Medical Immunology Campus Erlangen

MICE Letter *Spring 2011*

CONTENT

Scientific Highlights p. 2/3
- How Plasma Cells Reach the Bone Marrow
- Regulation of B Cell Signalling

News and Updates p. 3/4
- Second Phase of the Excellence Initiative
- Joachim Kalden Lecture 2011
- Joachim Kalden Lecture 2012

Upcoming Events p. 4
- Conferences (Co-)Organized by MICE Members
- Further Conferences of Interest

EDITORIAL

Dear colleagues and friends,

… Results of the preselection in the second phase of the Excellence Initiative …

On 2 March 2011, the Joint Commission appointed by the DFG and the German Council of Science and Humanities announced the results of the preselection in the second phase of the Excellence Initiative. 27 out of 107 submitted preproposals for a cluster of excellence have been selected for the final round. The preproposal of the Medical Immunology Campus Erlangen "From Target Identification to Immunotherapy", however, has not been chosen. Apparently, there was an extraordinary competition. In this year's round, only four biomedical preproposals – among them only one immunology draft from the University of Bonn – were successful. The MICE's key scientists involved in the preproposal have already been informed about the reasons for the decision. The statement of the DFG implies that our draft was discussed very controversially: The concept of a personalized medicine was evaluated as a highly potent idea by one group of the reviewers. However, another group of referees criticized this concept, considering a personalized medicine as not being sustainable and generating high expenses. The outlined allocation of resources and the existing infrastructure were positively evaluated, as well as structural aspects like knowledge transfer, promotion of young researchers, and gender equality which have been recognized as exemplary. The previous achievements and planned projects in the field of translational medicine were positively assessed and considered as internationally explicitly competitive. On the other hand, the scientific concept could have been more focused on a specific topic.

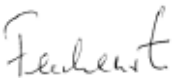
… Only four biomedical preproposals were successful …

… I wish to thank all the people involved for their dedication and motivation to design and set up the MICE preproposal …

On behalf of the writing committee, I wish to thank all the people involved for their dedication and motivation to design and set up the MICE preproposal. After all, our initiative appears to have left a good impression, even though we finally did not succeed in prevailing against the tough competition in this second phase of the Excellence Initiative.

…The MICE will continuously develop its existing tasks as an interdisciplinary center of the University …

We will continue to strive for support at the Federal state level to structurally improve the scientific region of northern Bavaria. The results from the Excellence Initiative have revealed once more that the presence of non-university research institutions is an absolute prerequisite for the success of a research site in a highly competitive environment in the long run. The University is dedicated to enable the founding of a Leibniz Institute for the Function and Deficiency of the Immune System. In the future, the MICE will continuously develop its existing tasks as an interdisciplinary center of the University.



Prof. Bernhard Fleckenstein Coordinator

SCIENTIFIC HIGHLIGHTS

How Plasma Cells Reach the Bone Marrow

Plasma Cell Homing Controlled by Krüppel-like Factor 2

Krüppel-like factor 2 (KLF2), a zinc finger- containing transcription factor, is crucial for proper homing of antigen-specific plasma cells to the bone marrow

WOLFGANG SCHUH · REBECCA WINKELMANN
HANS-MARTIN JÄCK
DIVISION OF MOLECULAR IMMUNOLOGY, DEPARTMENT OF INTERNAL MEDICINE 3 · NIKOLAUS-FIEBIGER CENTER

Long-lived plasma cells, which are generated in secondary lymphoid tissues, have to reach specialized survival niches formed by stromal and other cells in the bone marrow

Plasma cells are powerful micro factories producing thousands of antibody molecules per second and thereby protecting the organism from harmful pathogens and infections. Once a B cell encounters its specific antigen, a fascinating differentiation program is initiated that leads to morphological cellular restructuring and converting the B cell into an antibody-producing cell, the so-called plasma cell.

Plasma cells can be subdivided into short- and long-lived plasma cells. Short-lived plasma cells predominantly produce IgM and have a life-span of approximately one week; in contrast long-lived plasma cells continuously produce high affinity IgG or IgA molecules and survive for years.

Long-lived plasma cells, which are generated in secondary lymphoid tissues, have to reach specialized survival niches formed by stromal and other cells in the bone marrow. Still, it is puzzling how migration, homing and survival of these cells are controlled.

