Medical Immunology Campus Erlangen

An Interdisciplinary Center
of the Friedrich-Alexander-Universität
Erlangen-Nürnberg

Newsletter
Winter 2015/16

CONTENT

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

EDITORIAL

Dear colleagues and friends,

In the past months the news have been largely dominated by reports on the outflow of refugees from the Near and Middle East and from Africa. Tabloid papers started to stoke fears that the displaced people might bring dangerous infectious diseases to Central Europe and thereby jeopardize the health of the local population. None of this is true. At the same time, important event celebrating milestone results in infectious disease research has been largely ignored by the same media: the award of the *Nobel Prize in Physiology or Medicine* to Youyou Tu (China), to William Campbell (Ireland/USA) and to Satoshi Omura (Japan). The three scientists have been honored for their discovery and development of novel drugs against the tropical diseases malaria, onchocerciasis (which can lead to river blindness) and lymphatic filariasis (which can cause elephantiasis). All these diseases are highly prevalent in Africa and other areas of the world. At the beginning of the 70s, the pharmacist Youyou Tu succeeded in extracting artemisinin from annual wormwood (*Artemisia annua*) and later synthesized the compound dihydroartemesinin. Derivatives of dihydroartemisinin are nowadays used for the prophylaxis or treatment of *Plasmodium falciparum* malaria. The chemist and microbiologist Satoshi Omura developed new methods for the culture of bacteria and fungi. He specifically focused on *Streptomycetes*, which belong to the actinobacteria. Out of one of these cultures (*Streptomyces avermitilis*) the parasitologist and biochemist William Campbell isolated an agent (avermectin) which showed strong activity against parasitic diseases of domestic and farm animals. A chemical modification of avermectin led to the discovery of the more potent ivermectin, which nowadays is not only used in patients with onchocerciasis, but also for the treatment of several other worm infections (e.g. *Larva migrans cutanea*) or ectoparasites (e.g. scabies). There is no doubt that the work of all three researchers has helped tremendously to improve the quality of life of the people in endemic areas. Today, medical research on infectious diseases and immunity, the development of efficient and affordable drugs and vaccines and access to basic and advanced medical care remain critical factors that contribute to the social and political stability of countries around the world.

In the year 2015, the *Medical Immunology Campus Erlangen* succeeded in establishing a new Collaborative Research Center (CRC1181) funded by the DFG. Its first scientific retreat has just taken place at Schloss Banz, a former Benedictine monastery in the upper Main valley. In the 2015 DFG Funding Atlas, the FAU Erlangen-Nürnberg once again achieved a top rank (position 3 of all German universities, closely behind the MHH and the LMU) in the research area “microbiology, virology and immunology”. This not only reflects the huge efforts of the immunologists and infectious disease researchers at the FAU, but also underlines that the university and the faculties need to provide the infrastructure for a continuously growing community of immunologists.

I wish you and your families a Merry Christmas, some relaxing holidays and all the best for 2016.

Prof. Christian Bogdan

Chairman of the *Medical Immunology Campus Erlangen*

SCIENTIFIC HIGHLIGHTS

Dietary fatty acids have profound influence on T cell differentiation in the gut

Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine

RALF LINKER
DEPARTMENT OF NEUROLOGY, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Recent evidence points at a strong link between diet, microbiota composition, immune status and autoimmune disease. This concept is now strengthened by new evidence showing that medium and long-chain fatty acids (MCFA/LCFA), the most abundant type of fatty acid in the typical Western diet, can exacerbate disease in a mouse model of multiple sclerosis.

Adding the LCFA lauric acid (a C12 fatty acid) to naive mouse T cells increased the differentiation of T_H1 and T_H17 cells by ~50% under T_H cell-polarizing conditions and decreased the differentiation of regulatory T (T_{reg}) cells by about one third.

