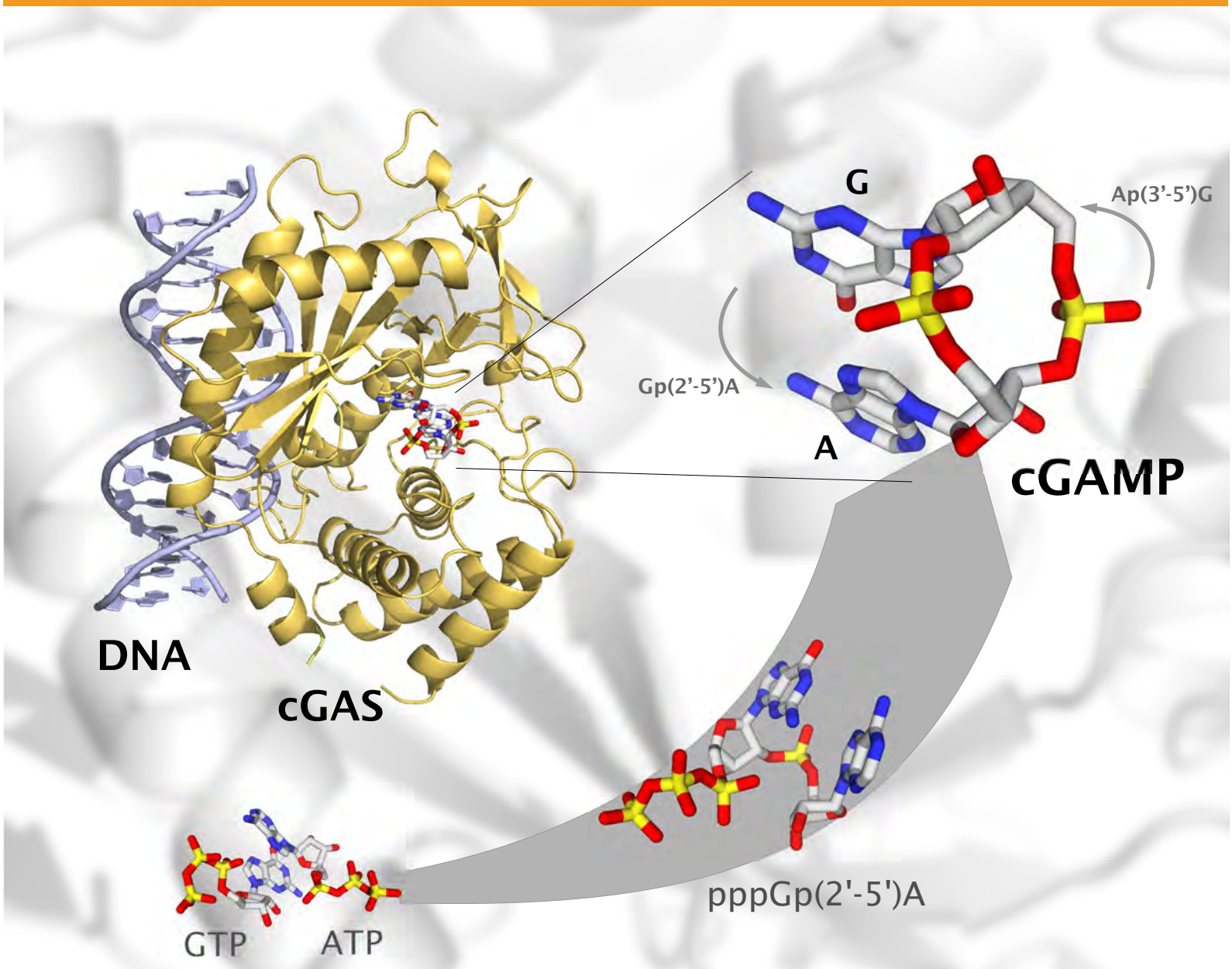
ImmunoSensation

the immune sensory system Bonn cluster of excellence

ANNUAL REPORT 2013



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LIMES Life & Medical Sciences Institute

DZNE German Center for Neurodegenerative Diseases within the Helmholtz Association

caesar center of advanced european studies and research

OVERVIEW

Preface

Preface

We can now look back on the first year of funding of our Cluster of Excellence ImmunoSensation by the German Research Foundation, DFG. Within the Cluster, we presented a conceptually new view of an immune sensory system beyond the boundaries of classical immunology, and it is truly exciting to see that our concept has found so much resonance within the international community. We also coined the term immune sensing to draw attention to the parallels with other sensory systems, and what was initially deemed unconventional has now entered the immunological parlance. Immune sensing is now frequently used worldwide and has almost eclipsed the former term “pattern recognition”.

Within our first year, we have made substantial progress in establishing a widely visible center for immunology in Bonn. Structural measures include the recruitment of the first Cluster professorship funded by the DFG (W2 Vascular Immunology, Dr. Wolfgang Kastenmüller from the NIH, USA), the formation of a central organizational structure, the Cluster Coordination Office, the establishment of the International Immunology Training Program, IITB, and the creation of support programs such as soft skill courses for students and young scientists and instruments for family and gender support. In scientific terms, we are proud to present what has been achieved in 2013, including groundbreaking discoveries as well as the development of innovative concepts and strategies which we expect will yield novel insights in the coming years.

Exciting work has been done in the Cluster, some of which is published in 2013 and reported in the following chapters. Other innovative project areas are just at the edge of a profound conceptual advance arising from new interactions within the Cluster, such as the one presented in the Feature Article. One example of the focus areas of the Cluster research is illustrated on the cover image. It is the identification of the founding member of a new family of metazoan cyclic heterodinucleotide second messengers, a key molecule in the DNA sensing pathway. One distinguishing feature of this new molecule is the 2´-5´ linkage, which differs from the 3´-5´ cyclic dinucleotides that are already well known in bacteria. This molecule is the long-sought missing piece in the puzzle of immune sensing of DNA (Gao et al., 2013a; Ablasser et al 2013a; Civil et al., 2013; Gao et al.,2013b). In the context of this new second messenger molecule, Cluster researchers also discovered a novel principle in innate immunity – that innate immune signals can be transferred via gap junctions. Gap-junction mediated transfer of cGAMP to bystander cells allows a rapid transcriptional-independent antiviral response in neighboring cells protecting them instantly from virus infection (Ablasser et al., 2013b). Another publication in this context clarified how oxidation of self DNA can lead to autoinflammatory disease (Gehrke et al., 2013). Altogether, DNA sensing was one of the most important topics in innate immunity in 2013, and the contributions made by ImmunoSensation Cluster were prominent at an international level.

We could not have had such a successful year without the collaborative effort of all our members. We would like to thank our scientists, young and “old”, for their enthusiasm and hard work in 2013. We thank the managerial team behind the Cluster for its great track record after only one year. We are grateful for the support

that we have received from the DFG and from the University of Bonn, specifically the Faculty of Medicine and the Faculty of Mathematics and Natural Sciences. The cooperation within the Cluster between the University and our two extramural institutions, the Max Planck Society-associated center of advanced european studies and research (caesar) and the German Center for Neurodegenerative Diseases (DZNE) has been central to breaking new ground in research on the immune sensory system. Finally, there is a great sense of scientific community in Bonn that extends beyond group, institutional and national borders. It is this atmosphere that makes science at ImmunoSensation so vibrant, dynamic and enjoyable.
(For references see Cluster publication list 2013.)

Overview Science and Structure

The concept of the ImmunoSensation Cluster is to address the immune system as a complex, yet incredibly efficient sensing device, which displays multiple characteristics of a sensory organ. Specialized receptors are in charge of sensing damage or danger, such as the receptors of the innate immune system, which are inherited and present from birth on. In addition, there are the highly variable receptors of B- and T cells that are acquired later in life, and which are characterized by constant renewal. Immune sensing receptors are not restricted to immune cells. Some of them are expressed in a wide range of human somatic cell types. They represent the center core of a multimodal sensory system that is well-equipped to distinguish self from non-self as well as harmless from harmful. An exact analysis and signal integration of the sensed information is essential in order to coordinate and execute an appropriate immune reaction and to protect the organism from damage. In healthy organisms, these sensing mechanisms are continuously active beyond the level of our awareness. This is comparable to other classical sensory systems that operate constantly without us taking notice of them. Intact and synchronized communications and connections of the immune system to other processes and structures of our body, like metabolism or the nervous system, are crucial to balance immune activity and to maintain health.

To efficiently investigate the complex network of the immune sensory system, research groups from different disciplines are working together within the ImmunoSensation Cluster. The Medical Faculty is leading this initiative jointly together with LIMES (Life and Medical Sciences Institute) of the Faculty of Mathematics and Natural Sciences. Immunologists closely work together with groups of genetics, biochemistry, biophysics, cell biology, neuroscience, and mathematics. The participation of research groups from the clinical departments foster translational research. Besides the University of Bonn, the Max Planck Society-associated center of advanced european studies and research (caesar) and the German Center for Neurodegenerative Diseases (DZNE) are equal partners of the Cluster. The German Aerospace Center (DLR) and the Hebrew University in Israel are Cluster-associated institutions. The Cluster closely cooperates with international research partners and institutions from the USA, UK, Ireland, Israel, and Japan.

Prof. Dr. med. Gunther Hartmann
Speaker

Picture
Prof. Dr. Gunther Hartmann

Overview:
Science and Structure

ImmunoSensation Cluster of Excellence an Introduction: Interview with Prof. Gunther Hartmann Speaker of the ImmunoSensation Cluster

Interview with Prof. Dr. med. Gunther Hartmann

ImmunoSensation:
Prof. Hartmann, what is the research focus of the ImmunoSensation Cluster of Excellence?

Gunther Hartmann:
Our approach is to view the immune system as an **immune sensory system**, in other words as an organ of perception that uses receptors to sense pathogens and cellular damage. This system should be seen in a broader context than just immune cells, since these immune sensing receptors are not restricted to immune cells and therefore this concept reaches beyond the classical immune system. We are also beginning to understand the extent to which the immune system is linked with the other functional systems in our bodies, such as the metabolism and the nervous system.

ImmunoSensation:
Which academic fields are involved in this type of research?

Gunther Hartmann:
A leading academic role has been taken by two facilities at the University of Bonn: the **Faculty of Medicine** and the **Life and Medical Sciences Institute (LIMES),** which is part of the Faculty of Mathematics and Natural Sciences. In addition, two extramural institutions are also part of ImmunoSensation: the **German Centre for Neurodegenerative Diseases** (DZNE) and the **center of advanced european studies and research** (caesar), which is associated with the Max Planck Society. Within the cluster, scientists in the fields of immunology, neuroscience and mathematics at the University of Bonn collaborate closely with research on neurodegeneration at the DZNE and the research on biophysics and molecular sensory systems at caesar. We also work together with international collaboration partners in the USA, UK, Ireland, Israel and Japan.

ImmunoSensation:
What exactly is meant by “the immune system as a sensory organ”? What is the connection to the other systems in the body?

Gunther Hartmann:
For most sensory organs, the signal integration takes place in the central nervous system. The immune system is also linked with the nervous system. However, its signal integration does not take place in the CNS but rather within the immune organs themselves. Most immune cells are mobile, and our research focuses on how these immune signals, how all of the information derived from multiple mobile cellular units, can be integrated in a way that the appropriate immune response is elicited. The immune response has to be sufficiently specific and directed to the cause of damage but not cause damage in this process. One particularly important topic within the cluster is sterile inflammation, in other words inflammation in the absence of microbial infection.

ImmunoSensation:
What has changed in our understanding of the Immunsystem in comparison with the previous models!

Interview with Prof. Dr. med. Gunther Hartmann

Gunther Hartmann:
Over the last few years, the field of Immunology has experienced several waves of research focuses. Until 1965 or so, researchers focused mainly on the humoral immune system, including B cells and the antibodies they produce. Then it became evident that B cells are mainly guided by T cells during the immune response. Both B- and T cells have the ability to recombine new genes within a human's lifetime. This is the learning process through which new receptors are produced that are able to recognize specific viral or bacterial structures even if the host has never been in contact with them before. This is also known as the adaptive immune system.

The next conceptual advance was that cells of the innate immune system, in particular dendritic cells, control and modulate the responses of the adaptive immune system. Immune sensing receptors recognize pathogens and activate T cells or induce tolerance. We see innate immune sensing receptors as well as T- and B cell receptors, including antibodies, as part of the immune sensory system because all of these receptors are highly specialized to detect danger and damage.

ImmunoSensation:
What roles do the receptors of the immune sensory system play in disease? What processes are beneficial and which are harmful for the host?

Gunther Hartmann:
There are many different families of receptors. Some receptors recognize viral nucleic acids. Others recognize molecules that are specific to bacteria. They detect the presence of microbial pathogens via their contact with specific molecules that are uniquely found in microbes but not in their human hosts. Thus, these receptors can activate an "early warning system" against a particular microbe and disease. Other receptors recognize molecules that are endogenous to the human host, when these are found at an unusually high concentration or have acquired molecular changes. One important example is the misidentification of endogenous nucleic acids, a process that is closely linked with the development of several autoimmune diseases.

ImmunoSensation:
Does this research offer new perspectives for therapeutic approaches to disease?

Gunther Hartmann:
Sterile inflammation plays a central role in several widespread diseases, which as atherosclerosis, Alzheimer's disease, rheumatic diseases, gout and type 2 diabetes. There are also genetic sterile inflammatory diseases that often have a devastating course without treatment, such as Muckle-Wells disease. In recent years, these diseases have become eminently treatable but only because we understand the molecular mechanisms behind them. Since we now know how endogenous stimuli can trigger inappropriate immune responses, we can also block these mechanisms. Thus, we can specifically suppress the inflammatory process and restore balance within the immune sensory system. By "restoring balance", I mean that we can treat the autoinflammation and still largely preserve the immune sensing of pathogens.

Our new understanding of the mechanisms that control and modulate the immune system also lead us to new possibilities for the treatment of malignant tumors. One particularly promising approach is the activation of the immune receptor RIG-I. In conjunction with the Cluster, we have established a biotech company, Rigontec GmbH, which is working to translate RIG-I-based tumor therapy into clinical application, specifically for cancer treatment. This is one example of a potential direct benefit of our research for patients.

ImmunoSensation:
What effect has the ImmunoSensation Cluster of Excellence had on research in Bonn in general?

Gunther Hartmann:
There are sizeable number of techniques that are important to basic and clinical research but require equipment with six-figure prices. No one lab can afford this kind of instrumentation. Sharing equipment and technical platforms does not only make machinery available. It also allows us to share and develop a high level of expertise. Often, the cooperative use of equipment also leads to scientific collaboration. Shared seminars and conferences also create a common space for intensive scientific discussions and exchange. Our programs to promote gender equality also make Bonn particularly interesting for women in science. We are devoting considerable resources to the training of young scientists, but also support for simple everyday problems, such as daycare. All this is important for the success of our scientists, and it also makes Bonn a highly attractive place for talented researchers.

Interview by the
Cluster Coordination office

DNA Sensing and Oxidative Damage

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Cytosolic DNA Sensing via the Innate Immune System

The Innate Immune System Distinguishes Friend from Foe

The most important role of the immune system is to preserve the integrity of the organism in the face of danger both from without and within, i.e. from both environmental pathogens and endogenous danger signals. To this effect, the immune system has developed a fascinating ability: it can reliably identify potentially dangerous microbes and eliminate them without misidentifying and damaging the body of the host. The underlying principle of this is a system of germline-encoded receptors that recognize molecular patterns intrinsic to dangerous organisms or processes, also known as immune-sensing receptors. As the name “innate” literally suggests, the host is born with these pattern-recognition receptors. As a whole, these receptors form an immune-sensory system.

Some of these receptors recognize invariant elements within microbial pathogens that are clearly distinguishable from the endogenous structures of the host, e.g. several immune- sensing receptors recognize elements of bacterial cell walls. Moreover, in the last few years, it has also been discovered that they can detect endogenous molecules. Here, the specific spatiotemporal subcellular localization of the receptors can play an important role. This means that under physiological conditions, immune-sensing receptors and their endogenous ligands are usually separated. This spatiotemporal principle is of particular importance for receptors that detect microbial nucleic acids, such as certain members of the Toll-like Receptor (TLR) family. TLR3, TLR7, TLR8 and TLR9 are all found in the endosome, where they can come into contact with the nucleic acids of phagocytosed microbes. Importantly, the endosome is usually free of endogenous DNA or RNA. However, in the course of an autoimmune disease, if there is an accumulation of endogenous nucleic acids in the endosomal compartment, this can also activate these TLRs and their pathways and initiate or aggravate the pathogenesis of the disease. In addition to changes in localization or concentration, structural modifications of endogenous molecules can also be indicative of cellular damage and lead to the activation of a particular immune-sensing receptor.

How can the Immune Sensory System Recognize that DNA is Foreign?

Since endogenous DNA is normally confined to the nucleus of the cell, the cytosolic localization of DNA is indicative of either cellular damage or the presence of pathogens. While it has been known for decades that the detection of cytosolic DNA leads to the release of type-I interferon, the precise receptors and mechanisms involved in cytosolic DNA recognition have remained elusive until very recently. At the end of 2012, James Chen (University of Texas) and his colleagues were able to identify a previously uncharacterized cytoplasmic enzyme that creates a second messenger cyclic guanosine monophosphate–adenosine monophosphate, or cGAMP, after binding DNA. Accordingly, the DNA-binding enzyme was named cGAMP synthetase, or cGAS (Figure 1). Before the discovery of cGAMP, bacterial cyclic dinucleotides were already known to be potent activators of the ER-adaptor protein STING (stimulator of interferon genes). STING activation initiates an antimicrobial “defense program”, which protects the cell against bacterial and viral infection. Interestingly, the importance of STING for

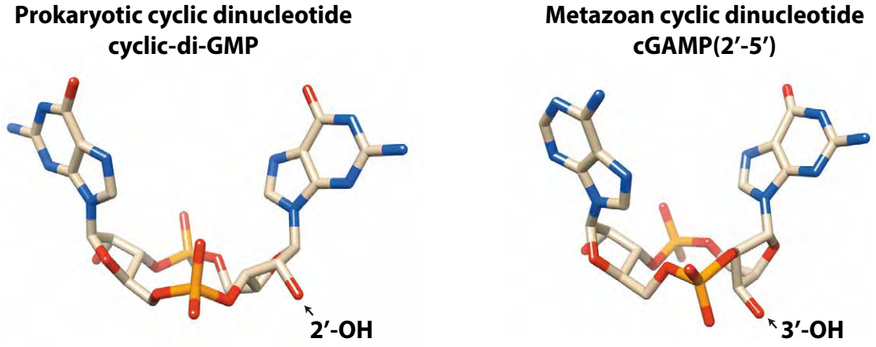

Figure 1 Three-dimensional structures of cyclic di-GMP and cGAMP(2'-5'). Carbon atoms are shown in beige, nitrogen in blue, oxygen in red, and phosphorus in orange.

DNA Sensing and Oxidative Damage

DNA-recognition was also well known before the discovery of cGAS. What remained unclear was how the DNA was actually recognized and how this recognition could lead to STING activation. Thus, the discovery of cGAS and its second messenger cGAMP finally allowed the puzzle to be solved: the enzyme cGAS catalyzes the formation of cGAMP after binding cytosolic DNA; then, cGAMP can subsequently bind to STING and initiate the antimicrobial immune response. Experiments with cGAS or STING-deficient cells confirmed the importance of this newly discovered axis of signal transduction. In the absence of cGAS or STING, certain DNA viruses are no longer identified as "foreign" and trigger an immune response. Thus, these viruses can replicate rampantly and unopposed by the immune system.

The Truth is in the Detail

Several members of the ImmunoSensation Cluster of Excellence were able to make significant contributions to the characterization of the cGAS – cGAMP – STING signal transduction cascade (Gao et al., 2013a; Ablasser et al., 2013a; Civil et al., 2013; Gao et al., 2013b). In two independent experimental approaches, the research groups of Hornung/Ablasser and Hartmann/Barchet were both able to show that there was an important molecular distinction between the metazoan second messenger formed by cGAS and previously discovered bacterial cyclic dinucleotides. In collaboration with Dinshaw Patel at the Rockefeller University in New York, Hartmann/Barchet were able to examine the crystal structure of DNA, cGAS and cGAMP, in order to more precisely characterize the cGAMP synthesis and its structure. Hornung/Ablasser used a mass-spectrometry approach, in vitro enzyme activity assays and NMR techniques to characterize the exact molecular structure of cGAS-sythesized cGAMP. Both complementary approaches came to the same conclusion: metazoan cGAS dependent cGAMP demonstrates an unusual phosphodiester linkage. The researchers discovered that one phosphodiester linkage in cGAMP is between the C2'-atom of the ribose in GMP and the C5'-atom of the ribose in AMP while the second phosphodiester linkage is 3'-5', as is typically found in nucleic acids. Not only is this molecule the first example of a combined 2'-5' / 3'-5' phosphodiester linkage in a natural nucleic acid, but this unusual linkage is also responsible for the more potent effect of DNA-dependent cGAMP on its receptor STING.

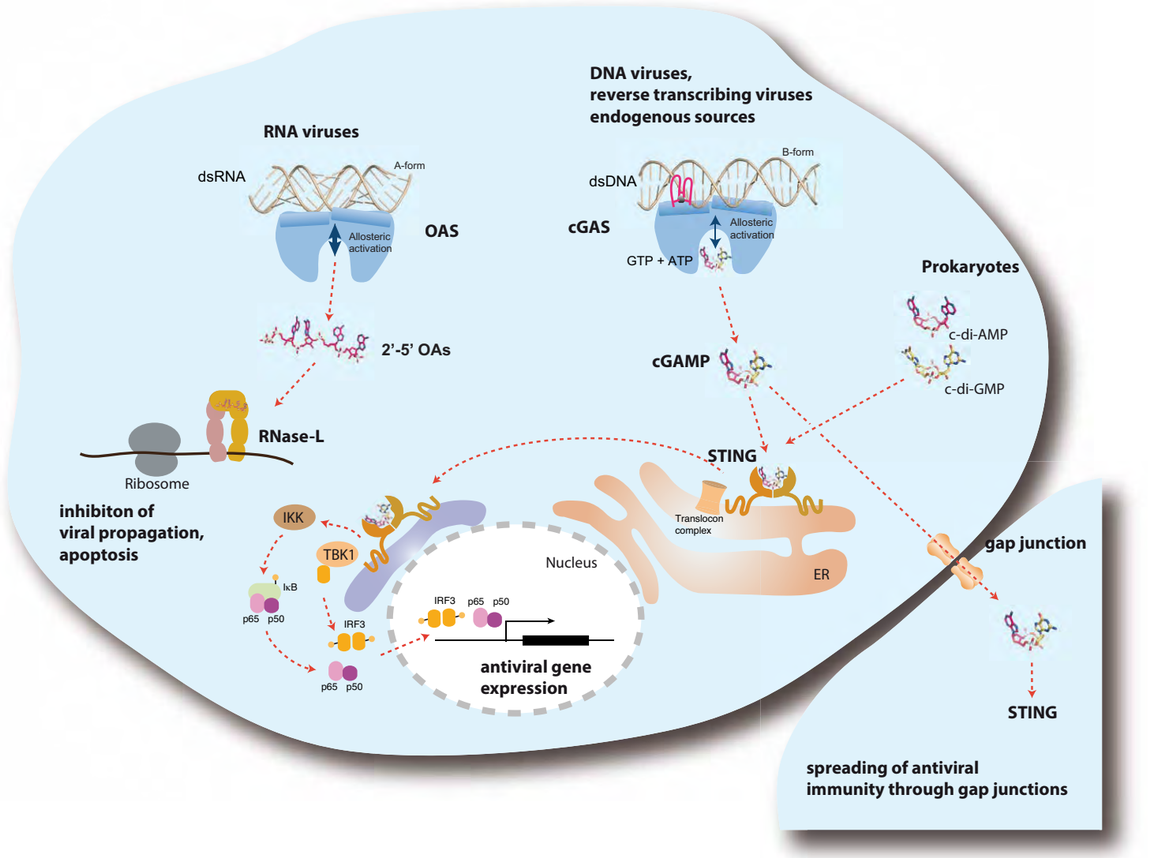

Figure 2 Schematic view of the OAS-RNase L pathway and the cGAS-STING axis. Upon recognition of double-stranded A-form RNA, OAS produces 2'-5' linked oligoadenylates (2'-5' OAs) that in turn bind and activate the latent endoribonuclease RNase L. Activated RNase L then degrades cellular RNAs and possibly also viral RNAs to induce cell death and to inhibit viral propagation. cGAS detects double-stranded DNA of the B-form configuration and subsequently produces the second messenger molecule cGAMP(2'-5') using ATP and GTP as substrates. cGAMP(2'-5') binds to and activates the ER-resident receptor STING, which results in its translocation to a perinuclear compartment where it achieves its signaling-competent state. This in turn results in the activation of antiviral and pro-inflammatory transcription factors that initiate antiviral gene expression. Next to its role in sensing the endogenous, cGAS-derived cyclic dinucleotide cGAMP(2'-5'), STING also functions as a PRR for exogenous, prokaryotic cyclic dinucleotides. Beyond its role in initiating a cell-intrinsic antiviral response, cGAMP(2'-5') can also diffuse to neighboring cells in a gap-junction dependent manner..

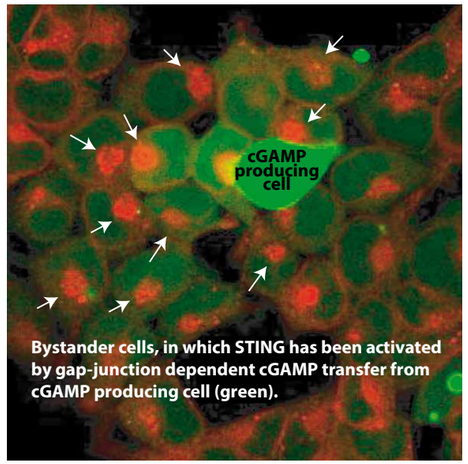

Figure 3 Microscopic image of a cGAMP-producing HEK cell loaded with calcein (bright green) co-cultured with HEK STING cells (red). Highlighted are bystander cells, in which STING has been activated (white arrows) by gap-junction dependent transfer of cGAMP(2'-5').

DNA Sensing and Oxidative Damage

Further studies in structural biology could also show that cGAS displays a striking resemblance to oligoadenylate synthetases (OAS). This enzyme family is activated by double-stranded RNA and produces oligoadenylates, short chains of 2'-5' linked adenosine monophosphates. These oligoadenylates then activate RNase L, an effector enzyme of the anti-viral immune response, which degrades viral RNA when activated. These discoveries demonstrate intriguing parallels in the innate immune response to intracellular nucleic acids: double-stranded nucleic acids activate enzymes with polymerase activity that produce 2'-5' second messengers and then initiate a very specific antiviral immune response (Figure 2).

A Neighborhood Watch Against Viruses

One distinctive feature of the cGAS-cGAMP-STING signaling pathway is the fact that the second messenger cGAMP can only be produced by cGAS and most likely uniquely serves as a ligand for STING. This lack of "signaling promiscuity" is rather unusual. Most second messengers are generated downstream from many different input signals, and they are themselves usually upstream of several signaling pathways.

However, the team of Veit Hornung was able to find a mechanism which offers a plausible explanation for this unusually strict signaling pathway (Ablasser et al., 2013b). Upon examining the activation of STING at a single-cell level, the researchers discovered that not only the cells with a direct cGAS activation showed STING-induced antiviral activity but also their neighbors. In other words, the activation of the cGAS-STING signaling pathway was not restricted to the one cell where cGAS had been activated, but rather the activation was "propagated" to neighboring cells in the tissue. In further studies, it could be show that this local activation was communicated by the transfer of cGAMP through small intercellular canals known as gap junctions. This newly discovered mechanism allows the host to directly and rapidly warn neighboring cells about a viral threat without waiting for cytokine production and release. This crucial time advantage allows for the more efficient containment of a viral infection (Figure 3).

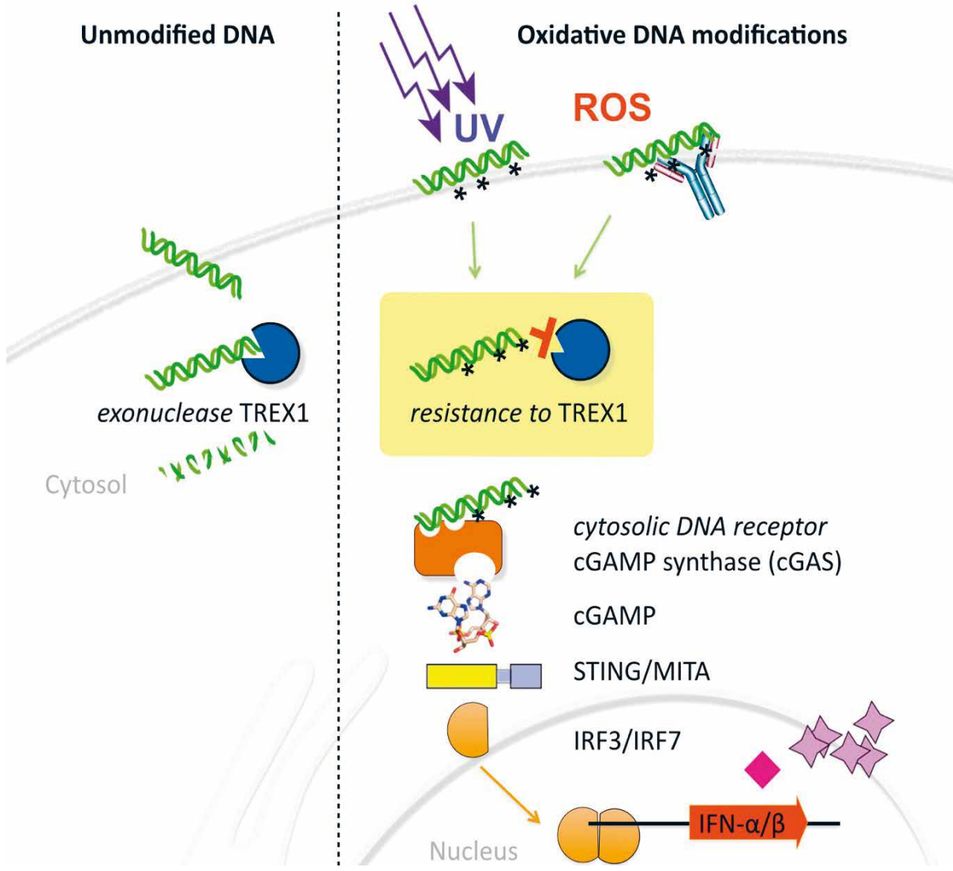

Figure 4 Oxidative damage of DNA confers resistance to TREX1 degradation and potentiates cGAS/STING dependent immune sensing Upon entering the cytosol, DNA is degraded by exonuclease TREX1, which limits potential immune activation (left panel). However, DNA that has incurred oxidative modifications e.g. as a consequence of UV damage or ROS exposure becomes largely resistant to TREX1 mediated degradation. Accumulating oxidized DNA engages the cytosolic DNA receptor cGAS, which via the second messenger 2',3'-cGAMP activates the STING dependent signaling cascade. STING signaling via TBK1 and IRF3/7 eventually leads to the secretion of type I IFN and other pro-inflammatory cytokines (right panel). This mechanism provides a potential explanation for UV-light induced phototoxicity prevalent in autoimmune lupus erythematosus (LE), and suggests that oxidative modifications of self DNA may act as trigger for the induction of LE skin lesions.

Oxidatively Damaged DNA Sounds an even Louder Alarm

DNA in the cytosol and outside of the nucleus is usually degraded rather rapidly by a variety of DNAses. Thus, unmodified DNA is a relatively weak stimulus for the cGAS-STING signaling pathway, and unphysiologically high concentrations of DNA are necessary to investigate the cGAS-STING pathway in vitro. The group of Hartmann/Barchet has discovered that oxidatively damaged DNA is a much more potent activator of the cGAS pathway than unmodified DNA (Gehrke et al., 2013). This oxidative damage can occur in physiological conditions via contact with UV-radiation from the sun or oxygen radicals after the activation of immune cells.

One important modification to DNA in an oxidative environment is the presence of 8-hydroxyguanosine. The researchers could show that this modification does not change its binding to cGAS but rather inhibits its eventual degradation via the cytosolic DNAse TREX1. This reduced degradation leads to an accumulation of oxidized DNA in the cytosol and thus a heightened activation of the cGAS pathway (Figure 4).

This mechanism has important consequences for our understanding of both physiological immune sensing and pathological autoinflammation. The group of Hartmann/Barchet could show that exposure to UV-irradiation leads to the presence of oxidized DNA in the skin of patients with cutaneous lupus erythematosus and that the ensuing inflammation contributes to the disease pathology. Moreover, they demonstrated that bacterial and viral DNA could be better identified if the DNA had been previously exposed to an oxidative environment, such as reactive oxygen species produced by immune cells.

Thus, the researchers were able to identify an important novel criterion that allows our immune system to distinguish endogenous and foreign DNA. Situations that lead to misidentification of endogenous DNA, such as the oxidative damage to DNA in lupus patients, lead inevitably to unnecessary inflammation and eventually to inflammatory disease.

Thus, DNA sensing was a central theme of several important research projects and a core research area of the ImmunoSensation Cluster of Excellence. In 2013, our researchers were able to make discoveries in this field which were both clinically relevant and groundbreaking on international level.

Reference Publications 2013

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Gao P., Ascano M., Zillinger T., Wang W., Dai P., Serganov A.A., Gaffney B.L., Shuman S., Jones R.A., Deng L., Hartmann G., Barchet W., Tuschl T., Patel D.J. Structure-Function Analysis of STING Activation by c[G(2‘,5‘)pA(3‘,5‘)p] and Targeting by Antiviral DMXAA. **Cell**. 154(4):748-62. 2013a.

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Gehrke N., Mertens C., Zillinger T., Wenzel J., Bald T., Zahn S., Tüting T., Hartmann G., Barchet W. Oxidative Damage of DNA Confers Resistance to Cytosolic Nuclease TREX1 Degradation and Potentiates STING-Dependent Immune Sensing. **Immunity**. 39(3):482-95. 2013.

Picture
Dr. Andrea Ablasser

Picture (f.l.t.r.)
Dr. Winfried Barchet, Prof. Gunther Hartmann, Prof. Veit Hornung, Thomas Zillinger

Local Immune Regulation in Tissues

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Introduction
Local Context Sensing

Immune cells located in peripheral organs are exposed to microenvironmental signals from neighboring non-immune cells, which may dramatically alter recruitment and mobility of immune cells, their ability to elicit an immune response and its quality. Our aim is to better understand how local particularities are integrated by the immune system when it decides which effector mechanisms are to be activated. This knowledge is critical for designing locally targeted immunotherapies that cause less adverse effects in other organs.

Migration of immune cells is guided by localized expression of chemoattractants and cell adhesion molecules. The expression of these immune regulators varies enormously between the different tissues of our body. Dendritic cells (DC) are attracted to peripheral organs through the action of chemokines and cell adhesion molecules. Upon activation through PRR ligands, dendritic cells change their chemokine receptor expression to follow different chemokine gradients in order to move to local draining lymph nodes and induce an appropriate immune response. The Kurts group discovered an unusually high number of dendritic cells in the cortex of the kidney, which were recruited through the local expression of the chemokine CX_3CL1 (fractalkine) by the kidney stroma. Immigration of dendritic cells into the kidney but not other organs was dependent on expression of the CX_3CR1 chemokine receptor. Blockade of CX_3CR1-dependent chemokine responsiveness selectively depleted dendritic cells in the kidney cortex and protected mice from development of glomerulonephritis (see article by Hochheiser et al., 2013). In addition, the group of I. Förster in cooperation with J.L. Schultze discovered a novel IFN-γ dependent pathway which regulates production of the chemokine CCL17 by dendritic cells differentially in the spleen versus the lymph nodes. Whereas organ-resident splenic dendritic cells were susceptible to IFN-γ dependent suppression of CCL17 expression, migratory dendritic cells in the lymph nodes specifically downregulated the IFN-γ receptor and expressed much larger amounts of CCL17, a chemokine which promotes T cell-dendritic cell interactions and inflammation (see Globisch et al., 2014).

The liver constantly receives immunostimulatory signals from the gut through microbial components or food constituents and plays an important role in detoxification of low molecular weight chemicals. To avoid unwanted overshooting immune responses in the liver, this organ has developed an immunosuppressive microenvironment, which is of major importance for induction of immunologic tolerance. On the other hand, in the case of acute or chronic viral infection of the liver, local expansion of virus-specific cytotoxic T cells is highly desirable, also in the liver. P. Knolle and coworkers made the striking observation that cytotoxic T cells were able to proliferate in microanatomical niches formed within the liver by TLR-activated intrahepatic myeloid-cell aggregates, so called iMATEs (Huang et al., 2013).

