Medical Immunology Campus Erlangen

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

Newsletter *Winter 2014/15*

CONTENT

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

EDITORIAL

Dear colleagues and friends,

A successful year for the *Medical Immunology Campus Erlangen* comes to an end. Earlier in May, the *Research Training Group 1660 "Schlüsselsignale der adaptiven Immunität"* (spokesman: Hans-Martin Jäck) was approved for a second 4.5 year funding period, for which the new PhD students have already been recruited. Around the same time the initiative of Georg Schett and Markus Neurath for a new *Collaborative Research Center CRC 1181 "Checkpoints for Resolution of Inflammation"* received a strong recommendation to proceed to a full application. During the past 6 months a volume of almost 400 pages has been compiled and has now been submitted to the German Research Foundation (DFG). The on-site review will take place in 8 weeks from now in February 2015. Many thanks go to the two designated spokesmen and the two dedicated assistants Sandra Jeleazcov and Martina Seidel, who spent many extra hours to bring the application into perfect shape. Finally, the *Clinical Research Unit 257 "Molekulare Pathogenese und optimierte Therapie von chronisch entzündlichen Darmerkrankungen"* run by Christoph Becker and Markus Neurath was recently very positively evaluated for a second funding period.

In October, Klaus Überla, Director of the Department of Molecular and Medical Virology at the Ruhr-Universität Bochum, informed the Dean of our Medical Faculty that he accepts the offered position as Chair of Virology and Director of the Institute of Clinical and Molecular Virology as of February 1, 2015. Klaus Überla will be successor of Bernhard Fleckenstein, who has headed the institute for more than 36 years. We cordially welcome Klaus Überla, who is an expert in vaccination immunology, as a new member of the *Medical Immunology Campus Erlangen* and will report on him in more detail once he has arrived in Erlangen.

Exciting news also came in just the other day, when our member Gerhard Krönke was announced as one of the recipients of the highly competitive starting grants from the *European Research Council* (ERC; 1.5 million € for 5 years). Congratulations to Gerhard and his group! We will feature this achievement in the next issue of the newsletter.

Thanks to the initiative of Hans-Martin Jäck the Council of the *German Society for Immunology* (DGFI) decided during its last meeting that the Annual Conference of the DGFI in 2017 (50th anniversary of the DGFI) will take place in Erlangen. The organisation of this conference will be a major challenge, but also an unprecedented opportunity for our *Medical Immunology Campus Erlangen.*

I wish you and your families a Merry Christmas and all the best for 2015.

Prof. Christian Bogdan

Chairman of the *Medical Immunology Campus Erlangen*

SCIENTIFIC HIGHLIGHTS

Fighting the Lernaean Hydra

From chronic lymphocytic leukemia cell metabolism to immune escape

REGINA JITSCHIN, MARTINA BRAUN, DIMITRIOS MOUGIAKAKOS
DEPARTMENT OF INTERNAL MEDICINE 5, UNIVERSITÄTSKLINIKUM ERLANGEN

Chronic lymphocytic leukemia (CLL) is the leukemia with the highest incidence among adults. Increasing evidence suggests that immune alterations negatively impact the disease course. Identifying the underlying mechanisms holds the potential for novel therapeutic approaches.

First, we investigated the role of myeloid derived suppressor cells (MDSCs). Accumulation of MDCSs has been reported in numerous mainly solid cancers. Several studies indicate the involvement of MDSCs in weakening anti-tumor immunity. We observed an increase of monocytic MDCSs. A hallmark of MDSCs is their suppressive activity, which we were able to show *in vitro* and to validate *ex vivo*: CLL MDSCs inhibited T-cell activation and induced regulatory T-cells (T_{Regs}) using indoleamine-2,3-dioxygenase. Furthermore, CLL-cells promoted the conversion of healthy monocytes into cells resembling functionally and phenotypically CLL MDSCs thus providing a potential explanation for their observed accumulation.

