EDITORIAL

Dear colleagues and friends,

a research motto that is attributed to Paul Ehrlich are his “four Gs” for success in science: Geschick, Geduld, Glück and Geld (skills, patience, luck and money). Although this list is by far not complete and could easily be extended by Gelegenheit, Gemeinschaft, Gunst and Gesundheit (opportunity, companionship, patronage and health), financial support is of critical importance for the work of researchers and leading-edge innovations. In this respect the Medical Immunology Campus Erlangen is very happy about recent approvals of consortial grant applications. Georg Schett (Director of the Medical Department 3), together with Andreas Maier (Chair for Informatics 5/Pattern recognition, FAU) and Prof. Silke Christiansen (Helmholtz Center for Materials and Energy, Berlin / Medical Valley Forchheim), received a 12.3 million € synergy grant for six years from the European Research Council (ERC) to develop a new X-ray microscope and tomograph for analyzing the pathogenesis of osteoporosis in humans. The German Research Foundation (DFG) decided to sponsor a new research unit on “Pathways triggering autoimmunity and defining onset of early rheumatoid arthritis” (PANDORA) with more than 3 million € for 3 years, which will be coordinated by Gerhard Krönke (Medical Department 3). Finally, the DFG also approved the new SFB 1350 of the University of Regensburg, which focuses on the (patho)physiology of the tubular system and interstitium of the kidney and in which six research groups of Universitätshäklinikum Erlangen and the FAU (Medical Department 4, Department of Nephropathology, Institute of Cellular and Molecular Physiology) are participating. Congratulations to all researchers for these fabulous achievements!

Three other highlights of the past months were the foundation and opening of the Deutsches Zentrum für Immuntherapie (DZI) here at the University Hospital (for details see the separate report in this newsletter), the official inauguration of the Harald zur Hausen Lecture Hall of the Medical Faculty (see separate report) as well as the presentation of the book on the 275 years’ history of the Medical Faculty of FAU (1743 – 2018), edited by Karl-Heinz Leven and colleagues, which is a real treasure also with respect to its account on the early development of immunological research in Erlangen.

After all these positive news I cannot fail to stress that Erlangen and the FAU are not the land of milk and honey. Thinking about the extended “G”-list and our opportunities for research it comes to my mind that immunologists and many other FAU researchers have been suffering now for months from the restricted access to important journals published by Elsevier. While we certainly understand the need for vigorous negotiations with the publisher, ordering of research articles via interlibrary loans is not a practical solution.

I wish you and your families a Merry Christmas, happy holidays and all the best for 2019.

Prof. Christian Bogdan
Chairman of The Medical Immunology Campus Erlangen
**Scientific Highlights**

**Novel factor in Treg differentiation**

**CD83 expression is essential for Treg cell differentiation and stability**

**Christina König, Alexander Steinkasserer, Matthias Lechmann**

Department of Immune Modulation, FAU Erlangen-Nürnberg,Universitätsklinikum Erlangen

Foxp3-positive regulatory T cells (Tregs) are crucial for the maintenance of immune homeostasis and keep immune responses in check. Upon activation, Tregs are transferred into an effector state expressing transcripts essential for their suppressive activity, migration, and survival. However, it is not completely understood how different intrinsic and environmental factors control Treg differentiation.

Interestingly, CD4+CD25+Foxp3+ Tregs rapidly and strongly induce the transcription of CD83 after activation. Using CD83eGFP reporter mice, we recently reported that CD83 protein expression is correlated to murine T cells that have highly up-regulated Treg-associated molecules. Additionally, human Tregs were also found to express CD83 at mRNA as well as at protein level. However, the precise functional relevance and the implication of endogenous CD83 expression specifically in regulatory T cells was still obscure. Since complete CD83 KO mice lack normal peripheral CD4+ T cell populations, we generated CD83 conditional knockout (cKO) animals, in which CD83 expression has only been deleted in Foxp3+ Tregs. Interestingly, Treg-specific CD83 deficiency in mice shifted the immune balance towards a pro-inflammatory phenotype, aggravated autoimmunity and impaired the resolution of inflammation. Noteworthy, we also discovered that CD83 is essential for Treg cell stability and late differentiation upon activation. Since Treg cells play a crucial role in the maintenance of immune tolerance and thus in the prevention of autoimmune disorders, our findings are also clinically highly relevant as we provide a new pathway to modulate T cell tolerance.