Regulation of immune responses through communication between immune and non-immune cell types also plays an important role in neuro-immune interactions. The group of N. Novak in the Department of Dermatology and Allergy now discovered that neurotrophins released by sensory neurons are able to stimulate the proliferation and migration of mast cells,

which in turn are able to produce neurotrophins themselves.
A dysregulation of this circuit appears to be responsible for a hereditary disease called mastocytosis, which leads to the abnormal accumulation of mast cells in the skin or gastrointestinal tract (Peng et al., 2013).
More detailed summaries of the main findings reported in the four selected key publications in 2013 are given below.

Organ-specific Cytokine Responsiveness and Expression of the Chemokine CCL17
(by Irmgard Förster)

Dendritic cells are important sentinels of the immune system and direct the quality and strength of adaptive immune responses in an organ-specific manner. The Förster group has characterized a subset of dendritic cells that produces the inflammatory chemokine CCL17, a ligand of the chemokine receptor CCR4. CCL17 not only mediates the attraction of activated T cells to antigen-presenting dendritic cells but also positively influences the migration of dendritic cells themselves. Using various mouse models, it has been shown previously that CCL17 promotes the pathogenesis of several allergic and inflammatory diseases, such as atopic dermatitis, inflammatory bowel disease, and atherosclerosis. However, CCL17 has also been shown to enhance cross-presentation of exogenous antigens by CD8-positive splenic dendritic cells and thereby may support anti-microbial or anti-viral immune responses.

Interestingly, the expression of CCL17 by dendritic cells is strongly influenced by the local tissue context. In the steady state, organ-resident splenic DC generally fail to express CCL17, whereas migratory, CD103-positive dendritic cells in lymph nodes are strong CCL17 producers.
In barrier organs, such as the skin or intestinal mucosa, CCL17 expression is induced by Toll-like receptor stimulation or allergic sensitization, even though the same stimuli do not induce CCL17 expression in the spleen. The only stimulus known so far to be able to induce CCL17 in the spleen is systemic CD1d-dependent NKT cell activation by glycolipid antigens, e.g. α-galactosylceramide (αGalCer). In collaboration with the group of J.L. Schultze, we performed global gene expression analysis to further explore the differential, organ-specific expression of CCL17. For this purpose, CCL17-negative dendritic cells from the spleen and CCL17-expressing dendritic cells from lymph nodes were purified by fluorescent cell sorting and characterized by global mRNA expression analysis. This analysis revealed a striking differential expression of IFN-γ inducible genes as well as the IFN-γ receptor (IFN-γR) itself, which were strongly downregulated in the lymph node compared with splenic dendritic cells, indicating the cytokine IFN-γ may be responsible for suppression of CCL17-expression in the spleen. To test this hypothesis, CCL17 reporter mice expressing the green fluorescent protein under control of the CCL17 promoter were bred with IFN-γR-deficient mice, rendering all dendritic cells insensitive to IFN-γ. Whereas IFN-γR deficiency, as such, did not lead to a major up-regulation of CCL17 expression in the spleen, a large proportion of splenic IFN-γR-deficient DC upregulated CCL17 expression by 50-fold when mice were stimulated with αGalCer. This positive induction of CCL17 was dependent on the cytokines IL-4 and GM-CSF, as shown by the application of IL-4- or GM-CSF-specific neutralizing antibodies as well as the analysis of GM-CSF-deficient mice. In contrast, absence of the type I IFN receptor did not impact on the level of CCL17 expression. Thus, dendritic cells locally regulate production of CCL17 through differential expression of the IFN-γR.

As splenic dendritic cells are organ-resident and may develop from local precursor cells, it is possible that the differential expression of the IFN-γR is determined by developmental differences between organ-resident and migratory dendritic cells. Alternatively, the local microenvironment of the spleen versus lymph node may regulate organ-specific gene expression programs. Obviously, the spleen as a filter of systemic blood borne antigens may have different requirements for initiation and control of immune responses than peripheral organs and their local draining lymph nodes.

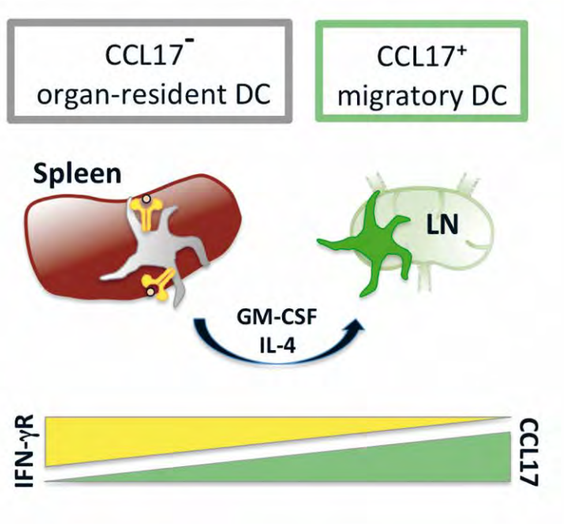

Figure Differential expression of the IFN-γR on splenic versus lymph node dendritic cells. IFN-γ mediates suppression of CCL17 expression in the spleen, whereas GM-CSF and IL-4 lead to upregulation of CCL17 expression, in particular in the absence of IFN-γR signaling.

Reference Publication 2013

Globisch T., Steiner N., Fülle L., Lukacs-Kornek V., Degrandi D., Dresing P., Alferink J., Lang R., Pfeffer K., Beyer M. Weighardt H., **Kurts C.**, Ulas T., **Schultze J.L.** and **Förster I.** Cytokine-dependent regulation of denditic cell differentiation in the splenic microenvironment. **Eur. J. Immunol.** 44, 500-510, 2014. Epub 2013 Dec 12.

Local Regulation of T Cell Immunity in the Liver
(by Percy Knolle)

The liver is constantly exposed to bacterial degradation products derived from the gastrointestinal tract. The Knolle group has characterized the consequences of TLR-signaling locally in the liver. It is well known that the liver contains many cell populations that provide strong innate immunity since they are equipped with immune sensory receptors. Moreover, since the liver harbors scavenger cell populations such as Liver Sinusoidal Endothelial Cells and Kupffer cells, these cell populations have a prominent role in eliminating pathogen-associated molecular patterns from the circulation, and, at the same time, they can mount potent innate immunity triggering local inflammation.

The Knolle group made the unexpected discovery that uptake of agonistic ligands for TLR4 and TLR9 in the liver and local inflammation in the liver both lead to a

dramatic expansion of CD8 T cells locally in the liver. TLR-ligands did not act on T cells directly to facilitate this enormous local expansion but instead facilitated the recruitment of myeloid cells to the liver. Comprehensive phenotypic analysis revealed that inflammatory monocytes were recruited to liver sinusoids and differentiated into inflammatory dendritic cells under the influence of continuous TLR-signaling. Interestingly, myeloid cells accumulated in cocoon-like structures that formed within 24 hrs of TLR signaling and disappeared again after 6 to 8 days. T cells migrated into these structures and proliferated locally. Since T cells did not proliferate elsewhere in liver tissue but only in these structures formed by myeloid cells, we termed them iMATE for intrahepatic myeloid cell aggregates associated with T cell expansion.

iMATEs were not only formed in response to application of TLR-ligands but were also observed during viral infection of the liver by RNA or by DNA viruses indicating that iMATE formation is a physiological response to viral infection. Importantly, prevention of iMATE formation by elimination of inflammatory monocytes also abrogates protective T cell immunity against viral infection suggesting that T cell expansion within iMATE is an important part anti-viral immunity. Since, during chronic viral infection of the liver, no iMATEs are observed, we reasoned that therapeutic iMATE induction by TLR9-L application might overcome chronic infection. Indeed, in combination with adoptive cell therapy or DNA vaccination, the induction of iMATE formation suffices to control and eradicate chronic viral infection. Thus, hepatic immune sensing has an important role for adaptive immunity by promoting strong proliferation of T cells outside of lymphoid tissues.

Reference Publication 2013

Huang L.R., Wohlleber D., Reisinger F., Jenne C.N., Cheng R.L., Abdullah Z., Schildberg F.A., Odenthal M., Dienes H.P., van Rooijen N., Schmitt E., **Garbi N.**, Croft M., **Kurts C.**, Kubes P., Protzer U., Heikenwalder M., **Knolle P.A.** Intrahepatic myeloid-cell aggregates enable local proliferation of CD8(+) T cells and successful immunotherapy against chronic viral liver infection. **Nat Immunol.**, 14(6): 574-583, 2013.

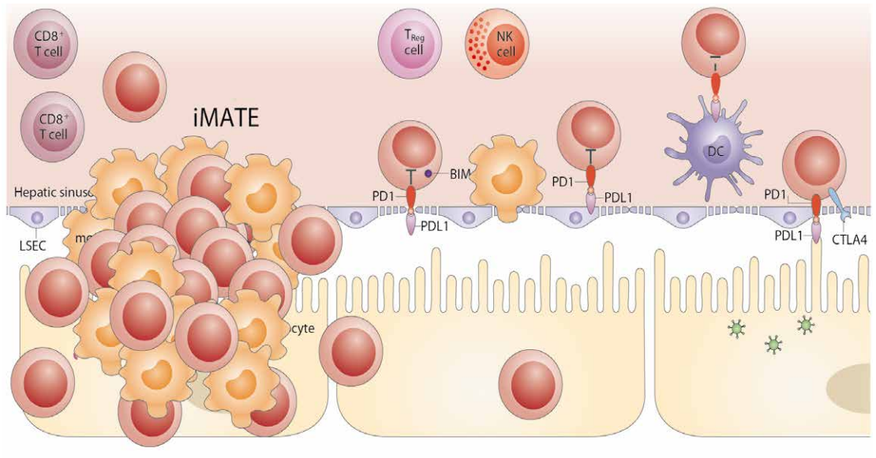

Figure Accumulation of inflammatory monocytes locally within the liver leads to formation of iMATEs that serve as expansion hub for activated CD8 T cells.

Exclusive CX3CR1 Dependence of Kidney DCs Impacts Glomerulonephritis Progression (by Christian Kurts)

As many as 4 million people in Germany suffer from chronic kidney disease (CKD), and its incidence is on the rise. For many patients, CKD eventually leads to kidney failure and the need for external blood filtration, known as dialysis. However, this treatment is not only extremely expensive but also reduces the life expectancy and the quality of life of patients. Currently, the only alternative to dialysis available is kidney transplantation, which requires major surgery followed by lifelong immunosuppression and, thus, carries its own risks.

CKD is often the result of a misguided autoimmune response directed at the basic filtration unit of the kidney and known as glomerulonephritis (GN). However, CKD can also result from other underlying conditions, such as diabetes mellitus and high blood pressure. Nonetheless, even if diabetes and hypertension are not primary autoimmune diseases, the immune system still plays an important role in their pathology in that it induces chronic inflammation and thus promotes the destruction of the renal parenchyma and its replacement with scar tissue.

In their previous work (Hochheiser et al., 2011), the Kurts group was able to show that dendritic cells (DCs) play a central role in the development of kidney disease. DCs are the “sentinels” of the immune system that collect and process antigens in the body and then present them to T cells in the lymph nodes. In addition, tissue resident DCs in the kidney and other organs modulate local immune responses via the regulation of infiltrating T-cells (Heymann et al., 2009; Riedel et al., 2012; Wakim et al., 2008).

The Kidney Depends on Fractalkine to Recruit Dendritic Cells

Recently, the Kurts group discovered that DCs depend on a particular chemokine receptor, known as the fractalkine receptor, or CX3CR1, in order to infiltrate the kidney. Even though DCs are present in virtually every organ, this dependence on CX3CR1 is specific to the kidneys, where it has a dramatic influence on DC influx. In mice deficient in CX3CR1, the number of DCs in the kidney is reduced by 75% while other organs in the body remain unaffected. Since DCs in other organs also express CX3CR1, this finding was initially quite surprising. However, further analysis revealed that the kidney expresses exceptionally high levels of CX3CL, the ligand of CX3CR1. CX3CL levels are higher in the kidney than in any other organ with the exception of the small intestine. This expression of CX3CL promotes the infiltration of the kidney with DCs and could explain the extraordinarily high number of DCs found in this organ.

In collaboration with the Institut national de la santé et de la recherche médicale (Inserm) in Paris and the University Hospital Eppendorf in Hamburg, Kurts and his group could show that CX3CR1-deficient mice were largely protected from crescentic GN in their model. Crescentic GN, also known as rapidly progressive GN, is a type of GN characterized histopathologically by the presence of cellular crescents and clinically by its rash progression and loss of renal function. This form of GN can develop idiopathically, i.e. without a known underlying cause, or as a clinical manifestation of several different autoimmune diseases, including systemic lupus erythematodes and Goodpasture syndrome. Thus, if an inhibitor of CX-3CR1 could be used to selectively reduce the number of DCs in the kidney without affecting other organs, such a therapy would not only be promising for the treatment of GN but also for many other systemic diseases that also affect the kidney.

A New Approach to Treatment

The striking selectivity of CX3CR1 dependence to the kidney makes this therapeutic approach particularly promising. Conventional immunosuppressive therapy for autoimmune GN and other autoimmune diseases brings unwanted systemic effects including a reduction of the general immune competence of the patient. The kidney itself can also be prone to infection under immunosuppressive treatment, in particular to a bacterial infection of the renal pelvis, known as pyelonephritis. As shown by previous work from the Kurts group (Tittel et al., 2011), DCs play a central role in combatting pyelonephritis. Thus, despite the lack of systemic effects, one potential problem with CX3CR1 inhibition could still be a potentially increased risk for kidney infections. However, Kurts and his group were able to show that the inhibition of CX3CR1 does not diminish the ability of the immune system to combat pyelonephritis. This surprising finding is due to a fortunate anatomic detail: the DCs that depend on CX3CR1 are predominantly found in the renal cortex, the site of the glomeruli and thus GN, and not in the renal pelvis, where pyelonephritis occurs.

Initial epidemiological studies indicate that these processes are conserved in humans, meaning that CX3CR1 is extremely promising as a potential target for GN therapy in human patients. Clinical studies are now needed to verify the role of CX3CR1 in human patients and hopefully translate this finding from the bench to the bedside.

Reference Publication 2013

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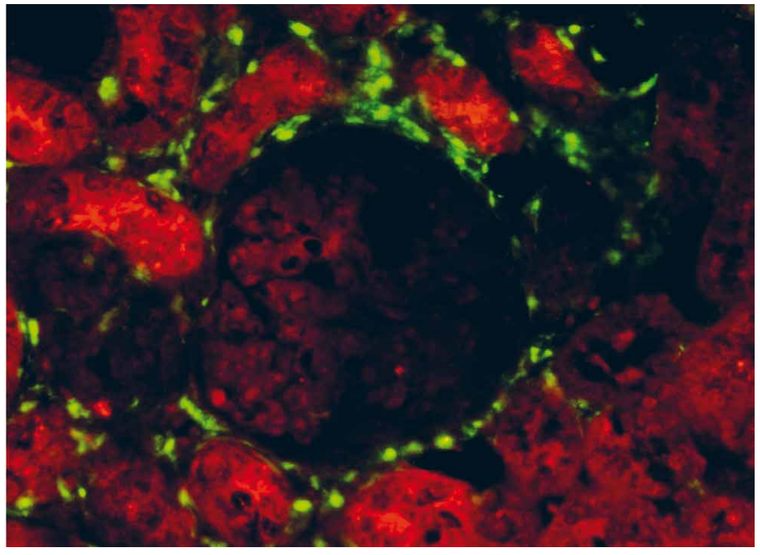
Figure A renal corpuscle from a kidney with glomerulonephritis: the Bowman's capsule and glomerulus (both red) are surrounded by dendritic cells (green).



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Local regulation of mast cell migration and activation in the skin and gut by neurotrophins in mastocytosis (by Natalija Novak)

Mastocytosis is characterized by a rapid mobilization of mast cells through exogenous and endogenous stimuli (Pardanani, 2012). Here, signals mediated by the neuro-immunologic network play an important role. Both activation as well as recruitment and migration of mast cells from the bone marrow via the blood to the peripheral organs are directed by soluble mediators and corresponding surface receptors. Neurotrophins are growth factors that were initially discovered in the nervous system and contribute to the development, maintenance and regeneration of nerve fibers (Arevalo and Wu, 2006). They include nerve-growth factor (NG-F)-β, brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3 and -4 (A). NTs promote the chemotaxis, maturation and survival of MCs (Tam et al., 1997). NT-expressing nerves are in close contact with mast cells, and mast cells, themselves, are also capable of producing NTs (Bruni et al., 1982; Groneberg et al., 2005; Nilsson et al., 1997; Peters et al., 2007; Quarcoo et al., 2009). This bidirectional interaction of NTs and mast cells suggests a contribution by NTs to diseases such as mastocytosis.

The three tropomyosin-related kinases, tropomyosin-related kinase A (TrkA), B (TrkB) and C (TrkC) are all high-affinity neurotrophin receptors. TrkA is a receptor for NGF-β; TrkB is a receptor for BDNF and NT-4, and TrkC is a receptor for NT-3. In this context, we were able to report for the first time the expression of TrkA, TrkB and TrkC on human skin mast cells (SMCs) as well as their increased expression on human SMCs of patients with mastocytosis. In addition, we observed that the intestinal mast cells of patients with mastocytosis expressed TrkA and TrkC but not TrkB.

We also investigated the expression of Trk isoforms in controls and mastocytosis patients. Full-length TrkA was not found on human SMCs. Only the exon-lacking TrkA I splice variant was expressed, both on SMCs from controls and from patients with mastocytosis. However, TrkB was expressed in both full-length (FL-TrkB) and truncated (TrKB-T1) isoforms on the

SMCs of both populations (B). Patients with mastocytosis nonetheless displayed differences in their gene expression profile of TrkB on human SMCs when compared with controls (Stoilov et al., 2002). Exons 1- through 4 and a major part of exon 5 encode the conventional 5´untranslated region (UTR) of the human TrkB gene and serve as transcription start sites. We detected a higher expression of the 5´UTR in SMCs of mastocytosis patients. However, SMCs of patients with mastocytosis and controls had the same mRNA expression level of exon 24, which encodes part of the FL-TrkB receptor containing the tyrosine kinase domain (exons 21-24). Although both FL-TrkB and TrKB-T1, the receptor variant without exon 22, were expressed on human SMCs, TrKB-T1-mRNA expression was increased in SMCs of patients with mastocytosis. In addition, SMCs of patients with mastocytosis displayed a higher mRNA expression of extracellular domain of TrkB than controls. Although the full-length isoform of TrkC was not expressed on SMCs of patients with mastocytosis or on control mast cells, a truncated isoform was detected in the SMCs of both populations. Moreover, the expression of this truncated isoform of TrkC was significantly higher on the SMCs of patients with mastocytosis

Local Immune Regulation in Tissues

NTs have been shown to exert chemotactic effects on different cells. In line with these observations, we demonstrated a significantly increased migration of $CD117^+$ mast cell progenitors toward an NGF-β gradient via TrkA, which was expressed by mast cells of the skin and gut, organs which are frequently infiltrated by mast cells in mastocytosis.

In addition, we could show for the first time higher circulating levels of NGF-β, NT-3 and NT-4. Together with the increased migration of $CD117^+$ progenitors from the blood toward an NGF-β gradient via TrkA, NTs might contribute to the augmented tissue infiltration by mast cells mediated by NGF-β as well as the stimulation and differentiation of mast cells, mediated by NT-3 and NT-4 (C). As we and others could show that mast cells themselves both represent a source of NTs as well as expressing the respective functional receptors, mast cells might augment these effects in an autocrine fashion.

Altogether, we could provide evidence for a crucial role for NTs in mastocytosis, and we elucidated a sophisticated network allowing communication between mast cell progenitors in the blood, mast cells in the skin and gut as well as soluble mediators of the nervous system. Further know-ledge about mechanisms promoting mast cell infiltration will help to identify structures which might be targeted in therapeutic approaches to prevent unwanted tissue infiltration by mast cells and mast cell overactivation, in mastocytosis and in other mast cell driven diseases, as well.

Reference Publication 2013

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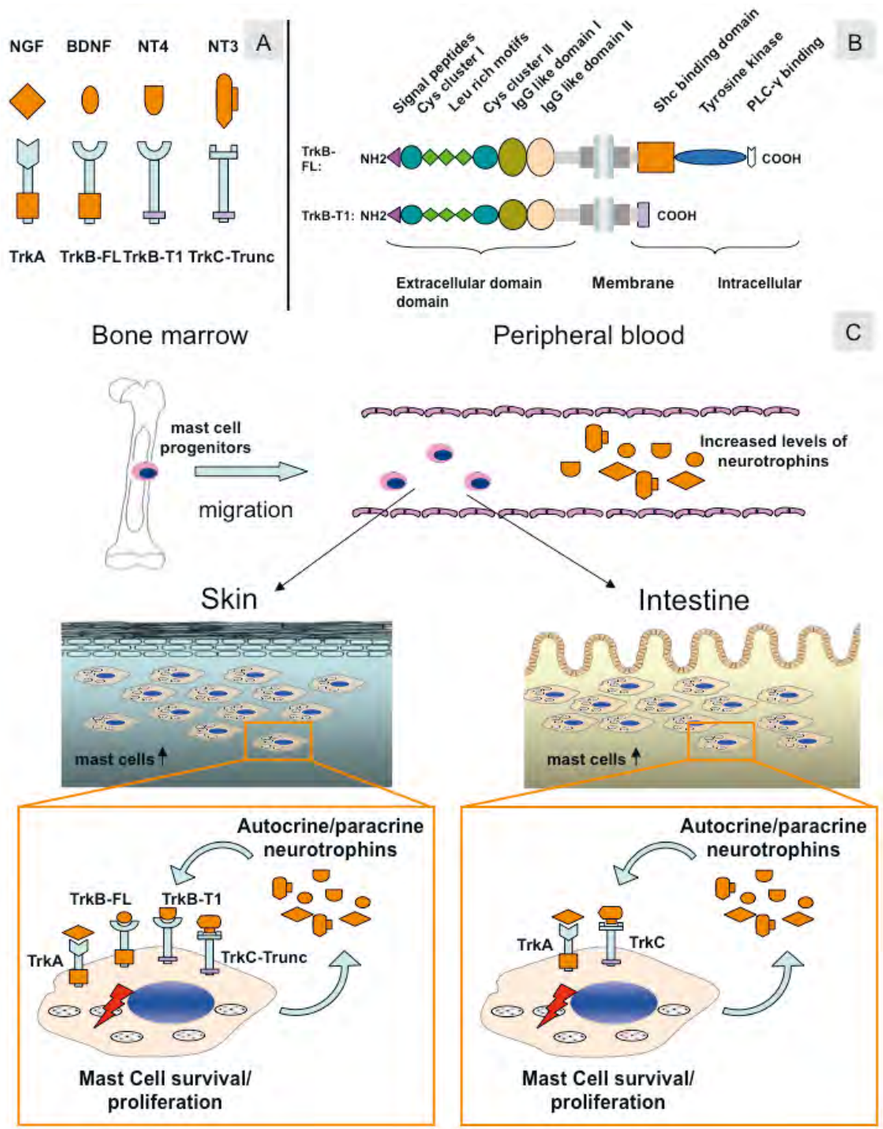

Figure (A): Overview of neurotrophins and respective tropomyosin-related kinase receptors. (B): Schematic drawing of TrKB-FL and TrkB-T1 isoforms expressed by human skin mast cells. (C): Summary of the proposed mast cell – neurotrophin network in mastocytosis.

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Picture (f.l.t.r.)
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Sterile Inflammation in Nervous System and Metabolism

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Sterile Inflammation in Nervous System and Metabolism

One of the crucial functions of the innate immune system is the initiation and execution of the acute inflammatory response. This response is our “first line of defense” against invading pathogens, and it is rapid, powerful, inherently non-specific and incredibly effective. Nonetheless, this incredible effectiveness and efficiency also comes at a cost. The non-specificity of the acute inflammatory response enables the immune system to efficiently recognize new pathogens, yet it also inherently harbors the potential of misidentifying threats and causing inappropriate immune responses. Moreover, the very effectiveness of the acute inflammatory response in killing and eliminating pathogens also makes it an intrinsically destructive force. Reactive oxygen species, porines, metalloproteases, etc. are not only highly effective means of targeting invading pathogens, but they also destroy host cells and scar parenchymal tissue.

In sterile inflammation, or inflammation in the absence of an infectious, microbial trigger, this destruction more often drives the pathology of the disease than curing it. There are a plethora of sterile stimuli that cause inflammation: crystals such as monosodium urate or cholesterol, ischemia, other types of cellular damage, aluminum salts, oxidized

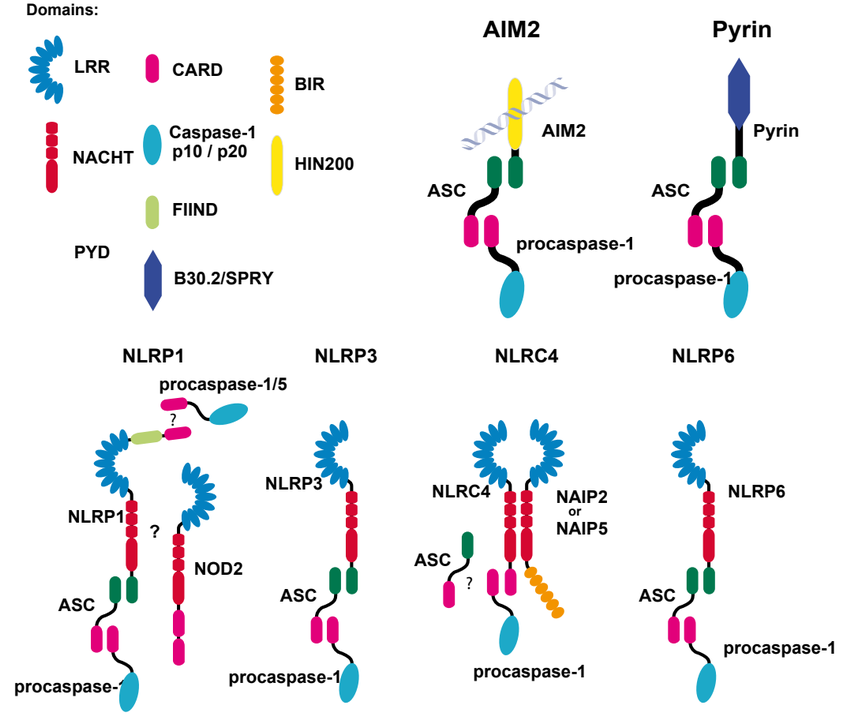

Figure 1 Inflammasome proteins. Pictured are several different multimeric protein complexes formed via homotypic domain interactions, e.g. Pyrin-Pyrin or CARD-CARD. All of the inflammasomes can binding and activate of procaspase-1 via CARD-CARD interaction.

DNA. Since these stimuli often do not pose an inherent threat, the inflammation and ensuing destruction is often "for naught". If intentionally applied in a limited quantity as an adjuvant, sterile inflammatory stimuli can be used to purposefully boost the adaptive response. However, these stimuli in larger quantities are rarely "cleared" by the immune system and are often the result of continuous processes within the host. Without clearance of the inflammatory trigger, there is also no possibility for the inflammation to resolve.

Sterile Inflammation and the Inflammasome

Many sterile inflammatory stimuli induce the release of the pro-inflammatory cytokines IL-1a and IL-1b. Activation of the IL-1 receptor, which is expressed on a wide variety of immune and somatic cells, enables the movement (diapedesis) of immune cells to the site of inflammation. It also causes fever, vasodilatation and hyperalgesia, which are responsible for the typical clinical symptoms of inflammation. IL-1b is expressed as an inactive pro-form, pro-IL-1b, which must first be transcriptionally upregulated, e.g. via NF-KB, and then cleaved to achieve bioactivity. This cleavage is closely regulated and requires the formation of the inflammasome, a multiprotein molecular platform. There are different inflammasome complexes that respond to a variety of sterile and infectious stimuli with the activation of caspase-1, which in turn activates IL-1b (Figure 1).

Although several inflammasomes most likely play an important role in sterile inflammation, e.g. AIM2 recognizes cytosolic dsDNA both of endogenous and microbial origin, the NLRP3 inflammasome has been implicated in the greatest number of human pathologies to date. The precise mechanism of NLRP3 activation still remains unknown. However, the NRLP3 inflammasome is downstream of any process that results in potassium efflux, such as bacterial toxins or extracellular ATP via the P2X7 receptor. In addition, it can be activated by a process known as lysosomal destabilization. The lysosome is a digestive compartment in cells. In immune cells such as macrophages, it is where phagocytosed material, whether pathogens or simply debris, is degraded. However, crystalline material as well as the accumulated aggregated proteins associated with several diseases are all "difficult to digest" leading to lysosomal rupture and NLRP3 activation (Table 1 and Figure 2).

Disease	Crystalline or Aggregated NLRP3 Activator
Alzheimer's disease	Amyloid-β*
Asbestosis	Asbestos crystals
Atherosclerosis	Cholesterol crystals*
Gout	Monosodium Urate Crystals (MSU)
Silicosis (Miner's Lung)	Silica crystals*
Type-II Diabetes Mellitus	Islet amyloid polypeptide

* ImmunoSensation Cluster Members have published important research on these mechanisms.
Table 1 Sterile inflammation contributes to the pathology of many diseases. Here, a list of diseases where NLRP3-mediated inflammation is involved and the corresponding NLRP3 stimulus.

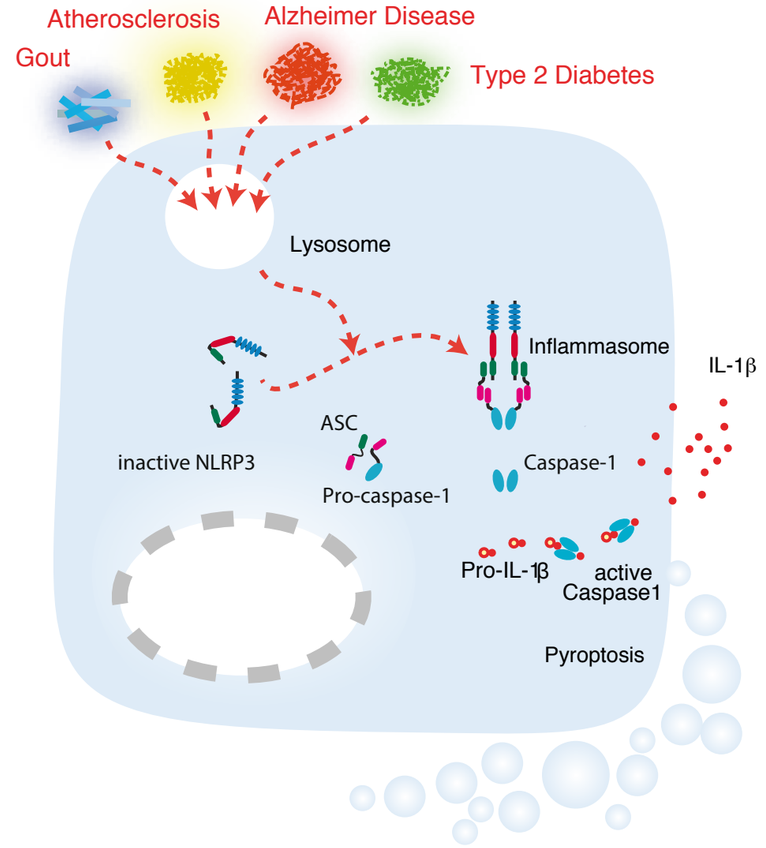

Figure 2 The accumulation of crystalline material is associated with many „lifestyle diseases". Phagocytosis of this material activates NLRP3 via lysosomal destabilization.

In 2013, the list of materials known to initiate sterile inflammation via NLRP3 was expanded to include the Amyloid-B protein found in the senile plaques of Alzheimer's patients. ImmunoSensation members Michael Heneka, Annett Halle and Eicke Latz were not only able to show that Amyloid-β can activate NLRP3 but also that the progression of Alzheimer's disease is NLRP3 dependent. This discovery is of particular clinical relevance since it raises the possibility of the use of pharmacological NLRP3 inhibitors to halt Alzheimer's progression. (For more information, please see page 43 of this chapter.)

Another publication from the ImmunoSensation Cluster focused on developing the tools necessary to execute high-throughput screenings for pharmacological inhibitors. Cluster members Veit Hornung and Eicke Latz have developed a proteolytic luminescent reporter for caspase-1 and IL-1b activation, allowing the measurement of inflammasome activation in high-throughput. Currently, both scientists are screening for new

TLR	Known Ligands	Immune Response
TLR1:TLR2 heterodimer	Lipomannans (mycobacteria) Lipoproteins	Pro-inflammatory cytokines (e.g. proIL-1, IL-6, TNFa, IL-8, IL-12)
TLR1:TLR6 heterodimer	Lipoteichoic acids (Gram-positive bacteria) Cell-wall B-glucans (bacteria and fungi) Zymosan (fungi)	
TLR3	Double-stranded RNA (viruses)	Pro-inflammatory cytokines, Type-I interferon
TLR4	LPS (Gram-negative bacteria) Lipoteichoic acids (Gram-positive bacteria)	Pro-inflammatory cytokines, Type-I interferon
TLR5	Flagellin (bacteria)	Pro-inflammatory cytokines
TLR7	Single-stranded RNA (viruses)	Pro-inflammatory cytokines, Type-I interferon
TLR8	Single-stranded RNA (viruses)	Pro-inflammatory cytokines, Type-I interferon
TLR9	DNA with unmethylated CpG (bacteria and herpesviruses)	Pro-inflammatory cytokines, Type-I interferon
TLR10	unknown	Pro-inflammatory cytokines

Table 2 Human TLRs, their known ligands and downstream immune response after activation. (Based on Kawai and Akira, 2011.

inflammasome-relevant pharmacological therapies. (For more information, please see page 46 of this chapter.)

Sterile Inflammation and the TLRs

The Toll-Like Receptor (TLR) family is a part of an ancient immune sensory system, which has analogs in insects and plants. All 10 currently known TLRs in humans are thought to each be responsible for the detection of a distinct group of molecules that are not normally found in healthy cells. (See Table 2)

The most important pathways downstream of the TLRs are NF-KB signaling, AP-1 signaling and IRF-dependent type-I interferon production. The production of type-I interferon is essential for the initiation of an anti-viral state in immune and somatic cells and is also downstream of cytosolic DNA sensing (p. 17). NF-KB and AP-1 are responsible for the transcription of pro-inflammatory cytokines. The transcriptional regulation of pro-IL1B and NLRP3 is of particular importance for sterile inflammation in response to crystalline material (see above). However, pro-inflammatory cytokines such as IL-6 are also part of the acute phase reaction and central to sterile and infectious inflammation.

Thus, the mediation of TLR-mediated transcriptional effects is a feasible "switch-point" for controlling inflammation. After stimulating the release of pro-inflammatory cytokines, TLR activation is often accompanied by a second wave of cytokines, lead by IL-10 which downregulates the release of further cytokines. The resolution and endogenous downregulation of TLR-mediated inflammation are currently important fields of research. Understanding the resolution of inflammation would create the possibility for therapeutic approaches that inhibit autoinflammation but still allow adequate host defense.

ImmunoSensation Cluster members Eicke Latz and Joachim Schultze have discovered a novel mechanism of TLR inhibition via High-density Lipoprotein (HDL), commonly known as "good cholesterol". The researchers discovered that HDL upregulates the transcriptional modulator ATF3, which in turn represses the transcription of pro-inflammatory cytokines after TLR activation. Thus, the anti-inflammatory effect of HDL is not only the result of its ability to remove pro-inflammatory cholesterol crystals, but also via a direct stimulation of anti-inflammatory processes. This discovery is not only important for our understanding of sterile inflammation in atherosclerosis but is a promising therapeutic approach for other inflammation-mediated diseases of both infectious and sterile origin.

Reference Publications 2013

Bartok E., Bauernfeind F., Khaminets M.G., Jakobs C., Monks B., Fitzgerald K.A., **Latz E.**, and **Hornung V.** iGluc: a luciferase-based inflammasome and protease activity reporter. **Nat. Methods** 1–10, 2013.

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Heneka M.T., Kummer M.P., Stutz A., Delekate A., Schwartz S., Vieira-Saecker A., Griep A., Axt D., Remus A., Tzeng T.-C., Gelpi E., **Halle A.**, Korte M., **Latz E.**, Golenbock DT. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. **Nature** 493, 674–678, 2012.

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Metabolic Regulation of Immunity by High-density Lipoproteins (HDL)

High-density lipoprotein (HDL) has protective functions in various diseases including atherosclerosis and type II diabetes. HDL is best known for its essential role in reverse cholesterol transport (RCT). During this important process HDL removes excess cholesterol from peripheral cells and transports it to the liver, thus promoting cholesterol excretion into the digestive tract. In addition to its role in RCT, HDL displays remarkable anti-inflammatory properties, which also likely contribute to its protective nature. However, the molecular mechanisms by which HDL can reduce inflammatory responses in immune cells have remained elusive.