Next, we focused on oxidative stress a metabolic condition harmful for immune cells and regularly seen in cancer. We found increased concentrations of markers for oxidative stress that were linked to significant immune alterations. CLL-cells exhibited an increased mitochondrial oxidative phosphorylation. As a result, the mitochondria of CLL cells abundantly produced superoxide and were the main source of reactive oxygen species (ROS). ROS led to an adaptive up-regulation of the antioxidant heme-oxygenase-1 (HO-1). Interestingly, HO-1 is an activator of the mitochondrial transcription factor A. That way, ROS, adaptation to it, and mitochondrial biogenesis (leading to more ROS production) appear to form a self-amplifying feedback loop. Taking advantage of their bioenergetic profile we were able to selectively target CLL-cells by blocking the mitochondrial F1F0-ATPase that led to a exuberant (lethal) ROS production.

Taken together we have obtained evidence for a crosstalk between CLL cells, MDSCs, and T_{Regs}. Furthermore, our data provides the rationale for therapeutic redox-modulating strategies (Figure).

R. Jitschin · AD. Hofmann · H. Bruns · A. Gießl · J. Bricks · J. Berger · D. Saul · MJ. Eckart · A. Mackensen · D. Mougiakakos

Mitochondrial metabolism contributes to oxidative stress and reveals therapeutic targets in chronic lymphocytic leukemia. Blood 2014;123(17):2663–72.

R. Jitschin · M. Braun · M. Büttner · K. Dettmer-Wilde · J. Bricks · J. Berger · M.J. Eckart · S.W. Krause · P.J. Oefner · K. Le Blanc · A. Mackensen · D. Mougiakakos

CLL-cells induce IDOhi CD14+HLA-DRlo myeloid-derived suppressor cells that inhibit T-cell responses and promote TRegs. Blood. 2014; 124(5):750–60.

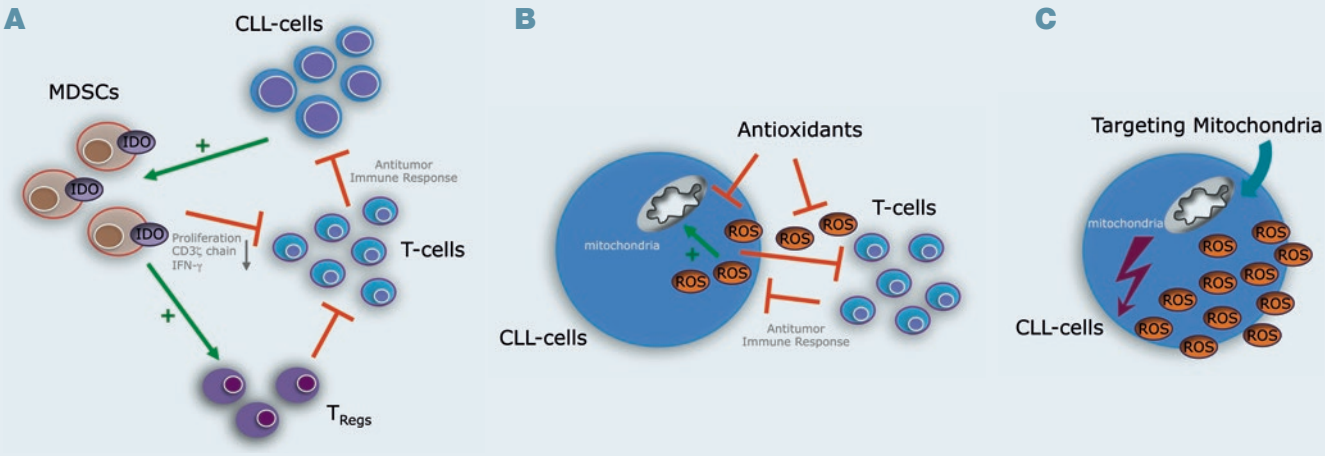

Figure: Suppressive crosstalk and metabolic targets in CLL. (**A**) Based on our *in vitro* and our *ex vivo* observations we propose the following model for CLL-cell-mediated immune suppression. CLL-cells promote the accumulation of monocytic myeloid derived suppressor cells (MDSCs). The MDSCs in turn (**A**) inhibit T-cells and at the same time (**B**) induce regulatory T-cells (TRegs) that efficiently abolish the function of effector T cells. Both direct T-cell suppression and TReg induction are mediated by the tryptophan depleting enzyme indoleamine-2,3 dioxygenase (IDO), which holds a prominent role in tolerance induction. These phenomena could weaken the T-cell-dependent anti-CLL immunity and thereby contribute to CLL immune escape. Furthermore, our data suggest two opposite redox-modulating strategies in CLL. (**B**) Using antioxidants could neutralize the negative ROS-mediated effects on T-cells and the overall antitumor immune response. At the same time it could breach the self-amplifying positive feedback loop established between ROS and mitochondrial biogenesis. (**C**) Substances interfering with the mitochondrial electron transport chain can cause a further increase of mitochondrial ROS production exceeding the "tipping point" of the compensatory mechanisms of CLL cells and thereby inducing cell death.