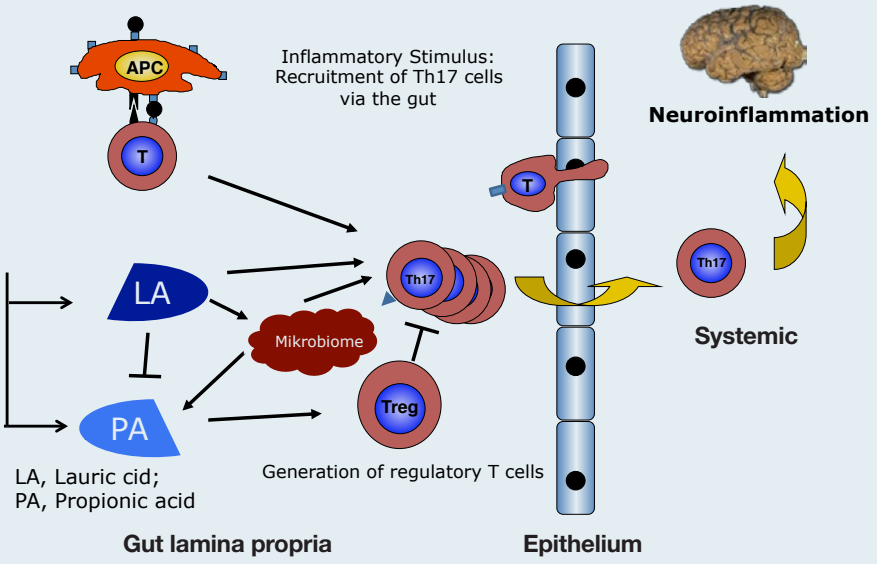
Looking at the involvement of downstream signaling pathways, the most differentially expressed genes between lauric acid-treated and untreated T_H17 cells include *Maf* and *Mapk14*. Lauric acid treatment of T cells under T_H17 cell-polarizing conditions increased p38 phosphorylation, and pharmacological or genetic blockade of p38 inhibited the effect of lauric acid on T_H17 cell differentiation. By contrast, the short-chain fatty acid (SCFA) propionate (C3) displayed a T_{reg} cell-stimulating effect on mouse and human naive $CD4^+$ T cells, which correlated with decreased p38 phosphorylation.

Using experimental autoimmune encephalomyelitis (EAE) as a model of T_H1 cell- and/or T_H17 cell-mediated disease, mice fed a diet rich in lauric acid suffered from a more severe disease than mice fed a control diet, with an increased frequency of T_H17 cells in the small intestinal mucosa, spleen and central nervous system at 7 days, 10 days and 14 days, respectively, after disease induction by antigen immunization. This T_H17 cell-enhancing effect of a lauric acid-rich diet involved changes to the intestinal microbiota – including decreased Prevotellaceae and families of Bacteroidetes – that correlated with increased levels of LCFAs and decreased levels of SCFAs in faeces. Faecal filtrates from lauric acid-fed mice enhanced T_H17 cell polarization *in vitro* and *in vivo* in a model of inflammation in the small intestinal mucosa. Daily oral gavage of mice with the SCFA salt propionate prevented the onset of EAE, which correlated with an increased frequency of T_{reg} cells that could transfer protection to recipient mice.

In summary, the data argue for a role of LCFA as a new environmental modulator of T cell differentiation in the gut, shifting the balance in favor of T_H1 and T_H17 cells and against T_{reg}cells via metabolic changes in the gut microbiota and p38 MAPK mediated pathways.

A. Haghikia, S. Jorg, A. Duscha, J. Berg, A. Manzel, A. Waschbisch, A. Hammer, D.H. Lee, C. May, N. Wilck, A. Balogh, A.I. Ostermann, N.H. Schebb, D.A. Akkad, D.A. Grohme, M. Kleinewietfeld, S. Kempa, J. Thone, S. Demir, D.N. Muller, R. Gold, R. A. Linker. 2015 Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine. *Immunity* 43:817-829

Dietary fatty acids modulate neuroinflammtion via the gut



SCIENTIFIC HIGHLIGHTS

How Human Antibodies work *in vivo*

Pathways Responsible for Human Autoantibody and Therapeutic Intravenous IgG Activity in Humanized Mice