In our study we demonstrated that Krüppel-like factor 2 (KLF2), a zinc finger- containing transcription factor, is crucial for proper homing of antigen-specific plasma cells to the bone marrow. In a mouse strain with a B cell-specific deletion of KLF2 we found a clear reduction of plasma cells in the bone marrow, whereas plasma cell numbers in the spleen and the blood were fairly normal, indicating that KLF2 plays an important role in homing of plasma cells to the bone marrow (Fig. 1). Since we found diminished levels of $\alpha_4\beta_7$ - Integrin and L-Selectin on KLF2-deficient B cells, we propose that KLF2 regulates plasma cell homing to the bone marrow via regulation of these two cell adhesion molecules. Future experiments using a plasma cell-specific GFP reporter mouse will clarify the role of KLF2 in humoral immunity and provide new ways to interfere with the generation of pathologic plasma cells in patients with multiple myeloma and autoimmune disease.

Supported by the IZKF Erlangen and the DFG

This research was originally published in **Winkelmann R, Sandrock L, Porstner M, Roth E, Mathews M, Hobeika E, Reth M, Kahn ML, Schuh W, Jäck HM:** B cell homeostasis and plasma cell homing controlled by Krüppel-like factor 2. Proc. Natl. Acad. Sci. U.S.A. 2011;108:710-5

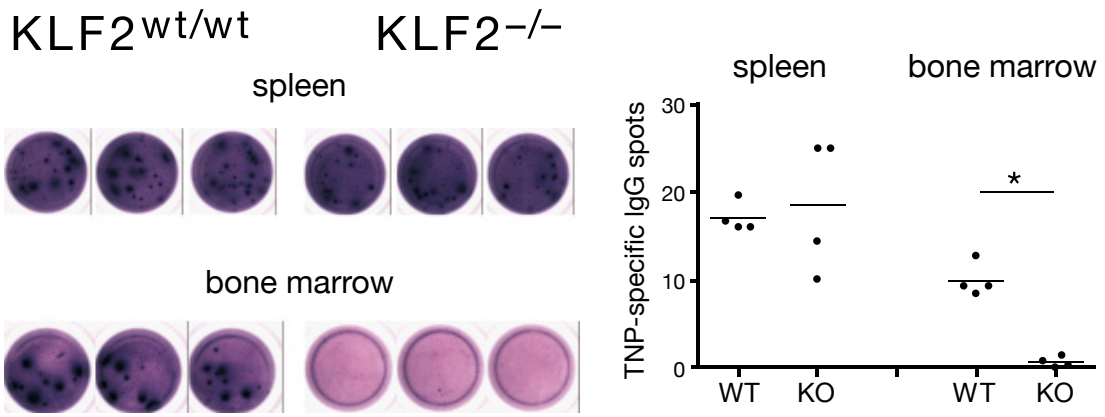


FIGURE 1 Elispot assay of TNP-specific IgG-secreting cells in spleen and bone marrow 14 days after boost immunization with TNP-KLH. A triplicate of one representative experiment is shown to the left, and results of all analyzed littermates are summarized with one dot representing the mean value of triplicates of one mouse is shown to the right.

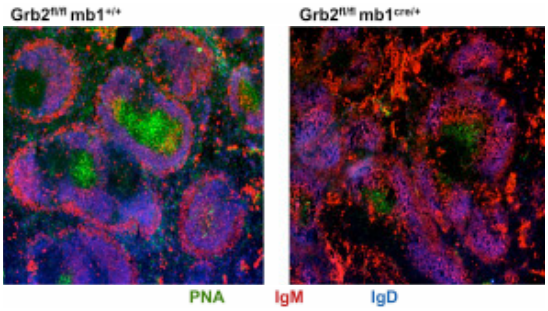
SCIENTIFIC HIGHLIGHTS

Regulation of B Cell Signalling

Grb2 Regulates B Cell Maturation, B Cell Memory Responses and Inhibits B cell Ca^{2+} Signalling.