SCIENTIFIC HIGHLIGHTS

Th9 cells play an important role in driving ulcerative colitis by regulating intestinal epithelial cells

T helper 9 cells expressing the transcription factor PU.1 (Spi 1) drive T cell-mediated colitis via interleukin-9 receptor signaling in intestinal epithelial cells

KATHARINA GERLACH, MARKUS NEURATH

DEPARTMENT OF MEDICINE 1, UNIVERSITÄTSKLINIKUM ERLANGEN

Crohn's disease (CD) and ulcerative colitis (UC) belong to inflammatory bowel diseases (IBD) and are characterized by inflammatory disorders of the gastrointestinal tract leading to diarrhoea and abdominal pain. Mucosal inflammation and ulcerations in IBD are driven by activated immune cells. In particular, T lymphocytes produce large amounts of cytokines and induce tissue damage in IBD patients. Recently, a new subset of T helper cells characterized by the production of IL-9 and named Th9 cells, has been identified. In particular, IL-9 gene transcription is controlled by PU.1, an ETS family transcription factor that is induced in T cells following TGF-β stimulation. Here, we discovered an expansion of PU.1$^+$ T cells in patients with ulcerative colitis (UC) (**Figure**) and found a higher expression of IL-9 in colitogenic lamia propria cells of patients suffering from UC, suggesting that Th9 cells are involved in the development of IBD. In experimental colitis models, citrine reporter mice showed an expansion of IL-9 expressing mucosal T cells. Furthermore, an IL-9- or PU.1-deficiency in T cells suppressed the activity of acute colitis in mice, which was manifested in a protection against inflammation. In our manuscript, an *in vivo* therapeutic approach with an anti-IL-9 antibody also led to the suppression of colitis. Thus, our findings suggest that Th9 cells play an important role in driving ulcerative colitis and emerge as an attractive target for future treatment of intestinal inflammation.

K. Gerlach · Y. Hwang · A. Nikolaev · R. Atreya · H. Dornhoff · S. Steiner · H.A. Lehr · S. Wirtz · M. Vieth · A. Waisman · F. Rosenbauer · A.N. McKenzie · B. Weigmann · M.F. Neurath. 2014.

Th9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signalingin intestinal epithelial cells. *Nature immunology* 15: 676 – 686.