CD83 is essential for maintaining tolerogenic mechanisms and promotes resolution of inflammation.
NFATc1 is a transcription factor activated by TCR (T cell receptor) and Ca²⁺-signaling that affects T cell activation along with effector and cytotoxic T cell functions. The cytotoxic properties of T cells are important for the process of cancer immunosurveillance resulting in the elimination of cancer cells which provides the rationale for currently applied immunotherapies. One novel promising immunotherapeutic approach is the inhibition of PD-1 (programmed cell death 1) by using checkpoint inhibitors (anti-PD-1 antibodies) promoting cytotoxic T cell functions and thus anti-tumor immune response.

Our recent findings show a progressive decrease of NFATc1 in tumor-infiltrating T cells of patients suffering from advanced stage NSCLC. Mice harboring conditionally inactivated NFATc1 in T cells showed increased lung tumor growth associated with impaired T cell activation. Furthermore, effector memory and CD103⁺ TRM (tissue-resident memory) T cells were found to be reduced underlining impaired cytotoxic T cell responses and a reduced TRM tissue-homing capacity in the presence of lung tumor. In addition, treatment of lung tumor-bearing wild-type mice with an anti-PD1 antibody resulted in a strong induction of NFATc1 in tumor-infiltrating T cells associated with increased anti-tumor cytotoxic functions. These results indicate that anti-PD-1 antibodies induce NFATc1 in tumor infiltrating lymphocytes resulting in T cell activation and improved T cell effector functions which promote the functional restoration of exhausted T cells (Figure).

Together, this study reveals a multi-faceted role of NFATc1 in the activation and function of T cells underlining the importance of this transcription factor for successful anti-tumor immune responses especially in the setting of lung cancer.

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by the loss of midbrain neurons. An accumulation of alpha-synuclein (aSyn) and inflammation are suggested to play a crucial role for neurodegeneration in PD. However, the mechanisms of their contribution to neuronal loss and their possible interplay during PD pathology remain elusive.

To model PD pathology in the human system, we differentiated neurons from patient-derived induced pluripotent stem cells (iPSC). We demonstrated that formation of small oligomeric aSyn aggregates caused reduced mitochondrial axonal transport and impaired axonal and synaptic integrity in human neurons, including iPSC-derived neurons from a PD patient carrying aSyn gene duplication. Axonal transport defects could be rescued by using a compound known to inhibit aSyn oligomer formation.

In a parallel study using human autologous co-culture of peripheral T cells and iPSC-derived midbrain neurons, we showed that T cells induced cell death of midbrain neurons in sporadic PD by IL-17, upregulation of IL-17 receptor and NFκB activation. Higher Th17 frequencies were also evident in the blood of PD patients and increased numbers of T cells were detected in postmortem PD brain tissues. Blockage of IL-17 or IL-17R rescued the neuronal death.

Possible involvement of IL-17-producing T cells in PD might revise our understanding of how PD neurodegeneration can be promoted by systemic inflammation. Since inflammation can affect axonal transport, a challenging possibility of aSyn oligomer-induced axonopathy as underlying mechanism of Th17-induced neuronal death in human PD pathology needs to be further investigated.


