS production in mb1creIL-4Rα-/lox mice, altogether leading to a protective type-1 immune response. Surprisingly, IL-4 production by B cells was induced as early as day 1 after infection leading to susceptibility in cutaneous leishmaniasis whilst in contrast, B cells unable to express or respond to IL-4 prevented *L. major*-induced disease in B cell-deficient μMT animals. Mixed-bone marrow chimeras further confirmed that B cell-derived IL-4 was important in regulating and assisting a detrimental Th2 response during *L. major* infection in BALB/c mice.

Conclusion : Together, this data demonstrate that early IL-4Rα-responsive B cells producing IL-4 influence early Th dichotomy towards detrimental Th2 responses, which leads to *L. major*-induced cutaneous leishmaniasis in BALB/c mice.

HIV-associated disruption of alveolar immune cell homeostasis in Malawian adults.

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Introduction: Chronic HIV infection impairs pulmonary immunity and increases susceptibility to lower respiratory tract infections. Unlike in peripheral blood, the immune cell populations that are impacted by HIV infection in the lung are less well defined. We aimed to characterise the impact of HIV infection on immune cell homoestasis in the lung as this might help explain the propensity for LRTIs in HIV-infected adults.
Methods: 20 healthy HIV-uninfected controls and 19 asymptomatic HIV-1 infected ART-naïve adults were recruited from Queen Elizabeth Central Hospital, Voluntary Counselling and Testing clinic. Bronchoalveolar lavage (BAL) fluid and peripheral blood was obtained from from the volunteers. Using immunophenotyping, lymphocyte and myeloid cell populations in BAL fluid and peripheral blood were characterised.
Results: Overall, the proportions of $CD8^+$ T cells, B cells, γδ T cell and intermediate monocytes were higher in HIV-infected adults compared to HIV-uninfected controls, while the the proportions of NK cells, classical monocytes and myeloid dendritic cells and alveolar macrophages were lower in HIV-infected adults compared to HIV-uninfected controls. However, we found no difference in the numbers of alveolar $CD4^+$ T cells in HIV-infected adults compared to HIV-uninfected controls, even though there was a significant reduction in peripheral blood $CD4^+$ T cell count ($p<0.0001$). We also found higher numbers of B cells ($p=0.0043$) and γδ T cell subsets ($p=0.0361$) in BAL fluid from HIV-infected adults compared to HIV-uninfected controls. In contrast, the numbers of classical monocytes were lower in HIV-infected adults compared to HIV-uninfected controls ($p=0.0172$).
Conclusion: Chronic HIV infection is associated with broad disruption of immune cell homeostasis, but does not lead to massive depletion of alveolar $CD4^+$ T cells in the lung. These findings suggests that dysregulation of alveolar immune cell homeostasis, beyond $CD8^+$ T cell alveolitis, may contribute to increased susceptability to lower respiratory tract infections in HIV-infected adults.

Novel insights into molecular basis of Autoimmune Lymphoproliferative Syndrome due to *FAS* defect revealed by the study of consanguineous patients.

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Autoimmune lymphoproliferative syndrome (ALPS) is a primary immunodeficiency disease due to impaired Fas-FasL apoptotic pathway. It is characterized by chronic non-malignant, non-infectious lymphadenopathy and/or splenomegaly associated with autoimmune manifestations primarily directed against the hematopoietic cells.
Herein, we report recent findings revealed by the study of consanguineous patients. Indeed, this peculiar genetic background favored the identification of the first example of a human AR ALPS with normal or decreased protein expression, expanding the spectrum of ALPS types and raising the possibility to revisit the classification of ALPS-FAS. In addition, rare mutational mechanisms underlying the splicing defects of *FAS* exon 6 have been identified in AR ALPS-FAS with lack of protein expression. These findings will undoubtedly allow gaining deeper insight into the fine-tuned regulation of FAS balanced alternative splicing. These descriptions should also prompt clinicians to search for such patients in consanguineous settings to allow early diagnosis, appropriate follow up and genetic counseling.

Complement deficiencies: Specific aspects for Tunisian patients.

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The discovery of individuals with inherited complement deficiencies (ICD) has greatly contributed to understand the importance of the complement system in host defence and homeostasis. Bacterial infections, autoimmune and renal diseases are the clinical conditions most frequently associated with ICD. Other diseases observed in complement deficient patients include hereditary angioedema and paroxysmal nocturnal syndrome.
Since 2005, our laboratory implemented a technical platform with antigenic, functional and genetic explorations to assess ICD in Tunisian patients.
One hundred forty two Tunisian adult patients with bacterial meningitis were screened for late complement component (C5-C9) and properdin deficiencies. ICD were found in 18 patients (12,7 %): 15 had late complement component deficiency and 3 had properdin deficiency. All deficient patients had meningococcal meningitis. A severe disease was frequently noted in deficient patients (66%). Recurrent meningitis were reported in one third of the patients. Genetic analysis revealed new mutations in *C5* (c. 957-959 del AAC DelK320) and *C6* (IVS9-1 G>A and IVS11+1 G>A) genes.
Hereditary angioedema (HAO) due to C1 inhibitor deficiency was detected in 35 patients (86% with type 1 HAO). Acquired AO secondary to anti-C1inhibitor deficiency was diagnosed in one patient with B lymphoma.
In Systemic lupus patients, type I C2 deficiency was diagnosed in 10 patients and C1q deficiency in 3 cases, two were related. A peculiar clinical presentation, with early disease onset, predominant cutaneous manifestations and susceptibility to infections, was frequently reported. A new mutation g.5580G4C in exon 1 of the C1q C chain gene (Gly61Arg) was revealed in the two related patients.
A multicentrer study was conducted on Tunisian adults and pediatric aHUS patient. Factor H and factor I deficiencies as well as acquired deficiency induced by anti-factor H antibodies were investigated. In FH gene, two novel anomalies have been detected: C.3310+144 C>T and c.3766delGATA. New mutations were also found in patients with FI deficiency. The frequency of anti-FH antibodies was similar to other cohorts but we noticed the absence of FH related genes R1 and R3 deletion, a molecular defect usually associated with anti-FH antibodies.
ICD are described as rare diseases but our results showed a high frequency mainly in Tunisian patients with meningococcal meningitis. Few cases of HAO were reported in our cohort reflecting a misdiagnosis of this fatal disease. Many molecular defects were found in aHUS patients reflecting the complexity of this disease on the physiopathology and the molecular diagnosis levels.

Celiac disease: A Tunisian perspective.

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Celiac disease (CD) is a chronic inflammatory disease which develops in predisposed individuals. The immune response to ingested gluten leads to inflammation, villous atrophy and crypt hyperplasia of proximal small intestine that are responsible of the principal manifestations of disease. During recent years CD has emerged as a public health problem in many countries. **Objective**: to elucidate epidemiological, serological, genetic and *in situ* cytokine expression in Tunisian CD patients.

We started by performing the first screening study of CD in 6286 schoolchildren from the north of Tunisia. We used for screening IgA anti tissue transglutaminase antibodies (IgA-tTG) by ELISA. Positive sera were assessed by immunofluorescence for the presence of IgA antiendomysium antibodies. Positive participants were called in for serological control, intestinal biopsy and biological exploration. The prevalence of CD was estimated of about 1/157 (0.63%). Most of the screened children showed an atypical and asymptomatic form, but even the typical forms were underdiagnosed. We also identified 5 asymptomatic children with positive IgA anti-endomysium and IgA-tTG but a normal intestinal histology that were considered as latent CD.

Few years later, we make our second screening study on 2064 schoolchildren from Djerba Island (south of Tunisia) by a whole blood rapid method. Children with positive results were tested for IgA-tTG and anti-endomysium by conventional tests. In positive children, intestinal biopsy was performed. Prevalence of CD was not statistically different from that in the north of the country (0.24-0.34%).

Regarding the genetic aspect of CD, we performed the first case-control study to elucidate the HLA DRB1, DQA1 and DQB1 polymorphism in Tunisian children with CD. We also aimed to compare the distribution of these alleles between symptomatic patients and CD children resulting from our first serologic screening study. We confirmed the high frequency of DQ2 haplotype in CD patients and we identified new protective alleles DRB1*13, DQA1*0102 and DQB1*06. However, HLA polymorphism seems to have no evident impact on clinical outcome of CD.

To better understand the physiopathology of CD, we assessed the expression of IFN-g, IL-10, MMP3, MMP12 and FOXP-3 in intestinal biopsies from latent CD patients compared to active forms by real time PCR. Our results demonstrated the absence of a Th1 inflammatory response which is in line with the lack of intestinal damage and villous atrophy in latent CD patients. However, there was a lack of evidence for IL-10 and FOXP-3 regulatory T cells involvement in the maintenance of intestinal homeostasis. The low number of latent CD patient is the major limitation of this study.

Conclusion: epidemiological and serological characteristics of Tunisian CD patients were similar to that reported in the literature. The description of new protective alleles as well as a peculiar cytokine profile in latent patients gives new insights in CD pathogeneses. Screening for CD is mandatory in Tunisian patients regarding the high proportion of atypical forms.

The intrathecal polyspecific antiviral immune response (MRZ reaction): a potential cerebrospinal fluid (CSF) marker for multiple sclerosis diagnosis.

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Introduction: In CSF of multiple sclerosis (MS) patients, the intrathecal synthesis (IS) of IgG class antibodies is classically revealed by CSF isofocusing test (detection of IgG Oligoclonal bands (OCB)), Total IgG Index and/or Reiber diagram. These routine laboratory tests could be unable to resolve the problem of many clinically confusing cases. Recently, the detection of a polyspecific intrathecal humoral immune response against the three most frequent neurotropic viruses: Measles (M), Rubella (R) and Varicella Zoster (Z), called "MRZ reaction" has gained a lot of interest in MS studies. It is reported to be highly specific to disease diagnosis, especially in OCB negative-MS patients.
The aim of this study was to investigate the clinical relevance of MRZ reaction in MS and to compare its diagnostic value to OCB detection.
Material and methods: In this study, 158 samples (79 couples of CSF/serum) were collected from 61 MS patients (46 OCB (+) and 15 OCB (-)), and 18 non-MS patients with other CNS inflammatory conditions (control group). Samples were analyzed for OCB using CSF isofocusing. Levels of total IgG and albumin were determined by nephelemetry for Total IgG Index calculation and Reiber Diagram interpretation. M, R and Z viruses specific-IgG levels were determined using a commercially available ELISA for anti-virus antibody determination in CSF and serum. The IS of IgG to M, R and Z viruses was detected by calculation of the corresponding virus-specific antibody Index (AI) according to Reiber's Formula. MRZ Reaction was considered as positive if at least 2 AI were ≥1.5. Statistical analysis was performed using SPSS.20 software.
Results: The MRZ Reaction in MS patients was more frequent than in control group (65.5% Vs 16.6%; $p<0.001$). The specificity and the sensitivity for MS diagnosis were 83.3% and 65.5% respectively. As expected, in MS group, each of the 3 specific AI was found more frequently positive and each median index value was higher in comparison with non-MS group, with a statistical significance for R and Z viruses. Regarding MS group, MRZ reaction was significantly associated to the presence of Total IgG IS in Reiber Diagram ($p<0.001$). This association was preserved for R and Z viruses when considering each anti-viral reaction alone ($p<0.001$ and $=0.001$ respectively). The AI values of these two viruses were correlated to the Total IgG Index. Interestingly, in OCB (-) MS subgroup, MRZ reaction was detected in 53% of patients with a specificity of 92.3% for the disease. In OCB (+) MS patients, the R specific AI value was correlated to the number of OCB detected in CSF by isofocusing test.
Conclusion: Our results confirm that MRZ reaction is overall the most specific CSF marker of MS disease with a special relevance in diagnosing OCB (-) MS patients. Especially, the R and Z reactions were found to be qualitatively and quantitatively correlated to the IS of Total IgG. While its high potential as a relevant diagnostic marker has been demonstrated, the unknown pathophysiological role of MRZ reaction may require further research.

Leptin decreases susceptibility of breast cancer cells to NK-lysis via PGC-1α pathway: Linking tumor progression with obesity.

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Introduction/Objectives: Large prospective studies have established a link between obesity and breast cancer (BC) development. Among the diverse adipocytokines secreted by hypertrophic adipose tissue, leptin is emerging as a key candidate molecule linking obesity and cancer. This study aims to explore the effect of leptin on tumor resistance to NK lysis and the underlying mechanism.

Materials/Methods: MCF-7 were treated with different concentrations of leptin (10: physiological; 100 ng/ml: obesity) and analyzed for several genes by Real-time PCR and Western-Blotting. The impact of leptin on the susceptibility of BC cells to NK92 mediated lysis was investigated by chromium release assay. Recombinant adenoviruses were used for PGC-α overexpression.

Results and Conclusions: We found that leptin promotes both MCF-7 resistance to NK92-mediated lysis and β oxidation, by the up-regulation of the Peroxisome proliferator activated receptor coactivator-1α (PGC-1α). Using adenoviral approaches, we show that an acute elevation of PGC-1α enhances the fatty acid oxidation pathway and decreases the susceptibly of MCF-7 cells to NK92-mediated lysis. Importantly, we identified the involvement of PGC-1α and leptin in regulating the expression of the hypoxia inducible factor-1 alpha (HIF-1α) by tumor cells. We further demonstrate that basal BC cells exhibit an increased PGC-1α mRNA level, an enhanced activity of oxidative phosphorylation and are more resistance to NK92 lysis in comparison with luminal BC cells.

This study shows, for the first time, how leptin could promote tumor resistance to immune attacks. Reagents blocking leptin or PGC-1α activity might aid in developing new therapeutic strategies to limit tumor development in obese BC patients.

Homozygous *TCF3* mutation is associated with severe hypogammaglobulinemia and acute lymphoblastic leukemia.

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TCF3 (E2A) gene encodes E12 and E47 transcription factors which are essential in differentiation process of common lymphoid progenitors into B-lineage cells and are key regulators of B-cell development. Herein, we report the first homozygous TCF3 patients. They presented reduced peripheral B cells, hypoagammaglobulinemia and acute lymphoblatic leukemia.

The two patients were born to Tunisian first cousin parents. Patient P1 had recurrent pneumonia and meningitis since early childhood and mild facial dysmorphia. At age 7 years he presented pancytopenia and splenomegaly, the diagnosis of B-ALL was confirmed. At the age of 10 years, he died despite chemotherapy was resumed.

Patient P2 suffered from recurrent pneumonia and failure to thrive. She also had facial dysmorphia. At age 14 years, she developed acute lymphoblastic leukemia. Immunological investigations revealed a very low number of peripheral $CD19^+$B cells in patient P1 and ~ 3% $CD19^+$ B cells in patient P2. All immunoglobulin classes were absent in patient P1, while borderline low IgG and significantly decreased IgA and IgM serum immunoglobulin levels were observed in patient P2.

Whole exome sequencing revealed a novel homozygous mutation within exon 9 of *TCF3* (c.C807T) and resulted in a premature stop codon (p.Q270X). Both parents were heterozygous. The truncated protein, with no helix-loop-helix (HLH) functional domain, was absent as shown by a western Blot.

In contrast to previous E47 deficient patients, patient P2 had normal expression of IgM but decreased levels of $CD27^+$ memory B cells as well as of switched memory $CD27^+IgD^-$ B cells. Detailed analysis of the T cell immunophenotype, revealed a significant increase in effectors memory $CD8^+$ T cells and absent terminally differentiated effector T cells (TEM_{RA}).

Considering the crucial role of TCF3 in the regulation of normal B cell development, it is not surprising that disruption of this transcription factor causes a profound B cell defect. Since TCF3 is also known to be affected (translocations and deletions) in B-ALL, this could explain the clinical phenotype herein observed. Indeed, a decrease in the level of PAX5 transcripts was observed in patient P1. This is consistent with data in mice showing that the loss of PAX5 in mature B cells leads to the development of aggressive progenitor B-cell lymphomas.

Immunodeficiency Diseases Related Scores and Leucocytes Explorations for the Diagnosis of Primary Immunodeficiency Diseases.

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Primary immunodeficiency diseases (PIDs) represent a large and heterogeneous group of more than 120 different entities, most of which have now been genetically characterized. The recent research allowed physicians and scientists to understand, and subsequently diagnose and treat PIDs with more and more accuracy. Clinical exploration based on the immunodeficiency diseases related (IDR) score is used to identify the likelihood of finding immunodeficiency among suspected patients. Nevertheless, IDR score alone do not predict systematically PID affections. Patients suffering from evocative clinical manifestations need to undergo explorations of the phenotype subsets and/or some functional parameters of blood leucocytes. However, the pathological mechanisms associated with these clinical manifestations can affect the values of the explored parameters even in patients with non-PIDs diseases.

In this lecture, we will analyse the IDR scores of PIDs suspected patients in parallel with the different biological parameters explored in our laboratory during the last 10 years in the framework of the biological diagnosis of DIPs. Analysis will be focussed on the non-PIDs patients suffering from DIPs-evocative clinical manifestations compared to PIDs confirmed patients. The output of this analysis will have an important interest in the improvement of the interpretation of the parameter values surrounding the threshold of the references intervals routinely used in the diagnosis of PIDs.

Abnormal repression of *SHP-1, SHP-2 and SOCS-1* transcription sustains the activation of the JAK/STAT3 pathway and the progression of the disease in multiple myeloma

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Sustained activation of JAK/STAT3 signaling pathway is classically described in Multiple Myeloma (MM). One explanation could be the silencing of the *JAK/STAT* suppressor genes, through the hypermethylation of *SHP-1* and *SOCS-1*, previously demonstrated in MM cell lines or in whole bone marrow aspirates. The link between such suppressor gene silencing and the bone marrow invasion degree or the treatment response has not been evaluated in depth. Using *real-time* RT-PCR technique, we studied the expression profile of three *JAK/STAT* suppressor genes: *SHP-1, SHP-2* and *SOCS-1* in plasma cells freshly isolated from the bone marrows of MM patients and healthy controls .Our data demonstrated an abnormal repression of such genes in malignant plasma cells and revealed a significant correlation between such defects and the sustained activation of the *JAK/STAT3* pathway during MM. The repressed expression of *SHP-1* and *SHP-2* correlated significantly with a high initial degree of bone marrow infiltration but was, unexpectedly, associated with a better response to the induction therapy. Collectively, our data provide new evidences that substantiate the contribution of *JAK/STAT* suppressor genes in the pathogenesis of MM. They also highlight the possibility that the decreased gene expression of *SHP-1* and *SHP-2* could be of interest as a new predictive factor of a good treatment response and suggest new potential mechanisms of action of the therapeutic molecules. Whether such defect help the progression of the disease from MGUS to MM remain, however, to be determined.

Urinary mRNA analysis as a biomarker of epithelial mesenchymal transition in renal allograft

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Introduction: Interstitial fibrosis and tubular atrophy are the major cause of chronic graft dysfunction leads to end-stage renal failure after transplantation. These lesions can be highlighted by epithelial phenotypic changes corresponding to partial epithelial-mesenchymal transitions (pEMT) at biopsy, which still an invasive approach in itself. In this prospective study, we investigate the hypothesis that specific renal tubular epithelial cell proteins could be a useful noninvasive urinary marker of early pEMT.
Materials and methods: Seventy-five stable kidney recipients from two clinical centers were included. Patients were subdivided in G1: 23 transplant from living donors (LD) and G2: 52 patients engrafted with a kidney from deceased donors (DD). The expression of vimentin (VIM) and β-catenin (βCAT) on the 3-mounth protocol surveillance biopsy was evaluated by immunohistochemistry. On the same biopsy day, urinary samples were collected and the mRNA expression of vimentin (VIM), CD45, Glyceraldehde-3-phosphate dehydrogenase (GAPDH) and Uroplakin 1A (Upk1a) in urinary cells was measured using real-time PCR.
Results: Using the formerly defined threshold of 10% of vimentin or b-catenin positive tubules to define positive pEMT, there were 28 pEMT positive and 47 pEMT negative patients. The mean of VIM and βCAT scores are statistically higher in the DD group than LD group (1.51 ± 0.16 versus 1 ± 0.17 for VIM score (p=0.07) and 1.48 ± 0.16 versus 0.96 ± 0.2 for βCAT score (p=0,046)). The Spearman's rank correlation analysis showed that both VIM and βCAT were significantly correlated with Banff scores (tubulit, capillarity peritubular tubular atrophy), proteinuria and graft dysfunction at 6 months (r=-0.239: p = 0.04), 1 year (r =-0.29: p = 0.011) and even 2 years for βCAT (r=-0.27: p = 0.03). On the other hand, the relative mRNA measurements of RT-PCR VIM and CD45 normalized by Upk1a were significantly correlated to biopsy VIM score (r=0.453: p = 0.0098 and r=0.592, p=0.02, respectively). The ROC curve of urinary VIM/Upk1A and CD45/Upk1A for the diagnosis of pEMT on the renal allograft biopsy showed an area under the curve (AUC) of 0.74 (95%CI=0.54-0.94) and 0.79 (95%CI=0.62-0.96) respectively.
Conclusion: Our results suggest that the RNA expression of the urinary VIM and CD45 is correlated with the presence of early pEMT. So these biomarkers could be used as a noninvasive tool to predict renal graft fibrogenesis.

Oral communications

Interleukin-22-binding protein (IL-22BP) regulates IL-22 functions during gut homeostasis.

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IL-22 is a cytokine mostly produced by CD4+ T cells and group 3 innate lymphoid cells that almost exclusively act on epithelial cells because of their restricted expression of membrane IL-22 receptor (IL-22R). IL-22 is consequently important for the crosstalk between immune and epithelial cells, particularly at barrier surfaces, including the gut. As such, a number of protective functions have been attributed to IL-22 during gut inflammation, notably because it strengthens epithelial barrier function through inducing antimicrobial peptides (AMPs) expression in intestinal epithelial cells (IEC), and by supporting their proliferation and regeneration.

Interestingly, emerging data suggest that IL-22 actions in the gut extend beyond inflammation and play critical functions to set up intestinal homeostasis, especially by defining AMPs mediated shaping and control of the microbiota. IL-22 binding protein (IL-22BP) is a soluble secreted inhibitor of IL-22 we previously showed to negatively regulate IL-22-dependent protective effects during acute colitis. Because IL-22BP is constitutively produced during steady state, we hypothesized it could act as a rheostat of homeostatic IL-22R activation. To test this hypothesis, we first analyzed expression of known IL-22-dependent genes in isolated IEC from ileum, colon and Payer's patches (PPs) of Il22ra2-/- rats vs. Il22ra2+/+ littermate controls. Concordant with our expectation of increased IL-22 signaling in IEC from Il22ra2-/-, we detected significant higher levels of the 2 AMPs REGIIIβ and REGIIIγ whereas IL-25 expression was down regulated. REGIIIs are major IEC-derived factors to control the growth of ileal IEC-adhering segmented filamentous bacteria (SFB), a group of Clostridium-related bacteria involved in Th17 cells induction and subsequent secretion of IL-17. Supportive of REGIIIs-induced altered growth of SFB, extensive phenotypic analysis of the gut immune system by flow cytometry revealed a specific decrease of IL-17-secreting CD4+ T cells in the ileum of Il22ra2-/- rats, whereas no defect could be observed in other T cells populations or myeloid cells.

Finally, owing to our newly generated IL 22BP-GFP reporter rats, we confirmed conventional dendritic cells as the major source of IL-22BP in rodent gut lamina propria and SLOs. Collectively, our data indicate that host microbiota interactions in the gut are under the control of a fine-tuning of IL-22R activation by cDCs-derived IL-22BP.

ITE, a nontoxic AhR ligand, activatesTh22 subsets and enhances *de novo* generation of regulatory T cells in humans

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The aromatic hydrocarbons receptor (AhR) is a ligand-dependant transcription factor that mediates a range of critical events in response to xenobiotics. Recently, several data pointed out its key and complex role in the regulation of immune responses. ITE was recently identified as a non-toxic endogenous AhR ligand. Several data provided evidence that ITE could be useful in+human therapy. Accordingly, ITE inhibits the symptoms of experimental autoimmune encephalomyelitis (EAE) in mice *via* the *de novo* generation of FoxP3+ Tregs. Herein, we aimed to decipher the effects of ITE on Tregs and T helper subpopulations in humans. We first analyzed the *in vitro* effect of ITE on T helper subpopulations by assessing the production of IFN-γ, IL-17 and IL-22 on peripheral blood mononuclear cells (PBMCs) isolated from 6 healthy volunteers and stimulated in the presence or not of ITE. Flow cytometry analysis showed that ITE was able to induce the production of IL-22 in a significant proportion of CD4P P T cells stimulated during 5 days. The percentage of IL-22-producing cells increased from a median of 1% in unstimulated conditions to a median of 5.2% in cells stimulated with ITE at 10µM (p= 0.0039). No induction of IL-17 or IFN-γ was showed after stimulation with ITE. The small percentage of T cells producing IL-22 after ITE stimulation may probably correspond to activated Th22 memory cells which are characterized by a high expression of AhR. Consistently, it has been shown that AhR is essential for IL-22 production by T cells. Interestingly, IL-22 not only increases the antimicrobial defense in mucosa and skin but also plays a tissue-protective role counteracting the deleterious effects of the immune response. Our findings further argue in favor of a beneficial effect of ITE in inflammatory diseases. We then analyzed the effect of ITE on regulatory T lymphocytes by studying the effect of this molecule either on *de novo* generated Tregs. Conventional CD4P+PCD25P- PT cell isolated from 4 healthy donors were stimulated during 5 days with anti-CD3/anti-CD28 antibodies in the presence of TGF-β. ITE was added during culture at different concentrations (0.1, 1 and 10µM) and its effect was assessed by studying the suppressive functions of generated Tregs and the expression of FoxP3 by flow cytometry. The suppressive effect of generated Tregs was significantly enhanced in the presence of ITE at all the tested concentrations (p = 0.04). The expression of Foxp3 was not altered in generated Tregs the presence of ITE, yet reinforced in the presence of ITE at 10µM ($p<0.05$). Our data demonstrated that ITE enhanced the suppressive functions of generated Tregs. Collectively, they bring new elements supporting the use of ITE in human therapy of inflammatory diseases.

RV0140-specific granzyme B, as an alternative biomarker, to discriminate different phases of *Mycobacterium Tuberculosis* infection.

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Introduction/Objectives: Two billion people are latently infected (LTBI) with *Mycobacterium tuberculosis (Mtb)*. This proportion represents a reservoir for the propagation of the disease. The accurate diagnosis and prophylactic treatment of LTBI cases are currently essential components of the global Post-2015 tuberculosis (TB) strategy. The IL12/IFN- γ axis is crucial for protective immunity to *Mtb*. However, the quantification of IFN- γ induced by antigens of the early stage of infection, as a biomarker, failed to discriminate different phases of the disease and to predict clinical outcome of the infection. Many alternative host biomarkers have been currently investigated. Particularly, recent studies pointed out the role of CD8+ T cell-secreted Granzyme B in preventing progression to active TB. Rv0140 is a reactivation-associated antigen of *Mtb*. In the current study, we aimed to investigate its specific cellular immune response in order to evaluate Rv0140-specific Granzyme B (GrzB) potential, as an alternative biomarker for TB progression.
Material and methods: A total of 55 volunteers were enrolled and distributed as follows: 17 patients with active TB before/less than 5 days of anti-TB treatment; 22 LTBI who have been in contact with an active TB patient, with a tuberculin skin test ≥15mm and without clinical signs; and 16 healthy individuals. We measured by ELISA, IFN-γ, TNF-α and GrzB secreted by PBMCs after stimulation with Rv0140, PPD, ESAT6 and PHA as positive controls for 24h in the presence of IL7. We further characterized by Intra cellular staining (ICS) the T cell subset source of GrzB.
Results: Our results showed that Rv0140 induces significantly higher IFNg amounts in LTBI group than in TB patients ($p < 0.0037$) as previously reported. No significant difference in Rv0140-induced TNF-α was observed in different study groups. Herein we showed, for the first time, that Rv0140 induces high amount of GrzB in LTBI. Interestingly, it seems that TB patients loose this cyto-toxic activity. Thus, the Rv0140-specific GrzB release assay allows important discriminative power ($p < 0.0009$) between LTBI and Active TB. ICS experiment showed that CD8 T cells are the source of Rv0140-specific GrzB.
Conclusion: The current study showed that Rv0140-specific GrzB could be a potential biomarker for the discrimination of different phases of TB disease.

Towards the development of a field-friendly point-of-care screening test for the diagnosis of TB disease in resource constrained settings

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Introduction: There is an urgent need for user-friendly, rapid, inexpensive yet accurate tools for the diagnosis of tuberculosis (TB) disease at the point-of-care (POC) in resource-limited settings. We evaluated the utility of host biomarkers detected in serum and plasma samples as tools for the diagnosis of TB disease, in a large multi-centred consortium project, comprising multiple African and European institutions.
Aim: To evaluate the usefulness of host biomarkers detected in serum and plasma samples as diagnostic candidates for TB disease
Methods: Individuals presenting with symptoms requiring investigation for TB disease were prospectively recruited at primary health care centers situated in six African countries, prior to clinical diagnosis. Using a pre-established diagnostic algorithm comprising of laboratory, clinical and radiological findings, participants were later classified as having TB disease or other respiratory diseases (ORD). Using a multiplex cytokine detection platform, we evaluated the concentrations of multiple host biomarkers in serum and plasma samples, and assessed their diagnostic potential for TB disease.
Results: Out of 716 participants enrolled from five study sites, 214 were diagnosed with TB disease, 487 had ORD whereas six had an uncertain diagnosis. A seven-marker serum biosignature comprising of CRP, transthyretin, IFN-γ, CFH, apolipoprotein-A1, IP-10 and SAA identified on a training sample set (n=491), diagnosed TB disease in the test set (n=210) with sensitivity of 93.8% (95% CI, 84.0-98.0%), specificity of 73.3% (95% CI, 65.2-80.1%), and positive and negative predictive values of 60.6% (95% CI, 50.3-70.1) and 96.4% (95% CI, 90.5-98.8%) respectively, regardless of HIV infection status or study site. In a smaller follow-up study, six-marker plasma biosignatures comprising of relatively new biomarkers in combination with some of the markers in the serum biosignature, diagnosed TB disease with a sensitivity of 100% and specificity of 89.3% irrespective of HIV status. Interestingly, an excellent correlation was observed between biomarkers detected in serum and plasma.
Conclusion: We have identified blood-based biosignatures with strong potential in the diagnosis of TB disease irrespective of HIV infection status or ethnicity in Africa. The development of a field-friendly POC test; adaptable to finger-prick whole blood, based on these biosignatures, is currently ongoing.

HIV co-infection affects expression and function of human lung tissue resident T-cells during TB disease.

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Tissue resident T cells are non-circulating T cells found in non-lymphoid tissues where they provide quick response against re-encountered infections thus accelerating pathogen clearance. Priming of T-cell responses to invading pathogens is disease specific and may take days during viral infections or weeks in *M. tuberculosis*. Upon inhalation of *M. tuberculosis* aerosol droplets into the lung alveoli, the bacteria are phagocytosed by resident macrophages and begin to replicate. The bacteria then transit to the lung parenchyma and continue replication in macrophages setting off inflammatory responses that recruits more innate cells. This initiates granuloma formation, although adaptive responses are required to complete granuloma development. Human studies rely primarily on peripheral blood T-cell responses to understand immune responses during *M. tuberculosis* infection. However, lung granulomas provide a better measure of the actual responses induced by *M. tuberculosis* at the site of disease. Indeed, data from non-human primate studies suggest that in animals with established active disease or latent infection, the systemic T-cell responses do not accurately reflect the local T-cell responses.

Using resected lung tissue from patients with active-TB disease, we sought to characterize the phenotype and functionality of resident T cells in the lung and compare with T cell responses observed in circulation. Patients with HIV coinfection were on anti-retroviral therapy. Lymphocytes from lung tissue and PBMC were isolated by gentle Macs Tissue dissociator (Miltenyi Biotec) and Percoll gradient isolation. The cells were stained for surface markers or stimulated with antigens followed by intracellular cytokine staining. Cells were acquired by flow cytometry and data analysed using flowjo. DNA was also isolated from both tissue and periphery for T- Cell Receptor (TCR) clonotyping.

Results show that T cells were depleted more in tissue than in circulation during HIV infection while antiretroviral treatment only restored T cells in circulation. HIV co-infection also increases TCR clonality in circulation but not in tissue. We also observed that tissue resident T cells (CD103+CD69+ cells) produce higher frequency of cytokines compared to non-tissue T cells (CD103-CD69- cells).

In conclusion, the expression and functionality of T cells in *M. tuberculosis* infected human lung is affected by HIV co-infection. Antiretroviral therapy does not restore T cells sufficiently in human lung where they are needed to fight TB disease.

Alternative quantiferon cytokines for diagnosis of children with active tuberculosis and HIV co-infection in Ghana.

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IFN-γ release assays (IGRAs) often present false-negative or indeterminate results in children with tuberculosis. HIV co-infection may contribute to decreased sensitivity of IGRAs by impairing T-cell IFN-γ expression. Measurement of alternative cytokines in Quantiferon® (QFT) supernatants can circumvent the IFN-γ-dependency and may improve QFT sensitivity. We aimed to identify additional cytokines from QFT supernatants for detection of *M. tuberculosis* infection in children with tuberculosis and HIV co-infection from Ghana. Concentrations of 18 cytokines in QFT supernatants from children (0-16 years) with tuberculosis concomitantly infected with HIV (n = 25) or without HIV (n = 24) from Ghana were measured using cytometric bead array (CBA).

29% of the children showed positive IFN-γ test results, and five cytokines, i.e. IL-6, IL-21, TNF-α, IL-1α and IP-10, detected *M. tuberculosis* infection with comparable or, for IL-6, with significantly higher sensitivity (59%). Increased age and HIV co-infection were associated with decreased cytokine induction, and especially IL-21 and IP-10 were less prevalent in HIV co-infected children with tuberculosis. Combined cytokine analyses increased proportions of positive tests, and a four-cytokine subset (i.e. IL-6, IL-21, IFN-γ, IL-1α) predicted 78% of the children with tuberculosis correctly.

Combined evaluation of IFN-γ and alternative cytokines improved IGRA-sensitivity in children with tuberculosis.

Visceral Leishmaniasis patients display altered composition and maturity of neutrophils as well as impaired neutrophil effector functions.

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Introduction: Immunologically, active visceral leishmaniasis (VL) is characterized by profound immune suppression, severe systemic inflammatory responses, and an impaired capacity to control parasite replication. Neutrophils are highly versatile cells, which play a crucial role in the induction as well as the resolution of inflammation, the control of pathogen replication, and the regulation of immune responses. Neutrophil functions have been investigated in human cutaneous leishmaniasis; however, their role in human VL is poorly understood.

Methods: In the present study we evaluated the activation status and effector functions of neutrophils in patients with active VL and after successful anti-leishmanial treatment by flow cytometry.

Results: Our results show that neutrophils are highly activated and have degranulated; high levels of arginase, myeloperoxidase, and elastase, all contained in neutrophils' granules, were found in the plasma of VL patients. In addition, we show that a large proportion of these cells are immature. We also analyzed effector functions of neutrophils that are essential for pathogen clearance and show that neutrophils have an impaired capacity to release neutrophil extracellular traps, produce reactive oxygen species, and phagocytose bacterial particles, but not *Leishmania* parasites.

Conclusion: Our results suggest that impaired effector functions, increased activation, and immaturity of neutrophils play a key role in the pathogenesis of VL.

Phlebotomus papatasi yellow-related and apyrase salivary proteins are candidates for vaccination against human cutaneous leishmaniasis

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Several experimental data demonstrate that pre-exposure to sand fly saliva confers protection against leishmaniasis. Our previous work in humans indicates that saliva of *Phlebotomus papatasi*, the vector of *Leishmania major*, elicit IL-10-producing CD8+ T lymphocytes. Blocking IL-10 enhanced the activation of IFN-γ-producing CD4+ T lymphocytes. Herein, we used a biochemical and functional genomics approach to identify the sand fly salivary components that activate a Th1 immune response in humans therefore constituting potential vaccine candidates against leishmaniasis. Fractionated *Phlebotomus papatasi* salivary extracts were first tested on T lymphocytes of immune donors. A proliferative response and IFN-γ induction was demonstrated for CD4+ T lymphocytes stimulated with the proteins with molecular weight higher than 30 KDa. Peripheral blood mononuclear cells from immune donors were transfected with plasmids coding for the most abundant proteins from *P. papatasi* salivary gland cDNA library. Our data showed that the "yellow related proteins", PPTSP42 and PPTSP44, and "apyrase", PPTSP36, elicit a cellular immune response with IFN-γ-production. Strikingly, PPTSP44 triggered the highest level of lymphocyte proliferation and IFN-γ secretion. Multiplex cytokine analysis confirmed the Th1-polarized immune response induced by such proteins. Importantly, recombinant PPTSP44 validated the results observed with the DNA plasmid, further supporting that PPTSP44 constitutes a promising vaccine candidate against human leishmaniasis.

Histological and immunological differences between zoonotic cutaneous leishmaniasis due to *Leishmania major* and sporadic cutaneous leishmaniasis due to *Leishmania infantum*

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Introduction/Objectives: In Tunisia, three forms of cutaneous leishmaniasis (CL) were described: the zoonotic cutaneous leishmaniasis (ZCL), caused by *Leishmania* (*L). major*, endemic in the Southern and Central region of Tunisia; the sporadic cutaneous leishmaniasis (SCL), caused by *L. infantum* in North Tunisia and the chronic cutaneous leishmaniasis (CCL) caused by *L. tropica* described first in South of Tunisia. In order to study the impact of *Leishmania* species on the lesion feature, we evaluated the histological and immunological differences between ZCL and SCL.

Materials/Methods: Skin biopsies specimens obtained from 20 patients with active ZCL and 32 patients with active SCL were used. Biopsies were divided into two parts: one was used for histological and immunohistochemical analysis and the second was used for the analysis of mRNA expression of IFN-γ, IL-10, and IL-13, IL-8 and MCP-1, granzyme B (GrB) and granulysine (Grly) using real-time quantitative polymerase chain reaction (RT-qPCR). Immunohistochemical staining was performed using anti-CD3, CD4, CD8, CD56, GrB and IFN-γ. Data analysis was performed using Graph-Pad Prism.

Results: Histological analysis showed a mild to moderate infiltrate within ZCL lesions. In contrast a massive infiltration of the dermis was observed within SCL lesions. Contrary to ZCL, infiltrates within SCL lesions were organized and showed granuloma composed of macrophages and lymphocytes. In addition, immunohistochemical analysis showed a predominance of $CD4^+$T cells within both of CL forms. Otherwise, IL-8 mRNA levels were significantly higher in ZCL lesions compared to SCL lesions. Conversely, IFN-γ mRNA levels were higher in SCL lesions. Levels of IL-10, MCP-1, GrB and Grly mRNA levels were comparables within SCL and ZCL lesions.

Conclusions: CL due to *L. infantum* (SCL) is characterized by a massive organized dermal infiltrate with a predominance of $CD4^+$ T cells and high levels of IFN-γ. However, in CL due to *L. major* (ZCL) the dermal infiltrate is moderate and lesions are characterized by an important density of neutrophils and high mRNA levels of pro-inflamatory chimiokine IL-8. Both lesions showed high levels of GrB and Grly mRNA, indicating a cytotoxic activity which might be involved in lesion establishment and killing of parasite.

Evaluating the role of early HIV-1 specific T and B cell phenotypes and function in determining the subsequent production of functionally relevant HIV specific antibodies.

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Background: The identification of broadly neutralizing antibodies in HIV-1 infection has renewed hope in the quest of an effective antibody based vaccine. It has been shown that HIV alters the B cell compartment, leading to an increase in activated and exhausted B cell subsets. To what extent these perturbations contribute to the delayed development of functional antibody responses remains unclear. Upon antigen encounter, naïve B cells differentiate into antibody secreting cells, a process that largely takes place in the germinal center (GC) and requires help from T follicular helper cells (TfH). It is therefore conceivable that the interaction of Tfh cells and B cells may contribute to the generation of antibodies with functional relevance. In this study, we seek to understand cellular mechanisms of Tfh cells and B cells that lead to the generation of desired antibody function. The identification of Tfh-like cell populations in peripheral circulation has enabled the study of these interactions using peripheral blood.

Objectives: We hypothesize that the frequency and quality of peripheral HIV-specific TfH cells and B cell subsets will predict the quality of subsequent antibody function (neutralizing and/or non-neutralizing function) in HIV-1 infection. Specifically, we seek to describe the phenotypes and functions of TfH cells and B cells in early HIV-1 infection and associate these to subsequent antibody function.

Methods: To do this, we will use flow cytometry to describe the frequencies of HIV-specific T cells(CD4 and CD8 subsets) and B-cell subsets in early HIV infection. For the HIV-specific T cells, PBMC cultures will be stimulated with clade A envelop peptides for 18 hours and stained with monoclonal antibodies including the activation markers CD25 and OX40 as previously reported. HIV-specific B cells will be detected using a gp120 probe. We will then perform antibody functional assays and compare HIV-specific Tfh and B cell phenotypes and interactions in individuals generating good or poor antibody function. Assay optimization on the characterization of HIV-1 specific Tfh cells and B cells is now complete. Results from this optimization and study samples, currently being analyzed, will be discussed.

Results and Conclusion: Our preliminary results demonstrate that using the activation markers (CD25 and OX40), we can detect HIV-specific Tfh like cells (CXCR5+CD45RA-CD4+) in peripheral circulation after stimulation with HIV peptides. Similarly, we can detect HIV-specific B cell subsets, using fluorescent gp120 probes that have two fluorophores, which improves specificity of the detection of HIV-specific B cell subsets.

Frequency of broadly neutralizing antibodies in HIV-1 chronically infected individuals in Ugandan Clades A and D

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Aim: The study was aimed at assessing frequencies of neutralizing antibodies in individuals affected with the commonest HIV-1 clades A and D in Uganda.

Methods: This was a cross- sectional study of 83HIV-1 chronically infected Anti- Retroviral Therapy (ART) naïve adults who were enrolled from Medical Research Council (MRC) cohort and The AIDS Support Organization (TASO) Clinic in Entebbe. Samples of Plasma were tested for the neutralization activity against a panel of 3 clade A and D viruses using the Neutralization Assays.

Neutralization assays were performed using Env pseudovirus viruses in the TZM-bl cell-based assay. Neutralization values were obtained as the plasma dilutions at which virus entry was inhibited by 50% compared to that in the absence of plasma (IC_{50}). A plasma sample was scored as displaying neutralizing activity against a particular virus if at least 50% inhibition of infection was recorded at the lowest plasma dilution tested (1: 20) in at least two independent neutralization assays.

Results: Clade A viruses are better neutralized compared to clade D viruses. Individuals whose titers were above 1080 (labeled red required further sample dilution. 51.81% of the participants had their antibody neutralization titers above 40. There was a significant difference between the proportion of clade A viruses neutralized and those of clade D as obtained statistically using the Mann- Whitney test with a p- value < 0.0001. The neutralization titers obtained for the individual clade A viruses Q23.17, Q769.d22 and Q842.d12 were much higher than those for clade D viruses QA013.H1, Q857.B3 and QD435.5B.

Conclusion: Generally, the frequency of neutralizing antibodies was found to be much higher in Clade A compared to Clade D. This implies that in case of a vaccine design, emphasis should be put on Clade D subtype since it's harder to neutralize naturally.

Filaria specific antibody response profiling in plasma from anti-retroviral naïve Loa loa microfilaraemic HIV-1 infected people.

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Introduction: In west and central Africa areas of endemic *Loa loa* infections overlap with regions of high prevalence of the Human Immunodeficiency virus type 1(HIV-1) infections. Here because people are exposed to filarial parasites from birth, most HIV-1 infected people as a consequence invariably also have a history of filarial parasite infection. Since HIV-1 infection depletes and maintains the immune system in perpetual inflammation this can hamper *Loa loa* filarial parasite mediated immune modulation leading to enhanced loaisis mediated immunopathology. In this study we have assessed in plasma from asymptomatic anti-retroviral (ARV) naïve *Loa loa* microfilaraemic HIV infected people the filarial antibody responses specific to a filariasis composite antigen consisting of Wbgp29-BmR1-BmM14-WbSXP.

Method: The antibody responses specific to a filariasis composite antigen consisting of Wbgp29-BmR1-BmM14-WbSXP was determined by enzyme linked immunosorbent assay (ELISA) in plasma from ARV naïve *Loa loa* microfilaraemicHIV infected participants. In addition the filarial antigen specific IgG antibody subclass profiles were also determined for both HIV-1 positive and negative people.

Result: Both *Loa loa* microfilaraemic HIV-1 positive and negative individuals showed significantly higher plasma levels of IgG1 ($P<0.0001$), IgG2 ($P<0.0001$) and IgM ($P<0.0001$) relative to microfilaraemia negative participants. A significant increase in IgE ($P<0.0001$) was observed exclusively in *Loa loa* microfilaraemic HIV-1 infected people. In contrast there was a significant reduction in the level of IgG4 ($P<0.0001$) and IgG3 ($P<0.0001$) in *Loa loa*microfilaraemic ARV naive HIV-1 infected individuals.

Conclusion: Thus *Loa loa* microfilaraemia in ARV naïve HIV-1 infected people through differential reduction of plasma levels of filariasis composite antigen specific IgG3, IgG4 and a significant increase in plasma levels of filarial antigen specific IgE could diminish *Loa loa* mediated immunoregulation. This in effect can result to increase loaisis mediated immunopathology in antiretroviral naive HIV-1 infected people.

Fluorescent isothiocyanate Dextran evaluates the permeability of blood-brain barrier in rabies infected mice model.

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Rabies is primarily a horrifying viral zoonosis that annually accounts for 55,000 deaths worldwide. Acute encephalitis develops as the rabies virus (RABV) enters to the central nervous system by crossing the blood brain barrier (BBB) which is a tight junction of endothelial cells.

In this study, three different molecular weights (70 kDa, 150 kDa and 200 kDa) of fluorescent isothiocyanate dextrans (FITC-Dextrans) were used to measure the extent of BBB damage and subsequent leakage patterns in brain tissues of rabies infected mice which were post-immunized with neutralizing antibodies to observe whether it has positive effect on infected mice by decreasing the death ratio.

The brains were processed for immunofluorescence to observe the neutralizing antibodies and its relevant compatibility with the leakage of FITC- Dextrans. Results showed that 70 kDa and 150 kDa FITC-Dextrans efficiently crossed BBB, and produced fluorescent illumination mainly in the cerebral cortex of brain. The enhancement of BBB permeability was significant at 5^{th} day of post-immunization, while the neutralizing antibody neutralized some rabies virus particles by crossing BBB, but it did not present enough treatment effect to the dying mice. These findings suggest that FITC-Dextran is an important fluorescent marker to investigate the integrity of BBB permeability in neurodegenerative diseases like rabies.

Cytokines and B cells responses during Behçet disease.

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Introduction/objectives: Behçet disease (BD) is a systemic inflammatory disorder with uncertain etiology. Behçet disease is considered as avasculitis with the presence of autoantibodies. In this study, we evaluated the implication of B cells in BD in relation with the major cytokines regulating their proliferation and/or differentiation.
Patients/methods: Peripheral blood was obtained from 96 patients and 35 controls. We assessed the levels of circulating B cells by flow cytometry, total antibodies (IgM, IgA, IgG) by nephelometry and auto-antibodies (ANCA, anti-phospholipids) by Luminex. IL-6, BAFF and APRIL levels were estimated by ELISA. Control Peripheral B lymphocytes were purified and cultured in RPMI 1640 complemented by 10% FBS and antibiotics in presence or absence of patients' plasma (20%). After 24h, cells' activation and/or differentiation markers were analyzed by flow cytometry (CD19, CD5, IgD, CD38). Mann-Whitney *U* test and Student T test were used for groups and markers comparison and Spearman test was used for correlation test.
Results: We observed a significant increased B cells and antibodies levels in comparison to control group ($p<0.01$). Patients showed different profiles according to the clinical data (activity: $p<0.05$, clinical expression: $p<0.01$). Autoantibodies indicated different profiles with no differences with controls in ANCA levels ($p>0.05$). In contrast, anti-phospholipids were higher during BD with anti-cardiolipins revealing a significant difference ($p<0.01$).Cytokines' analyses showed a significant increase in IL-6 and BAFF production during BD when compared to controls ($p<0.05$). In addition, a significant increase was observed for BAFF production during disease active stage ($p<0.01$). APRIL levels were not significantly increased in patients ($p>0.05$). However, we noticed with interest a correlation between APRIL and IgG levels in all BD patients ($r=0.760$, $p<0.05$). Furthermore, APRIL was significantly linked to retinal vasculitis ($p<0.05$).Peripheral B lymphocytes cultures' treatment with patients' plasma containing high amounts of BAFF induced a significant modification in the different markers' expression and B cell sub-population distribution ($p<0.05$).
Conclusion: Collectively, our results suggest the implication of BAFF and APRIL in humoral autoimmune responses during Behçet disease in relation with the clinical expression.

Interleukin-37 expression is decreased in Behcet's disease and is associated with inflammation

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Interleukin-37 (IL-37) exerts broad inhibitory properties on the innate inflammatory and acquired immune responses. This study was set up to investigate the expression of IL-37 in Behcet disease (BD) and to explore its possible regulatory role during inflammation.
IL-37 protein levels and mRNA expression in lipopolysaccharides (LPS)-stimulated peripheral blood mononuclear cells (PBMCs) from 50 BD (30 patients in active stage) patients and 20 healthy controls were assayed by real-time polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). Cytokines in the serum and the supernatants of stimulated PBMCs and $CD4^+$T cells were assayed by ELISA.
Active BD patients showed a decreased IL-37 expression and increased IL-1□, IL-6, and tumor necrosis factor-alpha (TNF-□) levels in serum and in PBMC culture supernatants. Active BD patients treated with corticosteroids showed an enhanced IL-37 production. Recombinant IL-37 (rIL-37) induced a significant decrease of inflammatory cytokines (IL-1□, IL-6, and TNF-□□). It also markedly decreased IL-17 expression in PBMCs and $CD4^+$T cells from active BD patients.
The present study suggests that a decreased IL-37 expression in BD patients is associated with an increased inflammatory response. Corticosteroid treatment of active BD patients is associated with an increased expression of IL-37 mRNA, which suggests that treatment may partly exert its immunosuppressive effect by regulating IL-37 production and reducing inflammatory cytokines.

Phenotypic analysis of lymphocytes and macrophages in bronchoalveolar lavage from patients with pulmonary sarcoidosis

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Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The lungs are affected in more than 90% of cases. A high CD4/CD8 ratio in Broncho Alveolar Lavage (BAL) is found in sarcoidosis but can also be observed in other interstitial lung disease (ILD). Nevertheless, Sarcoidosis is a disorder characterized by an accumulation of activated T cells and macrophages at sites of disease activity. This phenomenon involves increased expression of adhesion molecules on macrophages and an increase in the expression of the activation marker associated with the evaluation of disease activity.

The aim of this study was to evaluate a potential role of activation and adhesion markers in T cells and macrophages in BAL of patients with sarcoidosis.

We studied explored activation and adhesion markers in T cells and macrophages in BAL by flow cytometry within 28 patients with ILD including confirmed sarcoidosis and tuberculosis.

We found that the proportion of CD8 T cells was significantly lower in sarcoidosis and tuberculosis with a higher percentage of CD4 T cells a well as a high CD4/CD8 ratio.

In sarcoidosis patients, increased proportions of early (CD25) and late (HLA-DR) activation molecules were observed. Moreover, significantly higher central memory marker was found in BAL. No statistically significant differences were found in adhesion markers expression between the study groups.

Thus, a systematic evaluation of BAL activation and memory parameters could allow a diagnostic discrimination of sarcoidosis from other ILD entities.

Implication of FcεRI-IgE polynuclear neutrophils in the pathogenesis of malaria: possible association with the severity of disease and with cerebral forms of malaria

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Background: The role of polynuclear neutrophils (PNN) in the pathogenesis of human malaria is not yet well defined. In mice Plasmodium berghei ANKA model, it has been demonstrated that these cells were involved in the inflammatory response via FcεRI present on their surface and subsequent release of inflammatory mediators. In humans, FcεRI-IgE$^+$ PNN cells have been reported in atopic patients. In this study we aimed to investigate the potential role of these cells in human cerebral malaria and their association with the severity and outcome of disease.

Methodology: 53 patients (mean age 25 [11-64] years) were recruited in Hospital yearly from August till December during three years. Analysis included three groups: 17 patients with uncomplicated malaria and 36 with cerebral malaria hospitalized in the intensive care unit (ICU) and a group of 31 controls free of P. falciparum infection. Cerebral malaria cases included 9 patients with fatal outcome. Labeling of isolated neutrophils from peripheral blood was performed using the following monoclonal Abs: anti-CD16-Alexa 647, anti-CD49d-FITC, anti-CD203c-PerCP, anti-IgE-PE and PE-anti-FcRI. Data analysis, after acquisition by flow-cytometry, was done using Flow Jo® software for measurement of circulating FcεRI-IgE$^+$ PNN cells.

Results: Our results clearly showed the presence of FcεRI-IgE PNN$^+$ in patients with clinical malaria and a significantly higher proportions in the cerebral malaria forms ($p < 0.01$) than in uncomplicated malaria. Depending on the disease outcome, this cell population was found in significant higher proportion in patients who died ($p = 0.021$). Among survivors, the rate of circulating FcεRI-IgE PNN$^+$ cells significantly decreased between admission and the day of discharge from ICU ($p = 0.011$). Cytokine profiles showed higher IL-5 levels in uncomplicated malaria ($p=0.012$), no difference for IL-13 and lack of correlation between cytokines levels and proportion of FcεRI-IgE PNN$^+$.

Conclusion: This study demonstrates for the first time, the existence of FcεRI-IgE PNN$^+$ in patients with clinical malaria particularly in cerebral forms. It opens the way for a better understanding of the patho-physiological role of FcεRI-IgE PNN$^+$ and requires additional investigations concerning other clinical conditions.

Immunity profiling as a biomarker of integrated malaria control measures in Ivorian communities using: a Multiplex Assay.

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Introduction/objectives: Advances in malaria control have reduced the burden of disease, impacting the level of natural immunity. Therefore, it is increasingly important to monitor associated changes in immunity by measuring antibodies to an enlarged array of parasite antigens. We have validated a magnetic bead-based immunoassay (MBA) using 10 *Plasmodium* antigens and an *A. gambiae* salivary peptide to assess measurements of the decline of immunity and control measures by investigating symptomatic malaria in sentinels sites from Cote d'Ivoire.

Materiel/Methods: Recombinant proteins or peptides derived from liver or blood stages included: CSP, $LSA1_{41}$, LSA3, SALSA, PF13-DBL1α, GLURP, AMA1, MSP1p19, MSP4, CSP (*P malariae*), gSG6 (*A. gambiae*). Antigens were covalently linked to a color-coded microsphere (Luminex™ beads) in a multiplex assay. ELISA on plates was used for whole schizont extract (SE). A retrospective cross-sectional study was carried out using 298 sera sampled from 2010 to 2013, the majority in peri-urban sentinel (Abobo) and rural (Korhogo and Man) of Cote d'Ivoire.

Results: A high prevalence (7-93%) and high levels of antibody responses to most of the antigens were found. A longitudinal analysis in Abobo revealed only a marginal decreasing trend of Ab responses from 2010 to 2013 that did not parallel the observed reduction of clinical malaria prevalence following the implementation of intervention in this area. There was a significant inverse correlation between Ab responses and parasitaemia ($P<10^{-3}$, rho=0.3). Parasitaemia and Ab levels were inversely correlated, ranking individual immunity levels *ie* Korhogo> Man > Abobo. A high prevalence of IgG to *P. malariae* CSP underlined the importance of this specie in clinical burden of malaria in Cote d'Ivoire.

Conclusion: The multiplex assay provides for accurate high throughput monitoring of malaria immunity. Sero-surveillance from sentinel sites can provide important information about population time/site immunity level and its expected decline to monitor field exposure. In cross-sectional clinical malaria recruitment, the use of MBA can also clearly delineate different endemic sites where control measures have un-equal impact.

Host immunity to malaria infection: effects on malnutrition and anaemia amongst under-ten children, north region of Cameroon.

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Malaria, malnutrition and anaemia are key public-health challenges in Cameroon.However, little has been reported on the interaction between these interconnected health determinants. We hypothesized that protection against malaria will be indicated by high immunoglobulin gamma levels in the host, and malaria and malnutrition, the causes of anaemia. This study was designed to investigate the relationship between malaria, immunity, nutritional status and anaemia in under–ten children living in an area of intense seasonal malaria transmission in North Cameroon.

A Cross-sectional study was conducted in November 2013, in Pitoa and Mayo-Oulo Health Districts. Total, 368 children (6mths - 10 yrs) were enrolled. Finger-prick blood samples collected were used for haematocrit; IgG level determination using ELISA; malaria parasite presence, specie and density by microscopy; *Plasmodium* DNA extraction from filter paper for PCR. Anthropometric measurements taken using standard methods and Nutritional status assessed by calculating Height- for- age, Weight- for- age and Weight- for- Height Z-scores to determine stunting, underweight and wasting respectively. Data analysis was by SPSS 20 and Epi-Info 6.

Overall prevalences of malaria, malnutrition and anaemia were- 32.9%, 54.1% and 20.6% respectively. Stunting, underweight and wasting- 56.9%, 63.5% and 34.8% respectively. Globally, 46.4% of the children (95% CI: 41.1 - 51.8) were low anti-malarial Total IgG producers, 36.2% (95% CI: 31.2 - 41.5) low IgG_1 producers and 19.8% (95% CI: 15.7- 24.3) low IgG_3 producers. No statistically significant ($p>0.05$) association was seen between immunity and malaria for all categories of IgG. However, the production of IgG3 and Total IgG was independent of nutritional status ($P=0.077$). There was statistically significant evidence that more non-aneamic children were lower producers of Total IgG 49.6%, significantly ($P<0.05$) higher than that of aneamic children 34.8%.

Since no effect of malaria and immunity was observed in the low production of IgGs, IgG levels observed could not be an indicator of any protection against malaria but may have been due to humoral response to malaria infection.Malaria and malnutrition were not the causes of anaemia. Other factors may have accounted for anaemia. Therefore, results are suggestive anaemia observed may have been due to other presumptive causes like helminthes among others. Further studies need to be carried out to ascertain the exact cause of the IgG levels observed as well as the possible causes of anaemia in the children.

CSF Neopterin and CXCL13 are potential biomarkers for test of cure in the non-human primate model of human African trypanosomiasis.

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Background: Post-treatment follow-up is critical for confirming cure and early detection of treatment failure in human African trypanosomiasis (HAT) patients.The study aimed at investigating the feasibility of using the biomarkers neopterin and CXCL13 for staging and test of cure in a vervet monkey (*Chlorocebus aethiops*) model of HAT.
Methods: Six monkeys were infected intravenously with *Trypanosoma brucei brucei* and two uninfected monkeys acted as controls. Late-stage disease was induced by sub-curative treatment with diminazene aceturate (DA) administered 28 days post-infection (dpi). On relapse parasitaemia at 82 dpi, they were curatively treated with melarsoprol (MelB). Cerebrospinal fluid (CSF) and blood samples were collected at regular intervals for 39 weeks. The concentrations of neopterin and CXCL13 were determined by quantitative ELISA.
Results: Infected monkeys presented with a clinically similar disease as observed in humans with progression from early stage to late stage disease.Serum neopterin levels increased rapidly after infection in early stage disease, peaking at 14 dpi. Levels then dropped rapidly to pre-infection levels by 35 dpi where they remained for the rest of the experimental period. In contrast, there was a marginal increase in CSF neopterin during early infection, with a minor peak at 21 dpi. In late stage disease however, levels increased again from 42 dpi and peaked at 82dpi, coinciding with relapse parasitaemia. A fall in CSF neopterin occurred after curative treatment with MelB, to within pre-infection ranges. Serum CXCL13 increased rapidly from 7 dpi, peaking at 28 dpi, after which the levels dropped upon sub-curative treatment with DA. In CSF, CXCL13 increased gradually in early stage disease, and was not affected by sub-curative treatment. Peak levels coincided with relapse parasitaemia, followed by a gradual decline to pre-infection levels 105 days after curative treatment.
Conclusions: The changes in CSF neopterin and CXCL13 correspond to important time-points and stages of the disease. That peak levels coincided with time of relapses demonstrates the potential of these biomarkers in staging and detecting treatment failure. Moreover, the rapid fall in CSF neopterin after curative treatment confirms its great potential for use in development of a test of cure.

An investigation into the role of *Schistosoma Mansoni* infection on human *papillomavirus* (HPV) vaccine induced protective responses.

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In sub-Saharan African countries vaccines are administered to people who may suffer from multiple or co-infections. These infections that include exposure to helminth infections are known to modulate immune responses rendering some vaccines ineffective. The impact of helminth infections such as schistosomiasis on a recently introduced Human papillomavirus (HPV) vaccine that provides more than 90% protection, on populations infected or treated and the degree or duration of protection has not been determined

This study set out to investigate whether schistosomiasis compromises the efficacy of the HPV vaccine. A baboon model was used to define the immune mechanisms induced by Schistosomiasis and how this infection impacts on HPV vaccination strategies. A total of 12 Olive Baboons were divided into 4 groups each having 3 animals. Group 1 were infected with S. mansoni cercariae and allowed to develop to chronic infections before vaccination with HPV vaccine. Group 2 was also infected with S. mansoni cercariae, followed by treatment with Praziquantel (80mg/kg) and finally HPV vaccine administered. Group 3, the control arm, were not infected with Schistosomiaisis, however they were vaccinated in a similar manner.

The progression of the Schistosomiasis infection was monitored through the Kato Katz technique. Blood samples were collected at predetermined time points, serum and immune cells were isolated. Immunological assays included ELISA to determine total IgG antibodies present in the serum samples and levels of IL-4, IFN cytokines, lymphocyte proliferation assays, flow cytometry to determine their proliferation index. The data was analyzed using One-way ANOVA followed by Dunn/Berferonni multiple comparison tests for the treatments that show statistical difference, this was done using the GraphPad Prism software version 7.00 for Windows. The statistical level of significance was set at $p \leq 0.05$.

We observed no significant difference in the levels of HPV specific total IgG antibodies among the 3 groups of experimental animals (P= 0.4865). We are currently analyzing lymphocyte proliferation assays to determine if cellular responses are affected by HPV vaccine administration.

This study provides valuable information on the role anti-helminth therapy may play on vaccine responses.

Suppression of granulocyte functions in lymphatic *Filariasis*: Role of IgG4 antibodies.

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Introduction: Helminth parasites are renowned for their capacity to dampen inflammation to support their own survival, thus generating a modified Th2 immune response characterized by the presence of regulatory cytokines and high plasma levels of the non-cytolytic antibody IgG4. This particular isotype is described in both helminth and allergy models to inhibit diverse effector cells. How IgG4 molecules affect granulocyte activation and functions is still not well characterized.
Methods: Using isolated granulocytesand affinity purified IgG and IgG4 fractions fromplasma of endemic normals (EN), lymphatic filariasis pathology patients (CP), asymptomatic microfilaraemic (Mf+) and amicrofilaraemic (Mf-)infected individuals, we analyzed the impact of bulk plasma and IgG positive or negative fractions on IgE/IL-3 stimulated granulocytes by flow-cytometric analysis of CD66b/CD63/HLADR expression and ELISA assessment of histamine, eosinophil cationic protein and neutrophil elastase in culture supernatants. In addition, the IgG4-induced granulocyte modulation pathways were investigated by FcγRs blocking, immunofluorescence and western blot.
Results: Granulocyte activation and granules content release were significantly inhibited byplasma of EN and Mf+ individuals. This inhibitory capacity was abrogated upon depletion of IgGs from the plasma of Mf+ individuals but persisted in EN plasma. Interestingly, affinity-purified IgG4 molecules from EN, Mf+ and Mf-, but not those of CP, interact with FcγRI and FcγRII while significantly inhibiting granulocyte activation, especially neutrophils and basophils, in a Src, AKT and MEK dependent mechanism.
Conclusion: Our data indicate that, during filarial infections, Mf+ individuals display IgG4 antibodies with potent inhibitory activities on granulocytes, notably neutrophils and basophils. In addition, we have identified possible functional differences between IgG4 molecules from patients.

Foxp3+ Regulatory T Cells Require IL-4Rα Signalling To Control Tissue Inflammation and Immunopathology during Helminth Infections.

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Introduction: IL-4Rα mediated signalling has been puzzlingly suggested to have either a stimulatory or inhibitory role on Foxp3+ Treg cells. To address this conundrum, My PhD project sought to determine the role of IL-4Rα mediated signaling in Foxp3+ Treg cells by deletion of the il-4rα gene specifically in Foxp3+ Treg cells.
Methodology: To do so, we have successfully generated and characterized a novel Foxp3+ specific IL-4Rαdeficient mouse model (Foxp3cre IL-4Rα-/lox). We have checked the role of IL-4R on Foxp3+ Tregs during steady state and helminthic infection with either 100 S. mansoni cercaria or 500 L3 Nippostrongylus brasiliensis larvae. Immune and histopathological responses were investigated by Immunohistochemistry, FACS and ELISA
Results and conclusion: Our newly generated Foxp3+ specific IL-4Rα-deficient mouse model had no detectable physiological defects or significantly altered organ cellularities under steady-state amid a genetic, phenotypic, and functional impairment of IL-4Rα mediated signaling specifically in Foxp3+ Treg cells. Under diseased conditions, infection of Foxp3cre IL-4Rα-/lox mice with Schistosoma mansoni resulted in a significantly higher production of type 2 cytokines by mesenteric lymph node cells dominated by IL-13, IL-10, and IL-4 compared to infected littermate controls. Pathologically, the heightened Th2 immune response in schistosomiasis diseased Foxp3cre IL-4Rα-/lox mice translated into an aggravated egg-driven fibrogranulomatous inflammation and negatively correlated with Foxp3 infiltration within the liver granulomas. Similarly, specific removal of IL-4Rα from Foxp3+ Treg cells resulted in a higher mucus production in the lungs of Foxp3cre IL-4Rα-/lox mice following primary Nippostrongylus brasiliensis infection. Mechanistically, removal of IL-4Rα from Foxp3+ Tregs led to reduction in the level of suppressive capacity markers, Foxp3, Helios, and IRF4 expression per cell basis, and that has been confirmed in vitro as well. Together, these findings indicate IL-4Rα mediated signalling on Foxp3+ Tregs are required to control tissue inflammation and immunopathology during helminthic infection. A regulatory feedback loop of type-2 effector responses by Foxp3+ Tregs activated by type-2 cytokines is suggested and will be discussed.

The involvement of NOTCH signaling in the pathological behavior of cultured human rheumatoid arthritis fibroblast like synovicytes.

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Introduction: Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disorder that is characterized by synovial tissue proliferation and joint inflammation, leading to degradation of articular cartilage and joint destruction. Fibroblast-like synoviocytes (FLS) are activated during this pathology and have their phenotype changed and exhibit characteristics of transformed cells. Many signaling pathways might be involved in the onset of the transformed-like phenotype of RA FLS including the Notch signaling pathway. It has been reported that Notch signaling plays an important role in joint biology and physiopathology. An over-expression of Notch signaling family components has been reported in RA and osteoarthritis (OA). The effect of Notch signaling on FLS pathology remains poorly characterized. In the current study, we investigated the involvement of Notch in RA *in vitro* using a Notch inhibitor: DAPT on normal (NL), RA and osteoarthritis (OA) FLS. **Methods**: Synovial fluid samples were collected from knees of patients with active RA. OA synovial tissue samples were obtained from patients undergoing total knee replacement surgery. Normal synovial samples were obtained from cadavers knees with no history of joint diseases. NL, RA and OA FLS were treated with DAPT for 6 days. We analyzed the effect of Notch signaling inhibition on FLS extracellular markers [fibronectin (Fbn) and metalloproteinase 3 (MMP3)] and on Notch components (Notch1, Jagged1and HES1) in NL, OA and RA FLS by western blotting and/or qRT-PCR. **Results**: Cellular clusters were observed during the first few days of NL, OA and RA FLS cultures. After the first passage, successful RA cultures proliferated rapidly and formed a tissue-like structure. Our results suggest that Notch is responsible for the down regulation of Fbn expression in both NL and RA tissues. The inhibition of Notch signaling resulted in a significant increase in MMP3 expression in both OA and RA samples suggesting that Notch downregulates this protein during these pathologies. Moreover inhibition of Notch resulted in changes in the expression pattern of Notch pathway components: receptor Notch1, ligand Jagged1 and target gene HES1, which might play important roles in the progression of joint inflammation. **Conclusion**: the results of this study show significant effects of Notch pathway inhibition by DAPT treatment not only on RA FLS but also on OA FLS, confirming the involvement of Notch signaling mechanisms in joint pathology associated with RA progression.

Circulating fibrocytes in rheumatoid arthritis: is there a role for WNT5A pathways?

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Introduction: Fibroblast-like synoviocytes (FLS) represent one of the principal effectors of joint damage and inflammation in rheumatoid arthritis (RA). The transformed-like phenotype of RA FLS reflects activation of many signaling systems including Wnt5a signaling. The origin of the expanding FLS population is uncertain and alteration in proliferation or apoptosis rates alone cannot account for the kinetics of synovial hyperplasia. In fact, RA FLS expansion could be due to migration and differentiation of fibrocytes, a rare population of circulating progenitor cells comprising 0.1–0.5% of the total circulating leukocyte population, or expansion of a stem cell pool in the synovium.
Objective: The purpose of our study was to compare the expression of Wnt5a ligand, Wnt5a receptors/co-receptors and Wnt5a targets between RA fibrocytes, RA synovial tissue FLS and RA synovial fluid FLS.
Material and Methods: RA fibrocytes were purified from peripheral blood and cultured under the conditions described by Bucala et al. RA FLS were cultured from synovial fluid and surgical specimens of synovial tissue. Wnt5a, Wnt receptors/co-receptors (FZD4, RYK, LRP5, ROR2) and Wnt5a targets (IL8/CXCR2, IL6, IL1β, CXCL10, CCL2, COX2) were analyzed using qRT-PCR. All experiments were performed at least three times. Each qPCR reaction was performed in triplicate. Statistical significance was determined by Kruskal–Wallis test. Significance was defined at $p<0.05$.
Results: Wnt5a and Wnt5a receptors/co-receptors were expressed in the three cell populations. Baseline expression of IL8, IL1β, CXCL10 and CCL2 transcripts were higher in RA fibrocytes compared to RA synovial tissue FLS and RA synovial fluid FLS. RA synovial fluid FLS showed a higher level of IL6 compared to RA synovial tissue FLS and RA fibrocytes. CXCR2 was expressed in RA fibrocytes but not in RA synovial tissue FLS and RA synovial fluid FLS.
Conclusion: Although the expression levels of Wnt5a and Wnt5a receptors/co-receptors in RA fibrocytes are not higher than those in RA synovial tissue FLS and RA synovial fluid FLS, the principal targets of Wnt5a including IL8 are overexpressed by the circulating progenitor cells. This chemokine may be involved in fibrocyte migration to the inflamed joints and in synovial hyperplasia through its proliferative potential.

FcγR2A and FcγR3B polymorphisms and biotherapy outcomes in patients with chronic inflammatory rheumatisms

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Introduction: Despite the proven therapeutic value of TNFa antagonists, many patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) show low or no response. This heterogeneity may be due in part to polymorphisms of the Fcg receptors, resulting in a higher or lower affinity to the Fc region of Ig-based therapies with impact on their clearance and bioavailability. This study examines the role of FCGR2A and FCGR3B polymorphisms on anti-drug antibodies (ADAb) production and on a clinical response to biotherapy in RA and AS patients

Material and methods: A total 40 RA patients and 31 AS patients was investigated. Eleven patients treated with Adalimumab (ADL), 17 with Etanercept (ETA), 26 with Infliximab (INF) and 17 with Rituximab (RTX). Genotyping of FCGR2A R131H and FCGR3B NA1NA2 SNP's was performed by PCR-SSP. Antidrug antibody and drug levels were measured by ELISA (Promonitor®). Serum samples obtained after at least 6 months of biotherapy initiation. According to EULAR recommendations, patients were classified as not responding, if ([DAS]-28) is less than 1,2 in RA group (31%) and if BASDAI score is more than 4 in AS group (39%).

Results: The positivity of ADAb was observed in 28,2% of patients and was statistically higher in those receiving TNF than other biotherapy groups (p: 0,003). The ADAb positivity correlates also to lower drug levels in RA and AS patients (p: 0.004) and to worse therapeutic response in the two patients groups (p: 0,007). Regardless of the biotherapy type, homozygotes of the low affinity FCRG2A allele were significant predictors of the production of ADAb (p = 0.038) and were associated to higher levels of these antibodies (R/R: 4762,46 ± 1586,47 AU/ml, R/H 307,89 ± 94,96 AU/ml and H/H: 192,91 ± 112,167 AU/ml) (p = 0,066). However, adjustment for covariate factors (age, gender, type of biotherapy) in logistic regression models does not confirmed that FCGR2A R131H could constitute an independent susceptibility factor of biotherapy immunogenicity. No differences in FCGR3B genotype distribution were observed among ADAb producers compared to ADAb (-) patients and among EULAR non-responders compared to EULAR good responders. Nevertheless, FCGR3B NA1NA2 SNP's seems to affect the side effects of Ig-based therapies by increasing the allergic reactions risk (p = 0,031).