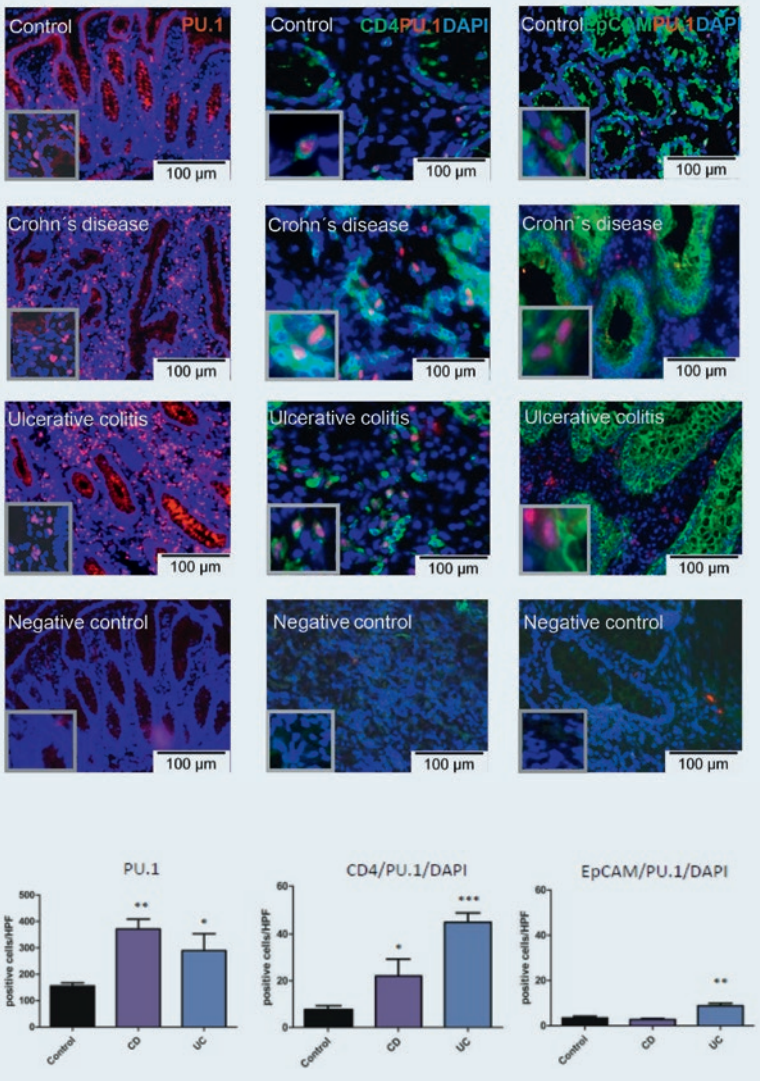

Figure: Enhanced expression of PU.1$^+$ T cells in the mucosa of IBD patients. Cryosections of colonic specimens were incubated with an anti-PU.1 antibody. Cells were counterstained with HOECHST dye. Statistical analysis revealed a higher number of PU.1$^+$ cells in the mucosa of IBD patients. In addition, double staining analysis for PU.1 and CD4 or PU.1 and EpCAM in the lamina propria of IBD patients was performed. Representative stainings are shown. PU.1$^+$ T cells were significantly higher expressed in the lamia propria of UC patients in contrast to CD patients and healthy controls, proposing the influence of Th9 cells on the development of IBD.

SCIENTIFIC HIGHLIGHTS

T cell costimulator (CD80/86) kills osteoclasts

CD80/86 inhibits osteogenesis by inducing apoptosis through the IDO/Tryptophan pathway

ALINE BOZEC, MARIO ZAISS, GEORG SCHETT

DEPARTMENT OF MEDICINE 3, UNIVERSITÄTSKLINIKUM ERLANGEN

Bone is continuously remodeled during life. This process needs a strict control since it regulates skeletal growth during adolescence, adaptation of bone to physical demands in adulthood and bone loss during aging. In our manuscript, we describe a new control mechanism of bone resorption by the adaptive immune system. CD80/86, a pair of co-stimulation molecules mediating binding of APCs to CD28 on T cells, represents also a strong inhibitory signal for osteoclast differentiation and thereby protects the body from uncontrolled bone resorption. Engagement of CD80/86 by the regulatory molecule CTLA-4 induces the expression of the enzyme indoleamine 2,3-dioxygenase (IDO) in osteoclast lineage cells, which is the rate-limiting enzyme of tryptophan catabolism and involved in cell apoptosis. Physiological regulation of bone resorption and preservation of bone mass by T cell CD80/86 co-stimulation molecules appear to have direct relevance in medicine since intervention strategies blocking as well as fostering CTLA-4-CD80/86 interactions are currently used for treatment of inflammatory diseases, transplant rejection and cancer.

A. Bozec · M.M. Zaiss · R. Kagwiria · R. Voll · M. Rauh · Z. Chen · S. Mueller-Schmucker · R. A. Kroczek · L. Heinzerling · M. Moser · A.L. Mellor · J.P. David · G. Schett. 2014.

T cell costimulation molecules CD80/86 inhibit osteoclast differentiation by inducing the IDO/tryptophan pathway. *Science Translational Medicine* 6:235ra260.