Using unbiased genomics approaches and bioinformatics analysis, Dr. Dominic De Nardo and Ms Larisa Labzin from the Latz laboratory, together with the laboratory of Prof. Joachim L. Schultze, have identified how HDL can affect the output of macrophages in response to various inflammatory stimuli, such as Toll-like receptor (TLR) ligands. In a concerted effort involving scientists from Germany, Japan, China, the USA and Australia, we identified the inducible transcriptional modulator, ATF3 as the key factor that mediates HDL's anti-inflammatory activities in macrophages. We could show that incubation of macrophages with HDL results in an upregulation of ATF3, which then acts to repress the transcription of key inflammatory cytokines, including IL-6, IL-12p40 or TNF.

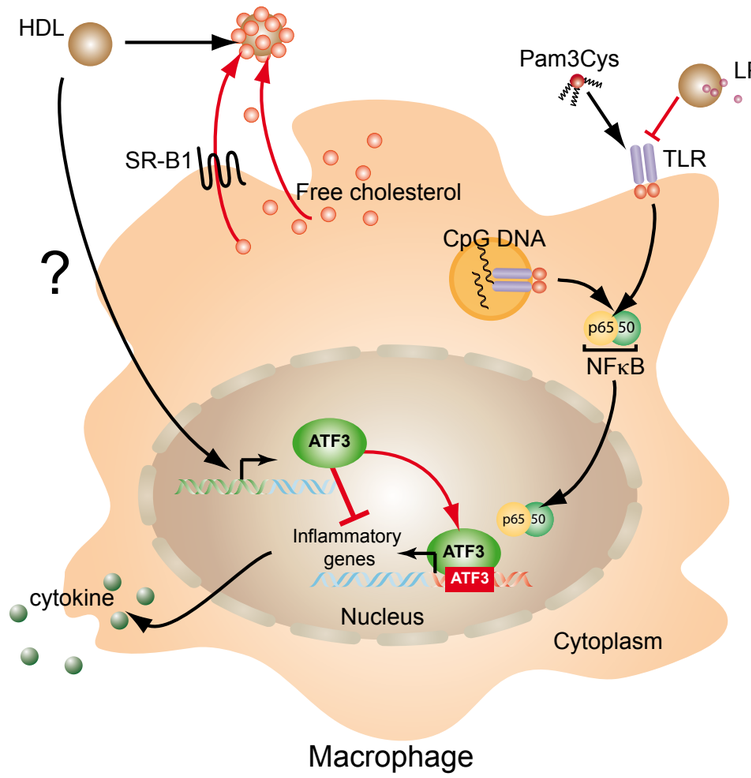

Figure HDL treatment of macrophages does not affect TLR-induced signaling, but rather induces the expression of the transcriptional modulator, ATF3, which then acts to directly inhibit the gene expression of numerous pro-inflammatory cytokines.

These studies have great relevance for the pharmaceutical industry as current efforts focus on the development of HDL-based therapies for the treatment of inflammatory diseases, particularly atherosclerosis. For example, successful in vivo treatment could potentially be evaluated by measuring the induction of ATF3 in blood cells of patients.

Reference Publication 2013

De Nardo D.*, Labzin L.I.*, Kono H., Seki R., Schmidt S.V., Beyer M., Xu D., Zimmer S., Lahrmann C., Schilberg F.A., Vogelhuber J., Kraut M., Ulas T., Kerksiek A., Krebs W., Bode N., Grebe A., Fitzgerald M.L., Hernandez N.J., Williams B., **Knolle P.A.**, Kneiling M., Rocken M., Lutjohann D., Wright S.D., **Schultze J.L.*, Latz E.***. HDL mediates anti-inflammatory transcriptional reprogramming of macrophages via ATF3. **Nature immunology**, 2014 15(2), 152-160, 2014. Epub 2013 Dec 8.

*equal contribution

Picture (f.l.t.r.)
Larisa Labzin, Prof. Eicke Latz and Dr. Dominik De Nardo from the Institute of Innate Immunity

NLRP3 is Activated in Alzheimer's Disease and Contributes to Pathology in APP/PS1 Mice

Alzheimer's disease is the most common cause of dementia worldwide. Moreover, as our life expectancy increases, the prevalence of this disease is only expected to rise further. Although much is known about the clinical symptoms and histopathological findings associated with Alzheimer's, little is known about the molecular mechanisms determining the disease's development.
Three members of the ImmunoSensation Cluster of Excellence, Prof. Eicke Latz (page 159), Prof. Michael Heneka (page 148) and Dr. Annett Halle (page 146), have approached Alzheimer's disease research from an interdisciplinary perspective and discovered that sterile inflammation is of central importance to

its pathogenesis. As they have discovered, Alzheimer's is not only a neurological disease but also an immunological one, as well.

β-Amyloid Causes Sterile Inflammation

One of the most prominent histopathological findings in Alzheimer's disease is the accumulation of the β-amyloid peptide in senile plaques in the brain parenchyma. However, it is less clear how these senile plaques actually cause brain damage. In their previous work, Annett Halle, a neurologist by training, and Eicke Latz, an immunologist, discovered that β-amyloid peptide can in fact provoke an inflammatory response in vitro from immune cells known as microglia.

These cells are the resident macrophages of the central nervous system. As phagocytes, microglia engulf debris and pathogens, including the β-amyloid aggregates found in senile plaques. Ideally, phagocytosis should lead to the removal of extracellular debris by delivering the engulfed material into a specific intracellular compartment, known as the lysosome, where they are digested. However, as Halle and Latz discovered, in the case of aggregated β-amyloid the cells are unable to fully digest this substrate. The incomplete removal of aggregated β-amyloid results in a destruction of the lysosomal compartiment. This in turn results in a leaking of lysosomal acidic content into the cytoplasm. Some of the released proteins represent potent danger signals causing the activation of an intracellular inflammatory pathway, the NLRP3-inflammasome. (For more information on the inflammasome, please see the introduction to Sterile Inflammation page 37.)

NLRP3 and Caspase-1 Activation in vivo

Up to now it has remained unknown whether NLRP3-dependent sterile inflammation by microglia is responsible for the progress of Alzheimer's disease.

Therefore, the team of scientists examined the role of NLRP3 and caspase-1 in a murine model of Alzheimer's disease (APP/PS1 mice). These transgenic mice express mutated versions of the amyloid precursor protein (APP) and presenilin-1 (PS1) which both highly correlate with the early development of Alzheimer's in humans. These modified mice develop senile plaques and show memory loss, cognitive dysfunction and hyperdynamic locomotion at the age of 6 months.

In order to investigate the role the NLRP3/caspase-1 pathway in Alzheimer's disease, NLRP3 and caspase-1 deficiency were each crossed with APP/PS1 mice, respectively. Lack of NLRP3 was sufficient to largely protect mice from memory loss and behavior deficits. In particular, NLRP3-deficient APP/PS1 mice performed as well as wild-type mice in the Morris-water maze test (spatial memory formation) and in the object recognition test.

A priori, these findings could simply be explained via the decreased sterile inflammation found in NLRP3-deficient APP/PS1 mice. However, Michael Heneka and his colleagues also discovered that NLRP3-deficient APP/PS1 mice in fact have less senile plaques than APP/PS1 mice. Upon further investigation, the researchers could show that APP/PS1 mice deficient in NLRP3 or caspase-1 could are in fact better able to phagocytose and dispose of β-amyloid. This may be the result of macrophage polarization or the enhanced survival of NLRP3 or caspase-1 deficient macrophages after contact with β-amyloid. (Activation of NLRP3 normally kills macrophages triggering a special form of cell death known as pyroptosis.)

Caspase-1 Activation in Human Alzheimer's Patients

In order to corroborate these results in human patients the cleavage of caspase-1 in the brain of patients with Alzheimer's disease was also examined. Alzheimer's disease patients exhibited increased cleavage of caspase-1 in their hippocampus and frontal cortex. The hippocampus is responsible for the consolidation of memories and is one of the first regions of the brain to be affected in Alzheimer's disease patients. The frontal cortex is associated with short-term memory, attention, planning, reward and motivation, and it has been shown in several studies that the frontal cortex also undergoes volumetric decline in Alzheimer's disease patients. Thus, these areas of the brain are exactly where one would expect to find Alzheimer-induced inflammation. Since APP/PS1 mice precisely recapitulate these findings, there seems to be a clear association between Alzheimer's disease and sterile inflammation in the brain in humans, as well.

A New Approach to Alzheimer's Therapy

Altogether, these results show a clear association between NLRP3/Caspase-1-induced sterile inflammation and Alzheimer's disease. There are BfArM-approved medications that are known to inhibit NRLP3, and screenings of new compounds is ongoing. Thus, via drug repurposing or discovery, NRLP3 inhibition is a novel and promising approach to ameliorate the symptoms of Alzheimer's disease.

Reference Publication 2013

Heneka M.T., Kummer M.P., Stutz A., Delekate A., Schwartz S., Vieira-Saecker A., Griep A., Axt D., Remus A., Tzeng T.-C., Gelpi E., **Halle A.**, Korte M., **Latz E.**, Golenbock DT. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. **Nature** 493, 674–678, 2013.

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Halle A., **Hornung V.**, Petzold G.C., Stewart C. R., Monks B.G., Reinheckel T. Fitzgerald K.A., **Latz E.**, Moore K.J., Golenbock D.T. The NALP3 inflammasome is involved in the innate immune response to amyloid-β. **Nature Immunology**, 9(8), 857–865, 2008.

Picture
Prof. Michael Heneka

iGluc: a luciferase-based inflammasome and protease activity reporter

The Role of IL-1 and the Inflammasome in Sterile Inflammation

The cytokine IL-1b is the most potent endogenous pyrogen known in mammals. However, it is also one of the most closely regulated. The cytokine itself must be transcriptionally upregulated and undergo proteolysis via caspase-1 and the so-called inflammasome complex before it can bind to its receptors. At the same time organisms are equipped with decoy receptors and receptor antagonists for IL-1b.

Nonetheless, despite this impressive arsenal of regulatory possibilities, IL-1b can still be inappropriately activated in organisms. For example, acute IL-1b release plays a central role in the pathogenesis of sepsis. However, chronic, lower-level activation of IL-1b and also significantly contributes to sterile inflammatory processes found in Alzheimer's, atherosclerosis, diabetes mellitus and gout (see figure 2 on page 39). Needless to say, better understanding both how IL-1b release is regulated and how it can be modulated pharmacologically would make a vital contribution to the development of new treatment strategies for many widespread illnesses.

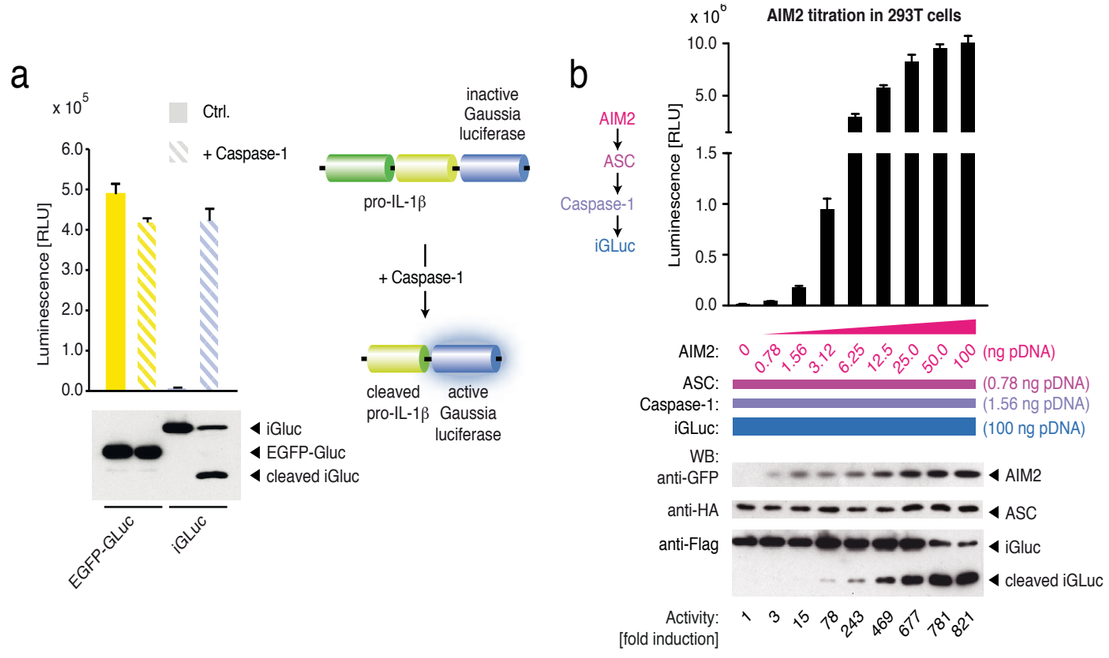


Figure 1 (a) iGluc only exhibits luciferase activity after proteolytic cleavage by caspase-1. (b) iGluc can be used as a readout for inflammasome activation. Aim2 inflammasome reconstitution via transient transfection in 293T HEK cells shown.

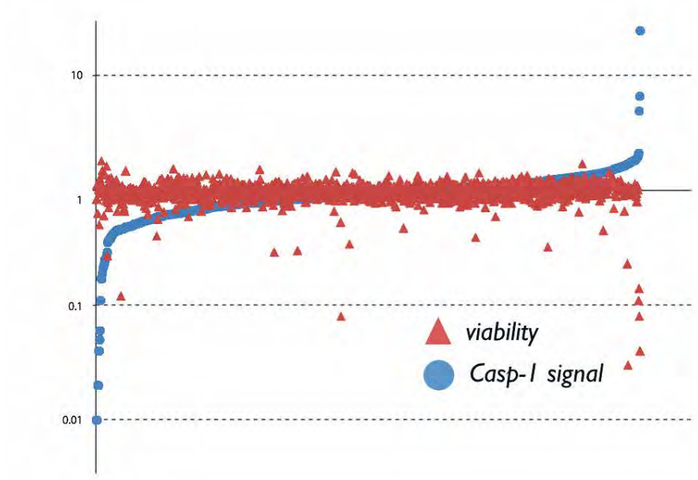


Figure 2 iGluc reporter macrophages screened for inhibitors of NLRP3 activity using the Prestwick commercial library. Approximately 1.5% of compounds demonstrated a significant inhibition of NLRP3 activation.

iGluc as a Sensor for Caspase-1 and Inflammasome Activity

Veit Hornung (page 152) and his lab members Eva Bartok and Franz Bauernfeind, in collaboration with Eicke Latz (page 159) have developed a proteolytic biosensor for activators upstream of IL-1b. The biosensor is based on murine IL-1b fused to a gaussia luciferase construct, known as iGLuc (Figure 1). Surprisingly, the gaussia luciferase in iGluc has little activity when fused to the full-length form of mmIL-1b. However, upon proteolytic cleavage of IL-1b, iGLuc exhibits a robust gaussia signal.

The activation of IL-1b is a complex process involving the formation of a multimeric protein complex known as the inflammasome. This complex activates caspase-1, which in turn cleaves IL-1b. (For more information on the "inflammasome", please see the introduction to this chapter.) However, measuring inflammasome formation is technically challenging, and the current "gold standard" read-out for inflammasome activation, immunoblotting for cleaved caspase-1, is a time-consuming technique.

In contrast, gaussia luciferase activity can be easily read in a luminometer after the addition of its substrate. In addition, the use of luciferases as reporters for transcriptional activity has a well-established methodology for high-throughput screenings (HTS). Thus, there is a clear rationale for the development of a gaussia-based proteolytic assay for inflammasome activation.

To this end, Veit Hornung and his colleagues decided to create a cell-based assay to measure inflammasome activation. Wild-type immortalized murine macrophages and cell lines deficient in inflammasome proteins were transduced to stably express the iGluc reporter. Upon inflammasome stimulation, these cells secrete active iGLuc into the cellular supernatant where they activity can be rapidly measured using a standard luminometer.

Screening the Inflammasome

Thus, it is now possible to screen thousands of novel compounds and clinically-approved medications for inflammasome activation and inhibition. This approach has enormous potential for drug repurposing and new drug discovery for all of the illness related to inflammasome activation. Given the prevalence and prognosis of these diseases (See figure 2 on page 39), new therapies could be of major clinical significance. Currently, Veit Hornung and his colleagues are using iGLuc to search for new therapeutic approaches to treating sterile inflammation (Figure 2).

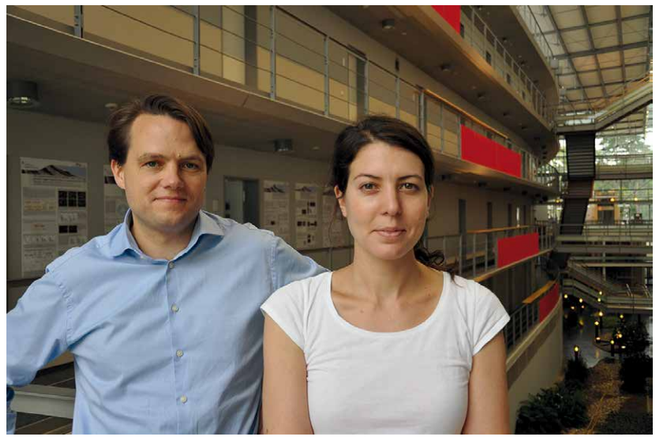
Reference Publication 2013

Bartok E., Bauernfeind F., Khaminets M.G., Jakobs C., Monks B., Fitzgerald K.A., **Latz E.**, and **Hornung V.** iGluc: a luciferase-based inflammasome and protease activity reporter. **Nat. Methods** 1–10, 2013.

Other Reference

Bauernfeind F., **Ablasser A.**, Bartok E., Kim S., Schmid-Burgk J., Cavlar T., and **Hornung V.** Inflammasomes: current understanding and open questions. **Cell. Mol. Life Sci.** 68, 765–783, 2010

Picture
Prof. Veit Hornung,
Dr. Eva Bartok



Immune Sensing and Responses in Tumor Biology

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University of Bonn

Prof. Thomas Tüting, MD
Department of Dermatology and Allergy
Medical Faculty
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Introduction

The immune system communicates with virtually all of the cell types in our body and is constantly surveying its integrity. Tissue injury causes the release of alarm signals, or DAMP molecules (Damage-Associated Molecular Pattern), that are sensed by patrolling immune cells and upon their recruitment initiate and coordinate a wound repair response. This physiological program is not only essential for the integrity and survival of multicellular organisms, but it also plays a critical role in several pathological conditions including chronic inflammatory diseases and cancer. It is well established that genomic alterations are key drivers of neoplastic cell proliferation. However, over the years, it has become clear that tumors also critically require the presence of non-transformed cells in their neighborhood for their survival. Cancer-associated fibroblasts and certain subsets of immune cells are of pivotal importance to this interplay among the various cell types present in the tumor microenvironment. Proinflammatory cytokines and growth factors, including TNF-α, IL-6, HGF and TGF-β are crucial soluble mediators of the physiological wound response and their aberrant release and activation is frequently detected in tumor tissues.

In this sense, cancers can be considered to be chronically wounded tissues that nevertheless manifest a metastable organization with established reciprocal interdependencies between neoplastic and non-malignant cells. From that point of view, the cytoreductive therapies used in the clinic such as genotoxic chemotherapies, targeted inhibition of oncogenic signaling or immunotherapies not only cause profound acute onset injury to the tumor tissue but also massively exacerbate the preexisting inflammation (Krysko et al., 2012). Dying cancer cells release large amounts of DAMPs that rapidly attract immune cells to the regressing and collapsing tumor tissue. This infiltration subsequently establishes a cytokine-driven regenerative proinflammatory

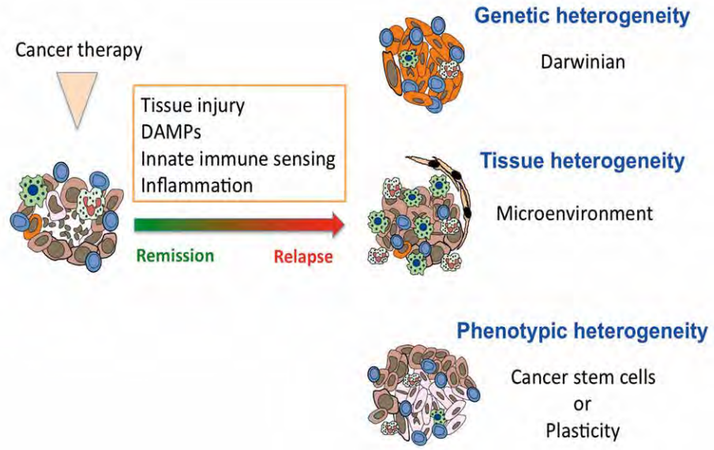

Figure 1 Links therapy between therapy-induced tumor tissue injury, innate immune sensing and the development of therapy resistance. A proinflammatory microenvironment supports different scenarios of therapy resistance.

tumor microenvironment that is believed to pave the ground for the survival of a few remaining tumor cells and ultimately lead to the relapse of the disease (Figure 1) (Hölzel et al., 2013).

Therefore, it is important to understand how therapy-related tumor tissue injury is sensed by the immune system and to identify the critical innate immune signaling cascades and cell types involved. This knowledge may help to substantially improve current cancer treatments by specifically targeting the microenvironmental survival signals sensed by remnant tumor cells after a cytoreductive therapy. However, despite this unified initial approach to understanding the outgrowth of resistant tumor cells in a proinflammatory environment, the scenario surrounding a particular tumor remains quite complex as different cancers are phenotypically and genetically heterogeneous (Gerlinger et al., 2012; Meacham and Morrison, 2013). Another layer of complexity is added by the inherent phenotypic plasticity of the tumor and immune cells themselves in response to proinflammatory signals (Aktipis et al., 2013). A prominent example of adaptive and protective cancer cell phenotype switching is the acquisition of mesenchymal traits by therapy-resistant epithelial tumors, termed as EMT-like states (epithelial-mesenchymal transition), with cancer stem cell-like properties (Zhang et al., 2012). Despite these advances, little is known about the in vivo dynamics of different tumor and immune cell subpopulations and how they interact with each other.

In conclusion, the innate immune sensing of DAMP release after tissue injury has emerged as a critical aspect of tumor biology in the context of tumor development and therapy resistance. The resulting inflammation is a potent influence leading to the “rewiring” of the phenotypes of neoplastic and non-malignant cells in the tumor microenvironment.

Report on key contributions 2012/13

Huang S., **Hölzel M.**, Knijnenburger T., Schlicker A., Roepman P., McDermott U., Garnett M.J., Grernrum W., Sun C., Prahallad A., Groenendijk F.H., Mittempergher L., Nijkamp W., Neefjes J., Salazar R., Ten Dijke P., Uramoto H., Tanaka F., Beijersbergen R.L., Wessels L.F., Bernards R. MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signaling. **Cell**, 151, 937–950, 2012.

Therapy-induced tumor tissue injury and inflammation is a trigger for regenerative wound responses, and EMT-like phenotype transitions at relapse have been linked to the activation of the TGF-β signaling pathway in the tumor microenvironment. Targeting the ALK and EGF receptor tyrosine kinases with specific inhibitors (EGFRi, ALKi) causes profound but transient responses in lung cancers harboring EML4-ALK translocations or activating mutations of EGFR. A significant subset of EGFRi resistant tumors indeed exhibits EMT-like transitions in clinical specimens at recurrence. In this study, we used an unbiased large-scale RNAi in vitro screen and identified that loss of MED12, a component of the transcriptional MEDIATOR complex and known mutated cancer gene, confers resistance to ALK and EGFR inhibitors (Huang et al., 2012). Unexpectedly, we could establish a novel link between MED12 and TGF-β signaling, and we found that cytoplasmically localized MED12 negatively regulates TGF-βR2 by direct binding. Reducing MED12 expression enhanced TGF-βR signaling, which is both necessary and sufficient for drug resistance. In this context, TGF-β was able to activate MEK/ERK signaling, and hence MED12 loss also reduced sensitivity to MEK and BRAF inhibitors in other cancers. In parallel, MED12 suppression caused an EMT-like phenotype switch, which we could also functionally link to chemotherapy resistance in colon cancer patients and to EGFRi in lung cancer. From a translational perspective, blocking TGF-βR signaling may be a promising target to enhance and restore multimodal drug responsiveness in different cancers by abrogating protective regenerative wound responses. Our study is in line with other reports showing an important contribution of the tumor microenvironment to resistance to cancer therapy (Straussman et al., 2012).

Landsberg J., Kohlmeyer J., Renn M., Bald T., Rogava M., Cron M., Fatho M., Lennerz V., Wölfel T., **Hölzel M.**, **Tüting T.** Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. **Nature**, 490, 412–416, 2012.

In order to understand how melanomas become resistant to immunotherapy, we used a genetically engineered mouse melanoma model that recapitulates clinical courses of regression, remission and relapse following adoptive transfer of cytotoxic T cells (ACT). Our model allowed us to successfully treat established primary melanomas with cytotoxic T cells (CTLs) that specifically target the melanocytic differentiation antigen gp100 (Kohlmeyer et al., 2009). Even though a gradual loss of CTL effector functions contributed to tumor relapses in this model, reactivating these memory T cells via a booster vaccination only temporarily enhanced tumor control, and we ultimately observed relapses in all cases. Importantly, we noticed a loss of the target antigen gp100 that was linked to an inflammatory microenvironment. Surprisingly, serial transplantation experiments and in vitro studies revealed that melanoma cells switch between differentiated and dedifferentiated subpopulations with or without melanocytic antigen expression, respectively. Subsequent experiments identified the proinflammatory cytokine TNF-α as major cause for the reversible shift of both mouse and human melanoma cells from a melanocytic to a non-melanocytic phenotype. Thereby, inflammation leads to TNF-α secretion by tumor-infiltrating immune cells and selectively impairs the recognition of the melanocytic antigens by the CTLs (Figure 2). However, it does not affect the recognition of non-melanocytic tumor antigens as demonstrated by matched pairs of human melanoma cell lines and respective cytotoxic T cells isolated from melanoma patients. Our work exemplifies the importance of the phenotypic plasticity of melanoma cells

Immune Sensing and Responses in Tumor Biology

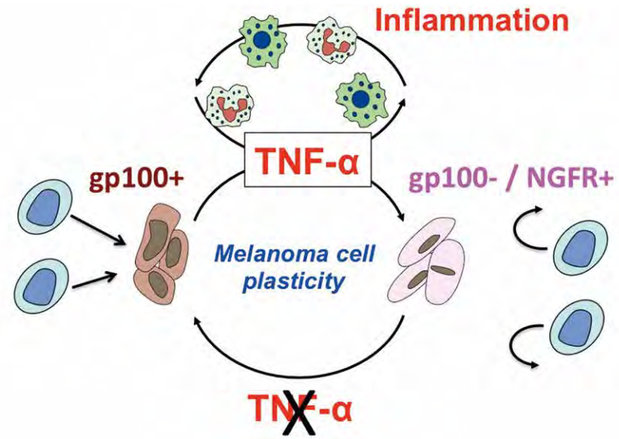

Figure 2 Model summarizing the mechanism of inflammation-induced reversible dedifferentiation that contributes to resistance to T cell therapy in melanoma. T cells killing the melanoma cells via the target antigen gp100 provoke a proinflammatory response in the tumor microenvironment that in turn leads to reversible dedifferentiation (antigen loss) and upregulation of the lineage precursor marker NGFR on the surface of the melanoma cells.

as a rapid adaptation to therapy-induced inflammatory signals in the microenvironment (Landsberg et al., 2012). Furthermore, it establishes a link between the loss of T cell effector functions with the immunoselection of reversible antigen loss variants through dynamic inflammation-induced phenotype switching of immune and tumor cells.

Hölzel M., **Bovier A.**, **Tüting T**. Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? **Nat Rev Cancer** 13, 365-76, 2013.

In this opinion article, we discuss concepts that reconcile the inflammation-induced adaptive plasticity of tumor and immune cells with the genetic heterogeneity of cancers in the context of therapy resistance. Following a careful review of experimental and clinical research, we were able to delineate similarities among the therapeutic approaches to different tumor types including chemotherapy, oncogenic signaling inhibition and immunotherapy. We propose that the course of regression and relapse represents a fast-track evolutionary setting as an approach to studying the interactions between different cell populations in a complex tumor tissue. In keeping with this analogy, we have integrated the concepts and terminology of ecological approaches and applied them both to specific cell populations as well as the tumor environment, as a whole. Cell populations can be regarded in terms of their “fitness” and ability to survive in the “niches” provided within the tumor environment. Furthermore, we discuss strategies to mathematically model the dynamics of these heterogeneous subpopulations that are both genetically and phenotypically diverse. Using our T cell therapy resistance model as a template, we have simulated the cell population dynamics with an adaptive Markovian model (Figure 3). We also discuss how we aim to incorporate our experimental results into such models in order to more comprehensively understand the evolution of complex tumor microenvironments consisting of tumor and immune cells during therapeutic selection pressure. This approach provides a mathematical framework for modeling T cell activation that may help us to better understand both endogenous antitumor immunity and T cell based immunotherapies by inhibition of negative immune checkpoints such as PD-1 or targeted immune-cell activation with RIG-I ligands.

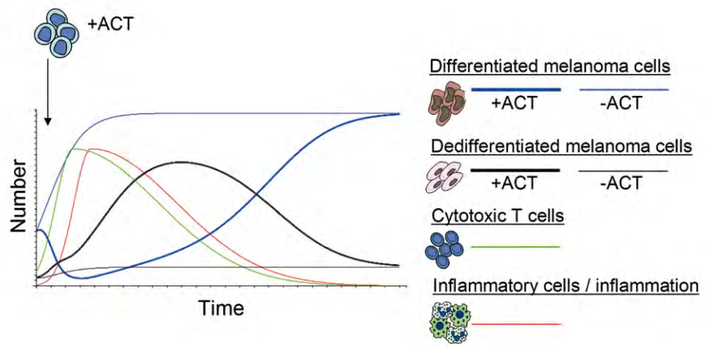

Figure 3 Results of a simulated T cell therapy using an adaptive Markovian dynamics model. A future goal is to implement mathematic modeling in therapeutic models to understand interactions between different cell populations.

Reference Publications 2012/13

Hölzel M., **Bovier A.**, and **Tüting T.** Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? **Nat Rev Cancer** 13, 365–376, 2013.

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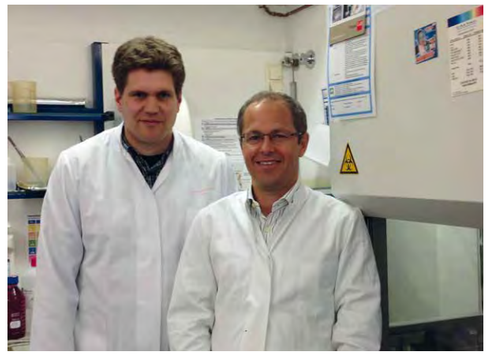

Picture (f.l.t.r.)
Prof. Michael Hölzel,
Prof. Thomas Tüting

Feature Article: Immunity and Aerospace Medicine

Prof. Waldemar Kolanus, PhD
Molecular Immunology & Cell Biology

Life and Medical Sciences Institute
University of Bonn

Salt Metabolism and Macrophages: Of Astronauts and Normal People

Manned space flight is not only expensive. It also causes a number of serious health problems for astronauts due to life at zero gravity for prolonged periods of time and exposure to intense radiation. Such issues - amongst others - are investigated at the DLR, the German Space Agency, at their site in Cologne. In the course of a number of studies, the immune system and immune cells have also come into focus. It turned out, for example, that ROS production, which is one of the major anti-microbial defense mechanisms of innate immune cells, is strongly altered in macrophages at conditions of zero-gravity. Such conditions are not only available in space but may also be caused during parabolic flights of aircrafts, because “free fall” – e.g. when the aircraft nosedives for a while - equals zero gravity. With the help of stationary devices that simulate the conditions of constant free fall for cells through the use of rotation and by employing centrifuges, which can easily generate conditions of excessive weight, it was then shown that gravity-dependent alterations of ROS production of macrophages can also be observed in “normal” laboratories, as well (Adrian et al., 2013). This raises important questions about the anti-bacterial defense mechanisms of astronauts during manned spaceflight and is the subject of further investigation.

Another related area in which my lab became involved is the general metabolism of astronauts (and, as will be shown, of ordinary people, too!). Specifically, I’m referring here to salt and water metabolism. Salt uptake is a long-known risk factor for systemic high blood pressure disease, which plays a major role in the development of atherosclerosis and can damage countless other organs in the body. It was observed, that astronauts “store” salt in their bodies during manned space flight, meaning that they don’t excrete enough of the NaCl taken up with their meals. This was then confirmed and extended by statistical analyses led by the physiologist Jens Titze (Erlangen University/Vanderbilt University, Nashville) using a real-life simulation of a manned Mars mission, which took place in Berlin. Here, the would-be astronauts lived for 500 days in a completely contained and controlled environment (the so-called “Mars 500 mission”). A very similar observation was made here, as well: test persons apparently store salt in their tissues. And this happens in a manner, which does not involve concurrent water uptake or a rise in aqueous volume. It thus remains “invisible” to the kidneys (Rakova et al., 2013). Where are these stores and how are they regulated? Titze and colleagues had shown before that tissue macrophages might play a role in this process (Machnik et al., 2009). Upon stimulation with high concentrations of salt (a 40mM excess, to be precise), skin macrophages induce the expression of the transcription factor NFAT5 (also called TonEBP), which is known to play a role in renal physiology, as well. The result of NFAT5 expression is the production of the lymphangiogenic growth factor VEGF, and lymphangiogenesis is indeed observed in the skin of rats that are fed on a high-salt diet (Machnik et al, 2009; Izzedine et al., 2009).

We hypothesized that macrophages might be able to sense salt stored in tissues in the form of gradients and devised a very simply system to test this idea. A so-called transwell system was employed by Silke Müller, a grad student at the lab of Dr. Ruth Hemmersbach at the DLR in the department of Prof. Rupert Gerzer. In the course of these studies,

Silke was trained by Dr. Thomas Quast in my team at the LIMES Institute.

The observations made by Silke were quite striking (Müller et al., 2013). Macrophages from several sources (cell lines, bone marrow derived and peritoneal macrophages) selectively migrated towards excess concentrations of salt present in the lower chambers of the transwell inserts. This was not due to osmotic stress since these cells did not migrate towards equi-osmolar concentrations of other solutes, such as the sugar mannitol. Also, these cells only became motile when the high salt conditions were present in the lower chamber, indicating a bona-fide chemotaxis. This response appears to be highly cell-specific, since dendritic cells, which are closely related to macrophages, are not able to perform salt-dependent chemotaxis under the same conditions in which they would normally migrate towards chemokines. With the help of Jens Titze, we were finally able to show that macrophages derived from mice which lack NFAT5 expression in macrophages (such mice acquire higher blood pressure when fed on a high salt diet!) surprisingly showed a normal migratory response to high salt concentrations (Müller et al., 2013). Apparently, macrophages possess a second, NFAT5-independent sensor system for the detection of high salt levels. And this seems at the very least to be related to their migratory responses *in vitro*. Our future studies of course aim at the elucidation of this sensor system. Macrophages appear to deal with a number of other (surprising) things, besides their well-known role in the killing of pathogenic microorganisms. Maybe, one day, clinicians will direct their efforts at the molecular structures of immune cells to treat high blood pressure.

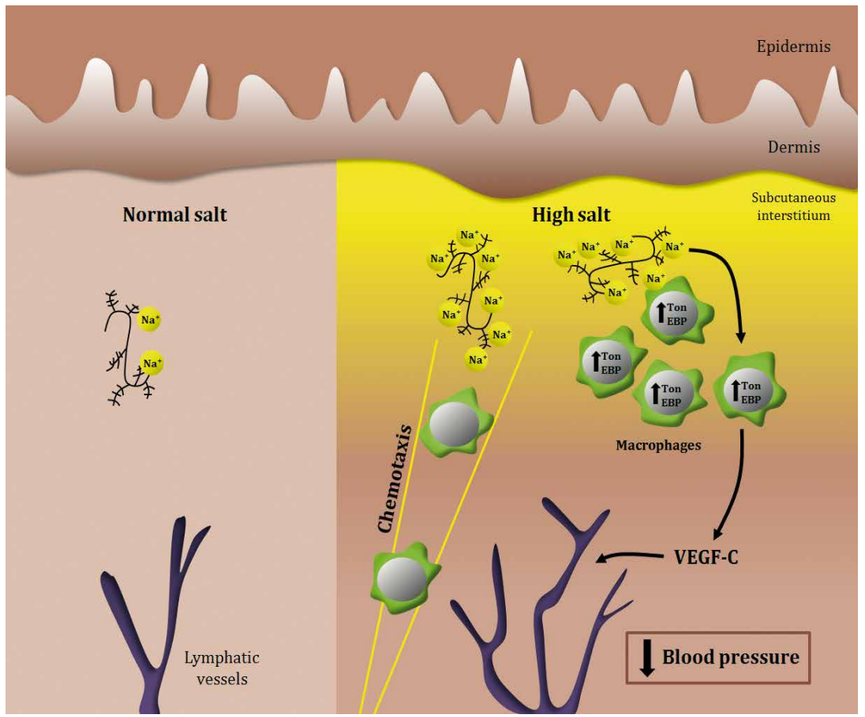

Figure Current model of the role of macrophages in the regulation of interstitial NaCl balance (modified from Izzedine et al, 2009)

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Salt Metabolism and Macrophages: Of Astronauts and Normal People

Picture (f.l.t.r.)
Dr. Thomas Quast, Prof. Waldemar Kolanus, Dr. Silke Müller (all LIMES), Prof. Rupert Gerzer, Dr. Ruth Hemmersbach (both DLR)

Interviews

Prof. Max P. Baur, PhD
Dean of the Medical Faculty
University of Bonn

Prof. Gunther Hartmann, MD
Institute of Clinical Chemistry & Clinical Pharmacology
Medical Faculty
University of Bonn

Prof. Waldemar Kolanus, PhD
Molecular Immunology & Cell Biology
Life and Medical Sciences Institute
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Dr. Katharina Hochheiser
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Larisa Labzin
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Dr. Elmar Endl
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Interview with Prof. Max P. Baur
Dean of the Medical Faculty

ImmunoSensation:
The University Hospital Bonn and its Faculty of Medicine connect and integrate medical departments, research institutes and teaching institutions. Thus, they can be seen as a “center of competence” for patient care, research and education.