Conclusion: Our preliminary results suggest that Fcg receptors polymorphisms may affect the outcome of biotherapy response. These findings could improve the optimization of pharmacologic approaches on chronic inflammatory rheumatisms.

CXCL4 in Tunisian patients with systemic sclerosis.

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Introduction: Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by excessive collagen deposition and vascular injury in the skin and internal organs. Clinical features, disease progress and prognosis are heterogeneous among patients with SSc. Therefore, biomarkers that can predict the type and the severity of organ involvements are required to detect patients with a high risk of disease progression. Among the recently studied biomarkers is the CXCL4, a chemokine with anti-angiogenic and pro-fibrosing action.

Objectives: First, to assess the CXCL4 level in patients with SSc comparing to healthy controls and to patients presenting other clinical conditions; Second to search correlations between the level of CXCL4 and the clinical manifestations of the disease.

Material/Methods: This was a retrospective study of 50 cases of SSc with no other connective tissue diseases associated, which were collected from the Internal Medicine department during the period from January 2011 to February 2017. All patients met the American college of rheumatology/European league against rheumatism classification criteria for SSc of 2013. Healthy controls were represented by 30 age- and sex-matched healthy persons. We also determined the levels of CXCL4 in 36 patients with systemic lupus erythematosus (SLE), 30 patients with rheumatoid arthritis (RA) and 27 patients with Sjögren's syndrome (SS). Levels of CXCL4 were determined using an enzyme-linked immunosorbent assay (R&D Systems®).

Statistical analysis used SSPSS software and a p value under 0.05 was considered significant.

Results: The SSc cohort was made of 47 women and 3 men; the mean age was 50.1 ± 10.4 years. The mean level of CXCL4 in patients with SSc was 47.80 ± 18.27ng / ml. It was significantly higher than the mean level in healthy controls (38.34 ± 15.83ng / ml), in patients with SLE (25.46 ± 16.09 ng / ml) and patients with RA (39.28 ± 11.91ng / ml) ($p = 0.021$, <0.001 and $=0.026$ respectively). There was no significant difference between the mean level of CXCL4 in patients with SSc and in patients with SS (45.60 ± 12.62 ng / ml).

In patients with SSc, the CXCL4 level was significantly lower in patients presenting arthralgia comparing to those who did not have arthralgia (p=0,041). There was no statistically significant correlation between CXCL4 levels and the various other clinical and paraclinical manifestations of the disease.

Conclusion: CXCL4 appears as a potential biomarker for SSc, however it is not correlated to the clinical phenotype of the disease in our cohort. Studies on larger cohorts are necessary in order to better study its role as an indicator of disease severity.

Diagnostic value of anti-Phospholipase A2 receptor (APLA2R) and anti-thrombospondine type1 domaine containing 7A (ATHSD7A) in membranous nephropathy: a Tunisian cohort.

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Introduction: Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in adults. MN can be primary or caused by infections, malignancies or auto-immune diseases. Defining the primary nature of MN can be challenging due to all explorations that need to be run to exclude secondary MN. The recent characterization of antigen targets in primary MN allowed important advances in understanding its pathophysiology. APLA2R and ATHSD7A are new interesting tools in the diagnosis of primary MN but no data are available on Tunisian patients.

Objectives: To assess the diagnostic and monitoring value of APLA2R in primary MN Tunisian patients. To evaluate the clinical usefulness of APLA2R serum subclass distribution and the relevance of ATHSD7A testing in APLA2R negative patients.

Patients and Methods: Study population consisted in 54 biopsy proven MN, 15 non-MN glomerulopathy, 15 active hepatitis B and 35 healthy donors (HD). Among MN patients 31 were diagnosed with primary MN. APLA2R and ATHSD7A antibody detection was performed by ELISA and/or indirect immunofluorescence (IIFT). APLA2R subtype distribution was assessed in all positive samples using monoclonal anti-IgG1, IgG2, IgG3 and IgG4 Anti-human antibodies. Considering higher sensitivity of IIFT and the mutual exclusive character of APLA2R and THSD7A, negative primary MN samples were tested to APLA2R and ATHSD7A by IIFT. Over 16 positive APLA2R primary MN patients, 7 had a re-assessment after a mean period of 2 years.

Results: Among primary MN patients, 54.8% (17/31) showed positive APLA2R by ELISA with a specificity of 98.9%. Over 14 primary MN negative samples, 3 were positive for APLA2R when tested by IIFT improving the biomarker's sensitivity to 64.5%. All 14 samples were negative to ATHSD7A. Primary MN samples with APLA2R high title displayed IgG4 subclass predominance, which was not the case in a patient with MN secondary to hepatitis B. Among patients re-assessed for APLA2R, 4 showed a good correlation between antibody level over time and clinical course. As the 3 remaining patients progressed to end stage renal failure, surrogate markers for disease activity couldn't be assessed.

Conclusions: APLA2R presents as sensitive and specific biomarker for primary MN, however positive APLA2R status doesn't allow the exclusion of secondary MN. Preliminary results show that subclass assessment may be interesting for guiding the diagnosis of secondary MN. APLA2R appears as a non invasive marker for disease activity over time. A study over a larger cohort is needed to determine ATHSD7A prevalence in MN.

The impaired role of monocytes and regulatory T cells in the pathogenesis of Hashimoto's thyroiditis.

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Introduction: Hasimoto's thyroiditis (HT) is an organ-specific autoimmune disorder characterized by reactivity to self thyroid antigens with a variable level of chronic inflammation. CD4+CD25+FoxP3+ regulatory T cells (Treg), a subset of CD4T that plays a major role in the maintaining of self-tolerance. Altered suppressor function of these cells or its global depletion leads to autoimmune diseases, such as Hashimoto thyroiditis. Monocytes, a major component of the innate immune system, may play a key role in the pathogenesis of HT. These cells are widely recognized to play an inflammatory and tissue destructive function and abnormalities in their phenotype and have been associated with a variety of autoimmune disorders. Little is known regarding the contribution of monocytes to the pathogenesis of HT. This study aims to explore the phenotypic profile of regulatory T cells and monocytes subsets in HT patients in comparison with healthy donors (HD).
Materials and methods: The frequencies of Treg cell and monocyte subsets in the peripheral blood of 35 HD and 27 HT were determined by flow cytometry using CD16 PE C14 FITC HLA-DR APC, CD4 PercP, CD25 APC, FoxP3PE and ObR FITC antibodies. Thereafter, Tregs were isolated by Magnetic-Activated Cell Separation (MACS) technology from 5 cases of TH patients and 5 healthy donors, their suppressive activity was evaluated in the coculture of CD4+CD25- T responder cells with Treg cells in presence or not of leptin.
Results: Compared with the control subjects, our results demonstrate that the proportion of Treg in HT patients was in average similar to that found for HD. However, Treg exhibit a significant increase in the expression of ObR, a leptin receptor that is involved in the regulation of the suppressive function of Treg cells, was observed on Treg of HT patients. Moreover, we showed that Treg purified from PBMC of HT patients were less suppressive than Treg from HD. In the same way, the absolute count of monocytes in patient with HT was higher than that in the HD group. Then, the proportions relative to total monocytes of each monocyte subsets were further examined. The intermediate subsets were found to be the most expended exhibiting a high level of HLA-DR in patients with HT.
Conclusion: Taken together, our data suggest that impairment of Treg and the increased count of monocytes may have a role in the autoreactive response toward the thyroid gland of HT patients.

Expression of T helper cells master regulators in Tunisian Pemphigus Foliaceus.

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Backgroung/Objectives: Pemphigus foliaceus (PF) is an autoimmune blistering skin disease. It is considered as a polar Th2 disease in the chronic phase, with a partial shift to Th1 during the acute phase. However, recent study suggests the involvement of Th17 in the pathogenesis of the disease. The aim of our study was to evaluate the mRNA expression of the key transcription factors Tbet (Th1), GATA3 (Th2), RORc (Th17) and FOXP3 (Treg) characteristics of Th lymphocyte subsets to assess the lymphocyte imbalance in skin biopsies and PBMCs of Tunisian PF patients

Material and Methods: PBMCs were extracted from the whole blood obtained from 5 patients in the acute phase and 4 healthy controls. Total RNA was extracted using Trizol reagents. Skin biopsies were obtained from 6 PF patients (group 1: 3 first discovery and group 2: 3 patients with corticoresistance) and 2 healthy controls. Total RNA was extracted using the 'Rneasy Fibous Tissue Mini Kit', Qiagen®. The mRNA expression of the transcription factors was analyzed using the TaqMan detection system. For the relative quantification, data were analyzed by the ΔΔCt method and normalized to the average of housekeeping gene GAPDH. Statistical analyses were carried out using GraphPad software.

Results: In skin biopsies, the specimens of first discovery patients expressed higher levels of GATA3 (0.03±0.02) and FOXP3 mRNA (0.0055±0.0026) compared to healthy controls (0.0056±0.00004 and 0.0011±0.000015; respectively). In specimens of patients with corticoresistance, the expression levels of GATA3 (0.200±0.07), RORc (0.057±0.03) and FOXP3 mRNA (0.045±0.024) were significantly higher than of healthy controls (FOXP3: 0.0031±0.004) ($p<0.05$). The transcriptions factor's ratios differed between patient's groups: (i) For the first discovery patients; GATA3 (0.7), FOXP3 (0.15), RORc (0.1) and Tbet (0.033) and (ii) for patients with corticoresistance; GATA3(0.57), RORc (0.22) FOXP3 (0.16),and Tbet (0.04), respectively. RORc mRNA expression in PF skin biopsies was significantly associated with the severity of the disease. The expression of these transcription factors in PBMCs does not differ statically between PF specimens and healthy controls ones.

Conclusion: These findings suggest the important implication of the Th cells imbalance in PF pathogenesis particularly the Th17cells that, potentially, may address a selective therapeutic approach targeting the IL23/Th17 pathway. However, the expression of the transcription factors in PBMC through different stages of the disease must be investigated to more elucidate the role of Th balance.

Ectoenzyme implication in neurological inflammatory disorders compared to autoimmune diseases.

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Introduction/Objective: Multiple sclerosis (MS) and Neuro-behçet (NB) are recurrent disorders affecting the central nervous system (CNS). It has been reported that effectors T cells involved in the pathogenesis of MS and NB are mainly TH1 and TH17 populations. To maintain homeostasis, these cells are suppressed by regulatory T cells. Recently, it became apparent that Tregs can be divided in two subsets based on the expression of CD39 an ectonucleotidase that catalyzes the conversion of pro-inflammatory extracellular ATP to adenosine which present a regulatory effect. CD39+ Tregs, but not CD39− Tregs, have the potential to suppress the pathogenic IL-17 producing CD4+ T cells. The purpose of our study is to characterize the CD39 population in the blood and cerebral spinal fluid (CSF) of MS and NB disease to determine the role of this ectoenzyme in these two disorders.

Materiel and methods: We quantified, using quantitative RT-PCR, the mRNA expression of IL-10, IL-4, GATA3, Foxp3, CD39 and CD73 in the PBMC and CSF of 21 patients with relapsing remitting multiple sclerosis (RRMS), 19 patients with Neuro-Behçet disease (NBD) and 22 healthy controls. CD39 and CD73 in blood and CSF were studied simultaneously with Foxp3 and CD25 extra and intracellular labeling by flow cytometry.

Results: Measurement of anti-inflammatory cytokines, showed no significant difference in the expression of IL-4, GATA3 and Foxp3 mRNA in the blood and CSF of the three studied groups. However, in CSF a significant higher IL-10 expression was observed in NBD patients compared to other groups ($p<0,001$). Concerning CD39 expression, our results revealed a significant decrease of CD39 in PBMC of RRMS compared to NBD (p=). Surprisingly, In the CSF we detected a high level of CD39 in RRMS and NBD patients ($p<0,001$) compared to controls. Moreover, we have demonstrated that this ectoenzyme is more expressed in the CSF of NBD compared to RRMS (p). To induce a regulatory effect, CD39 should be co-expressed with another marker named CD73 that cleaves AMP to adenosine. Our finding show, a high CD73 expression in the CSF of RRMS patients compared to NBD and controls. Moreover, cellular labeling indicates that CD39 in CSF RRMS patients isn't associated with regulatory markers like Foxp3.

Conclusion: To conclude, we show a strong involvement of CD39+ cells in the CSF of NBD and MS patients. It seems that this ectoenzyme have different functions depending on the inflammatory environment.

Circulating IL-10 producing B cells and T CD4 cells in CSF and blood of neuroimmunological disorders patients.

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Introduction/Objectives: Neuroimmunological disorders are a spectrum of diseases characterized by a chronic neuroinflammation causing neurologic lesions. The clinical course of the majority of these diseases is defined by periods of relapses and remission that suppose an interplay between self-reactive and immunoregulatory process. T and B cells are generally considered as effectors cells, but it is now clear that they are essential for inducing immune tolerance by regulating immune responses via IL-10 production. IL-10 producing B and T cells provide an antigen-specific mechanism for delivering IL-10 locally to sites of immune activation and inflammation. We first demonstrate an elevated IL-10 expression in the cerebrospinal fluid of patients with neuroinflammatory disease like neuro-Behçet. The aim of this work is to assess involvement of different cell subsets secreting Il-10.

Material/Methods: Blood and cerebrospinal fluid (CSF) samples from patients with CNS inflammatory diseases were collected at time of clinical relapse. Our study included controls with no neurological inflammatory process. Ethical clearance and written consent were obtained for all of them. Isolated PBMCs and CSF cells were immunostaining with a combination of anti-CD-19 (FITC) anti-CD4 (APC) and anti IL-10(PE) then analyzed using BD FACS DIVA.

Results and conclusion: We investigated using flow cytometry IL-10 producing B and T cells in the blood and CSF. The evaluation of the eventual source of this cytokine show us a higher IL-10 producing B cells proportion in the blood and the CSF of patients compared to healthy controls. Interestingly, the CD4 subset secretes lower levels of IL-10 in the two studied compartments of patients compared to healthy controls. In summary, our current findings suggest that IL-10 producing B cells are the major regulatory cells involved in neuroinflammatory environment.

Clinical significance of NOS2 expression in four types of tumor Tunisian patients: melanoma, nasopharyngeal, colorectal and breast tumors

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Introduction/Objectives: The type 2 nitric-oxide synthase (NOS2) is an enzyme dominantly expressed during inflammatory reactions. NOS2 products have ambivalent effects: Pro or anti-tumoral depending on concentration and micro-environment. Furthermore, our previous work in a mouse model of melanoma, a mice transgenic for the RET oncogene on the NOD background (NOD.RET^{+}), showed that the germline inactivation of the Nos2 gene was associated with a dramatically improved tumor prognosis. In consequence, in this work, we aimed to study the prognostic value of NOS2 expression in melanoma (M) as well as breast cancer (BC), colorectal cancer (CRC), and nasopharyngeal carcinoma (NPC) of Tunisian patients.

Material/Methods: The level of NOS2 was measured by RT-QPCR in tumor specimens, the correlation of NOS2 expression with clinico-pathological parameters was determined, and the NOS2 expression was localized by immunohistochemistry analysis.

Results: Overall, we showed that the expression of NOS2 was higher in breast compared to colorectal and nasopharyngeal tumors whereas in melanoma, the level of NOS2 expression was low. Furthermore, NOS2 expression correlated with the Breslow thickness, Clark level and histological subtype in melanoma while in NPC, significant association was seen with age at diagnosis, TNM, metastasis, response to treatment, and expression of COX-2. In CRC, the expression of NOS2 correlated with tumor size, TNM, tumor location, and histological type, and with tumor size, tumor stage, SBR grade and triple negative cases in BC. In melanoma and NPC samples, NOS2 immunoreactivity is found in stromal cells and tumor cells as well. In CRC specimens, the NOS2 immuno positivity is found mainly in the stromal cells and occasionally in tumor cells. However, in BC, the immunostaining is observed only in the cytoplasm of stromal cells.

Conclusion: These observations showed that an increased expression of NOS2 was associated with more severe clinical and histopathological characteristics and highlight that NOS2 is a reliable marker for advanced stage and aggressive behavior for the four types of cancer and might be a potentially promising therapeutic target.

Targeting Hsp27/eIF4E interaction with phenazine compound and its encapsulation: a promising alternative for prostate cancer treatment.

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Background: The actual strategy to improve current therapies in advanced prostate cancer involves targeting genes activated by androgen withdrawal, either to delay or prevent the emergence of the castration-refractory phenotype. However, these genes are often implicated in several physiological processes, and long-term inhibition of survival proteins might be accompanied with cytotoxic effects. To avoid this problem, an alternative therapeutic strategy relies on the identification and use of compounds that disrupt specific protein-protein interactions involved in androgen withdrawal. Specifically, the interaction of the chaperone protein Hsp27 with the eukaryotic translational initiation factor eIF4E leads to the protection of protein synthesis initiation process and enhances cell survival during cell stress induced by castration or chemotherapy. Thus, in this work we aimed at i) identifying the interaction site of the Hsp27/eIF4E complex ii) interfere with the relevant protein/protein association mechanism involved in castration-resistant progression of prostate cancer and iii) developed two encapsulated phenazine derivatives DOTAU-CL and DOUPEG-2000 to improve the solubility of the compound 14.

Methods: Towards this goal, combining in silico and BRET screening to found potential chemical compounds - “hits”- that disrupt the Hsp27-eIF4E interaction, we found one phenazine compound (#14) as « hit » compounds able to disrupt the interaction between Hsp27 and eIF4E. We tested the effect of compounds 14 on the inhibition of the interaction Hsp27-eIF4E by co-IP, cell proliferation, delivery for the cells, apoptosis and *in vivo* of CRPC models.

Results and Conclusion: We proved that eIF4E interacts with the C-terminal part of Hsp27, preferentially when Hsp27 is phosphorylated. We also observed that the loss of this interaction increased cell chemo-and hormone-sensitivity. In order to find a potential inhibitor of Hsp27/eIF4E interaction, BRET assays in combination with molecular simulations identified the phenazine derivative 14 as the compound able to efficiently interfere with this protein/protein interaction, thereby inhibiting cell viability and increasing cell death in chemo- and castration-resistant prostate cancer models *in vitro* and *in vivo*.

Investigation of inflammatory biomarkers in systemic and in cutaneous melanoma microenvironment: Xeroderma Pigmentosum as a model.

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Introduction: Melanoma cancer (MC) is a malignancy known for its low rate in Tunisia (0.5-0.7 per 100 000 inhabitants per year). Xeroderma Pigmentosum (XP) is a rare genetic disease that stands as the major familial predisposing factor to melanoma with a rate relatively high in Tunisia, 1/10000. Increasingly studies highlight the association of inflammatory response to the poor outcome of cancers. However, little is known about its involvement in MC development and especially in XP patients.

The aim of the study was to investigate major inflammatory pathways/Biomarkers in patients with Sporadic MC (SP-MC) and in XP patients developing MC (XP-MC), compared to healthy donors.

Methods: Inflammatory gene expression of 3 SP-MC patients, 3 XP-MC patients and 3 healthy donors were analyzed with real-time PCR arrays using total RNA extracted from MC tumors. A total of 84 genes were studied. Differentially expressed genes were verified by real-time quantitative PCR (RT-qPCR). In addition, we used multiplex flow cytometry to investigate candidate inflammatory biomarkers in blood, from 8 SP-MC patients and 4 XP-MC patients. A total of 18 inflammatory molecules were tested. This study has obtained the ethics approval (IPT/LR05/Project PCI/22/2012/v2) from the Institut Pasteur de Tunis.

Results: The gene expression analysis in SP-MC tumors show that 56 genes were differentially expressed compared to healthy skin, among which 53 were up regulated. Regarding XP-MC tumors, we found that 52 inflammatory genes were differentially expressed compared to healthy skin, among which 16 were down regulated.

The comparison between SP-MC and XP-MC tumors expression profiles reveals that 2 genes were significantly upregulated in SP-MC (HRH2, and C3), while one gene, the KLK1 was downregulated. Regarding XP-MC tumors, we found that KLK13, and IGF1 were up-regulated. After checking with regular rt-qPCR, only the KLK13 gene was over expressed in XP-MC whereas HRH2 is up-regulated, and KLK1 down-regulated in SP-MC tumors.

Results obtained by multiplex flow cytometry, showed low levels of inflammatory biomarkers in SP and XP patients. Only IL33, MCP1, and MIP1b molecules were statistically significant in both groups.

Conclusion: Our results may point to some new putative biomarkers obtained using multi-parametric analysis. The KLK13, which were upregulated in XP-MC, were previously suggested to be involved in cancer progression (Martins et al., 2011); and IL33, newly described as a novel cytokine that could have a role in tumorigenesis (Lu B et al., 2016). Further investigation of the roles that could play these biomarkers on melanoma cells will be performed.

Primary immunoideficiency patients are a reservoir for potentially neurovirulent vaccine-derived poliovirus strains in post-eradication era.

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Several outbreaks of poliomyelitis due to circulating vaccine-derived polioviruses (cVDPVs) have been reported. Patients with combined immunodeficiencies and predominately antibody deficiencies exposed to oral polio vaccine (OPV) may excrete poliovirus strains for months or years. The excreted viruses (Immunodeficient VDPVs (iVDPVs)) are frequently highly divergent from the parental OPV and have been shown to be as neurovirulent as wild virus. Thus these patients represent a reservoir for potentially neurovirulent polioviruses and a global risk to unimmunized contacts in post-eradication era. Thereby, assessing the risk associated with prolonged iVDPV excretion among PID patients is of critical importance for stakeholders and decision-makers to build an effective strategy for the polio endgame, including development of potential treatments such as antivirals. In support of WHO recommendations to better estimate the prevalence of poliovirus excreters among immunodeficient patients and characterize the dynamics of virus excretion and the genetic evolution of these strains, 635 patients from 13 OPV using countries were studied. Patients include 570 with primary antibody deficiencies and 65 combined immunodeficiencies. Two

stool samples were collected over 4 days and tested for enterovirus. Poliovirus positive samples were sequenced. Thirteen patients (2%) excreted VDPV strains, most for less than 2 months. Five patients (0.8%) from Iran, Tunisia and Turkey were considered iVDPV excreters based on the number of virus nucleotide changes which reflects duration of excretion. Five (0.8%) were classified as iVDPVs (only in combined immunodeficiencies and mainly due to poliovirus serotype 2). Non-polio enteroviruses were detected in 30 patients (4.7%). Patients with combined immunodeficiencies had increased risk of defect in the polioviruses clearance than primary antibody deficiencies. iVDPV divergence occurs in poliovirus excreters with combined immune deficiencies in a short period of time after OPV exposure, most for less than 6 months. Survival rates among PID patients are improving in lower-and middle-income countries and iVDPV excreters are identified more frequently. Surveillance for poliovirus excretion among PID patients should be reinforced until the use of OPV is stopped. Antivirals presently in development represent the only means to manage the treatment of excreters and the risk they present to the polio endgame.

State of effectiveness of protein quality control by the proteasome complex in dependence on the clinical status of Moroccan patients with blood cancer

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Background: The failure of the machinery of protein degradation namely "the ubiquitin-proteasome pathway" is involved in the onset of various diseases notably different forms of cancer including Hematologic malignancies linked to protein degradation, such as transcription factors, and cell cycle regulators or of tumor suppressor proteins. Mainly localized in the nucleus and cytoplasm of cells, the proteasome can be detected in the cell culture supernatant or in the peripheral blood of patients.

Objective: This study focused on a study in a large cohort of patients with Moroccan Hematologic malignancies in order to follow the evolution of the 20S proteasome in serum and intracellular according to clinical status.

Materials and Methods: Quantitative and functional analysis of the proteasome was conducted at the subcellular level and serum during a pathological phenomenon (hematologic malignancy) in 145 Moroccan patients (sex ratio: 1.10 / average age: 47.9 ± 15.3 years) with ELISA assay, and by following the fluorescence emitted after enzymatic digestion of specific peptides by the chymotrypsin-like activity.

Results: All patients (n=145) with Hematologic malignancies express proteolysis rate more pronounced in serum compared to the control. The evolutionary trend of subcellular proteasome is significantly linked to the rate of chymotrypsin-like activity. The entire population of 60 patients called back for a second blood test after three months of treatment reported a significant drop in the rate and the activity of the proteasome in serum and intracellular level.

Conclusion: The relationship between clinical condition and concentration of the proteasome has been reported in various diseases. The use of proteasome circulating assay as a biomarker of tumor and a tool that could be very satisfying to follow patients after remission to prevent a possible fall. So Intracellular dosage proteasome reveals important because it allows estimating the predictive score of the risk of toxicity.

Cytokines associated with Burkitt's lymphoma in western Kenya.

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Background: Burkitt's lymphoma (BL) is an aggressive non-Hodgkin lymphoma common among children in East and Central Africa. Chronic infections with Epstein Barr virus (EBV), *Plasmodium falciparum*, human immunodeficiency virus 1 or 2 (HIV-1/2) and other pathogens prevalent in the region are thought to drive inflammatory or anti-inflammatory cytokine responses and B-cell hyper stimulation. It is widely hypothesized that inflammatory immune responses due to infections indirectly or directly drive *c-myc* gene, a situation that can lead to neoplastic transformation and consequently BL tumours. This study attempted to describe cytokine patterns in children and adolescents with BL in western Kenya.

Methods: One hundred and four (104) clinical and histological diagnoses of non-Hodgkin's lymphomas patients at Moi Teaching and Referral Hospital (MTRH) were recruited. Their BL status was confirmed using a consensus immunohistochemistry (IHC) panel. Participants' plasma cytokines levels were estimated by BD CBA Human Th1, Th2 and Th17A Cytokine Kit and CBA Human TGF-β1 Flex Set kit. Complete blood counts were determined using Coulter® AcT5 Diff CP (Beckman Coulter, USA) for each subject.

Results: the participants were grouped into BLs' and non-BLs' based on their IHC staining pattern. The media plasma levels pg/ml of IL-6 (13.83) and IL-10 (8.98) were higher in BL participants compared toIL-6 (3.34) and IL-10 (1.50) in non-BL subjects. But the mean level pg/ml64.00 of IL-17A in non-BLs was higher compared to 17.38 for BL cases, though not statistically significant. Th1 cytokines -IFN-γ, IL-2 and TNF-α were lowly expressed in both BL and non-BL participants. The TGF-β1 levels were below detection of TGF-β1 BD CBA kit used in both the study groups. White, red and platelet counts differed marginally from normal but significantly so before and after treatment in both BL and non-BL participants.

Conclusion: Inflammatory and anti-inflammatory cytokines as a result of immune response to some or a combination of infectious agents prevalent in the study region may have a role in BL pathogenesis and may be potential therapeutic targets.

The role of IL-23/TH17 pathway in renal allograft rejection.

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Introduction: To investigate the role of interleukin 17 (IL-17)/ IL-23 pathway in the inflammatory process thus contributing to interstitial injury during acute allograft rejection, a IL-17 mRNA expression in renal allograft biopsy tissue and functional polymorphisms of IL-17A, IL-17F, IL-17 Receptor genes were evaluated.
Methods: A total of 93 kidney transplant recipients were included in this study. Overall 48 recipients (51.6%) experienced an acute rejection (AR). SNPs including -1507 C/T (rs18889570), 7384 A/G (rs2397084), 7469 C/T (rs11465553), and 7489 A/G (rs763780) of IL-17F gene were tested by direct sequencing. IL-17A A/G and IL-17 Receptor A/G polymorphisms were analyzed by PCR-RFLP. The gene expression of IL-17A in early allograft post-transplant biopsy (day 7: D7) was analyzed by quantitative real-time PCR (QUANTITEC IL-17A QIAGEN®) in 18 patients with acute rejection (GI) and 18 kidney recipients with stable renal function (GII) for at least one year. The relative expression for the target gene was given by $2^{-\Delta\Delta CT}$. ELISA R&D systems kits were used to test the IL-17A, Il-17F and IL-23 levels in plasma at the day of transplantation (D0) and (D7).
Results: Functional exploration of allograft biopsy tissue of renal transplant revealed that recipients with (AR) have a significantly increased mRNA expression levels of IL-17A in D7 compared to patients with stable renal function (p=0.037). Moreover, significant elevations of plasma IL-17A levels were noted in GI than in GII (p=0.002) and serial study of this cytokine confirmed that increased IL-17A levels between D0 and D7 correlate to acute renal allograft rejection (p = 0.06). Nevertheless, ROC curves, used to evaluate the performance of plasma IL-17A in detecting AR showed that given 100% specificity, the highest sensitivity was only 35.4% at cutoff value of 40.87 pg/ml. Genetic study revealed that IL-17 Receptor A/G carriers were significantly more frequent in patients with acute rejection as compared to patients without any sign of rejection and seems to be associated to lower graft survival (p = 0.018). However, no significant haplotype association was found to be a susceptibility factor to kidney lost. No impact of these functional SNPs on cytokines plasma levels was also noted.
Conclusion: Based on these findings, significant increase of IL-17A mRNA and protein levels in AR patients highlights the role of this cytokine that can be a useful clinical biomarker to predictearly acute renal allograft rejection.

Posters

Innate Immunity & Inflammation

P1. LEVELS OF CELLULAR ACTIVATION AND ANTIOXIDANT SYSTEM IN BREAST MILK AND BLOOD OF LACTATING MOTHERS

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Introduction: The present study compared the status of markers of oxidative stress in breast milk and corresponding blood samples of healthy lactating mothers.
Methods: Forty lactating mothers (22-36 years) volunteered to participate in this study. They were non-smokers and apparently healthy nursing mothers who had normal delivery without postnatal complications. Blood and breast-milk samples were collected from the lactating mothers between 6th and 18th weeks after delivery. Total antioxidant potential (TAP), total plasma peroxides (TPP) and malondialdehyde (MDA) were determined in both breast milk and blood of the mothers using spectrophotometric methods. Oxidative stress index (OSI) was determined as the percent ratio of the TPP and TAP.
Results: The results showed that TAP, TPP and OSI increased significantly ($p<0.001$) in breast milk when compared with the blood. The blood / breast milk ratios of TAP, TPP and OSI were 1:3, 1:5 and 1:2 respectively in the lactating mothers. The level of MDA was significantly ($p=0.01$) lower in the breast-milk, when compared with the blood. In the blood, levels of OSI correlated significantly with TAP ($r= -0.46$; $p= 0.015$) and TPP ($r=0.90$; $p<0.001$) while in the breast-milk, OSI correlated significantly with only the TAP ($r = -0.76$; $p<0.001$).
Conclusion: Different levels of cellular activation and antioxidant system occur in breast milk when compared with blood. Increased free radical generation in the breast milk could be beneficial against pathogens, while the bio-accumulation of antioxidants molecules regulates free radical load and avert the consequences of oxidative stress in the breast tissue.

P2. SIGNALING AND FUNCTION OF PKCδ IN PLATELET FUNCTION

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Background and Rationale: In the context of cardiovascular disease and more specifically in thrombotic reactions, our focus is on the role of PKCδ and the upstream GPIbα receptor. In a previous study, we have demonstrated that the PKCδ is essential for platelet function in response to collagen. Moreover, it's well established that the PKCδ is essential for platelet function in response to thrombin, which signals and activates platelets *via* protease-activated receptors (PARs) and GPIbα, the low/medium and high affinity receptors in human platelets, respectively. However, its role, following the stimulation of GPIbα by thrombin, remains to be discussed. The current research proposal aims to investigate the interplay between thrombin receptors and PKCδ in platelet function and thrombus formation. Accordingly, we propose to address the following hypothesis:

Hypothesis: GPIbα and PAR-1 negatively regulate platelet function *via* PKCδ in response to low doses of thrombin.

The specific objectives are : i) To determine *in vitro* the role of GPIbα in platelet signaling *via* the PKCδ, using a specific inhibitor; ii) To determine whether the PAR-1 is a cofactor for the GPIb; iii) To assess *in vivo* the effect of PKCδ on bleeding time and formation of micro-embolism in the $PKC\delta^{-/-}$ mice.

General Methods: Objectives (i) and (ii) will be done by assessing platelet function *in vitro*: aggregation, P-selectin expression, Flow Cytometry, ATP and ADP secretion with and without specific pharmacological agonists and antagonists of the thrombin receptors and PKCδ in isolated platelets from WT and PKCδ deficient mice. In addition, the phosphorylation of PKCδ will be assessed by WB and correlated with the platelet responses.

Objective (iii) will be carried out in vivo in a mouse model of thrombosis involving injury to the carotid artery. Thrombus will be examined in response to mild (2% $FeCl_3$), moderate (4% $FeCl_3$) and deep (6.5% $FeCl_3$) injury in WT mice ± a specific inhibitor of PKCδ and in PKCδ KO mice.

Significance: We expect to identify new mechanisms and pathways in platelet function that are regulated by PKCδ in response to thrombin. This study will also reveal the relative importance of the different thrombin receptors that may be clinically relevant for the control of platelet activation and thrombus formation.

P3. IL-8 AND MCP-1 CHEMOKINES CIRCULATING LEVELS IN SICKLE CELL YOUNG PATIENTS

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Introduction: Sickle cell disease (SCD) is the most prevalent genetic disease worldwide. The highest frequency is found in Sub-Saharan Africa. In Côte d'Ivoire, the prevalence rate is 12% and 50 - 75 % of children with SCD do not reach their fifth birthday.
Because accurate data on cytokines are lacking in SCD in Sub-Saharan Africa, our study evaluate, the serum levels of MCP-1 and IL-8 and their potential role in SCD.
Patients and Methods: 34 subjects (4 to 18 years) were prospectively enrolled in the study after an informed consent. The patients were assigned in 2 groups, patients in steady state and patients admitted for crisis. Serums were measured in San Diego Biolegend laboratory during Hands on training session by using LEGENDplex^{TM} Human Inflammation Panel assays.
Results: Thirty four patients with a diagnosis of sickle cell disease (SCD) comprising 18 young females (47, 06%) and 16 young males (52.94%) were evaluated in this study. Of the SCD patients, 13 (38.24%) were in crisis, and 21 (61.76%) were in a steady state condition and represented our stable control patients. Hyperleukocytosis was almost constant in SCD patients. No significative difference in monocytes and neutrophiles in steady patients versus crisis patients (monocytes : crisis 10.63+/- 3.4, steady state: 8.87+/-3.8, neutrophiles crisis 38.56+/- 19.73, steady state : 45.92+/-10.24). Higher levels of IL-8 were observed in steady-state patients compared to vaso-occlusive crisis patients (1675pg/ml versus 419pg/ml). The same applies for MCP-1. Level was higher in steady state patients (188.16 for crisis versus 288.9 for steady state) but not significative. In comparing the hemoglobin pattern, the same trend was observed in all hemoglobin type (SSFA2, SFA2, and AFA2).
Conclusion: This study reveals a chronic permanent inflammatory in children with SCD. The better understanding is essential to the development of new therapeutic approaches.

P4. IL-17 CIRCULATING LEVELS IN SICKLE CELL PATIENTS IN CÔTE D'IVOIRE

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Introduction: Sickle cell disease (SCD) is the most prevalent genetic disease worldwide. The highest frequency is found in Sub-Saharan Africa. In Côte d'Ivoire, the prevalence rate is 12%. Because accurate data on cytokines are lacking in SCD in Sub-Saharan Africa, our study evaluate, the serum levels of IL-17 A and their potential role in SCD.
Patients and Methods: 75 subjects (4 to 55 years) were prospectively enrolled in the study after an informed consent. The patients were assigned in 2 groups, patients in steady state and patients admitted for crisis. Serums were measured in San Diego Biolegend laboratory during Hands on training session by using LEGEND plex TM Human Inflammation Panel assays.
Results: Seventy-five patients with a diagnosis of sickle cell disease (SCD) comprising 37 females (49.3 %) and 38 males (50.7%) were evaluated in this study. Of the SCD patients, 38 (50.7 %) were in crisis, and 37 (49.3%) were in a steady state condition and represented our stable control patients. Hyperleukocytosis (11712.92 +/- 4589.984) was almost constant in SCD patients. No significative difference in monocytes and neutrophiles in steady patients versus crisis patients (monocytes: crisis 1090.1069 +/- 583.79537, steady state: 1393.6000 +/- 1701.99895, neutrophiles crisis 8403.5393 +/- 15521.07200, steady state : 5317.7697 +/- 2843.33521). Higher levels of IL-17A were observed in steady-state patients and vaso-occlusive crisis patients (10.0770 +/- 18.25056 pg/ml versus 9.2982 +/- 10.51591 pg/ml), but the difference was not significative. In comparing the hemoglobin pattern, the observed differences concerning IL-17 were significant in all hemoglobin type (SSFA2, SFA2, and AFA2), p=0,001.
Conclusion: This study reveals a chronic permanent inflammatory in patients with SCD even during the steady state. The better understanding is essential and suggests that the development of new therapeutic approaches should take care of crisis but also of the steady state in sickle cell disease.

P5. PREVALENCE OF NEW SEROLOGICAL MARKERS IN TUNISIAN ULCERATIVE COLITIS AND CROHN'S DISEASE

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Introduction: Several serological markers areused for the diagnosis and the discrimination between ulcerative colitis (UC) and Crohn's disease (CD). CD is associated with the presence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) and less frequently with anti-exocrine pancreas antibodies EPA (recently identified as anti-GP2 and anti-CUZD1 antibodies), while UC is usually associated with atypical pattern of Anti-Neutrophil Cytoplasmic Antibodies (a-ANCA), whose major target antigen "the DNA-bound Lactoferrin" (LFR) has recently been described, and rarely associated with anti-intestinal goblet cells antibodies (GCA).
Our aim was to identify the prevalence of these classical and new antibodies and to test the DNA-bound Lactoferrin (LFR) as a target of a-ANCA in sera of Tunisian UC and CD patients.
Material and Methods: Seventy five patients with IBD (32 CD and 43 UC) were consecutively recruited from the Gastro-Enterology Department and included in this study (35 women and 40 men; age average: 41 years). Diagnosis of CD and UC was established according to clinical, endoscopic radiological and histological criteria. ANCA screening (IgG, ethanol fixed-granulocytes), DNA-bound LFR testing (LFR granulocytes), characterization of ASCA (IgA, fungal smear), anti-GP2/anti-CUZD1 antibodies (IgG, transfected cells) and anti-intestinal goblet cells antibodies (goblet cells culture) were performed in sera samples by indirect immuno-fluorescence using a Mosaic substrate.
Results: The a-ANCA were detected in 22/43 patients with UC and 2/32 patients with CD. These antibodies were targeting the LFR in 15/22 ANCA-positive UC patients and in the 2 positive patients with CD. Regarding GCA, they were found in 13/43 UC patients (4 a-ANCA-negative patients) and in 2/32 CD patients. The classical ASCA were detected in 20/32 CD and in 3/43 UC patients. Anti-GP2 and anti-CUZD1 antibodies were identified in only 4 IBD cases (2/32 CD and 2/43 UC). Among them, one UC patient with pancolitis had only these antibodies as a serological marker.
Conclusion: Our results confirm that DNA-bound LFR is the major target antigen of a-ANCA in UC. GCA could be useful in case of a-ANCA negative UC. The low frequencies of the recently described EPA (anti-GP2 and anti-CUZD1) in our study may reflect their limited value for IBD diagnosis. However, further studies are needed to identify their promising prognostic value.

P6. ABERRANT EXPRESSION OF MUC1-C SUBUNIT IN INFLAMMATORY BOWEL DISEASE

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Introduction/objectives: Inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), affect more than two million people worldwide. Mucin 1 (MUC1) was recently described in serval IBD mouse model studies to play an important and as yet undetermined role in the immuno-pathogenesis of the disease and its progress to a cancer. Nevertheless, a few data examines the expression and the localization of MUC1in particularly the C-terminal subunit in IBD patients. This study proposes to analyze the localization and to quantify the expression level of MUC1-C in a cohort of Tunisian patients of IBD.

Material/methods: 18 biopsies from patients with a diagnosis of CD, UC or unspecific inflammation were reviewed by a pathologist and 1 colonic biopsy with inflammatory alteration was selected for staining. We also collected normal tissues adjacent to 13 cases as a control group. MUC-C expression was detected by immunohistochemistry method using a rabbit polyclonal antibody. The optic density that correlates with the antigen expression was calculated by Image FIJI.

Results: The positive expression rates of MUC1 in normal and inflamed tissues were 23% (3/13), 68% (13/18) respectively. MUC1 is significantly upregulated and its localization is altered in inflamed mucosa. Strong reaction involves apical membrane and cytoplasm of epithelial cells of glands in IBD cases

Conclusion: Even with a small number of cases, our data affirms the increase expression and altered localization of MUC1-C in inflamed mucosa. These results support the need for a larger, prospective study to elucidate MUC1-C signaling role during chronic and acute inflammation.

P7. EVALUATION OF THE INVOLVEMENT OF VASP AND PRDX2 PROTEINS IN PLATELET FUNCTION CAUSED BY CROHN'S DISEASE

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Platelets, in addition to their known role in coagulation, in inflammatory processes and the immunity modulation, also possess "restorative" properties. The aim of this work was the contribution to the evaluation of biochemical variations for Vasodilator Stimulated Phosphoprotein (VASP) and Peroxiredoxin 2 (PRDX2) involved in inflammation and recovery of hemostasis. The results showed a degree of platelet aggregation of the order of 80% in the presence of low concentration of collagen (0.5 µg/mL) through a chain/of more complex signaling cells and can intervene a whole set of biochemical reactions and which can generate positive results for the repair against inflammation for Crohn's disease (CD) subjects. For platelets stimulated for both healthy subjects and Crohn's disease subjects, the results obtained with Western Blott showed for VASP greater bands in CD subjects after A stimulation with a low concentration of collagen. These results have confirmed the importance of such stimulation which can lead to more interactions between platelets. Stimulation with collagen at 1 µg/mL shows a 5-fold increase in phosphorylation among CD subjects compared with healthy subjects, whereas the values were almost without phosphorylation in both CD and healthy controls.
Similarly, results among CD subjects have shown a maximum response of phosphorylated VASP after only 30 seconds of stimulation. As for the results of the phosphorylation rate of the PRDX2 protein, these latter show the same profile as that of the VASP since it plays the role of protector against the importance of the inflammation.

P8. IL-23R POLYMORPHISMS AND IL23 PLASMA LEVELS IN TUNISIAN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background: Th17 cells and their related cytokines (IL-17, IL-23) have been shown to be implied in pathogenesis and activity of inflammatory bowel diseases (IBD). Genome-wide association studies identified polymorphisms of Interleukin-23 receptor (IL-23R) as susceptibility or resistance factors for IBD. Therefore, we aimed to study the impact of an IL23Rfunctional polymorphismand the plasma IL-23 on IBD susceptibility and severity.
Methods: In this sense, IL-23R*rs11209026 (G/A) polymorphism were investigated together with quantification of plasma IL23 level in 54 IBD patients (47 with Crohn disease and 7 with ulcerative colitis) and 50 healthy control subjects matched in age, sex and ethnic origin.
Results: The frequencies of IL-23R mutant genotypes (*A/A and *G/A) and the IL-23R*Avariant allele were significantly lower in patients comparatively to controls, p=6.210 E-6 and p<10E-4, OR [95% CI] = 8.75 [2.35-38.42], respectively. Furthermore, IL-23 plasma levels were significantly higher in patients (325pg/ml) comparatively to controls (0 pg/ml), p=0.035. ROC curve was used to evaluate the performance of plasma IL-23 in detecting IBD. The area under the ROC curve was 0.731, 95% CI = 0.634-0.829; p=4.710E-5. Given 100% specificity, the highest sensitivity of plasma IL-23 was 46.3% at a cutoff value of 8.9pg/ml.
Analytic results did not show any correlation between IL-23R studied polymorphism and the clinical and the biological features of IBD. It was equally the case for the plasma IL-23 levels which did not influence the disease presentation.
Conclusion: The IL-23R*rs11209026 polymorphism (G/A) seems to be protective against IBD in Tunisian. Plasma IL-23 might be predictive of IBD occurrence.

P9. GENETIC POLYMORPHISMS OF INFLAMMATORY MOLECULES IN TUNISIAN INFLAMMATORY BOWEL DISEASES

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Introduction: As chemokines and adhesion molecules play a major role in the process by which leukocytes are recruited from the bloodstream into sites of inflammation, genetic variation in these production or activity molecules may influence susceptibility to inflammatory diseases.
Aim : To detect a possible association between the functional polymorphisms of these molecules and susceptibility to Crohn's disease (CD) and ulcerative colitis (UC) in Tunisian population.
Materials and methods: we have analysed polymorphisms of CCR5-delta32, CCR5-59029-A/G, CCR2-V64I, MCP-1 G/A (-2518), ICAM-1 G241R, PECAM-1 V125L, E-selectin L554F and L-selectin F206L in 194 Inflammatory bowel disease (IBD) patients and 169 healthy blood donors using PCR-RFLP and PCR-SSP methods. The patients were classified in 126 patients with CD and 68 patients with UC.
Results: A significant increase in allele frequency of 206L of L-selectin was observed in IBD patients compared with controls (OR: 1.53; 95%CI: [1.05-5.60]; *p*=0.02) but does not constitute factor influencing clinical manifestations. The genotypic and allelic frequencies of chemokine polymorphisms did not reveal significant differences between patients and controls, and among CD and UC patients. However, analysis of CD patients revealed that those carrying A/A and/or A/G CCR5-59029 genotypes are more frequently in remission compared to those with G/G genotype (OR: 0.4; 95%CI: [0.174-0.928]; *p*=0.03). Also, the frequency of the 64I CCR2 muted allele was statistically higher in CD patients in remission disease than those in active form (OR: 0.267; 95%CI: [0.09-0.78]; *p*=0.01). Adjustment for known covariates factors (age, gender and immunosuppressive regimen) confirmed these univariate findings and revealed that the A/G CCR5-59029 and V64I CCR2 genotype were associated to remission form of CD (OR: 2.63 ; 95%CI: [1.01-6.80] ; *p*=0.047 and OR: 4.64 ; 95%CI: [1.01-21.31] ; *p*=0.049 respectively).
Conclusion: The present study supports the involvement of chemokine receptor (CCR2 and CCR5) polymorphisms on the susceptibility to clinical course of IBD in Tunisian patients. However, further studies are needed to confirm the association of these diseases with allele L206 of L-selectin gene.

P10. THE ASSOCIATION BETWEEN TNF-αPROMOTER POLYMORPHISMS AND ANKYLOSING SPONDYLITIS IN MOROCCO

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Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that mainly affects the axial spine and sacroiliac joint. Several genes such as TNF-α have been checked as contributors to the pathogenesis of AS. This study evaluated the association between TNF-α promoter polymorphisms and disease susceptibility, or influence on clinical manifestations in Moroccan patients with AS. Six single nucleotide polymorphisms (SNPs) of the TNF-α promoter at positions –1031T/C, –863C/A, –857C/T, –367G/A, –308G/A, and –238G/A were analyzed.
This study included 51 males and 24 females. Clinical features of AS were obtained from reviews of medical records and interviews with patients using a standardized questionnaire. SNPs sequencing were genotyped by direct sequencing in 75 unrelated Moroccan AS patients and 100 ethnically matched healthy control. Allele and genotype distributions between groups were evaluated using the chi-square test or Fisher's exact test.
Forty eight (64%) patients were HLA-B27 positive. The frequency of homozygote –308 AA allele was higher in AS patients than in controls (P=0.0067). The frequency of -308 A was lower in patients with acute anterior uveitis (AAU; P=0.0005, OR=0.12, 95% CI=0.03-0.51) and extra-articular involvement (p=0.012; OR=0.28, 0.12 – 0.64). We did not detect any association between the polymorphisms at positions –1031T/C, –863C/A, –857C/T, –367G/A and–238G/A and susceptibility to AS or its clinical presentation.
Moroccan patients with AS had a significant higher frequency of -308AA, genotype independently from HLA-B27. We also found that this genotype and the A allele may have a protective effect in AS patients toward AAU involvement and extra-articular manifestations.

P11. SERUM LEVELS OF PROINFLAMMATORY CYTOKINES IN PSORIASIS PATIENTS IN CORRELATION WITH CLINICAL SEVERITY OF THE DISEASE AND EFFECT OF TOPICAL TREATMENT

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Introduction: Research into psoriasis is dominated by the hypothesis that it is an immunological disorder mediated through T lymphocytes. The study of the cytokine profile in psoriatic patients may provide therapeutic targets, diagnostic markers, prognosis or follow-up markers. We investigated the serum levels of the proinflammatory cytokines in psoriasis patients in correlation with disease severity and evaluated the effect of topical treatment on cytokine levels.

Patients and Methods: Psoriatic patients who have not received treatment for at least three months were recruited in the study. In all patients, dermatological examination with psoriasis severity assessment using Psoriasis Area and Severity Index (PASI), and Dermatology Quality of Life Index (DLQI) was performed. Patients were treated with calcipotriol-betamethasone dipropionate ointment (Dovobet®) once a day. Treatment efficacy was evaluated using an efficacy index. We assessed serum levels of proinflammatory cytokines in patients prior to initiation of therapy, after two months of topical treatment and in healthy controls. Interleukin (Il) 6, Il-8, Il-1β and Tumor Necrosis Factor-α were determined with the use of chemiluminescence. Il-22, Il-23 and interferon-γ were measured using ELISA (enzyme-linked immunosorbent assay) tests.

Results: Forty-two patients (53.7% plaque, 19.5% guttate, 17.1% association of guttate and plaque, 7.3% pustular, 2.4% plantar psoriasis) and forty-five controls were enrolled in the study. Il-22 serum levels were significantly increased in patients compared with controls (57.34 ± 90.9pg/mL vs 22.72 ± 13.39pg/mL respectively, p = 0.036). The PASI and DLQI correlated positively with serum levels of INF-γ (r = 0.374, p = 0.045) and Il-6 (r = 0.391, p = 0.015) respectively. Local treatment with calcipotriol-betamethasone dipropionate decreased the level of IL-23 from 1.72 ± 3.1pg/mL to 0.37 ± 1.23pg/mL after two months of regular application ((N = 11, p = 0.042). Efficacy of the treatment correlated positively with Il-8 levels measured before initiation of treatment (N = 14, r = 0.463, p = 0.048).

Conclusion: Therapeutics targeting Il-22 may have promise as a potential therapeutic target for treating psoriasis. It would be interesting to study the genetic background influencing Il-22 serum concentrations in psoriasis patients. Serum levels of Il-6 and INF- γ may be objective parameters for the disease severity. The local treatment with calcipotriol-betamethasone dipropionate decreased the serum concentrations of Il-23. Nevertheless, further clinical observations with larger cases are needed to confirm these findings.

P12. INTERLEUKIN-10 RECEPTOR 1 GENE POLYMORPHISM IN PSORIASIS

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Introduction: Interleukin-10 (IL10) is arguably the most potent anti-inflammatory cytokine. The inhibitory effects of IL10 on TNF production are crucial to its anti-inflammatory activities. It is weakly expressed in psoriasis, a systemic disease, with insufficient level of expression of anti-inflammatory cytokines to counterbalance pro-inflammatory effects. The interleukin-10 receptor subunit1 (IL10R1) is the ligand-binding subunit. The IL10R1 S138G loss-of-function single nucleotide polymorphism (SNP) has been associated with multiple diseases. We examined whether this SNP is associated with susceptibility to psoriasis in Tunisian patients.
Patients and methods: We investigated the genotype and allele frequencies at the IL10R1 S138G polymorphism in Tunisian psoriasis patients and in controls.
In all patients, dermatological examination with psoriasis severity assessment using Psoriasis Area and Severity Index (PASI) was performed.
Genotyping was performed using a multiplex allele specific polymerase chain reaction. The concentrations of TNF-α in serum were determined by solid phase chemiluminescent immunometric assay in patients.
Results: We examined forty-eight psoriatic patients (59.6% plaque, 17% guttate, 14.9% association of guttate and plaque, 8.5% pustular psoriasis) and forty-five controls. Genotypic frequencies were 47.9% AA, 47.9% AG, 4.2% GG for patients and 48.9% AA, 51.1% AG for controls. Allelic frequencies were 71.9% A and 28.1% G for patients and 25.6% G and 74.4% A for controls. No significant association between the genotypes ($p = 0.925$) or alleles ($p = 0.693$) of the studied SNP and susceptibility to psoriasis was observed.
The severity and age of onset of the disease were not influenced by Il10R1 genotype ($p = 0.791$ and $p = 0.914$ respectively). No significant difference was found in serum levels of TNF-α between the variant allele carriers (8.26 ± 3.09pg/ml) and the wild type allele carriers (8.89± 3.84pg/mL) in patients ($p = 0.58$).
Conclusion : The rs3135932 polymorphism of Il10R1 did not seem to be associated with psoriasis in the studied cohort. A larger number of patients and controls is although needed. Other polymorphisms of the interleukin-10 signal transduction pathway especially the Jak/stat system should be studied.

P13. CARD14 ALTERATIONS IN TUNISIAN PSORIASIS PATIENTS: FUNCTIONAL AND PREVENTION IMPACT

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Objectives: Psoriasis is a chronic inflammatory disease of the skin from multifactor origin. Rare highly penetrant gain of function mutations in caspase recruitment domain family, member 14 (CARD14) can lead to this pathology. Our aim was to investigate the contribution of rare CARD14 variants to psoriasis in the Tunisian population and expand knowledge of CARD14 variants in the European population.
Methods: CARD14 coding exons were re-sequenced in psoriasis cases (250 mostly military) and controls (250) from Tunisia and Europe. Novel variants seen in cases were evaluated for their effect upon NF-kb signaling.
Results: Rare variants in CARD14 were significantly enriched in Tunisian cases compared to controls. Three are collectively found in 5% of Tunisian cases and all affect the N terminal region of the protein harboring its CARD or coiled-coil domain. These variants are c.349G>A (p.Gly117Ser), and c.589G>A (p.Glu197Lys). c.589G>A (p.Glu197Lys) leading to upregulation of NF-kb activity in a similar manner to previously described psoriasis-associated mutations. On the contrary, the substitution c.205C>T p.Arg69Trp is responsible for seven fold down-regulation of NF-kb activity. One Tunisian case presented a c.1356+5G>A splice alteration that is predicted to lead to loss of exon 9 encoding part of the coiled-coil domain and hence abolishes CARD14 function.
Conclusions: These observations provide further insights into the genetic basis of psoriasis in the Tunisian population and functional information on novel CARD14 variants seen in cases from Tunisia and other populations. They indicate that gain and loss of CARD14 function might as well to the disease. They also ask the pertinence of genetic testing for prediction of the disease from the ethical point of view. Since psoriasis is a multifactor disease that occurs upon a risky genetic background and increases with continuous stress such as in military profession, it could be recommended to subjects carrying risk variants to avoid profession with stress.

P14. ASSOCIATION OF IL-10R1 S138G LOSS-OF-FUNCTION ALLELE WITH SUSCEPTIBLY TO BEHÇET'S DISEASE AND ITS CLINICAL FEATURES

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Introduction: Interleukin-10 (IL-10), a potent immunoregulatory cytokine, has been shown to be correlated with disease activity in patients with Behçet's disease (BD). It exerts its activity through its specific cell surface receptor complex, IL-10 receptor 1 (IL-10R1) and IL-10R2. The aim of this study was to investigate the IL-10R1 S138G loss-of-function polymorphism (rs3135932) with the susceptibility to BD and its clinical features in a series of Tunisian patients.
Methods: A total of 41 Tunisian BD patients (sex ratio 1.92; mean age: 38.41±10 years) and 45 control subjects (sex ratio 6.5; mean age: 30.92±12.9 years) were enrolled into this study. Genomic DNA samples were extracted from leukocytes and used to investigate the S138G polymorphism of the IL-10R1 gene by multiplex allele-specific polymerase chain reaction.
Results: The investigation of allelic and genotypic frequencies of the S138G polymorphism showed no statistically significant differences between patients and controls. Indeed, we noted that the allele A was the most frequent in both BD patients and controls [69.5% (57/90) and 75.6% (68/82), respectively]. The genotype frequencies of AA, GG and AG for BD patients were 58.5% (24/45), 2.4% (1/45) and 39% (16/45), respectively. Whereas, for the control group, the frequencies of the two observed genotypes (AA and AG) where 49.9% (22/41) and 51.1% (23/41), respectively. Our study showed no association between the S138G polymorphism and the clinical features in our series. Similarly, no association was found between this polymorphism and disease activity or the expression of the HLA-B51 molecule.
Conclusion: our results suggest that the S138G loss-of-function polymorphism of the IL-10R1 seems to be not associated with the susceptibility to BD or its clinical features. Further single-nucleotide polymorphisms on the IL-10R1 gene should be investigated to explore the immune mechanism involving IL-10/IL-10R signaling and possible influence on BD susceptibility or pathogenesis.

P15. CLINICAL RELEVANCE OF OXIDANT STATUE DURING BEHÇET DISEASE: A STUDY ON ALGERIAN PATIENTS

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Background/Objective: Behçet disease (BD) is a multisystem, chronic and inflammatory disorder. Mouth sores, genital ulcers and cutaneous lesions hallmark this disease. It may present with ocular, vascular, digestive and neurologic manifestations. In this study, we investigated the "oxidant/antioxidant" balance in Algerian patients and its relation with the disease clinical expression.

Patients and methods: We measured plasma levels of Nitric oxide (NO), Malondialdehyde (MDA), Advanced oxidized proteins products (AOPP) and superoxide dismutase (SOD) in Behçet Disease patients (n=78: 28 Active BD patients (ABP) and 50 Inactive BD patients (IBP)) and healthy controls HC (41). Mann-Whitney *U* test and Spearman test were used for statistical analyses.

Results: NO and AOPP levels significantly increased in ABP ($p<0.001$) compared to IBP and HC and in IBP ($p<0.001$) versus HC. Patients with inactive vasculitis showed no statistically differences in NO level ($p>0.05$) when compared to HC. MDA levels significantly increased in ABP ($p<0.001$) and IBP ($p<0.01$) versus HC while ABP exhibited a slight increase in MDA level ($P>0.05$) compared to IBP. SOD levels significantly decrease in ABP ($p<0.05$) related to IBP and HC while IBP did not show any statistical differences in SOD levels when compared to HC ($p>0.05$). Correlation studies showed that AOPP significantly and positively correlated with NO ($r=0.425$, $p<0.001$) and with MDA ($r=0.221$, $p<0.01$) in Behçet disease patients. In addition, we revealed a significant negative correlation between NO and SOD ($r= -0.27$, $p<0.05$), AOPP and SOD ($r= -0.533$, $p<0.001$) and a negative yet non-significant correlation between MDA and SOD ($r= - 0.196$, $P=0.0935$) amongst Behçet disease patients.

Conclusion: Our study highlight an imbalance in oxidant/ antioxidant system in favor of oxidant disorder. This oxidative stress may be in relation with granulocytes and monocytes hyperactivation in Behçet disease. Exploring others therapeutic strategies in Behçets disease aiming to strengthening antioxidant machinery and scavenging oxidant markers may be helpful for patients' recovery and disease control.

P16. OXIDATIVE STRESS STATUS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction/objectives: Familial Mediterranean Fever (FMF, OMIM 249100), the most common inherited inflammatory disease mainly affecting populations of Mediterranean origin, is characterized by recurrent attacks of fever and polyserositis. It is caused by mutations in the *MEFV* (MEditerranean FeVer) gene primarily, expressed in cells of innate immunity such as polymorphonuclear neutrophils (PMN) and encodes the protein called pyrin, which is involved in the regulation of inflammasome activity and IL-1 synthesis. FMF is an autoinflammatory disease which results from a dysfunction of innate immunity, where the neutrophils play a central role. In fact, during FMF attacks, there is a massive influx of PMN into the serosal membranes generating an oxidative stress by an overproduction of reactive species of oxygen and nitrogen, causing tissue and molecular damages. In this study, we aimed to investigate the oxidative stress status in Algerian FMF patients and in a group of healthy subjects.

Patients and methods: This study included twenty-one FMF patients who carried at least one mutation in *MEFV* gene and twelve controls without *MEFV* mutations. Three parameters were measured from plasma samples: nitric oxide (NO), malondialdehyde (MDA) and glutathione (GSH). The concentrations of NO were determined by using a Griess regent. Plasma MDA levels were measured with the thiobarbituric acid test and GSH levels were assayed with Ellman reagent.

Results and conclusion: FMF patients had significantly higher NO concentrations (35.92± 4.97 mM) than controls (30.54±2.33 mM) (p=0.0006). The plasma MDA level was higher in FMF compared to controls (4.66±1.18 mmol/ml *vs* 2.87±0.62 nmol/ml, p= 0.00004). These patients had a high GSH level (4.33±1.89 µg/ml) than controls (1.41±0.32 µg/ml) (p=0.00004). In addition, correlations between the measured parameters were searched. In our FMF patients, MDA was negatively and significantly correlated with GSH (- 0.5160 ; p= 0.017). We were also able to show a significant positive correlation between NO and GSH. However, the correlation between NO and MDA was positive (r = +0.2203) but not significant (p = 0.33). Thus, our study demonstrated increased oxidative stress in patients with FMF as compared to controls. However, despite high GSH levels, it appears that the antioxidant potential of patients is insufficient to neutralize the free radicals generated in these patients.

P17. DECREASED CD36 EXPRESSION BY PPARA INTERFERENCE ENHANCES CD34 IN DIABETIC PATIENTS WITH CARDIOVASCULAR DISEASES

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Introduction/objectives: Endothelial progenitor cells (EPCs) in Peripheral Blood Mononuclear Cells (PBMC), that express CD34 *play* a crucial role in the *development* and progression of atherosclerosis and Type 2 *diabetes* mellitus (T2DM). However, its association with low levels of circulating CD34 expression in T2DM, the scavenger receptor CD36 and Peroxisome proliferator-activated receptor-alpha (PPARα) had not yet been investigated.
Material/methods: The purpose of this study was to determine the expression of of CD34, CD36 and PPARα expressions in peripheral blood mononuclear cells (PBMC) in diabetic patients with and without CVD. Using real-time polymerase chain reaction (PCR), mRNA expression of PPAR-γ was found in PBMC from 20 diabetic subjects with CVD, 20 diabetic's without CVD and 5 healthy controls. Serum levels of glucose and lipid profiles were measured.
Results: In the diabetic patients with CVD, CD34 mRNA level was markedly increased compared to diabetics without CVD (1,72 ± 0.9 versus 1,17± 0.66). However, a strong negative correlation was found between CD34 and CD36 (r = -0,84 ; P<0.0001). Otherwise, a negative relationship was enregistered between CD36 and PPARα expressions (r=-0,43 ; P= 0,05). In contrast, the decline of mRNA CD34 expression level appeared not to correlate with CD36 level in diabetic patients without CVD (r = -1,17; P = 0,46).
Conclusions: Taken together, our study showed a significant improvement of circulating CD34 in diabetic patients with CVD in which the regulation of CD36 mediated PPARα seems to have a differential role.

P18. INTERPLAY BETWEEN STAT1 AND STAT6 IN MODULATING PPARγ EXPRESSION ON MONOCYTES INFLAMMATORY PHENOTYPES IN DIABETES'S TYPE 2 WITH OR WITHOUT CARDIOVASCULAR DISEASES

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Introduction/objectives: The transcription factor of peroxisome proliferator-activated receptor γ (PPARγ) is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. PPARγ is expressed in Peripheral Blood Mononuclear Cells (PBMC), like lymphocytes, vascular smooth muscle cells, monocytes and macrophages, where it plays a pivotal role in the regulation of lipid, glucose metabolism and inflammatory processes in diabetes type 2 (T2D) and atherosclerosis. Expression of CD36, a receptor for oxidized low-density lipoprotein (oxLDL), is activated by the transcription factor of PPARγ. Further, we investigate that inflammatory phenotype of monocytes CD14+ depends of PPARγ expression via STAT (signal transducers and activators of transcription) 6 and 1 as critical mediator of cytokine signaling. Notably CVD may be triggered and progressed by inflammation events.
Material/methods: Real-time PCR determinations were performed to quantify gene expression levels in PBMC of PPARγ, CD36, CD14, STAT1 and STAT6 in diabetes patients with or without cardiovascular diseases.
Results: We show, that PBMC gene expression levels of PPARγ ($P = 0.002$) and STAT6 ($P<0.0001$) were strongly upregulated in T2D patients compared to diabetic's with cardiovascular diseases (CVD). Among diabetic's, increased PPARγ expression depresses STAT1 ($P=0.01$). Additional, we demonstrate here that CD36 expression is positively correlated with PPARγ in both groups of diabetic patients without or with cardiovascular diseases (CVD), respectively r= 0, 66; r=0, 75.
Conclusion: Taken together, our results suggest that PBMCs commit towards proinflammatory phenotype in the pathogenesis of T2D with CVD. Furthermore, PPARγ downregulates proinflammatory mediators in circulating monocytes CD14+ and PPARγ act broadly to direct in an anti-inflammatory and anti-atherogenic pathway, in T2D patients without CVD.

P19. EFFECT OF RISK ALLELES IN CFH, C3, AND VEGFA ON THE RESPONSE TO INTRAVITREAL BEVACIZUMAB IN TUNISIAN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Purpose: The aim of this pharmacogenetic study was to evaluate the impact of high-risk alleles in factor H, factor C3 and vascular endothelial growth factor (*VEGF*) on the response to intravitreal bevacizumab in patients with neovascular age-related macular degeneration (AMD) in a Tunisian population.
Methods: Ninety patients with active neovascular AMD treated with intravitreal bevacizumab injections were enrolled in the study. Treatment response was evaluated by comparing BCVA at baseline and at 12 months. Patients were classified into either “poor responders” (PR) or “good responders” (GR). Single nucleotide polymorphism (SNP) genotyping was performed for rs1061170 in *FH*, rs2230199 in *C3* and rs699947, rs2010963 and rs3025039 in *VEGF*. The association between genotype and visual response at 12 months was assessed.
Results: Seventy-seven participants were assigned to the GR group and 13 to the PR group. No correlation was found between *FH*, *C3* and *VEGF* variant alleles and treatment response. However, haplotype analysis of rs699947 ((−2578) C/A), rs2010963 ((+ 405) C/G) and rs3025039 ((+ 936) C/T) SNPs revealed that the AGT haplotype was associated with a poor response at 12 months ($p = 0.048$). No association was found between treatment response and the cumulative effect of all high-risk alleles of *C3*, *FH* and *VEGF*. All three types of CNV were found in both groups at a comparable frequency.
Conclusions: The *VEGF* haplotype TGA could be used as a marker for poor visual prognosis in Tunisian patients with neovascular AMD treated with bevacizumab.

P20. USING NGS TO IDENTIFY INHERITED CAUSES OF THE ASSOCIATION OF RARE PHENOTYPE: RETINITIS PIGMENTOSA (RP) AND AGE RELATED MACULAR DEGENERATION (AMD) IN A CONSANGUINEOUS TUNISIAN FAMILY

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Purpose: To localize and identify the gene and mutations causing a complex overlapping phenotype expressed in a Tunisian family with retinitis pigmentosa (RP).
Methods: We performed a clinical and molecular genetic study of a consanguineous Tunisian family with twelve affected individuals. DNA sample from the index patient was subject to next generation sequencing (NGS) analysis, a specific hereditary eye disease enrichment panel of 63 genes. Variants identified were validated by Sanger sequencing. Familial segregation was performed. The pathogenicity of these mutations was determined by in silico analysis.
Results: The index patient was 72 years old and reported night blindness and visual loss that appeared at the 30 years of life. Visual acuity was limited to hand motion. Fundus examination revealed in the right eye a large macular atrophic-pigment scar associated with bone spicule-shaped pigment deposits in the periphery along with atrophy of the retina and in the left eye showed a fibrovascular scarring of exudative AMD with a few peripheral bone spicule-shaped pigment. NGS analysis demonstrated that the index patient carried two mutations: the first one is a heterozygous mutation c.[4165G>A],[=], p.[V1389I],[=] in *SNRNP200,* Involved in spliceosome assembly, activation and disassembly, the mutation was associated with autosomic dominant RP (MAF=0.005); the second is a hemizygous variant c.[2323 A>G],[0], p.[I775V],[0] in *RPGR* (MAF=0.001), is a X-linked retinitis pigmentosa gene and plays an important role in photoreceptor integrity. The segregation analysis in the family was complicated because of the heterogeneity in the phenotype, affected uncle have a severe phenotype (blind) and carry only one c.[2323 A>G], [0] mutation in *RPGR* and the affected sister was heterozygous for the c.[4165G>A],[=] mutation in *SNRNP200*.
Conclusion: An individual carrying both *SNRNP200* and *RPGR* disease causing mutations could explain a complex, overlapping phenotype associated with both RP and AMD. Further whole exome sequencing might help identifying the molecular origin of this disease.

P21. INVOLVEMENT OF INFLAMMATION IN PTERYGIUM DISEASE OF ALGERIAN PATIENTS: ROLE OF NITRIC OXIDE AND IL-17A

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Pterygium is a human ocular surface disease related to chronic ultraviolet exposure. Clinically, pterygium involves invasive centripetal growth and neovascularization. This disease results in altered ocular tissue invasion into the cornea. It is frequent in North Africa, particularly in Algeria. Recent studies reported a strong relationship between the pterygium and inflammation responses. In view of this, we aim to investigate cytokines (IL-17A, IL-6, IL-10) and nitric oxide production in sera and tears of patients (n=43). Besides, we conducted histological analysis and probed CD3, CD68 and Bcl2, expression in pterygium biopsies of the same patients. Additionaly, we analyzed local NO synthase 2 and NF-κB expression using anti inducible NO synthase (Sigma) and anti NF-κB/p65 (Santa Cruz, Biotechnologies), respectively. Our results show concomitant increases of (IL-6, IL-17A) and NO levels in patients tears and sera. Interestingly, we noted that NO synthase2 expression and NF-κB are located in infiltrated inflammatory cells and positively correlates with CD3, CD68 and Bcl2 expression. Taken together, our study indicates the concomitant involvement of antiapoptotic and inflammatory process in pterygium pathogenesis through Th17 and NO synthase 2 pathways. The inhibition of local inflammation is likely to be a novel strategy to prevent pterygium progression and recurrence.

P22.TOPICAL CYCLOSPORINE A 2% EYEDROPS IN THE TREATMENT OF VERNAL KERATOCONJUNCTIVITIS

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Introduction : Vernal keratoconjunctivitis (VKC) is a chronic, bilateral inflammation of the conjunctiva that mostly affects children and young adult males. Management of VKC is primarily aimed at reducing symptoms and preventing serious vision threatening sequelae.
The purpose of our study was to assess the efficacy of topical cyclosporine A (CsA) 2% on the signs and symtomps in the management of VKC.
Methods : Prospective study about three patients (6 eyes) who received 2% CsA. Topical steroids were initially associated with progressive degression. Efficacy, local and systemic tolerability were evaluated at 1 month and then every 3 months.
Resultat : Two women and one man whose average age is13 years. Ocular inflammation was controlled without steroids in 2 cases (66,7%) after 1 month, and in all patient at 3 months. One patient presented with a recurrence of inflammatory signs. This patient had active extraocular atopic diseases. Local and systemic tolerability was excellent.
Conclusion : Topical CsA 2% eye drops were safe and effective in the treatment of patients with VKC.

P23. EFFICIENCY OF INTERFERON ALPHA-2-B SUBCUTANEOUS PARASPINAL INJECTION IN REDUCING OF HERNIATED DISC TISSUE

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Purpose: The goal of this study was to evaluate the MRI-controlled efficacy of interferon alpha-2-b subcutaneous paraspinal injection on a size of regression of herniated disc tissue (HD) in patients with failure of conservative treatment.

Methods and Materials: A total of 22 patients were involved in this study. The MRI confirmed average size of HD was 10.6 mm (+-0.8). All patients have a previously failure of conservative treatments and have indication for surgery measures to remove the herniated tissue. The duration of study was 60 days. Patients receive interferon alpha-2-b subcutaneous paraspinal injection in herniated disc level area, every other day, during 30 days. In total 15 injections. The dosage of interferon was 3 million international units. All patients received anticonvulsants for pain relief on different dosages. VAS score was used to evaluate intensity of pain. MRI scans was made every 10 days during study for each patient. After 60 days, we evaluate the average size of herniated disc regression in all patients by compare MRI scans.

Results: In 4 patients, no significant changes were observed on MRI. In other 18 patients, we evaluate the significant herniated disc regression. The average size of regression was 5.7 mm (+-0.6). Also, we observed the changes of MRI signals in group that can be a precursor of further changes.

Conclusion: Interferon alpha-2-b has exerted effects through the induction of numerous IFN-stimulated genes and an immunomodulatory effect on innate and adaptive immune responses and possibly can accelerate the act of regression of HD that can be in some cases an alternative to surgery measures. This results call for further research focused on immunobiology of this process by means with MRI diagnostic.