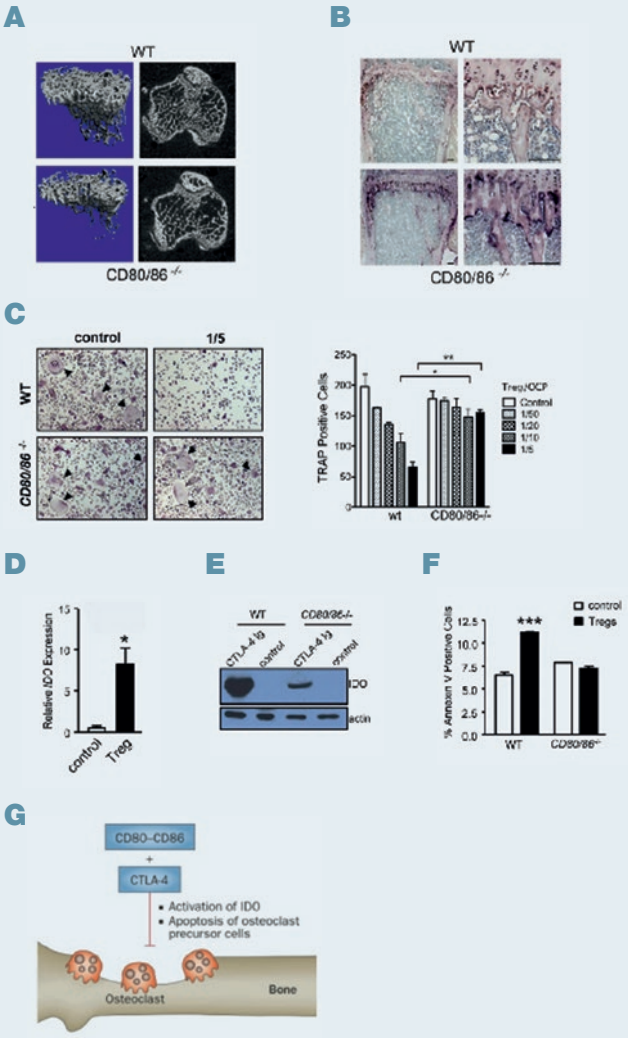

Figure: (**A**) Three-dimensional reconstructions of micro-computed tomography scans of the proximal tibia of CD80/86-/- mice and wild-type littermate controls. (**B**) Tartrate- resistant acid phosphatase (TRAP) stainings of tibial sections of CD80/86-/- mice and wild-type littermate controls (Left: original magnification x10, right: original magnification x40). (**C**) Tartrate-resistant acid phosphatase staining and quantification of osteoclast cultures from wild-type controls and CD80/86-/- mice cultures in absence (control) or presence of regulatory T cells (regulatory T cells/osteoclast precursors ratio = 1:5). (**D**) RT-PCR for indoleamine 2,3-dioxygenase (IDO) in wild- type osteoclast precursors stimulated with regulatory T cells (Treg; 1:5 ratio) (n=5). (**E**) Western blot for IDO expression in wild- type and CD80/86-/- osteoclast precursors stimulated with CTLA-4 (10 µg/mL) (n= 5). (**F**) FACS analysis for apoptotic annexin V positive osteoclast precursors after stimulating wild- type and CD80/86-/- osteoclast precursors stimulated with Treg (1:5 ratio) (n= 5). (**G**) Representative scheme of CD80/86 action on osteoclasts.

SCIENTIFIC HIGHLIGHTS

B cell inhibitory receptor critical to prevent autoimmunity

Siglec-G deficiency leads to more severe collagen-induced arthritis and earlier onset of lupus-like symptoms in MRL/lpr mice.

SUSANNE BÖKERS, LARS NITSCHKE
CHAIR OF GENETICS, DEPARTMENT OF BIOLOGY, FAU

Siglec-G is a member of the Siglec (sialic acid-binding immunoglobulin-like lectin)-family expressed on all B cells. Siglec-G deficient mice show a large expansion of the B1 cell compartment demonstrating the crucial role of Siglec-G as an inhibitory receptor on this cellular subset. While Siglec-G-deficient mice did not develop spontaneous autoimmunity, mice double-deficient for Siglec-G and the related Siglec protein CD22 showed autoimmunity at older age. In this study, we addressed the question whether loss of Siglec G on its own affects disease severity in animal models of rheumatoid arthritis and systemic lupus erythematosus (SLE). Siglec-G-deficient mice showed moderately increased clinical severity and higher inflammation of the knee joints following collagen-induced arthritis, when compared to control mice. The Siglec-G-deficient mouse was also backcrossed to the autoimmune prone MLR/lpr background. Although both Siglec-G-deficient and control MRL/*lpr* mice developed a lupus-like disease, Siglec-G-deficient MRL/*lpr* mice showed an earlier occurrence of autoantibodies, a higher lymphoproliferation of B- and T cells, and an earlier onset of disease as shown by proteinuria and glomerular damage in the kidney. Moreover, Siglec-G-deficient female mice showed a significantly reduced survival compared to female control MRL/*lpr* mice. Thus, the loss of the inhibitory receptor Siglec-G led to a moderate exacerbation of disease severity and early onset of both collagen-induced arthritis and spontaneous lupus nephritis in MRL/*lpr* mice.