In your opinion, what is the role of the Faculty of Medicine in terms of its status and its significance?

Max Baur:
The North-Rhine Westphalian Education Act defines universities and university hospitals as two different and independent public legal entities. The Medical Faculty is one of the seven faculties of the University of Bonn, meaning that its primary focus is on teaching and research. However, medical education and research are also inherently and inextricably linked to patient care at the University Hospital. As a result, the Medical Faculty represents the most essential link in the integration of patient care, research and education. We see our role as one of translation from the basic science of all the university faculties into diagnostics, therapy and prevention for both patients and the general population at large.

ImmunoSensation:
What is the significance of the ImmunoSensation Cluster of Excellence for the Faculty of Medicine?

Max Baur:
The decision to grant funding to the ImmunoSensation Cluster of Excellence awarded recognition to the long-term investment that has already been made in the creation of an internationaly-renowned center of immunological research. Through academic appointments, the creation of degree programs and their investments in research infrastructure, both the Faculty of Medicine and the Faculty of Mathematics and Natural Sciences have made Bonn a center of unrivaled immunological expertise. Our outstanding partner institutions (DZNE, caesar, DZIF, etc) have also made significant contributions to the research landscape. Awarding fund-

Prof. Max P. Baur, PhD
Dean of the Medical Faculty, University of Bonn
Since 04/2011
Dean of the Medical Faculty, University of Bonn
2004 – 2008
Vice-President (Prorektor) for Science and Research, University of Bonn
1974 - present
16 Projects (DFG, BMFT, BMG, BMBF, EU) 3.1 Mio € personal funding;
Two large research structures founded & led (DFG FOR 423, GEM platform in the National Genomics Research Network NGFN)
Total funding of 21.7 Mio €

ing to the Cluster of Excellence is not only the reward for the strategy we have pursued so far but also the obligation to make a continuing, enduring contribution in the future. Immunology is a field that impacts many others, e.g. neurosciences, infectious diseases, translational medical research. Thus, for both faculties, immunological research is a considerable impetus driving both external funding (DFG, BMBF, EU, et al) as well as the recruitment of outstanding students and scientists.

ImmunoSensation:
What are the advantages associated with a Cluster of Excellence?

Max Baur:
The advantage of a Cluster of Excellence lies in its focus on the creation of long-term, sustainable programs. The Cluster has enabled the recruitment of new professors, the establishment of junior research groups and the creation of an outstanding graduate program. Even if this funding comes to an end, the investment has a long-term value and will continue to provide for outstanding research and the excellent support of students and young investigators.

ImmunoSensation:
The Faculty of Medicine, the University Hospital and their associated institutions all make every effort to recruit outstanding physicians and scientists. In your opinion, why are there so few female professors in science and what could and should be done to improve the situation?

Max Baur:
This problem is fundamental to our society in general. Women are well represented at the undergraduate and graduate level, where they make up significantly more than 50% of students and are at least as successful as their male counterparts. However, after they complete their PhD, we often lose these outstanding women, because, for personal reasons, they decide not to pursue a career in academic science. This is a great loss both for science and for our greater society. Obviously, in our society, it still is not adequately recognized for couples to choose to take on three great responsibilities, i.e. pursuing two careers and raising children at the same time. The University Hospital, the University of Bonn and the Cluster of Excellence all go to great lengths to help outstanding women pursue careers in academic science through dual career programs, day care and numerous other programs.

ImmunoSensation:
The University Hospital has significantly expanded in recent years and continues to grow. Currently, the building of a new site for the German Center for Neurodegenerative Diseases (DZNE) and a new Mother and Child Center (ElKi) are in progress.
A second biomedical center (BMZ) is also in planning. What is the current stage of these plans?

Max Baur:
During the application period for the Cluster of Excellence, the Faculty of Medicine pledged to provide new professors with sufficient space for their research groups. We are especially proud that we have been able to advance and expedite the building of a second biomedical center (BMZ II) in close proximity to the first BMZ. Currently, architects and the future occupants of the BMZ II, including the Cluster of Excellence, are in the process of designing a new 5000-square-meter building with laboratories, offices, seminar rooms and core facilities. If all goes according to plan, the building should be ready for use by the end of 2016.

interviewed by
Cluster Coordination Office

Interview with Prof. Gunther Hartmann Speaker of the ImmunoSensation Cluster of Excellence

Prof. Gunther Hartmann
Speaker of the ImmunoSensation Cluster of Excellence
University of Bonn
Institute of Clinical Chemistry and Clinical Pharmacology, Director
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ImmunoSensation:
What is the quota of women within the ImmunoSensation Cluster?

Gunther Hartmann:
Right now about 331 students and researchers are involved in the Cluster. The percentage of female scientists is 47%. As in other research areas, the quota of women decreases with advanced career stages. At the student and postdoc level, the percentage of women is 54% and 48%, respectively. At the group leader level (including eight scientists with advanced degrees, Habilitation), the percentage declines to 23%. The 12% of Cluster professors exactly match the percentage of female professors at the Rheinische-Friedrich-Wilhelms Universität Bonn. The Cluster aims to significantly increase the quota of women. We decided to fill 50 percent of the advanced academic positions of the Cluster (group leaders and professors) with female candidates. However, there is a strong competition regarding the recruitment of excellent female scientists. For example, Andrea Ablasser, the most successful female group leader in our Cluster, just left and has been appointed a professorship at the ETH in Lausanne. We will further increase our efforts to offer women the best conditions for their career development.

ImmunoSensation:
Is the ImmunoSensation Cluster supporting women in a focused manner?

Gunther Hartmann:
Supporting women in their career development is a central task for the Cluster. In this respect, we are working on improving all aspects of career support and already started to develop the corresponding structures in the preparation phase of our application. Approximately 60 percent of the start-up money from the state of North Rhine-Westphalia before our application was approved, were already used to implement three research groups, and to fill the respective positions with young female scientists. One of them now moved on as professor in Switzerland. Furthermore, the first W3 professorship funded by the Cluster was given to Irmgard Förster, a renowned immunologist from Düsseldorf. We decided that of the other four advanced career positions, at least two will be filled with female scientists. In addition, we offer financial support for child care. Young mothers receive information and special offers for nursery as well as financial benefits. Moreover, there is a free nursing and child care service outside the core working hours. The Cluster offers special seminars on career opportunities, the coordination of family life and research and soft skill courses. Altogether, 400,000 € are available for these measures. In addition, 50 % of the graduate stipend program (2 million Euro) will be used to recruit female students.

ImmunoSensation:
In your opinion, what are the reasons for the low number of women at professorship level?

Gunther Hartmann:
This is a topic of intense discussions. The current picture looks as follows: with no doubt there are as many excellent young male and female scientists. There is no difference in talent or capabilities. However, all scientists face the fact that research is one of the most highly competitive jobs and requires 100 % personal commitment. First, cutting edge lab research takes long hours. Second, there is a high level of risk since advanced careers or professorships are not guaranteed. In fact, the number of attractive positions is rather limited, and there are many examples where even greatest commitment in time and efforts does not lead to an independent position in science. On the other hand, there is the wish to found a family and have children. In many cases, calculating the risk of a scientific career, many women come to the conclusion that family and an academic career at the forefront of science are mutually exclusive. We very often see that in principle women with young families want to stay in science but they decide to turn to less competitive areas like scientific management and coordination. In some cases, the male partner may step back and takes most duties of daily family life, but this is the exception. Now, is there a solution to this? I think yes, and we as a Cluster have a special responsibility to advance female academic careers. However, it is very clear that it requires a substantial amount of money to enable both partners to stay in science. It clearly requires specific measures, and it will cost an additional amount of money. Different levels of personal support have to make sure that parents see their children receive good care and attention to grow up the best possible way despite the time constraints of their parents. Important ways to support young parents are optimal day care, support in routine duties of daily life, and child care in situations of late hours of lab work or during times of travel. A political decision has to be made to provide the additional funds to young female scientists. An excellence Cluster is the ideal vehicle to spearhead such an initiative. Surely, questions will arise such as who personally and scientifically qualifies for this additional support, and for how long? But the Cluster can explore the best options, and establish the role model for other disciplines. Therefore, we as a Cluster will use parts of our Cluster funds to establish such a role model which specifically fosters the careers of female scientists and at the same time generate an even beneficial situation for their children.

interviewed by
Cluster Coordination Office

Prof. Gunther Hartmann
Speaker of the ImmunoSensation Cluster of Excellence
Winner of the Gottfried-Wilhelm-Leibniz-Preis 2012

Interview with Prof. Waldemar Kolanus Vice Speaker of the ImmunoSensation Cluster of Excellence

Prof. Waldemar Kolanus
Vice Speaker of the ImmunoSensation Cluster of Excellence
Life & Medical Sciences Institute (LIMES)
Molecular Immunology & Cell Biology, Director

ImmunoSensation:
The aim of the ImmunoSensation Cluster is to efficiently investigate the complex network of the immune sensory system. Therefore, research groups from different disciplines are working together. In your opinion, what are the advantages of that interdisciplinary approach?

Waldemar Kolanus:
The scope of the life sciences reaches very far these days. Our not so small ambition is to understand life from the atomistic detail of e.g. an isolated immune-receptor to the intricacies of systems biology both at the cellular and the organismic level. In a way this has always been the case, but the exciting thing is that the tools are now becoming available to actually meet such formidable challenges. This encompasses e.g. the structural resolution of complex receptor/signaling aggregates, the in vivo imaging of motile cells interacting with each other in their normal environments, and goes as far as carrying out genomic analyses from single cells. It becomes quite obvious that nobody can do all of this alone anymore. Interdisciplinary research does not only have strong advantages – it has become a necessity.

ImmunoSensation:
According to your experience, are there specific challenges concerning communication that come along with an interdisciplinary structure/program like the ImmunoSensation Cluster?

Waldemar Kolanus:
The Cluster was well prepared for this. Many of the Cluster scientists are members of the SFB 704 on “Local Immune Regulation and Chemical Modulation” and a strong hallmark of this initiative is the co-operative approach. But of course with the introduction of the Cluster, the scope widens even further and brings in neurobiologists, structural biologists, biophysicists and mathematicians. The communication styles and scientific cultures of these fields are quite different and it is therefore not always easy to establish good links. The only approach to this is to meet often and to communicate as openly as possible. Sometimes, listening to somebody from a different area can get you much further than talking to your bona-fide “expert”, who will usually share most of your views. For my taste, international scientific conferences are too frequently put together around fairly narrow subjects, although such meetings are important, too. We are changing this. A narrow perspective is not what the Cluster is about.

ImmunoSensation:
Are there particular outstanding examples for interdisciplinary co-operations within the ImmunoSensation Cluster?

Waldemar Kolanus:
The quality of the scientific productivity in the Cluster is very high and I could go on with this for a while. However, I take the liberty to highlight two recent examples. In the recent collaborative effort of Eicke Latz’s and Joachim Schultze’s groups it was discovered how HDL (low-density lipoprotein) triggers anti-inflammatory responses in macrophages via ATF transcription factors, and this paper was published in Nature Immunology. It was the combination of elegant in vivo models and an unbiased genomics and bioinformatics approach that led to the right targets and thus was a perfect mutual fit. Another example is the latest Nature publication from Thomas Tüting’s lab, which showed that UV radiation strikes twice in melanoma. As a first event UV generates mutations, and this is what we knew. But UV also drives cancer progression and development of metastases through the induction of inflammatory responses - and this was completely novel. My lab was able to contribute valuable new assays to prove that the angiotropic, migratory response of the melanoma cells were modulated by UV-driven inflammation. This study is also a good example for cooperation because it was only made possible by the contributions of many other Cluster members, including Irmgard Förster, Michael Hölzel, Wolfgang Kastenmüller and Bernd Fleischmann.

ImmunoSensation:
Prof. Dr. Max P. Baur, dean of the Medical Faculty Bonn, stated that the advantage of a Cluster of Excellence lies in its focus on the creation of long-term, sustainable programs. Do you think that the interdisciplinary co-operations will be continued beyond the Cluster’s framework?

Waldemar Kolanus:
Excellence Cluster initiatives are to a large degree structural programs, which means that it is one of our prime goal to convince excellent colleagues to come to Bonn, so that they can work in close association with us. This was already quite successful and underscored by the recent successful recruitments of Irmgard Förster, Wolfgang Kastenmüller and Michael Hölzel. The establishment of new permanent structures already means sustainability. As a program, the Cluster needs to acquire outside funds and I think we are on a good way to position ourselves strongly for reapplication. And even if different funding schemes emerge in the future, the novel scientific concepts generated within “ImmunoSensation” are very likely to prevail and make their way.

interviewed by
Cluster Coordination Office

Prof. Waldemar Kolanus and his group are interested in intracellular signal transduction events which control leukocyte adhesion, migration, and effector functions. One focus of their current research activities is the elucidation of the role of integrin adhesion receptors and the cytoskeleton in the functional adaptation of leukocyte motility to specific microenvironments.

Interview with Dr. Katharina Hochheiser

Dr. Katharina Hochheiser is a postdoc in the laboratory of Prof. Christian Kurts, where she also completed her PhD and diploma theses. Her PhD was awarded a summa cum laude in 2013.

ImmunoSensation
Katharina, what made you decide to go into science?

Katharina Hochheiser:
I'd been fascinated with biomedical research for a long time, but it wasn't the only thing I was interested in. At the end of my time at school, I started looking at degree programs online and found out that Bonn had a relatively new program "Molekulare Biomedizin" or molecular biomedicine. I talked to my parents about it. They're not researchers, but they still encouraged me to pursue whatever I was interested in.

ImmunoSensation:
Is that why you came to Bonn?

Katharina Hochheiser:
Yes, at the time, there weren't that many programs available that specialized in biomedical research, and Bonn had a good website. I became a student in the second year of their program.

ImmunoSensation:
And why did you decide to go into immunology?

Katharina Hochheiser:
During my studies, we had several good lecture courses on immunology. I found it fascinating. The body manages to develop immune responses to all sorts of different pathogens in all sorts of different places. It manages to discover them, distinguish friend from foe and eliminate the threat. The right cells have to get to the right places. It's a very complex, but very effective, choreography.

ImmunoSensation:
What brought you to Christian Kurts's lab?

Katharina Hochheiser:
In our degree program, there were quite a few lab rotations. Some were mandatory. Some were optional. My first rotation in Christian Kurts's lab was a required one, but I really enjoyed it, so I decided to come back for a second, optional rotation. After that, I decided to stay for my diploma thesis.

ImmunoSensation:
And you continued there, first as a PhD student and now as a postdoc. What made you decide to stay even longer?

Katharina Hochheiser:
I had received excellent training during my diploma thesis but also knew that I could still learn a lot in the Kurts lab. I also found the research focus or rather foci in the lab particularly interesting, and I wanted to continue working on them.

Now, as a postdoc, I am still following up on a few interesting questions that came up during my PhD. In addition to the work on CX3CR1, I still have a second project from my PhD that I'm working on. I'm also an advisor to a new PhD student, who has just started and who will continue on my projects when I go abroad by the end of the year.

ImmunoSensation:
Where are you going?

Katharina Hochheiser:
I'm planning to start a second postdoc in Thomas Gephardt's lab in Melbourne, Australia. During my diploma thesis, I also got the chance to spend some time in Melbourne as an exchange student in Richard Kitching's lab. The focus was also on nephrological research, and it was a great experience. That's why I decided to go back to Australia for a postdoc.

ImmunoSensation:
That sounds great. Congratulations! Not only on the postdoc in Australia, you finished your PhD in 2013 summa cum laude and published a really interesting paper in JCI as first and corresponding author. Could you tell us a bit about your PhD project and the JCI paper?

Katharina Hochheiser:
The project first started a couple of years earlier, when we decided to look at the role of dendritic cells, DCs, in a glomerulonephritis model. The previously published literature was relatively contradictory and controversial. We were able to show that DCs can take on different roles in the kidney depending on the context. In homeostasis, DCs have a more regulatory role. In glomerulonephritis, they mature and take on proinflammatory functions. We were already able to publish these results during the second year of my PhD.

However, this brought up a different, rather fascinating question. Most DCs in the kidney express CX3CR1, yet no one had ever looked at the function of this receptor. When we looked at CX3CR1-deficient mice, we saw that the number of DCs in the kidney were drastically reduced. This effect was the most pronounced in the renal cortex exactly where the DCs responsible for glomerulonephritis are also found. The DCs in the renal medulla weren't really influenced that much by the lack of CX3CR1, and this DC population is responsible for the immune response to infection. What's more, this CX3CR1 dependence also seems to be absent from other organs with the exception of the small intestine.

Dr. Katharina Hochheiser is first and corresponding author on a publication in 2013 in the Journal of Clinical Investigation, "Exclusive CX3CR1 dependence of kidney DCs impacts glomerulonephritis progression" 2013 Oct 1;123(10):4242-54.

ImmunoSensation:
So this brings us back to the idea of having the "right cells in the right places", doesn't it?

Katharina Hochheiser:
Exactly. CX3CR1 seems to be a kidney-specific homing receptor. However, in glomerulonephritis, we actually don't want these DCs in the renal cortex. They're responsible for inflammation and destruction of renal tissue. But we'd still like to keep the DCs in the renal medulla to protect us from infections like pyelonephritis. Since these DC populations differ in their dependence on CX3CR1, it's a really promising target for glomerulonephritis therapy. Inhibiting it could keep DCs out of the renal cortex but have few

side effects on other organs or on immune defense in the kidney.

ImmunoSensation:
Are you following up on this?

Katharina Hochheiser:
This is one of the projects I've continued on as a postdoc. Currently, I'm looking at whether specific inhibitors or antibodies against CX3CR1 can also prevent DC influx in glomerulonephritis or whether this effect is somehow specific to CX3CR1 knockout mice.

ImmunoSensation:
DCs have gotten a lot of attention in recent years. Steinmann won the Nobel Prize in 2011 for the discovery of their role in adaptive immunity. What made you decide to look at their role in the kidney?

Katharina Hochheiser:
DCs are really fascinating cells. They exist somewhere between innate and adaptive immunity. They integrate the signals coming from the innate immune system, the first line of defense, and present them to the adaptive immune system. Depending on their maturity, they can be regulatory or proinflammatory, which makes them a kind of central switchboard for the immune response. By influencing the function and migration of these cells, we could also potentially control the broader immune response.

ImmunoSensation:
And why in the kidney?

Katharina Hochheiser:
For quite a few reasons. Kidney disease affects many people because it can result from other widespread illnesses like diabetes and hypertension. It's clear that the immune system plays an important role here, but the exact mechanisms still aren't understood. This means that there are a lot of open questions for us to look at and that their answers may be of immediate practical relevance to patients. For me, it's an excellent combination of basic and applied research.

ImmunoSensation:
Your PI, Christian Kurts, and a co-author, Percy Knolle, are both members of the ImmunoSensation Cluster of Excellence. How was the Cluster involved in the CX3CR1 project?

Katharina Hochheiser:
The technical platforms were of great importance for the project, in particular "Flow Cytometry" and "Transgenic animal models". The core facilities are really helpful.

A second aspect, which is difficult to quantify, is the scientific exchange that occurs in the Cluster. This exchange is what gives you new ideas and impulses, whether it's during official talks or informal conversations.

ImmunoSensation:
The fact that we decided to interview you and Larisa Labzin has nothing to do with you being women. Rather, it was because you were both quite successful in 2013. However, the dean commented in his interview that the lack of women in academic science isn't the enrolment numbers at university, but rather that so few women choose to pursue academic science as a career afterwards. As a female postdoc, do you feel supported by the Faculty of Medicine? By ImmunoSensation?

Katharina Hochheiser:
To be fair, I haven't really needed any extra support so far. However, I do think that will become relevant later when I have children and take maternity leave. When that time comes, I would like to have support from my employer. It would be good if technical assistants can be hired, so that young mothers can continue their research even if they can't come into the lab for a period of time. The other really important thing is daycare. Women can't get back to the lab if there is no room in the daycare center. However, I know that ImmunoSensation is working on providing their female scientists with these services, and I think it will be of great help to them.

ImmunoSensation:
As someone who has chosen to stick with academic science, do you have any advice for the PhD students reading this interview?

Katharina Hochheiser:
Don't give up! Everyone has a time during their PhD when things just don't work. When that happens, take a break, keep your sense of humor and try to remember the fun side of doing research. If you try to work day and night for 3 or 4 years, you'll lose perspective. Take time to catch your breath and clear your head. It often helps you get a new perspective on a problem and that's when the best ideas occur to you.

interviewed by **Dr. Eva Bartok**

Interview with Larisa Labzin, PhD Student

Larisa Labzin is in the fourth year of her PhD in Prof. Eicke Latz's laboratory. A native of Brisbane, Australia, Larisa completed her B.Sc. Hon. at the University of Queensland while working in the laboratory of Matthew Sweet (TLR/NLR research).

Picture Larisa Labzin

ImmunoSensation:
So, Larisa, what brings an Australian all the way to Bonn?

Larisa Labzin
Eicke Latz. I came to Bonn because I definitely wanted to work in his laboratory. However, I had thought about coming to Europe before that. I spent a semester abroad in Berlin while studying for my bachelor's degree, and so I already knew some German. I thought it was a great way to combine spending time in Germany and working in a great lab.

ImmunoSensation:
If I remember correctly, you first worked in Prof Latz's lab as a research assistant. Then, after a few months, you decided to start your PhD here. What influenced your decision?

Larisa Labzin:
Well, when I came here, I already knew I was interested in immunology. My previous advisor was Matthew Sweet, who is also in innate immunity and a TLR researcher. I worked as a research assistant after finishing my bachelor's in Australia and though I'd continue that here and see if I wanted to pursue a PhD. However, after 3 months here, I was pretty sure that I was ready for that challenge. I asked Eicke if he had room for another PhD student, and he changed my contract immediately.

ImmunoSensation:
So, you've been in innate immunity since your bachelor's degree. What made you interested in it in the first place?

Larisa Labzin:
During my studies, there were lots of fields that I found interesting: cell biology, genetics, particularly epigenetic regulation, the biology of gene transcription. However, the biggest influence were the professors themselves. Some professors just exude this contagious enthusiasm for their research. That's why I started in immunology, at least, but I've stuck with it because it's a field of research that touches on just about everything else in biomedical research. Our paper was about the intersection between innate immunity and metabolism, with a focus on transcriptional regulation, so I could work on a few fields that I've always found interesting.

ImmunoSensation:
That brings me to my next question. You've obviously made the right decision coming to Bonn, and you've had a very successful year. Could you tell us something about the ATF3/HDL paper?

Larisa Labzin:
Of course. The short version is: we discovered a specific anti-inflammatory role for HDL that is separate from its direct role in cholesterol transport.

Just about everyone knows what HDL is and that it's somehow "good cholesterol" as opposed to "bad cholesterol" or LDL. There have been countless studies showing that high HDL levels correlate with a lower risk of cardiovascular events. Mainly, this has been attributed to the HDL's role in cholesterol efflux. However, there have also been studies that have shown that HDL is anti-inflammatory in general.

Our first question was if this effect is only due to cholesterol efflux or, perhaps, a more specific anti-inflammatory pathway. Although there are previous studies that show that HDL somehow dampens TLR-signaling, this has been attributed to non-specific effects. HDL really does bind LPS (lipopolysaccharide), which of course limits TLR4 signaling because it just removes the ligand. Another theory was that the cholesterol efflux simply disrupts lipid rafts, and the TLRs just can't signal properly. However, we wanted to investigate if HDL had a specific, pathway-mediated anti-inflammatory effect.

ImmunoSensation:
That's quite a broad question. What was your approach?

Larisa Labzin:
We chose to look at the role of HDL in normocholesterolemic macrophages where the effect of cholesterol efflux wouldn't be as important. We tested a wide variety of TLR activators instead of just looking at LPS. And we found that HDL inhibited TLR-signaling for all of them! Our gut feeling was that there was no way that HDL could just happen to bind this incredibly broad spectrum of ligands. Then, when we investigated the the TLR signaling pathways, we found that HDL didn't affect them, indicating that the lipid rafts were still intact, despite general cellular cholesterol depletion. We also saw that HDL reduced intracellular cytokine levels, indicating that it wasn't an effect on secretion. So we basically tried to narrow down where in the pathway HDL was mediating its effect.

ImmunoSensation:
Where did you go from there?

Larisa Labzin:
Our working hypothesis was that HDL was somehow involved at the transcriptional level. The earliest inhibitory effect of HDL that we saw was in cytokine mRNA levels. We thought that HDL might then repress a transcriptional activator or activating a transcriptional repressor. That's when Eicke approached Joachim Schultze's lab about a collaboration.

ImmunoSensation:
The paper was the result of a real Cluster Collaboration, wasn't it? What role did Joachim Schultze and his lab play in the publication?

Larisa Labzin:
They've been just brilliant, and the collaboration has been incredibly fruitful. We started with a microarray experiment in wild type macrophages to look for the global effect of HDL on CpG induced gene expression. They saw that HDL treatment induced a num-

Larissa Labzin and Dr. Dominic DeNardo shared first authorship of a recent publication in Nature Immunology "High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3" Epub 2013 Dec 8.

ber of transcription factors, and then, using various bioinformtaics approaches, were able to identify ATF3 as a potential HDL inducible transcriptional repressor. We confirmed that HDL did indeed induce ATF3 in our lab, and then we did some more experiments in ATF3-deficient mice to confirm that ATF3 was the key mediator of HDL's anti-inflammatory effect. We even did ChIP-seq (chromatin immunoprecipitation followed by DNA sequencing) using the ATF3-deficent macrophages as a background control, which gave us really clean, comprehensive data about where ATF3 binding was being induced by HDL across the genome. That was amazing! We had so many hypothesis at the start, and we could never investigate them all, so it was really nice to use an unbiased approach to identify ATF3 - and we could never have got that far without Joachim Schultze and his lab.

ImmunoSensation:
Where does it go from here? HDL seems to have quite a therapeutic potential.

Larisa Labzin:
One of the important things that researchers have realized is that not all HDL is alike. There have been lots of trials with HDL-raising drugs, which so far have been unsuccessful in treating cardiovascular disease. Probably a lot of this is because when it comes to HDL - its ‚quality versus quantity' - so you need the HDL to be really functional. We used a reconstituted form of HDL in our studies, which was a gift from CSL-Behring, and its basically really hungry HDL - its really good at removing cholesterol from cells. Its been shown to beneficial in animal models of sepsis, vascular inflammation and even rheumatoid arthritis, as well as in animal models of atherosclerosis. So, potentially, recombinant HDL could be beneficial for treating all sorts of inflammatory illnesses, not just atherosclerosis but also autoimmune illnesses like lupus or life-threatening inflammatory conditions like bacterial sepsis.

ImmunoSensation:
One of your other successes in 2013 was winning one of the first prizes at the ImmunoSensation Science Day. How was the meeting for you? Would you recommend it to other students?

Larisa Labzin:
It was actually a really cool meeting. It is always good to get experience presenting data in front of large audiences. And I was really impressed by my competition! There's so much great research going on in the other groups, and it was great to meet students from other institutes. The other important thing was seeing what a broad field immunology is. Normally, conferences deal with relatively narrow topics, but the meeting had everything from neuroscience to drosophila to molecular immunology. It's rare as a student to have the chance to give a talk in front of so many different professors. The questions and input were great, so I would definitely recommend it to every student who's interested. It was a great way of to getting input on my research from perspectives outside of my immediate field.

ImmunoSensation:
It's a bit off topic, but speaking of drosophila, do they have ATF3?

Larisa Labzin:
As a matter of fact they do, and the function is conserved! And that's not that off-topic. It's important to keep the evolutionary background of these pathways in mind, and Michael Hoch is one of my thesis advisors.

ImmunoSensation:
And, one last question, as someone who has come from very far away to do their PhD in a Cluster lab, what would be your advice to students thinking about coming to Bonn for our graduate program?

Larisa Labzin:
You should come! I've grown to really like Bonn. It's quite small, but it's pretty and that means you can walk and ride your bike everywhere. And, if you like having the big city life every once in a while, Cologne is only a half an hour away. I've also found that learning German has been a great experience for me. I've made some really great friends here, and I'm glad I can understand German and can appreciate some of the Rheinlandish humour.

The program for the students in the Cluster is also great. I've attended a communications seminar arranged by Astrid Draffehn, which was really helpful. There are technical courses. You meet other students from other labs.

And, of course, come for the research! Within the Cluster, there is funding, support and expertise that you can find almost nowhere else. So far, in my PhD, it's really been "if you can think it, you can do it". That's an incredibly valuable opportunity but it's also incredibly rare. Sometimes, I think the opportunities are almost daunting, but, then again, really, I wouldn't have it any other way.

interviewed by **Dr. Eva Bartok**

Interview with Dr. Elmar Endl
Head of the Flow Cytometry Core Facility

Picture Dr. Elmar Endl

ImmunoSensation:
Dr. Endl, you are the head of our Flow Cytometry Core Facility and you run the ImmunoSensation Flow Cytometry Platform. First of all, what is a “core facility”? And what is a “technical platform”?

Elmar Endl:
A core facility and a technical platform are basically two ways of expressing the same thing. They are a type of *research infrastructure* that is the combination of technical facilities, the current staff working there and the years of knowledge and experience the platform has accrued. Research infrastructures provide all researchers access to state-of-the-art instrumentation and ensure this access can be acquired in a simple and structured way like any good infrastructure, such a platform should be built to last and to serve generations of machines and scientists. It should be sustainable.

ImmunoSensation:
But the idea of a “technical platform” is actually rather recent, isn’t it?

Elmar Endl:
In the life sciences, it is relatively new. However, my background is in physics. If you look at a field such as particle physics, scientists have always had to share equipment since, well, time immemorial. A particle accelerator is phenomenally expensive and needs a lot of know-how if it’s to be used properly. CERN is a fantastic example of sustainable scientific infrastructure.

Outside of physics, these platforms have developed rather recently. In fact, they are part of a paradigm shift. The life sciences are in the process of a major transition between science driven by individuals, as practiced by the stereotypical mad scientist alone in his garage, and team-oriented science, where resources and knowledge are pooled. With the development of more and more advanced technology, machines are getting so expensive and so complicated that almost no one has the money and the know-how to operate them alone. Scientific knowledge is expanding too rapidly for any one individual to keep up with everything.

Thus, a technical platform is all about having open access to competitive science. Young investigators, in particular, would never be able to compete if we didn’t provide them with access to cutting-edge technology and teach them how to use it.

Universities and research institutions have also realized that these “platforms” make plain good sense, economically speaking. Equipment is used better and more efficiently. Platforms can negotiate prices with suppliers because they represent a larger user base. It is easier for younger scientists to obtain grants if they have an infrastructure supporting them, so it means more external funding for the university.

ImmunoSensation:
A sustainable infrastructure with open access sounds quite a bit different than just a shared collection of expensive machines.

Elmar Endl:
Absolutely. I can’t stress enough that a platform is not just the machines in it! The most valuable asset of a “technical platform” is the knowledge that comes with it, *what is around the machines*. You need an excellent staff both to maintain the machines and to make sure that users benefit from their full potential. Machines are expensive. However, my staff is invaluable.

ImmunoSensation:
And what about the head of a core facility?

Elmar Endl:
My technicians are excellent, so I don’t have to spend that much time with technical problems with equipment and such. The most important part of my job is in fact communication. The head of a core facility has to be not only an excellent communicator but also a reasonably good scientist. You have to know what the researchers on your campus are up to because you have to connect them with each other. You bring people together, and you foster collaborations.

You also have to connect scientists with companies. On the one hand, you can coordinate purchases with the administration by bundling and streamlining orders, and, as I said, this makes it far easier to negotiate prices with companies. On the other hand, you also have to know what techniques are on the market and what is in the pipeline, so that you can inform and advise your users. A lot of what I also do is put new products in perspective for scientists here because we know most of the old ones.

We also have an important role as educators and we’re part diplomat, part business man, part psychologist…

ImmunoSensation:
Part psychologist?

Elmar Endl:
Indeed. Our job isn’t only to tell people what works but also to tell them what doesn’t. The latter part is actually far more important because negative results are not what usually get published. One of the most important functions of a core facility is as a repository of negative data. You don’t see that many papers called “Technique X is overrated hype” or “Technique Y cost me two frustrating years of my life”…

Jokes aside, it’s essential to warn users about pitfalls, potential artifacts and even how their data could be misinterpreted. Sometimes you have to explain to the user that the validity of his or her data has to be questioned. If it’s at the beginning of someone’s project, then good enough,

but if someone's been working on something for a long time, and you're the bearer of the bad news that they've been doing it all wrong… That's the hard part of the job.

ImmunoSensation:
That brings me to another point. When should people come to you for advice?

Elmar Endl:
Well, there are two answers depending on your perspective: "whenever they want" and "as soon as possible". A core facility should be available to any user, anywhere, anytime,so to speak. We are happy to help users at all stages of their project whether it's the planning, the execution or the interpretation of data afterwards. However, it is usually easier for users if they get advice early on in their projects so that they can plan things as efficiently as possible.

In fact, sometimes my advice is not to use flow cytometry at all! FACS offers some fantastic techniques but it's not magic! There are many fascinating scientific questions that are nonetheless better answered with other techniques.

I'm also more than happy to hear what my colleagues are doing even if they have no initial intention of using my facility for their project. Sometimes I realize that we have a technique that could help them, but, all in all, it's simply my job to know what people are working on and what questions interest them. I have to keep informed and up to date if I want to make a relevant contribution to my colleagues' research.

ImmunoSensation:
Do you think your approach to your users is typical for the head of a "core facility"?

Elmar Endl:
There are definitely different approaches out there. There's the "fast-food model" so to speak. A fast-food restaurant may provide quick and reliable service, but you would never go to the staff for cooking lessons. My approach is more of a "Jamie Oliver or Tim Mälzer" style. It's to provide my users with the tricks of the trade, so that they have learned something for life. Small tips can often make a huge difference. In addition, the real challenge is trying to figure out what could help my users before they even realize that they need it. But that's also a really fun part of the job.

ImmunoSensation:
That brings us back to education.

Elmar Endl:
Education is one of the central missions of a core facility. It is also very important in the context of ImmunoSensation. As you know, we are working on an "Office of Shared Resources" within the ImmunoSensation Cluster, and this Office will, amongst many other things, help coordinate education for Cluster-associated scientists.

The measure of a core facility is not only the know-how of the staff that is there but also how qualified your former users have become.

Within the "Office of Shared Resources", meaning collaboratively between the technical platforms, one of our central goals is to standardize the education we give to young scientists. We would like to give our PhD students a minimum standard of knowledge in standard techniques before we send them off into the world.

Of course, I love teaching advanced courses, but, ultimately, I would like for all of our PhD students to at least have one introductory course from our facility before they graduate –even if their everyday life in the lab has nothing to do with flow cytometry. It's a basic skill in life-science research.

I know that means a lot of work for our facility. However, the quality of the Cluster will also be measured by the quality of the scientists we train.

ImmunoSensation:
I completely agree with you. But could you maybe briefly explain to our readers what the "Office of Shared Resources" is?

Elmar Endl:
The idea comes from the US, where federal funding is provided to establish such a central facility for the communication and organization of scientific research at a particular site or university. It's an official point of contact and exchange. The office keeps tabs on what resources available, for example, within the Cluster, and communicates this to researchers. I don't just mean instrumentation but also established techniques, reagents and most importantly know-how. People sometimes forget that the most valuable resource of a university is knlowledge.

ImmunoSensation:
That must be invaluable for new researchers.

Elmar Endl:
This Office is here to help scientists that are new to the Cluster, in particular. We're still at the beginning of things, but we are working on an information packet for new arrivals, whether they are PhD students or professors, detailing what platforms the Cluster offers, what facilities are available, and more importantly whom they should contact. The Office itself is in fact the default contact point if scientists don't know who to ask. Researchers can always start collecting information at the Office of Shared Resources, and we can direct to specific facilities or laboratories from there.

ImmunoSensation:
What are your plans for the Office and the Cluster in the coming years?

Elmar Endl:
Within the "Office of Shared Resources", we would like to coordinate and streamline the use of the technical platforms. It's important that the heads of the technical platforms are in close contact, not just for technical matters, but also so that we can have a coordinated uniform approach to education and young investigator support.