Huntington disease (HD) represents the most frequent polyglutamine disorder with late onset of overt neurodegeneration and death. The present work demonstrates in HD transgenic rats and mice that certain prodromal features of HD manifest in early life and could be amenable to therapeutic intervention at this stage. In the early postnatal period, both models showed a behavioural phenotype, which included reductions in ultrasonic vocalization and increases in risk-taking behaviour. Analysis of striatal gene expression in tgHD rats uncovered evidence of dopaminergic imbalance. In addition, neural stem cells from tgHD pups and BACHD embryos showed an impaired ability to differentiate into neurons and oligodendrocytes.

Our research consortium found that all aspects of this phenotype could be ameliorated by treatment with the HDAC inhibitor LBH589 (Panobinostat®) (Figure A). The findings of the study suggest that the prodromal phase of HD has a neurodevelopmental component that constitutes a novel therapeutic window bearing potentially novel targets.

Among these novel targets, further data revealed in HD rodent brains an upregulation of glutaminyl-cyclases (QCs) and dipeptidylpeptidase 4/CD26 (DPP4), which are checkpoints in controlling maturation and half-life of MCP1/CCL2 (Figure B). While QC-like enzymatic activity protects the N-terminus of MCPs by pGlu-MCP formation, in contrast, N-terminal truncation of MCP-1 by DPP-4 abrogates its activity, shortens half-life and therefore acts anti-inflammatory in certain inflammatory micro environments. This data exemplifies these “homeostatic” peptidase actions in complex disease and organ specific processes. The chemokine CCL2 is a key factor in recruiting monocytes to sites of neuroinflammation including but not limited to HD.
## PEOPLE

**Introducing our new members**

**Welcome Prof. Dr. Holger Hackstein**

Prof. Holger Hackstein is the new Head of the Department of Transfusion Medicine and Hemostaseology

Prof. Dr. Holger Hackstein

The Medical Immunology Campus Erlangen cordially welcomes its new member Prof. Holger Hackstein, who, as of April 2018, is the new Director of the Department of Transfusion Medicine and Hemostaseology, FAU Erlangen-Nürnberg, Universitätsklinikum Erlangen. As new director, he replaces Prof. Dr. Reinhold Eckstein, who headed the department for 26 years. Prof. Hackstein studied medicine at the Justus-Liebig University of Gießen and the Medical University of Lübeck. After spending nearly 4 years at the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh, PA, USA, as postdoc, he returned to the Justus-Liebig University of Giessen in the year 2002. Before taking over the Erlangen Department of Transfusion Medicine, Prof. Hackstein was instrumental in the merger of the two university clinics Gießen and Marburg, first as senior physician and later as deputy director of transfusion medicine. Prof. Hackstein’s main research focus is on the pharmacological modulation of dendritic cells and the immune regulation by extracorporeal photopheresis. At the Universitätsklinikum Erlangen, Prof. Hackstein plans to enhance the application of research into patient care and ultimately achieve self-sufficiency in blood products for the University Hospital.

## NEWS AND UPDATES

**Nobel Prize winner inaugurates FAU auditorium – Harald zur Hausen Lecture Hall**

On Thursday, July 12, one day before the opening ceremony of German Centre for Immunotherapy (DZI) in Erlangen (see article on page 7), Nobel Prize winner Prof. Dr. Harald zur Hausen came to the Friedrich-Alexander-University Erlangen-Nürnberg (FAU) to inaugurate the new lecture hall dedicated to him in the old university hospital.

After the welcome address by the Dean of the Medical Faculty, Prof. Dr. Jürgen Schüttler, who considers the lecture hall a lasting expression of our cordial solidarity with our ‘first’ Nobel Prize winner, Prof. Dr. Harald zur Hausen thanked the medical faculty and mentioned that it has always been a great pleasure for him to return to Erlangen, where he had spent five happy years. Looking at Erlangen from the outside he is very much impressed by the success and the excellent development of the Medical Faculty and the University.

The Harald zur Hausen lecture hall offers space for around 100 people and was renovated between 2011 and 2017 as part of the renovation work on the old university hospital. In the lecture hall, colloquia and meetings of the Medical Faculty as well as lectures for medical students and members of master study course Medical Process Management take place.