S. Bökers · A. Urbat · C. Daniel · K. Amann · K. G. Smith · M. Espéli · L. Nitschke. 2014.

Siglec-G deficiency leads to more severe collagen-induced arthritis and earlier onset of lupus-like symptoms in MRL/*lpr* mice. J Immunol. 192:2994 – 3002.

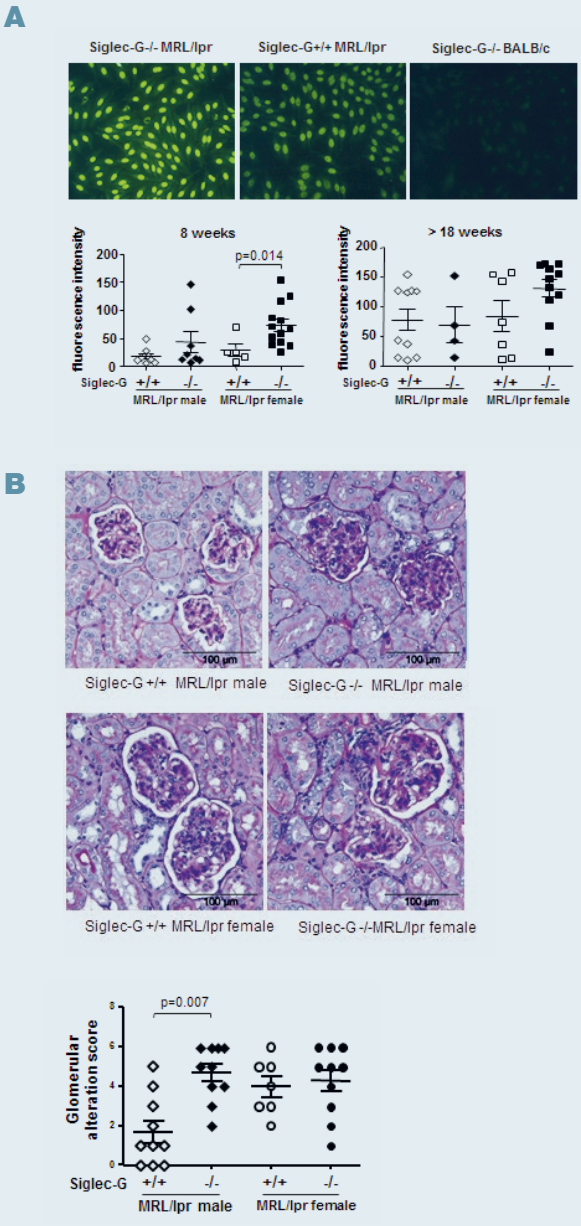

Figure: Increased anti-nuclear antibodies (ANA) and higher glomerulonephritis in Siglec-G-/- MRL/lpr mice. (**A**) Measurement of ANAs by Hep-2 slides representing examples of 8-week female mice of indicated genotypes. **Lower:** fluorescence intensity of ANA staining in 8-week and 18-20-week old mice. **B**) Representative sections of periodic acid-Schiff stained renal biopsies of 19-week old male and female MRL/lpr mice of indicated genotypes. **Lower:** Glomerular alterations were scored for typical changes observed in lupus nephritis.

NEWS AND UPDATES

The AspMetNet consortium of the first Infect-ERA call

Systematic identification of antifungal drug targets by a metabolic network approach

SVEN KRAPPMANN
MICROBIOLOGY INSTITUTE , UNIVERSTÄTSKLINIKUM ERLANGEN

Infectious diseases still account for vast numbers of morbidity and mortality worldwide. With the aim to foster research consortia addressing eminent topics of human infections on a European level, the Infect-ERA initiative was announced in 2013 to comprise several joint calls for transnational projects relating to basic aspects of human infection biology (www.infect-era.eu).