However, my ultimate goal is something that no one really has the blueprints for yet. We would like to collect detailed information on which researchers have established which techniques, so that their colleagues can contact them for help or advice. We would also like to have a reagent database, not only to share things like rare antibodies but also to share information about them, such as "Can you use this antibody to detect endogenous protein levels? Or for immunoprecipitation?" This information is not only important for the next experiment, it can also help us to negotiate prices with a supplier because it allows us to know which products really work. We also want to use social media or whatever else people are using to exchange information and ideas.

We will need a knowledge base and a user base. This is going to be the real challenge. We are in the process of creating a central database, where scientists can schedule the use of equipment and share information, a kind of central organization of innately decentralized things. This may just sound like a nice theory. However, it is in fact a practical approach to saving our researchers time, money and frustration so that they can do better science.

interviewed by **Dr. Eva Bartok**

Cluster Coordination Reports

Family Support & Gender Equality

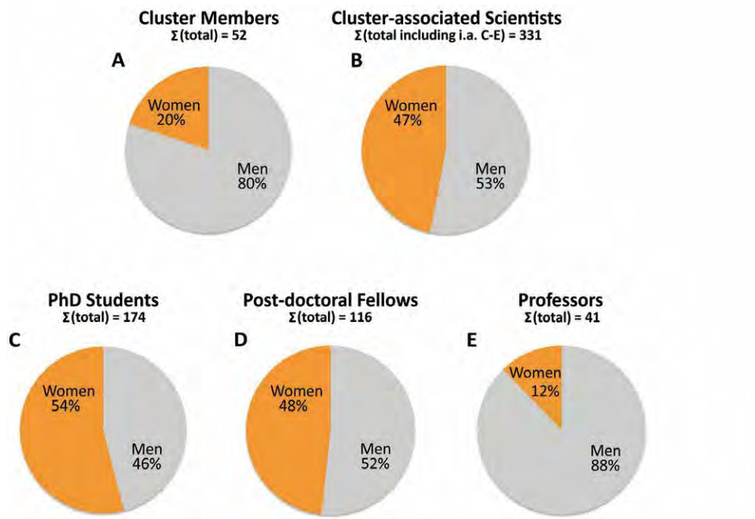
Women are clearly underrepresented in academic science. Although the number of female professors has increased significantly in the last few years, from 8 to 19 percent since 1995[1], in engineering, mathematics and the natural sciences ("MINT-Fächer"), women still only comprise only 9-12% of academic chairholders.
Importantly, this gender disparity is neither due to a lack of interest nor a lack of talent. In Germany, women comprise 44% of PhD students and even 48.5% of what the German National Academic Foundation (Studienstiftung des Deutschen Volkes) considers "highly talented" PhD students[2]. However, most of these talented young women do not go on to pursue successful academic careers. It is striking that the gender disparity begins immediately after women complete their doctorates: female academics only comprise 25% of post-doctoral researchers. Moreover, each further step in the career ladder also sees a further widening of the gender gap.[3] This underrepresentation of women has lead to a great loss of talent and expertise that is not only detrimental to women but to all of academia. Clearly, realizing the potential of our female researchers is key to realizing our greater scientific potential, which is why the ImmunoSensation Cluster of Excellence is committed to supporting female scientists, their career advancement and their scientific progress.

Gender Distribution: ImmunoSensation in Numbers

Currently, women make up **approximately 20%** of **Cluster members** (A) and **47%** of **Cluster-associated scientists** in general (B). Since (B) includes all of scientists within the research groups of Cluster members, the difference between (A) and

Endnotes

[1] Source: Federal Ministry of Education and Research, www.bfbm.de
[2] Source: German National Academic Foundation, www.studienstiftung.de
[3] Ibid (1)



(B) is largely due to the high percentage of **female PhD students, 54%** (C), and **female postdocs 48%**, (D). At the **professorial level**, the proportion of women drops to **12%** (E).
As the numbers indicate, the percentage of female professors in the Cluster currently corresponds to the national average in mathematics and the natural sciences. However, ImmunoSensation is actively seeking to recruit women to professorial positions, and we hope to have more women in leadership roles in the future. In addition, we see our relatively high proportion of female postdoctoral fellows in a very positive light. We hope that many of these women will become the professors of tomorrow, and one central priority of ImmunoSensation's gender support is helping these young women scientists fulfill their career potential.

Gender Support: Our accomplishments in 2012-2013

Ex-ante appointment of a Female W3 Professor

Irmgard Förster was recruited as the first ImmunoSensation Cluster Professor in 2012. Prof. Förster has the W3 chair "Immunology and Environment" at LIMES. Within ImmunoSensation, Prof. Förster is both a member of the central steering committee of ImmunoSensation and one of the leaders of the research area B, "Local Immune Regulation". Prof. Förster's research accomplishments in 2013 are highlighted in the chapter "Local Immune Regulation in Tissues" in this report (p. 81).

Appointment of Three Independent Female Junior Research Group Leaders

Andrea Ablasser, Susanne Buch and Annett Halle have all established independent research groups within the ImmunoSensation Cluster and have been able to establish productive laboratories in Bonn. In particular, Dr. Ablasser's group was exceptionally successful in 2013 with two publications in the prestigious journal Nature. Dr Ablasser's research accomplishments are highlighted in the chapter "DNA Sensing" of this report (p. 17).

Establishment of ImmunoSensation Office of Gender Support

In order to coordinate programs and initiatives for women within the Cluster, ImmunoSensation established an Office of Gender Support in 2013. This office is coordinated by Nicole Dahms and serves as a central contact point for female scientists. Here, women can find out about resources for them within the Cluster but also on a larger university-wide, national or even international level. In addition, the Office regularly reaches out to women in the ImmunoSensation Cluster to find out about their specific concerns in order to better tailor the Cluster's offers to the needs of its female scientists. On the basis of this valuable input from female Cluster scientists, the office arranged its first "gender communication" seminar, which took place in January 2014. Further seminars are planned for 2014.

Cooperation with the University of Bonn

The University of Bonn already has several facilities and programs in place to support women in academia. The Cluster closely cooperates with the gender equality office of the University of Bonn (Ursula Mättig) and the gender equality office of the University Hospital Bonn (Sabine Zander). One result of this cooperation is a **seminar series** that will start in 2014 with general and specific information on gender-related topics that are relevant to scientists, especially young scientists and students.
In addition, the Cluster will fund the participation of female scientists in the MeTra program, a mentoring and networking program for young women in academia. This program is part of a collaboration with the Maria-von-Linden program from the University of Bonn. In 2013, we were able to reserve and fund positions for eight female students in MeTra in 2014.

Childcare for Women in Science

Reconciling family and career obligations is particularly important for women in science. The Office of Gender Support invested considerable resources in 2013 to explore the available possibilities for childcare support for Cluster scientists. In April 2013, a survey was conducted among parents in the Cluster to better ascertain their childcare needs, and, on the basis of this input, the Cluster will offer two core services for parental support in 2014.

- The Cluster helps to fund regular childcare at the nursery "Max and Mary" (Venusberg). This childcare center is conveniently located at the Venusberg between the LIMES and the University Hospital Bonn.

- For urgent or emergency childcare, the Cluster cooperates with the "pme Familienservice" in Bonn. Using this service, it will be possible to provide childcare for emergencies and out-of-town conferences. In addition, there is also the possibility of participating in childcare programs during school holidays ("Ferienbetreuungsangebote").

Outlook for 2014 and Beyond

We hope to continue and to continually improve our programs for female scientists in 2014 with a specific focus on the following goals:

Further Recruitment of Talented Women Scientists to the Cluster

Here, the focus is on leadership positions. In particular, ImmunoSensation aims to recruit **one additional female W3 professor** and **one additional female W2 professor** and **one additional female junior research group leader**. In addition, our goal is to significantly increase the percentage of female members of the Cluster with the active recruitment of outstanding women in science.

Support for Scientists on Parental Leave

Great value is placed in a continuous relationship between the Cluster and its scientists even when an individual is on parental leave. In order to assist scientists who cannot continue their laboratory work due to parental obligations, special funding will be made available to hire student assistants. ("studentische/wissenschaftliche Hilfskraft"). This program will enable researchers to continue their work from home and facilitate their return to the laboratory after parental leave.

Children and the Future of Science

In order to inspire the female scientists of the future, the Cluster is also committed to promoting for children interested in science. Prof. Micheal Heneka, a member of the IS Steering Committee, will take part in the **Children's University Program** ("Kinderuni") in January 2014. ImmunoSensation will also participate in the **Girls' Day 2014.**
Moreover, ImmunoSensation is also planning its own programs for outreach in schools. In 2014, we are also planning an **Immunology Kindergarten** for children from 3 to 6 as well as other courses for older schoolchildren.

Continuous Improvement of Our Current Programs

A sustainable improvement in the representation of women in science is not achievable overnight. At ImmunoSensation, we are committed to the long-term support of our female scientists. We plan to carefully evaluate our progress and stay in close communication with the women within the Cluster in order to better adapt our programs to their changing needs.


universitätbonn
LIMES
Life & Medical Sciences Institute

Young Investigator Support

Immunology is a rapidly expanding field. For young immunologists, this means both an enormous variety of new career opportunities as well as a daunting amount of new information and new techniques which they are expected to acquire. In order to aid young scientists in this challenging field, ImmunoSensation has established a Young Investigator Support (YIS) program for young immunologists associated with the Cluster of Excellence.

Our Students and Young Postdocs

All of the PhD students and young postdocs associated with any of the 52 groups belonging to the ImmunoSensation Cluster members are eligible to participate in the YIS program. Currently, there are 170 PhD students and 87 young postdocs (< 2 years since PhD) from more than 20 countries of the world. These young scientists have research focuses as varied as the field of immunology itself. Within the 52 groups lead by Cluster members, our young researchers are active such fields as innate and adaptive immunity, neuroimmunology, genetics, bioinformatics and applied mathematics.

The diverse backgrounds of our young scientists poses unique challenges but is also an innate strength to the program, as it fosters interdisciplinary research and allows young scientists to meet a variety of colleagues with a variety of academic and professional backgrounds. Since this diversity reflects the diversity of scientific research itself, it is excellent preparation for their further careers.

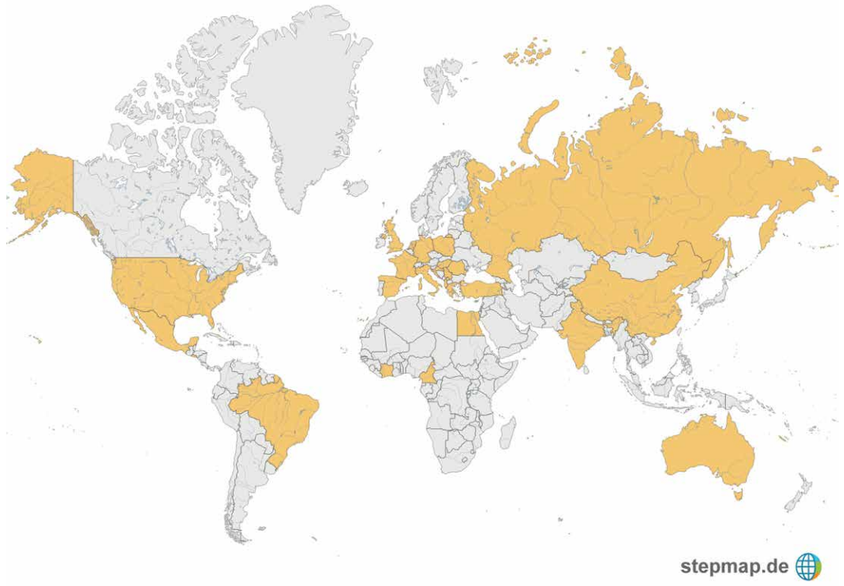


Figure Our young scientists come from all over the world: Native countries of current YIS participants shown in orange.

In order to get to know two of our young scientists more personally, we would encourage you to read our interviews with PhD student Larisa Labzin from Australia (p. 72) and young postdoc Dr. Katharina Hochheiser (p. 68) from Germany. Here, they also describe their experiences with the YIS program.

2013: Our First Year

In August 2013, Dr. Astrid Draffehn and Dr. Eva Bartok became jointly responsible for the YIS program. Dr. Draffehn is a scientist with bioinformatic background at the LIMES Institute of the University of Bonn. Dr. Bartok is a physician at the University Hospital with a background in basic immunological research. By representing two different faculties and professional and educational backgrounds, Dr. Draffehn and Dr Bartok hope to better support the diversity of young investigators within the Cluster.

In September and October 2013, the YIS conducted a large-scale survey among young scientists (app. 80 participants) to find out which techniques, programs and career support would help them most. Our young researchers reported that they were most interested in general courses such as statistics, data analysis and visualization, scientific writing and oral presentations. In addition, they were also particularly interested in soft skills to address conflict management in research and research groups. In terms of career support, students showed particular interest in visiting non-academic institutions and biotech companies. We have incorporated all of these wishes into our YIS program for 2014.

The first event organized by YIS was the Science Day 2013 on October 22. Science Day 2013 is the first of what will be an annual meeting for young scientists to present their work. In 2013, over 70 young scientists in the Cluster submitted their abstracts, and 22 of them were selected to present their work to an audience of 200 other scientists at a one-day meeting. The event was a resounding success and has been extended to three days in 2014. (For more details on Science Day, please see also p. 102).

During and after Science Day, at the end of October, YIS hosted 5 Israeli students and their advisor Prof. Hermona Soreq as part of our scientific exchange with Edmond and Lily Safra Center of Brain Sciences at the Hebrew University in Jerusalem. The students presented their research at Science Day as well as in internal laboratory meetings from member groups. This exchange will be continued in the future as a part of the YIS program.

In November 2013 the Cluster began its Meet-the-Expert series for young scientists. The first professor to participate was Prof. Irina Udalova, Kennedy Institute of Rheumatology, University of Oxford, who held a breakfast meeting with young investigators on November 20.

Our Plans for 2014

In keeping with the needs and wishes expressed by young scientists in the YIS, the following programs have been planned for 2014:

- Scientific Writing with Prof. Wild; MPI for Molecular Biomedicine/ Münster

- R Courses for data analysis & data visualization conducted by Science Craft/ Berlin

Young Investigator Support

Young Investigator Support

- Presentation skills workshop with Science Craft/ Berlin

- Conflict Management with Dr. Roos from ICCON/ Aachen

- General and need-suited FACS courses with Dr. Endl from the Institute of Molecular Medicine/ Bonn

- Proteomics workshop with Dr. Sylvester, Institute for Biochemistry and Molecular Biology/ Bonn

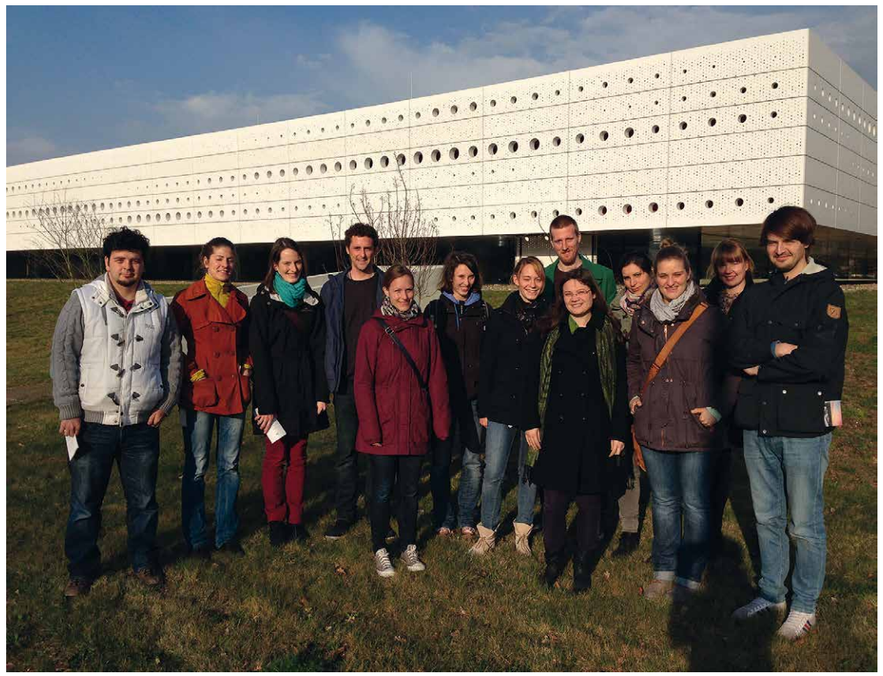
- Excursions to: envihab, the new research facility of the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt/ DLR), and to BAYER Pharma AG Wuppertal

- Continuation of the „meet-the-expert“ series

The International Immunology Training Program Bonn (IITB)

In the summer of 2014, ImmunoSensation will begin its graduate program the IITB, the International Immunology Training Program Bonn, which is affiliated with YIS. All young scientists associated with ImmunoSensation will have the possibility to apply for the IITB, which will provide graduate students and young postdocs with a structured program on immunology and methodology. Throughout the program, IITB participants will be guided by their supervisor and an additional mentor.

Beside these students who are already integrated in one the Cluster research groups, new IITB students funded by the ImmunoSensation Cluster's fellowships will be recruited in summer 2014. The students will perform a three-year experimental research project in one of the member groups of the ImmunoSensation Cluster.



Picture In front of the envihab, German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt/ DLR)
(f.l.t.r.) back row: Özkan Is, Hanna Nievendick, Anna Göbel, Fabian Gondorf, Sven Büttner, Katharina Meyer, Kathy Stein
front row: Christina Mertens, Janina Küpper, Michaela Wittlich, Lora Heffele, Meike Welz, Karl Komander

Picture: (f.l.t.r.)
back row: Sander Tuit, Peeyush Sahu, Kevin Baßler, Wolfgang Krebs, Thomas Ulas
front row: Kathrin Klee, Dr. Astrid Draffehn, Jil Sander

Public Relations

Communicating Science to the Public…

..is always a challenge. On the one hand, the subject matter is specialized. Even ideas and innovations that can bring fundamental change to society may require a lot of background information before they can be understood. On the other hand, scientists themselves may not have the time, interest or didactic know-how to communicate their discoveries to a larger public.

However, the public should not just be interested in science for their own sake. They also have a right to know how their tax money is being spent. Thus, as Kaite Pratt wrote on the Soapbox Science Editor, a community guest blog from nature.com: “Science has a PR problem.”

So, how do we solve it?

The ImmunoSensation Cluster of Excellence would like to reach out to the public. The field of immunology has seen many breakthroughs in the last decades that we feel are important to society at large. We now know that the immune system plays a central role in such widespread diseases as cancer, diabetes, atherosclerosis and Alzheimer’s. In addition, we have also made important progress in our understanding of the underlying mechanisms of autoimmune diseases such as systemic lupus erythematodes and glomerulonephritis. We believe that our research is relevant for society, and we would like to share our enthusiasm.

One central way of reaching out is the report you are now reading. If you read our Scientific Reports (p. 17-59) from 2013, you can see what important contributions we have made to the field of immunology in the last year. We encourage you to do so.

However, we would like to go further by offering a website, podcasts and a presence on social media that explain and promote our scientific successes to the public. We would like to inspire young people to go into our field, whether it is recruiting excellent young researchers or reaching out to school pupils. Furthermore, we would like to promote “ImmunoSensation” as a brand that is connected with successful science and is a fitting environment for young, ambitious and outstanding scientists. Ultimately, a modern and open image will help scientists, from students to professors, decide to become a part of our excellent research community.

What have we done so far?

Our most important “public relations tool” is the website: www.immunosensation.de

Here it is possible to get the latest information about Cluster publications, scientific talks, seminars and news with public outreach. Furthermore, students have the opportunity to get information about our programs and download the application form for the Cluster Graduate Program (IITB).

Podcasts

On immunosensation.de, there are pictures of Cluster events and podcasts about publications and topics of broader interest. These podcasts focus on communicating highly complex research ideas to non-scientists. In some podcasts, the basic research topic of a Cluster

member’s group is presented, so every interested person can comprehend what kind of research is done in that group.

Our podcasts about immunological research provide an entertaining way for the public to come into contact with our research.

Social Media

To announce news and podcasts, we use social media. In October 2013, the Cluster started a Facebook page and a Twitter account. These platforms provide an opportunity for interactive communication for all kinds of people interested in science. In terms of spreading news and getting a reaction to a posted content, social media platforms have become a common way of interaction.

Print Material

Last but not least, the Cluster provides printed materials, e.g. folders, flyers, and this annual report, about the Cluster’s performance and achievements. The Cluster uses a combined approach with online and print communication. In order to connect with scientists all over the world, most communication material is in English and translated from German if necessary.

The ImmunoSensation Cluster of Excellence has been internationally visible for scientists from the beginning – now, we are working on being visible for the greater public, as well.

Events

First Retreat of the ImmunoSensation Cluster

In May 2013, the ImmunoSensation Cluster of Excellence organized its first scientific retreat in St. Goar (Rhine valley), Germany. More than 45 Cluster members from the University of Bonn, LIMES, caesar, the University Hospital Bonn, and DZNE attended the meeting. A particular highlight was the chance to attend talks given by three outstanding national and international guest speakers: Prof. Hermann Wagner (Technical University Munich, Germany), Prof. Ola Winqvist (Karolinska Institute Stockholm, Sweden), and Prof. Hermona Soreq (Hebrew University of Jerusalem, Israel).

The retreat started with an informal hiking tour in the beautiful Rhine valley, giving the scientists the possibility to exchange ideas and discuss opportunities for new collaborations in an informal manner. In the evening the official opening by the Cluster speaker **Prof. Gunther Hartmann**

Prof. Hermann Wagner

was followed by the fascinating lecture of **Prof. Hermann Wagner** entitled “Immune-sensing of nucleotides: Why to abdicate TLR13?“. As a pioneering expert in Toll-like receptor signalling, he shared his personal perspective on the development in the field and presented new data from his work.

On the second day, **Prof. Ola Winqvist** opened the session with an inspiring presentation on “Tailored leukapheresis, a new approach for treating immune mediated diseases”. Prof. Winqvist presented a new clinical methodology, in which the active immune system is balanced by the removal of the proinflammatory cells which are directed against chronically damaged tissues, such as those found patients with autoimmune disease. For this work, he was recently awarded with the Athena prize, a highly prestigious award for clinical research.

Retreat May 2013, St. Goar

The session was then continued with scientific talks given by several Cluster members. They presented exciting

new data covering the different Cluster research topics ranging from the basic molecular and structural mechanisms of nucleic acid recognition by the innate immune system to the immunopathology of Alzheimer disease and lupus erythematosus.

Prof. Hermona Soreq

In the second session, **Prof. Hermona Soreq** presented intriguing insights into the crosstalk between the nervous system and the immune system in her lecture entitled “MicroRNAs in the interface between anxiety and inflammation”.

The session was continued with talks by Cluster members from on research area B: “Local Context Sensing”. The last part of scientific talks was specifically dedicated to the development of new analytical techniques and technological platforms used within the Cluster framework.

Altogether, the retreat gave an overview of the excellent scientific progress and development of the technological platforms in the Cluster. The positive feedback by the participants showed that the retreat fostered the communication among the Cluster members and initiated new interdisciplinary collaborations.

The open atmosphere and the lively scientific discussions made this first retreat of the ImmunoSensation Cluster of Excellence a great success, combining science with the inspiring atmosphere of the UNESCO world heritage Rhine Valley in St. Goar.

ImmunoSensation Cluster Seminars

July 1, 2013

Prof. Hans-Joachim Anders, MD
Medizinische Klinik und Poliklinik IV
Ludwig-Maximilians-University Munich

„NLRP3 and ASC in lupus-like systemic autoimmunity“

The NLRP3 inflammasome is a critical danger signalling platform in innate immunity. Little data is available on its role in adaptive immunity. We found that lack of NLRP3 and ASC aggravates systemic autoimmunity in a mouse model of lupus. This effect seems independent of canonical inflammasome signalling as lack of IL-1R or IL-18 did not share this phenotype. Potential explanations were discussed.

August 21, 2013

Prof. Jens Titze, MD
Vanderbilt University Medical Center
Nashville, TN, USA

„Electrolyte homeostasis: immunology beyond innate and adaptive stereotypes“

September 13, 2013

Prof. Matthew Sweet, PhD
University of Queensland
Australia

„Mapping TLR-inducible inflammatory and antimicrobial pathways in macrophages“

As key innate immune cells, macrophages use distinct families of pattern recognition receptors to respond to danger signals. This enables these cells to initiate effective host defence, but can also lead to inappropriate inflammatory

responses during acute and chronic inflammatory diseases. This talk focused on species differences in cellular responses initiated by the Toll-like Receptor (TLR) family of pattern recognition receptors, the role of TLR-inducible zinc trafficking in human macrophage responses against bacterial pathogens, and the roles of histone deacetylases in regulating TLR-mediated inflammatory responses. The findings from this work help us to understand how some bacterial pathogens overcome macrophage-mediated antimicrobial responses, and may provide opportunities for manipulating TLR signalling for therapeutic benefit.

September 16, 2013

Dr. Dirk Baumjohann, PhD
University of California, San Francisco (UCSF), USA

„MicroRNA Regulation of T Helper Cell Differentiation and Plasticity“

MicroRNAs are potent regulators of T helper (Th) cell differentiation. Here we show that global microRNA expression in T cells is required for the differentiation of naive CD4 T cells into T follicular helper (Tfh) cells, the prototypic Th cell subset that provides help to B cells for the production of high-affinity antibodies. Furthermore, we show that the microRNA cluster miR-17-92 regulates Tfh cells by promoting Tfh cell differentiation and by repressing subset-inappropriate gene expression.

September 16, 2013

Dr. Georg Gasteiger, MD
Immunology Program, Memorial Sloan-Kettering Cancer Center and Howard Hughes Medical Institute, New York, USA

„Help and Regulation: Cooperations at the Interface of Adaptive and Innate Immunity“

The talk was about the interactions between innate and adaptive lymphocytes; specifically, Prof. Gasteiger discussed how regulatory T cells control the function of natural killer cells, and how an „ILC-like“ population of NK cells expands in response to IL-2 in the absence of regulatory T cells, as well as in response to tumors and chronic viral infection.

October 29, 2013

Dr. Shamith Smarajiwa
Computational Biology Group

CRUK Cambridge Institute, University of Cambridge, UK

„Integrative computational approaches for systems immunology and regulatory genomics“

In order to understand complex biology associated with immunity, inflammation and cancer we have developed integrative systems biology approaches. This includes constructing computational resources to integrate, data-mine and understand pathways, networks and underlying regulatory relationships within these systems as well as modelling these systems. We presented examples of such computational resources for innate immunity and inflammation (interferome: the database of interferon regulated genes, tollome and interferonscape: systems models of TLR and IFN systems) and in cancer (models of p53 target gene networks, generated by integrating transcription factor binding and gene expression in phenotypes associated with p53 activity).

October 16, 2013

Prof. Owen Sansom, PhD
University of Glasgow, Beatson Institute for Cancer Research, Scotland, UK

„Investigating key pathways important for tumour initiation, progression and dedifferentiation in vivo“

International cooperation of the Cluster's graduate program IITB

Cooperation of the International Immunology Training Program Bonn (IITB)

Internationality and interdisciplinarity are important key factors for creating experienced and creative networks. To enable our young Cluster scientists to build up those networks and to broaden their knowledge beyond their own research focus, the Excellence Cluster ImmunoSensation has established a cooperation /an exchange with the Edmond and Lily Safra Brain Center, Jerusalem, Israel (ELSC). The ELSC was established within the Hebrew University of Jerusalem and aims to explore the relationships between gene function, brain neuronal circuits, and behavior.

In June 2013, the Dean of the Medical Faculty of the University of Bonn, Prof. Max P. Baur together with Prof. Gunther Hartmann and other professors of the Excellence Cluster visited the ELSC. In a joint effort, the Bonn scientists defined together with their Israeli colleagues the cornerstones of their shared international program for student exchange.

The program will include:

- **Elective courses**. Courses of the ELSC will cover topics like cognitive processes, methods in neurobiology, advanced physiology, neural networks, and computing statistics whilst courses of the ImmunoSensation Cluster will focus on basic immunology, methods in immunology, medical immunology, and medical microbiology.

- **Practical courses in technologies**. Three-week courses in high-end research techniques will be set up to share expertise and enable researchers to efficiently benefit from the provided technical platforms.

- **Exchange program.** PhD students can participate in the graduate program of the partner university and benefit from the expertise of the two institutions.

- **Collaborative research projects**. PhD students as well as group leaders of both collaboration partners will work together on a joint project using the excellent resources of both the ELSC and the Cluster.

- **Scientific meetings and retreats**. The young scientists of the ImmunoSensation Cluster as well as of the ELSC can participate at the scientific meetings and retreats of the other respective institution.

In a first exchange, Prof. Hermona Soreq (ELSC) and five of her Israeli students visited member groups at the University of Bonn and participated in the Cluster Science Day on October 22, 2013. At that event, Geula Hanin and Nir Waiskopf (both from ELSC) gave talks on their current research. (For more detailed information about the Science Day 2013, please see page 102).

Our collaboration with the ELSC gives us the unique opportunity to study the relationship between cognitive neuroscience and immunology. Although such an approach may seem unorthodox, we see great research potential in the intersection of these fields, and we are looking forward to future exchanges and collaborations with the ELSC.

left Picture: (f.l.t.r.)
Prof. Michael Heneka,
Prof. Hermona Soreq

right Picture: (f.l.t.r.)
Prof. Hermona Soreq,
Prof. Gunther Hartmann

Picture: (f.l.t.r.)
Prof. Max Baur,
Prof. Michael Heneka

Picture: (f.l.t.r.)
Prof. Andreas Zimmer,
Prof. Michael Heneka,
Prof. Gunther Hartmann

caesar

center of advanced
european studies
and research

DZNE
German Center for
Neurodegenerative Diseases
within the Helmholtz Association

Cluster Science Day 2013
Joint Meeting of Young Cluster Scientists

Cluster Science Day October 22, 2013

On October 22, 2013 ImmunoSensation held its first „Science Day“, a meeting dedicated to the young scientists of the ImmunoSensation Cluster. All students and young postdocs (< 2 years since PhD) working in Cluster member groups were invited to submit abstracts. We received 71 entries, all of which were excepted for publication in the conference book (available online at www.immunosensation.de). Twenty-two young scientists were also chosen to give oral presentations on October 22 at caesar (center of advanced european studies and research) and competed for a total of 5000€ in prize money. (Please view our profiles of the “Prizewinners” on page 105)

Student Participation
All submitted abstracts themselves were of impressive quality, and much of the research has been subsequently published. The scope of the abstracts covered not only “classical immunology” but also other disciplines from an immunological vantage point, including applied mathematics, biophysics, bioinformatics, genetics, dermatology, electrophysiology, neurology and developmental biology. Thus, the research of our young scientists also reflects the broad spectrum of topics and the interdisciplinary of the research in the Cluster. In addition to the 22 students selected for oral presentations, 120 young scientists attended the conference. Although this made for a large conference, even more attendees are expected in 2014.

The Conference
Altoghether over 170 Cluster-associated scientists attended Science Day. Thus, our young scientists were able to present their research to a full auditorium. During the question-and answer session after each talk, presenters had the opportunity to field questions from both young colleagues and renowned experts alike. This lively scientific discussion continued well into the coffee breaks, giving scientists “young and old” an excellent forum for scientific exchange. Many scientists also saw the conference as an opportunity to get up to date on research within the Cluster in general. We hope that this contact has also formed a basis for future scientific collaborations between Cluster scientists.

International Guests
We were very please to welcome Prof. Hermona Soreq from the Edmond and Lily Safra Institute in Jerusalem. Prof. Soreq was also accompanied by five of her Israeli students, Bettina Nadorp, Geula Hanin, Nadav Yayon, Shani Shenhar-Tsarfaty, and Nir Waiskopf. Two of Prof. Soreq’s group members were chosen to give talks on Science Day.

Geula Hanin: “Competing targets of microRNA-608 modulate risks of hypertension and anxiety”

Nir Waiskopf: “Semiconductor Nanoparticles for Biological Applications: The Promise and Challenges”.

In honor of our Israeli guests, everyone was invited to stay for beer and snacks after the conference in the foyer of caesar. Even though the scientific discussion continued, the atmosphere was relaxed, and many of the guests stayed well into the evening to chat with our guests.

Cluster Science Day October 22, 2013

Picture Lecture Hall at center of advanced european studies and research (caesar)

Picture (f.l.t.r.) Prof. Gunther Hartmann, Dr. Shani Shenhar-Tsarfaty, Geula Hanin, Prof. Hermona Soreq

Cluster Science Day 2013 Prizewinners

Science Day 2014

The popularity and success of this year's Science Day encouraged us to extend that event from one to three days in 2014 and to include not only oral presentations but also poster sessions. The next "Science Days" will take place in November and additionally host the scientific advisory board (SAB) of the ImmunoSensation Cluster. The Cluster's SAB includes:

Anthony Cerami (CEO Araim Pharmaceuticals, Ossining, USA)

Steve Cohen (Department of Cellular and Molecular Medicine, Copenhagen, Denmark)

Charles Dinarello (Division of Infectious Diseases, Aurora, USA)

Douglas T. Golenbock (University of Massachusetts Medical School, Worcester, MA, USA)

Herbert Jäckle (Max Planck Institute for Biophysical Chemistry, Göttingen, Germany)

Luke O'Neill (Trinity College Dublin, Dublin, Ireland)

Hidde Ploegh (Whitehead Institute for Biomedical Research, Cambridge, USA)

Brigitta Stockinger (MRC National Institute for Medical Research, London, UK)

Hermann Wagner (Technische Universität München, Munich, Germany)

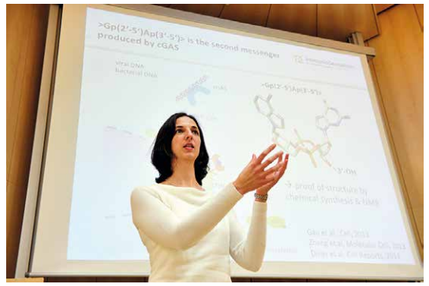
Tony Wyss-Coray (Stanford, CA, USA)

We are looking forward to ImmunoSensation's Science Days 2014 and would encourage you to attend.

Science Day: the Prizewinners in Profile

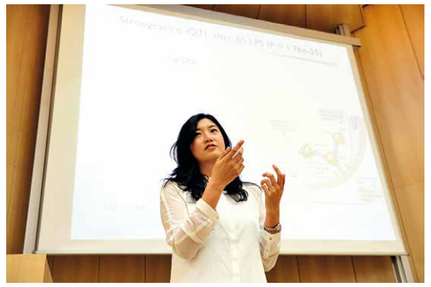
All of the Science Day presentations on October 22 were excellent, and the ImmunoSensation Steering Committee had quite a difficult time choosing the prizewinners. Ultimately, 10 participants were chosen for the "first" and "second" prizes with 6 "second prizes" (350€) and four "first prizes" (700€) being awarded. We would like to extend our sincerest congratulations to the winners, and we encourage you to read the profiles of our prizewinners and their outstanding research!

First Prize



Marion Goldeck
Marion is a PhD student under the supervision of Prof. Gunther Hartmann (p. 147) and Dr. Janos Ludwig. On Science Day, she presented her work on the chemical analysis, synthesis and bioactivity of STING ligands. Specifically, in collaboration with Dr. Andrea Ablasser (p.141) and Prof. Veit Hornung (p.152), the researchers were able to determine the precise endogenous ligand of STING downstream of the cytosolic DNA-sensing protein cGAS. This molecule, cyclic [G(2',5')pA(3',5')p], is the first example of a combined 2'-5' / 3'-5' phosphodiester linkage in a natural nucleic acid. Marion, Dr. Andrea Ablasser and Prof. Veit Hornung have published these results in Nature. (PMID: 23722158, "cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING", Nature 2013). For more information on this publication, please see the chapter "DNA Sensing" of this report (p. 17)

Sebastian Hückesfeld
Sebastian is a PhD student in Prof. Michael Pankratz's laboratory (p. 164) Sebastian presented his work on pathogen avoidance in Drosophila, a topic that is at the intersection of behavioral biology, electrophysiology and immunology. Sebastian was able to show that oral intake of food could be inhibited via a neural circuit under the control of neurons expressing the Hugin neuropeptide. Activating these neurons resulted in an increase in expression of the anti-microbial peptide Drosomycin, which is normally upregulated in response to fungal infection. Interestingly, Hugin has a mammalian homologue, NeuromedinU, which is also involved in inflammatory processes. Sebastian and his colleagues have since published a selection of these results in PloS Biology.w (PMID: 24960360, "Selection of motor programs for suppressing food intake and inducing locomotion in the Drosophila brain", PloS Biology 2014) More information on this publication will be included in the Annual Report 2014.