INESSA SCHWAB, FALK NIMMERJAHN

CHAIR OF GENETICS, DEPARTMENT OF BIOLOGY, FAU ERLANGEN-NÜRNBERG

Our knowledge of the pathways relevant for human autoantibody and intravenous IgG activity on the background of a genetically complex human immune system largely stems from indirect association studies. While inbred mouse model systems have been invaluable tools for dissecting the molecular and cellular pathways responsible for mouse IgG activity *in vivo*, differences between the mouse and human antibody and Fc-receptor system make it difficult to draw definitive conclusions with respect to the transferability of these results to the genetically diverse and outbred human population. To close this gap, we established the first humanized mouse model of an autoantibody dependent autoimmune disease (immunothrombocytopenia), which responds to IVIg treatment, a clinically relevant standard therapeutic intervention using polyclonal serum IgG preparations. These studies revealed that the human autoantibody constant region determines autoantibody pathology. Thus, human IgG1 and IgG3 subclasses were much more potent in inducing platelet depletion than IgG2 or IgG4 subclasses. Consistent with this Fc-dependent effect, humanized mouse colonies generated with hematopoietic stem cells from donors carrying different combinations of human activating Fcγ-receptor alleles, demonstrated that the presence of one high affinity FcγRIIIA-158V allele results in a higher level of autoimmune pathology. Moreover, blocking autoantibody access to human FcγRs and inactivation of the human mononuclear phagocytic network interfered with autoantibody activity, firmly establishing a critical role of cellular FcγRs *in vivo*. Apart from human autoantibody activity, we assessed how human immunomodulatory IVIg preparations suppress autoantibody activity. Our study demonstrates that IVIg did not result in a general blockade of activating FcγRs, but leads to a rather specific modulation of the mononuclear phagocytic system via highly sialylated IgG glycosylation variants.

Dr. Inessa Schwab was awarded for this work with the Hans Hench Award of the German Society for Immunology and the Award of the Staedtler Stiftung for an outstanding PhD thesis.