Patients with a compromised immunity are susceptible to infections by various opportunistic pathogens, including fungi that are omnipresent in the environment such as *Aspergillus* species. Accordingly, fungal infections pose a prevalent threat to such individuals. Especially aspergillosis is often diagnosed late due to non-specific clinical signs resulting from the infection and is hard to treat as current antifungals have limited efficacy, may display severe side effects, or have become ineffective due to evolved pathogen resistance. Pathways of fungal primary metabolism have been underrated as targets for antimycotic therapy. The major goal of the AspMetNet research consortium, which was recommended for funding during the highly competitive selection process of the first Infect-ERA call and that comprises four research groups from Austria, Germany, and Israel, is to explore the primary metabolism of the main pathogenic *Aspergillus* species, *A. fumigatus*, as essential virulence determinant. In the course of this joint project, that is coordinated by the German partner at the Erlangen University Hospital, the metabolic network of *A. fumigatus* will be reconstructed by mining genome and transcriptome data in order to identify key biosynthetic pathways. Following candidate prioritization, gene targeting and mutant generation efforts accompanied by extensive phenotypic analyses in an iterative manner will yield a refined metabolic network and, most importantly, promising target candidates to develop novel antifungal compounds. In a long-term perspective, these may be validated further to become applied to other fungal pathogens.

The AspMetNet project, being funded on the national level by the Federal Ministry of Education and Research (BMBF FKZ 031A408A), was launched in September 2014 with an expected duration of three years.

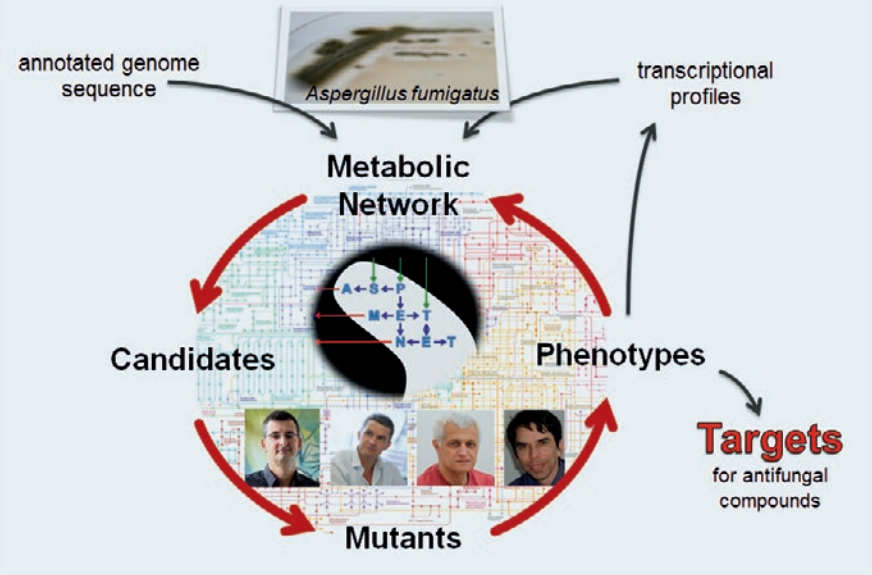

Figure: Schematic outline of the AspMetNet concept to identify novel targets of antifungal therapy by the systems biology approach of iterative metabolic network modeling. The consortium comprises as principal investigators (from left to right) Sven Krappmann (University Hospital Erlangen, Germany), Hubertus Haas (Innsbruck Medical University, Austria), Nir Osherov (Tell Aviv University, Israel), and Thomas Dandekar (University of Würzburg, Germany).