LARS NITSCHKE
CHAIR OF GENETICS, DEPARTMENT OF BIOLOGY

Grb2 is a ubiquitously expressed adaptor protein, which activates Ras and MAP kinases in growth factor receptor signalling, while in BCR signalling this role is controversial. In B cell lines it was shown that Grb2 can inhibit BCR-induced Ca^{2+} signalling. Besides, Grb2 also participates in other lymphocyte signalling pathways as a multifunctional adaptor protein. Nonetheless, the physiological role of Grb2 in primary B cells was still unknown. Therefore, the group of Lars Nitschke, Chair of Genetics, Department of Biology, generated a conditional B cell-specific Grb2-deficient mouse line. These animals had a severe reduction of mature follicular B cells in the periphery due to a differentiation block and decreased B cell survival. Moreover, several changes in important signalling pathways were found: enhanced BCR induced Ca^{2+} signalling, alterations in MAPK activation patterns and strongly impaired Akt activation, the latter pointing towards a defect in PI3K signalling. Interestingly, B cell specific Grb2-deficient mice showed impaired IgG and B cell memory responses, and impaired germinal centre formation (see figure). The defective memory response of B cell specific Grb2-deficient mice to hCMV derived virus-like particles was analysed in cooperation with the group of Thomas Winkler from the chair of Genetics. Thus, Grb2-dependent signalling pathways are crucial for lymphocyte differentiation processes, as well as for control of secondary humoral immune responses.



Spleen sections stained with PNA (green), IgM (red) and IgD (blue) 10 days after immunisation with sheep red blood cells. A spleen of a control mouse is shown on the left and a spleen of a conditional Grb2 KO mouse is shown on the right.

This research was originally published in **Ackermann JA, Radtke D, Maurberger A, Winkler TH, Nitschke L:** Grb2 regulates B-cell maturation, B-cell memory responses and inhibits B-cell Ca(2+) signalling. EMBO J. 2011 Apr 20;30(8):1621-33.

NEWS AND UPDATES

SECOND PHASE OF THE EXCELLENCE INITIATIVE

Evaluation of the First Round

After the first phase of the Excellence Initiative (2005 – 2012), the Federal and State governments agreed for a second phase (2010 – 2017) in June 2009. The deadline for preproposals was on 1 September 2010. According to the DFG, 98 draft proposals for graduate schools, 107 for clusters of excellence, and 22 for institutional strategies were submitted. A quarter (25 preproposals for graduate schools, 27 for clusters of excellence) up to a third of the preproposals (seven for institutional strategies) were preselected for the final round as announced by the Joint Commission appointed by the DFG and the German Council of Science and Humanities on 2 March 2011. Only 8 % of the selected preproposals for graduate schools and 15% of those for clusters of excellence have a biomedical background. The submission deadline for the initial full proposals, which will compete with the renewal proposals of the existing projects of the first phase, will be on 1 September 2011. It is expected that 10 – 20 clusters of excellence and up to five institutional strategies will be granted in addition to the existing projects. The final decision will be on June 15, 2012. More information: www.dfg.de/en/research_funding/programmes/excellence_initiative.

JOACHIM KALDEN LECTURE 2011

The Medical Immunology Campus Erlangen Honors Prof. Dr. Ralph Steinman

Prof. Steinman talking about “Dendritic Cell-targeted Protein Vaccinces” (left) and receiving the certificate for the Joachim Kalden Lecture 2011 presented by Prof. Gerold Schuler

With this year’s Joachim Kalden Lecture on 10 May, the Medical Immunology Campus Erlangen honored Prof. Ralph M. Steinman, who, together with Prof. Zanvil A. Cohn, described for the first time the dendritic cells in the early 1970ies.

Prof. Steinman is one of the leading immunologists and has received several highly reputated awards such as the Robert-Koch-Preis 1999, the Albert Lasker Award for Basic Medical Research 2007, the Albany Medical Center Prize 2009, and the Dr A. H. Heineken Prize for Medicine 2010.

In his lecture “Dendritic Cell-targeted Protein Vaccines” he talked about the discovery of dendritic cells, their characterization, and current research on the development of vaccines based on dendritic cells.

JOACHIM KALDEN LECTURE 2011

Abstract of the Talk by Prof. Ralph Steinman:

Dendritic Cell-targeted Protein Vaccines

The initiation and control of the immune response is central to vaccines, which already have provided many medical success stories. Most vaccines depend upon the induction of protective antibodies, but there is the potential to discover T cell-based vaccines to help resist global infections, and also to expand the scope of vaccine science to other medical fields like cancer. I would like to outline the demands of T cell-based vaccines, describe how we came to take a dendritic cell perspective to T cell science, and then explain the areas of dendritic cell function that our lab is trying to harness to develop new vaccines.