P24. A PIVOTAL ROLE FOR MMP9 IN NEURONAL LOSS: POST-MORTEM VASCULAR DEMENTIA STUDY

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Vascular dementia (VD) is the second largest cause of dementia, characterized by a series of cellular and molecular events leading to neuronal malfunction prior to neuronal loss and alteration of neuronal network. This post-mortem study aims to show the implication of MMP9 in human brains during VD as well as the underlying molecular mechanisms. In addition, it highlights some compensatory mechanisms deployed by the brain to minimize the consequences of neuronal loss.

P25. INVOLVEMENT OF PROTEASOME SYSTEM IN TISSUE INFLAMMATORY DISORDERS INDUCED BY SCORPION VENOM

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The inflammatory response is a key process in the genesis of the pathological events during scorpion envenomation. The activation and the release of proinflammatory mediators constitute a crucial event in the pathophysiology of scorpion envenomation. Protein degradation by proteasome system plays an important role in the modulation of the immune inflammatory processes. The involvement of this system in the induced cardiopulmonary inflammation response by scorpion venom has not been investigated.

The present study aimed therefore, to evaluate the potential involvement of proteasome system in this process. Indeed, high or low dose of proteasome inhibitor (bortezomib) was given 30 minutes before the envenomation of mice.

The inflammatory response was evaluated by assessing vascular permeability changes and inflammatory cell recruitment including polymorphonuclear and eosinophil cells into the cardiac and the pulmonary tissues. On the other hand, tissue disorders were evaluated by the measurement of oxidative/nitrosative stress markers such as nitric oxide, malondialdehyde and reduced glutathione but also by histopathological analysis.

The results showed that scorpion venom induced significant alterations of the cardiopulmonary tissues marked by an increase of vascular permeability and inflammatory cell recruitment, as well as, an increased nitric oxide levels and cardiopulmonary membranes lipid peroxidation concomitant with reduced antioxidant defense. Pretreatment with high-dose of bortezomib seemed to be more efficient in the prevention of the inflammatory disorders than the low dose. Significant reduction of the vascular permeability, the inflammatory cell infiltration and a marked prevention of oxidative/ nitrosative stress markers were observed.

Obtained results suggest the involvement of the proteasome system in the induced cardiopulmonary inflammatory response by scorpion venom probably by antigen presentation and NF-kB activation, which in turn, up-regulates the expression of the associated inflammatory genes.

P26. CARDIAC TISSUE INFLAMMATORY RESPONSE INDUCED BY SCORPION VENOM: ROLE OF ANGIOTENSIN II

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Activation of the immune system and the development of a severe inflammatory response play a major role in the pathogenesis of envenomation. However, the mechanisms behind the recognition of scorpion venom and the induction of mediators release still not well established. Thus, it has been reported that the immune response observed after scorpion stings include the activation of the toll like receptors (TLR2 and TLR-4) by the « VAMPs » (venom-associated molecular patterns). The release of various mediators (cytokines, eicosanoids, reactive oxygen species, and nitric oxide (NO)) and the activation of different systems such as the kinin–kallikrein and the complement systems but also the renin-angiotensin system (RAS), have also been reported. The RAS through its main effector peptide, Ang II, is involved in the development of cardiovascular diseases, heart failure and myocardial alterations.

The aim of this study is to evaluate the involvement of Ang II through its AT1 receptor in the immuno-inflammatory response developed in a model of cardiac dysfunction induced by *Androctonus australis hector (Aah)* scorpion venom, using an AT1R antagonist, Valsartan.

The inflammatory response was assessed by the measurement of the serum level of the proinflammatory cytokines (TNF-α and IL-6), the evaluation of the cardiac tissue polymorphonuclear cells infiltration and gelatinase (MMP-2 and MMP-9) activation. The cardiac tissue was also evaluated for oxidative/nitrosative stress markers (Nitrites, and H_2O_2, catalase and GSH) and for anatomopathology analysis.

Results revealed that scorpion venom induced an inflammatory response characterized by a marked elevation of the proinflammatory cytokines and an important MMPs expression, followed by the infiltration of the immune cells into the heart. This was accompanied by ROS generation concomitant with the alteration of the antioxidant system and severe myocardial alterations.

The inhibition of the AT1 receptor before envenomation resulted in the reduction of cytokine levels and the inflammatory cell infiltration. The prevention of the imbalanced redox status was also recorded. Furthermore, the histopathological analysis revealed the prevention of the myocardial alterations.

Obtained results reflect the involvement of Ang II throught the AT1R in the immuno-inflammatory response induced by *Aah* venom in the heart. However, further studies will be required to demonstrate the interactions between Ang II and the different components of the immune system in the envenomed models.

P27. IMMUNOMODULATORY EVALUATION OF GLIRICIDIA SEPIUM AQUEOUS LEAF EXTRACT IN WISTAR RATS

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Objective: *Gliricidia sepium* aqueous leaf extract is being used in the management of patients with sickle cell disease without considering its adverse effect on the users, hence this study aimed at investigating possible toxic effect the extract on some immunohematological parameters and lymphoid organs histology in Wistar rats exposed to the extract.

Methods: Acute oral and sub-chronic toxicity studies were carried out according to Organization for Economic Cooperation and Development Guidelines 420 and 407 respectively. At the end of each experiment, the rats were sacrificed and blood samples collected for immunohaematological parameters and lymphoid organs for histological examination.

Results: In the acute oral toxicity test, no death or sign of toxicity was observed in the rats after 24 hours and up to 14 days post-oral treatment. There was no significant difference ($p>0.05$) in the parameters between the test and the control groups. In sub-chronic toxicity study, there was no significant difference ($p>0.05$) between the test and control groups for all the parameters measured. Histology of thymus, spleen, and lymph node shows normal morphology as compared with the control.

Conclusion: In conclusion, the present findings have shown that aqueous leaf extract of *Gliricdia sepium* is relatively safe and is not likely to induce immunotoxic effect.

P28. EVALUATION OF THE MODULATOR EFFECT OF THE ETHANOLIC EXTRACT OF *Cola nitida* (STERCULIACEAE) ON HLA CELLS (HUMAN LEUKOCYTE ANTIGEN).

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Introduction: Sub-Saharan Africa stays the hardest hit region in the world, accounting for more than two-thirds (67%) of all people living with HIV. HIV prevalence among adults is less than 1% in three countries in West Africa (Cape Verde, Niger and Senegal), close to one out of 25 adults (3.9%) in Côte d'Ivoire lives with HIV (UNAIDS, 2008). The CD4 / CD8 cells receive the signal from the antigen presenting cells and the major histocompatibility complex MHC (Madden, 1995 ; Rammensee *and al*., 1993). These molecules play an important role in inducing an immune response. In contrast, MHC is involved in immune tolerance (Carosella *and al*., 1999). The genes of the HLA system control the synthesis of proteins, leukocyte antigens, which are found in lymphocytes, cells of the family of white blood cells. Our recent studies of ethanol extracts of cola nuts have increased the number of lymphocytes and neutrophils.
The general objective of this research is to evaluate the modulating effect of the ethanolic extract of *Cola nitida* (Sterculiaceae) on HLA (Human Leukocyte Antigen) cells.
Methodology : The ethanolic extracts obtained after several stages of preparations were used to study:

- Identify the different molecules present in this extract
- Isolate the molecule (s) responsible for its modulating effect

Expected Results : different molecules present in this extract will be available in the case of their using in short and medium term research
Conclusion : Cola nitida nut (Sterculiaceae) could be used as an Improved Traditional Medicine (MT A) for therapeutic and preventive purposes

P29. EFFECTIVE ACTIVITY ON IMMUNITY AND NEPHROPROTECTIVE ACTION OF AQUEOUS AND ETHANOLIC EXTRACTS OF Cola nitida (STERCULIACEAE).

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Introduction: Côte d'Ivoire is one of the countries producing nuts from Cola nitida (Sterculiaceae). The knowledge of some of its biological effects used in traditional medicine (against dysentery, bleeding, increases energy, strength and dissipates drowsiness) deserve to study to contribute to the valorization of our natural resources.
Objective: To evaluate the effector effect on the immunity and the nephroprotective action of the aqueous and ethanolic extracts of Cola nitida (Sterculiaceae).
Methodology: Cola nitida nuts (Sterculiaceae) harvested were cut and dried out of the sun and then powdered. The aqueous and ethanolic extracts obtained after several preparatory steps were used to study:
-The anti-inflammatory activity by the determination of the CRP and by the measurement of the edema of the rat paw induced by the carrageenan
-the evolution of the profile of the hemogram of the rabbits
-the protector effect of cola nitida nuts extracts on gentamicin-induced nephrotoxicity in rats.
Results: The anti-inflammatory activity is significant at 200 mg / kg of PC for the ethanol extract. The aqueous extract of Cola nitida is less effective than the ethanol extract. Similarly, the hemogram showed that the ethanolic extract of *Cola nitida* could improve hematopoiesis and stimulate the immune reaction. Also the ethanolic extract of Cola nitida attenuated the nephrotoxic effects induced by gentamicin.
Conclusion: *Cola nitida* nut (Sterculiaceae) could be used as an Improved Traditional Medicine (MTA) for therapeutic and preventive purposes, particularly in pathologies of inflammatory origin

P30. GASTRO-PROTECTIVE, THERAPEUTIC AND ANTI-INFLAMMATORY ACTIVITIES OF *PISTACIA LENTISCUS L.* FATTY OIL AGAINST ETHANOL-INDUCEDGASTRIC ULCER IN RATS

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In the present study, we investigated the anti-ulcerogenic activity of *Pistacia lentiscus* fatty oil (PLFO) on ethanol-induced gastric ulcers in rats. For this purpose, PLFO was orally administered to two experimental groups of rats before or after ethanol induction of gastric ulcer. The lesions of the gastric mucosa were evaluated by macroscopic and histopathological examination. In addition, the levels of nitric oxide (NO) and pro-inflammatory cytokines (interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)) were assessed in plasma and the supernatant of explants cultures of gastric mucosa. Finally, the mucus production and iNOS (inducible NO synthase) expression were determined by histochemical and immunohistochemical analysis respectively. Our results indicated that the PLFO pretreatment and treatment significantly reduced the gastric ulcerated and hemorrhagic areas. Interestingly, pretreatment and treatment with the PLFO highly reduced the plasmatic concentration of NO. Moreover, a significant decrease of NO, IL-6 and TNF-α levels was observed in explants culture supernatants. Interestingly, iNOS expression was also reduced in gastric mucosa. In contrast, mucus production by gastric cells was enhanced. Our results suggest that PLFO exhibited significant gastroprotective and therapeutic effects against gastric ulceration. Importantly, the mechanism underlying PLFO effects might involve inhibition of inflammatory responses during gastric ulcer.

Adaptative Immunity

P31. SOME IMMUNOLOGICAL AND NUTRITIONAL PROFILES OF ALMAJIRI (LESS PRIVILEGED CHILDREN) IN SOKOTO, NIGERIA.

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Introduction: The less privileged children popularly called Almajirisin Northern part of Nigeria are the street children without source of daily square meal and place of dwelling, they depend on alms for their survival. This study aimed at determining some immunological and nutritional profiles of Almajiris in Sokoto, Nigeria.
Method: Seven millilitres of blood samples were collected through clean venepuncture from 200 malealmajirisbelow the age of 18 years and 100 apparently healthy children of elites of the same age and gender who served as control, 4 ml into ethylene diamine tetra acetic acid (EDTA) specimen bottle for determination of haemoglobin (Hb), haematocrit (PCV), total and differential leucocytes count (WBC)andCD^4cells by flow cytometer. The remaining 3 ml of blood was dispensed into sterile plain specimen bottle, the blood was allowed to clot and the serum used for estimation of total proteinby Biuret, albumin byBromocresol Green and total cholesterol by enzymatic methods using Agape reagent kits.Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).
Result: The Hb, total WBC, CD^4, albumin and BMI values in Almajiris were significantly lower ($p<0.05$) than in elites' children (control group).
Conclusion: Our findings revealed that Almajiris' immunological and nutritional status are low and they may be susceptible to nutrition related diseases and infections due to poor diet and general living conditions.

P32 ACTIVATED MATURE B CELLS ARE ENRICHED IN THE LUNG OF HEALTHY MALAWIAN ADULTS

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Background: B cells play an important role in defence against pathogens. A lot of studies have defined the phenotype and proportions of the different B cell subsets in peripheral blood. However, there is not much that is known about the phenotype and proportions of B cell subsets in the lung. As such, we aimed to identify the phenotype and proportions of B cell subsets in the lung of healthy adults and how they compare to those in the systemic compartment.

Methods: We recruited 17 study participants from Queen Elizabeth Central Hospital VCT clinic in Blantyre, Malawi. All participants were healthy, asymptomatic adults (≥18 years old) who were HIV-1-uninfected with no clinical evidence of active disease. The participants underwent a bronchoscopy through which bronchoalveolar lavage (BAL) fluid was obtained. Peripheral blood was also obtained from the participants. BAL cells and peripheral blood mononuclear cells (PBMCs) were isolated from the BAL fluid and peripheral blood, respectively. Flow cytometry-based immunophenotyping was performed on the BAL cells and PBMCs to identify B cell subset.

Results: We found that activated mature B cells (36%) and resting memory B cells (39%) were the predominant subsets in BAL fluid, while naïve mature B cells (31%) and resting memory B cells (38%) were the predominant subsets in peripheral blood. The proportion of activated mature B cells was higher in BAL cells than in PBMCs (36% vs. 16%; $p<0.0001$). The proportions of naïve mature B cells (6% vs. 31%; $p<0.0001$), plasmablasts (0.7% vs 2%; $p=0.0069$) and immature transitional B cells (0.1% vs. 1%; $p=0.0312$) were lower in BAL cells compared to PBMCs. The proportions of resting memory B cells (39% vs. 38%; $p=0.5861$) and tissue-like B cells (6% vs. 5%; $p=0.6033$) were similar between BAL cells and PBMCs.

Conclusion: Our findings show B cell subsets are distributed differentially between the lung and peripheral blood compartments, with activated mature B cells being enriched in the alveolar space, a portal of entry for antigens. The higher proportion of activated mature B cells in the lung likely reflects the high exposure to multiple antigens in the respiratory tract.

P33. INVOLVEMENT OF T REGULATORY LYMPHOCYTES IN THE UNEXPLAINED INFERTILITY AND THE PROGNOSIS OF MEDICALLY ASSISTED PROCREATION

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Regulatory T cells (Treg) are among the most important cells involved in the establishment of immune tolerance against self antigens and antigens encountered in foreign grafts. They are required for the maternal immune system to tolerate the fetal allograft. In addition, there is evidence that a defect in Treg number or function may be involved in failures of pregnancy and pregnancy-associated diseases. However, the direct effect of such lymphocyte population on the outcome of the IVF remains a thorny subject in reproductive biology. Also, few data regarding the implication of these cells in the idiopathic infertility are available.

The aim of our present study was first to determine whether there was an association between the peripheral CD4+CD25+Foxp3+ Treg cells and the implantation success of patients undergoing in vitro fertilization (IVF). For this, a group of patients without any female pathology and undergoing in vitro fertilization (IVF) was selected and subdivided into 2 subgroups based on their pregnancy outcome. Our data showed that the initial rate of Treg does not influence the outcome of IVF in women free of any pathology. In addition, no significant correlation was found between Treg rate and the different parameters of IVF. A study including a larger cohort is needed to provide more conclusive results. Moreover, analyzing the increase of the peripheral rate of Treg cells 15 days after injection and/or in situ analysis of Treg cells would be more relevant.

In the second part of the study, we tried to objective a link between a quantitative decrease of Treg cells and the idiopathic infertility. Thus, the rate of Treg cells was compared between a group of women with idiopathic infertility and a healthy and fertile female group who had at least one normal pregnancy. Our data demonstrated a decrease in the rate of Treg cells in females with idiopathic infertility compared to control group, yet the difference was not significant. Our data suggested that the reduction of regulatory T cells may contribute to unexplained infertility. However, such data should be confirmed in a larger prospective study. The continuous increase in knowledge of Treg biology and function will further enlighten their role in pregnancy and may contribute to identify new therapeutic approaches in infertility.

P34. SPECIFIC IMMUNE RESPONSES IN MICE FOLLOWING SUBCHRONIC EXPOSURE TO ACETAMIPRID

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Aims: Acetamiprid (ACE) is an insecticide of the neonicotinoid family, the most widely used in the world. Herein, we assessed the effect of ACE on either the humoral or cellular immune responses of rodents. We also evaluated the role of curcumin in the restoration of altered immune responses after ACE treatment.

Main methods: Five groups of five Swiss Albino mice were immunized intraperitoneally with a recombinant protein, rCFP32. One group received ACE (5mg/kg) during 61 days, a second one received ACE associated with curcumin (100mg/kg). Three control groups were included; one untreated, the second received corn oil and the third received curcumin alone. The humoral immune response was assessed by ELISA testing the anti-rCFP32 antibody concentrations in the serum. The cellular immune response was assessed by analyzing the cellular proliferation of the splenocytes stimulated *in vitro* by a mitogen or rCFP32.

Key findings: The ACE-treated mice showed a significant immunosuppression of the specific humoral response with a restorative effect of curcumin when administered with ACE. Similarly, ACE significantly decreased the level of splenocyte proliferation after either a non specific or a specific activation. Curcumin partially restores the antigen specific cellular immune response but not that induced after mitogen activation. Moreover, when administered alone, curcumin significantly inhibits the proliferative responses to the mitogen confirming its anti-mitogenic effect commonly reported in the literature. Histological analysis showed alteration of spleens of mice exposed to ACE.

Significance: Altogether, our data indicated that sub-chronic exposure to ACE could potentially be detrimental to the immune system

Infection and immunity

P35. IMMUNE ABNORMALITIES IN HIV-EXPOSED UNINFECTED INFANTS: PILOTS STUDIES

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It is now well established that HIV-negative infants born to mothers with HIV are more susceptible to certain bacterial infections. Although Neutrophils are essential key in infants protection to bacterial infections, to date no study has investigated their profile in HIV exposed uninfected infants (HEU). Here we assessed : (1) the phagocytic ability of HEU infants' neutrophils using the nitroblue tetrazolium (NBT) reduction test, (2) HEU infants' baseline cytokines secretion by ELISA and (3) their complete blood count. Our investigations showed that about one-third (36%) of HEU infants have impaired phagocytic ability of neutrophils. The second one-third (36%) of HEU infants had high numbers of pre-activated neutrophils (producing ROS) and the rest (28) of HEU normal functioning neutrophils. The complete blood count done on HEU and HU infants showed that 80% of HEU infants against 25% in HU infants (cut-off set at 400000 cells/mm3), had "mild" thrombocytosis. Furthermore, HEU infants had significantly higher platelets count than HU-infants ($p \leq 0,01$). Also, the mean platelet volume (MPV) that gives an indication on bone marrow platelet production was significantly lower in HEU infants than in HU infants ($p<0,05$).

P36. THE IMPACT OF MDSC ON VACCINE IMMUNOGENICITY IN SOUTH AFRICAN HIV-INFECTED AND UNINFECTED MOTHERS AND THEIR INFANTS

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Background/Objective: Each year over 4 million infants die and suffer from vaccine-preventable infections, and the basis of reduced immunity is controversial. We hypothesized that myeloid-derived suppressor cells (MDSC) that might be induced during gestation, persist at birth leading to active suppression of infant-immune responses. We evaluated the ontogeny of MDSC and its effect on vaccine immunogenicity during early life.
Material/Methods: HIV-infected and uninfected mothers and their infants were recruited from Khayelitsha, Cape Town and followed-up for 1 year. In whole PBMC and after MDSC ($CD15^+$) depleted, we measured BCG, Hepatitis B, Tetanus toxoid and *Bordetella pertussis* vaccine-specific $CD4^+$ T cell proliferation by CFSE and IFN-γ responses using ELISpot assay.
Results: MDSC frequency was significantly higher in infants at birth, and decreased over time through 1 year of age. Neither HIV infection in mothers nor infant exposure had a significant effect on MDSC frequency. In infants and mothers, MDSC depletion had variable effects on $CD4^+$ T cell proliferation and IFN-γ production to deferent antigens, and MDSC depletion significantly increased responses to Tetanus, but not to BCG.
Conclusion: High frequencies of MDSC are present at birth, but decrease with age in infants. Therefore, MDSC effects on vaccine responses may be short-lived, and dependent on the type of antigen.

P37. TRENDS IN CD4+ T-CELL COUNT AND VIRAL LOAD AT DIAGNOSIS OF HIV INFECTION IN CENTRAL TUNISIA: ABOUT 76 CASES

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Introduction: Since the first case of HIV infection, declared in Tunisian 1987, the estimated number of people living with HIV (PLHIV) in 2015 is 2600. The prevalence of HIV infection in Tunisia is 0.013%, which classifies it as a low-level epidemic area. Yet, screening campaigns are few and early diagnosis remains a goal. HIV viral load is a good disease progression marker. The CD4 T-lymphocytes count is considered as the yardstick of the evolution of HIV infection. Evaluating this count at discovery of the infection reflects its evolutionary stage and thus can be a marker of the efficiency of the HIV/AIDS program in assuring early diagnosis.

Material and methods: Patients were included in this study on the base of laboratory analysis requests for HIV viral load, received on the laboratory of microbiology of Sahloul's university hospital in Sousse, from January 2015 to May 2017. All HIV viral load requests were screened. Only treatment-naive newly diagnosed patients were enrolled. Viral RNA extraction and viral load quantification were performed on Cobas®AmpliPrep and Cobas®TaqMan®instruments, Roche®, using HIV-1 Test, v2.0. Real-time reverse transcription PCR was used as the quantification method. The CD4 T-lymphocyte count was determined by Fluorescence Activated Cell Sorting (FACS) technique. Statistical analysis was performed using SPSS v21.0.

Results: This study included 76 patients, 48 males (63.2%) and 28 females (36.8%). The mean age is 31 years (5 months-82 years). The median CD4+ T-cell count at diagnosis among the population of study is 412/mm^3. When we examined this parameter by gender, we found a median of 444/mm^3 in males and of 329 /mm^3in females. It's hence lower in women. The median HIV viral load at diagnosis is 74 200 copies/ml. The statistical correlation between HIV viral load and CD4+ T-cell count is, as expected, significant.

Conclusion: PLHIV in central Tunisia are mostly diagnosed with CD4+ T-cell count under 500/mm^3. This work has implications for the analysis of the HIV program efficiency at both the local and national level. Evolution of markers such as viral load and CD4+ T-cell count at diagnosis is the most accurate reflection on how early this infection is diagnosed. Screening of HIV infection in apparently healthy people seems to be the next measure to prioritize.

P38. LEVELS OF CD4+ T-CELLS, NEOPTERIN, DNA-8-HYDROXYGUANOSINE AND TOTAL DOPAMINE IN HIV1-INFECTED NIGERIANS

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Background: There is a dearth of information on the association between macrophage activation, DNA damage, total dopamine status and HIV1-infection. In this study, levels of CD4+ T-cells, neopterin, DNA-8-hydroxyguanosine (8-OHdG) and total dopamine were determined in HIV-1 infected patients.
Materials and Methods: A total number of sixty HIV-1 infected patients participated in this study. Another 50 apparently healthy age and sex-matched individuals negative to HIV antibodies served as controls. Levels of CD4+ T-cells, neopterin, DNA-8-hydroxylguanosine and total dopamine (TD) were determined in all participants using flow cytometry and enzyme linked immunosorbent assay (ELISA) methods respectively.
Results: The results showed that 8-OHdG, TD and neopterin increased significantly ($p<0.05$) in HIV-1 infected patients when compared with the controls. CD4+ T-cells count was significantly lower in HIV-1 infected patients when compared with the controls. Plasma TD level correlated significantly ($r=-0.49$, $p<0.05$) with CD4+ T-cell counts in the patients. Neopterin and 8-OHdG showed no significant ($r=-0.14$, $p>0.05$; $r=-0.25$, $p>0.05$ respectively) correlations with CD4 T-cell counts in HIV-1 infected patients.
Conclusion: It could be concluded that HIV-1 infection has potential to induce oxidative DNA damage, macrophage activation and induce dopamine synthesis. Total dopamine increases with severity of HIV-infection (decrease in CD4+ T-cell count).

P39. IMMUNE REGULATION OF LANGERHANS CELLS IN HUMAN FORESKIN

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Background and rationale : Cells expressing CCR5 and CD4 receptor are primary targets of HIV infection. The foreskin mucosa comprises of largely HIV targeted cells, mostly Langerhans and CD4+ cells. However, the transcriptional and modulatory mechanism of LCs responsible for HIV infection and transmission are poorly understood. Thus, this study aims to evaluate the mechanisms of transcriptional control during immune activation and tolerance of human LCs.Furthermore, characterise LCs based on their ability to modulate HIV transmission.
Methodology : Foreskins of HIV negative men aged >18 will be collected at different local male circumcision clinics in the Western Cape, South Africa. Langerhans cells will be isolated using the crawl and liberate assay and evaluated for gene and protein expression. For gene expression, RNA from TNF-a stimulated LCs will be evaluated using RNA-seq. For protein expression, mass spectrometry will be used to characterise the proteins. Furthermore, flow cytometry will be used to identify the phenotypeof LCs during immune activation and tolerance.
Conclusion : Results from this study will give a detailed mechanism on how the transcription of Langerhans cells is controlled to shape strategies for HIV prevention as proteomes, genomic and transcriptomics provide a wealth of biological information.

P40. PARADOXICAL IMMUNOVIROLOGICAL RESPONSE IN PEOPLE LIVING WITH HIV STILL ANTIRETROVIRAL TREATMENT IN BURKINA FASO

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Introduction/objectives: Immunological surveillancein people living with H.I.V. knows its limits, because at the moment when immunological failure is observed, virological escapement has been evolving at low noise for several months or even years. The objective was to study the predictive factors of the paradoxical immunovirologic response in HIV-infected persons with less than 100 CD4 at 12 months of ambulatory follow-up on ART at the Bobo Dioulasso Day Hospital with good virological control.
Material/methods: It was a retrospective cohort study with an analytical focus over a period of 5 years from January 2008 to December 2012.Were included patients infected with HIV-1, aged at least 18 years, on antiretroviral therapy for 12 months,who received an undetectable HIV-1 plasma viral load in the 12th month of ARV treatment or virological success and who had a CD4 T cell count less than M0 and M12.
Results: 512 patients were included. 21 patients had less than 100 CD4 T cells with good virological control. The median age was 45 years (IQR 32.2 to 45.1); females represented 66.7% with a sex ratio of 0.5. The clinical manifestations were the reason for discovery of HIV status in 61.9% of patients. WHO clinical stages 3 and 4 accounted for 66.6%. At the initiation of therapy, the median CD4 T cells was 42 cells / l (IQR: 12-63) and 57.2% of patients had less than 50 cells/L. Patients received 2INTI + 1INNTI represented 85.7% against 14.3 % for 2INTI + 1IP. Combination therapy containing AZT were the most prescribed (61.9%)
Under ART treatment, 76.2% of patients had a high level adherence to treatment in the 12 months follow-up. Number median CD4 T cell increased from 42 to 76 cells/µL, a gain cell 34. In our study, 4.1% of patients were in response immunovirological paradoxical. Advanced age: ≥ 45 years (p = 0.0009), late clinical stage: WHO 3 and 4 (p = 0.0049) and profound decrease in CD4 T cells at the initiation of ART treatment : CD4 < 50 cells / µL (p = 0.00045) were predictive immunovirological of the paradoxical response.
Conclusion: Identification of paradoxical immunovirological response in people living with H.I.V.makes it possible to prevent a future therapeutic failure

P41. PROFILES OF PERIPHERAL CD4+T CELLS COUNT DURING ANTIRETROVIRALTREATMENT IN SENEGALESE ADULTS INFECTED BY HUMAN IMMUNODEFICIENCY VIRUS

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Introduction: Infection with Human Immunodeficiency Virus (HIV) remains a major public health problem despite advances in diagnosis and antiretroviral treatment. We aim to assess the immune reconstitution in Senegalese adults living with HIV.

Material and methods: At this end, we conducted across-sectional study on 82 HIV-positive subjects under highly active antiretroviral therapy (HAART) to evaluate the peripheral TCD4 profiles during treatment as well as sociodemographiccharacteristics.CD4 T lymphocytes count was performed by flow cytometry.

Results: Women were the most representative gender group (67%).The median age was 42 years at the inclusion and HIV-1 was predominant serotype (90%).

At the beginning of HAART, median CD4 count were 250 cells/µl; 44% of patients living with HIV (PLHIV) had presented the stages III and IÑ as defined by WHO. During the follow-up of 20 PLHIV1, we found a significant increase of CD4 counts with Combivir + Efavirenz (363 to 444 cells/µl; p = 0.023) and the combination Combivir + Nevirapine (n = 11) (266to 355 cells/µl (p = 0.021) and Tenolam + Efavirenz (n = 38) (258 and 465 cells/µl; p <0.001). However, no significant difference in CD4 count was observed for PLHIV-1 under Tenolam + Nevirapine (250 to 358 cells/µl; p = 0.108).For the Combivir + Kaletra second line treatment, median of CD4 count was 80% fold inPLHIV-2 and PLHIV-1+2 after 12months of treatment. We also found a positive change in the median CD4 count except forPLHIV-1+2 under Kaletra + Tenolam. We did not find association between the CD4 count and the duration of treatment (rho = 0.201 and p = 0.359). Poor adherence to treatment was observed in 13% of cases.

Conclusion: Our data have shown that CD4T cells counts is an important taspect of monitoring of HAART, suggesting that overall, the HIV-1 treatment lines used innational guideline improve live of patients through enhancement of immune reconstitution.

P42. SEOPREVALENCE AND RISK FACTORS OF HUMAN IMMUNE DEFICIENCY VIRUS (HIV) AND HEPATITIS C VIRUS INFECTIONS AMONG PREGNANT WOMEN ATTENDING ANTENATAL CARE CLINIC IN WESTERN ETHIOPIA

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Introduction: Human Immune Deficiency Virus and Hepatitis C virus (HCV) infections are global public health challenge. Both HIV and HCV share common modes of transmission and also have serious effects both on pregnant women and infants. However, there is limited information on sero-prevalence of HIV and HCV infection among pregnant women in West part of Ethiopia. Hence, this study was conducted to assess sero-prevalence and predictor factors of HIV and HCV infection among pregnant women attending antenatal care in West Ethiopia.
Methods: Institutional based cross-sectional study was conducted from July to September, 2014 among 421 pregnant women's attending antenatal care services in purposively selected health facilities, East Wollega Zone, Ethiopia. The HCV and HIV sero-markers were tested from aseptically collected serum samples. Hepatitis C virus was detected using an enzyme linked immunosorbent assay (ELISA). HIV infection was also detected using the national HIV test algorithms. The A pretested-structured questionnaire were used to collect socio-demographic data, and predictor factors of HIV and HCV infection. The collected data were analysis using SPSS version 20.
Results: The overall seroprevalence for HCV and HIV among the study population was about 8.1% (34/412 ; 95% CI : 5.7-10.7) and 1.0% (4/421; 95%CI: 0.2-2.0), respectively. The HCV-HIV co-infected prevalence was 0.23% (1/421). Among HIV infected women, the prevalence of HCV infection was 25%. The risk of HCV infection was significant low for urban residents (AOR=0.38, 95% CI : 0.16-0.90) compared to their rural counterparts. Significantly low risk of HCV infection was also observed among illiterate (AOR= 0.24, 95% CI: 0.06-0.85) population comparing to those attending higher level of education. For HIV infection, the history of blood transfusion was significant increase the risk (AOR = 19.52, 95%CI: 1.80-150.6).
Conclusion: The study showed that HCV and HIV infections are important public health problem in the study area. All pregnant women need to be screened for both HCV and HIV infection during antenatal care. Thus, HCV testing and diagnosis need to be included in the antennal care services, and awareness creation is need on the prevention and mode of transmissions HCV and HIV in general.

P43. IMMUNOLOGICAL PROFILE IN HIV AND TB COINFECTED PATIENTS, IN MOZAMBIQUE

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Introduction and Objectives: The HIV and TB coinfection is a problem of public health, and one of the challenges is to understand how the HIV affect the immune response to Tuberculosis. One of the pathways involved is the cellular recruitment, mediated by adhesion molecules and cytokines. This study had as main objective, to understand the role of the VLA-4 and LFA-1 integrins, CCL2 and CCL3 chemokines, and IFN-gamma in the HIV and TB coinfection.
Material and methods: We recruited at Hospital Geral de PolanaCaniço, nine patients coinfected HIV/TB and nine patients monoinfected TB, and in the Blood Bank of Hospital Central de Maputo, 17 health controls. All samples were tested at the Cellular Immunology Laboratory from INS, where was performed the separation of PBMC by Ficoll-Hypaque density method, CCL2 and CCL3 levels by ELISA commercial kit, IFN-gammaELISPOT and surface staining by flow cytometry. The comparisons were done using GraphPad Prism software, version 5.
Results: We found, as results, that the proportion of T CD8 cells that expressed LFA-1^{hi} and VLA-4^{hi} was higherin patients coinfected with HIV/TB when compared to patients monoinfected with TB and controls. The coinfected HIV/TB patients had lower ESAT-6 and CFP-10 response than TB monoinfected, and the plasmatic levels of CCL2 and CCL3 were similar between the coinfected HIV/TB, TB monoinfected and controls.
Conclusion: The coinfected HIV/TB patients respond less to TB peptides and has less T CD8 cells migrating than the monoinfected patients.

P44. ABERRANT PLASMA IL-7 AND SOLUBLE IL-7 RECEPTOR A LEVELS INDICATE IMPAIRED T-CELL RESPONSE TO IL-7 IN HUMAN TUBERCULOSIS

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T-cell proliferation and generation of protective memory during chronic infections depend on interleukin-7 (IL-7) availability and receptivity. Regulation of IL-7 receptorα (IL-7Rα) expression and signalling are key for IL-7-modulated T-cell functions. Aberrant expression of soluble and membrane-associated IL-7Rα molecules is associated with development of autoimmunity and immune failure in infectious diseases. We aimed to investigate the role of IL-7 and IL-7Rα on T-cell immunity in human tuberculosis.

We performed two independent case-control studies comparing tuberculosis patients (n_1 = 57; n_2 = 22) and healthy contacts (n_1 = 151; n_2 = 24). This was combined with follow-up examinations for a subgroup of tuberculosis patients under therapy and recovery. Blood plasma was characterised for IL-7 and soluble IL-7Rα level, while T cells were analysed for membrane-associated IL-7Rα expression. Further, IL-7-dependent T-cell functions were determined by analysing STAT5 phosphorylation and antigen-specific cytokine production.

Tuberculosis patients had lower soluble IL-7Rα (TB: 21.0 ng/ml ; Contacts: 33.1 ng/ml ; $p < 0.001$) and higher IL-7 (TB: 6.6 pg/ml; Contacts: 4.5 ng/ml ; $p < 0.001$) plasma concentrations as compared to healthy contacts. Both markers were largely independent and aberrant expression normalised during therapy and recovery. The rs6897932 single nucleotide polymorphism in the *IL7RA* gene was associated with the concentrations of soluble IL-7Rα in plasma ($p = 0.003$) but did not account for the differential level of soluble IL-7Rαseen between tuberculosis patients and contacts (minor allele frequency: TB: 7.3%; Contacts: 5.6%). For membrane-associated IL-7Rα, increased proportions of $CD4^+$ and $CD8^+$ T cells expressing low levels of IL-7Ra was seen in tuberculosis patients as compared to Contacts ($CD4^+$: $p = 0.006$; $CD8^+$ $p = 0.02$).Functional *in vitro* tests showed diminished STAT5 phosphorylation after IL-7-stimulation of $CD4^+$ cells ($p = 0.04$). In addition, IL-7-promoted cytokine production of *Mycobacterium tuberculosis*-specific $CD4^+$ T cells was impaired for tuberculosis patients ($p = 0.02$).

We conclude that diminished soluble IL-7Rα as well as decreased membrane-associated IL-7Rα expression in T cell sis associated with diminished T-cell sensitivity to IL-7 in tuberculosis patients. Altogether this suggests an impaired IL-7-signalling pathway in tuberculosis.

P45. KINETICS OF ALVEOLAR REGULATORY T CELLS DURING TREATMENT OF PULMONARY TUBERCULOSIS IN MALAWIAN ADULTS

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Background: Tuberculosis (TB) is a major public health challenge, particularly in sub-Saharan African countries where there is high HIV burden. Expansion of regulatory T cells (Tregs) during the untreated TB infection is associated with increased bacterial load and delayed onset of mycobacterium-specific $CD4^+$ T cell responses. In this study, we aimed to investigate whether the frequency of Tregs changes during treatment of microbiologically confirmed pulmonary tuberculosis.

Methods: We recruited 5 TB+/HIV- and 5 TB+/HIV+ participants, and 7 TB-/HIV- controls from Queen Elizabeth Central Hospital, Blantyre, Malawi. Bronchoalveolar lavage (BAL) was performed on participants at 2 months and 4 months into TB treatment. All HIV-infected individuals also received antiretroviral therapy (ART). To identify Tregs, BAL cells were stained with antibodies against CD4, CD25, CD127 and FoxP3 for flow cytometric analysis.

Results: We found that the frequency of Tregs was significantly higher at 2 months compared to 4 months into TB treatment (paired, 3.2 vs. 5.0%, p=0.0027). The frequency of Tregs was higher in HIV-infected TB patients compared to HIV-uninfected TB patients at 2 months (6.80% vs. 3.28%, p=0.049) and 4 months (4.64% vs. 1.66%, p=0.053) post TB treatment. The frequency of Tregs was similar between TB patients at 4 months post TB treatment compared to TB-negative controls (3.15% vs. 2.74%, p=0.69).

Conclusion: Our results show dynamic changes in the population of Tregs in the lungs of patients with pulmonary TB. These changes suggest that anti-TB treatment is associated with reduction in inhibitory anti-TB immune response through reduction in the proportion of Tregs in the lung. Subsequent work will explore whether this is linked to effective TB control and successful treatment outcome

P46. THE ROLE OF DENDRITIC CELLS IN CNS-TB FOLLOWING BCG INTRACEREBRAL INFECTION

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Introduction: Central nervous system tuberculosis (CNS-TB) is a rare and severe form of tuberculosis associated with 50% mortality. It primarily occurs in children but significantly increases in immune compromised adults such as those infected with HIV-1. Although *Mycobacterium bovis* Bacille Calmette-Guerin (BCG) vaccine is administered worldwide to prevent tuberculosis, it can cause disseminated disease. Specific cell types targeted for invasion by tuberculosis in CNS inflammation are mostly unknown and dendritic cells have been neglected due to their absence during homeostatic conditions.The objective of this study is to determine brain dendritic cell kinetics and the potential role of DCs in CNS inflammation subsequent to BCG intracerebral infection.

Materials and methods: Brains of C57BL/6 mice intracerebrally infected with *M.bovis* BCG were isolated and single cell suspensions were generated for flow cytometric analysis to calculate the relative recruitment and phenotypes of DCs and T cells. Bacterial burdens of brains, spleens and lungs were also determined to provide an indication of CNS inflammation and bacterial dissemination. Histological analysis was performed on all organs.

Results: BCG disease occurred in the brain causing inflammation that was significantly reduced six weeks post infection. BCG disseminated from brain to the spleen and lungs. There was an influx of conventional dendritic cells to the brain and migration to the cervical lymph nodes. MHCII+ dendritic cells presented antigens to T cells in the cervical lymph nodes, CD4 and CD8 T cells were recruited to the brain. Histology showed cellular infiltration.

Conclusion: This study shows that conventional dendritic cells contribute to bacterial clearance in CNS inflammation caused by BCG and that there is an occurrence of BCG disseminated disease. DCs are targeted for invasion by tuberculosis and this study suggests the potential of developing dendritic cell therapy for CNS-TB.

P47. MICA-STR AND HLA-CLASS II GENES DIVERSITY IN PATIENTS WITH TUBERCULOSIS IN SOUTH TUNISIA

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Introduction/objectives: *Mycobacterium tuberculosis* complex (MTBC) members are reported to infect about a third of the world's population but only 5-10 % are thought to develop active tuberculosis (TB) disease. Host immunity regulated by human leukocyte antigens (HLA) plays a central role in the regulation of the immune response and has an important determinant of the outcome of the infectious disease. Major histocompatibility complex (MHC) class I chain related gene A (MICA) is located 46 kb centromeric to HLA-B and encodes a stress-inducible protein. MICA allelic variation is thought to be associated with infectious disease susceptibility. We performed a case–control study to assess a genetic association of HLA class II genes and (GCT)n short tandem repeat of MICA gene (MICA-STR) with susceptibility to TB in South Tunisia.

Material and methods: Patients with a confirmed diagnosis of pulmonary TB (pTB) ($n = 30$), extrapulmonary TB (EPTB) ($n = 30$) and genetically related healthy controls ($n = 123$) were included in the study. HLA II class alleles typing was performed by polymerase chain reaction sequence-specific oligonucleotide (*SSO*) amplification and MICA-STR allelic variation was detected by fluorescent PCR–size genotyping.

Results: HLA-DRB1*01 and MICA*A4 alleles were significantly less frequent in TB patients than in controls (7% *vs* 19%, OR=0.31; p=0.03; 5% *vs* 14.6%, OR=0.82; p=0.05 respectively). HLA-DRB1*04 allele was significantly most frequent in old pTB patients (P = 0.05) whereas HLA-DQB1*05 was significantly higher in young pTB ones (0.007).HLA-DRB1*03 allele was significantly most frequent in EPTB patients compared to healthy controls (43.3% vs 24.4%, P = 0.04). HLA-DRB1*11, DRB1*13, HLA-DQB1*03 and MICA*A5 were significantly higher in the males TBEP patients, P= 0.05, 0.04, 0.02 and 0.05 respectively.

Conclusions: Our results suggest for a first time in the South Tunisia, that HLA-DRB1*01 and MICA*A4 alleles may be associated with resistance to TB and that HLA-DRB1*03 allele is associated with EPTB.

P48. ASSOCIATION OF TNF MICROSATELLITE ALLELES WITH TUBERCULOSIS IN SOUTH TUNISIA

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Introduction: Pathogenesis in tuberculosis (TB) is dependent on interactions between pathogen, host, and environment components, which contribute to an inter-individual variability of susceptibility to this disease and its clinical outcome. Host genetic polymorphism were intensely investigated for TB susceptibility in various populations. Studies have demonstrated that several functional polymorphisms in the TNF region modify the transcriptional regulation of the gene, vary the serum level of TNFα and therefore modulate the manifestation and development of TB. In the present case–control study, the association of TNF a-b-c microsatellite markers with susceptibility to TB in South Tunisia is investigated.

Material and methods: Patients with a confirmed diagnosis of pulmonary TB (pTB) (*n* = 30), extrapulmonary TB (EPTB) (*n* = 30) and genetically related healthy controls (*n* = 123) were included in the study. Genotyping for TNF a-b-c microsatellite alleles was accomplished by fluorescent PCR–size genotyping.

Results: The TNF*b4 allele was significantly most frequent in patients with pTB than in controls (OR = 2.71, p = 0.01). However, b3 and b5 alleles were significantly less expressed in pTB patients compared to controls with OR = 0.23 (p = 0.04) and OR = 0.30 (p = 0.005), respectively. A significant increase of the frequency of TNF*c2 allele was observed in EPTB patients when compared to controls (30% vs 53.6%; p=0.02; OR=0.37). Among EPTB patients, b3 allele was significantly more frequent in patients with lymphadenopathic TB compared with those with a non-ganglionic form (59% vs 8%, p = 0.01).

Comparison of TNF microsatellite alleles-distribution between TBP patients and those with EPTB revealed a significantly high frequency of the b3 allele in EPTB patients (37% vs 7%, p = 0.005). In contrast, alleles b6 and b7 were observed only in patients with pTB compared with EPTB patients (23.3% vs 0%, p = 0.02).

Conclusions: Our findings suggest for a first time in South Tunisia that the TNF*b3 allele is likely associated with decreased susceptibility to pTB whereas the same allele has an increased risk for lymphadenopathic TB. In addition, TNF*b4 allele is associated with pTB susceptibility.

P49. FIRST ANALYTIC EVALUATION OF THE LATEST QUANTIFERON GENERATION QFT GOLD-PLUS

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Introduction: The identification of the potential *Mycobacterium tuberculosis* (Mtb) carriers in candidates for immunosuppressive treatment is of a great value. Quantiferon tests (QFT) can detect latent Mtb infection (LTBI) by measuring the interferon gamma (IFNγ) released by Mtb specific T-cells after an *in vitro* incubation with Mtb antigens. Since 2000, 4 QFT generations have been developed : QFT Gold in tube (QFT-IT) and QFT Gold Plus (QFT+) are promising and have been successfully used. While a single mixture of high specific Mtb antigens stimulate a mainly CD4+ T-cell response in QFT-IT, QFT+ presents with 2 tubes TB1 containing peptides that mostly trigger a CD4+ T-cell response and TB2 having additional antigenstargetingCD8+ T-cells. The CD8+ T cell response was reported to be enhanced in subjects with active tuberculosis (TB), thus QFT+ has been described to detect both LTBI and active TB.
Objectives: We aim to analyse the diagnostic value of QFT+ in candidates for a biotherapy based on the TB1 and TB2 positivity profiles.
Material and methods: A total of 168 patients (107 females) were enrolled from September 2016 to August 2017. All patients had inflammatory rheumatisms and all except one were candidates for a biotherapy.QFT+ (Qiagen, Hilden, Germany®) assay was performed according to the manufacturer instructions. Results were considered positive when the IFNγ concentration was ≧ 0.35 IU/mL in one of the two antigen tubes (TB1 or TB2) or in both. A predominant CD8+ reactivity was defined by a minimum differential of 0.6IU/Ml between TB2 and TB1or an exclusive TB2 response. Clinical data were collected relating to TB contacts, suggestive clinical and radiological signs or treatment for TB.
Results: Twenty five patients(14.88%) tested positive to QFT+ with a sex ratio of 1.27.Thirteen of the positive patients were TB1+/TB2+, 3 of them had a differential of more than 0.6IU/mL. Four patients had an only TB2 response and 8 others were TB1+/TB2-. Among the seven patients with a predominant CD8+ reactivity, one patient had been treated for a tubercular uveitis, a second had clinical suspicion of TB unconfirmed bacteriologically and another had been considered as an LTBI and had received prophylactic treatment. TB contact was noted in 1 patient, although no TB signs were found. Two other subjects had no signs of TB and clinical data weren't available for 1 patient.
Conclusion: In our study, most patients with dominantCD8+ responses didnot present with active TB. This finding concords with published data. Further evaluations of QFT+ profiles are needed.

P50. CLINICAL, BIOLOGICAL AND THERAPEUTIC CHARECTERISTICS OF PATIENTS WITH AN 'UNDETERMINED' RESULT FOR THE QUANTIFERON TEST

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Introduction / Objective: The Quantiféron test is a qualitative and quantitative ELISA blood test used mainly for the assessment of latent tuberculosis. It is based on the quantification of the interferon γ secreted *in vitro* by the memory T-cells specific to the *Mycobacterium tuberculosis* complex. The 'undetermined' result of this test remains a major problem for a relevant therapeutic decision. In order to better understand the probable causes of this result, this work aims to investigate the clinical biological and therapeutic characteristics of patients for whom the Quantiferon test gives an 'undetermined' result.

Patients / methods: Fifty-six patients with chronic inflammatory diseases (mainly rheumatoid arthritis(n=36) and inflammatory bowel disease(n=8)) (12 males, 42 females, sex ratio F/M=3.5, mean age of 45.8±14.8 years) followed up in the Rheumatology, Gastroenterology and Internal Medicine departments of the CHU Fattouma Bourguiba of Monastir were enrolled in this retrospective study spread over two years (January 2015-January 2017). The Quantiféron test was performed in our laboratory.

Results: Our study showed that 47 patients had either positive (n=8) or Negative (n=49) result for the quantiferon test. Seven patients had an 'undetermined' test result. They are all females. They are younger then patients with positive or negative test (mean age: 30.7±14.5 years *versus* 47.96±13.6 years, p=0.03). Patients with an 'undetermined' result for the Quantiferon test have a higher erythrocytes sedimentation rate (ESR) than those with a negative or positive Quantiferon test (85.8±38.1 *versus* 60.9±29.8 mm/1st hour, p=0.09). Their C-reactive protein (CRP) was also higher for patients with an 'undetermined' Quantiferon result (126.8±210.2 *versus* 34.1±35.4 mg/L, p=0.019). Patients with 'undetermined' result of the Quantiferon test had inflammatory bowel disease (n=3), or RA (n=2) or rhupus syndrome (n=2). Knowing that all the cases of rhupus syndrome had an 'undetermined' result. Moreover, the immunosuppressive treatment and dose received seem to have a direct impact on the result of the Quantiferon since in our series all the patients who received Immurel (n=2) and all the patients who received Plaquenil (n=2) had an 'undetermined' result for the Quentiferon test.

Conclusion: Our study showed that younger age and elevated CRP and ESR may be associated with the 'undetermined' result for the Quantiferon test. Further investigation is needed to assess involvement of immunosuppressive drugs and other factors.

P51. PREDICTIVE VALUE OF TUBERCULINE SKIN TEST, QUANTIFERON AND INFG+874 SNP IN THE PROGRESSION TO TUBERCULOSIS DISEASE IN INFLAMMATORY BOWEL DISEASES PATIENTS

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Introduction: For a century, Tuberculin skin test (TST) was the unique available means for the diagnosis of latent tuberculosis infection (LTBI), until the recent development of interferon γ releasing assays. Among these tests, the QuantiFERON® TB Gold in Tube (QFT) is the most used. Genetic susceptibility may explain why a fraction of *Mycobacterium tuberculosis* exposed persons develop LTBI while others can completely eradicate this pathogen. The Interferon γ+874(T→A) polymorphism is associated with tuberculosis (TB), and affects the interferon-γ response.

Objective: to evaluate the predictive value of QFT and TST in the evolution of latent to active tuberculosis in immunosuppressed patients with inflammatory bowel disease (IBD), and to analyze the effect of *INFG*+874(T→A) SNP in this progression.

Material and methods: Ninety six IBD patients were enrolled on 2011-2012. The average age was 35 years, and the sex ratio was 1.1. Seven were with Ulcerative colitis, 89 have Crohn disease. TST and QFT were performed in all patients. The SNP genotyping was done by ARMS-PCR technique. From the year of inclusion to 2017, factors involved in TB reactivation including malnutrition (Body mass index<18.5) and immunosuppression therapy were recorded.

Results: At inclusion, 18 patients presented positive TST and/or QFT tests; 70 were negative for both and 8 patients had an indeterminate QFT. Among patients with positive tests, 6 were placed on prophylaxis for LTBI (1 patient for malnutrition, 4 under anti-TNFα therapy, and 1 under Corticoids and Azathioprine). One patient was diagnosed with active TB received anti-tuberculosis therapy. Clinical data were unavailable for one patient. The remaining 10 patients didn't receive TB prophylaxis. After 7 years of evolution, none of the TST-/QFT- group developed active TB despite the immunosuppressive treatments reflecting a high negative predictive value NPV of these tests (100%). TB reactivation was also not diagnosed in the 10 IBD patients, with TST and/or QFT positive tests, who didn't received TB prophylaxis. 7 patients were TST+/QFT-, 2TST -/QFT+ and 1 TST +/QFT+. Among them, 5 were homozygous for the susceptibility allele (A) of the SNP *INFG*+874.

Conclusion: This study confirms the high NPV of the TST-/QFT- profile in patients under immunosuppressive therapy. TST+/QFT- patients didn't progress to TB reflecting a poor predictive value of TST as false positivity could be due to vaccination. QFT+ patients didn't progress to active TB reflecting the involvement of others factors. Even though the *INFG*+874 (T→A) SNP has been frequently associated with active tuberculosis, it wasn't associated with the TB reactivation.

P52. EVALUATION OF THE EFFECT OF TUBERCULIN SKIN TEST ON SUBSEQUENT INTERFERON GAMMA RELEASING ASSAY RESULTS (QUANTIFERON TB)

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Tuberculin Skin Test (TST) has been the only diagnosis tool used in the detection of tuberculosis infection for long time. This test has several limitations and repeated TST was associated with boosting, conversions, and reversions phenomena in the test results. Recently, more specific in vitro blood assays (Quantiferon Tb and T-Spot TB) have been developed based on interferon gamma measuring. The aim of this study is to evaluate the effect of a preceding TST on subsequent Quantiferon Tb results.

QuantiFERON TB gold in tube (QTF) was performed in the Immunology laboratory of Mustapha Bacha University Teaching Hospital for 20 patients with suspected latent or extrapulmonary tuberculosis. For each patient, QTF were performed in the same week and 2 to 3 weeks after TST administration.

TST results were as follows : negative for 13 (65%) patients, positive for 5 (25%) patients and anergy for 2 (10%) patients. For 14 (70%) patients, no systematic change of QFT results was observed after TST administration (8 negative, 5 positive, 1 indeterminate) while conversion and reversion were found for 2 and 1 patient respectively. However, the existence of many factors that may interfere with QTF results (Within-subject variability, technical error...) makes difficult to establish a direct relationship between these variations and TST administration. For that, it appears safe to perform a QTF test before performing the TST.

P53. RELEVANCE OF THE USE OF TUBERCULIN SKIN TEST (TST) AND QUANTIFERON BEFORE THEPRESCRIPTION OF BIOLOGICAL AGENTS IN CHRONIC INFLAMMATORY DISEASES

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Introduction: The introduction of biotherapy to treat chronic inflammatory rheumatism (CIR) was shown to be able to reactivate latent tuberculosis. Our objectives are to evaluate the relevance of the use of tuberculin skin test (TST) and Quantiferon before the prescription of biological agents in CIR and to assess the clinical evolution accordingly.

Patients and methods: This retrospective study included 51 patients with CIR (Rheumatoid arthritis, primary ankylosing spondyloarthritis (AS), IBD associated AS, psoriasic rheumatism, Still disease and Sjögren's syndrome representing70.6%, 7.8%, 9.8%, 5.8%, 3.9% and 2% of cases, respectively). The mean age was 47.5 ± 13.6 years [24-69 years]. The patients were recruited during 3 years (2015, 2016 and 2017), and followed up at the rheumatology departments of the university hospitals of Monastir and Mahdia. The indication of biotherapy was a resistance (45 cases, 88.2%) or intolerance (4 cases, 7.8%)to conventional treatments, or severe extra-articular manifestations (2 cases). Two tests were used to assess latent tuberculosis: the TST was done in the rheumatology department and the Quantiferon was practiced in the laboratory of immunology.

Results: The TST was positive for 5 patients (9.8%). The Quantiferon was positive for 8 patients (15.7%), negative for 41 patients (80.4%) and undetermined for 2 patients. A significant correlation was found between the two tests ($r = 0.402$, $p = 0.003$). Hence, the two tests were both negative in 39 cases (76.4%) and both positive in 3 cases (5.8%) and discordant in 9 cases (17.6%) cases. Biotherapy was carried on systematically incase of two negative tests. while, an anti-tuberculosis treatment (based on Rifadine and Isoniazide during 3 months followed by 3 weeks without medication) was prescribed, in case of positivity of TST and/or Quantiferon, before starting biotherapy. The different biological drugs prescribed in our series (n=42) were Infliximab (23.5%), Etanercept (23.5%), Certolizumab (17.6%), Adalimumab (7.8%), Tocilizumab (3.9%) and rituximab (5.8%). In 17.6% of cases the type of biotherapy was not mentioned. The duration of follow up after biotherapy was variable: less than one year (35.3%), between one and two years (31.4%) and more than two years (29.4%). No patient had developed active tuberculosis.

Conclusion: Our study showed that TST and Quantiferon, used together, may constitute valuable tool to make the correct therapeutic decision in order to avoid problems related to the reactivation of latent tuberculosis under biotherapy.

P54. EXPLORATION AND VALIDATION OF THE ROLE OF *LEISHMANIA* GENES PUTATIVELY ASSOCIATED TO PARASITE VIRULENCE

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Introduction: *Leishmania* (*L.*) is a protozoan parasite transmitted through the bite of a sand fly vector and causes a group of diseases in humans commonly called Leishmaniasis. This parasite owes its survival in the human host cells to several complex and intricate strategies it successfully developed. Among these, the expression of virulence factors has been shown to play a role in the resistance to the host antimicrobial activities. Despite their importance, only few molecules have been clearly associated to virulence to date. The characterization of virulence factors and the study of the exact role they play in the parasite could hence help to better understand the mechanisms of intracellular survival of the parasite, as well as differences in the clinical expression of the disease.

Material/Methods: In this study, high-throughput differential comparison of gene expression between parasite field isolates showing contrasted severity in humans has been used to characterize novel putative virulence factors of *Leishmania* parasites. Based on RNAseq results, we are investigating the role of a candidate gene in *Leishmania* virulence by the creation of transgenic parasites able to over-express it. Our strategy is based on the integration of an expression construct bearing the gene of interest, together with suitable markers for both positive and negative selection, into a high transcripted region on the parasite genome. The transformed strains will allow the study of the candidate gene using *in vitro* and *in vivo* infection model.

Results: The gene of interest was amplified from the DNA of a *Leishmania* strain selected among our parasites bank. The amplified sequence was then cloned into a *Leishmania* expression system called pLEXSY vector, containing the Hygromycin resistance marker. The construct was verified after digestion by specific restriction enzymes and visualization on agarose gel. The pLEXSY vector has been produced in sufficient quantities to allow the parasites transfection and *in vitro* functional studies upon macrophage infection.

Conclusion: Determining the effect of over expression of the candidate gene on the virulence of the parasite, by performing functional tests, could likely contribute to the development of new strategies to fight *Leishmania* parasite survival and spread. This approach will be extended to other genes suspected to affect parasite virulence.

P55. INTEGRATIVE ANALYSIS OF THE MACROPHAGE MICRO RNA-MRNA RESPONSE TO *LEISHMANIA MAJOR* INFECTION

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Introduction: *Leishmania* (*L.*) parasites are able to survive and replicate in the hostile phagolysosomal environment of infected macrophages in human host. To establish a successful infection and ensure their own survival, these parasites have developed sophisticated strategies to subvert the host macrophage responses. Many of the mechanisms and molecules governing the interaction between *Leishmania* and macrophage as well as parasite internal thriving and survival are still being elucidated. Identifying factors that participate to this complex interplay is an important step towards better understanding of anti-parasite immune responses and clinical outcomes of leishmaniasis. Because miRNAs may be the upstream triggers of global changes observed in gene expression in *L. major*-infected macrophages, we conducted an integrated analysis of miRNA and mRNA expression profiles in order to identify the parasitic escape routes to the immune response.

Material/Methods: We established the miRNA and mRNA transcriptional profile of monocyte-derived human macrophages from healthy donors infected with *L. major* metacyclic promastigotes. This was realized using microfluidic cards and microarray set including 364 miRNAs and 17,838 mRNAs respectively. An integrated analysis based on the putative miRNA-target gene sets and the list of experimental differentially expressed genes from microarrays experiment was then applied to study the profile of host target genes that are under the control of both up- and down-regulated miRNAs in response to *L. major* infection.

Results : KEGG pathway analysis of up- and down-regulated miRNAs target genes allowed us to identify among the most highlighted pathways deregulated during the infection process, MAPK signaling pathways, PI3K-Akt signaling, as well as endocytosis and apoptotic pathways. These results suggest that modulation of such various cellular pathways is affected by the complex interaction between the miRNAs and their target genes during *L.major* infection.

Conclusion : Our data indicate that combining the two complementary mRNA and miRNA transcriptomic approaches may lead to better understand the involvement of key genes in deregulated pathways. This comprehensive approach is likely to allow the identification of new molecules and functional pathways that could be targeted to fight this parasitic infection.

P56. IMMUNE RESPONSES SPECIFIC TO PHOSPHOENOLPYRUVATE CARBOXYKINASE DURING INFECTION WITH *LEISHMANIA INFANTUM*

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Introduction/Objectives: Phosphoenolpyruvate carboxykinase (PEPCK) is conserved in all *Leishmania*, expressed in glycosomes of promastigotes and amastigotes, and elicited strong and dominant $CD4^+$T cell responses in infected mice and humans. Vaccination with PEPCK peptide (PEPCK335–351), DNA expressing full-length PEPCK, or *r*PEPCK induced strong durable cross-species protection in both resistant and susceptible mice. In the present study, we extend our findings and analyzed PEPCK-specific immune response in human subjects living in endemic area of *L. infantum* transmission in Tunisia and in dogs naturally infected with this parasite. *L. infantum* is responsible for human visceral leishmaniasis and canine leishmaniasis.

Materials/Methods: Sera from 26 subjects living in transmission endemic area of *L.infantum* and 5 healthy controls were included in this study. The anti-PEPCK IgG, IgG2, IgG3 and IgG4 levels were measured by ELISA. For analysis of PEPCK-specific immune response during canine visceral leishmaniasis (CVL) 45 dogs were used. Dogs were screened based on established serological, immunological and parasitological criteria. PEPCK-specific IgG, IgG1 and IgG2 titers were measured within dog's sera using ELISA and the cellular immune response was evaluated *in vitro* by analysis of the lymphoproliferative response after stimulation of PBMC with *r*PEPCK. In addition, the levels of IFN-γ, IL-10 and IL-4 in the culture supernatants were also determined by ELISA.

Results: The use of ELISA specific of PEPCK allowed us to distinguish between individuals non-infected with *L. infantum* (healthy controls) and those who had a previous contact with the parasite. The typing of the IgG subclasses showed a predominance of IgG3 in sera of the asymptomatic subjects in contrast to VL patients who showed higher levels of IgG2. Similar, high levels of IgG anti-PEPCK were measured within sera from infected dogs compared to those from healthy ones, with a predominance of IgG2 isotype. In addition, PEPCK-specific cellular immune response characterized by a weak lymphoproliferation with induction of IFN-γ and IL-10 was detected within asymptomatic dogs, indicating a mixed Th1 / Th2 response.

Conclusions: Our results showed the reliability of PEPCK-specific for the detection of a previous contact with *L.infantum,* which might constitute a tool for the serodiagnosis of human and canine visceral leishmaniasis. A mixed Th1 / Th2 cellular immune response was induced in response to stimulation of PBMCs from asymptomatic dogs with PEPCK indicating the immunogenicity of this antigen.

P57. IMMUNE CYTOKINE PROFILE OF LESIONS FROM CUTANEOUS LEISHMANIASIS PATIENTS USING A NEW NON-INVASIVE TECHNIQUE AT THE UNIVERSITY OF GONDAR HOSPITAL NORTH WEST ETHIOPIA

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The clinical presentation of cutaneous leishmaniasis (CL) varies in both type and severity; patients present with one of three different forms of cutaneous disease: localized CL (LCL) characterized by localized lesions on exposed skin; mucosal CL (MCL) affecting mucosa of the nose, mouth or pharynx; and diffuse CL (DCL) characterized by numerous non-ulcerating nodules. LCL can be self-healing, whereas persistent LCL, MCL and DCL require prolonged treatment and are associated with frequent relapse. Here we performed a proof of principle study to evaluate the use of a novel non-invasive sampling technique to measure the cytokine profile in the lesions of patients with different manifestations of CL.

Objective: To determine the arginase levels, protein levels and the cytokine profile (IL6, IL8, IL10, IL17A, CCL2, TNFα and IFNγ) in skin lesions of patients among cutaneous leishmaniasis and to compare differences among the samples

Matirials and Methods: A cross-sectional study was conducted at LRTC, University of Gondar from December 2015 to May2016. A total of 30 study participants were recruited. Ten standard D-Squame tape strips (2.2 cm in diameter) were sequentially applied onto skin lesions and nearby healthy skin with a constant pressure (Figure 1). The strips were each placed in an Eppendorf tube and frozen until use. An extraction buffer was used to extract the material collected on the strips, the protein content was determined using the BCA assay and the cytokine profile was measured by ELISA.

Result and Coclusions: IL6, IL8, CCL2, protein and arginase activity were detected in the skin of patients with different forms of CL. In future work researchers can use this noninvasive technique to study more immunological markers. In addition the first strip sample is recommended to recover cytokines, protein and arginase.

P58. GENE EXPRESSION PROFILES OF INDUCIBLE NITRIC OXIDE SYNTHASE (iNOS), IL-1β, AND IL-12 CYTOKINES DURING *IN VIVO* INFECTION OF MICE BY AUTOCHTHONOUS DERMOTROPIC STRAINS OF *LEISHMANIA* SPECIES

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Background: In Morocco, *Leishmania major* and *L. tropica* are the main dermotropic species responsible for cutaneous leishmaniasis (CL), which remains a public health problem. These species are associated with a significant clinical polymorphism of lesions in the human host. The cutaneous pathology is determined in part by the infecting *Leishmania* species, but also by host immune response factors resulting in different clinical outcomes. This response involves a diverse group of soluble mediators that may contribute to modulate *Leishmania* infection, such as nitric oxide (NO) and IL-1β or IL-12 cytokines. We already developed a murine model using Swiss mice, to study the physiopathology of *Leishmania* infection. Thus our goals are: i) to study the clinical evolution of mice infection by primary autochthonous strains of *L. major* and *L. tropica* ; ii) to determine the *in vivo* impact of these infections on iNOS, IL-1β and IL-12 genes expression.

Materials and methods: Female Swiss mice were injected subcutaneously at the foot-pad; control group is included (PBS injections). Two primary autochthonous dermotropic strains of *L.major* and *L.tropica* were used. Following the evolution of infection was carried out weekly by measuring the paw inflammation using a caliper. At 15 weeks post-infection, the parasite dissemination was evaluated by PCR (13a-13b primers) and gene expression of iNOS, IL-1β, IL-12 was analyzed by qRT-PCR on spleens' mice.

Results: Only the mice infected with *L.major* strain developed inflammation from week 3 post-infection that reached 1 mm diameter at week 13. Respectively 46% and 23% of spleens were *Leishmania* positive. Furthermore genes expression in mice spleens showed that both *L.major* and *L.tropica* infections resulted in a significant increase of IL-12 expression, but an iNOS inhibition. However IL-1β expression was differently modulated by these two strains.

Conclusion and discussion: On the whole our results show that Swiss mice infected by *L. major* develop inflammation and exhibit a resistant phenotype, while no dermal lesion was developed for *L. tropica* infected mice. The different IL-1β expression modulation in spleens during mice infections may explain the different physiopathology of *L. major* and *L. tropica* infection. Other experiments are ongoing to analyze the genes expression in other sites (infection site and draining lymph nodes) and at different infection times to complete the expression profile of the selected genes.

P59. ROLE OF TREG CELLS IN PATHOGENESIS OF POST KALA AZAR DERMAL LEISHMANIASIS

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Background: The persistence of post kala-azar dermal leishmaniasis (PKDL) in some patients has been difficult to explain. There are many gaps in knowledge concerning the pathogenesis of PKDL. This is a prospective, longitudinal study that was carried out between March 2010-April 2012. Setting**:** Patients from eastern Sudan were recruited for the present study. **Objective:** 1.to study the role of Treg cells in the pathogenesis of Post Kala-azar Dermal Leishmaniasis (PKDL). 2.To define the cell phenotypes and cytokines profile in tissues and peripheral blood of patients suffering from persistent PKDL before and after treatment.3. To correlate the pathology of PKDL lesions with the prognosis of PKDL (healing and non-healing)
Methods: Following informed consent, Sudanese PKDL patients from eastern Sudan were recruited. Patients were followed before and after treatment. From each patient, a clinical history was obtained and a clinical examination was conducted. Aspirations of bone marrow and lymph nodes were performed on patients who had lymphadenopathy, splenomegaly or fever. Smears of the aspirates were stained with Giemsa and examined for Leishmania parasites. Real time PCR assay was performed to detect and quantify the Leishmania Genome. The diagnosis of PKDL was made clinically on the basis of the characteristic type and distribution of lesions in patients recently treated for kala-azar. Skin biopsies were obtained under local anesthesia using 4 mm disposable punches. Tissue was fixed in 10 per cent neutral formal saline. The fixed tissue was embedded in paraffin; sections were cut and stained with haematoxylin and eosin (H&E). In haematoxylin and eosin stained sections, macrophages, lymphocytes, plasma cells, epithelioid granulomas and epithelioid not organized as discrete granulomas cells were scored semi-quantitatively. Immunohistochemical staining was then performed. PKDL lesions were classified into two groups depending on the types of inflammatory cells in the dermal infiltrate and the presence or absence of compact epithelioid granulomas. Blood samples were collected for flow cytometry.
Results: Hypopigmented papular skin rash was the most common presentation (55%), followed by maculopapular eruption (25%), followed by measles-like rash (15%) and nodular type (5%). Irrespective of clinical forms and histological groups the reaction in the skin usually consisted of a mixed inflammatory cellular infiltrate composed of lymphocytes, macrophages and epithelioid granulomas. In some cases the lesion consists mainly or entirely of lymphocytes and macrophages. Other cases showed mainly epithelioid granulomas. The epidermis shows hyperkeratosis and follicular plugging. In patients with hypopigmented lesions there is infiltration of the basal layer by lymphoid cells and vacuolar degeneration of the basal layer. The majority of cells infiltrating the lesions were CD3+ T cells and CD8 cells. There was a preponderance of macrophages (CD 68) over CD4 cells, and T reg cells. CD4 cells appeared more than T reg cells. B lymphocytes were completely absent. Patients with Type II reaction (epitheloid granuloma) had a significantly longer duration of the disease compared with those of mixed inflammatory type I reaction (p= 0.001). In peripheral blood samples of a subset of patients (n=20), the number of CD4 cells before treatment was high (SD=2200) followed by CD8 cells (SD=1900), followed by Treg cells (SD=900). The number of cells decreased in the same manner upon treatment. Both CD8 and Treg cells showed a significant difference in count before and after treatment (p=0.005).
Conclusion: Treg cells in PKDL have a major impact on our understanding of the pathogenesis and treatment of this disease. This study has provided evidence that Treg cells can influence the disease outcome and that UVB light plays an important role in the pathogenesis of PKDL by inducing Treg cells which suppress CD 8+ cells that are needed to damage the leishmania antigen-containing macrophages and epithelioid cells.
Recommendation: Understanding the pathology and the cell phenotypes interactions in PKDL lesions could be of paramount importance for the design of new strategies for therapeutic intervention in dampening inflammatory pathologies or by inhibiting the induction or function of T reg cells or conversely enhancing better functional immune responses to PKDL.

P60. AUTOCLAVED LEISHMANA MAJOR AND CAFFEIC ACID INDUCE HIGH LEVELS OF IGG2 AND RESTORE CUTANEOUS LESIONS IN INFECTED BALB/C MICE

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Introduction: Immunization with killed *Leishmania* promastigotes was considered as safe but gave variable levels of protection. Th2 cytokines, has been shown to play an active role in the progression of B-cell activation and switching of the isotype response with a predominant IgG1 production. On the other hand, IFN-γ (Thl cytokine) downregulates this activity and enhances IgG2 responses in mice. The aim of this study was to identify an appropriate *Leishmania* vaccine adjuvant based on high Th1 cytokine correlated with high value IgG2 antibody responses.
Material and methods: We performed 9 weeks infection of BALB/c mice treated with autoclaved *Leishmana major* (ALM) alone or in association with Freund's complete adjuvant (FA) or caffeic acid (CA), and then inoculated in a right hindpaw with a local strain of *L. major* promastigotes (LIPA1126). IFN-γ, TGF-β and total or IgG2 antibodies were quantified by enzyme-linked immunosorbent assay (ELISA).
Results: Indicated relatively lower type 1 cytokine responses following ALM-FA vaccination as well as in untreated mice, compared to ALM-CA or ALM immunization. Moreover, ALM immunization enhanced IFN-γ/TGF-β ratio. Therefore ALM-CA combination was more efficient, while ALM-FA was less effective, resulting in lower IFN-γ/TGF-β ratio correlated to persistent inflammatory foci. Significantly higher IgG2 antibody responses were associated with either ALM-CA or ALM immunization, indicating a Th1 polarisation.
Conclusion: The study concludes that ALM-CA could be used in *Leishmania* vaccine since it favours high Th1 cytokine and strong IgG2 antibody responses.

P61. DYSFUNCTION OF BLOOD NEUTROPHILS AND MONOCYTES IN CLINICAL VISCERAL LEISHMANIASIS

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Introduction/Objectives: Neutrophils and monocytes are rapidly recruited from the circulation to the site of *Leishmania* infection. The aim of this study was to investigate the response of blood neutrophils and monocytes to *Leishmania (L). donovani* and to ligands of Toll Like Receptors (TLRs) in visceral leishmaniasis (VL) patients.
Material/Methods: Using a whole blood-based assay, the response of neutrophils and monocytes of VL patients and endemic healthy controls (EHC) to *L. donovani* and to the TLR agonists LPS, MALP-2 and poly (I: C) was investigated by assessing the cell surface expression of CD62L and CD66b, phagocytic capacity, production of reactive oxygen species (ROS) and cytokine release. Cell activation markers, ROS production and phagocytic capacity were measured by using flow cytometry.
Results: Neutrophils of VL patients showed reduced response to *L. donovani* and MALP-2 regarding shedding of CD62L. Similarly, *L. donovani* induced degranulation (CD66b expression) was significantly lower in neutrophils from VL patient than in EHC. The phagocytic activity, ROS production of neutrophils and monocytes as well as the secretion of pro-inflammatory cytokines in response to stimuli was significantly compromised in VL.
Conclusion: The findings indicate a dysfunction of neutrophils and monocytes in VL which likely contributes to the development of life threatening disseminated disease after infection with *Leishmania donovani*.