The eponym, Prof. Dr. Harald zur Hausen, received the Nobel Prize for Medicine in 2008 for his discovery of the role of papillomaviruses in the development of cervical cancer. The foundations for his pioneering work were laid during his time at the FAU, where he was the founding director of the Virology Institute from 1972 to 1977. The physician has been closely associated with the university ever since - as a university councilor (1998 to 2002), as honorary senator of the FAU (since 2002) and as honorary doctor of the Medical Faculty (2005).
On July 13th, 2018, immunological research in Erlangen reached another milestone: the opening of the German Centre for Immunotherapy (DZI). The center bundles the competence of established research institutes to apply and further develop immunotherapies as well as diagnostic methods for disease detection and therapy monitoring for patients with cancer and chronic inflammatory diseases using the latest scientific methods and digital health technology.

The DZI – spatially accommodated on 1000 square meters with 24 consulting rooms in the internal medicine center of the Universitätseinrichtung Erlangen – provides a single point of contact for finding individual targeted immunotherapy through interdisciplinary cooperation between different disciplines. Only a few meters away one can find the Translational Research Center (TRC), where DZI researchers develop and test new therapeutic approaches against cancer and chronic inflammatory diseases in close clinical connection to the DZI outpatient departments.

The DZI opening ceremony took place at the Neues Hörsaalgebäude of the Universitätseinrichtung Erlangen. One of the two Spokesmen of the DZI, Prof. Dr. med. Georg Schett, Director of the Department of Medicine 3, introduced the center by emphasizing the potency of immunotherapy research. Prof. Schett explained that 15 years ago patients with advanced malignant melanoma were essentially sentenced to death, whereas today, there is a 30 to 40 percent chance of remission. This is mainly due to the rapid development of modern immunotherapies in recent years, said Schett. After Prof. Schett’s introduction, Prof. Dr.-Ing. Joachim Hornegger, President of FAU, gave a motivating welcome address referring to the center as a “beacon of medicine” and praising the interdisciplinary cooperation of various disciplines at the Universitätseinrichtung Erlangen. The dean of the Medical Faculty, Prof. Dr. med. Dr.h.c. Jürgen Schüttler also welcomed the audience and spoke of a dream come true for the Medical Faculty after 20 years of hard work and extensive research in the field of immunotherapy. The Medical Director of the Universitätseinrichtung Erlangen, Prof. Dr. med. Dr. h. c. Heinrich Iro presented the latest numbers and facts about the university hospital and sees the DZI as a magnet to attract outstanding researchers to Erlangen.

One of the highlights of the inauguration ceremony was Nobel Prize winner Professor Harald zur Hausen’s speech, who from 1972 to 1977 held the Chair of Virology at the Friedrich-Alexander-University Erlangen-Nürnberg. Prof. zur Hausen was awarded the Nobel Prize in Medicine in 2008 for his discovery of human papilloma viruses causing cervical cancer. Zur Hausen himself sees a “great potential for future developments” in the DZI. At the ceremony, he welcomed Professors Martin Röllinghoff, Joachim Kalden and Bernhard Fleckenstein, three long-standing companions who together led Erlangen’s immune research to international leadership. However, Adolf Kußmaul, the first person to describe panarteritis nodosa and FAU Chair of Internal Medicine from 1859 to 1863, is regarded as the ancestor of immunological research in Erlangen. During the past 10 years FAU and the Universitätseinrichtung Erlangen have been ranked amongst the top 3 institutions for immunological research in Germany, which certainly contributed to the establishment of the DZI.