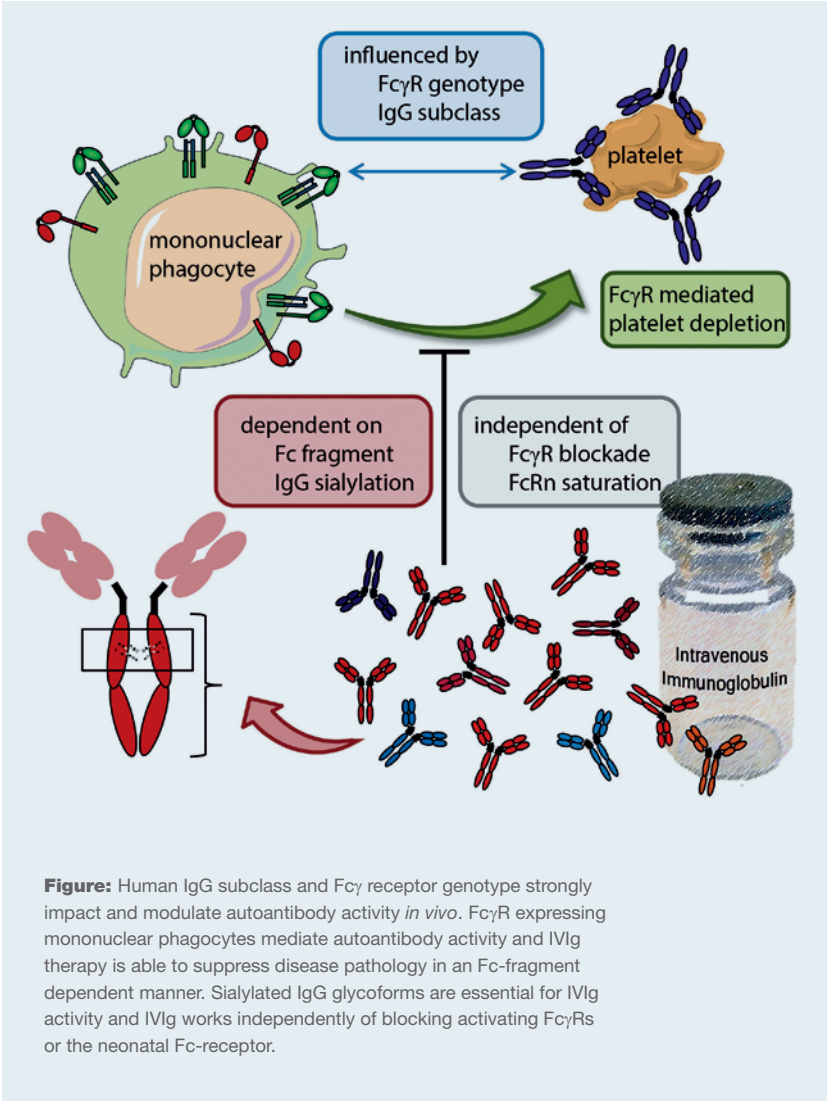


Figure: Human IgG subclass and Fcγ receptor genotype strongly impact and modulate autoantibody activity *in vivo*. FcγR expressing mononuclear phagocytes mediate autoantibody activity and IVIg therapy is able to suppress disease pathology in an Fc-fragment dependent manner. Sialylated IgG glycoforms are essential for IVIg activity and IVIg works independently of blocking activating FcγRs or the neonatal Fc-receptor.

I. Schwab, A. Lux, F. Nimmerjahn. 2015. Pathways Responsible for Human Autoantibody and Therapeutic Intravenous IgG Activity in Humanized Mice. *Cell Rep.* 20;13(3):610-20. doi: 10.1016/j.celrep.2015.09.013. Epub 2015 Oct 8.

SCIENTIFIC HIGHLIGHTS

Transcription factor ZEB1 confers therapy resistance in cancer

ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC-inhibitor Mocetinostat

THOMAS BRABLETZ
EXPERIMENTAL MEDICINE I, NIKOLAUS-FIEBIGER-CENTER FOR MOLECULAR MEDICINE, FAU ERLANGEN-NÜRNBERG

Therapy resistance is a major clinical problem in cancer medicine and crucial for disease relapse and progression. Therefore, the clinical need to overcome it, particularly for aggressive tumors such as pancreatic cancer, is very high. Aberrant activation of an epithelial-mesenchymal transition (EMT) and an associated cancer stem cell phenotype are considered a major cause of metastasis and therapy resistance. Recently, we identified the EMT-activator and transcriptional repressor ZEB1 as the crucial factor to confer metastasis, stemness and therapy resistance in cancer. Here, we demonstrated that ZEB1 represses expression of the microRNAs miR-200 and miR-203, both of which are strong inhibitors of a stemness phenotype. Particularly, re-expression of miR-203 induced differentiation and restored drug sensitivity in different cancer types. We applied a systematic, stepwise screening strategy to interfere with ZEB1 function, aiming to re-activate silenced target genes and thereby overcoming therapy resistance. This led to the identification of the class I HDAC-inhibitor Mocetinostat as epigenetic drug interfering with ZEB1 function, restoring miR-203 expression, repressing stemness properties and inducing sensitivity against chemotherapy. Thereby Mocetinostat turned out to be more effective than other HDAC-inhibitors, such as SAHA, indicating the relevance of the screening strategy. Our data encourage the application of mechanism-based combinations of selected epigenetic drugs with standard chemotherapy for the rational treatment of aggressive solid tumors, like pancreatic cancer.

S. Meidhof, S. Brabletz, W. Lehmann, B.T. Preca, K. Mock, M. Ruh, J. Schuler, M. Berthold, A. Weber, U. Burk, M. Lubbert, M. Puhr, Z. Culig, U. Wellner, T. Keck, P. Bronsert, S. Kusters, U.T. Hopt, M.P. Stemmler, T. Brabletz. 2015. ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat. *EMBO molecular medicine* 7:831-847.