Sarah Kim
Sarah is a medical resident in Human Genetics and performs research on the intersection between genetics and innate immunology under the joint supervision of Dr. Johannes Schumacher and Prof. Veit Hornung (p.152) Sarah's work examines genetic variants that influence gene expression under LPS stimulation (so called immune response expression quantitative trait loci (iQTLs)). In her study, she examined monocytes isolated from

Cluster Science Day 2013 Prizewinners

136 human volunteers and was able to map several novel iQTLs, which are active after TLR-4 stimulation. In particular, she identified iQTLs that confer risk to primary bililary cirrhosis (PBC), inflammatory bowel disease (IBD) and celiac disease. These findings could bring novel insights into the pathophysiology of these disorders.

Larisa Labzin
Larisa is a PhD student under the supervision of Prof. Eicke Latz (p. 159). Her research has focused on the anti-inflammatory role of HDL in normocholesterolemic individuals. In collaboration with Prof. Joachim L. Schultze (p. 165), Larisa and her colleagues were able to show that HDL activates the transcriptional repressor ATF3 in macrophages leading to a downregulation in the production of inflammatory cytokines. These results have since been published in Nature Immunology. (PMID: 24317040 “High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3”, Nature Immunology 2014.) For more information on this publication, please see the chapter on „Sterile Inflammation“ in this report (p. 42). In addition, Larisa was also kind enough to allow us to interview on her studies and research in Bonn (p. 72).

Second Prize

Tobias Bald
Tobias is a PhD student under the supervision of Prof. Thomas Tüting (p. 166). He presented his research on the effect of UV-induced inflammation on melanoma metastasis. In collaboration with Prof. Waldemar Kolanus (p. 157) and Dr. Thomas Quast, Tobias and his colleagues were able to show that a UV-induced neutrophilic inflammatory response promotes tumor cell migration along blood vessel surfaces and is associated with a higher number of metastases. These results have recently been published in Nature. (PMID: 24572365 “Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma”, Nature 2014.) More information on this publication will be included in the Annual Report.

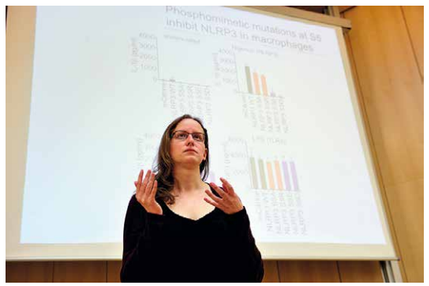
Felix Eppler
Felix is a PhD student under the supervision of Prof Waldemar Kolanus (p. 157). Felix presented his research about T-cell adhesion mediated by the small GTPase RAP-1 and the large GTPase Dynamin 2. RAP-1 is known to be an important regulator of integrin activity and cell polarization in leukocytes. However, Felix was the first to investigate the role of Dynamin 2 as a mediator of RAP-1 activation. Chemical inhibition as well as siRNA-mediated knockdown of Dynamin 2 resulted in deficient cell adhesion which could be rescued by RAP-1 overexpression. Thus, Felix was able to identify Dynamin 2 as a completely novel mediator of integrin dynamics and has elucidated a new layer of regulation in the complex process of leukocyte adhesion and migration.

Elvira Mass
Elvira completed her PhD in molecular biomedicine at the end of 2013 under the supervision of Prof. Michael Hoch (p. 149). In collaboration with Dr. Dagmar Wachten, Elvira was able to identify the gene Creld1 as key regulator of the calcineurin/nuclear factor of activated T cells pathway. Calcineurin and NFAT are well-known mediators of inflammatory responses and are the targets of the immunosuppressive drugs Ciclosporin A and Tacrolimus. In addition, Elvira and her colleagues were able to show that Creld1 deficiency leads to defective cardiac valve development and embryonic lethality in knockout mice, which most likely accounts for the known association between Creld1 mutations and atrioventricular septal defects in human patients. Thus, Elvira’s work is at the intersection of immunology and developmental biology. These results have since been published in Developmental Cell. (PMID: 24697899 “Murine Creld1 Controls Cardiac Development through Activation of Calcineurin/NFATc1 Signaling”, Developmental Cell 2014) More information on this publication will be included in the Annual Report 2014.

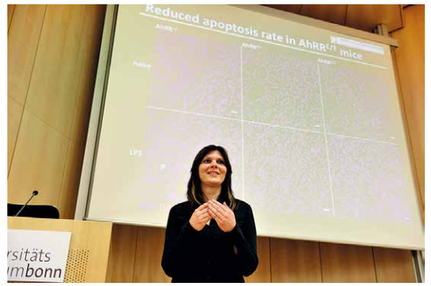
Jonathan Schmid-Burgk
Jonathan is a PhD student under the supervision of Prof. Veit Hornung (p. 152). Jonathan and his colleagues have developed a semi-automated high-throughput assembly platform for TALE nuclease genes and CRISPR gRNA plasmids. Using a ligation-independent cloning method developed by Jonathan, the researchers are currently working on the production of genome-wide libraries with the goal of pursuing genome-wide CRISPR screenings. Jonathan and his colleague have already published this cloning approach for TALE nuclease genes in Nature Biotechnology. (PMID:

Cluster Science Day 2013 Prizewinners

23242165 “A ligation-independent cloning technique for high-throughput assembly of transcription activator–like effector genes”, Nature Biotechnology 2013).



Andrea Stutz
Andrea Stutz is a PhD student under the supervision of Prof. Eicke Latz (p 159). Andrea presented her work on the regulation of NLRP3, a protein which is involved in the secretion of pro-inflammatory cytokines in response to bacterial toxins and endogenous danger signals. It is already known that NLRP3 is regulated on at the transcriptional and translational level. However, Andrea was also able to discover that NLRP3 may require dephosphorylation of a critical serine residue in order to activate downstream signaling. Since NLRP3 has been implicated in many widespread diseases including diabetes mellitus, Alzheimer disease and atherosclerosis, a better understanding of endogenous NLRP3-regulation could allow for novel therapeutic approaches.



Julia Vorac
Julia is a PhD student under the supervision of Prof. Irmgard Förster (p. 145). Julia presented her research on the Aryl Hydrocarbon Receptor Repressor(AhRR) and its role in the immune response to LPS. AhRR negatively regulates Aryl Hydrocarbon Receptor(AhR) activity by competing for their common binding partner ARNT. The expression of AhR is known to be induced by LPS-mediated NF-KB signaling. After generating an eGFP-reporter mouse for AhRR, Julia was able to demonstrate that many immune cells of barrier organs, such as the skin or the intestinal epithelium, constitutively express AhRR. Using eGFP-expressing AhRR-deficient mice, Julia could show that AhRR deficiency improved survival after LPS challenge and Citrobacter rodentium infection with lower systemic pro-inflammatory cytokine levels. Interestingly, the reduction of pro-inflammatory cytokines in the liver could be directly attributed to the smaller number of Kupffer cells (liver macrophages) found in AhRR-deficient mice. These results suggest that there is important crosstalk between the AhR/AhRR system and microbe sensing by the innate immune system.

Picture (f.l.t.r.)
Tobias Bald, Julia Vorac, Jonathan Schmid-Burgk, Sarah Kim, Marion Goldeck, Andrea Stutz, Sebastian Hückesfeld, Larisa Labzin, Felix Eppler

Cluster Science Day 2013 October 22, 2013

Prizewinners

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ImmunoSensation Publication List 2013

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ImmunoSensation Publication List 2013

List of Seminars and Meetings

Seminars and Meetings 2013

SFB 704: Epigenetic silencing of ATG5 in melanoma
April 10, 2013
Prof. Dr. Dr. Hans-Uwe Simon, Institute of Pharmacology, University of Bern

SFB 645: Role of Ceramides in Metabolic Diseases
April 25, 2013
Prof. Scott Summers, PhD
Duke-NUS Graduate Medical School, Singapore

Bonn Lecture Series in Neuroscience: Brain networks underlying episodic memory retrieval
May 14, 2013
Prof. Michael D. Rugg, PhD
Distinguished Chair in Behavioral and Brain Sciences
Co-Director of the Center for Vital Longevity, University of Texas
Institute of Physiology, University of Leipzig

SFB 704: Visualizing Type I Interferon producing cells – a matter of commitment?
June 11, 2013
Prof. Dr. rer. nat. Stefanie Scheu, Institute for Medical Microbiology and Hospital Hygiene, University Hospital Duesseldorf

SFB/TRR 57 CMM-lecture: Homodimers of the NF-kappB p50 subunit function as tumour suppressors in ageing- and carcinogen-associated liver disease
June 26, 2013
Prof. Dr. Derek Mann, Institute of Cellular Medicine, Newcastle University

Bonn Lecture Series in Neuroscience: Autonomous and non-autonomous regulation of axon integrity
June 27, 2013
Dr. Bogdan Beirowski, MD, PhD, Washington School of Medicine, Department of Genetics,
St Louis, Missouri

SFB 704: Studying Epstein-Barr Virus pathologies and immunosurveillance by reconstructing EBV infection in mice
June 28, 2013
Prof. Dr. rer. nat. Klaus Rajewsky, Max Delbrück Center for Molecular Medicine, Berlin

ImmunoSensation Seminar: NLRP3 and ASC in lupus-like systemic autoimmunity
July 01, 2013
Prof. Dr. med. Hans-Joachim Anders, Medizinische Klinik und Poliklinik IV
Ludwig-Maximilians-University Munich

Seminars 2013

SFB 704: CD4 T cells amplify innate immune response by dendritic cells for optimal anti-viral CTL immunity
July 09, 2013
Dr. Sammy Bedoui, University of Melbourne

ImmunoSensation Seminar: Electrolyte homeostasis: immunology beyond innate and adaptive stereotypes
August 21, 2013
Prof. Dr. Jens Titze, Vanderbilt University Medical Center, Nashville, TN, USA

ImmunoSensation Seminar: Mapping TLR-inducible inflammatory and antimicrobial pathways in macrophages
September 13, 2013
Prof. Matt Sweet, PhD, Department of Pediatric Haematology & Oncology, University of Queensland, Australia

ImmunoSensation Seminar: MicroRNA Regulation of T Helper Cell Differentiation and Plasticity
September 16, 2013
Dr. Dirk Baumjohann, University of California, San Francisco (UCSF), USA

ImmunoSensation Seminar: Help and Regulations: Cooperations at the Interface of Adaptive and Innate Immunity
September 16, 2013
Dr. Georg Gasteiger, Immunology Program, Memorial Sloan-Kettering Cancer Center and Howard Hughes Medical Institute, New York, USA

SFB 704: The growing family of NKT cells meet the growing family of lipid antigens
September 18, 2013
Prof. Dr. Dale Godfrey, University of Melbourne, Australia

SFB 704: Vaccination against chronic diseases
September 24, 2013
Prof. Dr. Martin Bachmann, The Jenner Institute, University of Oxford, UK

ImmunoSensation Seminar: Investigating key pathways important for tumour initiation, progression and dedifferentiation in vivo
October 16, 2013
Prof. Owen Sansom, PhD, Beatson Institute for Cancer Research, University of Glasgow, Scotland

ImmunoSensation Seminar: Investigating key pathways important for tumour initiation, progression and dedifferentiation in vivo
October 29, 2013
Dr. Shamith Samarajiwa, University of Cambridge, UK

Seminars 2013

SFB 704: Antibodies modulate immune highways and dendritic cell trafficking
November 05, 2013
Dr. Menna Clatworthy, Department of Medicine, Laboratory of Molecular Biology University of Cambridge, UK

SFB 704: Mechanisms of Gene Regulation in Immune Cells
November 11, 2013
Dr. Elke Glasmacher, Institute for Diabetes and Obesity Helmholtz Zentrum, München

SFB 704: Ab initio characterization of the immune system using massively parallel single cell RNA-Seq
November 14, 2013
Prof. Dr. Ido Amit, Laboratory for Immuno-Genomics, Weizmann Institute of Science, Rehovot, Israel

SFB 704: IRF5 expressing macrophages: regulation of inflammatory gene programme
November 19, 2013
Prof. Irina Udalova, PhD Kennedy Institute of Rheumatology, University of Oxford, UK

Bonn Lecture Series on Systems Biology - Kick-off Seminar: Regulatory RNAs
December 05, 2013
Prof. Dr. Nikolaus Rajewsky, Max-Delbrück-Center for Molecular Medicine, Berlin

Meetings 2013

SFB 704 Symposium: Immuno Regulation
April 22, 2013 - April 23, 2013
Speaker Prof. Tom Freeman, Division of Genetics & Genomics, University of Edinburg
Speaker Prof. Hans-Uwe Simon, Institute of Pharmacology, University of Bern

Retreat ImmunoSensation Cluster of Excellence
May 26-27, 2013, Schlosshotel Rheinfels, St. Goar

Cluster Science Day
October 22, 2013, research center caesar, Bonn

Roche Workshop 2013 for Young Scientists of the ImmunoSensation Cluster of Excellence
November 19-20, 2013, Life & Brain, University Hospital Bonn

Prizes & Distinctions

Prizes and Distinctions awarded within the ImmunoSensation Cluster 2013

June 29, 2013 University of Bonn awarded Prof. Hermann Wagner an honorary doctorate
Prof. Hermann Wagner from the Institute of Medical Microbiology at the Technical University Munich received an honorary doctorate from the Medical Faculty of the University of Bonn for his achievements in immunology.

July 01, 2013 ImmunOligo received third prize at Science4Life business plan competition
The GO-Bio funded project „RNA Therapeutics“ and its partner company ImmunOligo won third prize at the Science4Life annual business plan competition. The business plan was presented by Prof. Gunther Hartmann, Dr. Annegret de Baey-Diepolder, Dr. Christine Schuberth, Dr. Marcel Renn, Anna Schwickart.

August 05, 2013 Prof. Anton Bovier became a Fellow of the Institute of Mathematical Statistics (IMS)
Anton Bovier, Professor in Applied Mathematics at Rheinische Friedrich-Wilhelms-Universität Bonn, has been named a Fellow of the Institute of Mathematical Statistics (IMS). An induction ceremony took place at the Joint Statistics Meetings in Montreal, Quebec, Canada. Prof. A. Bovier received the award for his research into the theory of random media.

October 07, 2013 Dr. Andrea Ablasser and Prof. Veit Hornung received Pettenkofer Prize
Dr. Ablasser and Prof. Hornung from the Institute for Molecular Medicine, University Hospital Bonn won the prize granted by the Pettenkofer Foundation in Munich in recognition of their work on the activation of STING by the cGAS produced second messenger (see: Ablasser A. et. al. Nature 2013 June 0;498(7454):380-4).

October 24, 2013 Dr. Andrea Ablasser received Jürgen Wehland Prize
The Jürgen Wehland Prize is for junior scientists. Dr. Ablasser from the Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn was awarded the Jürgen Wehland Prize for her outstanding research on mechanisms of pathogen recognition by the innate immune system.

October 24, 2013 Prof. Michael T. Heneka received the Alzheimer Research Award
The Hans und Ilse Breuer Foundation awarded Prof. Dieter Edbauer (DZNE-Munich) und ImmunoSensation cluster member Prof. Michael T.Heneka (University of Bonn and DZNE-Bonn) with the Alzheimer Research Award. Prof. Michael T. Heneka was awarded in recognition of his research on neuroinflammatory diseases.

2013 Prof. Hermona Soreq from The Edmond and Lily Safra Center for Brain Sciences (Hebrew University of Jerusalem) became an Advanced ERC

Prizes and Distinctions awarded within the Cluster 2013

2013 Prof. Gunther Hartmann from the Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn became an elected member of the German National Academy of Sciences, Leopoldina

2013 Prof. Frank Bradke form the German Center for Neurodegenerative Diseases (DZNE) became an elected EMBO member The European Molecular Biology Organization elects members based on their outstanding achievements over the course of their scientific careers.

December 05, 2013 Carola Hertrich received the first prize from BONFOR for SciMed- scholars
Carola Hertrich is from the Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn. She was awarded for her work on " iFi203-An Important componen of cyclic dinucelotide sensing". Her advisors are Dr. A. Ablasser and Prof. V. Hornung.

December, 05 2013 Barbara Heinemann received the second prize from BONFOR for SciMed-scholars
Barbara Heinemann is from the Institute for Human Genetics, University Hospital Bonn, was awarded for her work on the "Analysis of genetic risk factors on KCTD13, a candidate gene for schizophrenia". Her work was done in the Institute of Human Genetics, which is under the supervision of Prof. M. Nöthen.

December 05, 2013 Maren Schmalenströr received the third prize from BONFOR for SciMed-scholars
Maren Schmalenströr from the Institute of Clinical Chemistry and Clinical Pharmacology (University Hospital Bonn), was awarded for her work on "Antitumoral CD8+ T cell response after therapeutic vaccination with whole-cell vaccines in syngeneic mouse models of ovarian cancer". Her advisors are the Cluster members Dr. W. Barchet and Prof. G. Hartmann.

December 05, 2013 Dr. Judith Kohlmeyer received the first prize from BONFOR for Gerok-scholars
Dr. Kohlmeyer from the Institute of Dermatology and Allergy, University Hospital Bonn, was awarded for her work on " TNF-alpha reversibly impairs recognition of melanomas by antigen specific T cells". Her advisor is Prof. T. Tüting.

December 05, 2013 Dr. Isabel Spier received the second prize from BONFOR for Gerok-scholars
Dr. Spier from the Institute of Human Genetics, University Hospital Bonn, was awarded for her work on the "Identification of candidate genes in intestinal polyposis".
Dr. Spier is a physician in the Institute of Human Genetics under the supervision of Prof. M. Nöthen.

December 05, 2013 Dr. Sebastian Zimmer received the first prize from BONFOR for junior research group leaders
Dr. Zimmer from the Department of Medicine/Cardiology, University Hospital Bonn,

Prizes and Distinctions awarded within the Cluster 2013

was awarded for his research on the Toll-like-rezeptor 3 in arteriogenesis, which he presented during the BONFOR-Symposium in Bonn. Dr. Zimmer's group is a part of the Medical Clinic II under the supervision of Prof. G. Nickenig.

December 05, 2013 Dr. med Laura Maintz received the second prize from BONFOR for junior research group leaders
Dr. Maintz from the Department of Dermatology and Allergy, University Hospital of Bonn, was awarded for her research on "Neuropeptide and Neurotrophin levels and the increased expression of their receptors in skin of patients with mastocytosis", which she presented during the BONFOR-Symposium in Bonn. Dr. Maintz's group is a part of Clinic of Dermatology and Allergology under the supervision of Prof. N. Novak.

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Annual Report 2013
ImmunoSensation Member List

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Life & Medical Sciences Institute (LIMES)
University of Bonn
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Annual Report 2013
ImmunoSensation Member List

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Zimmer, Andreas
Institute of Molecular Psychiatry (IMP)
Medical Faculty, University of Bonn, University Hospital Bonn
neuro@uni-bonn.de

Biosketches

Cluster Application Members

Dr. Andrea Ablasser, MD

Institute of Clinical Chemistry and Clinical Pharmacology

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Clinical Chemistry and Clinical Pharmacology

E-Mail: andrea.ablasser@uni-bonn.de

Research Expertise

Dr. Ablasser's main research focus is the immunorecognition of nucleic acids. Her work has contributed to identifying intracellular DNA sensors and to elucidating DNA-triggered antiviral signaling mechanisms.

Education / Training

University of Munich, Germany, Medicine, M.D., thesis, 2010
University of Munich, Germany, Medicine, M.D., state examination, 2008

Appointments / Positions Held

Since 2014
Assistant Professor, Global Health Institute, École Polytechnique Féderale de Lausanne, Switzerland

2011 - 2014
Junior Group Leader, Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Germany

2008 - 2011
Postdoctoral Research Fellow, Department of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Germany

2008
Visiting scientist, Division of Infectious Diseases and Immunology, University of Massachusetts, Worcester, USA

Honors / Awards

2014
Paul Ehrlich- und Ludwig Darmstaedter Prize for Young Researchers
2013
Max von Pettenkofer Prize
2013
Jürgen Wehland Prize

2010
Dissertation Price of the University of Munich (Münchener Universitätsgesellschaft)

2009
Fellow of the program "BONFOR", Medical Faculty, University of Bonn

2007
Fellow of the Munich-Harvard-Alliance
Fellow of the German Academic Exchange Service (DAAD)

2006
Graduate School 1202 "Oligonucleotides in cell biology an therapy", German Research Foundation (DFG)

2005
Fellow of the German National Merit Foundation (Studienstiftung des Deutschen Volkes)

10 Most Relevant Publications for Dr. Andrea Ablasser

1. **Ablasser A**, Hemmerling I, Schmid-Burgk JL, Behrendt R, Roers A, Hornung V. TREX1-deficiency triggers cell-autonomous immunity in a cGAS-dependent manner.
Journal of Immunology. 2014, in press
2. **Ablasser A**, Schmid-Burgk JL , Hemmerling I, Horvath G, Schmidt T, Latz E, Hornung V. Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP.
Nature 2013 Sep 29. doi: 10.1038/nature12640
3. **Ablasser A**, Goldeck M, Cavlar T, Deimling T, Witte G, Röhl I, Hopfner K-P, Ludwig J, Hornung V. cGAS produces a 2′-5′-linked cyclic dinucleotide second messenger that activates STING. Nature 2013 Jun 20;498(7454):380-4. doi: 10.1038/nature12306.
4. Civril F, Deimling T, de Oliveira Mann C. C, **Ablasser A**, Moldt M, Witte G, Hornung V, Hopfner K-P. Structural mechanism of cytosolic DNA sensing by cGAS.
Nature 2013 Jun 20; 498 (7454):332-7. doi: 10.1038/nature12305.
5. Cavlar T, Deimling T, **Ablasser A,** Hopfner KP, Hornung V. Species-specific detection of the antiviral small-molecule compound CMA by STING. EMBO J. 2013 May; 15;32 (10): 1440-50.
6. Kim S, Bauernfeind F, **Ablasser A**, Harmann G, Fitzgerald KA, Hornung V. Listeria monocytogenes is sensed by the NLRP3 and AIM2 inflammasome. European Journal of Immunology. 2010 Jun; 40 (6):1545-51.
7. **Ablasser A**, Bauernfeind F, Hartmann G, Latz E, Fitzgerald KA, Hornung V. RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nature Immunology. 2009; 10 (10):1065-72.
8. **Ablasser A**, Poeck H, Anz D, Berger M, Schlee M, Kim S, Bourquin C, Goutagny N, Jiang Z, Fitzgerald KA, Rothenfusser S, Endres S, Hartmann G, Hornung V. Selection of molecular structure and delivery of RNA oligonucleotides to activate TLR7 versus TLR8 and to induce high amounts of IL-12p70 in primary human monocytes. Journal of Immunology. 2009 Jun 1;182 (11): 6824-33.
9. Berger M, **Ablasser A**, Kim S, Bekeredjian-Ding I, Giese T, Endres S, Hornung V, Hartmann G. TLR8 driven IL-12-dependent reciprocal and synergistic activation of NK cells and monocytes by immunostimulatory RNA. Journal of Immunotherapy. 2009 Apr; 32 (3): 262-71.
10. Hornung V, **Ablasser A**, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Latz E, Fitzgerald KA. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC.
Nature. 2009 Mar 26; 458 (7237): 514-8.

Dr. Ashraf Al-Amoudi, PhD

German Centre for Neurodegenerative Diseases (DZNE) and center of advanced european studies and research (caesar)

German Centre for Neurodegenerative Diseases (DZNE) and center of advanced european studies and research (caesar)

E-Mail: ashraf.al-amoudi@dzne.de

Research Expertise

Structural biology, cryo-electron tomography, intercellular adhesion unctions, synapses, neurodegenerative diseases.

Education / Training

University of Lausanne, Switzerland, Life science/EM Structural, Biology, PhD, 2004
University of Lausanne, Switzerland, Physics, Science diploma, 1999
Birzeit University, West Bank, Palestine, Physics, B.Sc, 1997

Appointments / Positions Held

Jan 2010 - present
Group leader, Cryo-Electron Microscopy and Tomography in neurodegenerative diseases, German Centre for Neurodegenerative Disease (DZNE) and Center of Advanced European Studies and Research (caesar), Bonn
2005 - 2009
Postdoctoral fellow, Structural and Computational Biology Unit, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
2004 - 2005
Postdoctoral, Laboratory of Ultrastructure Analysis University of Lausanne, Switzerland

Honors / Awards

2014 – 2017
SFB, Transregio Collaborative Research, TRR83
2012 – 2017
Cluster of Excellence, ImmunoSensation, DFG
2010 - 2014
Wellcome Trust and MRC Career Development Awards - declined
2007 - 2009
Marie Curie Intra-European Fellowship
2006 - 2007
EMBO Fellowship
2005
Prize of excellence for young researchers for the PhD work, Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

10 Most Relevant Publications for Dr. Ashraf Al-Amoudi

1. **Al-Amoudi A**, Frangakis AS. 2013. Three-dimensional visualization of the molecular architecture of cell-cell junctions in situ by cryo-electron tomography of vitreous sections. Methods Mol Biol 961: 97-117.
2. **Al-Amoudi A**, Castaño-Diez D, Devos DP, Russell RB, Johnson GT, Frangakis AS. The three-dimensional molecular structure of the desmosomal plaque. Proc. Natl. Acad. Sci. 2011,108, 6480-5.
3. **Al-Amoudi A**, Diez DC, Betts MJ, Frangakis AS. 2007. The molecular architecture of cadherins in native epidermal desmosomes. Nature 450: 832-7.
4. Castano-Diez D, **Al-Amoudi A**, Glynn AM, Seybert A, Frangakis AS. 2007. Fiducial-less alignment of cryo-sections. J Struct Biol 159: 413-23.
5. **Al-Amoudi A**, Studer D, Dubochet J. 2005. Cutting artefacts and cutting process in vitreous sections for cryo-electron microscopy. J Struct Biol 150: 109-21.
6. **Al-Amoudi A**, Dubochet J, Norlen L. 2005. Nanostructure of the epidermal extracellular space as observed by cryo-electron microscopy of vitreous sections of human skin. J Invest Dermatol 124: 764-77.
7. Norlen L, **Al-Amoudi A.** 2004. Stratum corneum keratin structure, function, and formation: the cubic rod-packing and membrane templating model. J Invest Dermatol 123: 715-32.
8. **Al-Amoudi A**, Chang JJ, Leforestier A, McDowall A, Salamin LM, Norlen LP, Richter K, Blanc NS, Studer D, Dubochet J. 2004. Cryo-electron microscopy of vitreous sections. EMBO J 23: 3583-8.
9. Norlen L, **Al-Amoudi A**, Dubochet J. 2003. A cryotransmission electron microscopy study of skin barrier formation. J Invest Dermatol 120: 555-60.
10. **Al-Amoudi A**, Norlen LP, Dubochet J. 2004. Cryo-electron microscopy of vitreous sections of native biological cells and tissues. J Struct Biol 148: 131-5.

Prof. Regina Betz, MD

Institute of Human Genetics

Rheinische Friedrich-Wilhelms-Universität Bonn Institute of Human Genetics

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Research Expertise

The aim of our research is the identification and functional characterization of genes for monogenic and genetically complex hair loss disorders with a major focus on the autoimmune disorder alopecia areata (AA). We have the largest sample of AA patients available worldwide, which includes a current total of more than 2.200 individuals of middle European origin. We have been able to demonstrate the contribution of the HLA-complex and the genes PTPN22, TRAF1/C5 , CTLA4, IL13 and KIAA0350 to the disease risk using candidate gene studies. By the use of genome-wide association studies, meta-analyses, immunochips and further functional studies, we are currently aiming to identify new causative genes for AA and will thus contribute to a comprehensive understanding of AA.

Education / Training

University of Bonn, Germany Human Genetics, Habilitation, 2009
University of Bonn, Germany, Human Genetics, Medical Specialist, 2007
Karolinska Institute, Stockholm, Sweden University of Saarland Clinical Medicine, Medical license, 1999
University of Saarland, Germany, Medicine, MD thesis, 1998

Appointments / Positions Held

2010 - present Heisenberg Professorship, Institute of Human Genetics, University of Bonn, Germany
2009 - 2010 Research Scientist, Institute of Human Genetics, University of Bonn, Germany
2004 - 2009 Independent Head of a Junior Research Group, Institute of Human Genetics, University of Bonn, Germany
2002 - 2004 Postdoctoral fellow, Department of Medical Genetics, University of Antwerp, Belgium
2000 - 2002 Postdoctoral fellow, Institute of Human Genetics, University of Bonn, Germany
1999 - 2000 Research Scientist, Institute of Human Genetics, University of Bonn, Germany

Honors / Awards

2010 Heisenberg-Professorship from the DFG
2004 - 2009 Emmy Noether Independent Junior Research Group (DFG)
2008 PRO-SCIENTIA-Sponsorship Award of the Eckhart-Buddecke-Foundation for the advancement of basic medical research
2008 EP-Patent application 07 01 8871.9: “Maintenance of hair growth and treatment of hair loss.” (together with Prof. Nöthen, S. Pasternack Dipl.-biol., and Dr. Al Aboud)
2008 Lecture Prize at the Annual Meeting of the European Hair Research Society in Genoa, Italy
2006 Gottron-Just-Scientific Prize of the University and City of Ulm, Germany
2002 - 2004 Flemish Research Council Postdoctoral Fellowship
2000 - 2002 DFG Postdoctoral Fellowship

10 Most Relevant Publications for Prof. Regina Betz

1. Basmanav FB*, Oprisoreanu AM*, Pasternack SM*, Thiele H, Fritz G, Wenzel J, Größer L, Wehner M, Wolf S, Fagerberg C, Bygum A, Altmüller J, Rütten A, Parmentier L, El Shabrawi-Caelen L, Hafner C, Nürnberg P, Kruse R, Schoch S, Hanneken S, **Betz RC**. 2014. Mutations in POGLUT1, encoding protein O-glucosyltransferase 1, cause autosomal dominant Dowling-Degos disease. Am J Hum Genet 94:135-143.
2. Pasternack SM, Refke M, Paknia E, Hennies HC, Franz T, Schäfer N, Fryer A, van Steensel M, Sweeney E, Just M, Grimm C, Kruse R, Ferrándiz C, Nöthen MM, Fischer U, **Betz RC**. 2013. Mutations in SNRPE, encoding a core protein of the spliceosome, cause autosomal-dominant hypotrichosis simplex. Am J Hum Genet 92:81-87.
3. Jagielska D, Redler S, Brockschmidt FF, Herold C, Garcia Bartels N, Hanneken S, Eigelshoven S, Refke M, Barth S, Giehl KA, Kruse R, Lutz G, Wolff H, Blaumeiser B, Böhm M, Blume-Peytavi U, Becker T, Nöthen MM, **Betz RC**. 2012. A follow-up study of a genome-wide association scan in alopecia areata: replication of previously identified loci and identification of IL13 and KIAA0350 as new susceptibility loci supported with genome-wide significance. J Invest Dermatol 132:2192-2197.
4. Wen Y, Liu Y, Xu Y, Zhao Y, Hua R, Wang K, Sun M, Li Y, Yang S, Zhang XJ, Kruse R, Cichon S, **Betz RC**, Nothen MM, van Steensel MA, van Geel M, Steijlen PM, Hohl D, Huber M, Dunnill GS, Kennedy C, Messenger A, Munro CS, Terrinoni A, Hovnanian A, Bodemer C, de Prost Y, Paller AS, Irvine AD, Sinclair R, Green J, Shang D, Liu Q, Luo Y, Jiang L, Chen HD, Lo WH, McLean WH, He CD, Zhang X. 2009. Loss-of-function mutations of an inhibitory upstream ORF in the human hairless transcript cause Marie Unna hereditary hypotrichosis. Nat Genet 41: 228-33.
5. Pasternack SM, von Kugelgen I, Aboud KA, Lee YA, Ruschendorf F, Voss K, Hillmer AM, Molderings GJ, Franz T, Ramirez A, Nurnberg P, Nothen MM, **Betz RC**. 2008. G protein-coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. Nat Genet 40: 329-34.
6. Hillmer AM, Brockschmidt FF, Hanneken S, Eigelshoven S, Steffens M, Flaquer A, Herms S, Becker T, Kortum AK, Nyholt DR, Zhao ZZ, Montgomery GW, Martin NG, Muhleisen TW, Alblas MA, Moebus S, Jockel KH, Brocker-Preuss M, Erbel R, Reinartz R, **Betz RC**, Cichon S, Propping P, Baur MP, Wienker TF, Kruse R, Nothen MM. 2008. Susceptibility variants for male-pattern baldness on chromosome 20p11. Nat Genet 40: 1279-81.
7. **Betz RC**, Planko L, Eigelshoven S, Hanneken S, Pasternack SM, Bussow H, Van Den Bogaert K, Wenzel J, Braun-Falco M, Rutten A, Rogers MA, Ruzicka T, Nothen MM, Magin TM, Kruse R. 2006. Loss-of-function mutations in the keratin 5 gene lead to Dowling-Degos disease. Am J Hum Genet 78: 510-9.
8. Levy-Nissenbaum E, **Betz RC**, Frydman M, Simon M, Lahat H, Bakhan T, Goldman B, Bygum A, Pierick M, Hillmer AM, Jonca N, Toribio J, Kruse R, Dewald G, Cichon S, Kubisch C, Guerrin M, Serre G, Nothen MM, Pras E. 2003. Hypotrichosis simplex of the scalp is associated with nonsense mutations in CDSN encoding corneodesmosin. Nat Genet 34: 151-3.
9. **Betz RC**, Schoser BG, Kasper D, Ricker K, Ramirez A, Stein V, Torbergsen T, Lee YA, Nöthen MM, Wienker TF, Malin JP, Propping P, Reis A, Mortier W, Jentsch TJ, Vorgerd M, Kubisch C. 2001. Mutations in CAV3 cause mechanical hyperirritability of skeletal muscle in rippling muscle disease. Nat Genet 28: 218-9.
10. **Betz RC**, Lee Y-A, Bygum A, Brandrup F, Bernal AI, Toribio J, Alvarez JI, Kukuk GM, Ibsen HHW, Rasmussen HB, Wienker TF, Reis A, Propping P, Kruse R, Cichon S, Nöthen MM. 2000. A gene for hypotrichosis simplex of the scalp maps to chromosome 6p21.3. Am J Hum Genet 66:1979-1983.

Prof. Anton Bovier, PhD

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Research Expertise

The main focus of my work concerns the analysis of interacting stochastic systems of many components. This includes a special focus on models from statistical mechanics with an emphasis on disordered models, in particular spin glasses. Apart from classical aspects of equilibrium Gibbs measures I am particularly interested in aspects of long term dynamics such as metastability and aging. More recently I am also interested in application of methods from these areas in models of population genetics, ecology, and neurodegenerative diseases.

Education / Training

Technical University of Berlin, Germany
Mathematics, Habilitation 1995
The Swiss Federal Institute of Technology (ETH), Zurich
Physics, Dr. sc. nat., 1986
University of Bonn, Germany
Physics, Diploma, 1981

Appointments / Positions Held

2008 - present
Full Professor, Institute for Applied Mathematics
University of Bonn, Germany
2003 - 2008
Full Professor, Mathematics
Technical University, Berlin, Germany
1994 - 2008
Laboratory Head, and 2nd Deputy Director
Weierstrass-Institute for Applied Analysis and Stochastics (WIAS), Berlin
1992 - 1995
Deputy Laboratory Head
WIAS, Berlin
1991 - 1992
Research Associate, Mathematics Department
Bochum University, Germany
1988 - 1991
Research Associate, Physics Department
University of Bonn, Germany
1986 - 1988
Visiting Assistant Professor, Mathematics Department
University of California, Irvine, CA, USA
1982 - 1986
Assistant
Institute for Theoretical Physics
ETH-Zurich

Honors / Awards

2013
Elected Fellow, Institute of Mathematical Statistics
2012
Kloosterman Chair, University Leiden, NL
2010
Lady Davies Visiting Professor, Technion, Haifa, IL
2010
Plenary Speaker, Annual Meeting of the German Mathematical Association
2009
EURANDOM Chair, EURANDOM; Eindhoven, NL
2008
Member of the Selection Committee of the Minerva Foundation
2008
Member of the Review Board for Mathematics of the German Research Council
2006
Invited Speaker at the International Congress of Mathematicians, Madrid

10 Most Relevant Publications for Prof. Anton Bovier

1. Mayer, H., **Bovier, A**. 2014. Stochastic models of T-cell activation. J. Math. Biology: Online first.
2. Arguin, L.-P., **Bovier, A.**, Kistler, N. 2013. The extremal process of branching Brownian motion. Prob. Theor. Rel. Fields: 157, 535-574.
3. Hölzel, M., **Bovier, A.**, Tüting, T. 2013. Plasticity of tumor and immune cells: a source of heterogeneity and a cause for therapy resistance? Nature Reviews Cancer: 13, 365—376.
4. **Bovier A.**, den Hollander F, Spitoni C. 2010. Homogeneous nucleation for Glauber and Kawasaki dynamics in large volumes and low temperature. Ann Probab 38: 661–713.
5. Ben Arous G, **Bovier A.**, Cerný J. 2008. Universality of the REM for dynamics of mean field spin glasses. Commun Math Phys 282: 663–695.
6. **Bovier A**. 2006. Statistical mechanics of disordered systems. A mathematical perspective", 312 + xiv pp, Cambridge Series in Statistical and Probabilistic Mathematics Cambridge University Press Vol. 18.
7. **Bovier A**, Gayrard V, Klein M. 2005. Metastability in reversible diffusion processes II. precise asymptotics for small eigenvalues. J Europ Math Soc 7:69–99.
8. Baake E, Baake M, **Bovier A,** Klein M. 2005. An asymptotic maximum principle for essentially linear evolution models. J Math Biology 50: 83-114.
9. Ben Arous G, **Bovier A**, Gayrard V. 2003. Glauber dynamics of the random energy model. 2. Aging below the critical temperature. Commun Math Phys 236: 1-54.
10. **Bovier A**, Eckhoff M, Gayrard V, Klein M. 2002. Metastability and low-lying spectra in reversible Markov chains. Commun Math Phys 228: 219-255.