P62. SKEWING OF SAG MEDIATED THERAPY FOR A PREDOMINANT TH1 DURING VISCERAL LEISHMANIASIS ON TRIGGERING CD2 EPITOPE

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Introduction: Visceral Leishmaniasis is a macrophage associated disorder for the treatment of which antimony based drugs like SAG and SSG were the first choice in the recent past. The clinical value of antimony therapy is now declined against VL because increasing cases of Sodium Antimony Gluconate (SAG) resistance have reached outstanding proportion in Bihar, India.

Material Methods: Within this context we looked into the protein sequences of ABC transporters of *Leishmania spp* associated with Visceral Leishmaniasis that are known to play a crucial role in the development of multidrug resistance (MDR). We have also evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with 3 million parasites via-intra-cardiac route. Mice were treated with anti CD2 adjunct SAG subcutaneously twice a week for 4 weeks. Assessment for measurement of weight, spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments.

Results: Our studies consisting of ClustalW, Phylogeny and TCOFFEE have pinpointed that ABC transporters have enormously diverged during the process of evolution even within the identical species strains resulting in insignificant homology and subdued conservation amongst the amino acid residues. Moreover these amino acid residues remain susceptible to mutations in evolutionary era as indicated by high frequency of variations by the variability studies. Hence we predict that during the process of evolution a series of frequent mutations might have led to changes in the ABC transporters favorable to effluxing the drug thereby making the Leishmania species prone to resistance against the efficient first line drug SAG, used for combating VL. This selection has made them to survive efficiently in the adverse circumstances of antimony based anti leishmanial therapy regime The combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy ($p = 0.298$) but CD2 treatment even alone significantly influenced IFN- γ production than either SAG treatment ($p = 0.045$) or with CD2 adjunct SAG treatment ($p = 0.005$) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages. As shown, the super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Interestingly, the super-oxide generation ability remained intact in macrophage after treatment with immuno-chemotherapy even in mice infected with Leishmania resistant strain. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-α, resulting in resulting in most effective clearance of *L. donovani* from infected macrophages.

Conclusion: Our results indicate that CD2, which can boost up a protective Th1 response, might also be beneficial to enable SAG to induce macrophages to produce Leishmanicidal molecules and hence control the infection in clinical situation like Kala-azar. Drug resistance is the major impedance for disease control but the encouraging results obtained after infecting mice with resistant strain of the parasite strongly imply that this drug can be effective even in treating resistant cases of Kala-azar.

P63. IMMUNOLOGICAL STATUS TO HEPATITIS B VIRUS OF PREGNANT WOMEN IN DAKAR, SENEGAL

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Introduction/Objective: Hepatitis B represents major public health problems potentially mortal hepatic infection. Senegal is a highly endemic area for viral hepatitis and especially of hepatitis B. Despite implementation of hepatitis B national program since 1999 to fight against the infection, there are few efforts to evaluate efficacy of implemented policies. In this context, we decided to evaluate immunological status to hepatitis B virus of Senegalese pregnant women by screening HBs antigen.

Material and methods: The selection criterion of women was presence at the laboratory for biological exams of pregnancy follow-up. All volunteers for the study were screened for HBs antigen (HBs Ag). Investigation of chronic hepatitis B markers (HBe Ag, anti HBe, viral quantification) was performed in HBs Ag positive samples. The concentration of anti HBs antibodies was assessed in HBs Ag negative women.

Results: One hundred and fifteen (115) pregnant women were included in the study from July to October 2014. The mean age was 29 ± 6 years, ranging from 16 to 47. The seroprevalence of HBs Ag was 12% and the majority of women (90%) was not vaccinated. Any of the 14 HBs Ag-positive patients did not express serum HBe Ag, (marker of active viral replication) and all were anti-HBe antibodies positive. Their viral load (HBV / DNA) was undetectable and serum transaminases were normal. The anti-HBs antibodies titrated in HBs-Ag negative women serum revealed that only 46 had protective levels against HBV whilst 55 of them were unprotected.

Conclusion: It would be reasonable to promote vaccination before the pregnancy and to make a systematic screening of HBs Ag. Beyond vaccination of newborns from HBs Ag positive mothers, it is important to measure the viral load of HBs Ag positive and HBe Ag negative women to monitor the perinatal transmission risk and to prevent HBV by a neonatal seroprophylaxis. Advices on prevention of HBV transmission should also be provided to pregnant women positive for HBs Ag.

P64. QUANTIFICATION OF HVB-DNA AND HVC-RNA VIRAL LOADS: A COMPARATIVE STUDY OF TWO COMMERCIAL KITS

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Introduction: Hepatitis B virus DNA and C virus RNA quantification are a key determinant of anti-viral treatment. To date, many real-time PCR assays are commercially available. However, their performances are variable. The aim of this study was to compare the performances of QIAGEN kits to those of Sacace kits for viral nucleic acids quantification.

Material and Methods: 82 patients followed for viral hepatitis B (32 cases) or C (50 cases) were included. Viral markers were analyzed by enzyme-linked immunosorbent assay. The quantification of the viral loads was made according to two distinct protocols:

- Method 1 : extraction of viral nucleic acids by the NORDIAG Arrow (DiaSorin®) instrument and extraction kit: Viral NA Extraction Kit (DiaSorin®) followed by amplification with Sacace® HBV Real-TM Quant Dx or Sacace® kits HCV Real-TM Quant Dx.
- Method 2 : extraction of viral nucleic acids through the QIAcube (QIAGEN®) instrument and extraction kit: QIAamp DSP Virus Spin (QIAGEN®) and then amplification with artus® kits HBV RG PCR Kit or artus® HCV RG RT-PCR Kit.

Nonparametric tests were used to evaluate correlation between the two protocols.

Results: For patients with hepatitis B, the correlation between the two kits was statistically significant ($\kappa = 0.638$ and $p = 0.00028$). Thus, the viral loads quantified by the 2 kits were statistically correlated (Rho de Spearman = 0.838, $p < 10E-8$). The correlation was maximal (Rho de Spearman = 0.954) for Log IU / ml between 2 and 8. Nevertheless, discrepancies (Sacace (+) / QIAGEN (-)) have been revealed in 7 cases. These patients have chronic hepatitis B with anti-HBe seroconversion and HBV viral load (<2 log UI / ml). Such discrepancies probably reflect a relatively lower sensitivity of the QIAGEN kit compared to that of Sacace. The analysis of hepatitis C results showed a perfect concordance (100%, $\kappa = 1$ and $p = 10\text{-}12$) between the two kits. However, the average HCV viral load was statistically higher via QIAGEN kit than via Sacace kit ($p = 0.013$) with a greater coefficient of 3.8 to 5 x.

Conclusion: For the quantification of HCV-RNA, better performance has showen with the QIAGEN kit. So acquisition of this assay should be very interesting in our laboratory. Whereas, for hepatitis B, more investigations should be performed to confirm our preliminary results.

P65. TOLL-LIKE RECEPTOR 9 POLYMORPHISMS AND HEPATITIS B VIRUS CLEARANCE IN MOROCCAN PATIENTS

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Introduction/Objectives: Hepatitis B infection remain: a serious public health problem in the world. In connection with poorly defined defects affecting their immune competence, patients chronically infected with hepatitis B virus (HBV) cannot clear the virus. The outcome of infection depends primarily on the interaction between the virus and selected effectors of host immunity. Toll-like receptor 9 (TLR9) plays a crucial role in innate immunity against viral infections through detection of intra-cytoplasmic dsDNA. Defects in this system may result, therefore, in attenuated responses against HBV. Recent research has focused on the possibility of targeting the defects in TLR9pathwayas a novel approach for anti-HBV treatment. Our study aimed to assess the impact of both*TLR9*rs5743836and rs187084 polymorphisms on spontaneous HBV clearance in Moroccan patients.

Material/Methods: In this study, 239 chronic HBV (CHB) patients and 134 spontaneously resolved HBV (SRB) individuals were recruited and genotyped using a Taqman allelic discrimination assay.

Results/Conclusion: Remarkably, we observed dosage effect of both SNPs on viral loads. Atrs5743836, AA, AG and GG genotypes were significantly associated with a progressive increase of circulating HBV DNA whereas the inverse phenomenon was noticed with AA, AG and GG at rs187084. By contrast, there was no consistent association between *TLR9* polymorphisms and spontaneous clearance or persistence of HBV. To conclude, of Moroccan patients, no significant association of rs5743836 and rs187084 *TLR9*polymorphisms was observed with HBV natural clearance. Further studies on larger populations should shed light on the modulating effect of *TLR9* polymorphisms on HBV loads that remain a viral factor of paramount importance to predict HCC development.

P66. IMPACT OF TOLL-LIKE RECEPTORS 2 (TLR2) POLYMORPHISM IN HEPATITIS B

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Introduction/ Objectives: Toll-like receptors (TLR) play an important role in cell signaling and recognition of several pathogenic molecular motifs called PAMP polymorphisms within genes that code for proteins of the innate immune reponse are implicated in genetic susceptibility to several pathologies. In this context, the polymorphism-196 to -174 deletion affecting the TLR2 gene by modifying the activity of the promoter is associated with several diseases. This work deals with the implication of this polymorphism in the physiopathology of hepatitis B in the Tunisian population.

Material/methods: In total, 35 Tunisian patients suffering from hepatitis B who were in the department of gastroenterology at the military hospital of Tunis and 250 healthy volunteer donors of kidney transplant or blood donors within the same hospital. Genotyping of the deletion of the TLR2 gene is determined by a specific allele PCR reaction. We compared alleles and genotypes frequencies in patients versus controls.

Results: An analysis of the frequency of the genotypes insertion/deletion (Ins/Del) + deletion/deletion (Del/Del) was significantly different between the patients and the controls thus conferring a protective role of the deletion of 22 pb against HBV with [(p=0.0025; 95%) =0.31 (0.14-0.67)] hepatitis B, TLR2 polymorphism.

Conclusion: Our study showed a significant different between the patients and the controls thus conferring a protective role of the deletion of 22 pb against HBV. In fact our results should be confirmed by the enlargement of the cohort of patients in order to confirm or invalidate the implication of this polymorphism in the physiopathology of hepatitis B in Tunisia.

P67. IL28B RS12979860 POLYMORPHISM IN HEALTHY AND CHRONIC HEPATITS C TUNISIAN PATIENTS: PREVALENCE AND THERAPEUTIC VALUES

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Introduction and objectives: Hepatitis C virus (HCV) is a major world public health problem with over 120 million of individuals that are chronically infected and 350,000 patients die every year from HCV infection. In Tunisia, the standard care for HCVis based on pegylated-interferon alpha and ribavirin treatment. Recent pangenomic association studies have shown that human genetic variations in the interleukin-28B gene (*IL28B*) may explain differences in treatment outcomes of chronically HCV-infected individuals and may be useful as therapeutic response markers. Further, it was shown that the SNP rs12979860 in the *IL28B* gene had a strong association with the HCV bi-therapy in patients with chronic HCV genotype 1 infection in many populations. The aim of this study is to investigate whether this polymorphism shows complete linkage with bi-therapy response in Tunisian patients with chronic HCV genotype 1 infection.
Material and Methods: We conducted a prospective study that involved 30 patients chronically infected with HCV1 and having bi-therapy treatment. Viral RNA level was controlled during treatment to evaluate the bi-therapy efficiency. A second blood sampling was performed 6 months after the end of treatment to determine the result of sustained viral response. To determine the genetic status of the *IL28B* in Tunisian population we enrolled 161 healthy subjects as a control group with a negative history of cancer and hepatic diseases. A 400pb of genomic DNA containing the *IL28B* rs12979860SNP was amplified. Genotyping was performed mainly by PCR-RFLP. Statistical analysis was done using SPSS version 19.0.
Results and conclusion: No significant differences were found in the distribution of rs12979860 genotypes frequencies between HCV infected patients and healthy individuals (P=0,166). In contrast, the distribution of the rs12979860 alleles frequencie's showed a significant difference between the two populations (P=0,036).In our cohort, we report 48% of the success of treatment, 40% of relapse and 12% of non-response. In addition, patients with CC or TC genotypes had a high rate of sustained viral response (SVR) (respectively 62% and 55%) and low rate of relapse and non-response. By against patients with TT genotype had a high rate of non-response (60%) if we compare it with CC or TC genotypes (8% and 9%) with the null percentage of SVR and 40% of relapse. We have demonstrated that CC genotype correlates with SVR and TT with Bad response (P=0,048). Despite the low number of patients involved in this study, our results prove that TT genotype represents a bad predictor of SVR for bi-therapy treatment for HCV1 infected patients in our population.

P68. PREVALENCE OF ANTI-THYPEROXIDASE ANTIBODIES AND THYROID FUNCTION IN CHRONIC VIRAL HEPATITIS C RETROSPECTIVE STUDY OF 102 PATIENTS

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Introduction: Autoimmune manifestations, especially thyroïd ones, are frequently observed in patients with chronic viral hepatitis C. The prevalence of anti-thyroperoxidase antibodies in these patients (ATPO) varies from 2 to 15 % in the literature. The purpose of our study is to determine the prevalence of ATPOs and to study thyroïd function in patients with chronic hepatitis C.

Patients and methods: This is a retrospective study which included 102 patients with chronic hepatitis C, cirrhotic or not, who were hospitalized in Gastroenterology department B at La Rabta Hospital in 2016 .

Results: 102 cases of chronic hepatitis C were collected. The average age was 60.6 years (from 26 to 83 years). the sex ratio was 0.54. Dysthyroïdy was noted with 25 patients (24.5 %). It was a hypothyroïdism in 68 % of cases (N=17). Hyperthyroïdism (N=8) was noted with 32 % of patients. The prevalence of ATPOs in case of chronic HCV infection was 9 %. 3/4 of these patients developped thyroïd dysfunction. ATPOs were detected in case of hypo, hyper and euthyroïdism in respectively 26.6 %, 28.5 % and 3% of patients. Dysthyroïdy was significantly correlated with the presence of ATPOs (p=0.001) and female sex (p=0.03).

Conclusion: The prevalence of ATPOs in patients with chronic hepatitis C was 9 %. Their presence is associated with a higher risk of developping thyroïd dysfunction. In case of HCV infection, a systematic screening of these antibodies should be realised with a close monitoring of the thyroïd status of these patients.

P69. ANTIBODIES ASSESSMENT DURING MALARIA SUBSEQUENT EPISODES IN CHILDREN AND ADULTS LIVING IN MALARIA HYPERENDEMIC AREA OF BURKINA FASO

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Introduction: Exposure to repeated malaria infection allows acquisition of some immunity. In the present study we assessed the effect of subsequent episodes on malaria antigens specific antibodies production in a population living in malaria hyperendemic area and treated repetitively with Artemisinin-based Combination Therapies (ACTs).
Methods: In 2012, patients aged over 6 months, presenting uncomplicated malaria were recruited and allocated to receive ACTs and follow up to 2 years. Serum collected during each subsequent uncomplicated malaria episodes was used to assess antibodies titers against three *P.falciparum* antigens MSP3, GLURP-R0 and R2 by ELISA **.**
Results: A total of 371 volunteers were recruited allocated in two age groups as followed : 151 less than 5 years old and 220 with more than 5 years. During the follow up, 162 volunteers experience done episode, 94 did 2 episodes, 44 did 3 episodes, 42 were with 4 episodes and 29 of them did 5 episodes. Antibody concentration increased during subsequent episodes for GLURP R0 and R2. While, IgG to GLURP-R0 antigen showed a significant increase between episode 1 and episode 2 with respectively 3.8 AU and 5.89 AU (P=0.01). Antibodies concentration has doubled starting from 3.8 AU at episode 1 to 8.83 AU at episode 5. The same trend was observed in study participants over 5 years. No relationship was observed between drug regimen and antibodies profile.
Conclusion: In our study population naturally exposed to malaria, repeated episodes have a boosting effect on malaria humoral immune responses.

P70. IMPACT OF PLACENTAL PLASMODIUM FALCIPARUM MALARIA INFECTION ON THE CAMEROONIAN MATERNAL AND NEONATE'S PLASMA LEVELS OF SOME CYTOKINES KNOWN TO REGULATE T CELL DIFFERENTIATION AND FUNCTION

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Background: The impact of placental malaria (PM) infection on the expression profile of some cytokines known to regulate T cell differentiation and function and their influence on birth weight remain unclear. Moreover, there are noreports showing the relationship between PM and IL-27 or IL-28A. This study therefore sought to investigate whether placental *P. falciparum* infection alters the expression profile of the cytokines IL-28A, IL-27, IL-17E and IL-6 in mothers and their new born.

Methods: In a cross-sectional study conducted between 2013 and 2015 in Yaoundé, Cameroon, peripheral, placental and cord blood samples were collected from 108 women at delivery. Parasitaemia was determined microscopically and haemoglobin levels determined using a Coulter counter. Plasma levels of cytokines (IL-28A, IL-27, IL-17E and IL-6) were measured by luminex magnetic screening assay.

Results: Malaria parasite density in placenta impression smear associated negatively with maternal haemoglobin level ($P < 0.0001$) and baby birth weight ($P = 0.016$). While IL-17E, IL-27 and IL-28A levels were significantly higher in placental and cord plasma than in peripheral ($P < 0.0001$, < 0.001 and $P = 0.026$, respectively), an opposite relationship was observed with IL-6 ($P = 0.0018$). Multivariate analysis confirmed results of univariate analysis where the presence of malaria parasites or pigments in placenta tissue impression smears correlated with decrease levels of maternal IL-17E, IL-27 and IL-28A and neonate levels of IL-28A and IL-17E ($0.0001 \leq P \leq 0.02$). Placental and peripheral parasitaemias also correlated positively with peripheral plasma levels of IL-6 ($r_s = 0.18$, $P = 0.05$ and $r_s = 0.17$, $P = 0.07$, respectively). In addition, high maternal haemoglobin level associated with increasing levels of IL-17E, IL-27 and IL-28A in peripheral plasma ($0.002 \leq P \leq 0.018$) and high placental and cord plasma levels of these cytokines associated with increasing birth weight ($0.0001 \leq P \leq 0.0027$).

Conclusions: Placental malaria down regulates maternal plasma levels of IL-17E, IL-27 and IL-28A and neonates' plasma levels of IL-17E and IL-28A cytokines, which could help for parasite clearance and increase child birth weight. The study is expected to provide leads that should help identify potential biomarkers for improved birth weight and therapeutic interventions.

P71. INCREASED LEVELS OF PROINFLAMMATORY AND NTINFLAMMATORY CYTOKINES ARE ASSOCIATED WITH BRAIN SWELLING IN MALAWIAN CHILDREN WITH CEREBRAL MALARIA

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Introduction: Cerebral malaria (CM) is the deadliest complication of malaria in children with a case fatality rate of up to 25%. Recent studies have demonstrated that increased brain volume is common in children who die of CM but less common in survivors. Furthermore, pro-inflammatory cytokines have been associated with severe malaria. However, these studies have not been able to decipher the pathogenesis of brain swelling in CM. We hypothesized that high levels of plasma cytokines could be a risk factor for brain swelling. We aimed at describing the relationship between brain volume and cytokine levels in peripheral blood.

Methods: CM children aged between 6 months and 12 years were recruited (n=115) in Blantyre, Malawi. Concentrations of plasma cytokines (IL1β, IL6, IL8, IL10, IL12 & TNFα were measured during acute malaria using cytometric bead array. Brain volumes for CM children were measured using MRI scanner and grouped into normal brain volume (NBV) and severe brain volume (SBV). Grouped CM brain volumes were related to cytokine levels using *Mann-Whitney U test.*

Results: We found that IL6, IL10 and TFN-αlevels were significantly higher in SBV compared to NBV; IL6 (NBV median 139pg/ml interquartile range {IQR}[37.7-3890] vs SBV532pg/ml IQR [29.7-6590], *p* value 0.005), IL10 (NBV median 187pg/ml IQR [16.3-359pg/ml] vs SBV median560pg/ml IQR [75.5-860], *p* value 0.014) and TNF-α(NBVmedian18.5pg/ml IQR [9.15-39.3]vs SBV median 38.5pg/ml IQR [21.7-72.5], *p* value 0.007).

Conclusion: We have shown that increased levels of pro-inflammatory cytokines (IL6, TNF-α) and anti-inflammatory cytokine (IL10) are associated with brain swelling. The results suggest that these cytokines may be involved in the pathogenesis of CM. Furthermore, anti-inflammatory response mediated by IL10 might not have reached optimum level to down regulate pro-inflammatory driven pathology. Our findings provide new insight into the pathogenesis of CM in children.

P72. CEREBRAL MALARIA BRAIN SWELLING IS INFLAMMATION INDEPENDENT IN MALAWIAN CHILDREN

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Introduction: Cerebral malaria (CM) is the deadliest complication of malaria in children with a case fatality rate of up to 25%. Recent studies have demonstrated that brain swelling which leads to raised intracranial pressure is a predictor of death in African who present with CM. Furthermore, pro-inflammatory cytokines have been associated with severe malaria. However, these studies have not been able to decipher the mechanisms of brain swelling in CM. We hypothesized that high levels of plasma cytokines could be a risk factor for brain swelling. We aimed at describing the relationship between brain swelling and plasma cytokine levels.
Methods: We measured levels of plasma cytokines (IL1b, IL6, IL8, IL10, IL12 & TNFa) in Malawian children (n=195) with CM using cytometric bead array. Brain volumes for CM children were measured using MRI scanner and grouped into normal brain volume (NBV) and severe brain volume (SBV). Grouped CM brain volumes were related to cytokine levels using Mann-Whitney U test.
Results: We found that the levels of IL6, IL8, IL10, IL12 and TNFa were similar in NBV and SBV. Only IL1b levels were significantly higher in SBV compared to NBV; NBV median 0pg/ml interquartile range {IQR} [0-8.26] vs SBV 3.28pg/ml IQR [0-10.3], p value 0.03).
Conclusion: We have shown that CM brain swelling is independent of systemic inflammation except for cytokine IL1b which was associated with brain swelling. Our findings suggest that there could be other processes that are involved in the mechanisms of CM brain swelling in children.

P73. EFFECT OF HOOKWORM INFECTION AND ANTHELMINTIC TREATMENT ON *PLASMODIUM FALCIPARUM*-SPECIFIC ANTIBODY RESPONSES

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Background: The overlapping geographical and socio-economic distribution of malaria and helminth infection has led to several studies investigating the immunological and pathological interactions of these parasites. However, it is still not clear whether hookworm infection and anthelmintic treatmentmodify antimalarial immunity.
Aim: To determine the effect of hookworm infection and anthelmintic treatment on antibody responses against *P. falciparum*.
Methods: The study involved a total of 198 Ghanaians (4–88 years old) from the Kintampo North Municipality who were infected with either hookworm only (n=64), *P. falciparum* only (n=50) or both (n=39) and uninfected endemic controls (n=45). Serum samples were obtained prior to hookworm treatment with a single dose of albendazole (400mg) and two weeks after were studied. IgG1, IgG3and IgM antibody responses against malaria vaccine candidate antigens; merozoite surface protein (MSP3), glutamate rich protein (GLURP R0) and GMZ2 were measured using ELISA. Individual associations between nonscale variables were determined using the Mann–Whitney *U* rank sum and the Kruskal–Wallis tests. Wilcoxon Signed Ranks Test was used to compare the antibody levels in the individuals before and after albendazole treatment.
Results: Individuals with *P. falciparum* and *N. americanus* co-infection showed significantly stronger IgG3 responses to GMZ2 and GLURP R0 than those with *P.falciparum* only infection ($p<0.05$) at baseline. Two weeks after hookworm treatment there were significant decrease in levels of IgG1, IgG3 and IgM against GMZ2 ($p<0.05$), IgM and IgG3 for GLURPR0 ($p<0.05$), and IgG1against MSP3 ($p<0.05$). However, there were no observed significant changes inIgG3 and IgM levels against MSP3 antigen.
Conclusion: Treatment of hookworm infection resulted in significant reduction in malaria-specific IgG1 and IgG3 responses. The potential implications of hookworm infection and treatment on malaria vaccine efficacy needs to be assessed.

P74. DIFFERENCES IN IMMUNOLOGICAL PROFILE IN TWO WEST AFRICAN SETTINGS AS FUNCTION ENVIRONMENTAL CHANGES

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Background: Although variations of the immune system underlying disease protection or inflammatory disorders may follow genetically encoded programs, increasing evidences suggest that environmental influences, more than genetics, shapes immune system. Understanding the environmental impact on the immune system would be important to identify strategies to change trajectories toward long term, life-long protection from disease in specific geographical in the same experiments using identical reagents. Here we investigated the immunological profile in subjects from different rural settings of Africa.
Methods: Study participants were recruited from rural settings in Senegal (n=200) and Ghana (n=139) – two West African countries located respectively in a Sahelian semiarid zone hot and humid tropical environment – and screened for schistosomiasis, malaria, soil-transmitted helminths (STHs). From peripheral blood mononuclear cells (PBMCs), we investigated regulatory and activation phenotypes of dendritic cells (DCs), monocytes, T cells and T cells using flow cytometry. Following 3-day-culture with schistosomal worm and egg antigens, pro-inflammatory, ant-inflammatory cytokines as well as Th1 and Th2 cytokines were analysed from the culture supernatants using Luminex.
Results: The frequencies regulatory phenotypes PD-L1+ DCs and monocytes, CD163+ monocytes and Treg cells appeared significantly higher in Ghanaian whilst activation phenotype HLA-DR+ DCs and monocytes and CD25+ T cells were higher in Senegalese. Moreover, Senegalese elicited greater of TNF-α and lower IL-10 production as compared to Ghanaians. Taken together, these data indicate a greater activation and pro-inflammatory, and lower regulatory profile in Senegalese as compared to Ghanaian subjects.
Conclusion: Our results showed marked geographical differences in the magnitude of immune response, indicating that variation in immunological profiles might be attributed to environmental changes. Further investigations of the complex ecosystems underlying such difference would be important to identify strategies of protection from disease in specific geographical.

P75. PD-1+ T CELLS REFLECT ACTIVATED T CELL SUBSETS ASSOCIATED WITH LOWER REGULATORY PROFILE IN HIGH BURDEN OF HUMAN SCHISTOSOMIASIS

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Background: Beside regulatory T (Treg) cells, cell interactions include large variety of inhibitory signals that might be involved in modulating schistosome immune responses. The objective of this study was to investigate immunomodulatory axis using other immunomodulatory molecules involved in the interaction between innate and adaptive immune such as Program Death-1 (PD-1)/Program Death Ligands (PD-Ls) axis and B and T lymphocyte attenuator (BTLA) modulatory molecule.
Methodology: This study took place in northern Senegal where 200 individuals screened for schistosome infection and Schistosoma-related morbidity and distributed in four groups: 1) uninfected subjects (Neg, n = 37) single S. haematobium-infected (Sh, n = 25), single S. mansoni-infected (Sm, n = 46), and S. haematobium- and S. mansoni dual infected individuals (Mix, n = 92) presenting higher infection burden. Using flow cytometry, we investigated from the peripheral blood mononuclear cells (PBMCs) PD-L1, PD-L2 regulatory molecules and HLA-DR activation markers for antigen presenting cells (APCs) (dendritic cells (DCs) and monocytes) as well as PD-1, BTLA modulatory molecule, CD25 activation phenotype, and α4β7 gut homing maker for T cells.
Results: Our data have shown that frequencies of PD-1-expressing CD4+ and CD8+ T cells were significantly upregulated in mixed infection compared to controls and positively correlated with CD25 expression. The ratio PD-L1 or PD-L2 to HLA-DR in DCs, as well as BTLA to CD25 in CD4+ and CD8+ T cells showed significant lower regulatory profile in both APCs and T cells and significant higher α4β7-expressing Treg cells in mixed infection.
Conclusion: This the first study in human eliciting high PD-1+ T cells reflecting heightened activation state of T cells and lower regulatory profile in high schistosomiasis burden, which might coincide sequestration of Treg cells in tissues. Further investigation on the role of other immunomodulatory molecules may have implications in the control schistosomiasis.

P76. INTERLEUKIN (IL-6 AND IL-10) ARE UP REGULATED IN LATE STAGE *Trypanosoma brucei rhodesiense* SLEEPING SICKNESS

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Sleeping sickness due to Trypanosoma brucei rhodesiense has a wide spectrum of clinical presentations coupled with differences in disease progression and severity across East and Southern Africa. The disease progresses from an early (hemo-lymphatic) stage to the late (meningoencephalitic) stage characterized by presence of parasites in the central nervous system. We hypothesized that disease progression and severity of the neurological response is modulated by cytokines.

A total of 55 sleeping sickness cases and 41 healthy controls were recruited passively at Lwala hospital, in Northern Uganda. A panel of six cytokines (IFN-γ, IL1-β, TNF-α, IL-6, TGF-β and IL-10) were assayed from paired plasma and cerebrospinal fluid (CSF) samples. Cytokine concentrations were analyzed in relation to disease progression, clinical presentation and severity of neurological responses.

Median plasma levels (pg/ml) of IFN-γ (46.3), IL-6 (61.7), TGF-β (8755) and IL-10 (256.6) were significantly higher in cases compared to controls ($p<0.0001$). When early stage and late stage CSF cytokines were compared, IL-10 and IL-6 were up regulated in late stage patients and were associated with a reduction in tremors and cranioneuropathy. IL-10 had a higher staging accuracy with a sensitivity of 85.7 %(95% CI, 63.7%-97%) and a specificity of 100% (95% CI, 39.8%-100%) while for IL-6, a specificity of 100% (95% CI, 47.8%-100%) gave a sensitivity of 83.3% (95% CI, 62.2%-95.3%).

Our study demonstrates the role of host inflammatory cytokines in modulating the progression and severity of neurological responses in sleeping sickness. We demonstrate here an up-regulation of IL-6 and IL-10 during the late stage with a potential as adjunct stage biomarkers. Given that both cytokines could potentially be elevated by other CNS infections, our findings should be further validated in a large cohort of patients including those with other inflammatory diseases such as cerebral malaria.

P77. PREVALENCE OF DENGUE AND CHIKUNGUNYA VIRUS INFECTIONS IN NORTH-EASTERN TANZANIA: A CROSS SECTIONAL STUDY AMONG PARTICIPANTS PRESENTING WITH MALARIA-LIKE SYMPTOMS

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Background: In spite of increasing reports of dengue and chikungunya activity in Tanzania, limited research has been done to document the general epidemiology of dengue and chikungunya in the country. This study aimed at determining the sero-prevalence and prevalence of acute infections of dengue and chikungunya virus among participants presenting with malaria-like symptoms (fever, headache, rash, vomit, and joint pain) in three communities with distinct ecologies of north-eastern Tanzania.
Methods: Cross sectional studies were conducted among 1100 participants (aged 2-70 years) presenting with malaria-like symptoms at health facilities at Bondo dispensary (Bondo, Tanga), Hai hospital (Hai, Kilimanjaro) and TPC hospital (Lower Moshi). Participants who were malaria negative using rapid diagnostic tests (mRDT) were screened for sero-positivity towards dengue and chikungunya Immunoglobulin G and M (IgG and IgM) using ELISA-based kits. Participants with specific symptoms defined as probable dengue and/or chikungunya by WHO (fever and various combinations of symptoms such as headache, rash, nausea/vomit, and joint pain) were further screened for acute dengue and chikungunya infections by PCR.
Principal findings: Out of a total of 1100 participants recruited, 91.2% (n=1003) were malaria negative by mRDT. Out of these, few of the participants (<5%) were dengue IgM or IgG positive. A total of 381 participants had fever out of which 8.7% (33/381) met the defined criteria for probable dengue, though none (0%) was confirmed to be acute cases. Chikungunya IgM positives among febrile participants were 12.9% (49/381) while IgG positives were at 3.7% (14/381). A total of 74.2% (283/381) participants met the defined criteria for probable chikungunya and 4.2% (11/263) were confirmed by PCR to be acute chikungunya cases. Further analyses revealed that headache and joint pain were significantly associated with chikungunya IgM seropositivity.
Conclusion: In north-eastern Tanzania, mainly chikungunya virus appears to be actively circulating in the population. Continuous surveillance is needed to determine the contribution of viral infections of fever cases. A possible establishment of arboviral vector preventive control measures and better diagnosis of pathogens to avoid over-treatment of other diseases should be considered.

P78.TREATMENT WITH RECOMBINANT IL-12 PROTECTS AGAINST SECONDARY CYSTIC ECHINOCOCCOSIS

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Human cystic echinococcosisis a parasitic disease caused by the development in humans and other mammals by the larval form of Taenia *Echinococcusgranulosus*. It constitutes a serious public health problem in various parts of the world, particularly in Algeria. This parasitic helminth infection usually manifests as unilocular cyst(s) mainly located in the liver and/or lungs or other viscera of intermediate host. The variability and severity of the clinical expression of this parasitosis are associated with duration and intensity of infection. They are also related to the variety of human immunological responses to the hydatic antigens. The clinical evolution of these cysts is silent for several months, and the symptoms are not specific. Diagnosis is difficult and surgery constitutes the only therapy. The present studies aimed to identify anti hydatic molecules, which reduce the risk of relapse during hydatidosis. We investigate *in vitro,* Th1 (IFN-γ, IL-12); Th2 (IL-4, IL-13) and Treg (IL-10, TGF-β) effect on the protoscoleces of *Echinococcusgranulosus* in co-cultures with peripheral blood mononuclear cell (PBMC) and monocytes/macrophages (Mo/Mac) from hydatid patients (n=65). We observed 20 relapse cases. *Echinococcusgranulosus* protoscoleces were prepared from fertile hydatid cysts removed by surgery from hydatic patients. The supernatant was collected for nitrite (NO_2- +NO_{3-}) and arginine determination. PSC viability was assayed microscopically using eosin staining. Our results showed that NO levels were significantly higher in supernatants of co-cultures treated with IFN-γ, IL-12 when compared to untreated cultures supernatants ($p<0.01$). This production was concomitant with a decrease in the percentage of viable protoscoleces. However, the treatment of co-cultures with exogenous IL-4, TGF-β down regulated the NO production and enhanced protoscolices viability and arginine production. We observed with interest relapsing patients did not respond to protoscoleces stimulation and their PBMC and Mo/Mac did not secrete significant amounts of NO when stimulated with parasitic antigen. The reduction of nitrite production in relapsing patients correlates with the lack of IFN-γ and decrease in production of IL-12. Interestingly, addition of IL-12 to co-cultures of relapsing patients reduced protoscoleces viability. Collectively, our results show that IL-12 cytokines plays a relevant role in the scolocidal activity of mononuclear cells. Our finding may provide an alternative approach to the treatment of patients with hydatic disease.

P79. IMPAIRMENT OF MACROPHAGES PRESENTING ABILITY AND VIABILITY BY *ECHINOCOCCUS GRANULOSUS* ANTIGENS : OTHER FACETS OF THE IMMUNOSUPPRESSION

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Introduction/objectives: Despite advances toward an improved understanding of the evasive mechanisms leading to the establishment of cystic echinococcosis, the discovery of especially immunosuppressive mechanisms and related factors are of great interest in the development of an immunotherapeutic approach. Therefore we propose to elucidate immunosuppressive effects of bioactive factors contained in chromatographic fractions from hydatid cystic fluid (HCF) of *Echinococcusgranulosus*.
Material/Methods: Hydatid cystic fluid was fractionated by reverse phase chromatography. Non-specific Concanavalin A-driven proliferation of spleen cells was used to determine especially inhibitory fractions. Trypan blue exclusion test and flow cytometry analysis were performed to check whether highly inhibitory fractions and HCF have apoptotic effect on peritoneal macrophages. Western blot analysis was used to determine proteolytic effects of parasitic antigens on major histocompatibility complex (MHC) class II (I-a) contained in membrane proteins extract from macrophages.
Results: High concentrations of HCF and few of chromatographic fractions suppressed spleen cells proliferation. Fraction 7 and 35 were the highest inhibitory fractions. Specifically fraction 35 and to a lesser extend HCF induced apoptosis in peritoneal naive macrophages. However HCF and the fraction 7 altered proteolytically the expression of MHC class II molecules on peritoneal macrophages. The proteolytic molecule was identified as a serine protease. Macrophages taken at the chronic and end phase from cystic echinococcosis-infected mice were able to uptake and process C-Ovalbumine-FITC. These cells expressed a drastically reduced level of (I-a) molecules.
Conclusion: Among bioactive molecules contained in hydatid cystic fluid certain were able to trigger an apoptotic pathway in peritoneal macrophages while others altered proteolytically the integrity of MHC class II molecules expressed on these antigen presenting cells.The further molecular characterization of apoptotic and proteolytic factors might be useful to develop immunotherapeutic procedure leading to breaking down their inhibitory effects.

P80. A NOVEL HOMOZYGOUS CARD9 MUTATION IN A TUNISIAN PATIENT WITH DEEP DERMATOPHYTOSIS

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Deep Dermatophytosis (DD) disease is a severe, sometimes life threatening, fungal infection caused by dermatophytes and characterized by an extensive dermal and subcutaneous tissue invasion with frequent dissemination to the lymph nodes and occasionally to the central nervous system (CNS) Recently D Dhas been reported to be due, in the absence of immunosuppression, to an autosomal recessive (AR) CARD9 deficiency. Patients are also predisposed to recurrent mucocutaneous and invasive CNS infections by the *Candida species.*
Herein, we report the case of a 25-years old Tunisian female, born to non-consanguineous parents and with no family history of fungal infections. She has presented since early childhood with extensive and recurrent dermatophytosis. She had no history of recurrent oral thrush and was otherwise healthy. HIV infection was excluded and blood count revealed normal number of leukocytes with no lymphopenia and no eosinophilia. Immunological investigations, including immunophenotypic studies of lymphocytes populations, T-cell proliferation to mitogens and antigens, immunoglobulin levels and NBT test, were normal. Because of the extensive deep dermatophytic infection and the absence of HIV infection or immunosuppression, CARD9 deficiency was suspected and molecular investigation was conducted.
Patient's genomic DNA sequencing of *CARD9* gene revealed a novel homozygous missense variation (K179E) in the coil-coiled domain of the protein. The K179 residue is conserved across species. Moreover, the missense variation was predicted to be probably damaging with a score of 0.996by "POLYphen-2 and wasn't found in any of the various public databases searched (Human Gene Mutation Database, Ensembl) nor in 40 Tunisian healthy donors.
Most cases of CARD9 deficiency have been described in patients from North Africa. Recently, a homozygous mutation (Q289X) in the *CARD9* gene has been reported in 8 Algerian and 4 Tunisian patients from seven unrelated families with DD.A founder event responsible for this mutation has been demonstrated and estimated to have arisen approximately 975 years ago. Surprisingly, the patient herein reported, who belongs to the same geographic area as the four Tunisian patients described above did not bear the Q289X mutation but a novel variant. Familial segregation of this allele should be performed to confirm the AR inheritance and further investigations are needed to assess the consequence of this variation on protein function.

P81. TEMPORAL LINKS BETWEEN CYTOKINE PROFILE AND CANDIDA INFECTION IN TUNISIAN SEPSIS PATIENTS

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Introduction*:* Anti-inflammatory cytokines mainly IL-10, has begun to attract close attention in sepsis. The aim of our study was to investigate the kinetic of pro-inflammatory cytokine (TNF-α and IL6) and anti-inflammatory cytokine (IL10), produced during sepsis and their correlation with the Sequential Organ Failure Assessment Score (SOFA).

Patients and Methods: Sepsis patients were enrolled in a prospective descriptive study in the Military Hospital of Instruction of Tunis, Tunisia

Blood samples were collected at three times : hour 0 (H0),H24 and H48.H0 was the diagnosis time of sepsis. Serum levels of IL10, TNF-α and IL6 were measured with the technique of a solid-phase, two-site chemi-luminescent enzyme immune-metric assay (Immulite 1000, Simens, USA).

Results: Twenty six patients were included. We found that the SOFA score was not correlated with cytokines concentration, although a statistically significant difference was found in the IL6 levels between *candida* spp positive patients compared to *candida* spp negative (p=0.01) and a trend towards significance for IL-10 level at H24 (p=0.06).

Conclusions: Our findings highlight the role of IL6 and IL10at H24, in *candida spp* positive patients during sepsis.

P82. ADD TO PROCALCITONIN, ANTI-CARDIOLIPIN ANTIBODIES ARE THEY NEW BIOMARKERS OF SEPSIS?

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Introduction/Objective: The anticardiolipin antibodies (ACA) recognize cardiolipin, a major component of the inner membrane of mitochondria, but other anionic phospholipids : phosphatidylglycerol, phosphatidylinositol and phosphatidylserine. They are mainly associated with antiphospholipid syndrome (APS). The ACA has been reported in some infections. Their exact role in these cases is not completely understood. Few studies have investigated these antibodies in sepsis. The objective of our work is to study the evolution of ACA in sepsis and prognostic values.

Patients and methods: This prospective study was conducted in an intensive care unit over a period of 12 months. Two samples were taken for each patient at the time of diagnosis of sepsis (H0) and there after on the second day of hospitalization (H48). The enzyme immunoassay, indirect-type ELISA was used for the ACA highlighting to the two types of immunoglobulins IgM and IgG (Biosystem®, Barcelona, Spain). The normal value is 12 IU/ml for both isotypes. The SOFA score was calculated H0 and H48. We used SPSS version 11.0, and the Wilcoxon test software comparison nonparametric variables. It is considered statistically significantif $p < 0.05$. We also used the Pearson test for studying correlations.

Results: We collected 36 septic patients. In our study, three women and one man of 36were positive including two ACA IgG and two IgM. We noted a significant increase in IgG and IgM ACA between H0 and H 48 $P = 0.01$ and $P = 0.02$, respectively. We found a correlation between IgG ACA H0 to H48 and SOFA($R = 0.46$).

Conclusion: ACA may significantly increase in sepsis. They can be a contributing element to the management of septic patients. Their exact role in this disease remains to be determined. Further studies are needed to verify these results.

P83. ANTI-INFLAMMATORY EFFECTS OF THE POTASSIUM CHANNEL (Kv1.3) BLOCKER KALIOTOXIN IN EXPERIMENTAL MODEL OF SEPSIS: TOXINS TO THERAPEUTIC AGENTS

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Inflammation is a natural defense response that arises in any tissue against different harmful stimuli, including infection or exposure to microbiological toxins, such as lipopolysaccharide (LPS). Systemic inflammatory response syndrome caused by sepsis, which can lead to multiple organ dysfunction, is currently major issues that demand a prompt solution. Kv1.3 channels, highly expressed in T cells and macrophages, are attractive therapeutic targets to treat inflammatory and immunological disorders. Kaliotoxin2 (KTX2), a blocker of voltage-gated potassium channels (Kv) isolated from *Androctonus australis hector* scorpion venom, is highly selective for Kv1.3 channels. Therefore, we investigated the therapeutic properties of KTx2, via its immunosuppressive effects, to prevent the immunological disorders induced by lipopolysaccharide (LPS) administration in mice.

KTx2 was administered via the s.c. route, 30 min after the LPS (1 mg/kg; i.p.). The inflammatory response was assessed at 6 h after injection of LPS by evaluating NF-κB activity, vascular permeability changes, inflammatory cell infiltration, oxidative stress marker levels and histologic and functional analysis of the liver.

Obtained results revealed that LPS induced inflammatory disorders characterized by significant increase of NF-κB, activity, microvascular permeability, inflammatory cell infiltration and levels of nitric oxide in the hepatic homogenates. Moreover, significant alterations in the histological architecture of hepatic tissues were associated with increased serum levels of aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Treatment with KTx2, a selective blocker of Kv1.3, allowed to a significant reduction of inflammatory biomarker and prevents tissue damage induced by LPS.

We conclude that Kv channel blockers, such as KTx2, are a novel therapeutic target for treatment of inflammatory diseases.

P84. CROSS-PROTECTION STUDIES IN MICE IMMUNIZED WITH IRON-REGULATED PASTEURELLA MULTOCIDA SEROTYPE B: 3,4 VA

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Introduction/Objectives: Fowl cholera (FC) and Haemorrhagic septcaemia (HS) are specific economic diseases of avian and bovine species caused by certain serotypes of *Pasteurella multocida*. The FC causing serotypes include A:1, A:3, A:4 and A:5 and HS causing serotypes include B:1, B:2, B:3,4 and E:2. The immunological relationship between some of the common strains associated with FC and HS, and a prototype *P. multocida* vaccine strain B : 3,4 was evaluated using active mouse protection test.
Material/Methods: The cross-protective efficacy of the *P. multocida* serotype B:3,4 grown under iron-regulated condition, formalin-inactivated and adjuvanted with sodium alginate was examined in the mouse model by challenging the vaccinates with standardized virulent *P. multocida* serotypes A:1, A:4, B:2, B:3,4 and E:2.
Result: With the exception of serotype E:2, cross-protection with the prototype vaccine was observed against the challenge serotypes; and homologous protection was observed against serotype B : 3,4 challenge strain. All serotypes invariably produced death of the unvaccinated control mice. Whole cell bacteria proteins of the *P. multocida* B : 3,4 vaccine and the challenge serotypes were analyzed by SDS-PAGE and compared. The separation showed more than 12 clearly visible protein bands ranging from 26 to 100 kDa molecular weights. On the basis of stain intensity, the major protein bands occurred between the 30 kDa and 40 kDa of the strains.
Conclusion: From this limited study the prospect of a single-strain vaccine that is cost-effective and capable of inducing cross-protection and eliminating antigenic competition may be feasible for use in both poultry and cattle. Further research may be of value toward vaccine development.

P85. PREVALENCE OF INFECTIOUS AGENTS IN PATIENTS WITH AUTOIMMUNE DISEASES: A CASE-CONTROL STUDY ON *HELICOBACTER PYLORI, RICKETTSIA CONORII* AND *TOXOPLASMA GONDII*

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Introduction/objectives: Autoimmune diseases (AID) arise from the interaction of genetic susceptibility and environmental exposures. Among environmental factors, infectious triggers have been implicated and studied extensively. Several mechanisms by which infectious agents may cause AID have been proposed, these include molecular mimicry and epitope spreading. Among infectious agents implicated, *Toxoplasma gondii (T.gondii), Helicobacter pylori (H. pylori) and Rickettsia conorii (R. conorii)* have received particular attention.
We aimed to determine rates of seropositivity for IgG antibodies against a number of infectious agents in different AID groups: skin autoimmune bullous diseases "Pemphigus foliaceus (PF) (n=93) and Pemphigus Vulgaris (PV) (n=32), Inflammatory Bowel Disease (IBD) (n=25), Systemic Lupus Erythematosus (SLE) (n=51) patients and 146 healthy subjects from south Tunisia.
Materials/methods: Two hundred and twenty-six (226) patients with 4 AIDs collected from Hedi Chaker University Hospital of Sfax were recruited. All patients fulfilled the universal diagnostic criteria for each specific autoimmune disease. Serum IgG antibody against *H. pylori* was measured using enzyme-linked immunosorbent assays. IgM and IgG antibodies against *R. conorii* were detected by microimmunofluorescence test. Anti-T. gondii IgG antibodies were measured using immunochimiluminescence.
Results: There was a markedly significantly higher prevalence of *T. gondii* infection in IBD patients (52%, P<0.001), SLE patients (53%, P<0.001) and PV patients (68.75%, P=0.014) compared with controls (45.2%). The prevalence of *H. pylori* infection was significantly (P=0.038) lower in IBD patients (56%) than in controls (82.76%). There was no statistically significant difference between AID patient's groups for *R. conorii* infection.
Conclusions: Our study emphasizes the link between infection and several AIDs. Further, studies are needed to identify the mechanisms involved in this relationship.

Allergy

P86. THE IMPACT OF THE ENVIRONMENT IN THE DEVELOPMENT OF ALLERGIC DISEASES IN THE CASE OF THE CITY OF BENI MELLAL MOROCCO

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Background: Today, the number of allergy is increasing in industrialized countries. The World Health Organization (WHO) classifies allergic diseases to be the fourth in the world of affections. WHO considers that these diseases are a major public health problem in terms of quality of life, loss of work days, teaching, drug and even mortality cost.
The frequency of respiratory allergies including asthma and allergic rhinitis due to pollens is increasing in the young and urban dwellers in developed countries.
Methods: For this project, we chose Polydisciplinary Faculty of Beni-Mellal (PFBM) located in the center of Morocco as a place for the study of pollen allergy. It is a public institution of higher education that receives thousands of students from different parts of the region which is characterized by its vegetation richness**.**
The project was to study pollen allergy in PFBM in an effective sample of 529 randomly chosen within a range of about 7,000 students. A survey was made for descriptive studies.
Results: The percentage of students allergic to pollen surveyed in the PFBM was 39%. This percentage was within the confidence interval of all students in the allergic PFBM [35%; 44%] estimated 5% error risk. This result proves that our sample was representative. We also found that the allergic to pollen presents a significant percentage of 40.5% for female compared to 36.6% for male. Our study shows that the olive tree is the main allergen causing pollen allergy. The majority of the surveyed students are allergic to one or two types of plants. The most common symptoms of pollen allergy among its students are the nasal symptoms (sneezing and nasal itching).This study shows that most students have allergies in the spring season. Our study shows also that the cross-reactivity between pollen and food was the most dominant
Conclusions: The high percentage of students allergic to pollen surveyed in the PFBM might be explained by the wealth of the region in vegetation. We suggested that the difference seen between female and male is due to physiological and hormonal differences between the sexes. Olive tree was the main allergen; this can be explained by the richness of the region of Beni-Mellal-Khénifra with this plant.

P87. THE EFFECT OF CD14, TLR2 AND TLR4 GENE POLYMORPHISMS ON TUNISIAN ASTHMA

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Introduction: Allergic asthma is a multifactorial disease in which genetic and environmental factors are involved. Its mode of transmission is complex involving several genes identified by linkage and association studies requiring confirmation by functional studies.
Materials and methods: This case/control study was performed to identify A possible association between some SNPs and the susceptibility to allergic asthma as well as the response to the specific immunotherapy in Tunisian population. Thus, functional genetic polymorphisms: TLR2 (A753G), TLR4 (A299G), CD14 (-159 C/T), FcεR1-α (-95 T/C), FcεR1-β (-109 C/T) and PTPN22 (R620W) are analyzed in 213 asthmatic patients (105 adults and 108 children) and 323 normal control subjects.
Results: The results showed that TLR4 (A299G), CD14 (-159 C/T), FcεR1-α (-95 T/C) and FcεR1-β (-109 C/T) SNPs are not involved in allergic asthma predisposition in Tunisians. Nevertheless, TLR-2A and PTPN22 620W variant alleles were significantly more frequent in patients compared to controls. Analytical study showed the clinical impact of some SNPs with a significant association between homozygous wild genotype TLR-2 G/G and early onset of the disease ($p = 0.003$). In addition, correlation between the variant allele CD14 T and the positivity of total and specific IgE ($p = 0.028$ and $p = 0.011$ respectively) as well as the early onset of allergic symptoms is proved. The C/C (-95T /C FcεR1-α) genotype, is also, associated with uncontrolled severe asthma and lower levels of specific IgE compared to other genotypes ($p = 0.015$). However, no correlation was found between the different SNPs studied and the therapeutic response following desensitization cures.
Conclusion: TLR-2A and PTPN22 620W variant alleles deserve to be added to the immunogenetic factors spectrum of allergic asthma predisposition among Tunisians. The functional impact of CD14 (-159 C/T) and FcεR1-α (-95 T/C) SNPs should be confirmed by real-time quantitative studies in order to evaluate the variation of these molecules expression according to clinical presentation of the disease. A prospective cohort on a larger number of patients deserves to be carried out in order to elucidate the role of the innate immune receptor especially in the variation of the immune response following desensitization cures.

P88. ASSOCIATION BETWEEN VITAMIN D METABOLISM GENE POLYMORPHISMS AND RISK OT TUNISIAN ADULTS' ASTHMA

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Background: Several studies have shown a strong correlation between the serum vitamin D level and asthma severity, increased airway hyper responsiveness, reduced glucocorticoid response, and deficits in lung function.
Objectives: We aim to investigate whether the genetic background plays a role in the relationship between vitamin D level and the severity of asthma by targeting 5 SNPs of vitamin D metabolism pathway in a population of Tunisian adult asthmatics.
Material and Methods: We chose 3 genes encoding key components of the vitamin D pathway, which include: CYP2R1 (enzyme encodes the microsomal 25-hydroxylase that catalyses the C-25hydroxylation of vitamin D3), CYP27B1 (enzyme catalyzes the synthesis of active 1, 25-dihydroxyvitamin D3 in the kidney) and GC (coding for the vitamin D binding protein which transports 25(OH)D and other metabolites in blood to target organs). A case-control study including 154 Asthmatic Patients and 154 healthy subjects mean age (45.5+-9.83). Serum 25-hydroxyvitamin D level was measured by ELISA. The investigated polymorphisms of GC gene were analyzed using the PCR-RFLP method, while rs10741657 and rs12794714 for CYP2R1 gene and rs10877012 of CYP27B1 gene were genotyped using TaqMan PCR genotyping.
Results: We divided our participants into different subgroups according to Vitamin D level, sex, age, and smoking habits. We found that the presence of at least one copy of the rs12794714 allele was associated with lower risk of developing asthma [OR = 0.61, CI (0.38 -0.96).P =0.03]. We compare the association of asthma severity and SNPs' genotypes, we found that the rs12794714 is a protector factor against asthma severity (protector to having severe asthma [OR =0.5(0.27-0.95) P= 0.03)]. However, having TG genotype inrs10877012 of CYP27B1 gene is a risk factor for developing Mild or Moderate asthma for healthy controls [OR =1.89(1.09-3.29) P=0.02]. The subdivision according to smoking habit revealed that the presence of the rs10877012 TT genotype was associated with a higher risk of asthma development for the non-smoker patients [OR = 7.13(2.46-23.70) P=0.0001]. When we classified the population according to sex, our results showed that rs10877012TT was a risk genotype for women subjects [OR = 2.81(1.58 -5.05) P =0.0003].
Conclusion: In Addition of environmental factors and serum Vitamin D level in adults' asthmatics, we found that rs12794714 SNP of CYP2R1 gene and rs10877012 SNP of CYP27B1 gene were associated with asthma risk.

P89. NOD2 GENE VARIANT IN TUNISIAN CHILDHOOD ASTHMA

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Asthma is a heterogeneous inflammatory disorder characterized by hyper-responsiveness, obstruction, and infiltration of inflammatory cells in the airway. The nucleotide-binding and oligomerization domain 2 (NOD2) can activate antiviral responses of innate immunity after infection with respiratory syncytial virus that is associated with susceptibility to asthma. They also induces the activation of NF-κB and mitogen-activated protein kinases (MAPKs), subsequently leading to the production of proinflammatory mediators.
In our study, we aim to investigate the association of the 1007fs polymorphism with asthma susceptibility in the Tunisian population. 1007fs SNP is a frameshift alteration that contribute to a stop codon and then to truncation of the NOD2 protein.
Our population include 90 childhood asthmatic patients and 100 healthy controls. 1007fs variant was screened by Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) methods. We applied standard statistical procedures to assess associations between asthma or atopic phenotypes and CARD15 genotypes.
Our results did not found any association between 1007fs SNP and asthma susceptibility ($p>0.05$). We did not identify a characteristic mutation (Leu 1007fs insC: 3020insC in exon 11) in the Tunisian population. Stratification analysis did not show any significant association. Our findings showed that the frequency of the CARD15 1007fs variant in the Tunisian population is significantly lower than that observed in the German, Japanese, African Americans and Italian populations. These differences may result from racial and ethnic differences. Additionally, the NOD2/CARD15 gene has been described to be associated with diseases such as breast cancer, inflammatory bowel, rheumatoid arthritis and the chronic obstructive pulmonary disease (COPD).
In conclusion, this study showed that the distribution of *NOD2* rs2066847 genotypes is equally between Tunisian asthmatic patients and the controls.

P90. ASSOCIATION OF STIP1 VARIANTS WITH ASTHMA SUSCEPTIBILITYAND TREATMENT RESPONSE TO INHALED CORTICOSTEROIDS IN TUNISIAN WOMEN

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Background and Aims: Inhaled glucocorticoids are the most widely used medications to treat airway inflammation related to bronchial asthma. Pharmacogenetic studies have identified candidate genes that interact with response to Inhaled Corticosteroid treatment. Stress-inducible phosphoprotein 1(STIP1) genetic variants are found to be associated with response to glucocorticoid therapy in Caucasian asthmatic subjects. In this study we aimed to evaluate the association of STIP1 single nucleotide polymorphisms with asthma susceptibility and inhaled corticosteroid (ICS) response in Tunisian women.

Methods: We genotyped two single nucleotide polymorphisms of STIP1 in 101 asthmatics receiving ICS and 102 healthy controls. Furthermore, we analyzed the association of STIP1 variations with ICS response in 38 moderate-to-severe asthmatics.

Results: The TT genotype rs2236647 was associated with increased asthma risk (OR=2.51, 95% CI=2.203–5.417, P=0.0132), and independently associated with higher FEV1 baseline at the first measurement. The STIP1 rs2236648 TT genotype was significantly associated with asthma related phenotypes including higher ICS (step3 treatment according to GINA report), bad observance of treatment and higher risk of development allergy to dust in asthma patients.

Conclusions: STIP1 variations are associated with asthma susceptibility and asthma related -phenotypes in a Tunisian adult women. Moreover, STIP1 variations may affect ICS treatment response.

P91. SYSTEMIC PRODUCTION OF NITRICOXIDE DURING ALLERGIC RHINITIS, AND ALLERGIC ASTHMA: IMMONUMODULATION BY THE HELMINTH *ECHINOCOCCUS GRANULOSUS*

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Introduction/objectives: The effect of helminth infections on inflammatory and allergic diseases is still in conclusive.
Moreover, here is considerable evidence suggesting that nitricoxide (NO) plays a significant role in the physiopathology of allergic disease. In this sense, the aim of our study is to evaluate the production of NO in Algerian patients with allergic rhinitis, and allergic asthma. Moreover, we investigated *in vitro* the immunomodulatory effect of the laminated layer (LLs, outside layer of parasitic cyst) of the helminth *Echinococcusgranulosus* on NO production in PBMC from allergic patients.
Material/Methods: The NO production was evaluated in plasma and culture performed with peripheral blood mononuclear cells (PBMC) from patients with allergic rhinitis, allergic asthma and healthy donors. We have also investigated the effect of LLs and IL-4 on NO production by the same cells.
Results: Our results revealed a significant difference (P<0.01) in plasmatic NO levels between the two groups of patients (with asthma and allergic rhinitis) and the healthy subjects. In addition, no statistically significant differences were found between patients with allergic asthma (severe, moderate and mild) and allergic rhinitis. Interestingly, we observed that LLs reduced NO production *ex vivo*. Indeed, were ported a strong significant decrease (p<0.0001) of NO level in PBMC culture compared to the LLs-untreated culture. This result was confirmed using IL-4 which indicated the same effect such as LLs.
Conclusion: Our data confirm the implication of NO in the pathogenesis of allergic asthma and allergic rhinitis. They also support the hygienic hypothesis suggesting that *Echinococcus granulosus infection* like other helminthes prevents and/or modulates inflammation during inflammatory diseases like asthma. The potential therapeutic or preventive effect of the Laminated Layer in allergic diseases remains to be investigated in a mouse model of allergic diseases.

P92. COMPONENT-RESOLVED DIAGNOSTICS IN PEDIATRIC FOOD ALLERGY : BOS D8 AND GALD1 COMPONENTS ARE ASSOCIATED WITH SEVERITY AND/OR PERSISTENCE IN COW'S MILK AND HEN'S EGG ALLERGY

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Introduction: Accurate diagnosis of food allergies in children is important for assessing the risk of systemic reactions, evaluating the chances of tolerance induction and establishing the necessity of dietary restriction. We tested the usefulness of component-resolved diagnostic in Tunisian children with food allergy and /or sensitization.

Material and Methods: Our study included 24 children sensitized to the major pediatric food allergens (milk, egg, and peanut): 11 cases of allergy to cow's milk proteins, 6 cases of allergy to hen's egg white, 2 case of mixed food allergy (milk and egg) and 5 cases of peanut sensitization. A multiplex kit (Pediatric Profile) testing specific IgE to molecular subcomponents of cow milk (Bos d4, d5 Bos, Bos d8, Bos of Bos d6), egg white (Gal d2, d1 Gal Gal d3, d4 Gal), peanut (Ara h 1, Ara h2, h3 Ara, Ara h9) and Birch (Bet v 1) was used.

Results: Bos d8 and Gal d1 were associated with severity and/or persistence of respectively milk and egg white allergy: Sensitization to Bos d8 (casein) was found in all patients with severe persistent cow's milk allergy (7/10). Sensitization to Gal d1 (ovomucoid) was found in the only patient with severe hen's egg allergy.

Heat-sensitive components of egg white (Gal d2 and Gal d3) were responsible for sensitization in 5 patients, only one of them had an exclusive allergy to these components which suggests to him a solution with the egg cooking. No peanut components were detected in patients supposed to be sensitized to this food.

Conclusion: Our results confirm the diagnostic, prognostic and therapeutic interest of testing molecular subcomponents responsible for cow's milk and egg white allergy in children. Considering peanut sensitization, it seems to be rare in our pediatric population.

P93. COW MILK ALLERGY (CMA) IGE MEDIATED: ABOUT 30 CASES

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Introduction: Allergy to cow's milk proteins (APLV) occupies an important place in food pediatric allergology, it affect about 2 to 3% of infants. This is the most common and best known of the child's food allergies, since the young child is fed exclusively with milk for several years. Most often the mechanism involved is an IgE mediated hypersensitivity reaction, but it may also involve other classes of antibodies and / or cellular mechanisms. The associated symptoms are varied and may cover manifestations that affect the skin, respiratory system and digestive system. In the presence of a clinical symptomatology suggestive, the diagnosis of APLV is retained in the presence of a positive prick test and / or IgE specific cow's milk higher or equal to 0.35 KU / L The objective of our study is to determine, through this series of 30 Algerian children with APLV IgE mediated, the diagnosis aspects, the profile of allergenic proteins to cow's milk, to demonstrate possible food allergies Associated, and to identify cross-reactivity with soy protein. **Methods:** The serum of the 30 children with APLV were tested for anti-PLV-specific IgE, including IgE specific for cow's milk, but also for the specific anti-protein IgE constituting the milk: casein, β-lactoglobulin and A-lactalbumin. The assays were performed by chemiluminescence technique on Immulite 2000 xpi. **Results:** The distribution of patients according to sex shows that **23** patients (77%) are male and 7 patients (23%) are female, With a sex ratio of three man for a woman 3♂ / 1♀ (3.28≈3) in favor male Predominance. The frequence of family history of atopy is estimated to **50%** of cases. Skin manifestations are the most frequent, with 28 cases (93.33%), urticaria (73.33%), angioedema (30%), erythema (13.33) and Atopic dermatitis (10%) followed by digestive manifestations 8 cases (26.67%) with diarrhea type (16.67%), vomiting (13.33%) and oral syndrome %) And last asthma respiratory manifestations 7 cases (23.33%) and systemic anaphylactic shock 1 case (3.33%). **40%** of our patients had pricks tests and all returned positive and they a, Only one patient had a positive prick test with specific IgE values below the detection of the threshold. **29** patients (97%) had positive IgE specific IgE levels (≥0.35 KU / L) with only one patient (3%) **who returned negative** with a specific milk IgE level of whole negative cow (<0.35 UK / l). When we compered the positivity rate of specific IgE anti-casein, anti-α-lactalbumin and anti-β-lactoglobulin we did not find any significant difference,the same for the average but we note that the average of specific IgE against casein was the highest. So we conclude that **casein** is the most frequent allergen in our series. Most patients were sensitized to two or more proteins of cow's milk. The correlation between theaverageIgEspecificanti-casein, anti-α-lactalbumin and anti-β-lactoglobulin showed significant results **(P<0.0001)**, the casein Correlate perfectly with α-lactalbumin and it less Correlate with β-lactoglobulin . We conclude that sensitization to casein, α-lactalbumin and β-lactoglobulin appears to be closely related. We divided our patients into two groups according to age, in the first group the subjects had more than 2 years, while in the second group they had less than 2 years.There were 18 (60%) patients in Group 1 and 12 (40%) patients in Group 2.We did not find any significant difference between the specific IgE levels in the two different age groups **(P > 0.05)** but we found that the more than 2 years had specific IgE anti- Cow's milk, anti-casein and α-lactalbumin increased in comparison with the other group. As for the associated food allergies, we found that 26.67 % of our patients are sensitized to the proteins of the egg. The cross-reactivity with soy the Correlation between IgE specific levels for whole cow's milk and soya showed no significant differences .We note an associated sensitization between milk and soy is infrequent it concerns only 2 patients. And finaly we did not found any significant differences between IgE specific level anti-casein, anti-β-lactoglobulin and anti-α-lactalbumin levels in patients with digestive manifestations. However, the team of Paloma Poza-Guedes et al found that children with exclusive digestive manifestations were sensitized to β-lactoglobulin. **Conclusion:** APLV is a common condition and is one of the three most common food allergies in children. Its diagnosis is widely reported but rarely confirmed. In developed countries it is difficult to assess the prevalence of APLV since there is a large difference between the prevalence of APLV self-perceived by questionnaire and that of the confirmed APLV. In Algeria, the epidemiological, diagnostic and immunological aspects of ALPV are poorly defined due to the lack of studies based on high-performance diagnostic methods.

P94. INTERLEUKIN 4, INTERLEUKIN 13 AND GAMMA INTERFERON IN PATIENTS WITH FOOD ALLERGY

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Introduction: The food allergy (FA) is a problem of public health because of its high prevalence in the world. The objective of this work was on one hand to study total IgE in patients with FA and on the other hand, to measure three types of cytokines IL-4, IL-13 and interferon gamma (IFN-γ) and to determine the presence of a correlation between the total IgE levels and the titre of cytokines studied.

Patients and methods: The study included 97 subjects divided into 2 groups. The first one is a control group of 51 subjects. The second group consists of 46 patients with food or respiratory allergy or both. The study is conducted using a well-developed questionary. At the same time, biological tests (total Ig assay, IL-4, IL-13 and IFN-γ assays) were performed.

Results: The mean age of patients is 30 years and that of the control group 29 years. The mean of total IgE levels were 432.78 IU/ml in patients and 141.14 IU/ml in the control group. The mean of IL-4 titers in patients was significantly higher than that of the control group (180.21 vs. 116.54, p = 0.0003). The same result was found for IL-13 (32.44 vs 21.76, p = 0.04) and IFN-γ (19.01 vs 9.15, p = 0.003). A correlation was found between total IgE levels and IL-4 titers (r = 0.264) and between total IgE levels and IL-13 titers (r = 0.770). However, no correlation was found between total IgE levels and IFN-γ titres. The food that causes the most FA is shrimp (17.39%) followed by egg white (15.21%). Among 46 patients affected by allergy, 10 (21.73%) had an allergy to a single food. Allergy to two or three foods was present in 15 patients. 50% of peanut-allergic patients were also pea-allergic and 37.5% were soybean.

Conclusion: Due to the diversity of the allergens, the presence of cross-reactivity between foods and the sensitivity and specificity of the techniques used, it remains essential to establish an appropriate diagnostic approach to food allergy.

P95. FATAL CASE OF TOXIC EPIDERMAL NECROLYSIS CAUSED BY PRISTINAMYCINE

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Background: Pristinamycin is a streptogramin antibiotic with a similar spectrum of activity to macrolides and lincosamides for Gram-positive bacteria, with a reduced risk of drug resistance. Common side effects of Streptomycin include nausea, vomiting and stomach upset. Cutaneous side reactions due to pristinamycin, are rare and presenting as maculopapular eruption, erythroderma, and angioedema.

Method: Herein, we report a rare case of fatal pristinamycin-induced toxic epidermal necrolysis (TEN)

Results: A 76-year-old woman with a history of hypertension was admitted in Intensive Care Unit for Skin detachment. On admission, the patient's vital signs included temperature 39°c, pulse rate 125/min, blood pressure 110/90 mm Hg, and respiratory rate 20/min. The entire body skin was involved (approximately 70%) with positive Nikolsky sign. Biopsy and clinical features were consistent with TEN. The patient developed this mucocutaneous eruption 3 days after the onset of pristinamycin. Despite intensive care, the evolution was rapidly fatal and patient died at day 2 of multiorgan failure. TEN or Lyell's syndrome is a rare, potentially life-threatening mucocutaneous disease, usually caused by the administration of a drug and characterized by acute necrosis of the epidermis. The drugs most frequently incriminated are sulphonamides, nonsteroidal anti-inflammatory drugs, chemotherapics, lactam antibiotics, and anticonvulsants.

Death rate in TEN is high and can reach 25–35% mainly due to extensive areas of the affected body surface, fluid loss and electrolyte abnormalities and secondary infections. The patient's clinical state, and the time of medication therapy contribute to the mortality rate. In the literature only one case of fatal pristinamycin-induced-TEN has been described with difficulties of identifying the cause of this adverse drug reaction in polymedicated patient. In our case and according to the Naranjo probability scale, pristinamycin-induced TEN was probable.

Conclusion: TEN is rare during treatment with pristinamycin but clinicians should be vigilant of this side effect that can be rapidly fatal.

P96. SELECTIVE ALLERGY TO CEFAZOLIN CONFIRMED BY CUTANEOUS SKIN TESTING

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Background: Cefazolin is a widely used first generation cephalosporin especially in preoperative. Allergic reactions related to this molecule have increased. Skin testing is an easy and safe tool used in patients suspected of allergic reactions and to to determine the drug and / or the incriminated molecules and guide the prescription of another beta-lactam as a therapeutic alternative.
Case study: We report a case of 30-year-old female patient, with no relevant pathological history or allergy to drugs, who presented a pre-operative allergic reaction with a generalized rash and severe hypotension. The diagnosis of anaphylactic shock secondary to the administration of cefazolin was suspected. Skin prick tests were performed after 3 months of the reported event. Results were positive for cefazolin but were negative to amoxicillin, ampicillin, cefotaxime and cefuroxime. A reintroduction of amoxicillin was made without any incident.
Discussion: Allergy to penicillin and other beta-lactams is the most common cause of anaphylactic reactions. Cephalosporins can cause allergic reactions mediated by IgE. However, cephalosporin is known to be less allergenic than penicillins. The frequency of cutaneous reactions to cephalosporins is approximately 1 to 3% and the frequency of anaphylaxis is rare, ie 0.0001-0.1%. In cases of IgE-induced allergy to cephalosporins, skin tests may be helpful in the diagnosis. The risk of cross-reactivity to other beta-lactams necessitates an allergological investigation before prescribing another beta-lactam as an alternative. The first-generation cephalosporin has a structure that is more similar to that of penicillin, with the exception of cefazolin which has a side chain different from penicillin. In our case, it is a selective reaction to cefazolin without the involvement of other beta-lactams. This implies that the R1 side chain of cefazolines, rather than the beta-lactam nucleus, plays an essential role in IgE-type allergic reactions to this molecule.
Conclusion: A patient with a history of allergy to a cephalosporin such as cefazolin may receive another cephalosporin with a different side chain or even a penicillin drug. Skin tests are important to guide the choice of molecules.

P97.CLOZAPINE-INDUCED MYOCARDITIS COMPLICATED WITH DILATED CARDIOMYOPATHY AND HEART FAILURE

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Background: Clozapine is largely used for refractory schizophrenia. Nevertheless, its use is limited due to potentially life-threatening adverse effects, including leukopenia, fatal agranulocytosis and toxic megacolon. Myocarditis and cardiomyopathy are rarely reported complications of clozapine treatment. We report a case of clozapine-induced myocarditis complicated with dilated cardiomyopathy and heart failure .

Case report: A 45-year-old male with no cardiac history or cardiovascular risk factors, was stared on clozapine for resistant schizophrenia. Two weeks after the onset of drug therapy, he presented with dyspnea and tachycardia. The diagnosis of myocarditis was suspected and was confirmed due to an elevated cardiac enzyme levels and to transthoracic echocardiography showing heart failure with ejection fraction of 45 % and hypokinesia of the left ventricular. The diagnosis of clozapine-induced myocarditis complicated with dilated cardiomyopathy and heart failure was probable.

Discussion: Clozapine is an atypical antipsychotic drug, largely used in the treatment of refractory schizophrenia because of its greater efficacy and lesser tendency to induce extrapyramidal side effects when compared to conventional neuroleptics . However, several adverse effects are reported with the drug including cardiotoxicity. Hypersensitivity myocarditis and myocardipathy are a rare but serious life-threatening adverse effects of clozapine. Mortality averages approximately 25%. Myocarditis has been of particular interest because of its dose-independent outcome.The incidence of early (≤2 months) myocarditis ranges from <0.1 to 1.0 %. In our patient, the occurrence of myacarditis was within two weeks after clozapine initiation. Diagnosis was suspected on ECG changes, elevated cardiac enzyme levels and echocardiographic evidence of ventricular failure. Safety of clozapine rechallenge remains controversial. The exact mechanism by wich clozapine cause myocarditis remains uncertain: it is hypothesized that clozapine induces an IgE-mediated hypersensitivity reaction that is characterized by myocardial eosinophilic infiltrates. Some authors attribute the cause of myocarditis to direct toxicity of clozapine by drug accumulation on myocardiocytes.