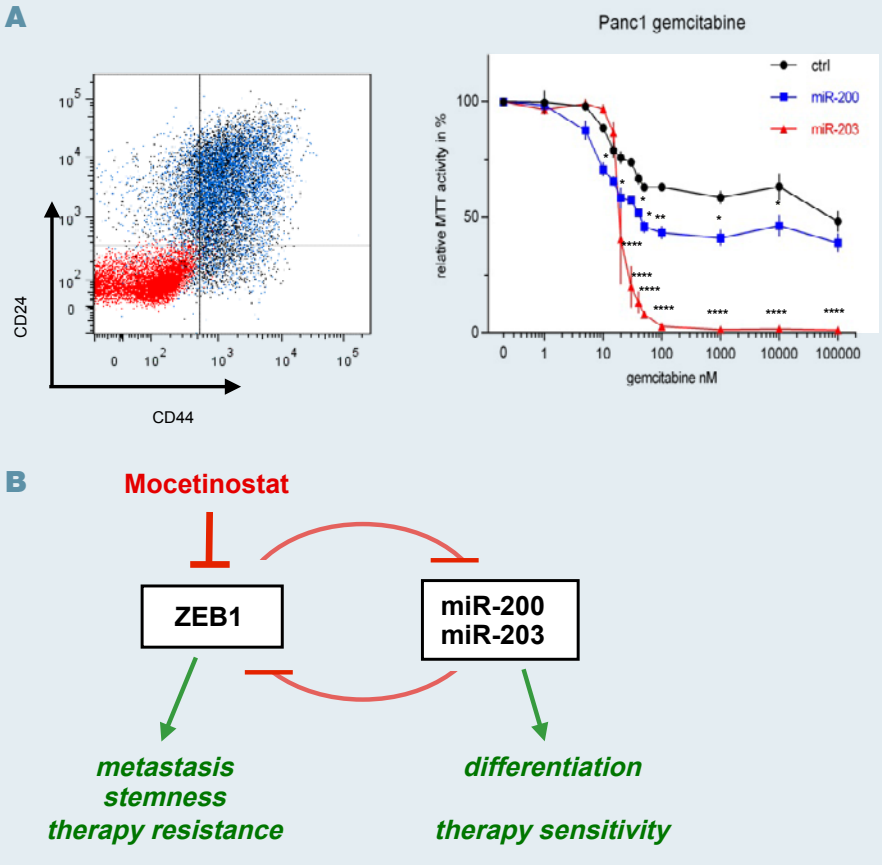


Figure:

A) Overexpression of miR-203 (red population) in aggressive and drug resistant pancreatic cancer cells induces differentiation indicated by a strong reduction of the CD24/CD44 double positive cancer stem cell pool (black population). This is associated with a highly increased sensitivity to chemotherapy, exemplified for the drug gemcitabine.

B) Summary: ZEB1 triggers metastasis, stemness and therapy resistance. The microRNAs miR-200 and miR-203 induce differentiation and therapy sensitivity. ZEB1 represses expression of both microRNAs, which themselves inhibit translation of ZEB1. Thus, both are linked in a double negative feedback loop, thereby stabilizing the associated phenotypes. The HDAC-inhibitor Mocetinostat inhibits the transcriptional repressor function of ZEB1, thereby inducing re-expression of silenced ZEB1 target genes and shifting the cancer cell phenotype to the right side of the feed-