Prof. Irmgard Förster, PhD

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Life and Medical Sciences Institute (LIMES),
Immunology and Environment, Director
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Research Expertise

Prof. Förster has special expertise in the functional characterization of macrophages and dendritic cells using conditional gene targeting techniques. She is interested in cell migration and immune regulation in barrier organs, and has profound experience with mouse models of atopic dermatitis, inflammatory bowel disease and bacterial infection.

Education / Training

University of Cologne, Germany
Genetics, PhD, 1988
University of Marburg, Germany
Human Biology, Diploma, 1985

Appointments / Positions Held

2012 - present
W3 Professor of Immunology and Environment Life and Medical Sciences (LIMES) Institute,
University of Bonn
2005 - 2012
Laboratory Head of Molecular Immunology
IUF - Leibniz Institute for Environmental Medicine at the University of Düsseldorf, Germany
2004 - 2012
C3 Professor of Molecular Immunology
Heinrich-Heine-University Düsseldorf
1998 - 2004
Head of the Volkswagen Foundation Research Group
Institute for Medical Microbiology, Immunology and Hygiene and the second Medical Clinic, Technical University of Munich
1997 - 1998
Assistant Professor, Institute for Genetics, University of Cologne
1993 - 1997
Postdoctoral Research Fellow, Institute for Genetics, University of Cologne
1990 - 1993
Postdoctoral Research Fellow, University of California, San Francisco, USA
1988 -1990
Research Fellow, Institute for Genetics, University of Cologne

Honors / Awards

1994
Bennigsen Foerder Prize, Ministry of Science and Research of North Rhine-Westphalia
1991 - 1992
Research grant from the DFG
1985 - 1988
Research Scholarship from the Fritz Thyssen Stiftung
1988
Awarded Summa cum laude for thesis titled „Studies on the characterization of Ly1-B-cell population"

10 Most Relevant Publications for Prof. Irmgard Förster

1. Globisch, T., Steiner, N.*, Fülle, L.*, Lukacs-Kornek, V., Degrandi, D., Dresing, P., Alferink, J., Lang, R., Pfeffer, K., Beyer, M., Weighardt, H., Kurts, C., Ulas, T., Schultze J.L and **Förster, I**. 2014. Cytokine-dependent regulation of denditic cell differentiation in the splenic microenvironment. Eur. J. Immunol. 44, 500-510.
2. Köhler, T., Reizis, B., Johnson, R.S., Weighardt, H. and **Förster, I**. 2012. Influence of hypoxia inducible factor 1a on dendritic cell differentiation and migration. Eur. J. Immunol. 42, 1226-1236.
3. Stutte S, Quast T, Gerbitzki N, Savinko T, Novak N, Reifenberger J, Homey B, Kolanus W, Alenius H and **Förster I.** 2010. Requirement of CCL17 for CCR7- and CXCR4-dependent migration of cutaneous dendritic cells. Proc. Natl. Acad. Sci. USA 107: 8736-41.
4. Semmling V, Lukacs-Kornek V, Thaiss C, Quast T, Hochheiser K, Panzer U, Rossjohn J, Perlmutter P, Cao J, Godfrey D, Savage P, Knolle P, Kolanus W, **Förster I*** and Kurts C* 2010. Alternative cross-priming through CCL17/CCR4-mediated CTL attraction towards NKT cell-licensed dendritic cells. Nat. Immunol. 11: 313-20.
5. Gross O, Gewies A, Finger K, Schäfer M, Sparwasser T, Peschel C, **Förster I** and Ruland J. 2006. Card9 controls a novel non-TLR signaling pathway for innate anti-fungal immunity. Nature. 442, 651-656.
6. Buch T, Polic B, Clausen BE, Weiss S, Akilli Ö, Chang CH, Flavell R, Schulz A, Jonjic S, Waisman A and **Förster I**. 2006. MHC class II expression through a hitherto unknown pathway supports T helper cell dependent immune responses: implications for MHC class II deficiency. Blood. 107, 1434-1444.
7. Alferink J*, Lieberam I*, Reindl W, Behrens A, Weiß S, Hüser N, Gerauer K, Ross R, Reske-Kunz A, Ahmad-Nejad P, Wagner H and **Förster I**. 2003. Compartmentalized production of CCL17 in vivo: strong inducibility in peripheral dendritic cells contrasts selective absence from the spleen. J. Exp. Med. 197, 585-599.
8. Lieberam I and **Förster I.** 1999. The murine beta-chemokine TARC is expressed by subsets of dendritic cells and attracts primed CD4+ T cells. Eur. J. Immunol. 29: 2684-2694.
9. Clausen BE, Burkhardt C, Reith W, Renkawitz R and **Förster I**. 1999. Conditional gene targeting in macrophages and granulocytes using LysMcre mice. Transg. Res. 8: 265-277.
10. Takeda K*, Clausen BE*, Kaisho T, Tsujimura T, Terada N, **Förster I*** and Akira S* 1999. Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils. Immunity. 10: 39-49.

*These authors contributed equally

Dr. Annett Halle, MD

center of advanced european studies and research (caesar)

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Research Expertise

Dr. Halle's group studies innate immune mechanisms and microglial function in Alzheimer's disease using cell culture techniques and mouse models of Alzheimer's disease.

Education / Training

Charité – University Medicine Berlin,
Medical Neuroscience, MD thesis, 2005
Free University Berlin, Humboldt University Berlin,
Clinical Medicine, MD, 2003

Appointments / Positions Held

2011 - present
Max-Planck Research Group leader
Center of Advanced European Studies and Research (caesar), Bonn, Germany
2009 - 2011
Research fellow and resident in Neuropathology
Department of Neuropathology, Charité – University Medicine Berlin, Germany
2005 - 2008
Postdoctoral fellow and instructor in Internal Medicine, Department of Infectious Diseases, University of Massachusetts, Worcester, USA
2003 - 2005
Medical dissertation and resident in Neurology, Department of Experimental Neurology, Charité – University Medicine Berlin, Germany
2000
Research internship, Department of Cell Biology, Harvard University, Boston, USA

Honors / Awards

2010
Ernst Jung-Career Award for Medical Research
2008
Lydia Rabinowitsch Fellowship for young scientists, Charité Berlin
2005 - 2007
Postdoctoral Fellowship, German Academic Exchange Foundation (DAAD)
2006
Young Scientist Award, Science Foundation Berlin, Germany
2006
Award for the best medical dissertation of 2005, Berlin Society for Psychiatry and Neurology
2005
Humboldt Prize (Prize for best dissertation of the year, Humboldt University Berlin)

10 Most Relevant Publications for Dr. Annett Halle

1. Schnaars M, Beckert H, **Halle A**. Assessing β-amyloid-induced NLRP3 inflammasome activation in primary microglia. Methods Mol Biol. 2013;1040:1-8.
2. Krabbe, G.*, **Halle, A**.*, Matyash, V., Rinnenthal, J. L., Eom, G. D., Bernhardt, U., Miller, K. R., Prokop, S., Kettenmann, H. and Heppner, F. L., Functional impairment of microglia coincides with Beta-amyloid deposition in mice with Alzheimer-like pathology. PLoS One 2013. 8: e60921.
3. Heneka, M. T., Kummer, M. P., Stutz, A., Delekate, A., Schwartz, S., Vieira-Saecker, A., Griep, A., Axt, D., Remus, A., Tzeng, T. C., Gelpi, E., **Halle, A.**, Korte, M., Latz, E. and Golenbock, D. T., NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 2013. 493: 674-678.
4. Stewart, C. R., Stuart, L. M., Wilkinson, K., van Gils, J. M., Deng, J., **Halle, A.**, Rayner, K. J., Boyer, L., Zhong, R., Frazier, W. A., Lacy-Hulbert, A., El Khoury, J., Golenbock, D. T. and Moore, K. J., CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat Immunol 2010. 11: 155-161.
5. Siednienko, J., **Halle, A.**, Nagpal, K., Golenbock, D. T. and Miggin, S. M., TLR3-mediated IFN-beta gene induction is negatively regulated by the TLR adaptor MyD88 adaptor-like. Eur J Immunol 2010. 40: 3150-3160.
6. **Halle, A.,** Hornung, V., Petzold, G. C., Stewart, C. R., Monks, B. G., Reinheckel, T., Fitzgerald, K. A., Latz, E., Moore, K. J. and Golenbock, D. T., The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol 2008. 9: 857-865.
7. **Halle, A.***, Zhou, S*., Kurt-Jones, E. A., Cerny, A. M., Porpiglia, E., Rogers, M., Golenbock, D. T. and Finberg, R. W., Lymphocytic choriomeningitis virus (LCMV) infection of CNS glial cells results in TLR2-MyD88/Mal-dependent inflammatory responses. J Neuroimmunol 2008. 194: 70-82.
8. Hornung, V., Bauernfeind, F., **Halle, A.**, Samstad, E. O., Kono, H., Rock, K. L., Fitzgerald, K. A. and Latz, E., Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 2008. 9: 847-856.
9. Jain, V., **Halle, A.**, Halmen, K. A., Lien, E., Charrel-Dennis, M., Ram, S., Golenbock, D. T. and Visintin, A., Phagocytosis and intracellular killing of MD-2 opsonized gram-negative bacteria depend on TLR4 signaling. Blood 2008. 111: 4637-4645.
10. **Halle, A**.*, Bermpohl, D.*, Freyer, D., Dagand, E., Braun, J. S., Bechmann, I., Schroder, N. W. and Weber, J. R., Bacterial programmed cell death of cerebral endothelial cells involves dual death pathways. J Clin Invest 2005. 115: 1607-1615.

*These authors contributed equally

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Research Expertise

The focus of research is the immunorecognition of nucleic acids, and its intersection with RNA interference. The group contributed to the immunobiology of TLR9 and CpG DNA, specifically the function of TLR9 in the human immune system. Furthermore, the group found that short interfering RNA molecules (siRNA) activate TLR7, and worked on the structural requirements for the detection of RNA by TLR7 and TLR8. The group identified the RNA ligand for RIG-I, and analyzed the signaling pathways of RIG-I, and resolved the crystal structure or RIG-I bound to its ligand 5´-triphosphate RNA. The group identified cyclic [G(2',5')pA(3",5")p] as the metazoan second messenger in the cGAS-STING pathway. The group applies immunostimulatory nucleic acids and siRNA for immunotherapy of cancer and viral infection.

Education / Training

University of Munich, Germany, Experimental Pharmacology and Toxicology Degree, 2006
University of Munich, Germany, Clinical Pharmacology, Degree, 2003
University of Munich, Germany, Clinical Pharmacology, Habilitation, 2001
University of Ulm, Germany, Clinical Genetics, MD thesis, 1994
University of Ulm, Germany, Clinical Medicine, MD, 1993

Appointments / Positions Held

2012 - present Speaker of the DFG-Excellence Cluster ImmunoSensation, University of Bonn, Germany
2008 - present Head of Research Committee BONFOR, University of Bonn, Germany
2007 - present Full Professor and Chair, Institute of Clinical Chemistry and Clinical Pharmacology with the Central Laboratory of the University Hospital, University of Bonn, Germany
2006 - present Member oft the Steering committee, Comprehensive Cancer Center Köln-Bonn (CIO), University of Bonn,
2005 Full Professor and Head, Division of Clinical Pharmacology, University of Bonn, Germany
2002 Assistant Professor, Division of Clinical Pharmacology, University of Munich, Germany
1999 - present Research group: Therapeutic Oligonucleotides, University of Munich, Germany
1998 - 1999 Postdoctoral Fellow, Department of Internal Medicine, University of Iowa, USA
1995 Research Fellow, Division of Clinical Pharmacology, University of Munich, Germany
1994 Research Fellow, Department of Internal Medicine, University of Munich, Germany

Honors / Awards

2013 - present Elected Member of the German Academy of Sciences Leopoldina
2012 Gottfried-Wilhelm Leibniz-Preis
2011 - 2012 Elected President of the Oligonucleotide Therapeutics Society (OTS)
2011 Dr.-Friedrich-Sasse-Preis, Berliner Medizinische Gesellschaft/ GoBio-Award of the Federal Ministry for Education and Research (BMBF)
2010 Elected Vice Speaker of the SFB 670
2009 Elected member of the committee Krebstherapie-Studien of the German Cancer Aid (Deutsche Krebshilfe)
2007 Wilhelm-Vaillant-Award for Medical Sciences
2004 Ludwig-Heilmeyer-Award (Ludwig-Heilmeyer Society, Internal Medicine, Germany) / Biofuture Award, of the Federal Ministry for Education and Research (BMBF) / Georg-Heberer Award, Chiles Foundation, Portland
2000 Paul-Martini-Award / Award "Young Master" of the German Society for Hematology and Oncology**"**

10 Most Relevant Publications for Prof. Gunther Hartmann

1. Gehrke N, Mertens C, Zillinger T, Wenzel J, Bald T, Zahn S, Tüting T, **Hartmann G,** Barchet W. Oxidative damage of DNA confers resistance to cytosolic nuclease TREX1 degradation and potentiates STING-dependent immune sensing. Immunity 2013 Sep 19;39(3):482-95.
2. Gao P, Ascano M, Wu Y, Barchet W, Gaffney BL, Zillinger T, Serganov AA, Liu Y, Jones RA, **Hartmann G**, Tuschl T, Patel DJ. Cyclic [G(2',5')pA(3",5")p] Is the Metazoan Second Messenger Produced by DNA-Activated Cyclic GMP-AMP Synthase. Cell 2013 May 23;153:1094-107.
3. Dann A, Poeck H, Croxford A, Pfeifer D, Maihoefer C, Endres S, Kalinke U, Knust M, Knobeloch KP, Akira S, Waisman A, **Hartmann G,** Prinz M. Systemic activation of RIG-I-like helicases limits Th1/ Th17-mediated autoimmunity in the CNS. Nature Neuroscience 2011;15:98-106.
4. Wang Y, Ludwig J, Schuberth C, Goldeck M, Schlee M, Li H, Juranek S, Sheng G, Micura R, Tuschl T*, **Hartmann G***, Patel DJ*. 2010. Structural and functional insights into 5'-ppp RNA pattern recognition by the innate immune receptor RIG-I. Nat Struct Mol Biol 17:781-7.
5. Poeck H, Bscheider M, Gross O, Finger K, Roth S, Rebsamen M, Hannesschlager N, Schlee M, Rothenfusser S, Barchet W, Kato H, Akira S, Inoue S, Endres S, Peschel C, **Hartmann G***, Hornung V*, Ruland J*. 2010. Recognition of RNA virus by RIG-I results in activation of CARD9 and inflammasome signaling for interleukin 1 beta production. Nat Immunol 11: 63-9.
6. Schlee M, Roth A, Hornung V, Hagmann CA, Wimmenauer V, Barchet W, Coch C, Janke M, Mihailovic A, Wardle G, Juranek S, Kato H, Kawai T, Poeck H, Fitzgerald KA, Takeuchi O, Akira S, Tuschl T, Latz E, Ludwig J, **Hartmann G**. 2009. Recognition of 5' triphosphate by RIG-I helicase requires short blunt double-stranded RNA as contained in panhandle of negative-strand virus. Immunity 31: 25-34.
7. Ablasser A, Bauernfeind F, **Hartmann G**, Latz E, Fitzgerald KA, Hornung V. 2009. RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nat Immunol 10: 1065-72.
8. Poeck H, Besch R, Maihoefer C, Renn M, Tormo D, Morskaya SS, Kirschnek S, Gaffal E, Landsberg J, Hellmuth J, Schmidt A, Anz D, Bscheider M, Schwerd T, Berking C, Bourquin C, Kalinke U, Kremmer E, Kato H, Akira S, Meyers R, Hacker G, Neuenhahn M, Busch D, Ruland J, Rothenfusser S, Prinz M, Hornung V, Endres S, Tuting T, **Hartmann G**. 2008. 5'-Triphosphate-siRNA: turning gene silencing and Rig-I activation against melanoma. Nat Med 14: 1256-63.
9. Hornung V, Ellegast J, Kim S, Brzozka K, Jung A, Kato H, Poeck H, Akira S, Conzelmann KK, Schlee M, Endres S, **Hartmann G**. 2006. 5'-Triphosphate RNA is the ligand for RIG-I. Science 314: 994-7.
10. Hornung V, Guenthner-Biller M, Bourquin C, Ablasser A, Schlee M, Uematsu S, Noronha A, Manoharan M, Akira S, de Fougerolles A, Endres S, **Hartmann G**. 2005. Sequence-specific potent induction of IFN-alpha by short interfering RNA in plasmacytoid dendritic cells through TLR7. Nat Med 11: 263-70.

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Prof. Michael Heneka, MD

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Clinical Neurosciences Unit, Director
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Research Expertise

Prof. Heneka is involved in basic science and translational research with focus on neurodegeneration and neuroinflammation. His major disease of interest and research topics include Alzheimer disease, amyotrophic lateral sclerosis, septic encephalopathy and multiple sclerosis. In clinical neurology, Prof. Heneka holds special expertise in neurodegenerative and autoimmune CNS disorders.

Education / Training

University of Bonn, Germany, Neurology, Professorial qualification (Habilitation), 2003
University of Bonn, Germany, Neurology, Specialty qualification, 2002
University of Tübingen, Germany, Medicine, M.D., 1996

Appointments / Positions Held

2008 - present
Full Professor (W3) for Clinical Neurosciences, Head of the Clinical Research Group 177 of the DFG, University of Bonn
2004 - 2008
Full Professor (C3) for Molecular Neurology, University of Münster
2004
Senior Clinical Fellow in Neurology, University of Bonn
1999 - 2003
Resident in Neurology, University of Bonn
1996 - 1999
Resident in Neurology, University of Tübingen
1992 - 1996
Predoctoral research fellow in the Dept. of Pharmacology, University of Cologne

Honors / Awards

2010 - present
Editorial Board Journal of Neurochemistry
2007 - present
Board Member of the Competence Network Degenerative Dementias (CNDD)
2008
Editorial board, Journal of Chemical Neuroanatomy
1998
Attempto Award - best Thesis of the University of Bonn

10 Most Relevant Publications for Prof. Michael Heneka

1. **Heneka MT,** Klockgether T, Feinstein DL. Peroxisome proliferator-activated receptor-gamma ligands reduce neuronal inducible nitric oxide synthase expression and cell death in vivo. J Neurosci 2000;20:6862-6867.
2. **Heneka MT**, Galea E, Gavriluyk V, Dumitrescu-Ozimek L, Daeschner J, O´Banion MK, Klockgether T, Feinstein DL. Noradrenergic depletion potentiates beta-amyloid induced cortical inflammation: Implications for Alzheimer's disease. J Neurosci 2002;22:2434-2442.
3. **Heneka MT**, Dewachter I, Sastre M, Dumitrescu-Ozimek L, Cuiperi K, a gonist pioglitazone and ibuprofen reduces inflammation and Aβ 1-42 levels in APP V717I transgenic mice. Brain 2005;128:1442-1453.
4. Schütz B, Reimann J, Dumitrescu-Ozimek L, Kappes-Horn K, Landreth GE, Schürmann B, Zimmer A, **Heneka MT**. The oral antidiabetic pioglitazone protects from neurodegeneration and ALS-like symptoms in SOD1-G93A transgenic mice. J Neurosci 2005;25:7805-7812.
5. Sastre M, Dewachter I, Rossner S, Bogdanovic N, Rosen E, Borghraef P, Evert BO, Dumitrescu-Ozimek D, Thal DR, Landreth GE, Walter J, Klockgether T, Van Leuven F, **Heneka MT** (2006) NSAIDs suppress BACE1 gene expression by the activation of PPARγ. Proc Natl Acad Sci USA 2006;103:443-448.
6. **Heneka MT**, Ramanathan M, Jacobs AH, Dumitrescu-Ozimek L, Debeir T, Sastre M, Bilkei-Gorzo A, Zimmer A, Galldiks N, Hoehn M, Heiss WD, Klockgether T, Staufenbiel M. Locus ceruleus degeneration promotes Alzheimer pathogenesis in APP transgenic mice. J. Neurosci 2006;26:1343-1354.
7. Weberpals M, Hermes M, Hermann M, Kummer MP, Terwel D, Semmler A, Berger M, Schäfers M, **Heneka MT** (2009) NOS2 gene deficiency protects from sepsis-induced long-term cognitive deficits, J Neurosci, 29:14177-84.
8. **Heneka MT**, Nadrigny F, Regen T, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch U, Kummer MP (2010) Locus ceruleus controls Alzheimer disease pathology by modulating microglial functions through norepinephrine. Proc. Natl. Acad. Sci. U.S.A., 107:6058-63.
9. Kummer MP, Hermes M, Delekarte A, Hammerschmidt T, Kumar S, Terwel D, Walter J, Pape HC, König, S, Roeber S, Jessen F, Klockgether T, Korte M, **Heneka MT** (2011) Nitration of tyrosine 10 critically enhances amyloid β aggregation and plaque formation. Neuron 71:833-44.
10. **Heneka MT**, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, Griep A, Axt D, Remus A, Tzeng TC, Gelpi E, Halle A, Korte M, Latz E, Golenbock DT (2013) NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 493: 674-678.

Prof. Michael Hoch, PhD

Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
Life and Medical Sciences Institute (LIMES), Managing Director, Genetics, Developmental Biology & Molecular Physiology, Director
E-Mail: m.hoch@uni-bonn.de

Research Expertise

Our aim is to identify new key regulators and genetic networks which control metabolism and cell and organ physiology. In particular, we elucidate the metabolism – innate immunity – gut microbiome axis, we investigate cellular (sphingo)lipid metabolism and body fat regulation, we study peroxisome and lysosome biogenesis and metabolic disorders (e.g. lipid storage diseases or neurodegeneration), and we analyse new regulators of cell-to-cell communication and tissue physiology. We use the fruit fly Drosophila, the mouse and zebra fish as genetic model organisms for our studies.

Education / Training

University of Munich, Germany, Developmental Biology PhD, 1992
University of Heidelberg, Germany, Biology Undergraduate (Dipl.), 1989

Appointments / Positions Held

2010
Visiting Research Professors, ASMeW Institute, Waseda University, Japan
2006 - present
Managing Director of the LIMES Institute, Chair Molecular Developmental Biology, LIMES Institute, University of Bonn, Germany
2000 - 2002
Director, Institute of Animal Physiology, University of Bonn, Germany
1999 - present
Full Professor, Chair of Molecular Developmental Biology LIMES Institute, University of Bonn, Germany
1996
Habilitation in Developmental Genetics & Cell Biology Technical University of Braunschweig, Germany
1994 - 1999
Group Leader, Dept. Mol. Developmental Biology (Head: Prof. H. Jäckle), Max Planck Institute for Biophysical Chemistry, Göttingen, Germany
1992 - 1994
Post-doc Fellow, Dept. Mol. Developmental Biology (Head: Prof. H. Jäckle), Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Honors / Awards

2014
Member of the Academic Senate of the University of Bonn
2013 - present
Member of the PhD fellowship selection committee of the German National Academic Foundation (Studienstiftung des deutschen Volkes)
2012 - present
Member of the Steering Committee of the Bonn Excellence Cluster ImmunoSensation (German Research foundation DFG)
2009 - present
Member of the Minerva Fellowship Committee of the Max Planck Society, Munich
2006 - 2009
Founding Head of the Section Molecular Biomedicine of the Faculty for Mathematics & Natural Science, University of Bonn
2005 - present
Speaker of the Collaborative Research Centre SFB 645 (German Research Foundation)
2003 - 2004
Head of the Section Biology of the Faculty for Mathematics & Natural Science, University of Bonn
2002 - 2004
Chairman of the Bonner Forum Biomedizin
2001 - 2004
Speaker of the Research Unit FOR 425, funded by the DFG
2000 - 2007
Member of the reviewer panel for the award of Post Graduate Fellowships of the DAAD (German Academic Exchange Service)
1996
Gerhard Hess Young Investigator Award (DFG)
1989 - 1992
PhD Fellowship of the Boehringer Ingelheim Fonds (Foundation for Basic Research in Medicine)
1986 - 1989
Member of the German National Academic Foundation (Studienstiftung des deutschen Volkes)

5 Most Relevant Publications for Prof. Michael Hoch

1. Mass E, Wachten D, Aschenbrenner AC, Voelzmann A, **Hoch M**. 2014. Murine Creld1 controls cardiac development through activation of calcineurin/NFATc1 signaling. Developmental Cell 28, 711-726. DOI: 10.1016/j.devcel.2014.02.012.
2. Becker T, Loch G, Beyer M, Zinke I, Aschenbrenner AC, Carrera P, Inhester T, Schultze JL, **Hoch M**. 2010. FOXO-dependent regulation of innate immune homeostasis. Nature 463: 369-73.
3. Loer B, Bauer R, Bornheim R, Grell J, Kremmer E, Kolanus W, **Hoch M**. 2008. The NHL-domain protein Wech is crucial for the integrin-cytoskeleton link. Nat Cell Biol 10: 422-8.
4. Behr M, Wingen C, Wolf C, Schuh R, **Hoch M**. 2007. Wurst is essential for airway clearance and respiratory-tube size control. Nat Cell Biol 9: 847-53.
5. Fuss B, Becker T, Zinke I, **Hoch M**. 2006. The cytohesin Steppke is essential for insulin signalling in Drosophila. Nature 444: 945-8.

Prof. Michael Hölzel, MD

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Institute of Clinical Chemistry and Clinical Pharmacology

E-Mail: michael.hoelzel@uni-bonn.de

Research Expertise

Michael Hölzel has long-standing research expertise in the field of tumor biology and functional genomics with a particular focus on neural crest derived tumors such as melanoma. Currently his group investigates how the immune system crosstalks with the tumor cells in response to danger and proinflammatory signals released by therapy-induced tumor tissue injury. A central hypothesis is that this reciprocal communication drives therapy relapse due to rewiring of survival and differentiation pathways in tumor cells. This knowledge is critically needed for the rational combination of immunotherapies and targeted signal transduction inhibitors in the clinic.

Education / Training

University of Munich, Germany
Medicine M.D. thesis, 2004
Universities of Munich, Germany
Medicine M.D., 2003

Appointments / Positions Held

2012 - present
W2 Professor, Unit for RNA Biology, Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Germany
2007 - 2011
Post-Doc, Laboratory of Rene Bernards, The Netherlands Cancer Institute, Amsterdam, The Netherlands
2003 - 2006
Residency Hematology/Oncology, University Hospital Munich (LMU), Germany

Honors / Awards

2014
Invited junior speaker, DFG cancer symposium “Hinterzartener Kreis”, Italy
2011
Invited junior speaker, DFG cancer symposium “Hinterzartener Kreis”, Italy
2002
Scholarship „Harvard-Munich Alliance“
1999
Scholarship “Studienstiftung des deutschen Volkes”

10 Most Relevant Publications for Prof. Michael Hölzel

1. Bald, T., Landsberg, J., Lopez-Ramos, D., Renn, M., Glodde, N., Jansen, P., Gaffal, E., Steitz, J., Tolba, R., Kalinke, U., Limmer, A., Jönsson, G., **Hölzel, M.**, Tüting T (2014). Immune-cell poor melanomas benefit from PD-1 blockade after targeted type I IFN activation. Cancer Discovery, 2014 Mar 3. Epub ahead of print.
2. Bald, T., Quast, T., Landsberg, J., Rogava, M., Glodde, N., Lopez-Ramos, D., Kohlmeyer, J., Riesenberg, S., van den Boorn-Konijnenberg, D., Hömig-Hölzel, C., Reuten, R. Schadow, B., Weighardt, I., Wenzel, D., Helfrich, I., Schadendorf, D., Bloch, W.,. Bianchi, M.E., Koch, M., Fleischmann, B.K., Förster, I., Kastenmüller, W., Kolanus, W., **Hölzel, M.***, Gaffal, G.*, Tüting, T* (*corresponding authors). (2014). Ultraviolet radiation-induced inflammation promotes angiotropism and metastasis in melanoma. Nature, 507, 109-13.
3. **Hölzel, M.**, Bovier, A., Tüting, T. (2013) Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? Nat Rev Cancer 13, 365-76.
4. Landsberg, J., Kohlmeyer, J., Renn, M., Bald, T., Rogava, M., Cron, M., Fatho, M., Lennerz, V., Wölfel, T., **Hölzel, M.**, Tüting, T. (2012) Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. Nature, 490, 412–416.
5. Huang, S., **Hölzel, M.**, Knijnenburger, T., Schlicker, A., Roepman, P., McDermott, U., Garnett, M.J., Grernrum, W., Sun, C., Prahallad, A., Groenendijk, F.H., Mittempergher, L., Nijkamp, W., Neefjes, J., Salazar, R., Ten Dijke, P., Uramoto, H., Tanaka, F., Beijersbergen, R.L., Wessels, L.F., Bernards, R. (2012) MED12 controls the response to multiple cancer drugs through regulation of TGFβ receptor signaling. Cell, 151, 937–950.
6. Heuckmann JM, **Hölzel M.**, Sos ML, Heynck S, Balke-Want H, Koker M, Peifer M, Weiss J, Lovly CM, Grütter C, Rauh D, Pao W, Thomas RK. (2011) ALK mutations conferring differential resistance to structurally diverse ALK inhibitors. Clin Cancer Res., 17, 7394-401.
7. **Hölzel, M.***, Huang, S.*, Koster, J., Ora, I., Lakeman, A., Caron, H., Nijkamp, W., Xie, J., Callens, T., Asgharzadeh, S., Seeger, RC., Messiaen, L., Versteeg, R., Bernards, R. NF1 is a tumor suppressor in neuroblastoma that determines retinoic acid response and disease outcome. Cell, 2010; 142, 218–229.
8. Burger K, Mühl B, Harasim T, Rohrmoser M, Malamoussi A, Orban M, Kellner M, Gruber-Eber A, Kremmer E, **Hölzel M.,** Eick D. (2010) Chemotherapeutic drugs inhibit ribosome biogenesis at various levels. J Biol Chem., 285, 12416-25.
9. **Hölzel M.**, Orban M, Hochstatter J, Rohrmoser M, Harasim T, Malamoussi A, Kremmer E, Längst G, Eick D. (2010) Defects in 18 S or 28 S rRNA processing activate the p53 pathway. J Biol Chem., 285, 6364-70.
10. Huang S, Laoukili J, Epping MT, Koster J, **Hölzel M.,** Westerman BA, Nijkamp W, Hata A, Asgharzadeh S, Seeger RC, Versteeg R, Beijersbergen RL, Bernards R. (2009) ZNF423 is critically required for retinoic acid-induced differentiation and is a marker of neuroblastoma outcome. Cancer Cell, 15, 328-40.

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Research Expertise

Prof. Hörauf is internationally renowned for his work in Tropical Medicine, specifically, for pioneering a new drug treatment for filariasis (a group of neglected tropical diseases). The new treatment exploits an endosymbiosis between the worms and bacterial endosymbionts called Wolbachia, which are susceptible to some classes of antibiotic. Prof. Hörauf’s group was the first to characterize a TLR2 ligand from Wolbachia, and established that blindness brought about by filarial antigens as the worm larvae migrate into the eye in onchocerciasis (or “river blindness”) is dependent on Wolbachia, and again mediated by the innate immune system. Prof. Hörauf’s second focus is in the field of infection immunity, where his group were the first to detect regulatory T cells in humans in an infection.

Education / Training

University of Erlangen, Germany, Clinical Immunology MD, 1989
University of Erlangen, Germany, Duke University, USA and Galaway University, Ireland
Clinical Immunology MD, with clinical rotations, 1989

Appointments / Positions Held

2003 - present
Full Professor and Director, Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Germany
2001 - 2003
Head, Department of Helminthology, Bernard Nocht Institute for Tropical Medicine, Germany
1995 - 2001
Independent Laboratory Head, Bernard Nocht Institute for Tropical Medicine, Germany
1990 - 1994
Fellow, Institute for Clinical Microbiology, Immunology and Hygiene, University of Erlangen, Germany

Honors / Awards

2012
President of the Paul Ehrlich Society for Chemotherapy e.V.
2010
Coordinator for the partner BonnCologne, Dt. Zentrum für Infektionsforschung (DZIF) – German Center for Infectious Disease.
2002
Main annual award, German Society for Hygiene and Microbiology (DGHM)
2001
Martini-Prize (bi-annual) for best clinical research of the University Clinic, Eppendorf/Hamburg
1999
Main bi-annual award, German Society for Tropical Medicine (DTG)
1984 - 1989
Recipient of the “Bavarian Gifted Scholarship”

10 Most Relevant Publications for Prof. Achim Hörauf

1. Mand S, Debrah AY, Klarmann U, Batsa L, Marfo-Debrekyei Y, Kwarteng A, Specht S, Belda-Domene A, Fimmers R, Taylor M, Adjei O, **Hoerauf A**. 2012. Doxycycline improves filarial lymphedema independent of active filarial infection: a randomized controlled trial. Clin Infect Dis. 55:621-30.
2. Specht S, Frank JK, Alferink J, Dubben B, Layland LE, Denece G, Bain O, Förster I, Kirschning CJ, Martin C, **Hoerauf A.** 2011. CCL17 controls mast cells for the defense against filarial larval entry. J Immunol 186:4845-52.
3. Taylor M, **Hoerauf A**, Bockarie M. 2010. Lymphatic filariasis and onchocerciasis.
Lancet 376: 1175-85.
4. **Hoerauf A**. 2009. Mansonella perstans--the importance of an endosymbiont. N Engl J Med 361: 1502-4.
5. Specht S, **Hoerauf A**. 2007. Does helminth elimination promote or prevent malaria?
Lancet 369: 446-7.
6. Taylor MJ, Makunde WH, McGarry HF, Turner JD, Mand S, **Hoerauf A**. 2005.
Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double- blind, randomised placebo-controlled trial. Lancet 365: 2116-21.
7. Brattig NW, Bazzocchi C, Kirschning CJ, Reiling N, Buttner DW, Ceciliani F, Geisinger F, Hochrein H, Ernst M, Wagner H, Bandi C, **Hoerauf A**. 2004. The major surface protein of Wolbachia endosymbionts in filarial nematodes elicits immune responses through TLR2 and TLR4. J Immunol 173: 437-45.
8. Saint Andre A, Blackwell NM, Hall LR, **Hoerauf A**, Brattig NW, Volkmann L, Taylor MJ, Ford L, Hise AG, Lass JH, Diaconu E, Pearlman E. 2002. The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. Science 295: 1892-5.
9. **Hoerauf A**, Mand S, Adjei O, Fleischer B, Buttner DW. 2001. Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. Lancet 357: 1415-6.
10. **Hoerauf A**, Volkmann L, Hamelmann C, Adjei O, Autenrieth IB, Fleischer B, Buttner DW. 2000. Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. Lancet 355: 1242-3.

Prof. Veit Hornung, MD

Institute of Molecular Medicine

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Molecular Medicine, Director
E-Mail: veit.hornung@uni-bonn.de

Research Expertise

Prof. Hornung has expertise in pattern recognition, innate immunology, macrophages, dendritic cells, RNA biology and genome engineering technologies.