Conclusion: Clinicians should be aware of the risk of myocarditis occurring during clozapine therapy. Its early onset should not delay the prompt management of this severe adverse event.

P98. IGE SENSITIZATION IN AUTISM CHILDREN

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Introduction: Autism Spectrum Disorder (ASD) includes a set of disorders characterized by a deficit in communication, social interactions and stereotypical behaviors. Recent studies suggest a higher frequency of atopic diseases (asthma, allergic rhinitis, food allergies ...). The aim of our study was to assess IgE sensitization to the most frequent allergens in children with ASD.

Material and methods: The study involved 30 children with ASD and 39 controls. The total IgE as well as the IgE specific to the food (FP2, FP5 and FP51) and respiratory (HP1 and GP1) allergen panels were determined in all children by chemiluminescence technique on the Immulite 2000Xpi.

Results: There was no significant difference between children with ASD and control in total IgE levels (high IgE level in 66.7% TSA vs 51.3%). Overall analysis of IgE sensitization to common allergens showed a higher frequency in ASD children (65.6% ASD versus 28.9% control, p = 0.002). Also, sensitization to house dust allergens (D1, D2 and I6) and to food allergens of FP5 panel (F1, F2, F4, F13 and F210) was more common in children with ASD (46.87% vs 21.05% and 37.5% vs. 13.16%, respectively, p <0.05). The most common sensitizing respiratory allergens were D1 and D2 mites in both populations. For eating allergens, egg white was the only allergen sensitizing in children with ASD.

Conclusion: Our study found an increased IgE sensitization to common respiratory and food allergens in ASD children.

Primary immunodeficiencies

P99. REFERENCE VALUES OF LEUCOCYTES EXPLORATIONS FOR THE DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES IN MOROCCAN POPULATION

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Primary immunodeficiency diseases (PIDs) represent a large and heterogeneous group of more than 120 different entities, most of which have now been genetically characterized. In the suspicion of immunodeficiency, the exploration of the blood lymphocyte subpopulations is the basic tools in the diagnostic process of PIDs. However, the reliable interpretations of the data resulting from this exploration require comparison of patient's results to reliable reference values. The routinely used reference values are established within representative populations of healthy subjects. Values for Caucasian cohorts are usually utilized, but could be inappropriate for Moroccan population. Furthermore, the biological explorations of the PIDs essentially concern patients suffering from evocative clinical manifestations of PIDs. However, the pathological mechanisms associated with these clinical manifestations can affect the values of the explored parameters even in patients with non-PIDs diseases.

The aim of this study is to establish the age-matched normal reference values of blood lymphocyte subpopulations for Moroccan population and to verify the accuracy of these reference values for the diagnosis of PIDs affection.

We measured lymphocyte subpopulations concentrations by flow cytometry for 75 healthy subjects and 322 non-PIDs patients suffering from DIPs-evocative clinical manifestations. We first compare the normal reference values of our population to those of other populations. We also compare values from patients with non-PIDs diseases to the normal reference values.

Moroccan normal reference values show to be slightly different from those of other populations. Furthermore, values from 44% of non-PIDs patients are significantly lower than normal reference values.

These results have an important interest in the improvement of the interpretation of the lymphocyte subpopulations concentrations values surrounding the threshold values of the references intervals routinely used in the diagnosis of PIDs within Moroccan population.

P100. MONOCLONAL GAMMOPATHY IN SCID PATIENTS PRIOR TO HEMATOPOIETIC STEM CELL TRANSPLANTATION: A REPORT OF 3 TUNISIAN PATIENTS

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Severe combined immunodeficiencies (SCID) are a group of genetic diseases characterized by a profound lack of both T and B cell immunity. SCID patients develop severe and recurrent infections. Monoclonal gammopathy (MG) is secondary to uncontrolled monoclonal B-cell activation and proliferation. MG may occur in SCID patients after hematopoietic stem cell transplantation (HSCT). Herein we report three SCID patients presenting with monoclonal gammopathy prior to HSCT.

The first patient had a history of BCG disease and presented at the age of 4 months with fever and cytopenia. Patient 2 was a 3 months old female who suffered from recurrent diarrhea and showed thymic atrophy with lymphopenia. Patient 3 was a 2 years old female with a history of cutaneous and respiratory infections as well as diarrhea. HIV infection was excluded in the three patients. Immunophenotype analysis of lymphocyte subsets as well as T-Cell mediated responses to antigens (Anti-CD3 and tuberculin) and mitogen (phyto-hemagglutinin: PHA) have been assessed in these patients. Serum protein electrophoresis and evaluation of immunoglobulin levels were performed. Immunofixation was also achieved.

All patients displayed a profound LcTCD3 count decrease and a very low response to mitogens and antigens matching with SCID clinical and biological picture. Patient 1 and Patient 3 had a T-B+NK+ profile and Patient 2 was T-B-NK+. Patient 1 and 2 displayed an unusual immunoglobulin distribution with elevated IgA. Serum protein electrophoresis and Immunofixation revealed IgA Lamba MG in Patient 1 and IgA kappa MG in Patient 2. Serum protein electrophoresis showed for Patient 3 a monoclonal peak in the gamma region and Immunofixation revealed an IgD lambda MG.

Only two cases of MG in SCID patient prior to HSCT have been reported to date. The mechanisms leading to MG in SCID are speculative. Maternal engrafted B cells with uncontrolled proliferation is one of the reported hypothesis. The decline of T-cell mediated surveillance in this context might pave the path to B-cell activation. Although benign, these MG raise the concern of malignant transformation.

P101. CHORIORETINAL DISEASES IN HUMAN IMMUNODEFICIENCY

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Introduction: Acquired human immunodeficiency virus (HIV) is now the best-known human virus. This affection affects all the organs of the individual by an opportunistic affection or a tumor. Of these organs, the eye is affected in more than 50% of cases. Chorio-retinitis (CR) involvement is the most frequent occurrence of ocular manifestations.
This study investigated the occurrence of chorioretinal diseases and the different therapeutic strategies in HIV infected patients.
Methods: Retrospective study carried out over a period of 11 years (between 2005 and 2016) comprising 25 patients diagnosed with HIV. All patients had a complete ophthalmologic examination. Fundus photos or angiography have been performed whenever posterior segment involvement occurs. For each case, all epidemiological, clinical, biological, therapeutic and evolutionary data were collected.
Results: Ten patients (40%) had CR involvement. Average age of our patients was 40 years. Sex ratio was 2.Sexual transmission was found in 80% of cases. Progressive decrease in vision was the reason for consultation in most cases. Disease was unilateral in 8 cases. Cytomegalovirus retinitis was present in 6 cases, toxoplasmosis in 1 case, cryptococcosis in 1 case and microangiopathies in 2 cases. The mean CD4 count was 66 E / mm3. Associated opportunistic infections have been reported in all cases. Antiretroviral therapy was administered in all cases associated with specific treatment. Four patients died after 7 months of onset of ocular involvement and three were lost to follow-up.
Conclusion: Ophthalmological examination in patients with acquired human immunodeficiency virus is now essential to preserve acceptable visual function in these patients whose survival is currently increased.

P102. THROMBOTIC THROMBOCYTOPENIC PURPURA REVELING PRIMARY COMBINED IMMUNODEFICIENCY

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Introduction: Thrombotic Thrombocytopenic Purpura (TTP) is a rare life-threatening multisystem disorder characterized by the association of microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction. In children, it is due in the majority of cases to a congenital deficit in ADAMTS13 protein. We report an original observation of PTT secondary to anti-ADAMTS13 antibodies revealing a primary immunodeficiency disease (IPD).

Observation: C.Z was a 9-month-old boy born from 1st degree consanguineous parents with a family history of death of his sister and 3 uncles. His disease was revealed at the age of 5 months by non febrile seizures after mild cranial trauma. Laboratory findings showed normochromic anemia and normal platelet levels.*Brain MRI showed* bilateral capsular and thalamic petechial hemorrhage injury. At the age of 9 months, he presented a petechial and ecchymotic purpura with hepatosplenomegaly. Peripheral blood smear showed evidence of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. Myelogram confirmed the peripheral origin of cytopenias. Direct coomb testwas positive. Thrombotic thrombocytopenic purpura (TTP) was suspected. ADAMTS 13 activity was remarkably low (<1%) with a positive inhibitory ADAMTS 13 antibody. The patient inderwent Infusion of high-dose fresh frozen plasma (30 mL/kg) associated to corticosteroid therapy.These medications have been maintained with an excellent response. Primary immunodeficiency has been suspected in this patientbecause of his family history, early autoimmune manifestations, and lymphopenia. Lymphocyte immuno-phenotyping showed significant CD4 lymphopenia with poor response to mitogens and specific antigens. HIV serology was negative. Immunoglobulin replacement therapy and anti-infectious prophylaxis were started with clinical stabilization in 2-years of follow-up.

Conclusion: Primary immunodeficiency is a multifaceted disease. Its prognosis could be improved by early management and good control of complications.

P103. HIGH PREVALENCE OF SEVERE COMPLICATIONS IN LATE-ONSET COMBINED IMMUNE DEFICIENCY: ABOUT THREE OBSERVATIONS

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Late onset combined immunodeficiency (LOCID) is a recently described variant of common variable immunodeficiency (CVID) defined by the presence of opportunistic infections and/or a decrease of a CD4+T cells count. These patients differ from classical CVID patients in several features including late onset of disease, higher prevalence of splenomegaly, granuloma, gastrointestinal disease, and increased risk of lymphoma. They may require more frequent antibiotics administration and hospitalization even on immunoglobulin substitution.
Herein, we present three unrelated Tunisian patients with LOCID: one female (P1) and two males (P2 and P3) aged 52, 28, 41 years respectively who presented with recurrent Ear-Nose-Throat and respiratory infections. Patient 1 had in addition developed polyarthritis. Patient 2 born to consanguineous parents developed bronchiectasis and at age 26 years a lymphoma which is currently in remission. Patient 3 had ethmoiditis and mediastinal polyadenopathies with presence of granuloma. Serum IgG, IgM and IgA levels in all patients showed a decrease of all three isotypes. Immunophenotyping of PBMCs revealed a marked decrease in CD4+T cell counts and a severe defect in naïve CD4 + CD45RA+T cells for all of them. The percentage of circulating B lymphocytes was markedly decreased (<0.5%) in P2 and P3. T-cell–mediated immune response to mitogen (PHA) was decreased for all.
It has been reported that LOCID patients differ from classical CVID patients in terms of clinical severity and immunologic features with a profound T-cell defect. Thus, T cell phenotyping may help identify such patient resulting in appropriate follow-up and timely treatment. Particularly, the risk of lymphoma which seems to be significantly increased in these patients should be assessed. The high rate of consanguinity reported suggests a possible autosomal recessive disease and the study of these patients in our highly consanguineous population may help unravel the molecular basis of this subset of CVID.

104. OUTCOME OF ECZEMA IN A PATIENT WITH WISKOTT-ALDRICH SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Wiskott-Aldrich syndrome (WAS) is an X-linked disorder characterized by the clinical triad of microthrombocytopenia, recurrent infections and eczema. This cutaneous manifestation is a delayed hypersensitivity reaction due to the activation in the skin of self-reactive T lymphocytes.

We report through an observation the outcome of allergic eczema after bone marrow transplantation in a patient with Wiskott Aldrich syndrome.

Observation: Y.A was a 2-moth-old boy who presented spontaneous bleeding with persistent thrombocytopenia from birth. His family history revealed an early neonatal deaths in a maternal uncle. Blood investigations showed peripheral microthrombopenia. Molecular analysis of the *WAS* gene confirmed Wiskott-Aldrich syndrome. During the initial examination at 2 months old, the infant presented a generalized severe eczema lesion resistant to conventional topical treatment. Laboratory findings showed hyper eosinophilia ranging from 3000 to 4000 elements/mm 3. Bone marrow was transplanted from geno-identical sibling donor at the age of 12 months with an excellent engraftment .Eczema was resolved since the beginning of the conditioning regimen. While elevated eosinophil counts and total serum IgE normalized.

Currently, at 10 months post transplant, the clinical examination of the infant is without abnormalities; the skin examination is normal and the eosinophil polynuclear level is normal.

Conclusion: Allogeneic HSCT ameliorated the infectious and atopic symptoms of WAS. A larger study should be carried to analyze the outcome of other allergic manifestations in terms of chimerism and immunological reconstitution following bone marrow transplantation.

P105. SEVERE DEFECT OF MEMORY B CELLS: REPORT OF 2 CASES OF PRIMARY ANTIBODY DEFICIENCIES (X-LINKED HYPER IGM SYNDROME AND CVID)

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Introduction/objective: Primary antibody deficiencies are the most common PID diseases. It is a heterogeneous group of disorders with various degrees of dysfunctional antibody production resulting from a disruption ofB-cell differentiation at different stages. In this study we addressed the question how immunoglobulin isotype switching is decreased in XHIM and CVID ; this led us to evaluate the predictive value of memory B cells in patient with hypogammaglobulinemia.
Materials/Methods: A male aged of 7 years and female aged of 16 years suspected of specific antibody deficiency were refered to our laboratory for exploration.
Biological investigation included:
- Measurement of serum IgG, IgA, IgM bylaser nephelometry.
-Lymphocyte immunophenotyping T, B, NK cells andB-cell subpopulations : memory(CD19+ CD27+ IgD-) and naïve B cells(CD19+ CD27- IgD+) by flow cytometry.
- Measurement of specific IgG antibodies against Diphtheria Toxoid and Tetanus Toxoid by Elisa.
Results: *First case*: Patient had a medical history of pneumonia, recurrent otitis, adenopathy, and chronic diarrhea he has decreased levels of IgG and IgA with normal IgM.
He shows altered vaccine responses to Diphtheria and Tetanus toxoids. Normal levels of T, B and NK cells. Phenotyping of B-cell subpopulations shows: 97% of naïveB cells and 0% of memory B cells. *Second case*: Patient developed angina, sinusitis, bronchiolitis, diarrhea, adenopathy, anemia. She has decreased IgG, IgA, and IgM. Very low vaccine responses to Diphtheria and Tetanus Toxoids. Normal level of T, NK and low level of B. Naive B cell76 % and 0% of memory B cells
Conclusion: Flow cytometric analysis revealed lacking of memory B cells in both XHIM and CVID patients, this finding provides evidence that lack of memory B cells as a cause of the impaired immunoglobulin production and low vaccine response, wich depends entirely on the immunological memory.

P106. A FOUNDER MUTATION UNDERLIES A SEVERE FORM OF PHOSPHOGLUTAMASE 3 (PGM3) DEFICIENCY IN TUNISIAN PATIENTS

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Phosphoglucomutase 3 (PGM3) protein catalyzes the conversion of N-acetyl-D-glucosamine-6-phosphate (GlcNAc-6-P) to N-acetyl-D-glucosamine-1-phosphate (GlcNAc-1-P), which is required for the synthesis of Uridine Diphosphate N-Acetylglucosamine (UDP-GlcNAc) an important precursor for protein glycosylation. Recently, mutations in PGM3 gene have been shown to underlie a new congenital disorder of glycosylation often associated to elevated IgE. Herein, we report twelve PGM3 deficient patients. They belong to three highly consanguineous families, originating from a rural district in west central Tunisia. The patient's clinical phenotype is characterized by severe respiratory and cutaneous infections as well as developmental delay and severe mental retardation. Fourteen patients died in early infancy before diagnosis supporting the severity of the clinical phenotype.

Laboratory findings in most patients revealed elevated IgE, CD4 lymphopenia and impaired T cell proliferation. Genetic analysis showed the presence, of a unique homozygous mutation (p.Glu340del) in *PGM3* gene leading to reduced PGM3 abundance. Segregating analysis using fifteen polymorphic markers overlapping PGM3 gene showed that all patients inherited a common homozygous haplotype encompassing 10-Mb on chromosome 6. The founder mutational event was estimated to have occurred approximately 100 years ago.

To date, (p.Glu340del) mutation represents the first founder mutation identified in *PGM3* gene. These findings will facilitate the development of preventive approaches through genetic counselling and prenatal diagnosis in the affected families.

P107. BONE MORROW FLOW CYTOMETRY ANALYSIS IN PATIENT WITH CONGENITAL AGAMMAGLOBULINEMIA : A CASE REPORT

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Background: Agammaglobulinemia is a rare primary immunodeficiency in which B cell development fails, leading to lack of circulating B-cells (<1%) and profound deficiency in all immunoglobulin isotypes. Characterized by an intrinsic defect in the maturation of pre-B-cells to B-cells and ultimately immunoglobulin-secreting plasma cells.
Purpose : evaluation of early B lymphocyte maturation arrest in congenital agammaglobulinemia.
Patient & Methods: A four-year-old boy, from east of Algeria, was found with profound hypogammaglobulinemia and absence of B lymphocyte in peripheral blood. Bone marrow aspirate from the patient was collected in ethylenediaminetetra acetic acid (EDTA) as an anticoagulant. The specimen was processed using a whole blood lysing system with ammonium chloride and stained with fluorochrome conjugated antibodies. The T, B and NK lymphocytes of peripheral blood and bone marrow analysis were performed by flow cytometry on **BD FACS CANTO II™** (3 lasers, 8 colors) and the measurement of serum immunoglobulins by using turbidimetry method on **SPA plus®**.
Results: He was well until the age of 6 months. During the age of 6 months to 4 years, he had recurrent episodes of infections leading to his hospitalization for pneumonia and chronic diarrhea. Other clinical features were otitis, periodontitis and hepatomegaly in physical examination.
Immunologic studies were performed with the following results: WBC 9,200/mm^3 (neutrophils 3,312/mm3, lymphocytes 5,336/mm3, monocytes 552/mm3), IgG 12,88 g/l (has been on IVIG), IgA: 0,02 g/l, IgM 0,11 g/l. Lymphocyte subsets by flow cytometry showed CD3+ T cells 99% (5283/mm^3), CD4+ T cells 42% (2241/mm^3), CD8+ T cells 35% (1868/mm^3), CD19+ B cells 0%, and CD56+ NK cells 1% (absolute count of 53/mm^3).
The bone marrow analysis revealed three populations, which are granulocytes (62.3%), lymphocytes (13.6%), and blasts (Represents 11.2% and which are $CD45^-$SSC low). The lymphocytes are characterized by the absence of expression of CD19 (absence of medullary CD19 + B cells).The blasts have a CD 19+ lymphoblastic population (or B-precursors), and are defined by expression of immaturity markers (TdT^+, $HLADR^+$, $CD10^+$, and $CD34^+$) with absence of expression of the intracytoplasmic μ chain, CD 22, CD79a, and sIgM.
Conclusion: These results indicate that patients with congenital agammaglobulinemia have a defect in maturation of pre-B cells, and suggest that some patients with acquired B lymphocyte deficiency may have lost the capacity to generate pre-B cells from stem cells.

P108. A NOVEL MUTATION IN THE BRUTON'S TYROSINE KINASE GENE CAUSING X-LINKED AGAMMAGLOBULINEMIA

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Introduction/Objective: X-linked agammaglobulinemia (XLA), also known as Bruton's disease, is caused by mutations in the gene coding for Bruton's tyrosine kinaseprotein (BTK), that lead to an arrest in early B cell differentiation. This disorder is characterized by a profound diminution of mature B, severe reduction in *al l*serum *Ig isotypes* and an increased susceptibility to encapsulated bacterial infections. In this study, we report the case of patient who was diagnosed as XLA at the age of 18 months. Genetic testing revealed a novel frame shift mutation "g. 101356256 delT", located inexon 15of the BTK gene.

Materials and Methods: An Algerian male patient aged of 18 months was referred to our laboratory to explore the cause of the recurrent infections he suffers from. The following immunological tests were performed:

-Measurement of IgG, IgA and IgM levels by laser turbidimetry.

-B and T lymphocytes were assessed on Beckman Coulter Flow Cytometry, using labelled anti-CD19 and anti-CD20 antibodies for B cells and anti-CD3, anti-CD4, anti-CD8 antibodies for T cells.

-Mutation analysis of the BTK gene was performed with BigDye 3.1, Applied Biosystem, once the informed consent had been obtained by parents

Results and conclusion: The patient presented recurrent infections of the upper respiratory tract, interstitial pneumonia and skin infections since the age of one year. XLA was diagnosed based on the combination of the clinical history,the profound hypogammaglobulinemia of all immunoglobulin isotypes (IgG< 0.17 g/l, IgA 0.023 g/l, IgM 0.15g/l), the absence of B-lymphocyte (0%) together and the male gender. The final diagnosis was confirmed by molecular DNA analysis. BTK gene sequencing revealed a deletion of a thymine at position g. 101356256, which would causes a frame shift at the 454th codon (Histidine)and premature termination at the30th downstream amino acid of the BTK protein (p.His454GlnfsX30).To our knowledge, this is the first report of the mutation"g. 101356256 delT" in the literature. This mutation, which is occurring in exon 15 that codes for the catalytic kinase domain (Src Homology 1 domain) of the BTK protein, induces the production of a truncated protein. Finally, BTK mutation analysis is helpful for the diagnosis of XLA. It may be used for subsequent genetic counseling, carrier detection and prenatal diagnosis.

P109. CGD DIAGNOSOS BY DHR TEST (PHAGOBURST): ABOUT A SERIES OF 6 PATIENTS

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Introduction: CGD is a rare inherited disorder of phagocytic cells that can be attributed to a variety of genetic mechanisms. The main characteristic is a defect in the enzymes that produce superoxide and other free radicals, resulting in a failure of phagocytes to destroy ingested microorganisms. Patients with CGD demonstrate vulnerability to infections caused by catalase positive organisms that are able to break down neutrophil and monocyte derived hydrogen peroxide. The lack of the formation of the superoxide free radical in CGD reduces the ability of the host's immune system to fight off infections. Most cases of CGD are inherited X-linked disorders, although examples of autosomal recessive CGD are also seen. Diagnosis is typically made by identifying the neutrophil oxidative burst activity. The dihydrorhodamine (DHR) 123 test uses flow cytometry to detect the oxidation of dihydrorhodamine 123 in activated neutrophils.

Material and Methods: Our study concerns the diagnosis of CGD in a series of 6 young patients: 3 females and 3 males, who were suspected having the disease. Two of patients are siblings (female and male). Four of our series benefited from an immunoglobulin assay and lymphocyte subpopulation phenotyping. The DHR test was performed for the whole series using heparin anticoagulated whole blood. Neutrophils were stimulated using different activators : Opsonized E. coli bacteria (particulate activator), phorbol 12-myristate 13-acetate (PMA) (High activator) and N-formyl-MetLeuPhe (fMLP) peptide (Low activator) separately. This initiates intracellular O_2-production and dihydrorhodamine 123 (DHR) is oxidised by the neutrophil reactive oxygen species (ROS) to rhodamine 123 (RHO) releasing a fluorescent green signal which can be measured by flow cytometry. Normal bloods produce a strong fluorescence whereas patients with an abnormality in O_2-production produce a weak level or no fluorescence at all.

Results: All our patients were diagnosed as CGD carriers including three in its X-linked form: Two boys and one girl. The histogram of the patient (a girl) with CGD in his X-linked form revealed the presence of two peaks. This explains the presence of a single defective CGD gene and a functionally normal gene. The absence of phagocytosis (0%) in his brother's histogram confirms the X-linked form for both. The third case of the CGD X-linked form noted in our study (male) was confirmed by the study of bactericidy in his parents. His father returned normal. As for her mom, it was noted that she was carrying a defective CGD gene.

Conclusion: This study was only able to include a small number of CGD and carrier state patient samples because of the scarcity of cases and the low number of requests for CGD screening tests. The method evaluated in our study was rapid; allowing the proportion of affected cells to be determined, and was able to identify the carrier state of X-linked CGD. In these cases the results show a strong positive peak and a separate weaker/negative peak. DHR is reportedly the most effective flow cytometric probe for assessing the oxidative burst in human granulocytes.

P110. IS THE OEDEMA BRADYKINIC BY DEFICIT IN C1 INH, A RARE IMMUNODEFICIENCY? THE EXPERIMENT OF BLIDA

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Introduction: The bradykinic angioedema by deficit in inhibitor of C1 esterase (C1inh) (AOB) is a rare immunodeficiency, with dominant autosomic transmission. It is characterized clinically by occurrence of crises of oedemas with localization primarily under cutaneous (face, ends). The acute abdominal painful crises and the laryngeal oedema make the gravity of the disease. Biologically, two types are described: type I secondary with a quantitative deficit of the fraction C1 inh ; who is the object of this work and type II related to a functional deficit in C1 inh.
Methods: The exploratory study since 2014 carried out on 3 families whose un questionable member introduced a symptomatology in favour of a OAB according to the assent of the patients, they were taken and profited from the examinations according to: an antigenic proportioning of C1inh, C4, C3 by laser nephelemetry and the proportioning of the CH50 by ELISA.
Results: 26 members among 75 were explored; the common clinical presentation between the patients was the quasi-constant presence of the facial dropsical crises and the members. The abdominal crises were variable of appearance and in intensity. Biologically concentration of C1inh and C4, as well as the rate of the CH50 fluctuated according to the presence the absence of the crises.
Conclusion: The deficit in C1inh is a pathology, which remains ignored being able to bring into play the vital prognosis of the patients reached, a interrogation deepened with a simple proportioning of C1inh and of C4 are sufficient to pose the diagnosis.

P111. MOLECULAR BASIS OF COMPLEMENT FACTOR H DEFICIENCY IN ATYPICAL HEMOLYTIC AND UREMIC SYNDROME PEDIATRIC TUNISIAN PATIENTS

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Introduction: Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy disorder characterized by the association of hemolytic anemia, thrombocytopenia and acute renal failure. The typical form is the most frequent in children occurring after an episode of diarrhea caused by *Esherichia Coli*. Atypical form (aHUS), which is less frequent and non-shigatoxin related, generally leads to final stage renal failure. This pathology is due to complement alternative pathway dyregulation. Complement factor H gene (*CFH*) mutations are the most reported and the most frequent genetic abnormality in aHUS patients.
Objective: To characterize genetic mutations in Tunisian pediatric Tunisian aHUS patients
Materiel & Methods: We conducted a study including 20aHUS patients (11 boys and 9 girls), with a mean age of 6 years. . Factor H antigen concentrations were measured by a "home-made" ELISA.A DNA extraction was performed followed by a PCR and *CFH* gene sequencing.
Results: Among the 15 sequenced and analyzed exons, 13 genetic abnormalities have been detected. Eleven SNPs have already been reported including one (rs534399) related to aHUS, 3 SNPs (rs1061147, rs16840522, rs203674)associated to an ocular pathology mediated by a disorder of the alternative pathway named AMD (Age-related macular degeneration). Among these 3 SNPs we noticed a frequent association of rs1061147 and rs203674 which can be aligned with a peculiar genetic profile of our patients. Two novel anomalies have been detected. The first one is an intronic substitution C.3310+144 C>T located in intron 20. According to the prediction in situ, it may have a consequence on the alternative splicing. The second one is an homozygous deletion, c.3766delGATA, resulting in coding stop TAG alteration. This leads to a prote in longer of 4aa. The abnormal protein produced is usually quickly degraded, which explains the low rate of FH in our patient.
Conclusion: We report two new mutations in Tunisian aHUS patients. Our study as well as two anterior studies identified deletions in the same region resulting in coding stop TAG alteration. These deletions occurred in a specific palindromic region sequence that might be a hot spot for deletions. Further studies would elucidate the consequences of c.3766delGATA on translation process. Assessing the frequency of genetic defects in healthy controls is required.

P112. TYPE I COMPLEMENT FACTOR I MUTATIONS IN TUNISIAN ATYPICAL HEMOLYTIC AND UREMIC SYNDROME

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Introduction: Complement factor I (CFI) is a soluble two-chain glycoprotein. It's a major regulator of complement alternative pathway (AP). In presence of cofactors such as complement factor H, CFI cleaves C3b and C4b on host healthy tissue and perform homeostatic balance. The impact of CFI mutation as well as those of AP regulator in atypical haemolytic and uremic syndrome (aHUS) is well established, since 60% of aHUS patients have at less one point mutation in these genes. Two types of CFI mutations are reported. In Type1, the mutant protein is absent or present in lower amounts while in type II the mutant protein is present in normal level in plasma with a functional defect.

Objective: to characterize molecular basis of type I CFI mutations in Tunisian aHUS patients.

Materials and methods: Thirteen aHUS patients were enrolled in this study. They were 6 adults (A1-A6) aged 32 to 42 years and 7 children (P1-P7) aged 2months to 11 years old. FI levels were assessed by a homemade sandwich ELISA and ranged between 12.5 and 60% in aHUS. Genomic DNA was amplified by way of a polymerase chain reaction (PCR) using intronic primers flanking the 13 coding CFI exons. Sequencing of the PCR products was carried by the dye terminator sequencing method. Molecular study was performed on parental DNA (F1, F2) for two pediatric dead patients. DNA extracted from 95 Tunisian healthy donors. Online *in silico* prediction tools were used to predict the impact of abnormalities.

Results: Eight substitutions in no coding region were detected: 3 in intron 1 (c.71+54G>A, c.71+181 T>A and c.71+185 A>G) respectively in P4, F4 and A4; c.482+6C>T in intron 3 in F3 and c.1429+33 G>A in intron 11 in patients A5 and A3. Three other substitutions were detected in 5' and 3'UTR regions: c.-132 G>C, c.-13G>A and c*.115C>T. Allelic frequencies of c.-132 G>C, c.-13G>A and c.71+181T>A were less than 1% in the control group. c.1429+33 G>A mutation was predicted to cause a potential alteration of splicing. In coding regions we report three substitutions c.1071T>G (Ile 357Met) in A1, A6, P7 and F2, c.1246A>C (Ile416Leu) in A5 and c.1642 G>C (Glu548Gln) in A2. Interestingly, allelic frequencies of c.1071T>G and c.1246A>C were less than 1% in tunisian controls with a probably damaging impact for the first one.

Conclusion: c.1071T>G was detected in approximatively one third of Tunisian aHUS patients. We report three new non coding mutations in intron 1 with two in 5'UTR region. Functional consequences of these mutations on RNA transcription/maturation and DNA methylation have to be elucidated.

P113. WEIGHTED GENE CO-EXPRESSION NETWORK ANALYSIS IDENTIFIES SPECIFIC MODULES AND HUB GENES RELATED TO ATYPICAL HEMOLYTIC HREMIC SYNDROME

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Background: The analysis of the potential molecule targets of atypical hemolytic uremic syndrome (aHUS) is critical for understanding the molecular mechanisms of disease. However, studies of global microarray gene co-expression analysis of aHUS still remain limited.
Methods: Microarray data of aHUS (GSE69090) were downloaded from Gene Expression Omnibus, including peripheral blood samples from patients anti-CD3 + anti-CD46 stimulation for 2hr Patient has a mutation in CD46 that leads to reduced cell surface CD46 expression and suffers from episodes of atypical hemolytic uremic syndrome (aHUS) . Limma package in R was used to identify the differentially expressed genes (DEGs) between aHUS and control samples. Using weighted gene co-expression network analysis (WGCNA) package in R, WGCNA was performed to identify significant modules in the network. Then, functional and pathway enrichment analyses were conducted for genes in the most significant module using DAVID software. Moreover, hub genes in the module were analyzed by isub pathway miner package in R and GenCLiP 2.0 tool to identify the significant sub-pathways.
Results: Total 3711 DEGs and 21 modules for them were identified in aHUS samples. The most significant module was associated with the pathways of nadequately regulated complement activation. In addition, the top 30 hub genes with high connectivity in the module were selected, and two genes (S1191L and V1197A) were taken as key molecules via sub-pathway screening and data mining.
Conclusions: A module associated with hypertrophic cardiomyopathy pathway was detected in aHUS samples. S1191L and V1197A were the potential targets in aHUS. Our finding might provide novel insight into the underlying molecular mechanism of aHUS.

P114. CFHR1/CFHR3 DELETION IN TUNISIAN AHUS PATIENTS WITH ANTI-FACTOR H ANTIBODIES

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Background: Atypical hemolytic and uremic syndrome (aHUS) is the prototype of disease secondary to complement alternative pathway (AP) dysregulation. In almost 60% of aHUS patients, mutations in the genes of AP regulators: Factor H (FH), factor I (FI) and membrane co-factor protein (MCP or CD46) were reported. Acquired FH deficiency due to autoantibodies against FH (anti-FH Abs) has been recently described. It is associated with a homozygous deletion of genes encoding FH-related protein 1 and 3 (CFHR1-R3) in 90% of cases. These deletion was correlated closely with the rs7542235 SNP A>G (r^2=0.98). Objective: to determine the frequency of anti-FH Abs in Tunisian aHUS patients and correlate the presence of these autoantibodies with CFHR1 and CFHR3 deletion.

Materials and Methods: We conducted a multicentrer study including 98 aHUS patients: forty eight children (25 boys and 23girls) and 50 adults (25 men and 25 woman). Fifty healthy subjects were also enrolled in this study.Functional activity of the classical pathway (CH50) and serum concentration of C3/C4 were determined by haemolytic assay and nephelometry respectively. FH and FI antigen concentrations as well as anti-FH Abs were measured by a "home-made" ELISA. CD46 membrane expression was assessed by flow cytometry. CFHR1 protein was characterized by western blot (WB)using a monoclonal antibody C18/3 known to bind both FH and FH related protein 1.To screen for CFHR1/R3 deletion, we also analysed rs7542235 by way of a polymerase chain reaction (PCR) and sequencing of the PCR products.

Results: Anti-FH Abs were found in 7 children and 7 adults. The mean age at onset of symptoms was 6 years in children and 34 years in adults. Children had a better prognosis than adults as only one among the 7 children reached end-stage renal disease (ESRD). Pediatric patients had an antibody title higher than that of adults. CFHR1/R3 deletion assessed by WB or by screening for the G allele of rs7542235 was found 4 cases. Six individual healthy donors (12%) had CFHR1/R3 deletion by WB.

Conclusion: To our knowledge this is the first report of Tunisian patients with anti-FH Abs. These Abs were associated with a mild progression in the paediatric cohort as reported in other studies. Anti-FH Abs were not frequently associated to CFHR1 deletion in Tunisian aHUS patients. Other contributing factors such as environmental agents may be involved in anti-FH Abs production.

P115. IDENTIFICATION OF HETEROZYGOUS INTRACELLULAR FAS MUTATIONS IN TWO TUNISIAN PATIENTS WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

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Autoimmune lymphoproliferative syndrome (ALPS) is caused by genetic defects altering Fas function and is characterized by lymphadenopathy/splenomegaly, autoimmune cytopenias, expansion of double negative T (DNT) cells and a high risk of malignancies. Homozygous *FAS* gene mutations have been previously described in ALPS Tunisian patients. Herein, we report two additional ALPS patients with heterozygous intracellular *FAS* mutations, suffering mainly from persistent thrombocytopenia. Patients P1 and P2 were aged 11 and 3 years respectively. They developed early in life thrombocytopenia, associated with anemia in the first patient. Both patients showed high percentages of DNT cells associated with high levels of sFasL. Elevation of plasma IL-10 was found only in the first patient. *FAS* gene molecular analysis of P1 identified a heterozygous glutamine to glycine transition at position 256 in the Death Domain (c.1009A>G/p.E256G). This mutation was predicted as probably deleterious by Polyphen 2 and SIFT softwares and was not found in 100 healthy Tunisian controls. Moreover, this mutation does not affect Fas protein expression. Interestingly, the E256G mutation, which has been associated with a Fas-mediated apoptosis defect, has been previously described in a patient with ALPS who developed an unusual T-cell lymphoma. Surprisingly, his paternal uncle bearing the same mutation developed Hodgkin's lymphoma with no clinical manifestations of ALPS. Genetic analysis of P2 identified a heterozygous substitution (c.926G>A/ E194K) in exon 7 that has not been found in healthy controls. This mutation resulted in a decreased Fas expression (24.5%) but normal Fas mediated apoptosis as compared to control. The E194K mutation was previously reported in a patient with a complex ALPS phenotype in association with a deletion in *XIAP* gene (1189delA) and a substitution in *UNC13D* gene (2768C>G). Thus, molecular study of other genes should be performed in P2 as well as a thorough functional investigation in order to better understand the discrepancy between the decrease of Fas expression and a normal Fas mediated apoptosis.

These descriptions highlight the clinical heterogeneity observed in ALPS patients and should prompt extensive genetic and functional study of all patients' family members. Strict follow up is required in some patients presenting molecular defects that seem to be particularly associated with the development of malignant proliferation.

Autoimmunity

P116. ANTI-NUCLEAR AUTOANTIBODY (AAN) PROFILE IN ALGERIAN LUPUS PATIENTS: ABOUT 106 CASES

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Introduction: Lupus disease is an auto-immune disease of connective tissue, systemic, inflammatory, chronic and recurrent, resulting from a rupture of immune tolerance towards the Ags of the self. Characterized by a large production of auto-antibodies affecting mainly the articulations, the skin, the kidneys, the nervous system and the blood. Occurrence results from a favorable genetic background and exposure to a particular environment.
The aim of our study is to determine the frequencies of auto antibodies in Algerian lupus patients.
Material and methods: The present work consists of an analysis of the autoantibody profile of 106 patients with SLE, diagnosed in different clinical services in the central region of Algeria, during a four-year period (2011-2015). All patients have at least four criteria from the American College of Rheumatology (ACR) revised in 1997. The average age of our patients is 37.8 years with extremes ranging from 10 to 75 years. The sex ratio F/M is 25.
Antinuclear autoantibodies (AANs) and anti-nDNA autoantibodies were investigated by the IFI technique on Hep2 cells and Crithidia Luciliae, respectively. While autoantibodies, antinucleosomes, anti histones and anti extractable nuclear antigens (ENA) have been identified by ELISA techniques.
Results: AANs were found in 100% of patients. Anti-nucleosome antibodies were most frequently found with 81.5% of cases, followed by anti-SSA (57.5%) and anti-DNA (50%).Anti-Sm and anti-RNP are found in 50% and 35.2% of cases, respectively.
Conclusion: Anti-nucleosome autoantibodies should be investigated in case of clinical suspicion of SLE, especially if the anti-nuclear antibodies are IFI positive without positivity of anti-native DNA antibodies**.**

P117. IMMUNOLOGICAL PROFILE OF SLE IN NIGERIAN PATIENTS

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Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-systemic involvement and the presence of autoantibodies.
It is proposed to evaluate clinical, immunological and clinico-immunological correlations in Nigerien patients with SLE.
Methods: This is a descriptive, retrospective study of 21 lupus patients followed in the department of internal medicine of the National Hospital of Niamey during the period January 2004 and October 2016. The diagnosis of LES was retained before the existence Of at least 4 criteria of the ACR 1997. The clinical-immunological correlation was also analyzed in these patients.
Results: There were 21 patients, 18 of whom were women and 3 men, a sex ratio of 6 : 1. The meanage was 32 with extremes ranging from 18-53 years. Immunologically, antinuclear autoantibodies were consistently found in our patients, followed by anti-SSA 13/21, anti-DNA 11/15, anti-SSB 8/21, and anti-Sm 8/21 and anti-phospholipids 3/21. Anti-U1-RNP autoantibodies were found in 9 of 21 patients. The presence of anti-DNA was correlated with renal involvement, 7 of the 9 patients with renal involvement had auto-Ab anti-DNA positive
Conclusion : The frequency of LES in our series is relatively low compared to that of the other series. This low prevalence is likely due to an under-diagnosis of this disease. The polymorphism of the clinical and immunological picture was the rule in our series as well as the female predominance. The presence of auto-Ab would be associated with renal involvement.

P118. AUTOANTIBODIES PROFIL IN LUPUS NEPHRITIS

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Introduction/ Objective: Systemic lupus erythematosus (SLE) is a nonspecific disease of organs characterized by the association of protean clinical manifestations and the production of a wide variety of antinuclear antibodies; some of them have a direct pathological implication. One of the alarming complications of SLE is lupus nephritis. In fact, 30% to 70% of lupus patients will develop nephropathy during the course of their disease**.** The objective is to determine the frequency and the titre of anti-dsDNA, anti-nucleosome, anti-histone, anti-C1q autoantibodies and C3, C4 complement fractions in patients with lupus nephritis.
Materials/Methods : Type of study: retrospective
Patients: Our study included 128 patients with at least four criteria of the American College of Rheumatology (ACR) for SLE diagnosis.
Techniques :
-Indirect immunofluorescence with HEP2 cells.
-Immunoenzymatique assay type ELISA.
- Laser nephelometry(C3, C4).
Results /Conclusion: In our series, renal disease was found in 58 of the 128 patients (ratio F: H = 4: 1). The average age is 35 +/- 13,11years (11-65).
In the 58 patients with lupus nephritis, we observed : Ab Anti-chromatin (76.47%), Ab anti dsDNA (73.52%), Ab anti-histone (70.58%), Ab anti C1q (58.8%); while among the 70 patients remaining the prevalences are respectively: 50%, 36%, 39% and 35%
-Hypocomplementemia is common during renal disease: 64.71% for C4 and 61.76% for C3 complement fraction, but it is found in 25% for C4 and 7.86% for C3 in lupus patients without renal disease.
Our study demonstrated statistically significant associationsbetween:
-Ab anti dsDNA and lupus nephritis ($P = 10^{-5}$, OR = 4,72),
-Ab anti-chromatin and lupus nephritis (p = 0.002, OR = 3.14),
-Ab anti histones and renal lupus patients (P = 0.0002; OR = 3.84).
-Abanti-C1q and renal lupus patients (P=0,005 ; OR=2,72).
Which confirm the role played by these antibodies in the pathogenesis of lupus nephritis.
C3 and C4 hypocomplementemia were significantly more pronounced in renal lupus compared to non-renal lupus ($P = 4.10^{-5}$ for Fraction C3, $P = 10^{-9}$ for C4), this is in agreement with the results of the various studies carried out on the subject.

P119. ANTI- PHOSPHOLIPASE A2 RECEPTOR ANTIBODIES IN MEMBRANOUS NEPHROPATHY

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CHU Mustapha Pacha

Introduction/objectives: Membranous nephropathy (MN) constitutes a major glomerulonephritis in adults. Recently the M-type phospholipase A2 receptor (PLA2R) was identified as the major target antigen in adult idiopathic membranous nephropathy (iMN).
The objectives of this study were to assess the prevalence and the specificity of anti-PLA2R antibodies (Abs) in a cohort of Algerian patients with iMN and to correlate the presence of anti-PLA2R Abs with clinical parameters reflecting the activity of the disease.
Material/methods: We measured anti-PLA2R Abs using an immuno-enzymatic assay (EuroImmune AG (Lubeck, Allemagne) in the serum of 40 patients with iMN, 09 with secondary MN and 10 with other forms of primary glomerular diseases. Anti-PLA2R Abs levels were correlated with other clinical parameters (proteinuria, serum albumin and serum creatinine) in patients with iMN. In 6 patients with iMN and anti-PLA2R positive, Abs levels were assessed at various stages of clinical disease (active, remission) and correlated with clinical disease activity.
Results and conclusion : Anti-PLA2R Abs were detected in 23/40 (57,5%) of patients with iMN, but not in those with secondary MN or other forms of primary glomerular diseases producing an overall specificity of 100%. In 24 patients with iMN, proteinuria was > 3 g/24 h at the time of PLA2R Abs measurement. 23 (91,66%) of these patients were positive for PLA2R Abs, while in 14 patients the proteinuria was < 3g/24h. Among them, only one patient (7,14%) was positive for PLA2R Abs. In patients with iMN, the Abs levels correlated positively with proteinuria (r=0,6 , *p*= 0,0004). Abs levels were negatively correlated with serum albumin (r=0,56, *p*= 0,0008). No correlation was found between Abs levels and serum creatinine. During the clinical course of the 6 anti-PLA2R positive patients, overall Abs levels correlated with cllinical status, which were high in the initial phase of active disease and decreased significantly during remission (*p*= 0,009).
Conclusion: these results suggest that PLA2R is a major target antigen in Algerian iMN and the detection of anti-PLA2R is a sensitive and specific test for iMN. Levels of circulating anti-PLA2R revealed a correlation with clinical disease activity, so, the detection and measurement of these Abs may provide a tool for monitoring disease activity.

P120. ANTI-PCNA ANTIBODIES: PREVALENCE AND DIAGNOSTIC VALUE

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Introduction: Autoantibodies (Abs) to proliferating-cell nuclear antigen (anti-PCNAs) are antinuclear antibodies (ANA) that target a protein (PCNA or cyclin) associated with the DNA polymerase enzyme. In the literature, these Abs are reported to be rare but with a high specificity for systemic lupus erythematosus (SLE). Their prevalence in the SLE does not exceed 5%. our Objective was to study the prevalence, the diagnostic and prognostic significance of anti-PCNAs.

Patients and methods: We conducted a retrospective study on 11520 patients sera sent from Internal Medicine department to our Immunology laboratory for ANA detection. Anti-PCNAs were detected using immunofluorescence on HEp2 cells. Confirmation was obtained using the immunoDOT.

Results: Among the 11520 sera studied, anti-PCNAs were found in 17 cases (0.15%): 12 females and 5 males with an average age 55±16 years (28-82 years). The principal clinical manifestations were represented by muco-cutaneous reactions in 9 cases (52.9%), rheumatologic manifestations in 7 cases (41.2%), vasomotor disorders in 3 cases (11.8%), pericarditis in 3 cases (17.6%), peripheral polyadenopathy in 2 cases (11.8%) and neurological signs in 1 case (5.9%). The ANA were speckled in 8 cases (47%), homogenous in 5 cases (29.4%), nucleolar in 3 cases (17.6%) and with anti-centromere aspect in 1 case (5.9%). Anti-PCNAs were isolated in 6 patients, associated with anti-RO52 and anti-DNAn in 29,5 and 17.6% of the cases respectively. Anti-nucleosome, anti-Sm, anti-RNP, anti-SSA, anti-PM-SCL, anti-ribosome and anti-centromere were positive but with lower frequency varing from 5.9 to 11.7%. Our patients were diagnosed with SLE in 3 cases, GSS in 2 cases, a rheumatoid arthritis in 2 cases, and undiffernciated connective diseases in 2 cases. Non systemic pathology were noted in 29.4% of patients: gout disease, venous thrombosis, myelodysplastic syndrome, a pancreatic neoplasm, uveitis. The etiology remained undetermined in 3 cases (17.6%). Our patients were followed-up during 12±12 months (0-40 months). The evolution was characterized by a relapse of the pathology in 2 cases (11.8%), the death in 1 case (5.9%). The rest of our patients were in remission**.**

Conclusion: The anti-PCNAs are characterized by their low prevalence, our results align with the literature. Nevertheless, our findings seem to be pleading for a lower specificity of the anti-PCNA for the SLE.

P121. ANTI-NUCLEOSOME ANTIBODIES: A NEW MARKER FOR SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction: Systemic lupus erythematosus (SLE) remains the most frequent autoimmune disease in the Tunisian population. Our main objective is to high light the usefulness of anti-nucleosomes antibodies in the diagnosis, follow-up and evolution of the disease.
Patients and methods: Our retrospective study was spread over 10 years. Eighty two patients were hospitalized in the Fattouma Bourguiba Hospital of Monastir in the Department of Internal Medicine / Endocrinology.
Results: The mean age was 35.38 + -13.3 years with a sex ratio of 9 women to one man. Seventeen patients (20.7%) had anti-nucleosomes antibodies. Anti-nucleosomes antibodies were associated with discoid lupus (p = 0.02), loco-pharyngeal ulcers (p = 0.044) and anti-SM (p = 0.02). A probable association is observed with anti-DNA (p = 0.06), respiratory involvement (p = 0.08) and vespertilio (p = 0.06).
Conclusion: The association of anti-nucleosomes antibodies with clinical and immunological signs of SLE is an argument in favor of its utility as a marker for diagnosis and follow-up of SLE. A wider study was needed to confirm our findings.

P122. IMPLICATION OF ANNEXIN A1 IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction: Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can affect many organs, including the skin, the central nervous system and the kidneys. Several factors and agents are implicated in the pathogenesis of SLE. In fact, Apoptosis and clearance of apoptotic cells/material are key processes in the physiopathology of SLE. As a result of the malfunction of these processes, the patient organism product different auto-antibodies that persist in circulation. Production of anti-annexin A1 antibodies was reported by few works.
The aim of this study is to compare the expression of annexin A1 auto-antibodies in SLE patients and healthy controls.
Materiel and Methods: We conducted a case-control study on 39 SLE patients and 39 healthy controls. All individuals were age- geographical origin- and sex-matched. The expression of annexin A1 antibodies IGg in sera was determined by home-made ELISA. Results were statistically analyzed using SPSS software.
Results: AnxA1 antibodies expression was significantly higher (< 0.001) in SLE patients' sera than in healthy controls. Whereas there is no correlation between the expression of these antibodies and any of the serological and clinical symptoms of SLE.
Conclusion: Our results which are concordant with results of previous study, demonstrate that anti-annexin A1 antibodies might be a candidate biomarkers of SLE. However this study have to be confirmed on a larger number of patients.

P123. USEFULNESS OF DETECTION OF DENSE FINE SPECKLED-70 ANTIBODIES IN SOUTH TUNISIAN PATIENTS

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Background/ Objectives: Dense fine speckled-70 (anti DFS70) antibodies (Abs) belong to the large family of anti-nuclear antibodies (ANA). In indirect immunofluorescence (IFI) on Hep-2 cells, they are characterized by a fine and very dense speckled fluorescence. The clinical relevance of these new Abs is still controversial. Recently, isolated anti DFS70 Abs have been reported to be protective factor against the development of systemic autoimmune diseases. The aim of our study was to assess the usefulness/clinical relevance/interest of anti DFS70 Abs in south Tunisian population.

Patients / methods: We conducted a retrospective study (January 2017 - June 2017). We included all samples for which an ANA screening was performed in our laboratory. Clinical an epidemiological data were collected retrospectively. ANA screening was performed using IFI on hep2 cells (Euroimmun®, Germany). Detection of anti DFS70 Abs as well as other ANA was performed by Immunodot (Euroline ANA Profile 3 plus DFS70).

Results: Four hundred and twenty four requests for ANA screening were received. Anti-DFS 70 was detected in 71 patients (17%), it was associated with other Abs in 24 cases. Twelve of Anti-DFS positive patients had confirmed connectivitis: 9 patients had systemic lupus erythematosus (SLE), 2 had Sjogren syndrome associated with SLE in 1 case and 1 patient had scleroderma. Among these 12 patients, 11 (92%) had other types of ANA associated to anti DFS70 Abs.

Pathologies other than connective diseases have been diagnosed: atypical nephrotic syndrome (n=5), Throiditis (n=4), Chronic urticaria (n=2), Rheumatoid arthritis (n=3), and Behçet's disease (n=2). Multiple sclerosis, Guillain-Barré syndrome, cerebral thrombophlebitis and cerebral vasculitis were found in one patient each.

More than half of the patients with positive anti DFS70 Abs (n=39), had no specific signs mainly articular (n=33), long-term fever (n=7), cutaneous signs (n=11) haematological signs (n=13), digestive signs (n=6).

Conclusion: Our study confirms the results described in the literature showing that, isolated anti-DFS 70 are rarely associated with connectivitis. However, the presence of anti-DFS70 does not allow us to exclude them formally. Accordingly, this analysis must be confirmed by a study on a larger sample.

P124. RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND INCREASED SERUM IL-21 IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Vitamin D deficiency and its relevance to the stability of the immune system are being increasingly considered a clinical problem of significant importance. Interleukin 21(IL-21) signaling pathway is involved in B cell differentiation into plasma cells and antibody production and has been suggested to play a role in systemic lupus erythematosus (SLE).
Objectives: To identify relationships between vitamin D serum levels and serum IL-21 levels and IL-21R In Patients with SLE.
Methods: 30 female Patients fulfilling ACR criteria for SLE together with 20 matched healthy controls were tested for serum concentrations of 25(OH) D3 by electrochemiluminescence immunoassay (ECLIA), IL-21 levels and IL-21R expression by Enzyme-linked immunosorbent assays (ELISA) and flow cytometry. All patients underwent complete medical history taking and thorough clinical examination; the disease activity was assessed by the use of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).
Results: Serum concentrations of 25(OH) D3 was insufficient (<30 nmol/L) in 17 SLE patients (56%) and in 14 (7%) of the controls participants (p = 0.001).Patients with insufficient 25(OH) D3 had higher levels of IL-21(199.8±61.11 pg/ ml) where it was lower in the controls participants with insufficient 25(OH) D3 (33.2±24.3 pg/ml).There was highly significant inverse correlation between vitamin D level and SLEDAI score in the patient group. There was no correlation between 25(OH) D3 level and IL-21R expression in B cells from patients when compared to controls.
Conclusion: Vitamin D deficiency is prevalent in SLE patients more than in healthy controls; vitamin D deficiency D is associated with a higher disease activity. The patients with SLE enrolled in this study showed an association between insufficient levels of vitamin D and higher levels of IL-21. Further research work is required to establish the levels of vitamin D needed to produce effects on the immunomodulation of these patients.

P125. UP-REGULATED EXPRESSION OF TOLL-LIKE-RECEPTOR 4 IN RENAL AND SKIN LESIONS IN LUPUS ERYTHEMATOSUS

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Objective: Toll-like receptor 4 (TLR4), a bacterial Lipopolysaccharide sensor, is an essential modulator of the innate immune response. It is expressed on both immune and non-immune cells and recognizes a panel of endogenous molecules released from injured cells and that may contribute to the cutaneous and renal manifestations during Lupus Erythematosus (LE). Studies conducted in vivo provide experimental evidence on the functional role of TLR4 in Lupus Nephritis (LN) but its implication in lupus skin disorders is still unknown. The purpose of this study is to analyze the role of TLR 4 in the pathogenesis of LN and cutaneous lupus erythematosus more precisely chronic (CLE) by evaluating its expression in renal and cutaneous biopsies of LE patients.

Methods: This study was carried out on 30 Renal biopsy specimens from LN patients compared to 11 healthy renal tissues from healthy subjects. Skin biopsies were obtained from 30 CLE patients and 15 normal individuals. All biopsies were taken for immunohistochemical staining of TLR 4.

Results: A strong and diffuse TLR4 expression throughout the epidermis combined to a labeled inflammatory infiltrate and an intense TLR4 expression in the dermis glands were observed in CLE patients' biopsies; while normal controls' skin expressed weakly TLR4 in the basal layer of epidermis and not at all in the dermis. We also showed an increased and more intense TLR4 expression respectively in LN glomeruli and tubules compared to normal controls where TLR4 expression was weak and rarely detected in glomeruli, diffuse and weak in tubules. A significant difference in TLR4 expression between LN classes, both in glomeruli and tubules was observed.

Conclusion: Our results clearly show an up-regulation of TLR4 expression in the affected tissues of CLE and LN patients and highlight the critical role of TLR4 in the pathogenesis of cutaneous and renal disorders in LE.

P126. ANNEXIN A1 IMPLICATION IN CUTANEOUS LUPUS

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Introduction: Lupus erythematosus (LE) is a multiorgan autoimmune disease with many clinical manifestations. The skin is one of the most affected organs in systemic lupus erythematosus (SLE) and may be the only affected one in cutaneous lupus erythematosus (CLE). Defective regulation of apoptosis is reported to play an important role in the development of LE. So that, we aimed in this study to investigate the expression of Annexin A1 (AnxA1), an anti-inflammatory protein implicated in apoptosis, in cutaneous biopsies of CLE patients.

Materiel and Methods: Our study was conducted on 18 CLE patients attending the Dermatology Department at the Hedi Chaker Hospital of Sfax and 6 normal individuals without autoimmune or inflammatory disease. Biopsies were stained by immuno-histochimestry to detect AnxA1 expression. The results were analyzed using SPSS version 20.

Results: In skin biopsies of CLE patients, the AnxA1 expression in epidermis showed a significant decrease compared with normal individuals (p=0.003). The AnxA1 was expressed in the 3 layers of epidermis in biopsies of normal controls whereas in CLE patients it was absent in 3 biopsies, limited to the basal layer of epidermis in 10 biopsies, expressed in basal and suprabasal layers of 4 biopsies and in the 3 layers of only one biopsy. There was also a difference between patients and controls in the localization of AnxA1 in the cell, it was nuclear in all control's biopsies with a cytoplasmic staining in only one. However, in CLE patient's biopsies, AnxA1-if present- was nuclear in 8 biopsies, nuclear and cytoplasmic in 4 biopsies and only cytoplasmic in 3 biopsies. Membrane localization, form in which AnxA1 is functional, was not noted in any biopsy.

Conclusion: Our results show that the expression of AnxA1 is defective in CLE patient's skin compared with healthy controls. As this protein is implicated in the resolution of inflammatory reaction and clearance of apoptotic debris, this lack of expression could explain the accumulation of apoptotic debris and the implication of this protein in the physiopathology of lupus. However, further studies exploring the functional aspect of this protein are necessary to confirm its real involvement in the disease.

P127. EVALUATION OF X CHROMOSOME INACTIVATION IN PEMPHIGUS FOLIACEUS AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Almost 5% of the world population develops an autoimmune disease (AID). Of this 5% approximately 78% are women and it is considered the fourth leading cause of disability for them. The rate between women and men in the most prevalent AID may vary from 9:1 in systemic lupus erythematosus (SLE) to 13:1 in Endemic tunisian pemphigus foliaceus (PF). Since, disorders of epigenetic processes, non-random X chromosome inactivation (XCI), have been reported in many female pre-dominant autoimmune diseases.
Here we test the hypothesis that women with PF and SLE display extremely skewed XCI.
Using methylation sensitive genotyping of the CAG short-tandem repeat (STR) polymorphism at androgen receptor (AR) gene exon 1, XCI profiles, were performed in peripheral blood mononuclear cells from 107 women with PF, 97 women with LES and 150 healthy women. XCI skewing was defined as having a ratio ≥ 80:20 of cells inactivating the same X chromosome. The analysis is based on differential I. 55 women with PF, 97 women with LES and 51 HC were, respectively, determined heterozygotes for the *AR* $(CAG)_n$ polymorphism. Evaluation of CXI is in progress. Differences in the size ratio of the heterozygous two-peak patterns indicate unequal methylation of the biparental X chromosomes, suggesting (i) nonrandom or skewed XCI when it is more than 90% , (ii) midly skewed when XCI 90% ≤XCI ≥70% and random XCI is equal 50%. The process of XCI needs to be considered as a potential factor in the predominance of females in most autoimmune diseases. It has been suggested that genes on the X chromosome might show linkage with AID.

P128. POLYMORPHISMS OF HLA MICROSATELLITE MARKERS IN TUNISIAN LUPUS ERYTHEMATOSUS

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Background and Objectives: Short tandem repeats (STR) are usually used as informative polymorphic markers for genetic mapping and for disease susceptibility analysis. The involvement of these microsatellite markers localized in the MHC region was reported in many auto-immune diseases. In this study we analyzed for the first time eight polymorphisms of microsatellite loci at the HLA region: D6S291, D6S273, TNFa, b and c, MICA, D6S265 and D6S2 7, in Tunisian systemic lupus erythematosus (SLE) patients.

Materials and methods: The microsatellite loci were amplified using specific primers labeled with NED, VIC, PET or 6-FAM and analyzed using GeneScan software 3.7. For the statistic analysis, we used SPSS software and we performed a sub-haplotype scoring test using the haplo.stats software developed in the R language. Sub-haplotype analysis included DRB1* and DQB1* loci.

Results: We found that two mean associated regions exist; the more important encompasses the 3 TNF markers (p=0.0003, OR=19.34); the latter covers the DR region (p=0.007, OR=5.31). In fact, when scoring haplotypes in 3 marker-sliding windows, the p value increased as we moved away from the TNF region and decreased again when we approached the DRB1 locus. We also established for the first time the negative association between alleles of D6S291 and SLE. The majority of clinical and serological correlations were noted with TNF alleles, TNFb4 was protective from lupus nephritis and TNFc2 was negatively associated with anti-Sm production.

Conclusion: Our results confirm the association between TNF and DRB1 polymorphisms and SLE. The association between alleles of D6S291 and SLE needs however to be verified by the analysis of other markers beyond this region.

P129. FREQUENCY OF CLASS II HLA ALLELES IN ALGERIAN LUPUS PATIENTS: ABOUT 58 CASES FOLLOWED AT BLIDA UNIVERSITY HOSPITAL

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Introduction: Lupus disease is an auto-immune disease which the etiology remains unknown, but probably involves complex interactions between hormonal, genetic and environmental factors. Genetic factors have been known to play a role in its pathogenesis. Most studies have focused on HLA genes, the most consistent associations that have been reported are those with HLA class II antigens.

Many studies on associations between leukocyte antigens (HLA) and susceptibility to systemic lupus erythematous (SLE) were performed. However, few protective associations with HLA-DRB1 alleles have been reported.The aim of this study is to evaluate the distribution of allelic frequencies for each locus and to determine the contribution of class II HLA antigens to the susceptibility as well as the search for protective alleles in Algerian lupus patients.

Material and methods: Prospective study carried out in the immunology laboratory of the CHU of Blida conducted over 4 years (2011-2015). The HLA class II typing was performed for 58 patients with SLE and 84 controls (organ donors, healthy without a history of auto-immune disease). HLA typing was realized by the molecular biology technique (PCR-SSP).

Results: A very significant frequency between the patients and the controls concerning homozygotes DRβ1*03/DRβ1*03 was found, however no control is homozygous for DRβ1*03. A non-significant increase in the frequency of the HLA DRβ1*03 allele was found in patients compared to controls. The frequency of the HLA-DRβ1*04 allele was significantly lower in lupus patients than in controls.

Conclusion: Data suggest the involvement of class II HLA molecules in the pathophysiological mechanisms of lupus disease.

P130. INTERLEUKIN-1-RECEPTOR-ASSOCIATED KINASE (*IRAK1*) GENE POLYMORPHISM IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease, characterized by the production of a wide range of autoantibodies and a broad spectrum of clinical presentation encompassing almost all organs and tissues. The etiology of this disease includes genetic and environmental factors. The aim of this study was to examine the association of a single-nucleotide polymorphism, rs3027898, of the *IRAK1* gene in a Tunisian population.
The study population consisted of 86 SLE patient and 137 healthy controls from Tunisia. The rs3027898 polymorphism was detected with the Ms PCR method. Statistical difference in genotype distribution was assessed by Chi-square test. $P < 0.05$ was considered significant.
The IRAK1 rs3027898 genotype distribution in patients with SLE (AA= 17.44%, AC= 33.73% and CC= 48.83%) did not significantly differ from those of the control subjects (AA= 10.94%, AC= 37.22% and CC= 51.84%) (p = 0.381). No association was observed between rs3027898 genotypes and the main clinical and biological features of the disease.
These findings suggest that the IRAK1 rs3027898 polymorphism is not a risk factor for the development of SLE in Tunisian population.

P131. ASSOCIATION STUDY BETWEEN *TNFAIP3* POLYMORPHISM (RS2230926) AND SYSTEMIC LUPUS ERYTHEMATOSUS IN TUNISIAN POPULATION

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by self-reactive antibodies resulting in systemic inflammation and organ failure. The TNF alpha-induced protein 3 (*TNFAIP3*) is an ubiquitin-modifying enzyme and an essential negative regulator of inflammation. We investigated the association of *TNFAIP3* gene polymorphism rs2230926 and SLE in Tunisian population.

A case-control association study was performed on the SNP rs2230926 in 122 SLE patients and 152 healthy controls. SNP rs2230926 genotypes were determined by the mutagenically separated polymerase chain reaction (Ms PCR). Association studies were analyzed using the chi-square test and $p < 0.05$ was considered statistically significant.

The TNFAIP3 rs22330926 T allele was detected in 85% of SLE patient and 80% of controls indicating that is not associated with SLE ($p = 0.23$). The rs22330926 genotype distribution was as follows (TT= 71.3%, TG= 27.1% and GG= 1.6%) in SLE patients compared to (TT= 65.5%, TG= 29.3% and GG= 5.2%) in control subjects. The distribution of the TT, TG, and GG genotypes did not significantly differ between the 2 groups (P= 0.23).

In conclusion, the *TNAIP3* rs2230926 was not associated with SLE in Tunisian population. A larger number of patient is needed to confirm this lack of association between *TNFAIP* 3 rs2230926 and SLE.

P132. POLYMORPHISMS OF TOLL-LIKE RECEPTOR 4 AND CD14 GENES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

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Introduction: Toll-like receptor 4 (TLR4) and its co-receptor CD14 play a major role in innate immunity by recognizing PAMPs and signal the activation of adaptive responses. These receptors can recognize endogenous ligands mainly auto-antigens. In addition, TLR4 (Asp299Gly) and CD14 (C/T -159) polymorphisms (SNPs) may modify qualitatively and/or quantitatively their expression. Therefore, they could be implied in autoimmune diseases and can influence both susceptibility and severity of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Patients and methods: TLR4 (Asp299Gly) and CD14 (C/T -159) SNPs were genotyped using polymerase chain reaction (PCR) in 127 SLE patients, 100 RA patients, and 114 healthy controls matched in age and gender.

Results: CD14*T allele was significantly more frequent in SLE patients (0.456) comparatively to controls (0.355), p=0.02 OR (95% CI) = 1.53 [1.04-2.24]. In RA patients, the higher frequency of CD14*T allele (0.405) failed to reach significance, p=0.28. Investigation of the TLR4 (Asp299Gly) SNP showed no significant association neither with SLE nor with RA. Analysis of these SNPs according to clinical and biological features showed a significant higher frequency of arthritis in SLE patients with CD14*T/T genotype (92%) comparatively to those with C/C and C/T genotypes (72.5%), p=0.04. Moreover, SLE patients carrying CD14*T/T / TLR4*A/A haplotype had significantly more arthritis (91.3%) than the rest of SLE group (73%), p=0,044 and confirmed by multivariable analysis after adjustment according to age and gender, p=0.01.

Conclusion: The CD14 (-159)*T allele seems to be associated with susceptibility to SLE and arthritis occurrence.

P133. CYP27B1-1260 PROMOTER POLYMORPHISM AND VITAMIN D STATUS IN TUNISIAN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction/Objectives: In addition to the classical effects of vitamin D (VitD) on mineral metabolism and skeletal health, new effects on the immune system have been recently described. Several studies have suggested a potential role for this hormone in the development of autoimmune diseases, especially in Systemic lupus erythematosus (SLE). In this study, our objective was to analyze the polymorphism of the CYP27B1-1260 gene which encodes for an enzyme involved in VitD metabolism and to study the VitD status in serum of Tunisian patients with SLE.

Material and Methods: This case-control study included 280 participants composed of 150 healthy volunteers and 130 patients who fulfilled the American College of Rheumatology criteria for SLE diagnosis (Internal medicine department of the Hedi Chaker university hospital). First, we performed a genetic association study of the C/A polymorphism within the CYP27B1-1260 gene with the susceptibility to SLE. Secondly, VitD serum levels were determined using electrochimiluminescence method (Cobas 6000, Roche®) in a group of 58 SLE patients, wherein values <20 ng/mL were considered to indicate VitD deficiency and levels ≥ 20 ng/mL were considered normal. The patients group was further classified into two subgroups: untreated group (a) composed of 10 newly diagnosed patients (34.5%), and treated group b composed of 38 SLE patients (65.5%). Statistical analysis was made using SPSS.20 Software.

Results: The observed CYP27B1 promoter (-1260) C/A polymorphism genotype frequencies were in accordance with the Hardy–Weinberg equilibrium in our 130 SLE patients as well as in the control group. The genotyping of this C/A polymorphism revealed that the CC genotype was roughly similar in SLE patients and in healthy controls (66% vs 67.3 % respectively). There was no allelic or genotypic significant difference between SLE patients and controls. In patients group, means of serum values of VitD in total participants was 13.98 ng/ml (minimum: 2.5 and maximum: 70.5 ng/ml). For the association between VitD levels and clinical and immunological variables, no association or correlation was observed, except for C3 level. By dividing patients according to vitamin D supplementation, there was significantly difference between the mean serum values of VitD in *group a* and *group b* patients (10.94 vs 23.91 ng/ml, p=0.005).

Conclusions: In our study**,** we found that there is a high prevalence of VitD deficiency in our cohort. This is in keeping with reports from other parts of the world, including Asia and Europe even though vitamin D varies with geographic location and season. CYP27B1-1260 promoter polymorphism is not associated with SLE patients.

P134. EXPRESSION OF IRF5 SNPS IS AT HIGH RISK OF DEVELOPING SLE AND RA IN ALGERIAN PATIENTS

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Introduction: Outside HLA region, IFN pathway genes, which encode cytokines with critical modulating effects on Immune response, represent a key component of genetic network leading to autoimmunity development. An overexpression of genes regulated by type 1 IFN, have been reported in peripheral blood cells in several autoimmune diseases, underlying the crucial role of IFN signaling pathway in this case. Many IRF5 gene SNPs, a major regulator of the type I IFN induction, have been associated with connective tissue diseases onset such as SLE and RA.

Objective: To analyze possible contribution of IRF5 gene SNPs in SLE and RA susceptibility among Algerian patients.

Material and methods: Our study included 745 subjects: 155 SLE patients, 355 RA patients and 235 healthy controls. The IRF5 SNPs were genotyped using TaqMan® technology. Allele and genotype frequencies in patients and healthy controls were compared using chi-square test. Furthermore, all genotyped SNPs were in Hardy-Weinberg equilibrium. We used Phase 2.1 software to generate haplotypes. IRF5 haplotypes based on the 3 SNPs tested were examined for association with SLE and RA.

Results and discussion: In our population, high susceptibility for SLE was associated with 2 IRF5 SNPs: allele T for IRF5 rs2004640 (-3835 G/T), allele C and genotype CC for IRF5 rs752637 (-2716 C/T). For RA patients, genotype CC was associated with high risk compared to healthy controls. Furthermore, ATC haplotype was at high risk for SLE developing in patients and AGT was more frequent in healthy controls than SLE patients were. Otherwise, these SNPs were associated with anti-DNA and anti-SSA/Ro production (ACT haplotype). We have found a few reports suggesting association between IRF5 gene SNPs and autoantibody production in SLE. Niewold et al, in 2012 define a novel risk haplotype of IRF5 that is associated with anti-dsDNA antibodies and show that risk of SLE due to IRF5 genotype is largely dependent upon particular autoantibodies production. Finally, production of ACPA, in RA patients, was associated with IRF5 rs729302 (-13176 A/C) SNP expression. Overall, our results are in line with the literature.

Conclusion: Our results provide evidence-implicating IRF5 in SLE and RA susceptibility. We also demonstrated that the two SNPs of IRF5 rs2004640 and rs752637 were associated with anti-ds DNA antibodies production in SLE patients and IRF5 rs729302 was associated with ACPA production in RA patients. These data provide new insight into the pathogenesis of SLE and RA, underlying the pivotal role of innate immunity and type I IFN pathway in connective tissue diseases onset.

P135. SHARED GENETIC EFFECTS IN AUTOIMMUNE DISEASES

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Introduction: Genome-wide association (GWA) studies have identifiednumerous, replicable, genetic associations betweencommon single nucleotide polymorphisms (SNPs) and risk of common autoimmune and inflammatory (immune-mediated) diseases,some of which are shared between two diseases. Along with epidemiological and clinical evidence, this suggests that some genetic risk factors may be shared across diseases.

Material and methods: In this work, weinvestigate the genetic commonality in immune-mediated inflammatory and autoimmune diseases by examining the contributions of associated genomic risk regions in five diseases: ulcerative colitis (UC), Crohn's disease (CD), autoimmune polyglandular syndrome type II (APSII), systemic lupus erythematosus (SLE) and type 1 diabetes (T1D). 138 SNPs were genotyped in a cohort of 337 patients (68 UC, 39 CD, 61 APSII, 93SLE and 76 T1D) and 162 controls from Southern Tunisia.

Results and conclusion: We find that several variants identified in GWA studies of an individual disease influence risk to at least twodiseases. Thesevariantsare involved in adaptive immunity (*PTPN2, PTPN22, PTPN*6…), in IL-2/IL-2RA-dependent regulatorypathway (IL-2RA, IL-2RB..) and in transcription pathway (CREM, IRF5, STAT4…), arguing for a genetic basis to co-morbidity.

P136. RHUMATOID POLYARTHRITIS, AUTOIMMUNE HEPATITIS TYPE ONE AND AUTO IMMUNE THYROIDITIS ASSOCIATION; CASE STUDY

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Introduction: Recently, the concept of multiple autoimmune syndrome has been introduced to describe patients with at least three autoimmune diseases. About 25 percent of patients with autoimmune diseases have a tendency to develop additional ones. If some auto immune diseases are frequently associated, other associations are less often diagnosed in the same patient and thus less described in the literature. In this case study, We describe a case of a young woman with a quite rare multiple autoimmune syndrome including Rheumatoid arthritis, autoimmune hepatitis type one and auto immune thyroiditis.