SCIENTIFIC HIGHLIGHTS

A novel mechanism of immune-complex-mediated bone loss

IgG-sialylation determines the pro-osteoclastogenic activity of IgG complexes

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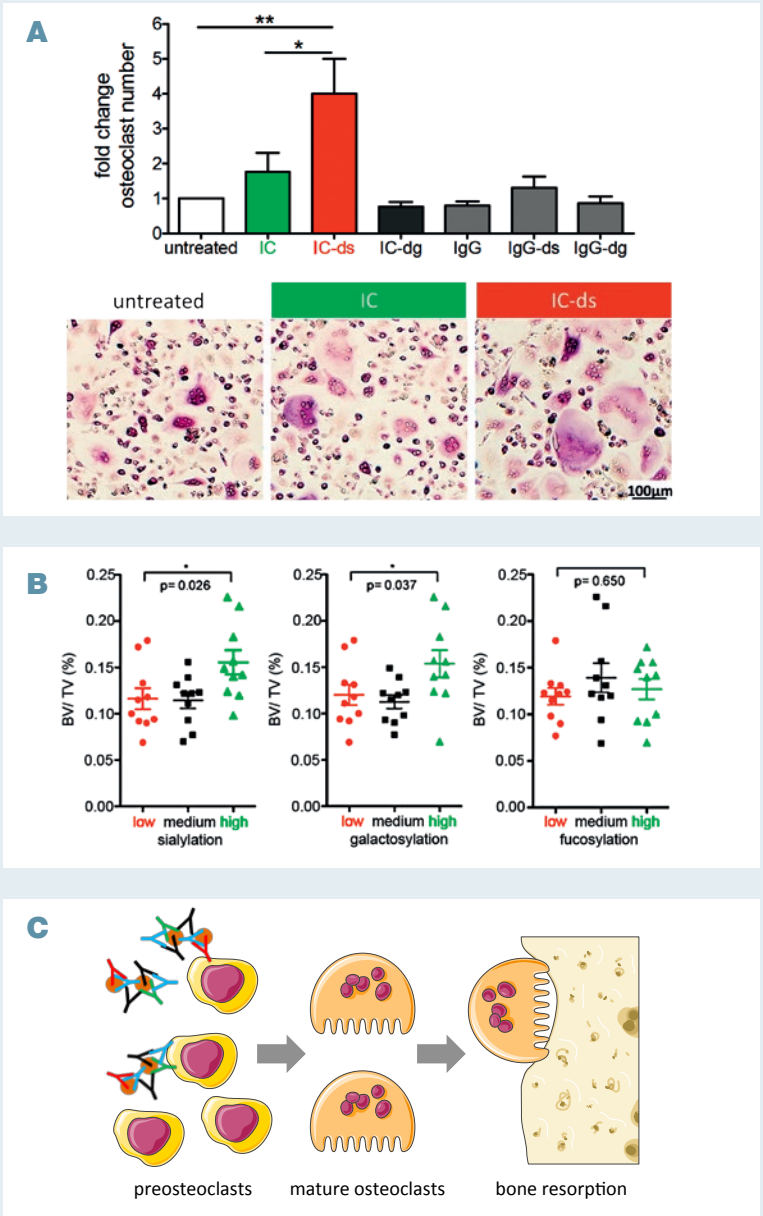
Autoimmune diseases are associated with bone loss. We speculated that bone loss may not only be triggered by inflammation but also by direct influence of immune complexes. Osteoclasts, the only bone resorbing cells in the body, express Fc receptors and are therefore susceptible for immune complexes. Furthermore, sialylation of immunoglobulin G (IgG) influences binding to Fc-receptors and therefore may modulate the effect of immune complexes on bone.

In our work, we show that immune complexes effectively trigger bone loss by stimulating bone resorbing osteoclasts. Furthermore, IgG sialylation determines the pro-osteoclastogenic capacity of immune complexes, as only desialylated, but not sialylated IgG complexes promoted osteoclastogenesis. By injecting sialylated and desialylated murine IgG complexes into knee joints, we further demonstrated that the enhancement of osteoclastogenesis by desialylated immune complexes is independent of inflammation. In accordance with these data, we found a correlation between the sialylation levels of both, random IgG and disease specific autoantibodies (ACPA), with bone structure in patients with rheumatoid arthritis and discovered that the pro-osteoclastogenic activity of ACPA relies on a low Fc-sialylation. Finally, the administration of the sialic acid precursor N-acetylmannosamine increased IgG sialylation and ameliorated bone loss in experimental arthritis.

Taken together, we describe a novel mechanism by which the immune system can influence bone.

U. Harre, S. Lang, R. Pfeifle, Y. Rombouts, S. Frühbeißer, K. Amara, H. Bang, A. Lux, C. Koeleman, W. Baum, K. Dietel, F. Gröhn, V. Malmström, L. Klareskog, G. Krönke, R. Kocijan, F. Nimmerjahn, R. Toes, M. Herrmann, H. Scherer, G. Schett. 2015. Glycosylation of immunoglobulin G determines osteoclast differentiation and bone loss. Nat *Commun*; 6:6651. doi: 10.1038/ncomms7651.



Figure

A) Osteoclast numbers after stimulation with native, desialylated (ds) or deglycosylated (dg) monomeric IgG or IgG complexes (IC). bar =100 µm

B) Bone volume per tissue volume (BV/TV) of rheumatoid arthritis patients with different ACPA glycosylation levels.

C) Schematic overview of the proposed model. Low-sialylated IgG immune complexes bind to Fc-receptors on osteoclast lineage cells and promote osteoclastogenesis and bone loss.