Dendritic cells were identified as distinct leukocytes specialized to initiate immunity, beginning with assays related to transplant immunity. At the time, leaders in immunology wondered how this powerful immune response was initiated. Dendritic cells were distinguished from other white cells including macrophages, and recent advances from many labs have described some of the driving forces for dendritic cell development in vivo. Once developed, a key feature is the abundance of dendritic cells in the T cell areas of lymphoid organs, where immunity begins. Another is the differentiation or maturation of dendritic cells in response to microbial and other stimuli, a central area of immunology that was discovered by Gerold Schuler. A new area of research is to learn to induce tolerance, including the induction of foxp3+ T reg, with dendritic cells.

To pursue the development of dendritic cell based vaccines, and to further understand their function in vivo, we focus on two types of receptors for "microbial patterns": receptors for antigen uptake particularly C-type lectins, and receptors for signaling innate immunity including toll like receptors. We introduce vaccine proteins of interest into monoclonal antibodies that target to dendritic cell lectins in vivo, and we combine these fusion antibodies with adjuvants that are agonists for innate immunity, particularly synthetic double stranded RNA or poly IC. The effects of poly IC in vivo will be illustrated, including our studies in healthy human subjects. This research benefits from progress worldwide on the intricate receptor systems involved in innate and adaptive immunity.

JOACHIM KALDEN LECTURE 2012

Call for Nominations

The next Joachim Kalden Lecture will be in 2012. The members of the MICE are cordially invited to make suggestions for a speaker. The person to be honored should be a distinguished representative from the field of immunology who is of interest to a broad, interdisciplinary audience. Please send your suggestion together with a short explanatory statement and the CV of the candidate to aegrohma@viro.med.uni-erlangen.de until 15 July 2011. We are looking forward to nominations!

Conferences (Co-)Organized by MICE Members

June 20 – 22, 2011
4th Weißenburg Symposium
Epigenetics and the Control of Gene Expression
Weißenburg
www.leopoldina.org/de/veranstaltungen/veranstaltungsdetails/article//epigenetics.html

Oct. 9 – 14, 2011
3rd Autumn School
"Current Concepts in Immunology" of the German Society of Immunology
Bad Schandau
www.herbstschule.de

Further conferences of interest

June 15 – 18, 2011
5. Deutsch-Österreichischer AIDS-Kongress (DÖAK 2011)
Hannover
www.doeak2011.com

Sept. 3 – 11, 2011
FEBS 16th International Summer School on Immunology:
Immune System: Genes, Receptors and Regulation
Hvar, Croatia
www.febs-hvar2011.org

Sept. 10 – 13, 2011
The EMBO Meeting
Vienna, Austria
www.the-embo-meeting.org

Sept. 22 – 24, 2011
19th Annual Meeting of the German Society for Immunogenetics
Berlin
www.berlin.dgiev.de

Sept. 22 – 24, 2011
25th Annual Meeting of the European Macrophage and Dendritic Cell Society (EMDS)
Brussels, Belgium
www.emds2011.eu

Sept. 23 – 24, 2011
International Symposium of the SFB854:
Molecular Organisation of Immune Cell Communication
Magdeburg
www.sfb854.de

Sept. 28 – Oct. 1, 2011
2011 Joint Annual Meeting of the Italian Society for Immunology (SIICA) and the German Society of Immunology (DGfI)
Riccione, Italy
www.immunology2011.it

Dec. 10 – 13, 2011
ASH Annual Meeting and Exposition
San Diego, CA, USA
www.hematology.org/Meetings/Annual-Meeting/

Jan. 16 – 20, 2012
IFReC-SIgN Winter School on Advanced Immunology
Awaji Island, Hyogo, Japan
http://ifrec-sign-winterschool.org

Medical Immunology Campus Erlangen

Publisher
Medical Immunology Campus Erlangen

Schlossgarten 4
91054 Erlangen

Phone +49.9131.85.2 67 84
Fax +49.9131.85.2 21 01

www.mice.uni-erlangen.de

Conceptual Design and Editor
Dr. Annette Grohmann
V.i.S.d.P.

Subscription via Email to:
aegrohma@viro.med.uni-erlangen.de

We are looking forward to suggestions for the next MICE letter.

Please send material to: aegrohma@viro.med.uni-erlangen.de