Objectives: Highlighting a rare multiple autoimmune syndrome which is the association of Rheumatoid arthritis, autoimmune hepatitis type one and auto immune thyroiditis in the same patient.

Patients and methods: A 53 years old female patient, previously thyroidectomised following an autoimmune thyroiditis, suffered from deep vein thrombosis and complained of arthralgia and arthritis, muscle pain, erythema and edema in the face and lower limbs.

In front of these symptoms panel, an immunological exploration looking for an autoimmune connective tissue disorders (Rheumatoid arthritis…) was carried out at the immunology unit of the Frantz Fanon hospital in Blida, Algeria.

The exploration involves electrophoresis of serum proteins, the search for anti-nuclear autoantibodies by indirect immunofluorescence on Hep2 cells, the search for anti-CCP, anti-actin, anti-TPO and anti-TG antibodies by immunoenzymatic technique as well as the search for auto-antibodies by indirect immunofluorescence on rat liver, kidney, stomach sections.

Results: The serum protein electrophoresis revealed an electrophoretic profile in favor of a chronic inflammatory syndrome.The autoimmunity tests revealed the presence of autoantibodies against CCP, anti-mitochondria and anti-actin at significantly positive levels.

After questioning the patient and comparing the biological and clinical data, the multiple autoimmune syndrome has been diagnosed in this patient.

Conclusions: The overlap syndromes of rheumatoid polyarthritis and organ-specific autoimmune diseases such as auto-immune hepatitis and autoimmune thyroiditis are poorlyreported, so these types of cases should be described more frequently in the literature in order to facilitate their studies and allow possibly the elucidation of the physio pathological mechanisms at the origin of these associations.

P137. ANTINUCLEAR ANTIBODIES IN RHEUMATOID ARTHRITIS, QUANTITATIVE AND QUALITATIVE ASPECTS

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Introduction: Rheumatoid arthritis (RA) is an autoimmune disease frequently associated with rheumatoid factors (RF) and anti-cyclic citrullinated peptides antibodies (ACCP). Nevertheless, antinuclear auto-antibodies (ANA) were reported in this disease. The aim of this study was to assessthe quantitative and qualitative aspects of ANA in ANA positive RA patients.

Patients and methods: This retrospective study included 28 ANA positive RA patients (24 female and 4 male, mean age: 52.22 ±13.6 years, 27-80 years), diagnosed according to the ACR/EULAR 2010 criteria. They were followed in the Rheumatology departments of Fattouma Bourguiba Monastir and Taher Sfar Mahdia hospitals. They were recruited from January 2013 to May 2017. ANA were screened using the immunofluorescence technique on HEp2 cells and typed using Immunoenzymatic assays.

Results: The mean duration of the disease in our series was 10.11±7.3 years [1-35 years]. The mean disease activity score (DAS28) was 5.38±1.33 [2.48-8.56]. Dix huit patients had very active disease (DAS 28>5.1). The Latex RF was positive in 17 cases (60.7%). The Waller Rose RF was positive in 12 cases (46.4%). The ACCP were positive in 19 cases (67.9%). The fluorescence pattern of ANA was homogenous in 10 patients (35.7%), speckled in 11 patients (39.2%), granular in one patient and nucleolarin another one. The titer varied from 1/100 to 1/800. It was low (≤1/200) in 13 patients (46.5%) and high (≥1/400) in 10 patients (35.8%). ANA titers were elevated in 5 patients with very active RA (5/18) and in 5 patients with lesser active disease (5/10). The typing was informative in only 3patients (10.7%): one patient had positive anti-nucleosome antibodies (ANA titer of 1/800). The second had positive anti-double stranded DNA and anti-Sm (ANA titer of 1/160). The third one had positive anti-double stranded DNA and anti-SSA (ANA titer of 1/100).These two last patients were diagnosed as having Rhupus Syndrome.

Conclusion: Our study showed that assessment of ANA in RA is important to be considerated. They may help to detect other associated auto-immune diseases even at low titers.

P138. COMPARAISON OF TWO DIFFERENT KITS FOR ANTI-CCP ANTIBODIES ASSAY BY ELISA TECHNIQUE

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Introduction: Anti-CCP antibodies (Ab) are bio-markers used in the diagnosis and monitoring of rheumatoid arthritis (RA). The most used technique is the ELISA technique marketed by different firms. In this regard, first, second and third generation kits have been developed and their diagnostic performance appears to vary depending on the antigen employed and the protocols recommended by each manufacturer.
Objective: It is proposed by this work to compare the performance of EUROIMMUN and INOVA kits for anti-CCP antibodies assay in patients with RA.
Material and methods: 50 patients followed for PR in Mongi Slim La Marsa hospital were recruited. At the same time, 39 healthy donors were also taken and served as control group. The anti-CCP assay in patients and healthy donors was carried out by two different kits: EUROIMMUN and INOVA QUANTA LITE CCP 3 IgG ELISA. Sensitivity and specificity for each kit were determined. The corresponding ROC curves were also plotted.
Results: According to the reference values recommended by the manufacturers, the INOVA kit showed a sensitivity of 76% and a specificity of 76% with a positive predictive value (VPP) of 80.85% and a negative predictive value (NPV) of 71.43%. The area under the curve (AUC) was 0.838. Similarly, the EUROIMMUN kit has a sensitivity of 74% and a specificity of 94% with a VPP of 94.87% is a VPN of 74%. The AUC for this kit was 0.903. The difference between the two AUCs was not significant.
Conclusion: Although the EUROIMMUN kit has a higher specificity than the INOVA kit, the difference is not significant. We recommend to continue using this kit. However, a determination of anti-CCP Ab Cut-off according to the studied population must be carried out before the introduction of a new kit.

P139. ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND CRP/ACPA POSITIVITY IN ALGERIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Introduction: Vitamin D (VD) displays immunomodulatory activities and has been proposed as a potential player in the pathogenesis of rheumatoid arthritis (RA).
Objective: The aim of this study was to estimate the prevalence of vitamin D deficiency in patients with rheumatoid arthritis as compared to healthy controls and to analyze the association between levels of vitaminD and CRP (C-reactive protein)/ACPA (anti citrullinated protein antibody) positivity.
Materials and methods: This is a retrospective study on data obtained from 115 patients fulfilling ACR 1987 criteria for RA and 104 healthy controls. All participants were not receiving VD supplements. Serum vitamin D levels were measured using the hemiluminescent immunoassay method (CLIA). Levels of VD at 30 and 10 ng/ml were the cut-off values for VD insufficiency and deficiency respectively. CRP (mg/dl) was measured by the nephelometric method and ACPA antibodies were evaluated using enzymatic linked immuno-assay (ELISA).
Results: In this study, the sex ratio F : M was 8 : 1. The average age of the participants was 47, 5±12 years. The mean value of VD was lower in healthy controls (15 ng/ml) compared to patients with RA (25 ng/ml). 60% of our patients were insufficient in VD, while 10% had a VD deficiency.
Our study showed a correlation between low VD values and positive CRP compared to patients with negative CRP (23 ng/ml vs 29ng/ml ; P=0,023). Moreover, a statistically significant association was also found between low VD levels and ACPA positivity (23ng/ml vs 28ng/ml ; P=0, 03).
Conclusion: The results of this analysis indicated that vitamin D deficiency is quite common in Algerian patients with RA.CRP and ACPA values are inversely related to 25(OH) D levels, which emphasizes its immunomodulatory role in innate and adaptive immunity.

P140. IS MATRIX METALLOPROTEINASE-3 (MMP-3) A GOOD BIOMARKER IN RHEUMATOID ARTHRITIS DISEASE ACTIVITY ASSESSMENT?

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Introduction/Objectives: Matrix metalloproteinase-3 (MMP-3) is a protease induced by inflammatory cytokines in rheumatoid arthritis (RA) synovium and degrades a number of extracellular matrix components of cartilage and bone. Its central role in RA joint destruction was especially highlighted from both pathophysiological and clinical studies. The aim of our study is to evaluate serum MMP-3 levels in RA patients compared to healthy subjects and control patients. Then we assess how this marker reflects disease activity in RA in correlation with inflammatory markers, erosion and autoantibodies status.

Material/Methods: Our study groups consisted of 116 RA patients (86% women, mean age 50±13years, mean disease duration 7±9years), 66 healthy controls and 47 control patients [33 undifferentiated connective tissue disease (UCTD) and 14 Chronic Inflammatory diseases (CID)]. MMP-3 serum measurement was based on a quantitative ELISA assay (Aeskulisa DF MMP-3, Aesku Diagnostics, Germany) with a cut-off point of 50 ng/ml (for men) and 30 ng/ml (for women). MMP-3 levels were correlated with: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease activity score-28 (DAS28), Rheumatoid factor (RF), anti-cyclic citrullinated antibodies (ACPA) and erosion status.

Results: Serum MMP-3 was significantly higher in sera of RA patients (49±46ng/ml) compared to healthy controls (18±14ng/ml) ($p<0.001$) and UCTD patients (17±16ng/ml) ($p=0.004$). There was no statistical difference with CID patients (43±58ng/ml). MMP-3 levels were increased in 56% of RA patients (both female and male) particularly in female patients with high DAS28 (58±44ng/ml) compared to those with moderate DAS28 ($p=0.03$). This statistical increasing values were found also with positivity of CRP ($p=0.02$), RF ($p=0.03$), ACPA ($p=0.02$) and erosive status ($p=0.009$). Finally, MMP-3 levels correlated positively only with RF ($p<0.0001$; $r=0.35$) and ACPA rates ($p=0.004$, $r=0.26$) but not with DAS28 in RA patients.

Conclusion: Measurement of serum MMP-3 provides a particularly useful marker of inflammatory activity in RA patients and may have a particular value in predicting the progression of erosive disease.

P141. CLINICAL, BIOLOGICAL AND RADIOLOGIC FACTORS ASSOCIATED WITH FAILURE OF CONVENTIONAL TREATMENTS AND THE RECOURSE TO BIOTHERAPY IN RHEUMATOID ARTHRITIS

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Introduction: The conventional treatment (DMARDS) in Rheumatoid arthritis (RA) can fail for some patients requiring recourse to biologic treatments. Factors associated with non response to DMARDS are still under investigation. The aim of this study wasto assess clinical, biological and radiologic factors associated with failure of conventional treatments and the recourse to biotherapy in Rheumatoid arthritis.

Patients and methods: This case control study included 37 RA patientscandidate to biotherapy (31 female and 6 male individuals, mean age of 48.14±12.6 years, [26-69 years]). The indication of biologic treatment was either a resistance (32 patients, 86.5%) or intolerance to DMARDS (3 patients, 8.1%) or a severe extraarticular manifestation (2 patients). The different biological drugs used in our series (n=35) were Infliximab (27%), Etanercept (29.7%), Certolizumab (24.3%), Adalimumab (5.4%) and rituximab (2.7%). We included also in this study 43 RA controlsstabilized under conventional treatments (40 female and 7 male individuals, mean age of 51,7±11,1years, [30-76]). The clinical, biological and radiologic characteristics of patients and controls were evaluated during their hospitalization in the Rheumatology departments of the university hospitals of Monastir and Mahdia.

Results: The mean duration of the disease was 11.75 ± 7.7 years [1-30 years] for patients and 12.1±8 years [1-35 years] for controls. The disease activity score (DAS28) was 6.21±1.2 [3.45-8.23] for patients and 5.33±1.3 [2.1-7.5] for controls (p = 0.005). Hence, 32 patients (70.2%) had a DAS>5.1 (high activity) *versus* 28 in controls (65.1%).The articular deformations were found in22 patients (59.5%) and 19 controls (44.2%) (p=0.01). The mean erythrocyte sedimentation rate (ESR) was 64±29.3 mm at first hour [12-135mm] for patients *versus* 50.3±27.5 mm at first hour [9-115mm] forcontrols (p=0.04). The rheumatoid factor (RF) was positive in 16 patients (43.2%) *versus* 31 controls (72.1%) (p=0.001).The radiologic involvement was present in28 patients (75.7%) *versus* 38 controls (88.4%) (p=0.04). The other disease features were similar between the two groups.

Conclusion: This study showed that patients candidate to biologic treatments had a specific profile with higher disease activity, higher ESR, lower RF positivity, lower radiologic involvement and more articular deformations.

P142. THE INFLUENCE OF METHOTREXATE ON THE KINETICS OF BIOLOGICAL MARKERS IN RHEUMATOID ARTHRITIS AND THEIR CORRELATION WITH DISEASE ACTIVITY

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Introduction: Biological diagnosis of Rheumatoid arthritis (RA) is based on the evaluation of the inflammatory markers: C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR), and auto-antibodies: Rheumatoid factors (RF) and anti-citrullinated peptide or protein antibodies (ACPA). Methotrexate (MTX) is the most used drug in the treatment of this pathology. The influence of this drug on RA biomarkers remains controversial, especially for auto-antibodies. Our prospective study aimed to follow the kinetics of the RA biological markers under treatment with MTX, for one year.

Material and methods: Our study included 54 recent-onset RA patients (47 women and 7 men, mean age: 44,26 ± 14,41 years) treated with MTX (15,05 ± 2,40 mg) associated with a low dose corticosteroid (4mg/day), for one year. Disease activity was evaluated using the Disease activity score 28 (DAS28)- CRP. RA biological markers and DAS28 were evaluated at the time of diagnosis (T0), and after 6 (T6) and 12 months (T12) of MTX therapy. CRP level was measured by nephelemetry (Behring), while auto-antibodies levels (RF-IgM and anti-CCP3 antibodies-IgG) were determined by the immunoenzymatic test ELISA (INOVA).

Results: CRP, ESR and DAS28 significantly decreased between T0 and T6 ($p<0,001$). However, no difference was found during the second semester of treatment. The comparison of RF-IgM and ACPA mean levels before and after MTX therapy didn't show any significant difference. However, a positive correlation was found between those two auto-antibodies, at the three times. No correlation was found between DAS28 and ACPA contrary to FR-IgM which showed a positive correlation with DAS28 at diagnosis ($p=0,03$, $r=0,31$).

Conclusion: CRP and ESR levels significantly decrease after MTX treatment, while auto-antibodies level didn't change after one year therapy. Consequently, it is useless to repeat the evaluation of these auto-antibodies in RA after treatment by MTX. The association between RF-IgM and basal disease activity confirm the prognosis value of these auto-antibodies in RA.

P143. TOLL-LIKE RECEPTOR 2 (–196 to 174) DEL POLYMORPHISM IS ASSOCIATED WITH RHEUMATOID ARTHRITIS IN TUNISIANS

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Introduction/objectives: Toll-like receptors (TLRs) are implicated in the innate immune system recognition of microbial Pathogens, they play important roles in the signalization of many pathogen-related molecules and endogenous proteins associated with immune activation. The aim of this study was to investigate the role of TLR2 –196 to –174 insertion/deletion (Ins/Del) polymorphism in the occurrence of rheumatoid arthritis disease in Tunisians.
Material/methods: Using PCR-based method, 72 RA patients and 100 healthy controls were investigated. We compared alleles and genotypes frequencies in RA patients versus controls.
Results: Our results showed a significant association between a deletion of 22pb (–196 to 174) on the gene coding for Toll-like Receptor 2 and the occurrence of RA. Indeed, this allele confer a protective effect against occurrence of RA (P = 0.046, OR = 0.546). A higher protective role of the Del was observed when patients with polyarticular onset RA were compared to controls (P = 0.012, OR = 0.351).
Conclusion: Our study suggest that –196 to –174 Del affects the TLR2 gene and alters its promoter activity involving the initiation of cytokine production and other tissue-destructive mediators. Targeting TLR2 could be a potential bio-therapy of RA.

P144. INVOLVEMENT OF -3771C/T AND -1659C/T INOS GENE POLYMORPHISMS IN SUSCEPTIBILITY TO RHEUMATOID ARTHRITIS IN AN ALGERIAN COHORT

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Introduction: Nitric oxide (NO) is a very potent endogenous vasodilator, which plays a role in many biological systems. It acts as a mediator of signal transduction pathways and participates in inflammatory response. NO is generated from L-arginine catalysed by nitric oxide synthases (NOS). iNOS is the inducible isoform responsible for most inflammatory joint damage in Rheumatoid Arthritis (RA). Several polymorphisms of this gene have been associated with various infectious and autoimmune diseases. The SNPs of iNOS are localized in the promoter region of the gene (transcription-regulating region) and could have consequences on the pro-inflammatory and antibacterial activity of NO via iNOS activity.
Material and methods: To understand, we investigated whether functionally relevant iNOS gene polymorphisms are associated with the susceptibility/resistance to RA in a cohort of Algerian patients. Genomic DNA from 228 RA patients and 188 ethnically matched healthy individuals were genotyped for iNOS -3771C/T and -1659C/T polymorphisms. Chi-square test was used to estimate the contribution of each allelic variant in disease susceptibility/resistance.
Results and discussion: nalysis of -3771C/T allelic frequencies showed that the T allele was significantly more frequent in the RA patients than healthy controls (Pc=0.05; OR=1.45, CI95%: 1.02-1.76) suggesting that this allele is a risk factor in RA. Analysis of genotypic frequencies revealed no statistical differences between patients and healthy controls with a limiting tendency of significance concerning TT genotype (Pc=0.09). For -1659C/T, the results showed no significant differences between patients and healthy controls in the distribution of alleles and genotypes.
Conclusion: Our data assume that -3771C/T polymorphism contributes to genetic susceptibility to RA while -1659C/T polymorphism shows no association with genetic susceptibility to disease in Algerian patients.

P145. IRAK1 IS NOT ASSOCIATED WITH RHEUMATOID ARTHRITIS IN THE TUNISIAN POPULATION

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Background: Rheumatoid arthritis (RA) is characterized by the production of an array of proinflammatory cytokines through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathway. The interleukin-1 receptor (IL-1R) and Toll-like receptors contain a common cytoplasmic motif the Toll/IL-1R (TIR) homology domain. This motif is required for NF-kB activation. IL-1R-associated kinase 1 (IRAK1) is a key adapter molecule recruited during the signaling cascade of the TIR.

Objectives: We investigated the role of the IRAK1 single-nucleotide polymorphism (SNP) rs3027898 (IRAK1 rs3027898) in Tunisian patients with RA and their association with C reactive protein (CRP), rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP) antibodies, and erosion.

Patients and Methods: In a cohort of 172 adult RA patients and 224 matched controls, IRAK1 rs3027898 genotyping was determined by mutagenically separated polymerase chain reaction (MS-PCR) with newly designed primers

Results: The IRAK1 rs3027898A allele was detected in 67% of RA patients and 70% of controls indicating that it is not associated with RA in codominant, dominant, or recessive models even after stratification by age and gender.

Conclusion: The IRAK1 rs3027898 was not associated with RA. Our results need to be confirmed in a larger cohort.

P146. ASSOCIATION OF MIR-146A WITH RHEUMATOID ARTHRITIS IN THE TUNISIAN POPULATION

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Objective: We investigated the role of the IRAK1 single-nucleotide polymorphism (SNP) of miR-146a SNP rs2910164 (miR-146a rs2910164) in Tunisian patients with RA and their association with C reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and erosion.
Patients and Methods: In a cohort of 172 adult RA patients and 224 matched controls, miR-146a rs2910164 genotyping was determined by restriction fragment length polymorphism PCR (RFLP-PCR).
Results: The miR-146a rs2910164 G allele was detected in 76% of RA patients and 68% of controls, thus the C allele confers some protection based on a dominant model [CC+GC (odds ratio (95% confidence interval) = 0.6 (0.3–0.9), p = 0.03)]. No association with CRP, RF, anti-CCP, or erosion was found for either SNPs.
Conclusion: The C allele of miR-146a rs2910164 was found to be protective. Functional studies are required to investigate the exact role of miR-146a rs2910164 during RA.

P147. VASCULAR ENDOTHELIAL GROWTH FACTOR GENE POLYMORPHISMS AND SUSCEPTIBILITY TO RHEUMATOID ARTHRITIS IN ALGERIAN POPULATION

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Introduction: Rheumatoid arthritis (RA) is a multifactorial chronic inflammatory autoimmune disease, with genetic and environmental predisposition, characterized by a synovial angiogenesis as an outstanding stage in its pathogenesis. VEGF is the most potent pro-angiogenic molecule promoting the angiogenic phenotype of RA, it's one of the most potent proangiogenic factors, which expression is potentiated in response to the hypoxic state in the rheumatoid joints and by several of pro and anti-inflammatory cytokines. Therefore, VEGF has a great role in pathological conditions that are associated to autoimmune diseases such as RA. The aim of this study was to investigate the association of VEGF SNPs polymorphisms and susceptibility to RA.

Material and methods: 228 RA patients and 188 healthy subjects were inspected for -1154 A/G, -2578 A/C and -634 G/C VEGF gene polymorphisms by TaqMan SNP genotyping assay.

Results and discussion: We analysed SNP-2578 A/C, -1154A/G, and -634G/C of the VEGF gene and identified the first two as polymorphisms significantly associated with RA susceptibility. These results indicate that VEGF may be a factor of risk for the pathology, whereas SNP-634G/C has been shown to be unrelated to RA in the Algerian population. The allelic and genotypic frequencies for SNP-2578A/C indicate that the C-allele and the wild-type CC homozygous genotype show a significant difference between RA and healthy subjects (Pc=0.015, OR=1.5; Pc= 0.002, OR=1.91) respectively, this difference represents a risk factor for RA, Whereas the A allele and the heterozygous CA genotype protect against the disease (Pc= 0.015, OR=0.67; Pc= 0.001, OR=0.51). Identical results were observed for SNP -1154G/A (allele G: Pc=0.03, OR=1.53; genotype GG: Pc= 0.004, OR=1.90) and (allele A: Pc= 0.03, OR=0.65; genotype AG: Pc= 0.001, OR=0.47). Statistical analysis of the allelic and genotypic frequencies of SNP-634G/C doesn't indicate an association between predisposition or protection against the disease and this polymorphism. As for the VEGF gene, we propose to continue our study on a larger number of patients and to analyse the haplotypic frequencies (of the 3 SNPs) between patients with RA and healthy subjects.

Conclusion: Present findings indicate that VEGF genetic polymorphisms may be associated with the susceptibility to RA in the Algerian population.

P148. IL-17A, IL-17RC POLYMORPHISMS AND IL-17 SERUM LEVELS IN TUNISIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Interleukin-17 (IL-17), a cytokine mainly secreted by Th17 cells, seems to play a significant role in the pathogenesis of rheumatoid arthritis (RA). Functional genetic polymorphisms in IL-17 and its receptor genes can influence either qualitatively or quantitatively their functions. Therefore, we aimed to study the impact of IL17-A and IL17RC polymorphisms on serum level of IL-17 and RA susceptibility and severity.
Methods: In this context, IL-17A*rs2275913 (G/A) and IL-17RC*rs708567 (G/A) polymorphisms were investigated together with quantification of IL17 serum level in 115 RA patients and 91 healthy control subjects matched in age, sex and ethnic origin.
Results: No statistically significant association of the IL-17A and IL-17RC studied polymorphisms with the susceptibility to RA. In contrast, IL-17A serum levels were significantly higher in patients (55.07 pg/ml) comparatively to controls (4.75 pg/ml), p<10E-12. ROC curve was used to evaluate the performance of serum IL-17 in detecting RA. Given 100% specificity, the highest sensitivity of serum IL-17A was 61.7% at a cutoff value of 18.25 pg/ml; p=0.023, CI = [0.849-0.939]
Analytic results showed that bone erosions were more frequent in patients carrying the IL-17A*A/A genotype (38.9%) comparatively to those with *G/G and G/A genotypes (9.1% and 17.6%) although the difference was not significant, p=0.07. Besides, even lacking significance, the frequency of the positivity of IgM-rheumatoid factor and anti-CCP antibodies was lower in IL-17RC*A/A genotype carriers than in *G/G and *G/A patients.
Otherwise, IL-17 serum levels analysis showed a significant association with the activity of RA (DAS28≥5.1 = 74.71 pg/ml vs. DAS28<5.1 = 11.96 pg/ml), p<10E-6.
Conclusion : The IL-17A*rs2275913 (G/A) and IL-17RC*rs708567 (G/A) polymorphisms did not seem to influence RA susceptibility in Tunisian, but may influence its severity. Serum IL-17A seems to be predictive of severe RA occurrence.

P149. A1298C AND C677T GENE POLYMORPHISMS OF THE METHYLENE TETRAHYDROFOLATE REDUCTASE IN RHEUMATOID ARTHRITIS IN ALGERIA

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Introduction: Methotrexate (MTX) is the most used drug in rheumatoid arthritis (RA) treatment. However, it shows variability in clinical response, which is explained by an association with genetic polymorphisms. This study aimed to elucidate the role of the two gene polymorphism C677T and A1298C of the methylenetetrahydrofolate reductase (MTHFR) in response to MTX in Algerian RA patients.
Material and methods: Our study included 54 recent-onset RA patients (47 women and 7 men, mean age: 44,26 ± 14,41 years) treated with MTX for one year. MTX efficiency and toxicity were evaluated at 6 and 12 months respectively and the two gene polymorphisms were genotyped using a real time polymerase chain reaction (RT-PCR) method.
Results: No association was found between A1298C polymorphism and MTX toxicity. However, T allele of the C677T polymorphism was associated with the occurrence of MTX adverse effects (p=0,019, OR: 3,63, 95% CI [1,12–12,80]). No association was found between C677T polymorphism and MTX efficiency, while A allele of the A1298C polymorphism was associated with good and moderate responses (p=0,02, OR=3,28, 95% CI : [1,11 – 9,42]).
Conclusion: Our study suggests that MTHFR C677T and A1298C genotyping are associated with MTX toxicity and efficiency, respectively, in RA patients. This offers new perspectives in the personalization of RA treatment in Algeria.

P150. HAPLOTYPE STUDY: DETECTION OF A SUSCEPTIBILITY REGION WITHIN HLA-CLASS I FOR PRIMARY SJOGREN SYNDROME

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Introduction and objectives: Primary Sjogren syndrome (pSS) is considered a multifactorial condition with complex interactions between genetic and environmental factors. The HLA carries the major genetic influence on susceptibility to this disease. Other genes in the region of the short arm of chromosome 6 may be involved.
To test the hypothesis of the existence of a HLA haplotype predisposing to pSS, we conducted an association study using HLA loci (A, B and DRB1) and 10 microsatellite polymorphic markers spanning HLA region in pSS patients compared to healthy individuals.
Materials and methods: Forty four patients responding to the European criteria of pSS and 123 healthy unrelated subjects were analyzed for their HLA class I and class II haplotypes. HLA class I typing was performed using a standard microlymphocytotoxicity method. For HLA class II typing, HLA-DRB1 genotyping was performed using PCR-SSP. We studied the polymorphism of 10 microsatellite markers from telomeric to centromeric HLA region for both groups : D6S276, D6S265, C3.2.11, MICA, C1.2.C, TNFb, TNFa, TNFc, D6S273 and D6S291. The haplotype analysis was performed using "Haplo.stats'' package implemented in R language.
Results: We described for the first time a positive association of HLA-B15 antigen and pSS in our Tunisian population (15.91% vs 2.44%; *p*=0.004; OR=7.57 [IC: 1.8-30.7]). The comparison of the frequencies of DRB1 alleles in pSS patients and controls confirmed DRB1 * 03 allele association with pSS (43.18% vs 24.39%; *p*=0.02; OR=2.36 [IC: 1.14-4.86]).On the other hand, the association study of microsatellite markers showed that the a9 allele of D6S265 marker and the a20 of C1.2.C were found to be positively associated with pSS compared to controls: (20.45% vs 2.44%; p= 0.0003; OR=10.29 and 25% vs 6.5% ; p=0.001 ; OR=4.79 respectively).
Using the "Haplostat" software analysis, we found that the most associated region was located in the HLA class I region and limited by A and B loci. The distribution of haplotypes showed a significant difference between pSS patients and healthy controls for three haplotype combination: A-D6S265 (*p*=0.00056), D6S265-C3.2.1 (*p*=0.017) and B-MICA (*p*=0.036).
Conclusion: The results of this study support the hypothesis of the existence of a susceptibility gene to pSS located in the HLA class I region. However, more studies are necessary to prove the general relevance of this polymorphism for pSS.

P151. ALL TRANS RETINOIC ACID IMMUNOMODULATES NITRIC OXIDE PRODUCTION DURING PRIMARY SJOGREN'S SYNDROME

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Introduction/objectives: Primary Sjögren's syndrome (pSS) is an autoimmune epithelitis hallmarked by mononuclear cell (MNC) infiltration of exocrine tissue. Evidence suggests that this autoimmune disorder is associated with secretion of inflammatory mediators. All-trans retinoic acid (ATRA) is a bioactive derivative of vitamin well-known to have diverse immunomodulatory actions. In our study, we investigated, the *ex vivo* immunomodulatory effect of ATRA on NO pathway using peripheral blood mononuclear cells (PBMCs) from Algerian pSS patients.

Material/methods: PBMCs isolated from Algerian pSS patients and healthy controls were treated (or not) with different concentrations of ATRA. NO production was estimated with the Griess method. Expression of iNOS in PBMCs was examined by fluorescence immunostaining.

Results*:* Our findings revealed higher NO production in SS patients compared to healthy controls. Interstingly, we observed that ATRA decreases both NO production and NOS2 expression in pSS patients comparing to healthy controls.

Conclusion: Collectively, our results highlight an immunoregulatory effect of ATRA in pSS patients and a potential value in new strategies to improve the therapy.

P152. SCREENING FOR IGG4-RELATED SYSTEMIC DISEASE IN PATIENTS WITH SICCA SYNDROME

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Introduction: IgG4-related systemic disease (IgG4-RSD) is a recently individualized uncommon pathological entity of incidence probably underestimated because of its ignorance and the difficulty of its diagnosis. It has been recently characterized by the association of a focal or diffuse enlargement in one or more organs, elevated levels of serum IgG4 and histopathological findings including prominent infiltration of lymphocytes and IgG4-positive plasma cells. Multiorgan lesions can occur usually after 50 years of age such as sialadenitis and dacryoadenitis. Sicca syndrome is one of the most frequent sign in Sjögren's syndrome (SS). It has also been described in IgG4-RSD.The aim of this work was to measure IgG4 level in patients with sicca syndrome.

Material and methods: This was a 7-year retrospective study (2011-2017) in which we collected 79 patients with sicca syndrome (xerostomia, xerophthalmia, abnormal shirmer test and pathological break-up time) from internal medical department. We measured the IgG4 level by immunoturbidimetry (normal values:0.03-0.85g/L) (The Binding Site®). Statistical analysis used Med-calc software and a p value under 0.05 was considered significant.

Results: Our 79 patients were 9 men and 70 women (sex ratio M/W 0.12) with a mean age of 47.76 ± 13.28 years (23-76). There was no correlation between the level of IgG4 and age. Nevertheless, the level of IgG4 was higher in female (0.177 *vs* 0.08; p=0.006). Patients were divided according to the diagnosis of SS which was confirmed in 52 patients (group 1). Among them, 51% had positive anti-SS-A/Ro60 and/or anti SS-B antibodies. In 27 cases, SS was eliminated and an IgG4-RSD was suspected (group 2).The mean level of IgG4 was higher in group 2 than in group 1 (0.212g/L± 0.3 *vs* 0.143± 0.15; p <0.001). Patients with anti-SSA and anti-SSB positive antibodies had higher level of IgG4 (0.170g/L±0.18 *vs* 0.107± 0.09; p=0.002). We have gathered 3 patients with a high level of IgG4 > 0.85 g/L, two of them belong to group2.

Conclusion: Although IgG4 mean level was higher in patients with suspected IgG4-RSD, this level doesn't reach the threshold described by japanese research committee in 2011 (> 1.35g/L). This result should be confirmed in a larger cohort including healthy controls to evaluate the mean level of IgG4 in Tunisian general population.

P153 AUTOANTIBODIES IN SYSTEMIC SCLEROSIS AND THEIR CLINICAL CORRELATION

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Introduction: Systemic sclerosis (SSc) is a heterogeneous connective tissue disease with a broad range of manifestations. The presence of serum autoantibodies (aAb) directed to multiple intracellular antigens is a serological hallmark of SSc. Some of these aAb are specific and others are associated to SSc. Recent studies suggest that they are also associated with distinctive clinical subsets, specific patterns of organ involvement, and different prognostic features.
Objective: to study the correlations between the aAb in SSc and the different clinical manifestations of the disease.
Material/Methods: This was a retrospective study of 50 cases of SSc with no other connective tissue diseases associated, which were collected from the Internal Medicine department during the period from January 2011 to February 2017. All patients met the *American college of rheumatology/European league against rheumatism classification criteria for SSc of 2013*. The aAb were detected by immunodot (Euroimmun®) searching for specific aAb (anti-topoisomerase I aAb (ATA), anti-centromere (anti-CENP) A and B, anti-RNA polymerase III (anti-RP11 and anti-RP155), anti-fibrillarin, anti-Th/To) and associated aAb (anti-NOR-90, anti-PM-Scl100, anti-PM-Scl75, anti-PDGFR, anti-Ku, anti-Ro52).
Statistical analysis used SSPSS software and a p value under 0.05 was considered significant.
Results: There were 47 women and 3 men; the mean age was 50.1 ± 10.4 years. Forty seven (94%) patients had at least one specific or associated aAb. ATA was statistically correlated with the extent of skin fibrosis (p=0.026). Presence of telangiectasias was statistically correlated to anti-Th/To antibodies (p=0.047) and presence of pigmentation abnormalities was statistically correlated to anti-fibrillarin antibodies (p=0.038). Digital necrosis was more frequent in presence of anti-CENP A and B (p=0.031 and 0.047 respectively). Interstitial lung disease was statistically more frequent in patients with ATA (p=0.001) and in absence of anti-CENP A (p=0.028). Pulmonary arterial hypertension was statistically more frequent in presence of anti-NOR-90 aAb (p=0.006). The disorders of the esophageal peristalsis were statistically more frequent in absence of anti-NOR-90 aAb (p=0.019).
Conclusion: We reported a high frequency of aAb in Tunisian patients with SSc. These aAb are associated with distinctive clinical phenotypes, allowing detecting patients with high risk of severe visceral manifestations with a view to achieving closer monitoring.

P154. A RARE ASSOCIATION BETWEEN ANTI-CENP A AND B, ANTI-NOR 90 AND ANTI-PM-SCL IN A PATIENT WITH LIMITED SYSTEMIC SCLEROSIS

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Systemic sclerosis (SSc) is a chronic autoimmune rheumatic disease of unknown etiology characterized by microvascular abnormalities, cutaneous and visceral fibrosis all accompanied by signature immune abnormalities. SSc patients are classified as diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc). Both forms are different in terms of clinical and serological findings.The presence of serum autoantibodies directed to multiple intracellular antigens is a serological hallmark of SSc. These antibodies are present in more than 95% and are helpful in establishing an early diagnosis of SSc. Interestingly, the different antibodies are associated with distinctive clinical subsets, specific patterns of organ involvement, and different prognostic features. They are, thus, considered to be mutually exclusive. Some studies have describedrare cases of patients with two coexisting antibodies but the simultaneous presence of three antibodies has been rarely described.

We report the case of a 61-year-old woman who presented an acrosyndrome in both hands, a polyarthralgia affecting the large joints and a dysphagia, without skin involvement.Indirect immunofluorescence on Hep2 cells showed a fine-speckled fluorescence of the cell nuclei (> 1/1280).The characterization of the antinuclear antibody target antigens by immunodot showed the presence of three antibodies: anti-CENPA/B (+++), anti-PM-Scl 100 (+) and anti-NOR 90 (+). These data concurred with alcSSc sine scleroderma diagnosis. Accordingly, anti-CENPA/B is classically associated with lcSSc, while anti-PM-Scl which is less specific, is linked to both lcSScandoverlap syndrome with polymyositis. NOR 90 antibodies are also associated with lcSSc. Although the patient did not exhibit polymyositis symptoms, a long term follow-up is required.

Nowadays, the detection of two coexisting antibodies in patients with SSc is increasing, which is probably due to the current use of more sensitive immunologic tests. However, few authors have described the simultaneous presence of three antibodies in patients with SSc. A larger database of SSc patients could help tobetter define the disease subtype associated with multiple coexisting antibodies.

P155. ANTINUCLEOLAR ANTIBODIES IN PATIENTS LACKING CLINICAL FEATURES RELATED TO SYSTEMIC SCLEROSIS

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Introduction: Antinucleolar antibodies (ANoA) constitute a heterogeneous group of antibodies and are usually found in the sera of patients with systemic sclerosis (SSc). However, nucleolar immunofluorescence staining is not synonymous of SSc as it can occur in various autoimmune diseases without evidence of clinical manifestation related to SSc. As the target of ANoA in autoimmune disease other than SSc are not defined, we aimed to determine the specificities of ANoA in the sera of patients showing a nucleolar staining in indirect immunofluorescence (IIF) without clinical features related to SSc.

Materials and methods: We enrolled sera of patients without SSc clinical manifestations and presenting nucleolar pattern referred to our laboratory on a period of 3 years (2015-2017). IIF patterns were screened on HEp-2 cells (Biorad®) with a positive cut-off at 1:100 serum dilution. Target antigens of ANoA were assessed by immunodot (SSc profile, Euroimmun®) searching for anti Scl70, anti RP11, anti RP155, anti Th/To, anti NOR90, anti Pm Scl-75, anti Pm Scl-100 and anti Fibrillarin antibodies.

Results: There were 42 patients with overage age of 51.28 years and sex ratio (M/F) 0.61. Based on their clinical findings, patients were split up into groups: 26 patients referred for suspicion of connective tissue disease (CTD), 10 patients for autoimmune liver disease, 4 patients for inflammatory bowel disease and 3 patients for inflammatory nervous system disease. Twenty eight patients (68%) had at least one ANoA detected by immunodot. The frequency of ANoA was as follows: 73%, 70%, 75% and 0% in the four groups respectively. Among ANoA, anti-Th/To and anti NOR90 were the most frequent ANoA found in 13 patients (43%), most of them belong to CTD group (61% and 69% respectively). However, anti Scl70 was the less frequent ANoA as it was detected in only one patient with CTD. Moreover, association of ANoA was found in 16 patients (57%). Four sera (25%) showed association of 4 different ANoA, including 3 patients from CTD group.

Conclusion: Our finding indicate that sera of patients without Scc dot not recognize nucleolar targets usually considered specific of this disease such as Scl70. On the other hand the most frequent target recognized are usually considered associated to Scc and frequently present in CTD which was the case in this study. Clinical relevance of these antibodies should be tested in a longitudinal study to see if these patients will develop Scc in the future.

P156. CD146 AND CD146s: ACTORS AND TARGETS OF SCLERODERMA

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Summary: Systemic Sclerosis is a connective tissue disease characterized by excessive fibrosis of the skin and organs and the presence of autoantibodies in the serum. Among the new potential targets, CD146, which is a component of the endothelial junction, involved in signaling. A soluble form (CD146s) is generated either by proteolytic cleavage of the membrane form or by alternative splicing. This form is detectable in human serum. Its serum concentration varies during pathologies related to vascular dysfunction. Among the cell lines used in relative scleroderma research, HUVECs are mature human endothelial cells isolated from the umbilical cord vein. They therefore have the characteristics of endothelial cells of the venous type. They also express the set of markers specific for endothelial cells, including surface antigens CD31, CD144 and KDR, as well as vWF, expressed intracytoplasmic and of course CD146. We recently discovered a subpopulation of T cells called Memory Effectory T Cells, wich express CD146 and have a greater potential for cells migration to the inflammation site and secretion of proinflammatory cytokines.

Objective: The detection of auto-anti-CD146 antibodies in the sera of 50 Tunisian patients affects systemic scleroderma. The effect of these autoantibodies on the cell migration of Human Umbilical Vein Endothelial Cells (HUVECs). The determination of the molecular weight of the anti-CD146 and finally the subpopulations of T cells in PBMCs of patients with autoimmune diseases.

Materials and methods: ELISA did the auto-anti-CD146 antibody assay, using Rh-CD146s. ELISA and cultivation of HUVECs carry out the study of their effects on cell migration in two stages: depletion of autoantibodies of sera in the presence or absence of autoantibodies. The RT-PCR technique allowed us to demonstrate the distribution of T lymphocyte subpopulations in various autoimmune pathologies.

Results and conclusion: Decreased anti-CD146 autoantibody levels in TUNISIAN patients with scleroderma. The depletion technique eliminated 85% of the autoantibody from sera, which were subsequently cultured with HUVECs. The depleted sera allowed a more rapid cicatrization of the lacteated HUVECs. RT-PCR are not yet discussed (we will do it as soon as possible and send you an updated abstract).

P157. PTPN22 GENE POLYMORPHISM IN ALGERIAN SYSTEMIC SCLEROSIS PATIENTS

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Introduction: The present study investigated whether protein tyrosine phosphatase 22 (PTPN22) gene polymorphism was involved in the genetic predisposition to systemic sclerosis (SS) in Algerian patients.

Methods: The PTPN22 (rs2476601) single nucleotide polymorphism (SNP) was directly genotyped in 117 SS patients and 120 healthy controls by real time -polymerase chain reaction method (TaqMan Assays). The relationships between anti-Scl70, anti-centromere and anti-topoisomerase antibodies positivity and genotypes were statistically analyzed.

Results: The comparison of the allelic frequencies of the PTPN22 gene between patients and the control group shows a significant difference between patients and controls (0.42% vs 5% for the T allele, 99% vs 94% for the C allele, $P < 0.05$). The same result was showed for the genotype frequencies, a significant difference for the CC genotype and CT genotype was observed (99 vs. 90%, 0.85% vs. 9%, $P < 0.05$). The stratified analysis according to the antibodies positivity (anti-Scl70, anti-centromere and anti-topoisomerase) revealed no significant association with the PTPN22 alleles.

Conclusion: The functional polymorphism PTPN22 reported as associated with many autoimmune diseases seems to be involved in a genetic susceptibility to systemic sclerosis in the Algerian population.

P158. AUTOANTIBODIES IN PATIENTS WITH INFLAMMATORY MYOSITIS : ABOUT 108 CASES

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Introduction: Idiopathic inflammatory myopathies (IIM) such as dermatomyositis (DM) and polymyositis (PM) are inflammatory diseases of the skeletal muscle. In these diseases, autoimmune mechanisms play an important role and several autoantibodies (autoAb) are detected. Most of them are used in the classification criteria of these diseases. There are myositis specific autoantibodies (MSA) such as anti-SRP, Mi-2, Jo1, PL7, PL12, EJ and OJ; and myositis associated autoantibodies (MAA) such as anti-Ro-52, PM-Scl and Ku.
Objective: to study the prevalence of these autoAb and analyze their clinical correlation in patients with IIM.
Material and methods: It is a three years study (2014-2016) including all patients referred to our laboratory for suspicion of IIM. Antinuclear antibodies (ANA) were screened by Indirect Immunofluorescence on HEp2 cells (Biorad®). The specific and associated autoAb were analyzed using the immunodot technique (Euroimmun®). Statistical analyses used Chi square of Pearson and a p value under 0.05 was considered significant.
Results: There were 108 patients with an average age of 47 years and sex ratio M/F of 0.48. The clinical signs motivating the prescription of the research of these autoAb were the following: proximal myalgia (35%), rhabdomyolysis (23%), muscle weakness (21%), interstitial syndrome (6%), orbital damage (6%), distinctive skin rash of DM (4%), diffuse interstitial pneumopathy (3%) and suspicion of anti-synthetase syndrome (2%).
ANA were detected in 69 patients (64%) and IIM AutoAb were identified in 57 cases (53%): 13 MSA, 28 MAA and 16 association of the two types of autoAb.
Among MSA, anti-SRP was the most frequent (12%) followed by anti-Mi-2 (6%), PL12 (4%), Jo1 (3%), PL7 (3%), EJ (2%), and OJ (2%). The association of two MSA was found in 4 patients (2 SRP/PL12, SRP/PL7 and PL7/EJ).
Among MAA, the Ro52 specificity was frequently isolated (13%), followed by Ku (9%), PM-Scl75 (6%) and PM-Scl100 (5%).
The anti-Mi-2 was significantly associated with DM (p=0.005). Anti-Ku was significantly associated with rhabdomyolysis (p=0.027). Neither Anti-Jo-1 nor anti-SRP was significantly associated with clinical signs. All patients with orbital damage hadn't IIM autoAb. Seven IIM patients had an associated scleroderma; 5 of them had anti-Ro52 and anti-PM-Scl.
Conclusion: In contrast to the literature, the association of two MSA was described in our Tunisian patients and the anti-SRP was the most frequent of those autoAb. As expected, the anti-Mi-2 was specific to DM. The research of IIM autoAb isn't recommended in orbital damage.

P159. BIOLOGICAL CHARACTERITICS OF ANTI-TIF1γ AUTO-ANTIBODIES IN DERMATOMYOSITIS: TOWARD A NEW PROGNOSIS BIOMARKER

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Objective: Anti-TIF1γ auto-antibodies (aAbs) are strongly associated with paraneoplastic dermatomyositis (DM), raising questions about the link between cancer and autoimmunity. This study aimed to determine the clinical profile and biological predictors of cancer and death for anti-TIF1γ$^+$ DM patients.

Methods: A quantitative immunoassay (ALBIA) was developed to measure and characterize anti-TIF1γ aAb levels. Patients with age > 18 years at DM diagnosis and scoring positive (> 2 UA/mL) for anti-TIF1γ aAb using this assay were included. Level of aAb and IgG subclass was determined wih ALBIA. Data were compared using Fisher's exact or Mann-whitney test, as appropriate.

Results: Sixty patients with DM were included (65% women). Statistical analyses are given for the first 33 patients analyzed. Full data will be presented. Median age at diagnosis was 61 years [43-72]. Median duration of follow-up was 18 months [9-36]. Overall mortality during the follow-up period was 36%, with 9.5 month [4-15] median survival duration. Cancer was present in 64% of the 33 patients. Each of them had both typical skin and muscle involvement. Dysphagia was present in 85% of patients; 30% of them needed a feeding tube. Respiratory failure concerned 24% of patients, among whom 75% died. Presence of cancer was associated with higher age (64 vs 47 years, p=0.013), asthenia (OR=6.4, IC 95% [1.3-30.6]), a muscular repercussion on walking (OR=8.4, IC95% [1.5-44.9]), mortality (OR=12, IC95% [1.3-111]) and higher anti-TIF1γ aAb level (34 vs 9.6 UA/mL, p=0.02). Median aAb level was 34 UA/mL at initial time point. Characterization of anti-TIF1γ IgG subclasses allowed to classify patients among one of the six following different patterns of partition of IgG subclasses: IgG1 (32%), IgG1+2 (16%), IgG2 (23%), IgG1+3 (10%), IgG3 (3%) and IgG1+2+3 (16%). IgG2, IgG1+2 and IgG1+2+3 subclasses patterns are associated to an increased risk of cancer (OR=5.7, CI95% [1.2-28.4] and mortality (OR=28.6, IC95% [3.3-326.1]. When IgG2 are present, survival was significantly decreased (15 months vs undefined survival, HR=5.9, CI95% [1.9-18.6]).

Conclusion: This study highlights the severity and poor prognosis of anti-TIF1γ aAb-positive DM. Interstingly, higher aAb levels and IgG2 subclass appeared as cancer predictors. The higher intensity of the anti-TIF1γ aAb response may suggest a persistant cancer-associated antigenic stimulation, supporting the hypothesis that cancer could trigger the auto-immune response and associated myopathy. Quantification of aAb level and characterisation of IgG subclasses are necessary in anti-TIF1γ positive DM to estimate the risk of malignancy and mortality.

P160. A RARE ASSOCIATION BETWEEN AN Mi-2, PL-7 and PL-12 ANTIBODIES IN A PATIENT WITH DERMATOMYOSITIS

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Dermatomyositis (DM) is a connective tissue disease characterized by specific inflammatory lesions in muscle biopsy. It predominantly affects the adults and is characterized by both cutaneous and muscle involvement. A similar clinical entity has been described called anti-synthetase syndrome (ASS) characterized by a milder muscle involvement, a higher proportion of interstitial lung disease with poor outcome requiring more aggressive therapy, as well as polyarthritis, fever, Raynaud's phenomenon and mechanic's hands. Anti-Mi-2 antibodies are rather specific for DM. Moreover, patients with anti-Mi-2 usually respond well to steroid treatment, have a good prognostic value and do not manifest lung involvement or polyarthritis. In contrast, anti-aminoacyl transfer RNA synthetases (ARS) including Jo-1, EJ, OJ, PL-7, and PL-12 autoantibodies, considered as markers of ASS clinical phenotypes, are frequently found in patients with interstitial lung disease.

Herein, we report the case of an exceptional association between anti-Mi-2, anti PL-12 and anti-PL-7 antibodies in a 29 year-old women who presented muscle weakness, an erythematous rash in her anterior chest, face and fingers. Interestingly, the patient did not present any interstitial lung disease or associated cancer. The biological exploration showed a ten times increase of the Creatinin Phospho Kinase (CPK) activity. The muscle biopsy showed specific inflammatory lesions. Indirect immunofluorescence on Hep2 cells showed a fine-speckled fluorescence of the cell nuclei (> 1/1280). The antibodies to extractable nuclear antigens (ENA), assayed by ELISA, were negative. Dot-blot (Myositis ®**)** with recombinant antigens showed PL7, Mi-2 and PL-12 reactivity. Treatment with corticosteroid alone resulted in the resolution of muscle weakness and the normalization of serum CPK level. To our knowledge, there is no case reporting a simultaneous presence of these three antibodies. In fact mutual exclusion was noted between autoantibodies anti-synthetases and Mi-2. However, sporadic cases of coexistence of two myositis-specific antibodies are reported and lead apparently to a more complex and severe disease expression.

P161. AUTOANTIBODY PROFILE OF CONNECTIVE TISSUE DISEASE WITH CUTANEOUS MANIFESTATIONS

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Objective: Report the autoantibody profiles of 60 patients with cutaneous connective tissue disorders.
Patients and methods: 60 sera from patients with connective tissue disease (53 women and 07 men with an average age of 35 ± 14 years), of which 63.33% had malaria rash, rash and erythema; 26.66% had sclerodactyly lesions and cutaneous sclerosis; 16.66% Raynaud's syndrome; 5% of mucocutaneous lesions; 3.33% an acrosyndrome; 3.33% suffered from cutaneous hyperpigmentation; 1.66% had discoid lupus lesions and alopecia. The detection of anti-nuclear antibodies (ANA) was performed by indirect immunofluorescence on HEp-2 cells. The detection of anti-soluble nuclear antigen (anti-ENA) antibodies and of anti-DNA antibodies was carried out by flow immunofluorometry (Luminex).
Results: The ANA assay was positive for all the sera studied and revealed a heterogeneity of autoantibodies as follows: 51.66% were speckled, 31.66% homogeneous, 6.66 % Nucleolar aspect, 5% centromeric aspect and 5% mixed appearance (homogeneous + nucleolar). The search for anti-ENA antibodies gave the following results: 45% for anti-SSA, 20% for anti-U1RNP, 16.66% for anti-Sm / RNP, 13.33 % For anti-Scl70, 10% for anti-SSB, 8.33% for Jo-1, 6.66% for anti-Sm, 5% for anti-PmScl, and 1.66 % For anti-PCNA. The search for anti-DNA antibodies was positive for 28.33% of the sera.
Conclusion: In the light of our results, we conclude that cutaneous manifestations have highly polymorphic clinical manifestations with very heterogeneous autoantibody profiles.

P162. USEFULNESS OF ANTI-DESMOGLEIN 1 AND 3 ENZYME-LINKED IMMUNSORBENT ASSAY IN PEMPHIGUS VULGARIS AND FOLIACEUS IN SOUTH TUNISIA

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Introduction: Pemphigus is an autoimmune blistering disease of skin and mucous membranes. Pemphigus foliaceus (PF) and pemphigus vulgaris (PV) are the two major subtypes of pemphigus characterized by intraepithelial blisters caused by the production of autoantibodies directed against desmosomes. Two transmembrane desmosomal proteins are specifically targeted by patients' autoantibodies (Abs): desmoglein (Dsg) 1 and 3.
We aimed in this study to determine the usefulness of anti-Dsg1 and 3 Abs in the diagnosis and follow-up of patients with PF and PV in south Tunisia.
Methods: We analyzed retrospectively 134 serum samples taken from 82 patients with PF and PV followed in the dermatology department of Hedi Chaker University Hospital of Sfax between 1992 and 2015. We measured anti-Dsg1 and anti-Dsg3 antibodies by ELISA at least once during the course of the disease.
Results: Our study included 82 patients: 52 patients with PF and 30 with PV. The sex ratio (F/M) was 8.1 and the mean age was 42 years (18 – 84 years). The mean follow-up period was 21 months. There were significant correlations between anti-Dsg1 Abs with PF (p=0.02) and anti-Dsg3 Abs with PV (p<0.001). In PF, initially high titers of anti-Dsg1 antibodies were associated to lesions spread (p=0.02), to short delays of remission (p=0.02) and healing (p=0.3). However no similar correlations were found between anti-Dsg3 Abs and PV. After first line treatment, anti-Dsg1 titers showed a significant decrease (p=0.01) in PF but not in muco-cutaneous PV (p=0.3). Anti-Dsg3 titers, by contrast, did not show a significant association with mucous PV disease activity (p=0.07). In PF, patients with persistent anti-Dsg1 high titers were more likely to have relapses compared to those with negative Abs (2.4 relapses vs 0.8 respectively; p=0.06). All patients with PV had their anti-Dsg3 Abs remained positive.
Conclusion: Antibodies against Dsg1 and 3 are useful for adjusting the diagnosis of the type vulgaris or foliaceus of pemphigus. Unlike anti-Dsg3 Abs, anti-Dsg1 titers seem to better correlate with PF activity, predict long term relapses and may be therefore a valuable tool to plan the schedules for tapering the drugs.

P163. AHR TRANSCRIPTION IS DECREASED IN SKIN OF VITILIGO PATIENTS

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Vitiligo is a chronic depigmentary skin disorder resulting from a selective destruction of melanocytes. The pathogenesis of the disease is still incompletely deciphered. Along with the auto-immune mediated destruction, several pathomechanisms could be responsible of the loss or destruction of melanocytes in vitiligo. Herein, we analyzed the role of aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor which plays a key role in melanocyte homeostasis and pigmentation after UVB stimulation. Through the transcriptional analysis of the related gene, we revealed a significantly decreased expression of the AhR transcripts in the non-lesional skin of vitiligo patients compared to the normal skin of healthy controls. Moreover, a progressive increase in the AhR transcription from the normal skin to the perilesional and the lesional skins of vitiligo patients has been noticed. This may be ascribed to a feedback response to counteract the deleterious inflammatory response. However, the AhR mRNA level in the perilesional and lesional skins of vitiligo patients did not reach this of the normal skin of heathy controls. The significant decrease of the baseline AhR transcription in the skin of vitiligo patients is of great interest as it could represent a susceptibility factor for the development of vitiligo. It could also explain the variable efficiency of UVB therapy in vitiligo patients. Evaluating the level of AhR transcription could, thus, be a predictive factor of the response to such therapy. Furthermore, we may suggest the use of the most potent AhR ligands as an alternative treatment in vitiligo patients with decreased levels of epidermis AhR.

P164. ASSOCIATION OF ANTI-PHOSPHATIDYLSERINE AUTO-ANTIBODIES WITH THE RISK OF THROMBOSIS IN WOMEN WITH ANTI-PHOSPHOLIPID: OBSTETRIC SYNDROME

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Introduction: Anti-phospholipid syndrome (SAPL) is an autoimmune disease characterized by recurrent fetal loss, arterial and venous thrombosis, and thrombocytopenia.
Biologically, the presence of anti-cardiolipin, anti-B2GPI (IgGand / or IgM) antibodies and lupus anticoagulant was noted at least twice, at 12-week intervals.
Objective: Evaluation of the association of anti-phosphatidylserine antibodies with the risk of thrombosis in women with repeat abortions and in whom SAPL is suspected.
Materials and methods: 194 patients with an average age of 39 years (19-59), with suspicion of obstetric SAPL were recruited from the Beni-Messous hospital ; All patients had ≥ 2 abortions. The detection of the antibodies was performed by enzyme-linked immunosorbent assay (ELISA).
Results and discussion: Our study showed that 47 patients (24%) were positive for at least one anti-phospholipid antibody (cardiolipin/β2GP1).
Anti-phosphatidylserine antibodies IgG and IgM isotypes were positive in 55 (61%) and 73 (81%) patients with obstetric SAPL and thrombosis versus 34 (33%) and 58 (56%) patients with obstetric SAPL without thrombosis (P= 0.0007 and 0.0001 for IgG and IgM isotypes respectively). Anti-phosphatidylserine antibodies potentiate the activity of antibodies directed against prothrombin (a vitamin K-dependent glycoprotein involved in the coagulation processes) by increasing their affinity as the latter is recognized more efficiently when linked to phosphatidylserine, Hence the association of anti-phosphatidyl serine with the risk of thrombosis during the course of obstetric SAPL.
Conclusion: Anti-phosphatidylserine antibodies are associated with the risk of developing thrombosis in women with obstetric SAPL.

P165. IMMUNOLOGICAL STUDY AND CLINICAL PRESENTATION OF ANCA VASCULITIS

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Introduction: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis comprises microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA). Major target antigens of ANCA associated with vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is related to MPA and EGPA, and PR3-ANCA is the marker antibody in GPA.
Objective: Report the clinical-immunological characteristics of 92 patients with positive ANCA vasculitis
Material and methods: 92 patients (64 Female et 28 male), with ANCAvasculitis according to the Chapel Hill classification. ANCA was performed by indirect immunofluorescence, supplemented by immunodot to determine their specificity MPO/PR3.
Résultats: The mean age of patients was 51 years, the diagnosis was: 14 cases of GPA, 21 cases of microscopic polyangiitis (MPA), 04 cases of EGPA, 53 subjects had signs of overlap between the GPA and MPA.
The clinical picture was dominated by renal disease followed by lung disease and rheumatologic signs. Some patients had cardiac involvement.
71 patients had p-ANCA (77,17%), of which 43 were anti-MPO specificity (46.73%), 21 patients had c-ANCA (22.83%), including 9 with a specific anti-PR3 (9, 78%) , patients showed no 2 searched specificities (44.44%).
Conclusion: ANCA vasculitis is rare, clinical and immunological spectrum is very heterogeneous. The demonstration of ANCA directed vis-a-vis PR3 and MPO specific as an aid in the diagnosis of systemic vasculitis

P166. PR3 AND MPO-ANCA AUTOANTIBODY IN PATIENTS WITH SUSPICION OF VASCULITIS

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Introduction: Antineutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against constituents of neutrophil granulocytes. Detection of these autoantibodies is critical for the diagnosis and monitoring of the ANCA-associated vasculitis. The two major autoantigen targets are Proteinase 3 (PR3) and myeloperoxidase (MPO). The purpose of this work was to describe the results of the ANCA research addressed to our immunology laboratory and to determine the clinical spectrum associated with positive ANCA.

Methods: It was a retrospective study carried out for all sera sent to our laboratory of immunology of the LA RABTA hospital from January 2013 to January 2016 and in which a research for ANCA was requested. ANCA were detected by indirect immunofluorescence (IIF) assays using ethanol and formalin fixed human neutrophils (Euroimmun®). ANCA specificity was determined by ELISA and /or immunodot (Euroimmun®) which were used to detect PR3 or MPO antibodies.

Results: The study included 1711 unique patient samples, of which 314 were IIF-ANCA positive. Of these, 159(50.6%) were C-ANCA, 89(28.3%) were P-ANCA, 14(4.5%) were C-ANCA atypical, 45(14.3%) were P-ANCA atypical and 7 (2.2%) were both P and C-ANCA. Renal failure, lung damage and ischemic stroke were the most associated diseases (14.8%, 6.7% and 6.7% respectively). Thus, of the 159 C-ANCA samples, 28.9% were positive for anti-PR3 and 11.9% were positive for anti-MPO, and of the 89 P-ANCA positive samples, 44.3% were positive for one of these two specificities. Importantly, only 3 of 59 samples with an atypical IIF-ANCA pattern were positive for anti-PR3. Two patients had an atypical P-ANCA on IIF and one patient had an atypical C-ANCA, with no clinical or radiologic evidence of vasculitis. Anti-PR3/C-ANCA was significantly associated ($p<0.0001$) with renal-limited rapidly progressive glomerulonephritis. Thirty percent of patients presenting P-ANCA with MPO had renal failure and 20% presented signs of vasculitis. In patients with suspicion of vasculitis, 50% of C-ANCA were directed against PR3 whereas 44.4% of P-ANCA recognised MPO.

Conclusion: A positive ANCA with an anti-MPO or anti-PR3 antibody confirms the diagnosis of vasculitis when suggestive clinical signs are present. In our study more than one third of sera with IIF positive results were negative for anti-MPO and anti-PR3, so that other antigenic targets of ANCA (minor antigens) should be investigated to explore the positive results with IIF method.

P167. TARGET ANTIGENS FOR ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES IN TUNISIAN PATIENTS

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Introduction: The major target antigens recognized by anti-neutrophil cytoplasmic antibodies (ANCA) in ANCA-associated vasculitis are proteinase 3 (PR3) and myeloperoxidase (MPO), which occur in the azurophilic granules of neutrophils. PR3-ANCA is the major antigen associated with the C-ANCA fluorescence pattern while MPO-ANCA cause a P-ANCA pattern. Besides the two main ANCA antigens, there are other antigens more rarely involved. The aim of this work was to look for these minor antigens in C-ANCA or P-ANCA positive patients with negative anti-MPO and anti-PR3 antibodies.

Methods: It is a retrospective study performed in 44 patients presenting P-ANCA or C-ANCA and negative anti-MPO and anti-PR3 antibodies. ANCA were detected by indirect immunofluorescence (IIF) assays using ethanol and formalin fixed human neutrophils (Euroimmun®). MPO and PR3 specificities were determined with both methods: ELISA and immunodot (Euroimmun®). ELISA method (Euroimmun®) was used to detect other autoantigens: Lysosyme, Bactericidal Permeability Increasing Protein (BPI), Elastase, Lactoferrine, Cathepsine G and Peroxidase.

Results: Of the 44 patients presenting P-ANCA or C-ANCA and negative anti-MPO and anti-PR3 antibodies, 24 were male and 20 were female, with an average age of 61.6 ± 54.1 (range 11–96) years at diagnosis. Seventeen patients had renal failure, 10 were with lung damage, 9 with suspicion of vasculitis, 4 with Wegener and 4 patients presented peripheral neuropathy. Among our 44 patients, 29 (65.9%) had C-ANCA and 15(34.1%) had P-ANCA. Only nine patients (20.45%) were positive for one antigen directed against BPI or Elastase. The highest prevalence of target antigens was observed against BPI which was detected in 5 patients with C-ANCA and 2 patients with P-ANCA. Anti-BPI antibody was detected in patients who presented: renal failure (n=2), lung damage (n=2), Wegener (n=2) and peripheral neuropathy (n=1). The antibody anti-Elastase was detected twice in persons who had a renal failure. All patients with Wegener (n=4) were detected C-ANCA, 2 patients were anti-BPI.

Conclusion: Given the very small number of minor antigen reactivity of positive ANCA sera, two main hypotheses can be discuss: either there were false positive results detected by IIF due to no specific neutrophil antibodies, or there were antibodies directed against other neutrophil antigens that must be explored and that doesn't exist in the list of antibodies used in this study.

P168. THE FREQUENCY OF THYROID AUTO-ANTIBODIES DURING BIERMER'S DISEASE

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Introduction: Biermer's disease is an autoimmune atrophic gastritis which is behind a vitamin B12 deficiency. The association of Biermer's disease with other autoimmune diseases is frequently found.

Objective: The aim of this study was to estimate the frequency of the association Biermer's disease-Autoimmune thyroid disease (AITD) in patients with Biermer's disease by investigating the prevalence of TPO (thyroid peroxydase) and TG (thyroglobulin) antibodies among a population which is diagnosed to have Biermer's disease.

Material and methods: 62 patients with Biermer's disease (a median age of 52 years and sex ratio women/men: 3/1), and 68 healthy controls (a median age of 34 years and sex ratio of 2/1) were included in this study. The dosage of TPO and TG antibodies was done by chemiluminescence technique.

Inclusion criteria of the patients was Biermer's disease confirmed by gastritis autoimmunity with 100% positive APCA (antibodies against parietal cells), 24% positive IF (intrinsic factor) antibodies.

Results: Among the 62 Patients, 24 patients had positive TPO antibodies (39%) and 5 patients had positive TG antibodies (8%).

TPO antibody was found higher in patients compared to the normal group (39% vs 10%, p=0.0001. OR= 5.50. IC: 95%: [2.025 - 16.430]). However, no significant differences were noted for the frequencies of anti-TG antibodies (8% vs 7 %, P> 0.05).

Conclusion: In our population, the association of AITD with Biermer's disease is highly probable, for this reason it is recommended to perform a regular screening in patients with Biermer's disease.

P169. POLYMORPHISM -308 OF THE TNF-A GENE IN ALGERIAN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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Introduction: Autoimmune thyroiditis (TAI) is one of the most common organ-specific autoimmune diseases, with Hashimoto's thyroiditis (TH) and Graves-Basedow's disease (GB), the most common clinical expressions. TH is characterized by hypothyroidism associated with thyroid destruction by thyroglobulin-specific self-reactive T lymphocytes. In contrast, GB disease, is characterized by hyperthyroidism due to excessive production of thyroid hormones induced by thyrotropin receptor-specific autoantibodies. Cytokines are key regulators of the immune and inflammatory response; and therefore polymorphisms at the genes encoding cytokines are potential risk factors for the development of TAI.
Materials and methods: The SNP polymorphism of the gene of proinflammatory cytokine TNF-α-308 A/G was studied by PCR-SSP. This was a case-control study of 41 patients with autoimmune thyroiditis (27 HT and 14 GD) and 35 healthy subjects in the control population.
Results: The GG genotype and the TNF A-308A / G high phenotype were more common in TAI vs. control (OR = 3.29, IC [1.02-11.04], p = 0.048) and in TH patients (OR = 3.87, IC [1.06-14.94], p = 0.039). Genotype AG TNF A-308 was more common in TAI males.
Conclusion: Our study reports an association between the polymorphism of the TNF-α gene and the development of TAI, highlighting the relevance of the polymorphisms of genes related to inflammation in the etiopathogenesis of TAI.

P170. INTEREST IN THE RESEARCH OF ANTITHYROID ANTIBODIES DURING THE DIAGNOSIS OF A CETOSIC ACIDIC DIABETES

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Introduction: Diabetic ketosis is an acute complication of diabetes that consists of an accumulation of ketone bodies in the blood, associated or not with acidosis. Ketosis is usually secondary to type 1 diabetes, which makes it necessary to look for other autoimmune diseases. The objective of our study is to investigate the interest of the determination of thyroid antibodies in the diagnosis of ketotic acute diabetes.
Patients and Methods: This is a retrospective and exhaustive study conducted in a Department of Endocrinology and Diabetology at the Farhat Hached Hospital of Sousse concerning patients diagnosed with an inaugural ketoacidosis over a period from January 2010 to August 2016. The study population was divided into 2 groups according to the presence or absence of anti-pancreatic autoimmunity evidenced by the positivity of the anti-pancreatic antibodies. Group 1: all patients with proven pancreatic autoimmunity, and group 2 patients without autoimmunity (Ac anti GAD and Ac anti IA2 negative). The search for antithyroid autoantibodies was done in both groups.
Results: These were 391 patients, the sex ratio was 266 men / 125 women, mean age 34 years with a standard deviation of 14.33 years and extremes ranging from 13 years to 77 years. Family history of type 2 diabetes, hypertension, and obesity were significantly more common in group 2. Family history of type 1 diabetes and familial autoimmunity were significantly more common in group 1. A ketosis precipitating factor was found in 77.7% of the overall study population, significantly more frequent in group 1 than in group 2. Serum autoimmune exploration performed in group 1 during hospitalization revealed a significant predominance of anti-GAD present in 90.5% of cases compared to anti-IA2 present in 39.2% of cases. Anti-celiac antibodies were also assayed (anti-Gliadin anti, Endomysium anti and anti-transglutaminase) with a positivity of 2%, significantly more present in group 1 than in group 2: 4.4% against 1.3%. A search for anti-thyroid antibodies showed the presence of anti-TPO and anti-TSH receptor present in 3.3% and 3.6% of cases respectively in the general population with a significant predominance in group 1 : 6.3% vs 1.3% in group 2 for anti-TPO and 7.6% vs. 0.9% respectively for groups 1 and 2 for anti-RTSH.
Conclusion: Antithyroid autoantibodies were predominantly present in type 1 ketotic patients with a family and personal bundle of autoimmunity.

P171. ANTI-PANCREATIC ANTIBODY PROFILE DURING THE DIAGNOSIS OF TYPE 1 DIABETES

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Introduction: Type 1 diabetes (T1D) is an autoimmune disease characterized by anti-pancreatic autoantibodies. The diagnosis can be made by the positivity of at least one of the antibodies. Nevertheless, the serological profile is not identical in all patients.The objective of our study is to evaluate the frequency and type of anti pancreatic autoantibodies in the diagnosis of the disease.

Patients and methods: This is a retrospective study of diabetes mellitus with insulinopenia at the time of insulin use. The autoimmune character is evidenced by the positivity of the anti-pancreas antibodies: anti glutamyl acid decarboxylase GAD and / or anti-tyrosine phosphatase antibody IA2.

Results: Our series covered 359 patients: 209 men and 150 women, aged between 10 and 69 years with an average age of 28.75 years. The clinical presentation was ketotic in the majority of cases n = 336 (93.6%), with an inaugural ketosis in 313 cases (87.2%). The duration of insulinopenia varies between one week and 36 months, with an average duration of 3.75 months and a standard deviation of 6.8 months, exceeding 6 months achieving a slow form and prior oral treatment in 24% of cases. In terms of weight, there is an average BMI of 22 (range : 15 and 39), greater than 30 in 22 patients. A precipitating factor was found in 256 patients (71.3%) with physical and / or psychological stress in 103 patients (40.2%). The average blood glucose level = 16.40 mmol / L and mean HbA1C = 12.32%. The anti-pancreatic antibodies were directed against the GAD-65 antigen in 334 patients (93%) while the anti-IA-2 antibodies were present in only 84 patients (23.4%).

Conclusion: Anti-GAD antibodies remain the most common and most prevalent antibodies in the diagnosis of type 1 diabetes. The presence of anti-IA2 alone is rare but possible.

P172. AUTOANTIBODIES DIABETES AND MICRONUTRIENTS IN TYPE 1 DIABETICS AND SIBLINGS OF ABIDJAN DISTRICT, CÔTE D'IVOIRE

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Introduction: the presence of diabetes autoantibodies has been reported as a factor of predisposition of diabetes in siblings of type 1 diabetics.
Objective: Search autoantibodies of diabetes anti-ICA, anti-GAD, anti-IA2 in type 1 diabetics and their siblings of district of Abidjan, Côte d'Ivoire, associated with the dosage of micronutrients such as phosphorus, magnesium and calcium.
Materials and methods: The study population consisted of 49 people, including 19 type 1 diabetics (T1D) and 30 siblings whose first degree of the blood was taken. T1D were recruited to University Hospital center (U.H.C) of Yopougon and Treichville and two NGOs. Serum obtained allowed the determination of anti-islet cell autoantibodies (anti-ICA) detected by the immunofluorescence method on monkey pancreas, anti-glutamic acid decarboxylase autoantibodies (anti-GAD) and anti- phosphatase IA2 detected by ELISA. The dosage of phosphorus, magnesium and calcium was made by the cobas 6000 Roche/Hitachi.
Results: Anti-ICA was positive to 5.26% in T1D and absent in siblings, anti-GAD were positive in the T1D to 57.89% and 3.33% for the siblings. The anti-IA2 was positive in the T1D to 47.36% and 16.66% for siblings. The anti-ICA-GAD-IA2 combination was present in 5.26% of T1D and absent in the siblings. The GAD-IA2 combination was present in 31.57% of T1D and 3.33% among siblings. The average phosphorus in T1D was 1.86±1.06 mmol/L versus 2.39±1.51mmol/L in the siblings; twice higher than normal values.
Conclusion: Autoantibodies diabetes in siblings is a marker for the imminence of autoimmune diabetes. Phosphorus is an important marker for the detection and follow up T1D.