NEWS AND UPDATES

Joachim Kalden Lecture 2015

The *Medical Immunology Campus Erlangen* honors Prof. Alain Fischer, M.D. Ph.D.

From left: Prof. Joachim Kalden (former Director of the Department of Medicine III), Prof. Alain Fischer holding the certificate of the Joachim Kalden Lecture and Prof. Christian Bogdan (Speaker of the *Medical Immunology Campus Erlangen* and Director the Microbiology Institute). Source: Universitätsklinikum Erlangen

The seventh Joachim Kalden Lecture 2015 of the *Medical Immunology Campus Erlangen* took place on December 1, 2015 and was delivered by Professor Alain Fischer, Director of the Research Institute for Genetic Diseases at the Hôpital Necker-Enfants Malades, Paris, France. Dr Fischer's main research interests are the development of the lymphoid system, the genetics of immunological disorders, primary immunodeficiencies of the adaptive immune system and their gene therapy. Over the last 20 years, he and his colleagues have identified approximately 30 unique genetic defects each of which accounts for an immunodeficiency phenotype in children. Being an author of more than 600 papers in various journals, Alain Fischer has received many scientific awards (such as the Louis-Jeantet Prize for Medicine). In 2014, Prof. Fischer together with Prof. Jean-Laurent Casanova received the renowned Robert-Koch-Award.

In his lecture entitled "Primary T cell immunodeficiencies: from pathophysiology to therapy", Prof. Fischer talked about a primary immunodeficiency named X-linked severe combined immunodeficiency (X-SCID). This genetic disorder is caused by a mutation of the common gamma-chain of the cytokine receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 and results in a complete absence of T cells and natural killer (NK) cells. The affected children show an extremely high susceptibility to very serious infections and cannot survive without bone marrow transplantation or gene therapy. Initially, Alain Fischer described his development of a first strategy for a genetic therapy of X-SCID. Using retroviral vectors, it was possible to restore the T cell compartment leading to survival rates of 90%. Unfortunately, genotoxic effects generated 50% T cell leukemias after gene therapy. However, the research group of Prof. Fischer succeeded in improving these retroviral vectors to the point of losing their oncogenic potential. The improved retroviral vectors have been applied to 44 patients who have so far shown no signs of leukemia. Although the reconstitution of T cell populations was achieved by gene therapy, the NK cell population remained defective. However, with the exception of papillomavirus-infection no other severe infectious diseases were observed. Prof. Fischer is convinced that gene therapy is an effective approach to treat other primary immunodeficiencies as well.

Bright Sparks in Immunology

The "Bright Sparks in Immunology" event during the 4th European Congress of Immunology (ECI) in Vienna gave 24 young immunologists the great opportunity to present their research to a large audience. These 24 speakers were selected anonymously by a review panel out of 2786 submitted abstracts. 8 selected speakers came from labs located in Germany, and with Katharina Pracht (Jäck Lab) and Dr. Tamar Mechedlidze (Wirtz Lab) Erlangen was represented by two speakers. All of the 24 speakers received the Biolegend Bright Sparks Award in the amount of 500 Euros. We congratulate all Bright Sparks speakers, especially those two young and promising scientists from Erlangen.

Written by Dr. Agnes Giniewski

Bright Sparks at the ECI 2015 with Dr. M. Mechedlidze (3rd from the left) and K. Pracht (5th from the left).

PEOPLE

Dr. rer. nat. Inessa Schwab

Dr. Inessa Schwab received the Hans-Hench PhD award for Clinical Immunology of the German Society of Immunology (DGfI) as well as the PhD award of the Staedtler Foundation

From left: Prof. Dr. Jürgen Wienands (President of the DGfI), Dr. Inessa Schwab and Prof. Dr. Hans-Hartmut Peter (Hans-Hench-Foundation)

Inessa Schwab studied Biology at the FAU and completed her PhD in the group of Prof. Dr. Falk Nimmerjahn at the Chair of Genetics, Department of Biology, FAU Erlangen-Nürnberg in 2014. Her outstanding dissertation on “Untersuchung des Mechanismus der anti-inflammatorischen Aktivitäten von intravenösem Immunglobulin” was honored on two separate occasions this fall. On September 8, the German Society of Immunology (DGfI) awarded Dr. Schwab with the Hans-Hench PhD award for Clinical Immunology worth 2000 € at the DGfI members’ assembly of this year´s European Congress of Immunology in Vienna, Austria. And on October 15, Dr. Schwab received the annual Staedtler PhD award worth 3500 €, which was handed over to her in a festive arrangement at the Staedtler headquarters in Nürnberg. Since finishing her thesis “summa cum laude”, Inessa Schwab has been working as a Post-Doc in the lab of Prof. Falk Nimmerjahn, where she has recently published two first-author manuscripts in high ranking scientific journals.