Last but not least, the second spokesperson of the DZI, Prof. Markus Neurath, Director of the Department of Medicine 1, outlined the latest research developments in the field of immunotherapy, which targets significantly increasing diseases such...
Ceremonial opening of the German Centre for Immunotherapy (DZI) in Erlangen

as asthma (4.8 million cases in Germany), psoriasis (1.2 million), rheumatism, multiple sclerosis and Crohn’s disease. Prof. Neurath explained that in the past, cortisone was considered a blessing in immunotherapy, but with many side effects. Before the turn of the millennium, the first monoclonal antibodies reached clinical application, but still – especially considering 480,000 new cancer cases per year in Germany – new diagnostic and therapeutic procedures are urgently needed. Prof. Neurath further mentioned that new imaging techniques and treatment strategies have been developed in the medical departments, the dermatology clinic and the children’s hospital. In addition, numerous partners have joined the DZI, including Siemens, the local Fraunhofer and Max Planck Institutes, Miracum and Medical Valley.

The Medical Immunology Campus Erlangen congratulates the spokesmen Prof. Georg Schett and Prof. Markus Neurath for their achievement and thanks them for their dedication and tireless effort in increasing Erlangen’s visibility in the field of immunology on a national and global scale.

**UPCOMING EVENTS**

**Immunological Colloquium of the Medical Immunology Campus Erlangen – Winter 2018/19**

**Tuesdays, 5.15 pm**

**08.01.2019**
Prof. Sven Hammerschmidt
Department of Molecular Genetics and Infection Biology, Universität Greifswald
*Function and immunogenicity of Streptococcus pneumoniae surface proteins*

**22.01.2019**
Prof. Joachim Hauber
Heinrich-Pette-Institut, Leibniz-Institut für Experimentelle Virologie, Hamburg
*Antiviral Therapy of Persistent Viral Infection using Genome Editing*

**29.01.2019**
PD Dr. Isis Ludwig-Portugall
Institut für experimentelle Immunologie (IEI), Uniklinik Bonn
*Innate lymphocytes (ILCs) respond to crystal-deposition and promote local inflammation and fibrosis*

**05.02.2019**
Prof. Philip Rosenstiel
Institut für Klinische Molekularbiologie, Christian-Albrechts-Universität zu Kiel
*Mechanisms of homeostasis at the intestinal barrier*

**Conferences and Events of Interest**

**February 24 – 26, 2019 - Berlin**
1st Immunology & Inflammation (I & I) Conference
www.mdcb-berlin.de/immunology-inflammation-2019

**February 25 – 27, 2019 - Göttingen**
71st Annual Meeting of the German Society of Hygiene and Microbiology
www.dghm-kongress.org

**February 27 - March 1, 2019 - Heidelberg**
20th International AEK Cancer Congress
www.aek-congress.org

**March 20 – 23, 2019 - Düsseldorf**
29th Annual Meeting of the Society for Virology
www.virology-meeting.de

**March 23 – 25, 2019 - Erlangen**
10th Cellular Therapy Meeting
www.cellular-therapy.de

**March 27 – 29, 2019 - Burg Rothenfels**
23. Symposium “Infektion und Immunabwehr”
www.dgfz.org/arbeitskreise/ak-infektionsimmunologie/meeting

**April 4 – 6, 2019 - Munich**
Conference on Tropical Medicine and Global Health
dtg2019.usernet.mwn.de

**April 28 – May 1, 2019 - Rotterdam/Netherlands**
7th Meeting of The European Society for Virology (ESV)
www.ecv2019.com

**April 29, 2019 - Day of Immunology**
June 12 – 14, 2019 - Tübingen
Novel Concepts in Innate Immunity
www.innate-immunity-conference.de

**September 4 – 6, 2019 - Cottbus**
21st Joint Meeting of the German Society for Immunology (DGfI) and the Italian Society of Immunology, Clinical Immunology and Allergology (SIICA)
www.immunology-conference.de

**September 10 –13, 2019 - München**
II Joint Meeting of the German Society for Immunology (DGfI) and the Italian Society of Immunology, Clinical Immunology and Allergology (SIICA)
www.immunology-conference.de

**September 12–14, 2019 - Marseille/France**
33th Annual Conference of the European Macrophage and Dendritic Cell Society (EMDS)
www.emds2019.com