P173. CORRELATION BETWEEN DIABETES AUTOANTIBODIES AND ENVIRONMENTAL PARAMETERS IN TYPE 1 DIABETICS AND THEIR SIBLINGS IN ABIDJAN DISTRICT, CÔTE D'IVOIRE

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Introduction: environmental parameters are known as releases or accelerator of the autoimmune process of type 1 diabetes.
Objective: The aim of this work is to determine the correlation between the presence of diabetes autoantibodies and certain environmental parameters and diet in type 1 diabetics (T1D) and their siblings.
Material and Methods: The study population consisted of 49 people, including 19 with T1D and 30 siblings of first degree whose blood and faeces were collected. T1D were recruited from two University hospital centres in Cote d'Ivoire. Serum obtained allowed the determination of anti-ICA autoantibodies by the immunofluorescence method, anti-GAD and anti-IA2 detected by ELISA. Blood parasites were sought by the drop of thick and blood smears. Intestinal parasites were searched by the direct method, Kato and Ritchie techniques. Yeasts isolation was done on Sabouraud chloranphénicol and identifying by the chromatic Candida medium. Pinworms were sought by the anal scotch test technique. Vaccines and food were mentioned on a survey sheet.
Results: The 3 diabetes autoantibodies were present in T1D and 2 combinations anti-GAD-IA2 among siblings ($p<0.0001$). Hand pinworms, DT1 and their siblings infected with blood parasites are respectively, intestinal parasites, yeast. The diet of T1D significantly different from that of siblings ($p=0.031<0.05$).
Conclusion: There is no correlation between the presence of diabetes autoantibodies and blood and intestinal parasites, yeasts, pinworms among siblings of diabetics. Their diet should be balanced to avoid the installation of diabetes.

P174. IMMUNOGLOBULIN GENES AND THE RISK OF TYPE 1 DIABETES: STUDY OF 59 FAMILIES

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Introduction: Immunoglobulins (Ig) are a bipolar molecules produced by plasmocytes in response to an immunogen. This molecule function's as an antibodies (Ac) that bind specifically to one or more related (Ag) antigens, providing host protection. By redirecting the pathogen to the secondary lymphoid organs, IgM can stimulate the healing of infection by the confinement of IgM-Ag immune complexes in the lymph nodes and spleen, thereby stimulating their degradation by macrophages. In fact, the immune complexes formed can also trigger an autoimmune response in the presence of a self Ag. In healthy individuals, self-reactive LBs are normally present, with a high level of natural and self-reactive IgM. The binding of self-reactive IgM to an auto-Ag may also be expected to result in complement activation (C) and the formation of Ag-IgM-C complex. Then, this immune complex, increases the auto-Ac production and seems to trigger an autoimmune disease. In this study, we studied 9 SNPs of the IGHM, IGHD and IGHG genes, coding for the constant region of the heavy chain mu (μ), delta (δ), gamma (γ) of the IgM, IgD, IgG isotype and 2 SNPs of the IGHV gene which codes for the variable region of the heavy chain H.
Methods: The study group consisted of 255 individuals from 59 families (23 multiplex families and 36 simplex families), including 86 children with T1D (mean age, 12 ±6.36 years with a range of 2-45 years) and 169 of their biological first degree relatives (mean age, 30 ±10.60 years with a range of 3-57 years). DNA of all patients and their relatives were genotyped using Sequenome's iPLEX Gold technique. The FBAT (Family Based Association Test) was used for the statistical transmission study.
Results: our results indicate a difference in the transmission of the G allele and the AG genotype of the rs1956596 polymorphism of IGHM gene rs1956596 from parents to affect children (Allele G, p = 0.04, Z = 2.018, Genotype, AG, p = 0.007, Z = 2.65). In addition, the GT genotypes (p = 0.032, Z = 2.14) and AA (p = 0.029, Z = 2.17), respectively, of the polymorphisms rs2180790 and rs1808152 are also more frequently transmitted than expected from parents to diabetic patients.
Discussion: these preliminary results show that the IGHM gene could be implicated in susceptibility to T1D in southern Tunisia. A case-control study on a larger sample would confirm whether or not this gene is involved in the predisposition to this pathology.

P175. LACK OF ASSOCIATION BETWEEN ACE I/D GENE POLYMORPHISM AND TYPE 1 DIABETIC NEPHROPATHY IN THE TUNISIAN POPULATION

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Background: Diabetic nephropathy (DN) is one of the leading causes of end-stage renal disease. Genetic predisposition plays a role in the development of DN as only a portion of patients with diabetes will have renal disease.
Objectives: The aim of this study was to evaluate the association between Angiotensin-converting enzyme (ACE) Insertion/Deletion (I/D) and Angiotensin II Type 1 Receptor A1166C (*AGTR1* A1166C) gene polymorphisms and Diabetic Nephropathy in Tunisian Type 1 diabetes (T1D).
Methods: The study included 90 T1D patients without ND and 45 T1D patients with DN. The investigation of the ACE I/D gene polymorphism was done using Polymerase Chain Reaction (PCR) method. The identification of the AGTR1 A116C gene polymorphism was determined by mutagenically separated polymerase chain reaction (MS-PCR). Association studies were analyzed using the chi-square test and $p < 0.05$ was considered statistically significant.
Results: The ACE I/D genotype distribution was as follows (DD=55.55%, ID=37.78% and II=6.67%) in DN group compared to (DD=62.23%, ID=28.89% and II=8.88%) in patients without DN. The distribution of the D/D, D/I, and I/I genotypes did not significantly differ between the 2 groups (P=0.563). The AGTR1 A1166C genotype distribution in patients with DN (AA=53.5%, AC=27.9% and CC=18,6%) also did not significantly differ from those without DN (AA=69.76%, AC=22.1% and CC=8.14%) (P=0.117).
Conclusion: This case-control study show that ACE I/D and AGTR1 A1166C gene polymorphisms are not genetic risk factors for DN in Tunisian type 1 diabetes.

P176. GENETIC POLYMORPHISM IN INTERFERON GAMMA (IFN-γ) IN ALGERIAN TYPE 1 DIABETES PATIENTS

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Introduction: Type 1 diabetes (T1D) is a multifactorial autoimmune disease with complex genetic inheritance where cytokines play prominent roles. To identify additional genetic markers, we tested polymorphisms in regulatory regions of interferon gamma gene in our population. These polymorphism exhibit functional consequences for expression and function.
Methods: IFN γ single nucleotide polymorphisms at positions +874 (T or A), were examined in 70 T1D patients and 74 healthy controls using Polymerase Chain Reaction *Sequence Specific Primers* (PCR- SSP).
Results: Our results show significantly decreased T allele frequency in patients when compared with control (48% vs 64%, P =0.004). Genotype analysis shows that TT genotype is also decreased in T1D than control (p= 0.007) the ORs (95% CI) were 0.38 (0.18- 0.78).
Conclusions: Our preliminary results suggested that the IFN γ +874 A/T genetic variant may be involved in Algerian type 1 diabetes susceptibility.

P177. INCREASED PREVALENCE OF COELIAC DISEASE IN DIABETES

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Introduction: The co-occurrence of celiac disease and type 1 diabetes has been reported as 5-7 times more prevalent than celiac disease alone. The clinical presentation of celiac disease in patients with type 1 diabetes may vary considerably. Less than 10% of patients with type 1 diabetes and celiac disease show gastrointestinal symptoms. Celiac disease is more prevalent in type 1 diabetic patients than in the general population in Algeria country. As follows the ESPGHAN guidelines, diagnosis of celiac disease is based on the presence of villous atrophy and crypt hyperplasia by intestinal biopsy and the presence of antibodies against tissue transglutaminase.
Material and methods: In a total of 420 diabetic adults were screened for coeliac disease by simultaneous detection of human IgA isotype antibodies directed against tissue transglutaminase, gliadin and deaminated peptide of gliadin by FIDIS Celiac DPG kits (Theradiag).
Resultats: Forty diabetic adults were positive for IgA class transglutaminase and a Deaminated Peptide of Gliadin antibody, all underwent biopsy of the small intestine. Twenty two cases of coeliac disease were found; all of these adults had characteristic biopsy establishing partial or total villous atrophy.
Conclusion: It was concluded that IgA class transglutaminase and deaminated peptide of gliadin antibody were a good marker of coeliac disease for screening tests of high risk populations. The prevalence of coeliac disease in Algerian diabetic population was 5.2% and we suggest that diabetic adults be screened routinely for antibody for coeliac disease at diagnosis of type 1 diabetes, every year in the first five years of follow-up.

P178. CELIAC DISEASE SCREENING IN AN ALGERIAN COHORT OF CHILDREN WITH TYPE 1 DIABETES

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Background: Patient with type 1 diabetes (T1D) are at increased risk of coeliac isease (CD). The aim of this study is to determine the prevalence of tissue transglutaminase antibody (IgA/IgG) in children with T1D from the central region of Algeria
Methods: A cohort of 78 children with T1D (38 males and 40 females) aged between 2 and 16 years were screened for CD using the enzyme-linked immunosorbent assay (ELISA) for IgA and IgG anti-tissue transglutaminase (tTG). An IgA antiendomysial antibody (EmA) was determined by immunofluorescence
Results: Anti-tTG antibody (IgA and IgG) were positive in 2 subjects (2.5%). While all patients were asymptomatic of CD at the time of screening. Both patients with positive tTG antibodies were positive for EmA. The intestinal biopsy was not done yet
Conclusion: The prevalence of CD (based on serology) in diabetic children in central region of Algeria was found to be lower than in several studies. However, more investigation on a larger number of patients will be done to confirm these results

P179. PREVALENCE OF AUTOIMMUNE ENDOCRINOPATHIES IN CELIAC DISEASE (CD): ABOUT A RETROSPECTIVE SERIES

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Introduction: CD is an autoimmune inflammatory enteropathy that can be accompanied by various extra-intestinal manifestations. Endocrine autoimmune manifestations are not rarely observed during this pathology. The aim of this study is to specify the prevalence of autoimmune endocrinopathies (AIE) during CD and to specify its types.
Methods: A retrospective study carried out in the department of gastroenterology B of the Rabta hospital and reporting all the consecutive cases of CD in a period of 20 years (from January 1996 to December 2016). AEIs and their characteristics were investigated.
Results: Eighty CDs were collected. The mean age was 35.1 years (16 to 67 years) with a sex ratio (M / F) of 0.25. Ten patients had at least one AIE associated with CD, a prevalence of 12.5%. They were 9 women and a man of average age of 33.8 years. AIE was: type I diabetes (N = 7), autoimmune dysthyroidism (N = 3) and autoimmune adrenal insufficiency (N = 1). One patient had 2 EAI associated (diabetes and hypothyroidism) with CD. The remaining 9 patients had only one AIE. The discovery of diabetes preceded in all cases the CD in average delay of 6 years. The 3 dysthyroides were observed in women. It was hypothyroidism with anti-thyroperoxidase antibodies positive in 100% of the subjects. In one case, the discovery of the thyroid involvement preceded by 15 years that of the CD. The two affections were concomitantly recognized in 2 other patients. One patient had an autoimmune adrenal insufficiency related to Addison's disease, the discovery of which preceded that of CD. Despite the small size, the presence of diabetes during CD was correlated with the existence of associated dysthyroidism ($p = 0.0224$).
Conclusion: During CD the prevalence of AIE is 12.5%, and it is dominated by type I diabetes, followed by dysthyroidism. In a celiac patient, the presence of diabetes appears to increase the risk of associated dysthyroidism.

P180. PREVALENCE OF INFRAMMATORY BOWEL DISEASES (IBD) DURING CELIAC DISEASE (CD)

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Introduction: The association of celiac disease (CD) with inflammatory bowel disease (IBD) is rare. The objective of this study is to determine the prevalence of IBD during CD.
Methods: A retrospective study carried out in the department of gastroenterology B at The Rabta Hospital compiled all the cases of CD diagnosed between January 1996 and December 2016. The prevalence, the type and the characteristics of the IBD associated with the CD were investigated.
Results: This study involved 80 patients with CD. The mean age was 35.1 years with sex-ratio (M / F) equal to 0.25. The mean follow-up was 9.5 years. Three cases of IBD associated with CD were noted which corresponds to a prevalence equal to 3.75%. It was about two women and one man aged 19, 20 and 21 years, respectively. These cases are represented by ulcerative colitis (UC, N = 1) and by Crohn's disease (N = 2). In all three patients, CD was suspected because of symptoms of chronic diarrhea associated with a mosaic pattern of the duodenal mucosa. The diagnosis was confirmed by the presence of tissue transglutaminase antibodies (N = 1) and anti-endomysial antibody (N = 2) and by the histological evaluation of duodenal biopsies revealing complete villous atrophy. The diagnosis of IBD was concomitant with the diagnosis of CD in UC's patient. It was suspected by the presence of bloody stools. Crohn's disease, was suspected alongside CD in 1 case, in front of the presence of complex anoperineal lesions. In the second patient, the diagnosis was made 12 years after the diagnosis of CD, based on bloody stools and a segmental involvement of the ileum and the sigmoide on endoscopy.
Conclusion: In this series, the prevalence of IBD during CD was 3.75%. This rate is higher than in the general population. In case of CD, a systematic search for IBD should be carried out by a complete exploration of the digestive tract.

P181. PREVALENCE OF VIRAL HEPATITIS C (VHC) IN CELIAC DISEASE (CD): ABOUT A RETROSPECTIVE SERIES

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Introduction: CD is characterized by a gluten-induced damage of the small bowel in sensitive individuals that may cause malabsorption. The prevalence of HCV infection among coeliac patients is 0.6%. The purpose of this study is to specify the prevalence of VHC during CD.
Methods: A retrospective study was performed in the Gastroenterology B department of the Rabta Hospital, collecting all consecutive cases of CD diagnosed over a period of 20 years (January 1996 to December 2016). Epidemiological, clinical, biological and endoscopic data were collected. VHC serological screening was performed in patients with abnormal liver function tests.
Results: Eighty consecutive CD patients were collected. The mean age was 35.1 years (16 to 67 years) with a sex ratio of 0.25. VHC was diagnosed in 2 patients, a prevalence of 2.5%. The diagnosis of CD was suspected in patient with carential anemia in the first case, and chronic diarrhea in the second case. It was confirmed by histology: subtotal villous atrophy with a positivity of the anti-endomysium and anti-transglutaminase antibodies. In the two patients, the diagnosis of VHC preceded that of the CD of 24 and 12 months respectively.
In the first patient: A cytolysis at 1.5 N suspected the diagnosis of VHC. The results showed : a viremia at $1.55X10^4$UI / ml, a genotype 2, an A1F2 score at fibrotest and negative autoimmune markers. Pegylated combinated therapy for 6 months resulted in a sustained virological response. Hepatocellular carcinoma was diagnosed 10 years later and was treated with radiofrequency. In the 2nd patient: Cirrhosis confirmed the diagnosis of hepatitis C infection. The results showed: a viraemia at $5X10^5$ IU / ml, a genotype Ib and a positivity of anti-nuclear, anti-mitochondrial and anti-smooth muscle antibodies with the presence of mixed cryoglobulinemia. Due to a depression contraindicating the interferon the patient was not treated. The evolution was marked by the worsening of cirrhosis.
Conclusion: Prevalence of HCV infection among celiac patients is 2.5%. It is higher than that found in the tunisian general population (1.2%). Etiopathogenic links between the two affections deserve to be sought by prospective studies.

P182. DIAGNOSTIC VALUE OF ANTI-F-ACTIN ANTIBODIES

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Introduction: Anti-smooth muscle antibodies (SMA) are known to recognize several components of the cell cytoskeleton. Their antigenic targets can be microfilaments (actin and vinculin), intermediate filaments and microtubules. SMA with F-actin specificity characterize type 1 autoimmune hepatitis (AIH). They are present in 85% of patients with AIH, either alone (35%) or in conjunction with antinuclear antibodies (50%) but are not specific to this disease. In fact, some studies report that anti-F-actin antibodies can be also found in non AHI diseases essentially celiac disease, connective tissue diseases and infectious hepatitis. The objective of this study was to determine the diagnostic value of anti-F-actin antibodies.

Materials and methods: Our study was carried out over a period of four years (2014-2017). Patients were selected on the basis of the presence of F-actin SMA detected by indirect immunofluorescence (IIF) on rat liver–kidney–stomach sections (Biosystems®). All sera were also tested by IIF on Hep2 cells (Bio-Rad®) and an immunodot was used to attest Actin specificity. Serologic testing for celiac disease included antitissue transglutaminase antibodies (IgA-tTG) by ELISA (Innova®) and IgA anti-endomysial antibodies by IIF (Biosystems®). Clinical data were recorded when available.

Results: Two hundred patients were included with sex ratio 0.3 and mean age of 45 years (6 months – 88 years).

Study of patients medical records showed that they can be divided into five groups: 104 cases (52%) with suspicion of AIH (Group1), 23 patients (11.5%) had celiac disease (Group 2), 16 patients (8%) with connective tissue disease (Group 3), 12 patients (6%) had positive viral hepatitis serology (Group 4) and in 45 cases (22.5%) a specific diagnosis was not available (Group 5). We noted that in the first group 73% was female, mean age 43 years and 17 patients had associated autoimmune liver disease: 11.5% primary biliary cirrhosis and 2% primary sclerosing cholangitis. In the second group most of patients were adult with mean age of 37 years and 8 cases (34.8%) presented extra-digestive manifestations. In the third group a predominance of cases with systemic lupus erythematosus was noticed (50%). In the fourth group; 10 cases (83%) were HCV positive of which 50% were already at cirrhosis stage. Finally in the last group we should note that 27 cases (60%) had a correct liver function (no cytolysis nor cholestasis).

Conclusion: We conclude that anti-F-actin antibodies can be found in numerous diseases setting, including both liver and non liver diseases where they may reflect an autoimmune status or a chronic activation by viral infection.

P183. PREDICTIVE VALUE OF ANTI-MITOCHONDRIA ANTIBODIES TYPE 2 IN PATIENTS WITHOUT PRIMARY BILIARY CIRRHOSIS

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Introduction: Anti-mitochondria antibodies type 2 (AM2) are often described as specific markers of primary biliary cirrhosis (PBC). They are found in almost all cases of BPC including asymptomatic forms. They can therefore be detected early even before the appearance of clinical signs. However, the characteristics and natural history of patients having AMA2 with no declared PBC are not well understood.

Objective: To evaluate the predictive value of anti-mitochondria antibodies type 2 in patients without PBC.

Patients and Methods: It was a prospective study including all patients whose sera were addressed to the immunology department of La Rabta Hospital between 2010 and 2012, and in which AMA2 were detected fortuitously by Indirected Immunofluorescence (IIF) on HEp2 cells (BioRad®) or on Liver/stomach/kidney tissues (Biosystems®) and confirmed by immunodot (Euroimmun®).

Were excluded from this evaluation, patients with at least one of the following signs: cholestasis, cirrhosis or histopathologic evidence of PBC.

Results: There were 14 patients (12 females and 2 males) with a median age of 61.9 ±9.8 years. Among associated pathologies, the most common founded were respiratory diseases (4 cases), hypothyroidism (4 cases) viral hepatitis (4 cases) Sjogren syndrome (3 cases) vasculitis (2 cases) anemia (1case) and systemic lupus erythematosus (1 case).

Hepatic assessment was normal in 9 patients and showed a cytolysis in 2 cases.

AMA2 were positive using IIF on HEp2 cells in 9 patients and on tissue rat sections in 5 patients with median AMA2 title 1:100.

Using immunodot, AMA2 and M2.3E were positive in 100% and 60% respectively and 5 patients had anti-nuclear antibodies with high specificity for BPC such as GP210 and SP100.

During the follow-up, only one case of PBC was reported. It was women aged 63 years suffering from polyarteritis nodosa. The immunodot result was positif for AMA-M2, M2-3E, SP100 and PML.

Conclusion: The majority of patients with positive AMA2 did not develop CBP. These antibodies seem to be related to an autoimmune state since it was detected in patient with autoimmune diseases or produced after hepatitis injury during viral infection. This "cholestasis negative" form could also correspond either to a very early stage of PBC or to a subgroup with a different natural history.

P184. AUTOANTIBODIES BY LINE IMMUNOASSAY IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Aim: To determine the sensitivity of line immunoassay for the detection of serological markers of primary biliary cholangitis (PBC).
Patients and methods: Fifty-three PBC patients (45 woman, 8 men, median age 53 years 2 months) were studied. Sera were collected between 2013 and 2017 from 3 hospitals in the center of Tunisia. The inclusion criteria was the positivity of anti-mitochondrial antibodies (AMA) by indirect immunofluorescence. A line immunoassay was used to determine antibodies to AMA-M2, M2-3E (BPO), Sp100, gp210 and PML.
Results: The frequency of anti-AMA-M2, anti-M2-E3, anti-Sp100 and anti-gp210 was 96.2%, 100%, 28.3% and 34% respectively. Only one patient had anti-PML. Twenty-eight out of 53 patients (52.8%) had anti-Sp100 and/or anti-gp210. Only five patients out of 53 (9.4%) had both anti-Sp100 and anti-gp210.Ten patients out of 53 (18.9%) had anti-Sp100 but not anti-gp210 and Thirteen patients out of 53 (24.5%) had anti-gp210 but not anti-Sp100. In all PBC patients and in female patients, the frequency of anti-Sp100 was significantly lower than that of the combination anti-Sp100-anti-gp210 (28.3% vs 52.8%, p = 0.01 and 24.4% vs 53.3%, p=0.005 respectively). The frequency of anti-gp210 was lower than that of the combination anti-Sp100-anti-gp210 but reaching a borderline significance (34% vs 52.8%, p = 0.05).
Conclusion: The combination anti-Sp100-anti-gp210 increases the sensitivity of these tests from 28.3% and 34% respectively to 52.8%.

P185. CLINICAL AND IMMUNOLOGICAL PROFILE OF PATIENTS WITH NuMA ANTIBODIES: ABOUT 14 CASES

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Introduction: Anti-Nuclear Mitotic Apparatus (NuMA) antibodies 1 and 2 belong to the family of auto-antibodies against mitotic spindle apparatus (MSA), a subtype of antinuclear antibodies (ANA). Anti-NuMA1 and anti-NuMA2 differ by their antigenic target, anti-NuMA1 targeting the NuMA and anti-NuMA2 the Kinesin Eg5 (HsEg5).
They are reported to be associated with several conditions, mainly connective tissue diseases, autoimmune liver disease and infections. In the present study, we assessed the prevalence and the clinical significance of anti-NuMA antibodies from a monocentre serie of 14 patients.
Material and methods: We retrospectively collected and analyzed clinical and immunological data of 14 patients with positive anti-NuMA.NuMA Antibodies were detected using an indirect immunofluorescence on HEp-2 cells.
Results: Our population included 11 women (79%) and 03 men (21%) with a mean age of 53,64 ±20.15 years. NuMA Antibodies were Anti-NuMA1 in all the patients (100%).
A definite autoimmune disease was established for 9 patients (63%). Four patients (29%) had a systemic lupus erythematosus, Sjögren syndrome in 01 patient, a systemic sclerosis in 1 patient, a AHAI in 1 patient and one patient with SAPL. A Biermer anemia was present in one patient. Non autoimmune conditions were present in 5 patients. They comprised three Inflammatory rheumatism, a IgA nephropathy in 1 patient and nephrotic syndrome in one patient. Anti-NuMA1 antibodies were associated with other ANA in 6 patients (42%), including 3 patients with positive anti-ENA, i.e. anti-SSA in 1 patient, anti-SSB in 1 patient, anti-Scl70 in 1 patient and anti-Jo-1 in one patient, and 3 patients with positive anti-dsDNA.
Conclusion: Detection of anti-NuMA antibodies is very uncommon. When present, they are mostly associated with connective tissue disease. Clinicians may be aware that in these latter conditions, anti-NuMA antibodies may be the single serological marker.

P186. AUTOIMMUNE LIMBIC ENCEPHALITIS: IMMUNOLOGICAL DIAGNOSIS

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Introduction: Autoimmune limbic encephalitis (ALE) has common characteristics, associating various neurological and psychiatric symptoms of rapid evolution. It can be of origin:
- Infectious: mainly due to Herpes viridae infections.
- Autoimmune: we can distinguish two groups of ELA :
- On the one hand, the ALE linked to the presence of antibodies directed against an intracellular neuronal antigen (CV2, PNMA2, Hu ...).
- On the other hand, the ELA related to the presence of antibodies directed against a membrane antigen (NMDA-R, VGKC, GABAb-R ..).

Goal: The interest of immunological exploration in the diagnosis of Autoimmune limbic encephalitis and the determination of the frequency and specificity of autoantibodies during Autoimmune limbic encephalitis.

Patients and Methods: The present study is performed on a sample of 21 Algerian patients (21 sera and only 06 CSF) with suspicion of an ALE, which we analyzed and explored at the Laboratory of Neuro-Immunology Department of Immunology of the Pasteur Institute of Algeria:
- An immunological analysis: quantitative (dosage of albumin and immunoglobulins GAM in sera and CSF by laser nephelemetry) and qualitative (isoelectric focusing) of CSF
- The search for anti-neuronal antibodies: Screening by indirect immunofluorescence on cerebellar monkey cut : "INOVA" and identification by Immunoblot/indirect immunofluorescence on transferred human embryonic kidney HEK293 "EUROIMMUN".

Results and discussion: Among the 06 CSF tested, 03 CSF (50%) show an inflammatory profile. Among the 21 patients in our serie antineuronal antibodies were detected in 43% of cases (09 patients) : -29% of the antibodies are directed against intracellular antigens : Anti PNMA2 (n = 04), Anti Yo (n = 02) and 14% of the antibodies directed against membrane antigens : Anti-VGKC (n = 02) including anti-LGI1 (n = 01), and anti-CASPR2 (n = 01), Anti-NMDAR (n = 01)).

Conclusion: The detection of intracellular and membrane target autoantibodies allowed the redefinition of the concept of Autoimmune limbic encephalitis, which is probably underdiagnosed. The coming years will therefore see the description of new autoantibodies that appear as tools for understanding the physiopathological mechanisms underlying the symptoms associated with Autoimmune limbic encephalitis.

P187. PERFORMANCE OF ANTI-AQUAPORINE 4 (AQP4- IgG) IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS DIAGNOSIS

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Introduction: Neuromyelitis optica (NMO) is an inflammatory demyelinating autoimmune disease of the central nervous system (CNS) that affects the optic nerves and spinal cord. Neuromyelitis Optica Spectrum Disorders (NMOSD) is a proposed term to unify neurologic disorders including limited forms of NMO (Optic Neuritis (ON) or myelitis). In this context, anti-aquaporine 4 (AQP4-IgG) a.k.a. anti-NMO-IgG has been described as a useful biomarker.
We aim to study the prevalence of AQP4-IgG in Tunisian patients with ON and/or myelitis.
Material and Methods: We performed anti-NMO-IgG screening using Anti-Aquaporin-4 IIFT kit (Euroimmun®, Germany) in 67 patients with ON and/or myelitis (17 to 71 years; sex-ratio M/F=0,29). ON was detected in 59 cases and myelitis in 46 cases. The 2 neurological signs were associated in 39 cases. Anomalies of brain's white mater were found in 57 cases. A clinical follow up was made until a final diagnosis for each patient.
Results: Among the 67 patients, Anti-AQP4-IgG were positive only in 2 women aged 29 and 46 years, for which the diagnosis of NMO/NMOSD was made. In one case, ON and myelitis were associated and in the other case myelitis was isolated. Brain's Magnetic Resonance Images (MRI) were normal in both cases. The diagnosis of NMO was made for a third patient despite anti-AQP4-IgG negativity (a woman aged 58 years with ON and myelitis). for the other patients, the diagnoses included 45 cases of Multiple Sclerosis, 3 cases of other CNS inflammatory diseases, 2 cases of CNS non inflammatory diseases and 14 cases of clinically isolated syndromes.
Conclusion: Anti-AQP4-IgG seems to be rare in Tunisian patients with ON and/or myelitis. Patients with such neurological disorder cannot currently be easily classified. Clinical and radiological follow-up, re-analysis of sera and use of novel biomarkers should be informative.

P188. A STUDY OF CORRELATION BETWEEN ACETYLCHOLINE RECEPTOR NITRIC OXIDE IN A SMALL COHORT OF ALGERIAN MYASTHENIA GRAVIS PATIENTS

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Introduction: Myasthenia gravis (MG) is an autoimmune disease characterized by fluctuating muscle and abnormal fatigability. MG is caused by the presence of antibodies (Abs) against components of the muscle membrane at the neuromuscular junction (NMJ), mainly Abs against acetylcholine receptor (AChR). AChR Abs can induce myasthenic symptoms by complement-dependent lysis of the postsynaptic muscle membrane, increased AChR degradation and direct inhibition of acetylcholine binding to AChR. An active inflammatory state has been observed at the peripheral level of AChR-positive MG patients and it has been reported that skeletal muscle exposed to AChR antibodies may serve as a source of nitric oxide (NO) in experimental autoimmune myasthenia gravis (EAMG). However, the exact molecular alterations leading to the development and maintenance of the autoimmune process in MG patients are unknown.
Our aim is to investigate if there is a correlation between sera nitric oxide level correlation with acetylcholine receptor antibodies level in Algerian myasthenia gravis patients.
Materials and Methods: Ten Algerian anti-AChR antibody-positive MG patients (male/female: 5/5, n=10) with generalized MG were included in this study. Half patients were treated at Ait Idir neurosurgery hospital and the other half at Sidi Belloua Hospital. Nitric oxide was measured using a modified Griess. Absorbance was assayed at 543 nm and compared with a standard curve obtained using sodium nitrite ($NaNO_2$). Dependency between any two variables was evaluated using Spearman's rank correlation coefficient. *p* values less than 0.05 were considered significant.
Results: No correlation was found between AChR levels and NO levels. (All p values were greater than 0.05). Sera nitric oxide levels do not seem to have any correlation with AChR antibodies levels in myasthenia gravis patients.
Conclusion: However, in order to have results that are more representative we aim to widen our sample size and include more patients that are not undergoing immunosuppressive treatment.

P189. PREVALENCE AND CLINICAL SIGNIFICANCE OF ANTI-NUCLEAR ANTIBODIES IN MULTIPLE SCLEROSIS

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Introduction: Multiple Sclerosis (MS) is an immune-mediated disorder of the central nervous system. The prevalence of auto-antibodies in MS patients and their clinical associations vary according the studies.
We aim to evaluate the prevalence and the relevance of ANA in Tunisian MS patients.
Material and Methods: We performed ANA screening using indirect immunofluorescence (IIF) on HEp-2 cells (Biosystem®) in 52 MS patients (40 cases of relapsing remitting MS (RRMS) and 12 cases of progressive MS). For ANA positive samples (titer≥1/160), ds-DNA screening (IIF on *Crithidia luciliae* (Biosystem®)) and extractable nuclear antigen typing (immunodot (Euroimmun®)) were performed.
Results: ANA were positive in 19/52 MS patients (36,5%): The titer was ≥1/320 in 8/19 patients. No antigenic target was detected for positive ANA using our typing techniques. None of patients had extra-neurological manifestations. No correlation was found between ANA and age, sex, category of MS, disease duration, clinical presentation, disability, IgG index nor IgG oligoclonal bands profil. Regarding RRMS, ANA positivity was more frequent in patients in relapse (48%) than in patients in remission (13,3%) (p=0,026). ANA-positive patients had a lower annual relapse rate compared to ANA-negative patients.
Conclusion: Our results showed that ANA positivity in MS disease is not rare. ANA occurrence in MS probably reflects ongoing immune dysregulation and cannot be a diagnosis exclusion criterion of the disease.

P190. TUNISIAN FEMALE PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS HAVE SEVERE DEFICIENCY OF 25-HYDROXYVITAMIN D3

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Introduction: A number of environmental factors contribute to the susceptibility to multiple sclerosis (MS) disease, a demyelinating inflammatory disease of the central nervous system. During the last years, vitamin D (VitD) has become a topic of interest in immune regulation, especially in the context of MS. A substantial evidence base now exists supporting an association between VitD and MS, primarily illustrated by a latitudinal gradient of MS prevalence, a month of birth effect, an interaction of VitD with MS-associated genes and the fact that high VitD levels have been associated with a reduced MS risk. Recent research also points to a possible role for VitD in neuroprotection and myelin repair.
The aim of this study is to analyze VitD status in Tunisian MS patients and to test the correlation of this parameter with clinical, radiological and biological features.
Patients and methods: In this prospective study, we included 90 South Tunisian patients with definite diagnosis of MS according to McDonald criteria (70 with Relapsing remitting MS (RR-MS) and 20 with progressive forms). This MS cohort was composed of 66 women and 24 men, with a mean age of 35 years old (19-59 years). Patients supplemented in VitD were excluded. Serum levels of VitD (25-hydroxyvitamin D3) were performed by electrochimiluminescence method (Cobas 6000, Roche®; Normal value ≥30 ng/ml). Patients with abnormal levels were classified as insufficient (vitamin D level <30 ng/ml) or deficient (vitamin D level <20 ng/ml) in VitD. A level <10ng/ml was considered as a severe deficiency. Statistical analysis was made using SPSS.20 software.
Results: The mean rate of VitD in patients was 9.85 ng/ ml (min=3 ng/ml; max=42.2 ng/ml) with levels <10 ng/ml (severe deficiency) in 61 (67.7%) patients (93.2% were women). Mean rates were significantly lower in women (7.4 ng/ml) than in man (16.6 ng/ml) ($p<0.001$). Levels of vitD were negatively correlated with age. Patients with RR-MS had a mean rate of VitD (8.4 ng/ ml) lower than patients with progressive forms (11.2 ng/ ml) ($p=0.08$). There was no significant difference of VitD levels between groups of RR-MS patients regarding the radiological features, the activity of the disease and the presence or not of IgG oligoclonal bands in CSF.
Conclusion: Our study emphasizes the emerging role of VitD status in MS susceptibility, especially in its RR form and in female patients. These results are concordant with different observational studies which reported reduced level of VitD in the blood as a risk factor for developing the disease. Thus, these findings deserve to be confirmed in a larger group of MS patients and to be completed by including a healthy control group.

P191. USE OF HEVYLITE ™ ANTIBODIES IN CSF DIAGNOSIS

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Introduction: Neuromyelitis optica (NMO) is an inflammatory demyelinating autoimmune disease of the central nervous system (CNS) that affects the optic nerves and spinal cord. Neuromyelitis Optica Spectrum Disorders (NMOSD) is a proposed term to unify neurologic disorders including limited forms of NMO (Optic Neuritis (ON) or myelitis). In this context, anti-aquaporine 4 (AQP4-IgG) a.k.a.anti-NMO-IgG has been described as a useful biomarker.
We aim to study the prevalence of AQP4-IgG in Tunisian patients with ON and/or myelitis.
Material and Methods: We performed anti-NMO-IgG screening using Anti-Aquaporin-4 IIFT kit (Euroimmun®, Germany) in 67 patients with ON and/or myelitis (17 to 71 years; sex-ratio M/F=0,29). ON was detected in 59 cases and myelitis in 46 cases. The 2 neurological signs were associated in 39 cases. Anomalies of brain's white mater were found in 57 cases. A clinical follow up was made until a final diagnosis for each patient.
Results: Among the 67 patients, Anti-AQP4-IgG were positive only in 2 women aged 29 and 46 years, for which the diagnosis of NMO/NMOSD was made. In one case, ON and myelitis were associated and in the other case myelitis was isolated. Brain's Magnetic Resonance Images (MRI) were normal in both cases. The diagnosis of NMO was made for a third patient despite anti-AQP4-IgG negativity (a woman aged 58 years with ON and myelitis). for the other patients, the diagnoses included 45 cases of Multiple Sclerosis, 3 cases of other CNS inflammatory diseases, 2 cases of CNS non inflammatory diseases and 14 cases of clinically isolated syndromes.
Conclusion: Anti-AQP4-IgG seems to be rare in Tunisian patients with ON and/or myelitis. Patients with such neurological disorder cannot currently be easily classified. Clinical and radiological follow-up, re-analysis of sera and use of novel biomarkers should be informative.

P192. ASSOCIATION BETWEEN TUMOR NECROSIS FACTOR ALPHA-308 G/A POLYMORPHISM AND MULTIPLE SCLEROSIS IN ALGERIAN POPULATION

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Tumor necrosis factor alpha (TNFα), proinflammatory cytokine, has been considered the prototypic cytopathogenic cytokine in multiple sclerosis (MS). A bi-allelic single nucleotide substitution of G (TNFA1 allele) with A (TNFA2 allele) polymorphism at −308 nucleotides upstream from the transcription initiation site in the TNF-α promoters associated with elevated TNF-α levels and MS susceptibilities.We investigated the association between TNFα -308G>A (rs 1800629) polymorphism and susceptibility to multiple sclerosis development, also, the association between this polymorphism, intrathecal secretion of IgG and HLA-DRB1*15 allele.
The study included 56 Algerian patients with defined MS, who were recruited to the neurology department of Mustapha Pacha University Hospital (Algiers). The control population was composed of 34 healthy subjects; all these subjects are free from any inflammatory or autoimmune pathology.Single Nucleotide Polymorphism (SNP) analysis was performed using a real-time PCR (taqman technology).
Comparison of genotypic, allelic and phenotypic frequencies between patients and controls found no statistically significant difference. Our results remain statistically insignificant after stratification of patients according to: sex, age of onset of illness, clinical form of MS and intrathecal synthesis.However, our study showed a significant difference between HLA DRB1*15 patients and non-HLA DRB1*15 patients: the frequency of 308 GG genotype was significantly higher in DRB1*15 patients (89% vs 65%, P = 0.049): the frequency of the G allele is significantly higher in DRB1*15 patients versus non-DRB1*15 patients (95% vs. 77%, P = 0.02), while the A allele is significantly higher in non-DRB1*15 patients versus DRB1*15 patients (23% vs. 5%, P = 0.02).The GG genotype and the G allele are significantly associated with the DRB1*15 allele in our MS patients.
The results of our study did not reveal an association between the -308 G> A polymorphism of TNFα and MS, but it seems that the G allele predisposes to MS in the subgroup of HLA DRB1*15 patients and the A allele predisposes to MS in the subgroup of non-DRB1*15 HLA patients.

P193. CRYOGLOBULINEMIA IN TUNISIAN PATIENTS

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Introduction: Cryoglobulins are immunoglobulins that precipitates in vitro at temperatures below 37° and redissolves after rewarming. Reversible precipitation upon exposure to low temperatures allows laboratory detection of cryoglobulins.
Presence of cryoglobulinemia can remain an isolated biological abnormality or be responsible of vasculitis of small vessels, with skin, joints, peripheral nervous system and kidney manifestations. Our aim was to describe the etiological, epidemiological and clinical characteristics among patients with cryoglobulinemia followed in internal medicine department.
Patients and methods: This is a retrospective study including patients with cryoglobulinemia hospitalized in internal medicine department of the university hospital of Sfax-Tunisia between 2014 and 2016. Cryoglobulins were detected by our Immunology laboratory. We described the epidemiological, clinical characteristics, and the etiologic profile in those patients.
Results: Our study included 36 patients: 30 women and 6 men (sex-ratio: 0,2); the mean age was 45+/- 13 years. The principal clinical manifestations were represented by: arthralgia (33%), arthritis (32%), dry syndrome (27%), Raynaud phenomenon (8%), glomerular nephropathy (11%), vascular purpura (5%) and peripheral neuropathy (3%). An inflammatory syndrome was noted in 32% of the cases and an hypocomplementaemia in 14.7%. The rheumatoid factor was positive in 14.7% of the cases. Immunochemical typing highlighted cryoglobulinemia type III in 17 cases, type II in 8 cases and type I (monoclonal)in 11 cases. Cryoglobulinemia was due to a systemic disease in most cases: sjogren's syndrome in 10 cases (28%), systemic lupus erythematosus (1 case), scleroderma (2 cases), rheumatoid arthritis (4 cases) and a sarcoidosis (1 case). Cryoglobulinemia was also detected in 3 patients who had a Kikuchi disease, a HSV infection and a viral hepatitis B respectively. It was essential in 15 cases (41%). Management of patients was based on a treatment of underlying diseases.
Conclusion: The etiologic orientation of cryoglobulinemia is determined by its immunochemical type and the etiologies are reported to be dominated by VHC infections, followed by lymphoid blood disease B and autoimmune affections. Our study was characterized by a high frequency of connective diseases particularly the sjogren's syndrome (28%), this is probably due to a sampling biases of the patients.

P194. ANTI-DRUG ANTIBODIES AND ANTI TNF ALPHA TROUGH LEVELS: IS THERE A CLINICAL RELEVANCE FOR PATIENTS WITH CHRONIC INFLAMMATORY DISEASES?

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Introduction: Anti-TNF alpha are the most widely used biological therapeutic agents in treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and Crohn's disease (CD). One limitation for the use of therapeutic antibodies is immunogenicity. The development of antidrug antibodies (ADAbs) has a varying impact on the clinical efficacy and drug survival of biologic agents. We aimed to determine whether trough level of Adalimumab and Infliximab and ADAbs are associated with clinical response.

Materials and Methods: A multicentre prospective study was performed. We enrolled all patients diagnosed with RA, AS or CD and treated with Adalimumab or Infliximab as a first biotherapy since at least 6 months. Plasma samples of all enrolled patients were collected just before the injection and were stored at – 80°C until use. Adalimumab and Infliximab trough level and ADAbs were measured by ELISA (Lisa-tracker, Theradiag®, France). For statistical analysis, Simcalc software was used and a p value under 0.05 was considered as significant.

Results: A total of 76 patients were enrolled in the study, including 45 men and 31 women. The mean age was 42 years (19-76 years). Forty were treated by Infliximab and 36 by Adalimumab. Sixteen were diagnosed RA, 27 AS and 33 CD. Twenty patients (26.3%) lost response to Infliximab and fifteen patients (19.7%) lost initial response to Adalimumab. There was no significant difference regarding the mean of trough level between responders and non responders (1.67 *vs* 1.65 µg/ml for Infliximab and 4.73 *vs* 3.16 µg/ml for Adalimumab respectively). ADAbs were detected in 16 patients treated with Infliximab (40%) and in 9 patients treated with Adalimumab (25%). There was no significant correlation between the presence of ADA, the though level of Adalimumab nor Infliximab and the clinical efficacy. There was no correlation between the mean trough level of Adalimumab and the presence of ADAs. However, the mean though level of Infliximab was significantly higher in patients without ADAs (2.59µg/ml vs 0.22µg/ml; $p<0.0001$).

Conclusion: As reported in many studies, anti TNF alpha efficacy seems to be not correlated neither with the absence of ADAs, nor with high trough level. Further studies assessing complexed bioactive anti TNF alpha are needed to clarify this lack of association.

P195. ANTI-ERYTHROPOIETIN ANTIBODIES: PREVALENCE AND CLINICAL IMPACT IN HEMODIALYZED PATIENTS

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Introduction: Recombinant erythropoietin (rhEPO) has revolutionized the management of anemia in patients with chronic renal insufficiency (CRI) by reducing significantly the use of blood transfusions. However this therapy presents an immunogenic risk with the appearance of anti-erythropoietin antibodies (anti-EPO). In this context, a research for these antibodies in Tunisian hemodialyzed patients was carried out in order to determine their prevalence and their clinical impact.

Materials and methods: 176 hemodialyzed patients (95 women and 81 men), treated by rhEPO were included. According to the response to the treatment, patients were subdivided in 2 groups: G1 : 86 patients who kept low hemoglobin counts requiring blood transfusion despite good observance for at least one year and G2: 90 who responded well to treatment. An enzyme-linked immunosorbent assay (home-test) was used for the research of the anti-EPO antibodies.

Results: The anti-EPO antibodies were positive in 21 patients (12%) with a statistically significant difference between the two groups (19 cases in GI versus 2 cases in G2) (P=0.0001). These antibodies were more prevalent in males compared to females (p=0.008) while their positivity does not appear to be influenced by neither the average age nor the duration of dialysis. Moreover, although the optical densities of most anti-EPO positivities were low, a resistance to EPO has been demonstrated in a young woman in G1 who has been diagnosed with moderate erythroblastopenia by a myelogram.

Conclusion: The anti-EPO antibodies were relatively prevalent in our study. Nevertheless, their prognostic value deserves to be studied in a prospective cohort involving larger number of patients.

Cancer immunity

P196. CIRCULATING TNFα, IL-6 and IL-10 AS A POTENTIAL PROGNOSTIC MARKERS: A PROSPECTIVE STUDY IN 60 BREAST CANCER PATIENTS

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Introduction: Breast cancer is the most common of feminine cancers. Early Breast cancer screening improved prognosis but high mortality still linked to metastasis. Novel sensitive tools are needed to identify these complications. Some authors suggest that cytokines in the tumor microenvironment drive metastatic development and their serum levels might mirror the ongoing inflammatory reaction at the tumor site.
The aim of this study was to measure circulating inflammatory cytokines (IL 6, TNF α) and immunosuppressive cytokine IL10 and to assess the potential role of their serum levels as prognostic indicators.
Methods: Serum samples were prospectively collected from a cohort of sixty breast cancer patients after surgery in the military hospital of instruction of Tunis. Circulating levels of the inflammatory cytokines, TNFα and IL6 were measured with the technique of a solid-phase, two-site chemi-luminescent enzyme immune-metric assay (Immulite 1000, Simens, USA) and IL10 were measured with the technique of ELISA sandwich.
Results: The mean age of patients were 47years, 19 patients were metastatic. The mean level of cytokines Il6, IL10 and TNFα military hospital of instruction of tunis were respectively: 3.31 +/- 4.07pg/ml (min 1, max 29.30pg/ml); 6.560+/- 3.50 pg/ml (min 0.880, max 17.925 pg/ml) and 6.90 +/- 2.99 pg/ml (min 3, max 20.30 pg/ml).
We observed significant Higher circulating TNF-α level in the group involved (N+) compared to uninvolved lymph node (N-) (p=0.01). We found a correlation between IL6 and the metastatic invasion (P=0,046). In addition we revealed a correlation between IL10 and tumor size (P=0,048)
Conclusion: We found that cytokine were correlated with clinico-pathological features such as tumor size, lymph node involvement and metastatic invasion. Our results highlight the role of these circulating cytokines as potential prognostic biomarkers in breast cancer patients. Future, larger studies are needed to evaluate this approach in breast cancer patients.

P197. PLASMA HOMOCYSTEINE, FOLATE, VITAMIN B12 AND RISK OF BREAST CANCER IN WOMEN

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Background: Homocysteine is associated with oxidative damage and metabolic disorders, which may lead to carcinogenesis. Folate and B12 vitamin are required in homocysteine metabolism and are essential for nucleotide biosynthesis, DNA replication, synthesis and repair. Thus, several studies have demonstrated a relationship between these three parameters and the risk of developing breast cancer.
Materials and methods: A case-control study was conducted with 45 patients diagnosed with breast cancer and 35 healthy women. The serum levels of vitamin B12, folate and homocysteine were compared between the two groups in order to find a correlation between these levels and the risk and the evolution of breast cancer. The two populations considered had the same age range.
Results: The mean age at diagnosis was 47 years [28-71]. Half of patients were menopausal. Twenty one patients (44%) had a family history of cancer including 10 cases of breast cancer. The tumor was localized in 73% of cases. Invasive ductal carcinoma was found in 89.60%. The mean homocysteine level in patients with breast cancer was 9.88 µmol /l [2.73-22.79] whereas it was 7.36 µmol /l in the control group [2.47-17] and the difference was statistically significant ($p = 0.007$). B12 vitamin levels were also significantly higher in breast cancer than controls with mean of 358.35 pg/ml [119-1500] versus 243.57 pg/ml [11-680] ($p = 0.018$). Folate levels were significantly higher too in breast cancer patients with a mean of 10.22 ng/ml [4.79-24] versus 6.48 ng/ml [2-15] ($p = 0.001$). Furthemore, a significant relationship was observed between vitamin B12 and the histological tumor type with $p = 0.042$, and between obesity and this vitamin ($p= 0.037$). Also, we found a significant association between folate and SBR grade ($p = 0.013$) whereas there was no significant correlation with other factors.
Conclusion: In our study, hyperhomocysteinemia was associated with an increased risk of breast cancer. However, higher levels of folate and vitamin B12 found in cancerous women were due to the therapeutic effects of cytotoxics. The increased risk of breast cancer associated with these parameters warrants further investigation.

P198. PREDICTIVE VALUE OF SOLUBLE INTERLEUKIN-2 RECEPTOR α (IL2-Rα) DURING CHEMOTHERAPY IN BREAST CANCER PATIENTS

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Introduction: Breast cancer (BC) is the most common cancer among women. The treatment based immune responses will be associated to current therapies such as chemotherapy. Before using this combination, a better understanding of the effects of chemotherapy in immune system is important and can be use as biomarker. Treg cells expressing CD25 (IL2-Rα), were widely associated in cancer development and may be influenced by the chemotherapy. This may reflect the immune status of BC patients during treatment.
Objectives: To highlight immunological biomarkers in BC, we assessed the serological profile of soluble IL2-Rα and the clinical evolution during chemotherapy.
Methods: Thirty-four (34) Senegalese women with BC treated with Doxorubicin associated to cyclophosphamide, during three cycles per patient and 42 healthy women controls (HC) were selected. Peripheral blood samples were taken before each cycle and levels of IL2-Rα were evaluated by ELISA.
Results: Before treatment; levels of IL2-Rα were not different between patients and HC (223.87 *vs* 221.33 pg / ml, $p = 0.363$) and we did not evidenced significant relationships between IL2-Rα concentrations and patient's or tumors' characteristics. However, IL2-Rα levels increases significantly after the first cycle of chemotherapy in the group of patients. This change concerns mainly patients that having a recurrent BC after the third cycle of chemotherapy. Compared to partially or completely recovered women, patients with recurrent BC, have shown the highest levels of IL2-Rα after the third cycle of chemotherapy ($p = 0.034$). In the group of recovered patients, no significant variation was found during the treatment.
Conclusion: ours finding show the prognostic value of IL2-Rα levels during BC treatment. Some previous studies were reported that this biomarker increase significantly in serum of women with recurrent BC after radiotherapy. Our results moving towards further exploration of Treg cells such as $CD3^+CD4^+CD25^+Foxp3^+$ and cytokines release.

P199. PREDICTIVE VALUE OF SOLUBLE GALECTIN-3 DURING CHEMOTHERAPY IN SENEGALESE WOMEN WITH BREAST CANCER

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Introduction: Breast cancer (BC) constitutes an important medical, social and economic problem worldwide, particularly in women. It is well-documented that galectin-3 (Gal-3) expression has many functions in cancer progression and would be largely associated with cancer cells evasion and metastasis. In BC several previous studies have reported these pro-tumoral actions of Gal-3. It has been proposed that high levels of Gal-3 in blood were associated to bad prognostic during treatment.

Methods: Our main objective aim was to determine the profile of Gal-3 levels in blood from women with BC, in order to assess the prognostic value of this protein during chemotherapy. Gal-3 levels were evaluated by enzyme immunoassay (ebioscience®) in 70 women with BC, treated with doxorubicin/Endoxan and followed in the Oncology Department of Hospital Aristide Le Dantec in Dakar. Forty two (42) healthy women diagnosed tumor-free were used as controls.

Results: Before treatment, the median level of Gal-3 was significantly higher in women with BC compared to healthy controls (6.58 versus 1.58 ng /ml, $p < 0.001$). According to the SBR grade, no significant variation of Gal-3 concentrations was found in BC patients ($p = 0.385$). However, the tumor size evaluated at the enrollment, was positively correlated with the circulating levels of Gal-3 ($rho = 0.571$, $p = 0.021$). This relationship was confirmed by logistic regression analysis taking into account age and clinico-biological data ($p = 0.002$) such as TNM score. During treatment, we found a significant decrease of the Gal-3 levels only in women with SBR I ($p <0.035$). At the end of the treatment, the tumor regression appears marked by a low level of Gal-3 in the patients with a favorable issue.

Conclusion: Our results support a prognostic value of Gal-3 detection in BC. Since this protein is often described as implicated in tumor angiogenesis and lymphocyte apoptosis, it would be appropriate to evaluate this involvement in women with a rapid evolution of BC.

P200. SMAD3 ASSOCIATION TO HIGH-GRADE TUMORS AND A HIGH PROLIFERATION INDEX IN (ERα+ERβ+) and PR+ BREAST CANCER

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Introduction: TGF-β is a multifunctional cytokine that plays a crucial role in such biological processes as cell proliferation, differentiation and apoptosis. Its expression found to be related to many pathologies including breast cancer which is largely dependent on hormone receptors such as ERa, ERb and PR. Thence, deciphering the relationships between TGF-β and the molecular distribution of estrogens and progesterone receptors in mammary tumours' needed to be fulfilled.
Methods: In the current study we aimed to assess the expression patterns of SMAD3, ERα, ERβ and PR in 32 breast tumor tissues using qRT-PCR as method. Furthermore, the Ki-67 status has been determined by Immunohistochemistry.
Results: Our results showed a decrease in the expression of SMAD3 in 22 cases (68.75%) and an increase in 10 cases of mammary tumors (31.25%) (p=0.005). The over-expression of SMAD3 is associated with high tumor grades (SBRII and SBRIII). In addition there is a highly significant positive correlation of SMAD3+ with a high proliferation index (p=0.001). On the other hand SMAD3+ is negatively correlated with the infiltration of the lymph nodes (metastasis) (p=0.02). The expression of SMAD3 versus the molecular subgroups (ERα, ERβ) shows a significant difference in this distribution, in fact 7 cases from 10 were (ERα+, ERβ+), 2 cases were (ERα +, ERβ -) and 1 case is (ERα-, ERβ +) (p = 0.009). Similarly, a significant association of SMAD3+ with PR+ was recorded (p=0.02). Moreover, the analysis of the molecular subgroups (ERα+, ERβ+, SMAD3+) expression and (PR+ SMAD3+) in the light of clinical and pathological records underlined the significance of such association with high grade tumors (p = 0.001 and p = 0.0003 respectively) and its correlation with the high proliferation index (>5%) (p=0.03 and p= 0.01 respectively). On the other hand, no significant association with lymph node infiltration was recorded.
Conclusion: Overall, it was concluded that SMAD3 could promote tumor progression and proliferation of cancer cells in breast tumors (ERα+, ERβ+) and PR+.

P201. CYTOKINES BIOMARKERS ASSOCIATED TO GYNECOLOGICAL CANCERS

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Introduction and Objectives: Actually, the role of inflammation in the development and progression of cancer is of great scientific and public health interest. It is well established that cytokines play key regulatory role through determination of the predominant pattern of the host response in the majority of inflammatory and multifactorial diseases such as tumoural diseases.This study aims to evaluate a large numbers of both pro-inflammatory and anti-inflammatory cytokines, including interferon gamma (IFNγ), tumour necrosis factor (TNF), interleukins IL-1, IL-10, IL-6; their receptors and others implicated in the promotion and tumour growth such as vascular endothelial growth factor (VEGF) as biomarkers for cervical and ovarian cancers.

Material and methods: Several bio-technologies approaches: PCR, PCR-RFLP, PCR-ARMS, RT-PCR and sequencing are used for quantification and molecular typing of these biomarkers in Tunisians women with cervical and ovarian cancers.

Results: TNF-α -308A allele was significantly associated with heightened risk of ovarian and cervical cancer. Specific IL-10 (rs3024490, rs1800872, and rs1800871), VEGF (rs699947 and rs1570360) variants and IL-1β (-511C>T) may also contribute to the development of cervical cancer among Tunisian women. In addition significantly higher minor allele frequency of IL-6 rs1880242 was seen in ovarian cancer patients compared to healthy women

Conclusion: The obtained results have allowed the identification of biomarkers that may help to identify women at greatest risk for developing ovarian or cervical cancer, and therefore refine those who would most benefit from increased screening based on their inflammatory profiles.

P202. PENETRANCE OF THE MUTATIONS OF *D-LOOP* AND *CYTOCHROME B* IN THE OCCURRENCE OF OVARIAN CARCINOMES IN SENEGALESE WOMEN

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Introduction: In Senegal, cancer pathologies are today at the top of the causes of death. Ovarian cancer accounts for 5.8% of cancer deaths and is the fifth leading cause of malignant tumor death. The strongest risk factors currently involved in the ethology of this cancer are those of genetic order, with specific mutations.
Aim: The aim of this study is to analyze the incidence of *D-loop* and *cytochrome b* (*Cyt b*) mutations in the ovarian cancer occurrence in Senegal.
Methodology: We studied the variability of the two genes (*D-Loop* and *Cyt b*) by PCR-sequencing in thirty Senegalese patients suffering from ovarian cancer. For each patient we worked with the healthy ovary and the cancerous ovary. The search for mutations, the evaluation of the degree of variability of the mitochondrial genomes and the genetic differentiation was carried out with the MITOMAP database and the BioEdit software version 7.2.0, MEGA 6 version 6.05, DnaSP version 5.10.01 and Harlequin Version 3.1.
Results: It should be noted in this study that the D-Loop is more variable than the *Cyt b* with 81 new variations of which 41.28% show significant differences ($P < 0.05$) for the D-Loop against 19 new variations for *Cyt b*, 19.23% of which show significant differences. Our results also showed a significant increase of tryptophan in cancerous tissues, a slight increase in alanine and arginine levels, but also that *Cyt b* was under positive selection.
Conclusion: Any increase in tryptophan, arginine and alanine levels in cancerous tissues may be correlated with an increased risk of developing ovarian cancer on one side and arginine on the other. Alanine could play an important role in the treatment of ovarian cancer.

P203. HUMAN PAPILLOMAVIRUS 16 SEROPREVALENCE AMONG TUNISIAN WOMEN WITH NORMAL CYTOLOGY AND SQUAMOUS INTRAEPITHELIAL LESIONS

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Genital HPV infection is one of the most common sexually transmitted infections in the world. Several types of HPV can infect the genital tract, especially types HPV-6, -11, -16 and -18. Low-risk non-oncogenic HPV are responsible of acuminated condylomas (HPV 6 and 11) and high-risk or oncogenic HPV are responsible of the development of precancerous and cancerous lesions (HPV 16/18).

In the present work, our objective was to carry out a sero-epidemiological study of HPV infection among Tunisian women with no intraepithelial lesion (NIL) and women with squamous intraepithelial lesions (SIL) using a sandwich linked immunosorbent assay (ELISA).

Human sera and cervical samples were collected from 335 non-vaccinated women attending the National Office of Family and Population of Monastir and the Center of Maternity and Neonatology of Monastir for regular gynecologic control. A glutathione S-transferase (GST)-capture-enzyme ELISA was developed to detect anti-HPV-16 IgG, IgM and IgA antibodies. Cervical HPV-DNA was detected using real-time PCR.

Among NIL women seroprevalence of HPV-16 specific antibodies according to HPV status showed that, both IgG and IgA seroprevalence were significantly higher among HPV-DNA positive women than HPV-DNA negative women (39% *versus* 21%; p=0.005; OR: 2.49 [1.33-4.65] and 20%*versus* 7%; p=0.008; OR: 3.30; [1.42-7.68]; respectively). Inversely, among SIL women, IgG seroprevalence was higher among HPV-DNA negative women (50%) than HPV-DNA positive women (27.3%) (p=0.27, OR= 0.43 [0.11-1.71]). HPV IgM seroprevalence was higher in women with high-grade SIL than in women with low-grade SIL (28% *versus* 18%; p=0.4, OR= 0.52 [0.11-2.31]). Moreover, univariate analysis showed that IgG and IgA seroprevalence were significantly associated with HPV infection (p=0.021, OR=1.86[1.09-3.17] and *p=0.03*, OR =2.46 [1.14-5.33], respectively) and a multi-partner lifestyle (p=1.10^{-4}, OR = 2.76 [1.60-4.76] and p=0.021, OR =2.59 [1.17-5.75], respectively). In multivariate analysis, HPV infection was the only independent risk factor for both IgG and IgA seroprevalence.

In conclusion, our results showed a strong association between IgA and IgG seroprevalence and HPV infection

P204. THE PROFILE OF IL-6 ACTIVATION MEDIATED BY STAT3 and AKT SIGNALING PATHWAYS IN HUMAN PROSTATE PATHOLOGIES

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Introduction : The major signaling transduction of the pro-inflammatory cytokine IL-6 is through the transcription factor STAT3. However, PI3-K/AKT signaling pathway can also activated by IL-6 under prostate pathological conditions.
Objectives : The aim of this study is to evaluate the tissues levels of STAT3/IL-6/ AKT axis signaling in prostate tissues from patients with Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (PC).
Material and Methodes : Immunohistochemical analyses for IL-6, Gp130, pSTAT3 (Tyr705) and pAKT (Ser473) were carried out in 25 samples of BPH, 16 samples of PC.
Results : Immunoreactivity to IL-6 was consistently observed in stroma compartment of BPH and cytoplasmic epithelial cell in PC samples. pAKT was mainly expressed in membrane and the cytoplasm in PC compared to BPH. Immunoreactivity for pSTAT3 (Tyr705) was found in the stroma and the nucleus of epithelial and tumoral cells. No significant association was determined (r=0.153, *P*=0.518) when IL-6 and pAKT(S473)were analyzed within BPH patients; whereas a positive correlation emerged between pSTAT3(Tyr705) in the stroma and pAKT(S473). In PC patients, significant relationship was documented between IL-6 and pAKT (S473) (r=0.725, *P*=0.02). In addition, the correlation between pAKT (S473) and pSTAT3 (Tyr705) as well as detected in the nucleus and the stroma were significant.
Conclusion : This suggests that IL-6/AKT axis could be one of mechanism to activate STAT3 by facilitating inflammatory cell migration and chronic inflammation in BPH and promote cancer progression by promoting cell growth in PC.

P205. THE IL-17A/IL-10 BALANCE AND PSMA/PSA DUALITY IN PROSTATE CANCER PATIENTS

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Introduction/Objective : Treg cells are an obstacle for immune surveillance in cancer by virtue of their ability to control cancer-associated inflammation in an IL-10-dependent manner. Treg cells are susceptible to convert to the proinflammatory Th17 phentotype. IL-17A is produced in large quantities in Th17 cells. Most Th17-mediated effects are attributed to this cytokine. The objective of this study was to investigate the balance of IL-10/IL-17A and its association with PSMA and PSA tissue expression in prostate cancer (PC) patients.
Material/Methods : Peripheral blood and tissues were collected from 23 cases of PC patients. ELISA assay was conducted to detect expression levels of IL-10 and IL-17A. Immunihistochemestry technique was performed to analyze PSMA and PSA expression.
Results : The expression levels of IL-17A and IL-10 cytokines were detected in a scanty sera PC patients (5 and 3 of 23 PC group, respectively). In sera PC patients, the levels of IL-17A were 106.65±192.39 pg/mL ; while the levels of IL-10 were 652±560.43 pg/mL. Most of sera PC patients (16 of 23 patients) were IL-17A^{neg}/IL-10^{neg}. This group of PC patients exhibited very abundant PSMA tissue expression and a low PSA tissue imunoreaction. The PSMA was overexpressed in all of IL-17A^{neg}/IL-10^{neg} PC group. However, PSA was only present in 6 of 16 IL-17A^{neg}/IL-10^{neg} PC group.
Conclusion : Our data indicated that the balance IL-17A/IL-10 was broken in peripheral blood of PC patients. And these data suggest that PSMA and PSA promoted the imbalance of IL-17A/IL-10 leading to suppression of immune response in PC patients.

P206. INTERPLAY BETWEEN SOLUBLE IL-6, TNF-α AND PSA LEVELS AND ITS RELEVANCE IN PROSTATE CARCINOMAS

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Introduction/Objective: Cytokines bias in the tumor microenvironment can be predictive of immune response in prostate carcinoma (PC). The role of some cytokines such as IL-6 and TNF-α in immune function in the context of prostate tumorigenesis is ambivalent. For this purpose, we aim to endow the correlation between IL-6 and TNF-α and its link to PSA expression levels in prostate carcinomas**.**
Material/Methods: Serum was collected from 22 PC patients. ELISA was performed according to the manufacture's instructions.
Results: The expression levels of IL-6 were more abundant than TNF-α by 2.53 folds in sera PC patients. The levels of IL-6 in sera PC patients were 17,47±33,12 pg/mL ; while the levels of TNF-α were 6.89±5.06 pg/mL. Depending on the levels of IL-6, we have identified two sera PC groups : IL-6 levels ranged between 2 and 10 pg/mL (in 16 of 22 PC patients) and IL-6 levels >10 pg/mL(in 6 of 22 PC patients) groups. The expression levels of TNF-α increased by 2.31 folds between IL-6 levels ranged between 2 and 10 pg/mL and IL-6 levels >10 pg/mL groups. Increased of TNF-α levels between IL-6 sera groups were associated with up-regulation of sera PSA levels.
Conclusion: Collectively, our study concluded that elevations of IL-6 was concomitant with increased of TNF-α and sera PSA levels in peripheral blood of PC patients. All these changes may be one of the possible immune mechanisms that promoted the development of prostate cancer.

P207. THE EFFECT OF LEPTIN ON THE MIGRATION OF PROSTATE CANCER CELLS

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Introduction/Objectives: Adiposity is associated with prostate cancer (PC) aggressiveness; however the underlying mechanisms remain not clear. Emerging evidence has suggested that leptin, an adipokine involved in metabolic regulation, plays a role in cancer growth and metastasis. The purpose of this study was to investigate the role of leptin and its receptor (ObR) on the development of PC.

Materials and methods: The expression of the adipokine receptors genes : leptin receptor (ObR), adiponectin receptor (AdipoR1 and AdipoR2) and genes involved in hypoxia (HIF-1α, HIF-2α) and angiogenesis such as VEGF by tumor biopsies was assesed for 13 patients with Prostate Cancer (PC) and 24 patients with BPH (Begnin Prostate Hyperplasia) by RT-PCR. The migration assay: Wound-healing was used to study the effect of different doses of leptin on PC cell lines: PC3 and DU-145 migration. The analysis was carried out by optical microscopy using phase contrast. Analysis of the results was done by Image J and statistical tests by SPSS.

Results: We first demonstrated an overexpression of ObR and a downregulation of AdipoR1 and AdipoR2 genes by PC biopsies in comparison with BPH patients. Next, we investigated the role of leptin in tumor cell migration and showed that *in vitro* leptin stimulates the migration of PC3 and DU-145 cells. This induction could be explained by the overexpression of HIF-1α and the phosphorylation of STAT-3, a transcription factors involved in tumor development and metastasis.

Conclusion: Leptin and its receptor ObR may be involved in PC development by promoting cell migration and metastasis. Blocking leptin/leptin receptor signaling may represent a potential therapeutic alternative to treat PC patients.

P208. EXPRESSION OF HUMAN SERUM HSP27 IN PROSTATE CANCER IS CORRELATED WITH THE GLEASON SCORE

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Purpose: Prostate cancer is a major healthcare problem. Clinical outcome at diagnosis is heterogeneous and not easy to predict; thus, predictive and diagnostic markers are needed. Heat shock proteins (Hsps) such as Hsp27 are up-regulated in several malignancies. Hsp27 plays a role in apoptosis control in tumor and cell protection including the immune response. The basal rate of Hsp27 in most human tissues is low compared to the high rates present in the tumors.

We here investigated concentrations of serum Hsp27 antigen in subjects with prostate cancer and assessed potential associations with the gleason score.

Materials and Methods: Circulating Hsp27 from 45 patients with prostate cancer and from control was assessed by enzyme-linked immunosorbent assays (Elisa).

Results: Serum Hsp27 levels were significantly ($p<0.001$) higher in patients with prostate cancer compared to the control. The results showed an over-expression of Hsp27 in tumors and indicated that malignant tumors expressed higher Hsp27 concentrations than benign tumors. Concentrations of Hsp27 were also correlated with the gleason score

Conclusion: Elevated levels of Hsp27 antigen in human serum occur in prostate cancer and are related to the prostate cancer malignancy level suggesting its use as a diagnostic marker.

P209. TARGETING MENIN AS A NEW THERAPEUTIC STRATEGY IN CASTRATION-RESISTANT PROSTATE CANCER

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Background: Prostate cancer (PC) is one of the most common malignancies in industrialized countries, and the second leading cause of cancer-related deaths in the United States. Previously we have shown that Hsp27 is highly overexpressed in castration-resistant prostate cancer, and developed a Hsp27 inhibitor (OGX-427) currently tested in phase I/II clinical trials as a chemosensitizing agent in different cancers.
Using large scale proteomic approach, we found that Menin is a new Hsp27 client protein that might drive cancer progression. Interestingly, we found that CRPC progression correlates with Menin overexpression. To define Menin's function, we have developed and worldwide patented a Menin antisense oligonucleotide (ASO). The treatment with our Menin ASO inhibits cell proliferation and induces cell cycle arrest in castration-resistant (CR) PC3 cultured cells and inhibits the growth of CR tumors in vivo in mice.

P210. POLY(I:C) POTENTIATES BACILLUS CALMETTE-GUÉRIN IMMUNOTHERAPY FOR BLADDER CANCER

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Introduction: Non-specific immunotherapy consisting of intravesical instillation of Bacillus Calmette-Guérin (BCG) is currently the best available treatment to prevent non-muscle-invasive bladder tumor recurrence and progression. This treatment however is suboptimal, and more effective immunotherapeutic approaches are needed. Toll-like receptors (TLRs) play a major role in the activation of the immune system in response to pathogens and danger signals but also in anti-tumor responses. We previously showed that human urothelial cells express functional TLRs and respond to TLR2 and TLR3 agonists.
Objectives: In this study, we analyzed the potential of polyinosinic: polycytidylic acid [poly(I:C)], a TLR3 agonist, to replace or complement BCG in the treatment of non-muscle-invasive bladder cancer.
Results: We observed that poly(I:C) had an anti-proliferative, cytotoxic, and apoptotic effect in vitro on two low-grade human bladder cancer cell lines. Poly(I:C) induced growth arrest at the G1-S transition. Poly(I:C) also increased the immunogenicity, inducing the secretion of MHC class I molecules and of pro-inflammatory cytokines. The combination poly(I:C)/BCG was much more effective in reducing MBT-2 tumor growth in mice than either treatment alone. It completely cured 29% of mice and also induced an immunological memory response.
Conclusion: our study suggests that adding poly(I:C) to BCG may enhance the therapeutic effect of BCG.

P211. CYTOKERATIN-21-FRAGMENT (CYFRA 21-1) AND β2-MICROGLOBILIN (β2M) MARKERS IN NASOPHARYNGEAL CANCER: A CASE-CONTROL STUDY

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Introduction: Nasopharyngeal carcinoma (NPC) is a relatively frequent cancer in Tunisia which is often diagnosed at advanced stages. Currently, there is no reliable biological marker validated in common investigation for this cancer. Cyfra21-1, fragment of cytokeratin 19 expressed especially in the malignant epithelial cells, is recognized as a tumor marker of non-small cell lung carcinomas. β-2-Microglobilin (β_2M) is a cell membrane protein ubiquitous to nucleated cells that reflects cell turn-over. It can be elevated in a variety of hematologic malignancies.
Our aim was to analyze the clinical usefulness of Cyfra 21-1 and β_2M as diagnostic and prognostic markers of NPC in Tunisian patients.
Patients and methods: This prospective study (2014-2017) included 101 Tunisian individuals: 50 patients with histologically confirmed primo-diagnostic of NPC and 51 healthy controls matched for age and sex. Patients group, composed of 36 men and 14 women, had a mean age of 44.5 years old (11-76 years). Serum values of Cyfra 21-1 marker were performed using an immuno-chemiluminescence method. Serum levels (H: high; L : low) were determined considering a cut-off of 3.3 ng/ml. Serum values of β-2-microglobilin were performed using immuno-nephelometry considering a cut-off of 1.8 U/ml. Statistical analysis was made using SPSS.20 software.
Results: Overall, 41/50 (82%) NPC patients had at least one positive marker. Considering Cyfra 21-1 marker, the mean serum value was significantly higher in patients than in controls: 13.69 ng/ml versus 1.32 ng/ml (p=0.005). Interestingly, none of the control individuals had a high level of this marker. In patients group, the level of Cyfra 21-1 was high in 34 cases (68%). The radiological extension to the pterygoid was significantly associated with high levels of Cyfra 21-1 (p=0.004). Furthermore, Patients with endocranial extension had a significantly higher mean value of Cyfra 21-1 compared to patients without extension (p=0.008). Both levels and mean values of the marker were correlated with advanced stages of the disease (≥III) (p=0.026 and <0.0001 respectively). Regarding β_2M, 29 patients (58%) had a high level of the marker. Among them, 22/29 were aged above 40 years (p=0.04). Interestingly, this marker was positive in 7/16 Cyfra-negative patients. No correlation with disease stages/TNM classification was detected.
Conclusion: Our study supports the diagnostic and prognostic value of the initial evaluation of Cyfra 21-1 and β_2M serum levels in NPC patients. However, our results need to be validated in a larger sample of patients and should be followed by the study of the usefulness of these biomarkers in the monitoring of the disease.

P212. NITRIC OXIDE LEVELS IN PLASMA OF PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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Nasopharyngeal carcinoma (NPC) is a malignant tumor of the nasopharyngeal mucosa characterized by its multifactorial etiology. In Tunisia, the NPC is a major public health problem. As part of the search for markers of NPC diagnosis, we are interested in nitric oxide (NO), a free radical produced by many cell types by three different nitric oxide synthase isoenzymes (NOS): neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). Nitric Oxide (NO) is one of the most multifunctional gaseous molecules involved in various biological and pathological functions.

The objective of this study is to determine the Nitric Oxide plasma levels in patients with NPC and its association with clinical and pathological parameters.

Our study population included 130 unrelated NPC patients originating from the middle coast of Tunisia. All patients had the undifferentiated NPC histological type (type III, World Health Organization classification) and were recruited from the Department of Cancerology and Radiotherapy of CHU Farhat Hached, Sousse, Tunisia. Total NO production (NOx) was quantified indirectly by measuring Nitrate and Nitrite levels by Nitric oxide colorimetric assay kit (Biovision, USA) according to the manufacturer's protocol. The absorbance was detected at 540 nm. Statistical analysis was carried out using SPSS v.23.0.