Dr. rer. nat. Jenny Ostrop

Dr. Jenny Ostrop was awarded PhD prize of the German Society for Hygiene and Microbiology (DGHM)

Prof. Dr. Mathias Herrmann (President of the DGHM) and Dr. Jenny Ostrop shortly after receiving the PhD prize certificate.

Jenny Ostrop, former PhD student at the Microbiology Institute (in the group of Prof. Roland Lang), FAU Erlangen-Nürnberg, Universitätklinikum Erlangen, recently received the PhD award of the German Society of Hygiene and Microbiology (DGHM) for her excellent PhD thesis titled “Aktivierung humaner antigenpräsentierender Zellen durch den mykobakteriellen Cord Faktor und das Glykolipid-Adjuvans Trehalose-6,6’- dibehenate”. Dr. Ostrop received the PhD award worth € 500 at his year’s annual conference of the DGHM in Münster. Dr. Ostrop, who was a fast-track PhD student within the DFG graduate school 1660 “Regulators of Adaptive Immunity” (Speaker: Prof. Hans-Martin Jäck), is currently continuing her research as a Postdoctoral Fellow at the Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology in Trondheim, Norway since fall 2015.

UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Winter 2015/16

Tuesdays, 5.15 pm

12. 01. 2016
Filip Swirski, PhD
Harvard Medical School
Boston, USA

"Growth factors link B cells with macrophages in inflammation and metabolism"

19. 01. 2016
Dr. Helmut Jonuleit
Department of Dermatology
Johannes Gutenberg-University
Mainz

"IL-6 modifies immunoregulation of T cell responses in Multiple Sclerosis"

26.01.2016
Dr. Chiara Romagnani
Deutsches Rheuma-Forschungszentrum (DRFZ)
Berlin

"Adaptive traits of NKG2C+ NK cell expansions in HCMV seropositive individuals"

02.02.2016
Prof. Ernst Werner
Innsbruck Medical University
Center for Chemistry and Biomedicine (CCB)

"Tetrahydrobiopterin: Impact on ischemia-reperfusion injury, allograft rejection and lipid metabolism"

Further Conferences and Events of Interest

February 25 – 27, 2016
5th Translational Immunology School
Schwielowsee, Potsdam
web.dgfi.org/translational-school/2016/index.html

February 28 – March 4, 2016
12th Spring School on Immunology
Ettal
web.dgfi.org/spring-school

April 7 – 9, 2016
International Conference – Infectious Disease Immunology Meets Molecular Microbiology on the Occasion of the 150th Anniversary of the Foundation of the Institute
Erlangen

To celebrate next year´s 150th anniversary of the Microbiology Institute in Erlangen, we will host an international conference titled Infectious Disease Immunology Meets Molecular Microbiology. The number of participants will be limited to 120. There will be no parallel sessions. The conference will comprise 16 invited main talks and 16 to 18 short talks given by scientists from the University of Erlangen and other parts of Germany working in the field of microbiology, infectious diseases and/or immunology.
www.mikrobiologie.uk-erlangen.de/kongress

August 21 – 26, 2016
International Congress of Immunology
Melbourne, Australia
www.ici2016.org

September 11 – 14, 2016
68. Jahrestagung der DGHM
Ulm

September 27 – 30, 2016
46th Annual Meeting of the German Society for Immunology
Hamburg
www.immunology-conference.de

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Dr. rer. nat. Sonja Pötzsch (Scientific Coordinator)

Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene

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Please note that the authors are responsible for the content of their contributions.

We are looking forward to suggestions for the next MICE newsletter. Please send material to: Sonja.Poetzsch@uk-erlangen.de

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