PEOPLE

PD Dr. Dimitrios Mougiakakos

Dimitrios Mougiakakos was awarded the Vincenz-Czerny Prize for Oncology

The president of the DGHO, Prof. Dr. Mathias Freund (right), hands over the Vincenz-Czerny-Preis for oncology to PD Dr. Dimitrios Mougiakakos. SOURCE: DGHO

Dr. Mougiakakos, head of the Max-Eder Junior Research Group at the Department of Medicine 5, Universitätsklinikum Erlangen, received the Vincenz-Czerny Prize for Oncology for his outstanding finding on the role of the mitochondrial metabolism of lymphocytes during chronic lymphocytic leukemia (CLL). Dimitrios Mougiakakos discovered that mitochondria in CLL cells were the main source for abundant reactive oxygen species (ROS). Using substances which interfere with the mitochondrial electron transport chain can cause a further increase of mitochondrial ROS production reaching the "tipping point" of the CLL-cells' compensatory mechanisms and thereby inducing cell death.

The Vincenz-Czerny Prize for Oncology, one of the most prestigious science awards in the field of hematology and oncology in Germany, is worth 7,500€ and was handed over to Dr. Mougiakakos during the Annual Conference of the Society for Hematology and Oncology (DGHO) in Hamburg in October 2014.

Prof. Dr. Dr. h.c. mult. Joachim R. Kalden

Honorary doctorate for Prof. Joachim Kalden

Prof. Joachim Kalden, director emeritus of the department of Medicine 3, Universitätsklinikum Erlangen, has received a honorary doctorate from the Medical University of Hannover. In the 1970s, after spending several years abroad, Prof. Kalden worked as assistant physician in Hannover, where he also received his first professorship and finished his internal medicine training.

UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Winter 2014/15 Tuesdays, 5.15 pm

16. 12. 2014
Joachim Kalden Lecture 2014
Prof. Dontscho Kerjaschki
Clinical Institute of Pathology, Medical University Vienna, Austria
"Lymphatics in Inflammation"

13. 01. 2015
David Sancho, Ph.D.
CNIC- Fundación Centro Nacional de Investigaciones Cardiovasculares "Carlos III", Madrid, Spain
"Novel aspects on Regulation of Th1 immunity by Dendritic cells"

14. 01. 2015
Special seminar
Prof. Michael Dustin
Kennedy Institute, Oxford, UK
"Title to be announced"

20.01. 2015
Anne Dudeck, PhD
Institute of Immunology, Technical University Dresden
"MASTer the danger – Mast cells as sensors of cell stress linking innate and adaptive immunity"

27.01. 2015
Dr. Till Strowig
Helmholtz Center for Infection Research, Braunschweig
"Living on the edge – The intestinal microbiota and local inflammatory responses"

23. 02. 2015
Prof. Sankar Ghosh
Columbia University, USA
"Regulation of NF-kB in inflammation and Immunity"

UPCOMING EVENTS

Further Conferences and Events of Interest

February 19 – 21, 2015
13th B Cell Forum
Hitzacker (Elbe)
www.b-lymphocytes.de/Hitzacker_info_2015

February 26 – 27, 2015
Workshop of the DGHM Specialized Group "Eukaryotic Pathogens"
Erlangen
The forthcoming annual workshop of the special interest group on Eukaryotic Pathogens is scheduled to take place at the Institute of Microbiology (Organizer: Sven Krappmann) to give especially young scientists a platform to present their research and recent achievements. Topics will include virulence and resistance of fungal and parasitic pathogens, host immunity mechanisms, as well as diagnostics of infections; furthermore, Dr. Elaine Bignell, deputy director of the *Manchester Fungal Infection Research Group* will present aspects of her exciting work on *Aspergillus* and beyond.

March 8 – 13, 2015
11th Spring School on Immunology
Ettal

March 19 – 20, 2015
Cellular Therapy 2015
Erlangen
www.cellular-therapy.de

March 19 – 21, 2015
4th Translational Immunology School
Schwielowsee, Potsdam

March 19 – 21, 2015
Tagung Arbeitskreis Infektionsimmunologie
Burg Rothenfels

April 29, 2015
Day of Immunology

March 18 – 21, 2015
25th Annual Meeting of the Society for Virology
Bochum
www.virology-meeting.de

September 6 – 9, 2015
4th European Congress of Immunology
Vienna, Austria
www.eci-vienna2015.org

September 11 – 13, 2015
29th Annual Conference of the European Macrophage and Dendritic Cell Society (EMDS)
Krakow, Polen
www.macrophage.de/meetings.htm

September 27 – 30, 2015
67. Jahrestagung der DGHM
Münster

October 4 – 9, 2015
7th Autumn School – Current Concepts in Immunology
Merseburg

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