Our results indicate that plasma NOx concentrations were significantly higher in untreated patients than those receiving radiotherapy (P=0,007). Moreover, lower levels of NO were observed in patients without metastasis than patients with metastatic NPC (P=0,007). However, there is no significant association between NOx levels and others parameters (age, gender, tobacco use, alcohol use, tumor extension, regional lymph node extension and TNM stage).

In summary, our results suggest a possible role of NO in NPC risk. However, further studies are needed to validate these findings.

P213. CYTOKINES PATTERN OF UNTREATED PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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Nasopharyngeal carcinoma (NPC), a malignant neoplasm of the head and neck, constantly associated with Epstein-Barr virus (EBV), is rare in most parts of world but endemic in the Southern China and Southeast Asia. Tunisia is one of Mediterranean countries characterized with an intermediate incidence in which, in contrast to high-risk area, a juvenile form of NPC occurs in addition to the adult one. NPC patients are commonly diagnosed as advanced metastasis disease due to its deep pathogenic site and vague symptoms.

The specific cytokine pattern in NPC has not been well elucidated, in particular among patients in intermediate incidence area. The purpose of this study was to examine plasma cytokine profile of nasopharyngeal carcinoma.

The plasma levels of interferon gamma (IFN-g), tumor necrosis factor (TNF)-a, interleukin 6 (IL)-6, and IL-10 were detected by enzyme-linked immunosorbent assay (ELISA) among 56 untreated NPC patients and 32 controls.

Compared to healthy controls, plasma levels of TNF-a and IL-10 were significantly higher in patients with NPC (p = 0,007 and p < 0,001 respectively); but the interferon gamma (IFN-g) levels were significantly lower (p < 0,001). No significant difference for IL-6 were observed. Interestingly, the levels of TNF-a elevated in patients with advanced clinical stage (p = 0,045). Furthermore, high levels of IFN-g and IL-10 correlated significantly with metastasis (p = 0,044 and p = 0,014 respectively). IL-6 levels were significantly higher when patients with cancer metastasis were compared to healthy controls (p = 0,036). Taken together, the patients with higher levels of IFN-g, TNF-a, IL-6, and IL-10 had worse prognosis, suggesting the implications of these cytokines in the pathogenesis of NPC.

Our results suggest strongly that inflammation is a critical component of NPC tumor progression.

P214. IL-10 AND TLR2,3 AS BIOMARKERS FOR HEAD AND NECK CANCERS

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Introduction and Objectives: Head and neck cancers (HNC) are leading cause of mortality in worldwide. Recent evidence supports the importance of immunogenetic factors in the pathogenesis of tumoral diseases, including HNC. This study aims to evaluate three IL-10 promoter variants, altered IL-10 plasma levels, TLR2 (-196 to -174 ins/del) and TLR3 (1377 C>T) variants as potential biomarkers for HNC.

Material and methods: We performed a case control study including 246 HNC patients [174 nasopharyngeal cancer (NPC) and 72 laryngeal cancer (LC)] and 250 healthy controls. Genotyping of rs1800896 (-1082A>G), rs1800871 (-819T>C), and rs1800872 (-592A>C) IL-10 variants was performed by real-time PCR; IL-10 levels were measured by EAISA. TLR genotyping was done by PCR-RFLP.

Results: Carriage of rs1800896 A/A genotype was more frequent in HNC and NPC cases, but was less frequent in controls than LC patients. Significant differences in IL-10 levels was seen between rs1800896A/G genotype-carrying NPC cases and controls. Positive association with NPC and LC was seen for rs1800871C/C, and carriage of rs1800872C/C genotype and A allele were associated with higher risk of HNC and NPC, but not LC. TG rs1800896-rs1800871 haplotype was more frequent among HNC and NPC cases than controls. Positive association was found between TA haplotype and LC. In addition, increased risk for HNC, NPC and LC cancers was associated with TLR2 ins/del and del/del genotypes. TLR3 T/T genotype is associated with HNC susceptibility. Significant increased frequencies of T-ins, C-del and T-del haplotypes were revealed for HNC and NPC and T-del for LC.

Conclusion: rs1800896, rs1800871, and rs1800872 IL-10, and TLR2 (-196 to -174 ins/del) and TLR3 (1377 C>T) variants may represent biomarkers for early detection of HNC.

Keywords: Head and neck cancer; Interleukin-10; Toll-like receptors; laryngeal cancer; nasopharyngeal cancer; Tunisia

P215. PROGNOSTIC VALUE OF TUMOR-INFILTRATING LEUKOCYTES IN NASOPHARYNGEAL CARCINOMA

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Nasopharyngeal carcinoma (NPC) is a malignant tumor with an epithelial origin, consistently associated with Epstein Barr virus (EBV). This tumor is characterized by a very abundant leukocyte infiltrate. In this study, we were interested in the leukocyte infiltrate of 43 NPC biopsies.We analyzed tumor infiltration (intratumoral and peritumoral) by immunohistochemistry (IHC) using the following antibodies: Anti-CD3, anti-CD138, anti-CD68 and anti-CD303.

We found intense intratumoral infiltration by T lymphocytes (LT) (47% of cases), plasma cells (45% of cases), tumor-associated macrophages (TAM) (35% of cases) and no infiltration by plasmacytoid dendritic cells (pDC). In peritumoral space, we observed LT and plasma cells infiltration rates are similar to tumor space, but an increasing TAM and pDC infiltration, 67% and 48% respectively.

Moreover, the survival curve analysis showed that patients with low leukocyte infiltration (LT, plasma cells, TAM and pDC) had the lowest survival rates.

In conclusion, Leukocyte infiltration regardless of its localization (intratumoral or peritumoral) is a marker of good prognosis.

P216. EXPRESSIONS OF TOLL-LIKE RECEPTOR 9 IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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Introduction*:* Nasopharyngeal carcinoma (NPC) is a tumor derived from the epithelial cells. The endemic nature, as well as, the carcinogenesis of NPC, is considered a consequence of Epstein-Barr virus (EBV) infection, which is one major etiological factor. During viral infection, the innate immune system is the first line of defense. The family of Toll-like receptors (TLRs) is important factors mediating the interaction between viral agents and host immune response. Human TLR9 is a DNA receptor that recognizes unmethylated nucleic acid contains (CpG) motifs present in bacteria and viruses. This receptor is one of the key sensors for the antiviral immunity (e.g. EBV). Therefore, any variation in TLR9 expression may alter the susceptibility as well as the severity of the viral disease.

Objectives: The main aim of this study was to evaluate the expression levels in the peripheral blood mononuclear cells (PBMCs) of NPC patients and controls.

Material and methods*:* Quantitative real-time PCR (qPCR) was used to evaluate *TLR9* mRNA expression in the PBMCs from both patients and controls. For normalization, the housekeeping GAPDH gene was used as an internal control and the relative expression of TLR9 mRNA was determined using the $2^{-\Delta\Delta CT}$ method.

Results: We studied TLR9 mRNA expression in PBMCs from 49 NPC patients and 30 control subjects. The results showed that TLR9 mRNA expression was significantly higher in control subjects than in NPC patients ($p<0.01$). Moreover, the results showed that the relative expression of *TLR9* mRNA was inversely correlated with tumor size ($p=0.008$; $r= -0.385$) at diagnosis.

Conclusion: According to our results, it appears that PBMC from NPC patients are unable to appropriately express the *TLR9* gene.

P217. NOS2 IS A KEY FACTOR OF EPITHELIAL-MESENCHYMAL TRANSITION AND MMP-9 ACTIVITY IN LARYNGEAL CARCINOMA

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Laryngeal carcinoma (LC) is a highly invasive tumor of the head and neck. LC carcinogenic process is associated with chronic inflammatory conditions implicating oxidative and nitrosative stress responses. In several cancers, nitric oxide (NO) dependent inflammatory reaction has been incriminated in the epithelial-mesenchymal transition (EMT) and acquisition of angiogenic and metastatic capacities via the regulation of matrix metalloproteinase-9 (MMP-9) activity. Our study aimed to identify possible correlations between NOS2 expression levels and EMT as well as the MMP-9 activity in LC patients.

NOS2, EMT markers (E-cadherin, β-catenin and vimentin), NFkB and MMP-9 expression was evaluated by immunohitochemistry (IHC) in invasive LC (n=20), adjacent in-situ carcinoma (n=9) and normal epithelium (n=10). Plasmatic NO levels were assessed in LC patients (n=40) and donors (HD) (n=20) using the modified Griess reaction and plasmatic MMP activity was evaluated by zymography.

We observed a significant increase of NOS2 expression in invasive LC which correlates with NFkB activation ($r= 0.37$, $p= 0.10$). IHC analysis revealed that EMT features were prominent in invasive LC, epithelial markers (E-cadherin and membranous β-catenin) correlated negatively with NOS2 expression and NFkB activation while strong positive correlations were found between mesenchymal markers (cytoplasmic β-catenin and vimentin) and NOS2 as well as NFkB activation. In plasma of LC patients both latent and active MMP-9 forms were detected with a major increase in MMP-9 levels in LC patients compared to HD ($p<0.0001$). MMP-9 was importantly expressed in invasive tumor tissue compared to in-situ carcinoma and adjacent normal epithelium. Interestingly, plasmatic MMP-9 expression and activation correlated negatively with NO synthesis in CL patients ($r= -0.43$, $p=0.005$) ($r = -0.27$, $p = 0.084$) respectively. Our results suggest that NFkB signal pathway induces NOS2 overexpression favorable to EMT switch in invasive CL. Furthermore, NO activity would be involved in pro-MMP-9 upregulation and its conversion to active MMP-9; therefore showing that the NOS2 dependent inflammatory reaction would contribute to laryngeal carcinoma metastatic progression.

P218. INVOLVEMENT OF THE FONCTIONAL DELETION (rs111200466) OF THE *TLR2* GENE IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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Background: The mammalian Toll-like receptor (TLR) family consists of 13 members, and recognizes specific patterns of microbial components, called pathogen associated molecular patterns (PAMPs).TLR-dependent recognition of PAMPs leads to activation of the innate immune system, which subsequently leads to activation of antigen-specific adaptive immunity.Epstein–Barr virus (EBV) infection contributes to tumorigenesis of various human malignancies including nasopharyngealcarcinoma (NPC). EBV triggers innate immune and inflammatory responses partly through TLRsignalling.EBV activates TLR2 in transfected HEK293 cells. The insertion/deletion polymorphism (rs111200466) at position -196 to -174 del/ins of the untranslated 5' region in *TLR*2 gene has been shown to affect the *TLR*2 gene function. This 22 bp nucleotide deletion in *TLR2* gene, is associated with reduced transcriptional activity of the promoter.

Objective: The aim of the present study was to investigate the association of *TLR2* (-196 to -174 ins/del) polymorphism with NPC in a case control study and to explore the effects of this polymorphism on the *TLR*2 expression among healthy blood donors.

Methods: DNAfrom 325 patients with NPC and 200 healthy controls were analysed by real-time quantitative PCR.Quantitative real-time PCR was used to evaluate *TLR2* mRNA expression in the PBMCs from 30 controls.

Results: The case-control study showed no significant association with the risk of NPC development, for both allelic and genotype frequency distrubutions.Survival analysis showed that patients carrying the "del" allele have better overall survival than patients with the ins/ins genotypes.The analysis of the *TLR2* mRNA expression in the PBMCs showed no correlation between *TLR2* genotypes and *TLR2* gene expression levels.

Conclusion: These findings indicate that there is no association between the TLR2 polymorphisms tested and NPC susceptibility in Tunisia. We suggest using other TLR functional SNPs to investigate the possible relationship between innate immunity deregulation and potential NPC development.

P219. ANTI-SOX1 ANTIBODY: AN ONCONEURONAL ANTIBODY FREQUENTLY ASSOCIATED WITH LUNG CANCERS

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The onconeural antibodies are directed against intracellular antigens and are highly specific markers of neoplasies in patients with neurological symptoms. Although the pathogenic role of onconeuronal antibodies is still largely unknown, the detection of such antibodies in a patient with neurological symptoms should lead to prompt investigation for cancer which could lead to earlier diagnosis of cancer and therefore earlier treatment.Nowadays, most of these antibodies are well-characterized (antibodies against Hu, Yo, Ri, CRMP5, amphiphysin, Ma2 and Tr) and are in common use for the diagnosis of definite paraneoplastic syndrome (PNS).Recently, a new anti-glial antibody associated with PNS has been described and SOX1 has been identified as the corresponding antigen.

SOX1 antibodies have been reportedin patients with Lambert–Eaton Myasthenic Syndrome (LEMS) in association with voltage-gated calcium channel antibodies as serological markers of lung cancer, especially small cell lung cancer (SCLC). They also have been described in association with Hu antibodies in patients with SCLC.

Herein, we report the case of a 54 year-old man, smoker, alcoholic, who exhibited a LEMS along with other neurological symptoms such as a cerebellar syndrome.His symptoms were, at the beginning, linked to his alcoholism, and he was treated for itwith a slight improvement.At the first signs of recurrence of his neurological symptoms, immunological exploration showed the presence of anti-SOX1 antibodies (+++) associated with anti-HU antibodies (+) in the serum. This led to a cancer screening and to the discovery of a pulmonary mass. This patient died shortly after before any further investigation was conducted.

We present this case to introduce the anti-SOX1 antibody and its association with LEMS in patients with SCLC and also, to underline the importance of onconeural antibodies testing in patients with PNS, which could save lives by detecting certain cancers in time.

P220. JAK 2 GENE POLYMORPHISM IN LUNG CANCER

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Genetic variants in Janus Kinase (JAK) / signal transducer and activator of transcription (STAT) signaling pathway genes have been associated with the development of various tumors, but not have been widely investigated in non small lung cancer (NSLC).
In the present case-control study, we investigate the association between the rs2230724 polymorphism in the *JAK* 2 gene and the lung cancer susceptibility. We analyzed the distribution of the *JAK* 2 rs2230724 genotypes in 103 NSLC and 103 healthy controls by using predefined Taqman genotyping assays.
Our results revealed that the presence of the rs2230724 GG genotype was associated with an increased risk of lung cancer development [OR =2.48; CI: 1.02 – 6.03, *P* = 0.042]. The rs2230724 G allele is a risk factor for the development of lung cancer in the Tunisian population. When we stratified our population according to clinical factors, our results indicated that the presence of GG genotype was associated with higher lung cancer risk for the men subjects [OR =3.27; CI: 1.10 – 9.77]. The most frequent cancer subtype in the Tunisian population was the Adenocarcinoma of the lung (49%), when compared to others subtypes. However, we did not find any association between the presence of the rs2230724 SNP and the predisposition to the development of any lung cancer subtypes.
The *JAK* 2 rs2230724 polymorphism was associated with a higher lung cancer risk in the Tunisian population, particularly in the men subjects.

P221. PROTEASOME: A NEW BIOMARKER OF MELANOMA IN DMBA-INDUCED SKIN CARCINOGENESIS

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Background: angiogenesis is a complex process that depends on many biological factors: genetic alterations, cell function or protection systems against oxidation, or change in protein metabolism. The ubiquitin-proteasome system, responsible for the degradation of the majority of cellular proteins involved in the regulation of many biological processes such as cell cycle regulation, apoptosis and control of proteins integrity. The dysregulation of the UPS has been involved in neurodegenerative diseases and various types of cancer like multiple myeloma and hepatocellular carcinoma. Furthermore, Plasmatic Proteasome level is a potential marker in patients with solid tumors

Objectives: The aim of this work is to analyze the quantitative and functional changes of the 20S proteasome in serum and subcellular, in DMBA-induced skin carcinogenesis on comparison to control mice.

Methods: the skin carcinogenesis was developed using topical applications of DMBA and croton oil. The Proteasome levels were measured using a sandwich ELISA assay.

Results: the results obtained demonstrate that following to the applications of DMBA and croton oil, 100% of mice developed melanomas compared to controls. In addition. The serum proteasome level are significantly elevated in carcinogenesis mice (2759.44 ± 71.73ng/mL ; $\rho < 0.001$), agonist control mice (1130.11 ± 81.31 ng/mL). Like serum proteasome level, a higher intracellular level was detected in carcinogenesis mice (4702.22 ±109.1 ng/mL; $\rho<0.001$), contrary to (1845 ± 119.55 ng/mL) in control mice. the mean serum (1264 ± 601 ng / ml).

Conclusion: Our results confirm the presence of the 20s proteasome both in serum and sub-cellular, in all groups of mice although it is mainly localized in the cytoplasm and in the nucleus of eukaryotic cells. Also, Like the other tumor (myeloma, lymphoma, hepatocellular carcinoma), the proteasome could be a key element in differentiation and malignant melanoma development

P222. CIRCULATING AND SUB-CELLULAR PROTEASOME LEVELS: POTENTIAL BIOMARKERS OF MELANOMA IN DMBA-INDUCED SKIN CARCINOGENESIS

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Proteasomes are nonlysosomal proteolytic structure localized both in cytoplasm and in nucleus in eukaryotic cells, it's correspond to the main pathway responsible for degradation of more than 80% polyubiquitinated proteins including this involved in vital functions, like cell cycle progression, differentiation, immune defense and the stress response. As the major cellular protease, the proteasome is a key player in eukaryotic protein homeostasis. The dysregulation of the UPS has been involved in neurodegenerative diseases and various types of cancer like multiple myeloma and hepatocellular carcinoma. Furthermore, Plasmatic Proteasome level is a potential marker in patients with solid tumors. In this study we examined the involvement of proteasome using a DMBA-induced melanoma in mice. Plasmatic and sub-cellular proteasome were measured using an enzyme-linked immunosorbent assay (ELISA) technique. Our objectives were four-fold: 1). Determine whether there were differences in Circulating and sub-cellular proteasome levels between normal and carcinogenesis mice; 2). Linking the stage of melanoma and that of the Circulating and sub-cellular proteasome levels; 3).To compare and correlate the proteasome activity with proteasome levels in normal and carcinogenesis mice ; and 4). Analyze the molecular structure of proteasome using two antibodies which detect different epitopes: Ac MCP 20 that recognize only the α6 subunit and Ac MCP 231 which recognizes both the 7 "α" subunits of the proteasome.

P223. IMMUNOHISTOCHEMICAL EXPRESSION OF P53 AND VEGF PROTEINS IN A MOROCCAN SAMPLE OF GLIOBLASTOMA PATIENTS

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Introduction: Glioblastomas are the most aggressive tumors of adult central nervous system. Treatment options are limited and the prognosis is very dim regarding these malignancies that account for about 15% of all brain tumors.
This study aimed to evaluate the expression of the tumor suppressor protein p53 and the angiogenic factor VEGF in Glioblastoma tumor tissues. And to assess the association between the expression of these proteins and patients related histoclinical factors
Material and methods: Using Formalin Fixed Paraffin Embedded (FFPE) tumor tissues from 33 Moroccan Glioblastoma patients, we performed immunohistochemistry using antibodies targeting either the mutated p53 or the over- expressed VEGF. We then investigated possible associations between these proteins' expression and 4 histoclinical factors which are: age, sex, histologic type and tumor localization.
Results: We conducted our study on a Moroccan sample of 33 patients, with a mean age of about 52 years old and a sex-ratio of 1.54 in favor of men over women. Our results showed a p53 expression in 19 cases out of 33 (58%), and a VEGF expression in 22 cases out of 33 (67%). Our univariate analysis indicated that p53 and VEGF expressions were not significantly associated with the histoclinical factors.
Conclusion: This study is the first of its kind in our country. Our results are to be further utilized in order to increase the data available regarding glioblastomas in Morocco.

P224. IMMUNOHISTOCHEMICAL EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR VEGF AND p53 IN HUMAN NEUROBLASTIC TUMORS: MOROCCAN EXPERIENCE

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Introduction & objectives: Peripheral neuroblastic tumors (pNTs), comprising neuroblastoma (NB), nodular ganglioneuroblastoma (nGNB), intermixed ganglioneuroblastoma (iGNB) and ganglioneuroma (GN), are the most common solid tumors of childhood arising from neural crest and responsible of 15 % of pediatric cancers deaths. Several factors define whether the prognosis is favorable or unfavourable such as clinical factors (age at diagnosis, tumor staging), histological factors (INPC classification, MKI) and the genetic factors (MYCN proto-oncogene). p53 is a nuclear phosphoprotein and a tumor suppressor gene, it is reported that around 50% of human cancers p53 is genetically altered. Vascular Endothelial Growth Factor (VEGF) is a homodimeric glycoprotein, it plays a huge part on the stimulation of the angiogenesis and a crucial role in tumor growth. The aim of this study was to evaluate the expression of p53 and VEGF proteins in pNTs patients and to assess potentiel associations between their expressions and some clinical and histological characteristics.
Material & methods: Formalin fixed paraffin-embedded blocks from 28 pNTs patients, diagnosed from January 2007 to December 2010. The blocks were analyzed using immunohistochemistry in order to evaluate the expression of the two markers. The Pearson chi- square and the Fischer's exact test carried out the statistical comparisons. The statistical analysis was performed by the SPSS software ($p<0.05$).
Results: p53 expression was observed in 82.14% of the neuroblastic tumors. High expression of VEGF was found in 50% of the tumors. Association between age, histologic types, INPC classification, primary site, metastasis, INSS stages and MKI index were all no statistically significant.
Conclusion: In contrast to our results, several studies demonstrated the association between the expression of p53 and the MKI, and between the expression of VEGF and advanced disease stage, INPC classification and histologic types. However, our results remain in concordance with data from literature in term of percentages of positivity.

P225. INCREASED OXIDATIVE STRESS MARKERS AND PURINE CATABOLISM IN ALGERIANS WITH GALL BLADDER CANCER

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Introduction: Gallbladder carcinoma (GBC) ranks the 5th worldwideincidence as a cancer of gastrointestinal tract. The poor prognosis of this lethal malignancy is related to its silent progression, as well as rapid growth and metastasis. This study aimed to investigate oxidative stress status and purine catabolism in Algerians GBC patients.

Materials and methods: Sera from 40 gallbladder cancer patients at TNM stage IVand 40 controls were sampled and used for oxidative stress and purine catabolism evaluation. Malondialdehyde (MDA) level was measured by the thiobarbituric acid reactive substances (TBARS) concentration.Nitric oxide (NO) levels were determined by the measure of nitrites, the stable end products of NO using Griess reagent. Adenosine deaminase (ADA) and xanthine oxidase (XO) activities weredetermined by Bertholet reaction and hypoxanthine oxidation method, respectively.Reduced glutathione (GSH) was measured by Ellman's method.

Results: Our results showed seric levels of MDA increased by 69%, while those of GSH stores decreased by 45% ($p < 0.001$), in GBC patients, compared to controls.

Sericnitrites levels ($p< 0.001$), ADA ($p< 0.001$) and XO ($p< 0.01$) activities enhanced by 2.0, 2.69and 1.26 fold, respectively in GBC patients, compared to controls. The receiving operating curve (ROC) showed an optimal cut-off for nitrites levels, ADA and XO activitiesof 21.21µM, 17.02 U/l and5.41 U/l, respectively. Spearman linear regression analysis revealed a positive correlation between nitric levels and ADA activity ($r=0.3419$, $p< 0.05$) and between seric ADA and XO activities ($r=0.5487$, $p< 0.001$), while no significant correlation was found between nitrites level and XO activity, in GBC patients.

Conclusion: Taken together, our results strongly suggest that oxidative stress and purine catabolism are actively involvedin the pathogenesis and progression of GBC.

P226. POMEGRANATE PEELS DECREASES ABERRANT CRYPT FOCI DEVELOPMENT AND ASSOCIATED OXIDATIVE STRESS IN DISTAL COLON OF 1, 2-DIMETHYHYDRAZINE- INITIATED MICE

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Introduction: Colorectal cancer is a malignant neoplasm of the large intestine with few to no symptoms. Dysplastic aberrant crypt foci (ACF) are reversible precancerous lesions of colon. ACF chemoprevention offers a valuable approach to control the incidence of colon cancer.
This study evaluated the efficacy of pomegranate peel aqueous extract (PPE; *Punica granatum L.,* from Biskra, South Algeria) supplementation on colonic aberrant crypt foci (ACF) formation, lipid peroxidation, and antioxidant defense in 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in mice.
Material and Methods: Colon carcinogenesis was initiated in two groups (2 and 3) of mice by subcutaneous injection of DMH (20 mg/ kg body weight), once a week, for 2 weeks. Groups 3 received orally PPE at 25 mg/ kg/ day, for 2 weeks. Control mice received the vehicle. At week 6, colon mice were recovered and evaluated for ACF formation, lipid peroxidation (malondialdehyde, MDA), and antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) activities.
Results: Our results showed that in DMH-treated mice increased number of ACF was accompanied by an increase in the colonic lipid peroxidation and decrease in SOD and CAT activities. PPE supplementation to DMH-treated mice decreased the number of ACF by 51% and inhibited colonic lipid peroxidation by 57%. PPE prevented SOD and CAT activities alteration, respectively by 46% and 51.79% compared to DMH-treated mice.
Conclusion: The results indicate that PPE supplementation interfere with chemically-induced promotion of colon carcinogenesis in mice by preventing ACF formation, mucosal oxidative stress.

P227. GENETIC VARIATION OF PD-1 IS ASSOCIATED WITH THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION

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Introduction/Objectives: Hepatitis C virus (HCV) persistence and pathobiology result from the interplay between viral replication and host immune responses. Programmed cell death-1 (PD-1) is an important immune effector with co-inhibitory activity involved in the progression of chronic viral infections. Our aim was to investigate the influence of the functional single nucleotide polymorphism (rs10204525) in the 3'-UTR of PD-1 on the susceptibility and outcomes of hepatitis C virus infection including disease progression in Moroccan patients.
Material/Methods: A total of 200 healthy controls, 101 spontaneous resolved HCV patients and 300 chronic HCV subjects (95 patients with mild liver disease, 131 individuals with advanced liver disease and 74 patients with hepatocellular carcinoma, HCC) were enrolled in this study and genotyped for rs10204525 using TaqMan allelic discrimination.
Results and Conclusion: Multivariate logistic regression analysis showed the significant association of rs10204525 with susceptibility to infection (P = 0.039), but a lack of association with spontaneous clearance (P > 0.05). In addition, the T allele at rs10204525 was related to an increased risk of HCC among patients with chronic HCV infection (OR= 1.528, 95% CI = 1.022–3.284, P = 0.038). These findings underline the importance of the functional polymorphism in PD-1 in the installation of HCV infection and its subsequent contribution to disease progression including the development of HCC.

P228. MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE: A CONTRAINDICATION FOR LIVING KIDNEY DONATION?

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Introduction: Kidney transplantation is the most effective option in patients with chronic renal failure in terms of survival and quality of life. During the last few years, the number of living donor kidney transplants (LDKT) has increased and this form of transplantation is currently the only option in some patients. Due to the growth of LDKT, new scenarios have been developed in which decisions on the feasibility of kidney transplantation can be difficult to make. We report a cases of living donor kidney transplantation in which the donor carried monoclonal gammopathy of undetermined significance.

Material/methods: The patient was a 17 -year-old Caucasian woman without toxic habits. She was affected by chronic renal failure stage V secondary to renal polycystic disease under renal replacement therapy with hemodialysis. The patient had no contraindications for kidney transplantation. A possible kidney living donor (father) was studied. He was a 50-year-old Caucasian man and showed no contraindication for donation. In our laboratory, in addition to usual immunological tests: HLA typing and HLA antibodies identification with Luminex technology, crossmatch tests. We realized protein electrophoresis and serum immunofixation for donor.

Results: Crossmatch was negative but protein electrophoresis and serum immunofixation of donor have shown a monoclonal proteins. The monoclonal protein was IgG lambda and the bone marrow examination showed 3% plasma cells. The M-protein concentration in the serum was 13.2 g/**L.** Kidney transplantation was carried out in Janury 2016 with no complications and renal function progressively improved. To date, the patient has no immunological or infectious complications. Serum protein electrophoresis and serum immunofixation have shown no monoclonal proteins.

The donor's renal function is currently normal, no complications have been detected and there is no evidence of MGUS progression to MM

Conclusion: In the foreseeable future, living kidney donation from donors with MGUS may no longer be exceptional due to the high incidence of MGUS, the increasing number of LDKT and the acceptance of greater age in donors and recipients. Due to the favorable results obtained in our cas until now, we no longer consider MGUS in the donor as a contraindication for LDKT. However, protocols should be established to optimize the approach in this situation.

P229. A CASE REPORT OF A TRICLONAL GAMMAPATHY OF UNDETERMINED SIGNIFICANCE

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Monoclonal gammapathy of undetermined significance (MGUS) is the most common plasma cell disorder, occurring in more than 5% of individuals past 70 years. It is characterized by the presence of a monoclonal protein (M-protein) in the serum <30mg/L or urine, bone marrow (BM) clonal plasma cells <10% with no end organ damage, such as hypercalcemia, renal insufficiency, anemia, bone lesions and no evidence of B-cell lymphoma or other disease known to produce an M-protein. The size and the type of the M-protein, the number of BM plasma cells and the serum Free Light Chain (FLC) ratio are all helpful in identifying patients at higher risk of progression. Herein, we report the case of a 70-year-old female, who was referred for the evaluation of a thyroid goiter. The patient complained of epigastralgia and arthralgia and did not return any other pathological history. Imaging studies showed an ulcerated bulbite and anatomopathological examination revealed the presence of *Helicobacter pylori* (*H. pylori*) bodies. The patient was treated with triple therapy. Osteodensitometry and radiography showed osteoporosis without lytic bone lesions and thyroid function was normal. In the framework of the supplementary examinations, serum protein electrophoresis and serum immunofixation revealed a triclonal gammapathy (TG) (IgG K, IgG **λ** and IgA **λ**). Nephelometric quantification of serum immunoglobulins was normal except for; IgA 5.58 g/L (0.7–3.6), FLC kappa (fk) 40.04 mg/L (3.3_19.40), FLC lambda (fl) 114.94 mg/L (5.71_26.3) with a normal FLC ratio k/l 0.34 (0.26–1.65). The other analyzes showed a mild anemia, haemoglobin 11.6 g/L and a Beta 2-microglobulin at the upper limit with a normal BM plasmocytosis 0.3%. Triclonal gammapathy is rarely reported. In fact, such clonal modifications are habitually induced by chemotherapy, BM transplantation and infections or could be an indication of myeloma progression. Interestingly, some studies have focused on the hypothesis that antigenic stimulation by different infectious agents, particularly *H. pylori*, could be involved in the development of a MGUS and that the eradication of the bacteria could lead to resolution of the gammapathy and normalization of the M-protein spike. Thus, post-treatment control of the infection and long-term monitoring is necessary in order to link the *H. pylori* infection to the development of the MGUS.

P230. INTEREST OF THE FREE LIGHT CHAIN IN THE RATIFICATION OF THE RISK AMONG PATIENTS PRESENTING A MULTIPLE MYELOMA

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Introduction: The multiple myeloma (MM) is characterized by a clonal proliferation of malignant plasmacels invading bone marrow. The survival varies according to the patients. Although there remains incurable to date, the MM knew these last years of important progress allowing an improvement of the therapeutic assumption of responsibility of the patients.
Objectives: Study of the implication of the free light chains, inthe survival of the patients reached of multiple myeloma in unvarié and multivariate (associate with the score International Survival Staging System (ISS).
Methods: Retrospective study realized on the serums of 52 patients presenting a multiple myeloma lasting the year 2013. All our patients profited from the proportioning of the total serum protids, of electrophoresis of serum proteins, serum and urinary immunofixation. And of the gravimetric measuring of the albumin of the immunoglobulines (IgG, IgA, IgM), of the freelight chains κ, and λ. as well as proportioning, the β2microglobuline.
Results: The median age of our patients was of 67 years with the extreme ones going from 42-89 years.The sex ratio was of 1.3. Average a Kappa Report (RKL) lower than 0.03 and higher than 32 was found among 23 patients is 55%. According to classification ISS our patients are classified as follows : 11 patients are classifiedwith stage I, 16 patients at the stage II, and 33patients at the stage III.
Conclusion: The application of score ISS associated withthe RKL revealed a new group of patients called at very high-risk whose average survival does not exceed 12 months.

P231. UTILITY OF SERUM FREE LIGHT CHAIN MEASUREMENT IN THE DIAGNOSIS AND FOLLOW-UP OF RANDALL'S DISEASE (ABOUT 03 CASES REPORTS)

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Introduction: Randall's disease or monoclonal immunoglobulin (Ig) deposition disease (MIDD) is a rare complication of plasma cell disorders, defined by linear Congo red-negative deposits of monoclonal light chain (LCDD), heavy chain (HCDD) or both (LHCDD) along basement membranes.

Renal involvement is almost always present in MIDD. Patients typically present with renal insufficiency and proteinuria, often accompanied by nephrotic syndrome

The monoclonal light chains, in LCDD are mainly of the kappa isotype (92%), which produced by monoclonal proliferation of plasma cells. To measure the concentration of this monoclonal light chains in sera, sensitives techniques are required, like the immuno-nephelometric or immuno-turbidimetric techniques. The abnormality of the ratio κ/λ is indicative of an excess of monoclonal production.

Observations: We report 3 cases of Randall's disease, all males with a mean age of 28 years. The clinical presentation is dominated by impure nephrotic syndrome, Renal Biopsy showed nodular glomerulosclerosis, which is a typical lesion of Randall's disease.

The bone marrow aspiration revealed a plasmocytosis less than 5%, which is in favor of monoclonal gammopathy of renal significance.

Electrophoresis of serum proteins did not reveal a monoclonal component. The turbidimetric assay of the free light chains (FLC) of kappa and lambda immunoglobulins (Ig) with determination of the κ/λ ratio confirmed the isotype of the monoclonal light chain which is of the Kappa type in the 3 patients, the mean concentration of the light chain Monoclonal "Kappa" measured by the "Freelite" assay is 254.76 mg/l. The κ / λ ratio “RFLC” was 8.84 at the time of diagnosis.

The dFLC represents the difference between the involved FLC and the not involvedFLC, reflects the tumor mass, it is also used to evaluate the response to treatment.

At the time of diagnosis (T0) the median estimated dFLC concentration was 667.38 mg/l, after treatment this value decreased to 230.94 mg/l indicating partial response to treatment.

Conclusion: The contribution of the FLC assay as a diagnostic marker, as an indicator of the tumor mass and as a therapeutic follow-up is no longer to be proved. It therefore seems pertinent to suggest a serum FLC assay once a diagnosis of Randall's disease is suspected.

P232. CYTOKINE PROFIL IN TUNISIAN MULTIPLE MYELOMA PATIENTS

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Introduction: In multiple myeloma (MM), several factors influence the growth of malignant clone through direct and indirect mechanisms. The aim of this study was to investigate associations between polymorphisms in IL-6, IL-1β, TNFα, IL-1Ra and VEGF genes, disease susceptibility or severity and to determine the functional impact of these SNPs on cytokines serum levels variation in Tunisian MM patients.

Methods: A cross-sectional case control study including 65 patients with MM and 100 healthy sex-matched volunteers was established. Cytokine genotyping was performed using molecular biology methods (PCR- SSP, VNTR, RFLP and direct sequencing) and serum concentrations were measured using an ELISA methodology.

Results : The first interesting finding of the present study was that individuals with IL-1 haplotype combination (IL-1β+3954 T / IL-1β +511 T / IL-1α-889 T) had a higher risk for MM susceptibility. Besides, a significant association between "higher producer" TNF-α genotypes profile or CCA (+936 C / +405 C / -2578 A) VEGF haplotype and renal failure was found.

Paradoxically, "high producer" IL-10 or TGF-β genotype's profile was more prevalent in multiple myeloma patients with advanced stage of the disease. However, no association between IL-6 variants and clinical evolution of multiple myeloma was observed.

Plasmatic study showed that patients who developed renal failure have higher TNF-α and VEGF serum levels, whereas high IL-1Ra serum levels might have a protective effect on such disease complications.

Conclusion : We conclude that differences in cytokine milieu may influence the disease pathogenesis of MM. Accordingly, pro-inflammatory (TNF-α and IL-1β) and angiogenic (VEGF) cytokines might have a prognostic value whereas anti-inflammatory cytokines (IL-1Ra) could play a protective role.

P233. NITRIC OXIDE US MEDIATOR AND MARKER OF INFLAMMATION- IS THERE A RELATION TO EXTENSIVE LAMBDA FREE LIGHT CHAIN PRODUCTION IN PATIENTS SUFRING OF MULTIPLE MYELOMA FROM EST OF ALGERIA

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Introduction: Nitric oxide (No) is formed by a variety of oxidative mechanisms; it is sensitive indices of inflammation and injury that are generated by products of cellular metabolism. Nitric oxide is widely associated with risk neoplasia and cancer development.
The free light chain (FLC) assay is a nephelometric measurement of lambda and kappa free light chains that circulate as monomers or dimers light chain and is not bound to immunoglobulin heavy chain. The quantitation of the lambda and kappa FLC and the calculation of the FLC λ/κ ratio are sensitive and specific prognostic marker of diseases produced by monoclonal gammopathies, such as multiple myeloma which is a hematologic malignancy characterized by the clonal proliferation of malignant plasma cells in the bone marrow.
Objectives: The aim of this study is to assess whether the level of serum (NO) associated with the serum lambda free light chains production in myeloma patients from the East of Algeria.
Material/methods: the serum of 38 MM patients aged between 35 and 60 from three Wilayas in the East of Algeria has been taken in 2014 and 2015 and analysed with colometric assays to evaluate (No) concentration ,Serum FLCs were measured by automated immunoassay and quantified using freelite™ reagent sets from the bindingsite.
Rresults and conclusion: The results obtained show a large interindividual variability in subjects where immunoglobulin concentration was between [lambda λ](5.36g/l_12000 g/l) means [1498±51.01061g/l] and NO production was higher in the population (58.66887µM /±40.2285 µM) Moreover, (NO) production secretion do not present any correlation with (λ FLc) secretion (r= -0.07005; P = 0.6760). Our results suggest that in this study no relationship was observed between NO production and serum myeloma (λ FLc) concentration in myeloma patients from the East of Algeria.

P234. EPIDEMIOLOGICAL AND IMMUNOCHEMICAL PARAMETERS OF MONOCLONAL PLASMA CELL DYSCRASIAS OF 2121 CASES IN ALGERIA

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Introduction : Plasma cell dyscrasias are a heterogeneous group of diseases characterized by the expansion of monoclonal bone marrow plasma cells that produce a monoclonal immunoglobulin (M-component).

Purpose: it's a retrospective study that describe epidemiogical, immunochemical features and etiology of monoclonal gammopathy diagnosed between1998 and december 2016 at the Teaching Hospital Beni-Messous of Algiers.

Material and Methods : 2121 cases of monoclonal gammapathy (MG) were collected during this period, Serum/urine protein electrophoresis , Serum/urine immunofixation and serum free light chain measurement were used to demonstrate M protein.

Results: The middle age of the patients at the time of the diagnosis was 62.96 ± 13.19 years with extremes ranging from 07 to 99 years and median to 64 years. The study included 1013 (47,76%) men and 1108 (52,23%) women with a sex ratio 0,91. Isotype repartition was : IgG (69.91 %), IgA (17.91 %) ,IgM (6.6 %), IgD (1.03 %) and IgE with 0.09% of cases . Moreover, 10.46 % of the patients were Kappa and Lambda-chain positive. Additionally, 2.82 % of patients had a biclonal gammopathy and 0.14 % had a triclonal gammopathy. The most frequent diagnosis were: Multiple Myeloma (55.20 %), followed by MGUS (34.13 %).

Discussion: The mean age was 62.96 years, in neighbours countries the average age was a bit closer to that found in this present study, for instance in Tunisia, Morroco and Egypt , it was 62,7, 60,21 and 58,5 years, respectively.

In our population, Females ' percentage was slight higher than males with a sex ratio 0,91, these resultsdid'nt agree with literature data. It could be do to the women predominance in older population. In study by Mseddi and al, IgG was the most common , followed by IgA and monoclonal light chains , these findings are similar to our data.

In international data, IgM isotype was frequent, for instance, in USA, Spainand France (Rennes and Blois hospitals), it was 19.6 %,13.6%, 31.9 and 25.7% respectively, however, in the present study and Mseddi and al study, the IgM was less frequent, it was 6.6% and 8.86% respectively, it could be due to the low frequency of WM in our region compared to the Western countries. Light chain proteinemia is frequent in our serie (10.46 %), these data are similar to the tunisian and egyptian studies. The most frequent diagnosis in western studies was monoclonal gammopathy of undetermined significance. However, the studies conducted by Mseddi and al, Ouzzif and al and our study , MM was the most frequent diagnosis, it can be explained by the lack of awareness about the diagnosis of MGUS in our country, which will evolve eventually to MM.

Conclusion: The pattern of monoclonal gammopathy observed in the algerian population show some particularities like the women percentage, which was found to be slightly higher than men, also the low frequency of IgM in this population and the high frequency of light chain multiple myeloma compared to other studies.

P235. THE IMMUNOLOGICAL DIAGNOSIS OF ALPHA HEAVY CHAIN DISEASE

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Introduction: The alpha heavy chain disease (αHCD) (also called : IPSID Immunoproliferative small intestinal disease) is an immunoproliferative syndrome characterized by the secretion of abnormal IgA molecules, made of incomplete α heavy chains without associated light chains. The majority of the diagnosed cases are from the Mediterranean basin and the Middle East, aged between 15 and 30 years of both sexes. The clinical manifestations are dominated by malabsorption, exudative enteropathy, diarrhea and vomiting. Hypoprotidemia and hypoalbuminemia are almost constant. The duodeno-jejunoscopy is the gold standard test for the diagnosis of this disease. The pathological protein consists of polymers of α heavy chains with variable size and devoid of light chains. The monoclonal peak in the serum protein electrophoresis is rarly present due to the heterogen size and charge of the pathological proteins. The immuno-selection is the reference technique to detect these proteins (in 20-90 % of cases), using anti-Kappa and anti-Lambda light chain antisera to precipitate the normal IgA, then the addition of an anti-heavy chain α reveals an anodal migration arc.

First observation: A 25-year-old man with chronic diarrhea since 2 years, not improved by the gluten-free diet of 6 months. The oeso-gastro-duodenal fibroscopy showed an ulcerated and micro-nodular duodenum. Serum protein electrophoresis showed a significant increase in the beta-globulin fraction with hypogammaglobulinemia and hypoalbuminemia. The immunoglobulins quantification showed an increase in IgA at 29.7 g/l (standards 0.7-4 g/l) and a hypo IgG at 4.49 g/l (standards 7-16 g/l). The immuno-selection disclosed the presence of heavy chains α. The screening for anti-nuclear antibodies, anti-polynuclear neutrophil antibodies, was negative. On the other hand, we have noticed a non-specific positivity of anti-gliadin, anti-transglutaminase and anti-saccharomyces cerevisiae IgA (ASCA) explained by the polyclonal increase of serum IgA.

2nd observation: A 24-year-old man with IPSID since 6 years, diagnosed with oeso-gastroduodenal fibroscopy and biopsy. Serum protein electrophoresis showed a monoclonal component in the gammaglobulins position at 9 g/l, the immuno-typing revealed the presence of an IgGκ. The serum immunoglobulins quantification showed an increase in IgA at 9.69/l (standards 0.7-4 g/l) and IgG at 22.6 g/l (standards 7-16 g/l). The immuno-selection technique revealed the presence of α heavy chains. The patient probably has an MGUS and αHCD.

Conclusion: The immuno-selection technique revealing the free α heavy chains is the gold standard test for the immunological diagnosis of αHCD.

P236. GAMMA HEAVY CHAIN DISEASE (A CASE REPORT)

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Introduction: Gamma heavy chain disease (ϒ HCD) is a rare lymphoproliferative disorder of B cells characterized by the production of heavy chain fragment of IgG without associated light chains.

Less than 150 patients have been discribed in the worldwide littérature, but ϒ HCD is currently underdiagnosed. In recent series, the median age at diagnosis is 51 to 68 years, and there is a clear female predominance. The lymphoplasma-cells may be located in the bone marrow or have an extramedullary localization, the most frequent was the skin involvement, but other localisations have been reported such as the thyroid gland, the oropharyngeal cavity, and the gastrointestinal tract, the most frequent manifestations include lymphadenopathy and hepatosplenomegaly, fever, and recurring infections.

The disease may be associated to autoimmune desorder such as rheumatoid arthritis, Sjögren syndrome, Lupus, myasthenia gravis autoimmune hemolytic anemia, and thyroiditis.

Observation: A 35-year-old woman presented with normochromic normocytic anemia, bones pain, cervical lymphadenopathy and history of autoimmune thyroiditis. The thyroid biopsy revealed *lymphocytic thyroiditis and the laboratory* tests were positives for anti-thyroglobulin antibodies. Renal biopsy showed infiltration of the lymphoplasmacytic lineage expressing CD20, which is in favor of lymphoplasmacytic lymphoma of renal localization.A vertebral compression at D5 region diagnosed with MRI, a thoracic computed tomography showed images suggestive of pulmonary and bone infiltration associated with osteolysis of the vertebral body of T5 region, but bone marrow biopsy showed no obvious lympho plasmacytic infiltration.The electrophoresis of serum proteins showed the a monoclonal peak of low concentration in the Beta region The serum immuno-fixation disclosed a heavy gamma chain without associated light chains.A deep hypogamma-globulinemia was also noted at 2.82 g/l.The free light chain assay (freelite®) showed an abnormal Kappa/Lambda ratio in favor of the Kappa light chain (RFLC=7.11, CLKappa:85.39mg/CLLambda:12mg./l).. The electrophoresis of the urinary proteins showed an albumin band with another band in the beta position, the urinary immuno-fixation has disclosed a heavy monoclonal gamma chain without associated light chains.

Discussion: The diagnosis of MCL gamma is based on the demonstration of a gamma isotype monoclonal heavy chain without associated light chains at the serum and / or urine by the immuno-fixation technique. The free light chain assay showed an abnormal kappa / Lambda ratio in favor of a light Kappa chain in this patient, confirming the hypothesis that light chains are produced by plasmocytes but incapable to binding to heavy chains. The heavy chains are altered and contain deletions, insertions, and point mutations that are acquired during somatic hypermutation. These alterations typically result in loss of a large portion of the constant-1 (CH1) domain of theimmunoglobulin heavy chain molecule responsible for light chain binding.

Conclusion: Gamma heavy chain disease is a rare B lymphoproliferative disorder, characterized by medullary or extra medullary lympho-plasmacytic infiltration. It can also be accompanied by an autoimmune disease, in our case it is an autoimmune thyroiditis. The diagnosis of this disease is essentially immunochemical by the detection of the heavy chain gamma without associated light chains.

P237. CORRELATION OF LACTATE DEHYDROGENASE AND LYMPHOMA IN ALGERIAN CHILDREN

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Objective: This study aimed to evaluate the relation of Lactate dehydrogenase (LDH) levels with stage of the disease and it role in monitoring tumor response to therapy in lymphoma patients.
Methods: LDH levels were evaluated on 65 diagnosed Algerian children and compared to healthy control.
Results: Our results revealed that LDH levels were significantly higher in untreated children with both hodgkin's and non hodgkin's lymphomas compared to control. Moreover, it was observed that the higher is the stage of disease, the more serum LDH level will be. However, there was a significant fall in serum LDH activity by completion of the chemotherapeutic courses.
Conclusion*:* LDH plays an important role in tumor initiation and maintenance. The elevated serum LDH may reflect, release of the enzyme from malignant cells and suggest that they may reflect tumor burden and therefore correlate with disease progression.

P238.THE ALTERNATIVE COMPLEMENT PATHWAY IS ASSOCIATED WITH THERAPY OUTCOME IN B CELL NON HODGKIN LYMPHOMA

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Introduction : Hypocomplementemia and overproduction of complement regulators (Stoiber H. et *al. Leukemia* 2013, *Hematologica* 2013) were pointed out in the therapeutic failure of B cell non-Hodjkin's lymphoma (BCNHL).
Aim : Propose and evaluate the alternative complement pathway (ACP) as prognostic factor for therapy response in BCNHL.
Experimental Design : A longitudinal kinetic follow up of 30 BCNHL patients was performed with monitoring of ACP and fH functional activities. The results were expressed as % of human normal plasma activity (NHP) and values above to 80 % NHP were considered as normal.
Results : We found a marked decreases in AH_{50} in the first group -Failure to therapy- (m_1=74.38 ± 9.99) compared to the second one -remission- (m_2= 84.38 ± 11.01 HNP%; p=0.001), parallel to FH increase (m_1=91.84 ± 5.4, m_2= 86.62 ± 5.08%, p=10^{-3}). Unexpectedly and in contrast to failure group where AH_{50} still stable through cures, in remission group, AH_{50} increases was observed in fashion with cures number (R^2=0.19; p=10^{-3}). Accordingly, a multivariate Cox model adjusted to BCNHL prognostic factors was used to verify whether hypocomplementemia could be associated with therapy response. In fact, the hazard ratio of high AH_{50} adjusted to age, sex, tumor localization and performance status to have remission was HR=5.3 $IC_{95\%}$[2.176-12.812]; p=10^{-3}.
Discussion : The current study confirms the findings of *Laura M. Rogers et al. (Blood 2017)* who have shown that higher fH levels correlating with inferior therapeutic response. Our data are in line with previous reports showing fH overexpression for cancer cells evasion to complement-mediated tumor killing (*M.M. Markiewski et col. Trends in Immunology 2009 ; Junnikkala S et al., J Immunol 2000)*. Interestingly, as shown by *Bridget Charbonneau (Am. J. Hematol. 2012),* we have identified that patient with high ACP activity is associated with therapeutic response and improved progression-free survival (PFS).the current study suggest that ACP activity could be considered as a strong candidate predictive biomarker to therapy outcomes.
Conclusion; Our study reinforces the previous data of Evidence-Based-Medicine and proposes AH_{50} as a prognostic biomarker for therapy outcome in BCNHL

P239. JAK2 V617F MUTANT ALLELE QUANTIFICATION IN MYELOPROLIFATIVE NEOPLASMS : EFFECTS ON PHENOTYPE AND THROMBOTIC EVENTS

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Introduction: Activating JAK2 V617F mutation is an independent risk factor of chronic myeloproliferative neoplasms (MPN). However, current data about thrombotic risk in patients harboring the JAK2 V617F mutation remain controversies. In this study, we aimed to investigate the correlation between the mutant allele burden and the risk of thrombosis in MPN patients.
Material and methods: Thirty-eight MPN patients carried the JAK2 V617F mutation (screening by PCR-RFLP and confirmed by direct sequencing) were explored. Real Time-PCR (ipsogen® RGQ PCR, QIAGEN®) was used for quantification the JAK2 mutant allele which was tested for correlation with the clinical presentation and type of chronic MPN.
Results: The JAK2 mutational load was statistically higher in patients with polycythemia vera (PV) (64,76% ± 32,54%) compared to patients with unclassifiable MPN (33,49% ± 24,34% and with essential thrombocythemia (ET) (23,73 ± 15,74) (p = 0.013). The highest JAK2 V617F mutation levels was also statistically correlated to the risk of evolution to myelofibrosis in both PV and ET patients (p = 0,03). However, no association between the mutational load and thrombosis was found and the V617F quantification was not correlated to hemoglobin levels, platelet counts or cardiovascular complications.
Conclusion: The above observations supported the lack of an increased risk of thrombosis associated with JAK2 V617F mutation. Nevertheless, quantification of mutational load appears to be useful for stratification of MPN patients and clinical evolution.

P240. JAK2 V617F MUTATION FREQUENCY AMONG PATIENTS WITH BUDD CHIARI SYNDROME AND OTHER SPLANCHNIC VEIN THROMBOSIS

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Introduction: Splanchnic vein thrombosis (SVT) involves thrombosis that occurs in the trunk of the portal vein, including the left and right branches as well as possible extension to the splanchnic vein, the upper mesenteric artery or the intra-hepatic branches of the portal vein. Budd-Chiari syndrome (BCS) is a rare disorder characterized by hepatic venous outflow obstruction, which presentation depends upon the extent and rapidity of hepatic vein occlusion. JAK2 V617F mutation is an important diagnosis tool of myeloproliferative diseases (MPDs). Some recent reports have suggested the possibility of latent MPDs in patients with splanchnic vein thrombosis, including BCS. The aim of this study is to determine the JAK2V617F mutation frequency in patients with BCS and other splanchnic vein thrombosis.
Material and methods: Our study included 110 patients : 32 (29%) patients with BCS, 38 (34%) with portal vein (PV) thrombosis, 3 patients had a superior mesenteric vein (SMV) thrombosis, 2 patients with splenic vein (SV) thrombosis, and 35 patients (32%) with more than one veinous thrombosis. Our population included 69 women (63%) and 41 men (37%) with a mean age of 46,42 ±15,79 years. JAK2 V617F mutation was detected using a Real-time PCR method (TaqMan Technology, Applied Biosystems).
Results: The most frequent clinical features were : splenomegaly (52%), asthenia (40%), hepatomegaly (32%) and weightloss (20%). In the other hand, leukopenia (32%), thrombocytopenia (30%) and Hypochromic microcytic anemia (28%) were the most biological features reported in our population. The JAK2 V617F mutation was found in 23 patients (21%). No difference was found by comparing the mutation frequencies according to the localization of vein thrombosis. In addition, osteomedullary biopsy was conclusive for 7 patients (6%) who show clinical and biological signs of MPDs. However, JAK2 V617F mutation was found in 5 patients among them.
Conclusion: In our study, JAK2 V617F mutation was found in 21% of patients with BCS and other splanchnic vein thrombosis. The detection of this mutation may be useful specially for latent MPDs patients screening, who require a tight follow-up.

Transplantation

P241. DONOR SPECIFIC ANTIBODIES AGAINST NATIVE AND DENATURED HLA: THE HIDDEN FACE OF CLASS I HLA MOLECULES

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Background: Class I HLA donor-specific antibodies (DSAs) are detected with Luminexsingle-antigen beads (LSAB) but their clinical relevance isstill not clearly defined. The LSAB express both class I HLA native antigens (nHLA) (Ag) and altered molecules of modified conformation called denatured HLA (dHLA). As patients' sera can contain anti-HLA antibodies specific for either one of the two forms, and as only the nHLA molecules are expressed on the cell surface, the anti-dHLA antibodies (Ab) could be considered as falsely positive and they actually do not seem to be pathogenic in vivo.
The aim of our study was to determine the prevalence ofde novo class I anti-dHLAandnHLA DSA in organ transplanted patients who were not HLA-sensitized pre-transplant, expecting that only anti-nHLA DSA would occur.
Methods: Serapositive forde novo class I DSA (mean fluorescence intensity MFI>1000) were retested after acid treatment of the beads to transform bead nHLA into dHLA. The DSA category was determined according to the ratio between the MFIfor treated and untreated LSAB as follows : anti-Dhla when d≥1,2n, anti-nHLA when d≤0,2n and intermediate anti-HLA when 0,2n<d<1,2n. These sera were tested in T-cell flow cytometry crossmatch (T-FCXM) against surrogate cells (from current donors) harboring only the DSA target antigen as a serum/cell mismatch, when adequate serum/cell combinations could be found,as original donors' cells were not available.
Results: At the moment, as this project is not yet finished, we have performed 74 tests from 41patients, covering the A1, A2,A26, A30, B8,B35,B41, B58, C4, C7 and C10 Ag, using the serum at the discovery of the DSA. Among them, 62%, 19%and 19%were anti-nHLA, intermediate anti-HLA andanti-dHLA, respectively. Most sera were tested on more than one cell (range 1-4) with consistent results. Positive T-FCXM (signal at least 1,5 fold the background) were obtained respectively for 28% of anti-dHLA, 50%of intermediate anti-HLA and 43% of anti-nHLA.
Conclusion: Only 42% of the sera provided positive FCXM, suggesting that the antigen that triggered the de novo LSAB DSA is not always nHLA. In addition, 19% of sera contained a dHLA reactivity according to LSAB definition, which again was against our starting hypothesis.As a possible explanation, the anti-HLA response can be complex and anti-HLA can bind to epitopesbelonging to both HLA forms, being therefore positive in all assays. Hence, epitope identification (e.g. with HLA-matchmaker and/or bead/cell serum adsorption experiments) should clarify these cases.

P242. COMPARISON OF HLA ANTIBODY SCREENING METHODS FLOW CYTOMETRY VERSUS LUMINEX®

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Introduction: Human leukocyte antigen (HLA) antibodies are a major cause of allograft loss, as research has clearly established. These antibodies have been traditionally detected by cytotoxicity techniques and more recently by flow cytometry.
Currently, the solid-phase immunoassay (Luminex®) using coated beads with HLA antigens offers a higher level of sensitivity in the detection of donor specificantibodies (DSA).
Objective: In this work, we designed a simple experimental approach to correlate flow cytometry results with data from the Luminex ® in order to compare the two methods.
Methods: We selected 28 sera already screened with solid-phase immunoassay and containing anti-HLA classI (anti HLA-A and -B) antibodies only. These sera were incubated with lymphocytes from four different patients expressing only one of the HLA class I antigens recognized by the serum to be assayed. We have correlated flow cytometry cross-match outcomes with results from Luminex®assays. The Concordance ratio was determined using comparisons of the Luminex®single antigen MFI and NBG ratio results with flow cytometry cross-match results. All calculations were performed using SPSS for Windows, version 21.
Results: We performed 12 flow cytometry cross-matches by combining 8 sera (among 28 luminex tested sera) with cells from four different patients typed for HLA class I, so that each of the sera samples presentedreactivity against only 1 of the HLA antigens expressed by lymphocytes. Among our 8 sera, the three negative luminex sera (MFI < 2000) were also negative by cytometry. Three luminex highly positive sera (MFI > 5000) were also positive by cytometry. The flow cytometry cross-match was negative in two cases, although the MFI value of the first serumagainst HLA-A32 was 10101and for the second one against HLA-B17 was 5542. A HLA-A2 luminex positive serum (MFI > 5000) was tested by fow cytometry cross-match against two different HLA-A2 cells. It was revealed positive in only one case. Our study will be completed to includeall of our 28 sera that will be tested by flow cytometry against a panel of HLA class I typed cells.
Conclusion: Luminex technology is more sensitive than flow cytometry for the identification of anti-HLA antibodies. Furthermore, it offers a high resolution typing of DSA epitope specificity.

P243. MICA AND RENAL TRANSPLANTATION: ANTIBODIES AND MICA-TM GENOTYPING IN A COHORT OF SOUTH TUNISIAN PATIENTS

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Introduction: Major histocompatibility complex class 1 chain-related antigen A **(**MICA) antibodies have been associated with renal graft loss. Solid organ transplantation poses the challanges of a possible mismatch for MICA between the donor transplant and the recipient. However, genotyping is not performed routinely.
The present study examined the frequency of the various alleles for MICA gene via genotyping of exon 5 MICA microsatellite among donors, compared to recipients and healthy individuals.
Materials and Methods: We examined the sera of patients who had received a kidney transplant graft from a related living donor between 2011 and 2016. Sera were collected before and/or after transplantation. MICA antibodies were screened using LABScreen assay (LSM12) by Luminex technology (One Lambda®).
Retrospectively, we studied the polymorphism of exon 5 MICA microsatellite for each donors, recipients and healthy controls.
Results: From 2011 to 2016, 19 patients were positive for anti-MICA antibodies screening, from whom six were detected after transplantation. A mis-match was detected in three cases between donor and recipient genotyping of MICA microsatellite. Concerning anti-MICA antibodies detected before transplantation, 10 mis-matches were detected. The statistical analysis of phenotypic MICA microsatellite polymorphism in the recipient, donor and healthy control showed that: -the MICA A4 was significantly associated with recipient group compared with healthy control group (p=0.001; 42% vs 14%).-MICA A6 and MICA A5.1 were more frequent in healthy control group compared to recipient group (p=0.01; 36% vs 69%) and donor group (p=0.01; 15% vs 45%) respectively. We observed a low frequency of the MICA A5.1 allele in our transplant donor population (n=3, 15.7%). This result is in contradiction with literature results.
Conclusion: The immune impact of MICA mismatch in kidney transplantation remains mostly uncovered. More data on the impact of MICA on renal grafts outcome are needed.

P244. RENAL TRANSPLANTATION IN A SUBJECT WITH ANTIBODIES TO THE GLOMERULAR BASEMENT MEMBRANE

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Introduction: Anti-glomerular basal membrane (anti-MBG) autoantibodies are specific for Goodpasture's syndrome (SGP). This syndrome is characterized by a hemorrhagic pneumo-renal syndrome that can lead to serious complications such as chronic terminal renal failure (CRTI).
Material and methods : We report the case of a 23-year-old patient with CRTI whose causal nephropathy is a Goodpasture syndrome with the presence of anti-glomerular (anti-MBG) antibodies.
Results: The patient was transplanted from the kidney of his monozygotic twin brother who does not have any particular pathological history. A renal pre-transplantation immunoassay was carried out, the latter comprising: HLA typing carried out by a molecular biology technique (PCR-SSO), anti-HLA antibody analysis carried out by fluorescent immunofluorometry (Luminex) and cross-match made by lymphocytotoxicity dependent supplement (LCT). The HLA typing of the patient showed the presence of a Goodpasture syndrome susceptibility gene which is HLA DRB1*15, this gene is present in one third of patients with this syndrome.
Conclusion : Recurrence of anti-MBG autoantibody disease is found in 50% of patients with circulating antibodies at the time of transplantation, but only in 5 to 15% of patients receiving a graft 6 months after the disappearance of antibodies. Recidivism were also described. The treatment is identical to that of Goodpasture diseases on native kidneys (corticoids, cyclophosphamide, plasma exchange).

P245. GNETIC POLYMORPHISMS OF CYP3A5 AND PHARMACOKINETICS OF THE CALCINEURIN INHIBITORS CYCLOSPORINE AND TACROLIMUS

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Introduction: The bioavaibility and metabolism of the calcineurin inhibitors (cyclosporine (CsA), tacrolimus (Tac)) are principally controlled by the cytochrome P-450 (CYP) isoenzyme system. Previous pharmacogenetic studies have reported an association between CYP3A5 genotype and variation of tacrolimus pharmakinetics. However, to date, these results still controversial. The aim of this study was to investigate the impact of CYP3A5 6986A>G polymorphism and its correlation on the calcineurin inhibitors metabolism in renal post-transplant phases of Tunisian recipients.

Material and methods: Ninety-one patients were recruited: 50 kidney recipients were receiving Tac (GI) and 41 patients CsA (GII). Blood samples were prospectively collected for therapeutic drug monitoring during early (1 to 90 days) or late (over 90 days) post-transplant phases. Through blood concentration (C_0), blood concentrations at one hour and three hours after drug administration (C_{1h} and C_{3h}) and area under the curve (AUC_{0-12}) were measured for GI and C_0, C_{2h} (blood concentration two hours after drug administration) and AUC_{0-12} were measured for GII. PCR-RFLP was used for CYP3A5 6986A>G genotyping and dose-adjusted C_0 and AUC_{0-12} were correlated with the corresponding genotype CYP3A5 6986A/A (CYP3A5*1/1) or CYP3A5 6986A/G (CYP3A5*1/3) or CYP3A5 6986G/G CYP3A5*3/3).

Results: Tac C_0 and AUC_{0-12} showed a significant difference between CYP3A5*1 carriers (mean C_0 = 4,47 ng/ml and AUC_{0-12} = 100,421 ng.h/ml) and homozygous CYP3A5*3/3 (mean-C_0 = 8,45 ng/ml and AUC_{0-12} = 167,680 ng.h/ml) (p = 0.003 and p = 0,010, respectively) in early and late post-transplant phases. Tac dose-adjusted trough C_0 (C_0/D) and AUC_{0-12} (AUC/D) were similar in the two groups (CYP3A5*1/1 or CYP3A5*1/3 and CYP3A5*3/3) before the first 3 months of transplantation and tend to be significantly different in the late post-transplant phase (p = 0, 06). However, in the GII, no difference between CsA bioavaibility markers and CYP3A5 6986A>G polymorphism was shown in Tunisian recipients.

Conclusion: Our results confirm that CYP3A5 polymorphism assessment could be useful to determine the therapeutic dose of Tac in pre and post kidney transplantation to minimize the risk of under or over immunosuppression. Our group and others have demonstrated that CXCL10 is a sensitive marker for both subclinical and clinical TCMR in adults.However, the data in pediatric renal transplantation is not avaible yet.

P246. CORRELATION BETWEEN ELEVATED CXCL10 URINARY LEVELS AND BKV INFECTION IN KIDNEY ALLOGRAFT RECIPIENTS

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Introduction: Recent data have demonstrated that CXCL10 (or IP10: interferon gamma induced protein 10) is a sensitive marker for both subclinical and clinical T cell-mediated rejection (TCMR). However, this association remains controversial by other authors. Therefore, our goal was to verify if elevated urinary CXCL10 levels could predict allograft damage in kidney transplantation.

Patients And Methods: Thirty-five patients with concomitant clinical and histopathologic data were included. 88 urine samples were prospectively and serially collected for CXCL10 ELISA (R & D systems) on day 7 (D7), one, three, six months (M1, M3, M6) post-transplantation. The inclusion criteria were all former and new transplant recipients. They were categorized according to clinical surveillance, BK Virus Real-time monitoring and Banff biopsies criteria as: normal (G1: 27 patients), acute rejection (G2: 3 patients) or suspected to have BK Virus nephropathy (G3: 5 patients).

Results: No association between elevated urinary CXCL10 levels and acute rejection was found. However, a significantly higher concentration of this marker was observed in G3 compared to the two other groups (Mean levels: 112,56 ± 65,92 pg/ml in G3 versus 27,58 ± 8,16 pg/ml in G1 and 7,78 ± 3,15 pg/ml in G2, respectively) ($p = 0.001$). The area under receiver operating curve for the positivity of PCR BKV-DNA was 0.78 [0.66 – 0.90] ($p = 66 \times 10^{-5}$). This corresponded to a sensitivity-specificity of 0.65-0.81 for PCR BKV positivity at CXCL10 cutoff of 4.3 pg/ml.

Conclusion: The above observations do not confirm that the noninvasive urinary CXCL10 quantification is a useful marker of acute rejection in our population. Nevertheless, it could potentially be used to identify and to purser patients with suspicion of BK Virus nephropathy.

P247. RECOMBINANTION IN HUMAN LEUKOCYTE ANTIGEN REGION IN TUNISIAN BONE MARROW RECEIVERS AND RELATED DONORS

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Introduction: Recombination or chromosomal crossing over is the exchange of genetic material between homologous chromosomes that may generate novel haplotypes. Even though recombination in human leucocyte antigen (HLA) region is a rare event, the resulting haplotypes could decrease the chance for a bone marrow receiver to find a suitable matched donor. We aimed in this study to investigate the recombination frequency and its location in HLA region.

Material and Methods: During a period of 12 years (2005- July 2017), bone marrow receivers and related family members were HLA typed at class I-A, B and class II- DR, DQ using serology and molecular methods (polymerase chain reaction- sequence specific oligonucleotides/sequence specific primes PCR-SSO/SSP). The genotyping of four short tandem repeat (STR) markers located in the short arm of chromosome 6 (D6S291, D6S273, D6S265, D6S276) was performed using ABI Prism 310 sequencer. HLA and STR haplotypes were analyzed for each case and recombination location was identified.

Results: Among 691 families, recombination in HLA region was identified in 13 families (1,88%). Each of the thirteen families had one member with recombinant haplotype. Crossing over was found in 5 bone marrow receivers and 8 related potential donors. The recombination was located between HLA-A and B loci in 8 cases and between HLA-B and DR loci in 4 cases. STR genotyping refined the crossing over localization in these 12 cases and allowed the identification of a recombination telomeric to HLA-A locus in one case.

Conclusion: Our study shows the importance of a careful interpretation of HLA typing results and the interest of STR genotyping in the context of bone marrow graft.

Miscellaneous

P248. THE CONTRIBUTION OF NON-CLASSICAL METHODS IN THE LEARNING OF MEDICAL IMMUNOLOGY: PRELIMINARY STUDY AT THE FACULTY OF MEDICINE OF ORAN

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Introduction: Medical immunology education is a major challenge for faculties of medicine around the world.
Objective: To study the impact of strengthening the classical method (CM) by active methods, called non-classical methods (NCM).
Material and Methods: 154 dental medicine students were studied for learning by lectures (CM) followed by Brainstorming (BS) learning then Problem-Based-Learning (PBL) and finally Quizzes-Based-Learning (QBL). The assessment focused on: (1) direct evaluation of the acquisition of scientific skills, and (2) student evaluation of each NCM according to its respective parameters. The analysis concerned 3 questions: Do the different NCMs work in synergy? Do NCMs increase exam scores? Does this reduce failure rates?
Results: Our study showed that CM was failing in 5/19 parameters: discussion, student active participation, course density, practical knowledge, data redundancy (median <6 points). BS has improved the control of immunology learning (p=0.044), active participation of students (p=0.023), practical knowledge (p = 0.011) and knowledge organization (p=0.045). A significant improvement in the BS and BPL examination scores was observed (p=0.00). The PBL improved test of knowledge (71.43%), development of the critical spirit (100%) and the benefit of the collective intelligence (64,28%).
Discussion: We confirm the results of Freeman S et al. 2014 that active learning is a strategy that improves student achievement and learning outcomes. The current study is consistent with previous reports that showed the contribution of NCM to improved cognitive performance and the final grade (Freeman S 2007, Walker JD 2008, Pyburn DT 2014). We found that NCM has a greater impact on students' mastery of cognitive skills. (Haukoos GD, Penick JE (1983), Martin T, Rivale SD, Diller KR (2007), Cordray DS, Harris TR, Klein S (2009), Jensen JL, Lawson A (2011).
Conclusion: The use of NCMs dramatically consolidates the complex knowledge and concepts that characterize medical immunology education.

P249. MALADIE DE TAKAYASU A PROPOS DE 3 CAS A L'HOPITAL NATIONAL DE NIAMEY

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Introduction /objective: the aim of our study is to evaluate the different epidemiological clinical radiological and therapeutic, aspects of Takayasu's disease.
Methods: We report three cases of Takayasu disease collected from HNN between 2005 and 2016. The parameters studied are age sex clinical and paraclinical signs as well as therapeutic and evolutionary models.
Results: Of the three patients, two were women and the age of onset was 27 years in one case and 33 years in the other two cases. Clinically, abolition of at least one peripheral pulse was constantly observed.
We find a predominance of the involvement of the supra-aortictrunks (3 cases) and less of the abdominal aortic involvement (1 case).
Moreover, our series is distinguished on the one hand by a case revealed by a stroke in a male subject and on the other by the frequency of thrombosis in two cases.
Corticosteroids were successful with clinical improvement and stabilization of the disease in the short and medium term.
The revascularization performed in two of the patients was complicated by short-termthrombosis in one case.
Conclusion: TA is uncommon disease that must be evoked before a symptomatology aspecific coaches and lead to check the pulse.
Ischemic complications are already presen tat the time of diagnosis. We have found a high frequency of arterial thrombosis in our series.

P250. MARCKS PROTEIN OVEREXPRESSION IN INFLAMMATORY BREAST CANCER

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Background: Inflammatory breast cancer (IBC) is the most aggressive form of locally-advanced breast cancer. Despite multimodality treatment, the 5-year survival remains around 50%. Identification of new therapeutic targets is crucial. We previously reported MARCKS mRNA overexpression in IBC in the largest transcriptomics study reported to date (1). Here, we evaluated MARCKS protein expression in IBC and non-IBC clinical samples.

Patients and methods: We retrospectively analyzed MARCKS protein expression by immunohistochemistry (IHC) in a series of 502 tumors, including 133 IBC and 369 non-IBC, from Tunisian and French patients. All samples were pre-therapeutic tumor samples. We searched for correlations between MARCKS expression and IBC versus non-IBC phenotype and metastasis-free survival (MFS).

Results: Using 0% of stained tumor cells as positivity cut-off, 89 samples (18%) exhibited a positive MARCKS expression (≥1% of stained cells), whereas 413 (82%) were MARCKS-negative. Among the 502 samples tested, 148 samples (34 IBC and 114 non-IBC) were previously analyzed for MARCKS mRNA expression on DNA microarrays; there was a correlation between protein and mRNA expression (p=7.0E-03).

Importantly, MARCKS expression was more frequently positive in IBC than in non-IBC (p=1.4E-09). The percentage of MARCKS-positive cases was 36% in IBC versus 11% in non-IBC, and was not different between the Tunisian and French IBC samples (42 versus 30%, p=0.21). *In multivariate analysis* integrating all significant variables, MARCKS protein expression remained associated with the IBC phenotype (p=6.9E-04), suggesting discriminating value independent from other variables including the molecular subtypes.

In IBC (N=94), MARCKS expression was associated with poor. The 5-year MFS rate was 35% [95CI, 20-59] in the MARCKS-positive group versus 64% [95CI, 52-79] in the MARCKS-negative group (p=3.6E-02, log-rank test).

Conclusion: MARCKS overexpression might in part explain the poor prognosis of IBC. As an oncogene associated with poor MFS, MARCKS might represent a new potential therapeutic target in IBC.