Education / Training

University of Munich, Germany, Clinical Pharmacology MD thesis, 2004
University of Munich, LMU, including exchange rotations at Harvard University, USA, and University of Zürich, Switzerland, Clinical Medicine, MD, 2003

Appointments / Positions Held

Since 2014
Director (W3) Institute of Molecular Medicine, University Hospital, University of Bonn
2008 - 2013
Professor of Clinical Biochemistry, Institute for Clinical Chemistry and Clinical Pharmacology, University of Bonn, Germany
2006 - 2008
Postdoctoral research fellow, Division of Infectious Diseases and Immunology, University of Massachusetts, USA
2005 - 2006
Group leader, Division of Clinical Pharmacology University of Munich, Germany
2003 - 2005
Research Fellow, Division of Clinical Pharmacology, University of Munich, Germany

Honors / Awards

2013
Pettenkofer Prize of the Max von Pettenkofer Foundation
2010
GlaxoSmithKline Foundation Prize for basic medical research
2010
Paul-Martini-Prize of the Paul-Martini-Foundation
2007
Heinz Maier Leibnitz Prize of the German Research Foundation
2006
Graduate-Scholarship of the Novartis-Foundation for Therapeutical Research
2002
Study Scholarship of the Munich-Harvard-Alliance
2000 - 2003
Fellow of the German National Academic Foundation ("Studienstiftung des deutschen Volkes")

10 Most Relevant Publications for Prof. Veit Hornung

1. Ablasser, A., J. L. Schmid-Burgk, I. Hemmerling, G. L. Horvath, T. Schmidt, E. Latz and **V. Hornung.** Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP Nature, 2013;
2. Ablasser, A., M. Goldeck, T. Cavlar, T. Deimling, G. Witte, I. Rohl, K. P. Hopfner, J. Ludwig and **V. Hornung.** cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activa- tes STING Nature, 2013; 498: 380-384.
3. Bartok, E., F. Bauernfeind, M. G. Khaminets, C. Jakobs, B. Monks, K. A. Fitzgerald, E. Latz and **V. Hornung.** iGLuc: a luciferase-based inflammasome and protease activity reporter Nat Methods, 2013; 10: 147-154.
4. Schmid-Burgk, J. L., T. Schmidt, V. Kaiser, K. Honing and **V. Hornung.** A ligation-indepen- dent cloning technique for high-throughput assembly of transcription activator-like effector genes Nat Biotechnol, 2013; 31: 76-81.
5. Duewell, P., H. Kono, K. J. Rayner, C. M. Sirois, G. Vladimer, F. G. Bauernfeind, G. S. Abe- la, L. Franchi, G. Nunez, M. Schnurr, T. Espevik, E. Lien, K. A. Fitzgerald, K. L. Rock, K. J. Moore, S. D. Wright, **V. Hornung*** and E. Latz*. NLRP3 inflammasomes are required for athe- rogenesis and activated by cholesterol crystals Nature, 2010; 464: 1357-1361.
6. Ablasser, A., F. Bauernfeind, G. Hartmann, E. Latz, K. A. Fitzgerald and **V. Hornung.** RIG- I-dependent sensing of poly (dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate Nat Immunol, 2009; 10: 1065-1072.
7. **Hornung, V.**, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D. R. Caffrey, E. Latz and K. A. Fitzgerald. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC Nature, 2009; 458: 514-518.
8. **Hornung, V.***, F. Bauernfeind*, A. Halle, E. O. Samstad, H. Kono, K. L. Rock, K. A. Fitz- gerald and E. Latz. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization Nat Immunol, 2008; 9: 847-856.
9. **Hornung, V.**, J. Ellegast, S. Kim, K. Brzozka, A. Jung, H. Kato, H. Poeck, S. Akira, K. K. Conzelmann, M. Schlee, S. Endres and G. Hartmann. 5'-Triphosphate RNA is the ligand for RIG-I Science, 2006; 314: 994-997.
10. **Hornung, V.**, M. Guenthner-Biller, C. Bourquin, A. Ablasser, M. Schlee, S. Uematsu, A. Noronha, M. Manoharan, S. Akira, A. de Fougerolles, S. Endres and G. Hartmann. Sequence-specific potent induction of IFN-alpha by short interfering RNA in plasmacytoid dendritic cells through TLR7 Nat Med, 2005; 11: 263-270.

*These authors contributed equally

Prof. Jörg C. Kalff, MD

Department of Surgery

Rheinische Friedrich-Wilhelms-Universität Bonn
Department of Surgery, Director
E-Mail: kalff@uni-bonn.de

Research Expertise

The focus of research are the immunological consequences of operative trauma and their recognition and regulation in postoperative dysfunction of the gastrointestinal tract. The group described and elucidated the immunological pathomechanism of postoperative ileus. Furthermore, the group found that the gastrointestinal field effect - a panenteric inflammation following localized abdominal surgery - is mediated by an immunological response involving resident intestinal macrophages, mesenteric dendritic cells and memory TH1 cells.

Education / Training

University of Bonn, Germany, Surgery, Habilitation, 1999
University of Aachen, Germany, Intensive Care , MD thesis, 1988
University of Aachen, Germany, Clinical Medicine, MD, 1987

Appointments / Positions Held

2010 - present
Full Professor and Head, Dept. of Surgery, University of Bonn, Germany
2009
Head, Division of Transplant Surgery, University of Bonn, Germany
2003
Professor of Surgery, University of Bonn, Germany
1999 - 2001
Visiting Research Professor, Dept. of Medicine, University of Pittsburgh, USA
1995 - 1998
Research Fellow, Department of Surgery, University of Pittsburgh, USA
1995
Clinical Fellow, Department of Surgery, University of Bonn, Germany
1989
Resident, Department of Surgery, University of Bonn, Germany

Honors / Awards

2006
Fellow of the American College of Surgeons (FACS)
2003
Elected Speaker of the KFO 115
2000
Ferdinand Sauerbruch Award, Berlin, Germany
2000
Young Investigator Award, American Motility Society
2000
BONFOR Young Investigator Research Award

10 Most Relevant Publications for Prof. Jörg C. Kalff

1. Pantelis D, Beissel A, Kahl P, Vilz TO, Stoffels B, Wehner S, **Kalff JC.** 2011. Colonic anastomotic healing in the context of altered macrophage function and endotoxemia. Int J Colorect Dis 26:737-46.
2. Engel DR, Koscielny A, Wehner S, Maurer J, Schumak B, Limmer A, Sparwasser T, Hirner A, Knolle P, **Kalff JC***, Kurts C* (*joined corresponding authorship). 2010. T helper type 1 memory cells disseminate postoperative ileus over the entire intestinal tract. Nat Med. 16:1407-13.
3. Wehner S, Buchholz BM, Schuichtrup S, Rocke A, Schaefer N, Lysson M, Hirner A, **Kalff JC.** 2010. Mechanical strain and TLR4 synergistically induce cell-specific inflammatory gene expression in intestinal smooth muscle cells and peritoneal macrophages. Am J Physiol Gastrointest Liver Physiol 299:G1187-97.
4. Pantelis D, Kabba MS, Kirfel J, Kahl P, Wehner S, Buettner R, Hirner A, **Kalff JC.** 2010. Transient perioperative pharmacologic inhibition of muscularis macrophages as a target for prophylaxis of postoperative ileus does not affect anastomotic healing in mice. Surgery 148:59-70.
5. Wehner S, Straesser S, Vilz TO, Pantelis D, Sielecki T, de la Cruz VF, Hirner A, **Kalff JC.** 2009. Inhibition of p38 mitogen-activated protein kinase pathway as prophylaxis of postoperative ileus in mice. Gastroenterology 136:619-29.
6. Wehner S, Behrendt FF, Lyutenski BN, Lysson M, Bauer AJ, Hirner A, **Kalff JC.** 2007. Inhibition of macrophage function prevents intestinal inflammation and postoperative ileus in rodents. Gut 56:176-185.
7. Wehner S, Schwarz NT, Hundsdörfer R, Hierholzer C, Tweardy DJ, Billiar TR, Bauer AJ, **Kalff JC.** 2005. Induction of IL-6 within the rodent intestinal muscularis following intestinal surgical stress. Surgery 137:436-46.
8. Schwarz NT, **Kalff JC**, Turler A, Speidel N, Grandis JR, Billiar TR, Bauer AJ. 2004. Selective jejunal manipulation causes postoperative pan-enteric inflammation and dysmotility. Gastroenterology 126:159-69.
9. **Kalff JC**, Türler A, Schwarz NT, Schraut WH, Lee KKW, Tweardy DJ, Billiar TR, Simmons RL, Bauer AJ. 2003. Intra-abdominal activation of a local inflammatory response within the human muscularis externa during laparotomy. Ann Surg 237:301-15.
10. Engel BM, Eskandari M, **Kalff JC**, Grandis JR, Bauer AJ. 2002. Lipopolysaccharide preconditioning and cross-tolerance: the induction of protective mechanisms for rat intestinal ileus. Gastroenterology 123:586-98.

Prof. Wolfgang Kastenmüller, PhD

Institute of Molecular Medicine

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Molecular Medicine
E-Mail: wkastenm@uni-bonn.de

Research Expertise

The scientific focus of his group are cellular interactions and cell-cell communication in the context of acute infections. Central techniques are live intravital imaging and histocytometry.

Education / Training

Laboratory of Systems Biology NIH/USA,
Ronald N. Germain, 2008 - 2011
Technical University of Munich, Germany, Specialization, Infectious Disease 2008
Technical University of Munich, Germany, Medicine, M.D. thesis, 2003
Technical University of Munich, Germany, Medicine,
1997 - 2002
Universities of Regensburg, Germany, Medicine,
1995 - 1997

Appointments / Positions Held

2013
Associate Professor, University of Bonn, Germany
2008 - 2012
Post-Doc, NIH/Besthesda USA
2002 - 2008
Clinical Fellow/Post-Doc, Technical University of Munich, Germany

Honors / Awards

2012
CIG – Best Paper Award NIH
2003
Dietmar-Zumpf-Promotions Preis

10 Most Relevant Publications for Prof. Wolfgang Kastenmüller

1. Bald T, Quast T, Landsberg J, Rogava M, Glodde N, Lopez-Ramos D, Kohlmeyer J, Riesenberg S, van den Boorn-Konijnenberg D, Hömig-Hölzel C, Reuten R, Schadow B, Weighardt H, Wenzel D, Helfrich I, Schadendorf D, Bloch W, Bianchi ME, Lugassy C, Barnhill RL, Koch M, Fleischmann BK, Förster I, **Kastenmuller W**, Kolanus W, Hölzel M, Gaffal E, Tüting T. Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. Nature. 2014 Mar 6; 507 (7490):109-13.
2. Schiwon M, Weisheit C, Franken L, Gutweiler S, Dixit A, Meyer-Schwesinger C, Pohl JM, Maurice NJ, Thiebes S, Lorenz K, Quast T, Fuhrmann M, Baumgarten G, Lohse MJ, Opdenakker G, Bernhagen J, Bucala R, Panzer U, Kolanus W, Gröne HJ, Garbi N, **Kastenmuller W**, Knolle PA, Kurts C, Engel DR.: Crosstalk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium. Cell. 2014 Jan 30;156 (3):456-68.
3. Honda T, Egen JG, Lämmermann T, **Kastenmuller W**, Torabi-Parizi P, Germain RN.: Tuning of antigen sensitivity by T cell receptor-dependent negative feedback controls T cell effector function in inflamed tissues. Immunity. 2014 Feb 20; 40 (2): 235-47.
4. Lämmermann T, Afonso PV, Angermann BR, Wang JM, **Kastenmuller W**, Parent CA, Germain RN.: Neutrophil swarms require LTB4 and integrins at sites of cell death in vivo. Nature. 2013 Jun 20; 498 (7454): 371-5.
5. **Kastenmuller, W**, Brandes, M., Wang, Z., Herz, J., Egen YG., Germain, RN.: Peripheral pre-positioning and local CXCL9-mediated guidance orchestrate rapid memory CD8+ T cell responses in the lymph node. Immunity, 2013, Jan 24.
6. **Kastenmuller, W**, Torabi-Parizi, P., Subramanian, S., Lammermann, T., Germain, R.N.: A spatially-organized multicellular innate immune response in the lymph node limits the systemic spread of tissue-invasive pathogens. Cell, 2012, Sep 14; 150 (6):1235-48.
7. Gerner, M.Y., **Kastenmuller, W**, Ifrim, I., Kabat J., Germain, R.N.: Histo-Cytometry: in situ multiplex cell phenotyping, quantification, and spatial analysis applied to dendritic cell subset analysis in lymph nodes. Immunity, 2012 Aug 24; 37(2): 364-76.
8. **Kastenmuller W**, Gasteiger G, Subramanian N, Sparwasser T, Busch DH, Belkaid Y, Drexler I, Germain RN. Regulatory T Cells Selectively Control CD8+ T Cell Effector Pool Size via IL-2 Restriction. J Immunol. 2011 Sep 15;187 (6): 3186-97.
9. Kastenmuller, K., Wille-Reece, U., Lindsay R. W. B., Trager L. R., Darrah P. A., Flynn B. J., Becker M. R., Udey M. C., Clausen B. E., Igyarto B. Z., Kaplan D. H., **Kastenmuller W**, Germain R. N., and Seder R. A. Protective T cell immunity in mice following protein-TLR7/8 agonist-conjugate immunization requires aggregation, type I IFN, and multiple DC subsets. J Clin Invest. 2011 May 2; 121 (5): 1782-96.
10. **Kastenmuller W**, Gasteiger G, Subramanian N, Sparwasser T, Busch DH, Belkaid Y, Drexler I, Germain RN. Regulatory T cells selectively control CD8+ T cell effector pool size via IL-2 restriction. J Immunol. 2011 Sep 15; 187 (6): 3186-97.

Prof. U. Benjamin Kaupp, PhD

center of advanced european studies and research (caesar)

center of advanced european studies and research (caesar), Molecular Sensory Systems, Scientific Director and Head of Department
E-Mail: u.b.kaupp@caesar.de

Research Expertise

Biophysics of sensory systems. Physiology of receptors and ion channels in cellular signaling. Cell motility and chemotaxis. Development of chemical tools for kinetic techniques in cell biology.

Education / Training

University of Osnabrück, Biophysics, Habilitation, 1983
Technical University of Berlin, Chemistry, PhD, 1979
University of Tübingen and Technical University of Berlin Chemistry, Diploma, 1974

Appointments / Positions Held

2010 - 2011
Director of the Max-Planck-Institute for Neurological Research, University of Cologne, Germany
2008 - present
Professor of Molecular Neurobiology, University of Bonn, Germany
2008 - present
Scientific Director of caesar and Head of Department Molecular Sensory Systems (Center of Advanced European Studies and Research)
2007 - present
Scientific Member of the Max-Planck-Society, Max-Planck-Society
2000 - present
Whitman Investigator, Marine Biological Laboratory (MBL), Woods Hole, USA
1988 - present
Professor of Biophysical Chemistry, University of Cologne, Germany
2006 - 2009
Director of the International Helmholtz Research School of Biophysics and Soft Matter, Research Centre Jülich
1988 - 2007
Director at the Institute of Neuroscience and Biophysics Research Centre Jülich
1987
Feodor-Lynen-Stipend at the Department of Medical Chemistry, University of Kyoto, Japan
1985 - 1988
Assistant Professor of Biophysics, University of Osnabrück
1982 - 1985
Hochschulassistent, University of Osnabrück
1981
Postdoctoral Fellow, SUNY Stony Brook, USA

Honors / Awards

2013 Member of the North Rhine-Westphalian Academy of Sciences
2005 Member of the “German Academy of Sciences Leopoldina”
1999 Novartis Lecture, University Regensburg
1999 Keynote lecturer on international conferences
1994 Alcon Research Award
1987 Feodor-Lynen-Fellowship
1978 Member of the Academic Senate Technical University Berlin

10 Most Relevant Publications for Prof. U. Benjamin Kaupp

1. Alvarez L, Dai L, Friedrich BM, Kashikar ND, Gregor I, Pascal R, **Kaupp UB**. (2012) The rate of change in Ca2+ concentration controls sperm chemotaxis J. Cell. Biol. 196, 653-663.
2. Strünker T, Goodwin N, Brenker C, Kashikar ND, Weyand I, Seifert R, **Kaupp UB**. 2011. The CatSper channel mediates progesterone-induced Ca2+ influx in human sperm. Nature 471: 382-386.
3. **Kaupp UB**. 2010. Olfactory signalling in vertebrates and insects: differences and commonalities. Nat. Rev. Neurosci. 11: 188-200.
4. Schröder-Lang S, Schwärzel M, Seifert R, Strünker T, Kateriya S, Looser J, Watanabe M, **Kaupp UB**, Hegemann P, Nagel G. 2007. Fast manipulation of cellular cAMP level by light in vivo. Nat. Methods 4: 39-42.
5. Strünker T, Weyand I, Bönigk W, Van Q, Loogen A, Brown JE, Kashikar ND, Hagen V, Krause E, **Kaupp UB**. 2006. A K+-selective cGMP-gated ion channel controls chemosensation of sperm. Nat Cell Biol 8: 1149-54.
6. **Kaupp UB**, Solzin J, Hildebrand E, Brown JE, Helbig A, Hagen V, Beyermann M, Pampaloni F, Weyand I. 2003. The signal flow and motor response controling chemotaxis of sea urchin sperm. Nat Cell Biol 5: 109-17.
7. Stevens DR, Seifert R, Bufe B, Müller F, Kremmer E, Gauss R, Meyerhof W, **Kaupp UB**, Lindemann B. 2001. Hyperpolarization-activated channels HCN1 and HCN4 mediate responses to sour stimuli. Nature 413: 631-5.
8. Körschen HG, Beyermann M, Müller F, Heck M, Vantler M, Koch KW, Kellner R, Wolfrum U, Bode C, Hofmann KP, **Kaupp UB**. 1999. Interaction of glutamic-acid-rich proteins with the cGMP signalling pathway in rod photoreceptors. Nature 400: 761-6.
9. Gauss R, Seifert R, **Kaupp UB**. 1998. Molecular identification of a hyperpolarization- activated channel in sea urchin sperm. Nature 393: 583-7.
10. **Kaupp UB**, Niidome T, Tanabe T, Terada S, Bönigk W, Stühmer W, Cook NJ, Kangawa K, Matsuo H, Hirose T, et al. 1989. Primary structure and functional expression from complementary DNA of the rod photoreceptor cyclic GMP-gated channel. Nature 342: 762-6.

Prof. Percy Knolle, MD

Institute of Molecular Immunology

Technische Universität München (TU)
Institute for Molecular Immunology, Director
Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Molecular Medicine, Director (until 2012)
E-Mail: percy.knolle@tum.de

Research Expertise

The focus of Prof. Knolle's research group is on the molecular and cellular mechanisms governing local immune control in tissues. In his laboratory the relevance of local antigen presentation by organ-resident liver cells was demonstrated for induction of immune tolerance in naïve CD4 and CD8 T cells. The development of novel cell separation techniques allowed to study the mechanisms and functional relevance of different liver cell populations at a new level of resolution and to compare the immune function of these non-professional antigen presenting cells with myeloid professional antigen presenting cells such as dendritic cells or macrophages. His group has discovered novel stimulatory pathways that are initiated by unique immune sensory mechanisms in liver-resident antigen presenting cells that trigger local T cell immunity in the liver. The lab has developed an interest in local mechanisms determining regulation of CD4 T cell differentiation with particular reference to the impact of nuclear receptors that also impact on the metabolic state of T cells.

Education / Training

University of Mainz, Germany, Internal Medicine Specialist, 1997
German Cancer Research Centre, Heidelberg Applied Immunology, M.D. thesis, 1990
Universities of Frankfurt, Paris, Birmingham (UK), Strasbourg, and Geneva, Medicine, M.D., 1988

Appointments / Positions Held

2013 - present
Director Institute of Molecular Immunology, TU Munich
2006 - 2012, University of Bonn
Vice-speaker of the Collaborative Research group 704
2002 - 2012
Director Institutes of Molecular Medicine and Experimental Immunology, University of Bonn, Germany
2002
Professor of Molecular Medicine and Immunology, University of Bonn, Germany
1997 - 2002
Independent Group Leader, Center of Molecular Biology Heidelberg (ZMBH), University of Heidelberg, Germany
1991 - 1997
Physician at the 1st Medical Department, University of Mainz, Germany
1990 - 1991
Postdoctoral Fellow, BASF Bioresearch, Corporation, Cambridge, USA

Honors / Awards

2001
Award by the Volkswagen Foundation (1.5 Million €)

10 Most Relevant Publications for Prof. Percy Knolle

1. Schiwon M, Weisheit C, Franken L, Gutweiler S, Dixit A, Meyer-Schwesinger C, Pohl JM, Maurice NJ, Thiebes S, Lorenz K, Quast T, Fuhrmann M, Baumgarten G, Lohse MJ, Opdenakker G, Bernhagen J, Bucala R, Panzer U, Kolanus W, Grone HJ, Garbi N, Kastenmuller W, **Knolle PA**, Kurts C, Engel DR. Crosstalk between Sentinel and Helper Macrophages Permits Neutrophil Migration into Infected Uroepithelium. Cell 2014, 156(3): 456-468.
2. **Knolle PA**, Thimme R. Hepatic Immune Regulation and its Involvement in Viral Hepatitis Infection. Gastroenterology 2014, in press.
3. De Nardo D, Labzin LI, Kono H, Seki R, Schmidt SV, Beyer M, Xu D, Zimmer S, Lahrmann C, Schildberg FA, Vogelhuber J, Kraut M, Ulas T, Kerksiek A, Krebs W, Bode N, Grebe A, Fitzgerald ML, Hernandez NJ, Williams BR, **Knolle P,** Kneilling M, Rocken M, Lutjohann D, Wright SD, Schultze JL, Latz E. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nature immunology 2014, 15(2): 152-160.
4. Huang LR, Wohlleber D, Reisinger F, Jenne CN, Cheng RL, Abdullah Z, Schildberg FA, Odenthal M, Dienes HP, van Rooijen N, Schmitt E, Garbi N, Croft M, Kurts C, Kubes P, Protzer U, Heikenwalder M, **Knolle PA**. Intrahepatic myeloid-cell aggregates enable local proliferation of CD8(+) T cells and successful immunotherapy against chronic viral liver infection. Nature immunology 2013, 14(6): 574-583.
5. Bottcher JP, Schanz O, Wohlleber D, Abdullah Z, Debey-Pascher S, Staratschek-Jox A, Hochst B, Hegenbarth S, Grell J, Limmer A, Atreya I, Neurath MF, Busch DH, Schmitt E, van Endert P, Kolanus W, Kurts C, Schultze JL, Diehl L, **Knolle PA.** Liver-primed memory T cells generated under noninflammatory conditions provide anti-infectious immunity. Cell reports 2013, 3(3): 779-795.
6. Abdullah Z, Schlee M, Roth S, Mraheil MA, Barchet W, Bottcher J, Hain T, Geiger S, Hayakawa Y, Fritz JH, Civril F, Hopfner KP, Kurts C, Ruland J, Hartmann G, Chakraborty T, **Knolle PA**. RIG-I detects infection with live Listeria by sensing secreted bacterial nucleic acids. The EMBO journal 2012, 31(21): 4153-4164.
7. Wohlleber D, Kashkar H, Gartner K, Frings MK, Odenthal M, Hegenbarth S, Borner C, Arnold B, Hammerling G, Nieswandt B, van Rooijen N, Limmer A, Cederbrant K, Heikenwalder M, Pasparakis M, Protzer U, Dienes HP, Kurts C, Kronke M, **Knolle PA**. TNF-induced target cell killing by CTL activated through cross-presentation. Cell reports 2012, 2(3): 478-487.
8. Huang LR, Gabel YA, Graf S, Arzberger S, Kurts C, Heikenwalder M, **Knolle PA**, Protzer U. Transfer of HBV genomes using low doses of adenovirus vectors leads to persistent infection in immune competent mice. Gastroenterology 2012, 142(7): 1447-1450 e1443.
9. Protzer U, Maini MK, **Knolle PA**. Living in the liver: hepatic infections. Nature reviews Immunology 2012, 12(3): 201-213.
10. Kern M, Popov A, Kurts C, Schultze JL, **Knolle PA**. Taking off the brakes: T cell immunity in the liver. Trends in immunology 2010, 31(8): 311-317.

Prof. Waldemar Kolanus, PhD

Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
Life and Medical Sciences Institute (LIMES), Molecular Immunology & Cell Biology, Director
E-Mail: wkolanus@uni-bonn.de

Research Expertise

Prof. Kolanus and his group are interested in intracellular signal transduction events which control leukocyte adhesion, migration, and effector functions. The main emphasis of their current research activities lies in elucidating the role of integrin adhesion receptors and the cytoskeleton in the functional adaptation of leukocyte motility to specific microenvironments, some of which include force-dependent slow migration of immune cells on and across barriers, versus force-independent, fast migration in the interstitium.

Education / Training

University of Hannover, Molecular Biology, PhD, 1987
University of Hannover, Biology, Chemistry, State examination, 1984

Appointments / Positions Held

2002 - present
Full Professorship, Molecular Immunology, University of Bonn
1999 - 2002
Associate Professor, Biochemistry, University of Munich (LMU)
1999
Habilitation in Biochemistry, Faculty of Chemistry, University of Munich (LMU)
1994 - 1999
Independent Group Leader, Gene Center Munich, University of Munich (LMU)
1990 - 1993
Post-doc Fellow, Molecular Immunology, Harvard Medical School
1988 - 1990 Post-doc Fellow, Immunology, Hannover Medical School

Honors / Awards

2009
US Patent 20090105286, Low molecular inhibitors of cyohesin-family guanine nucleotide exchange factors
2007
US Patent 20070287153 - Methods for identification and validation of functional intracellular targets with intramers or in vivo selection
2004
US Patent 20040170990 - Intracellular nucleic acid inhibitors of small guanine nucleotide exchange factors
US Patent 20040029775 - Methods and compounds for influencing beta3-integrin- dependent intracellular processes
2003
US Patent 20030138410 - Targeted cytolysis of HIV-infected cells by chimeric CD4 receptor-bearing cells
2002
US Patent 20020176851 - Redirection of cellular immunity by protein-tyrosine kinase chimeras
1996
US Patent 6573362 - Cytohesin-PH peptides that affect the ability of integrins to adhere
1994
Munich Gene Center Junior Group Leader 5-year-Award, BMBF and University of Munich

10 Most Relevant Publications for Prof. Waldemar Kolanus

1. Bald T, Quast T, Landsberg J, Rogava M, Glodde N, Lopez-Ramos D, Kohlmeyer J, Riesenberg S, van den Boorn-Konijnenberg D, Hömig-Hölzel C, Reuten R, Schadow B, Weighardt H, Wenzel D, Helfrich I, Schadendorf D, Bloch W, Bianchi M.E, Lugassy C, Barnhill RL, Koch M, Fleischmann BK, Förster I, Kastenmüller W, **Kolanus W**, Hölzel M, Gaffal E, Tüting T. 2014.Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. Nature. 507,109-13.
2. Salt-dependent chemotaxis of macrophages. 2013
Müller S, Quast T, Schröder A, Hucke S, Klotz L, Jantsch J, Gerzer R, Hemmersbach R, **Kolanus W**, PLoS One. 16 :e73439.
3. Ulbricht A, Eppler FJ, Tapia VE, van der Ven PF, Hampe N, Hersch N, Vakeel P, Stadel D, Haas A, Saftig P, Behrends C, Fürst DO, Volkmer R, Hoffmann B, **Kolanus W**, Höhfeld J.
Cellular mechanotransduction relies on tension-induced and chaperone-assisted autophagy., Curr Biol., 2013, 23, 430-435.
4. Quast T, Eppler F, Semmling V, Schild C, Homsi Y, Levy S, Lang T, Kurts C, **Kolanus W.** CD81 is essential for the formation of membrane protrusions and regulates Rac1-activation in adhesion-dependent immune cell migration., Blood, 2011, 118, 1818-1827.
5. Loer B, Bauer R, Bornheim R, Grell J, Kremmer E, **Kolanus W**, Hoch M. 2008. The NHLdomain protein Wech is crucial for the integrin-cytoskeleton link. Nat Cell Biol 10: 422-8.
6. Hafner M, Schmitz A, Grune I, Srivatsan SG, Paul B, **Kolanus W,** Quast T, Kremmer E, Bauer I, Famulok M. 2006. Inhibition of cytohesins by SecinH3 leads to hepatic insulin resistance. Nature 444: 941-4.
7. Shamri R, Grabovsky V, Gauguet JM, Feigelson S, Manevich E, **Kolanus W**, Robinson MK, Staunton DE, von Andrian UH, Alon R. 2005. Lymphocyte arrest requires instantaneous induction of an extended LFA-1 conformation mediated by endothelium- bound chemokines. Nat Immunol 6: 497-506.
8. Boehm T, Hofer S, Winklehner P, Kellersch B, Geiger C, Trockenbacher A, Neyer S, Fiegl H, Ebner S, Ivarsson L, Schneider R, Kremmer E, Heufler C, **Kolanus W**. 2003. Attenuation of cell adhesion in lymphocytes is regulated by CYTIP, a protein which mediates signal complex sequestration. EMBO J 22: 1014-24.
9. Geiger C, Nagel W, Boehm T, van Kooyk Y, Figdor CG, Kremmer E, Hogg N, Zeitlmann L, Dierks H, Weber KS, **Kolanus W**. 2000. Cytohesin-1 regulates beta-2 integrin-mediated adhesion through both ARF-GEF function and interaction with LFA-1. EMBO J 19: 2525-36.
10. **Kolanus W**, Nagel W, Schiller B, Zeitlmann L, Godar S, Stockinger H, Seed B. 1996. Alpha L beta 2 integrin/LFA-1 binding to ICAM-1 induced by cytohesin-1, a cytoplasmic regulatory molecule. Cell 86: 233-42.

Prof. Christian Kurts, MD

Institute of Experimental Immunology

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Experimental Immunology, Director
E-Mail: ckurts@uni-bonn.de

Research Expertise

Prof. Kurts and his group are interested in the mechanisms governing antigen-presentation and the ensuing immune response in the defense against infections and in immune-mediated disease. Their main research projects focus on the mechanisms of antigen cross-presentation to cytotoxic CD8 T cells, peripheral immune tolerance of T and B lymphocytes against self antigens, and the role of dendritic cells in diseases, especially in kidney disease.

Education / Training

University of Göttingen, Germany
Medicine M.D., 1991

Appointments / Positions Held

2013
Co-speaker SFB 704 “Molecular Mechanisms and Chemical Modulation of Local Immune Regulation“ University of Bonn, Germany
2012
Co-speaker SFB TR57 “Organ-Fibrosis”, representing the Bonn site, University of Bonn, Germany
2009 - present
Director Institute of Experimental Immunology, University of Bonn, Germany
2003 - 2008
Full Professor of Molecular Immunology University of Bonn, Germany
2002
Visiting scientist, Stephen Schoenberger Group
La Jolla Institute for Allergy and Immunology, CA, USA
2000 - 2003
Research group leader, Dept. of Nephrology and Clinical Immunology, University of Aachen, Germany
1998 - 2000
Medical Officer and Research Fellow, Hannover Medical School, Germany
1997 - 1998
Postdoctoral Research Fellow, Dept of Microbiology, Monash Medical School, Melbourne, Australia
1995 - 1997
Postdoctoral Research Fellow, Thymus Biology Unit, The Walter and Eliza Hall Institute for Medical Research (WEHI), Melbourne, Australia
1991-1995
Medical Officer and Research Fellow, Hannover Medical School, Germany

Honors / Awards

2012
Gottfried-Wilhelm-Leibniz-Prize of the DFG
2010
Hans-U.-Zollinger-Award of the German Society for Nephrology
2000
Heisenberg-Fellowship of the Deutsche Forschungsgemeinschaft
1999
Sir Hans Krebs award for basic medical research
1992
Annual award of the German Society of Nephrology for best doctoral thesis
1986 -1991
Fellowship Studienstiftung des deutschen Volkes (German National Academic Foundation)

10 Most Relevant Publications for Prof. Christian Kurts

1. Schiwon M, Weisheit C, Franken L, Gutweiler S, Dixit A, Meyer-Schwesinger C, Pohl J, Maurice NJ, Thiebes S, Lorenz K, Quast T, Fuhrmann M, Baumgarten G, Lohse MJ, Opdenakker G, Bernhagen J, Bucala R, Panzer U, Kolanus W, Gröne HJ, Garbi N, Kastenmüller W, Knolle PA, **Kurts C***, Engel DR*. 2014. Cross-talk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium. Cell, 156:456–68; (*joint senior authorship)
2. **Kurts C**, Panzer U, Anders HJ, Rees A. 2013. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol, 13(10):738-53.
3. Hochheiser K, Heuser, C Krause TA, Teteris S, Ilias A, Weisheit C, Hoss F, Tittel AP, Panzer U, Knolle PA, Engel DR, Tharaux PL, **Kurts C**. 2013. Exclusive CX3CR1-dependence of kidney cortex dendritic cells identifies a therapeutic target in glomerulonephritis. J Clin Invest, 123(10):4242-54.
4. Gottschalk C, Damuzzo V, Gotot J, Kroczek R, Yagita H, Murphy KM, Knolle PA, Ludwig-Portugall I, **Kurts C**. 2013. Batf3-dependent renal lymph node DCs maintain immune-homeostasis against circulating antigens; J Am Soc Nephrol, 24:543-9.
5. Gotot J, Gottschalk C, Leopold S, Knolle PA, Yagita H, **Kurts C***, Ludwig-Portugall I*. 2012. Direct PD-1-mediated suppression of autoreactive B cells by regulatory T cells. PNAS 109(26):10468-7. (*joint senior authorship)
6. Tittel AP, Heuser C, Ohliger C, Yona S, Hämmerling GJ, Engel DR, Garbi N, **Kurts C**. 2012. Functionally relevant neutrophilia in CD11c-diphteria toxin receptor transgenic mice. Nat Methods 9(4):385-90.
7. Engel DR, Koscielny A, Wehner S, Maurer J, Schiwon M, Schumak B, Limmer A, Sparwasser T, Hirner A, Knolle PA, Kalff JC, **Kurts C**. 2010. Th1 memory cells disseminate postoperative ileus over the entire intestinal tract. Nat Med, 16(12): 1407–1413.
8. Semmling V, Lukacs-Kornek V, Thaiss CA, Quast T, Hochheiser K, Panzer U, Rossjohn J, Perlmutter P, Cao J, Godfrey DI, Savage PB, Knolle PA, Kolanus W, Forster I, **Kurts C**. 2010. Alternative cross-priming through CCL17-CCR4-mediated attraction of CTLs toward NKT cell-licensed DCs. Nat Immunol 11: 313-20.
9. **Kurts C**, Robinson BW, Knolle PA. 2010. Cross-priming in health and disease. Nat Rev Immunol 10: 403-14.
10. Heymann F, Meyer-Schwesinger C, Hamilton-Williams EE, Hammerich L, Panzer U, Kaden S, Quaggin SE, Floege J, Grone HJ, **Kurts C**. 2009. Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. J Clin Invest 119: 1286-97.

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Research Expertise

The Latz Lab has a longstanding interest in deciphering the molecular mechanisms of innate immune receptor activation. In particular, the lab is interested in understanding how innate receptors interact with their ligands and how this molecular interaction leads to receptor activation. Recently, we have also focused on the molecular details of the mechanisms that lead to the activation of the NLRP3 and AIM2 inflammasome. The NLRP3 inflammasome can respond to a broad range of cellular stressors and to substances that indicate metabolic derangements such as aggregated peptides, crystals of monosodium urate (forming in gout) or crystals of cholesterol that are found in atherosclerotic plaques. One goal of the research is to translate the molecular understanding of innate immune receptor activation into the generation of molecular tools that could lead to the development of specific diagnostics for inflammatory materials. Another goal is to devise means to pharmacologically interfere with the activation of innate immune receptors in order to develop novel approaches to treat inflammatory diseases such as Alzheimer’s disease or atherosclerosis.

Education / Training

Humbolt University of Berlin, Germany, PhD, 2001
Free University of Berlin, Germany, Molecular Medicine, Hematology, M.D., 1998

Appointments / Positions Held

2009 - present Full Professor of Medicine, Founder and Director of the Institute of Innate Immunity, University of Bonn, Germany
2011- present Leader, Cooperation Unit Innate Immunity in Neurodegeneration, DZNE, Bonn, Germany
2003 - present Assistant Professor of Medicine UMass Medical School
2008 Adjunct Professor II, Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology
2007 Founder and Co-Director of UMassNanoMed, UMassNanoMed Institute
2003-2006 Assistant Research Professor, UMass Medical School
2001 - 2003 Postdoctoral Fellow, Division of Infectious Disease UMass Medical School
2001 Postdoctoral Fellow, Evans Biomedical Research Center, Boston University of Medicine
1999 - 2001 Research Fellow, Molecular Sepsis Research Laboratories, Charité University Hospital, Humboldt-University of Berlin
1998 - 2000 Internship and Residency (Intensive Care) Department of Surgery and Surgical Oncology, Charité University Hospital, Humboldt-University of Berlin
1998 Visiting Scientist, Department of Lipid Biochemistry, Merck Research Laboratories

Honors / Awards

2013 ERC Consolidator Grant
2011 GlaxoSmithKline Clinical Science Award
2009 Dana Foundation Award
2004 Federation of Clinical Immunology Societies (FOCIS) Award
2001 Postdoctoral Training Grant of the German Academic Exchange Program (DAAD)
2001 PhD Thesis awarded “summa cum laude”
2000 Scholarship of the Japanese Society for Endoscopy
2000 Award of the Japanese Society of Surgery, Tokyo National Cancer Center

10 Most Relevant Publications for Prof. Eicke Latz

1. De Nardo D*, Labzin LI*, Kono H, Seki R, Schmidt SV, Beyer M, Xu D, Zimmer S, Lahrmann C, Schildberg FA, Vogelhuber J, Kraut M, Ulas T, Kerksiek A, Krebs W, Bode N, Grebe A, Fitzgerald ML, Hernandez NJ, Williams BR, Knolle P, Kneilling M, Rocken M, Lutjohann D, Wright SD, Schultze JL* and **Latz E***. (2014). High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol, 15(2), 152-160.
2. Heneka MT*, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, Griep A, Axt D, Remus A, Tzeng TC, Gelpi E, Halle A, Korte M, **Latz E*** and Golenbock DT*. (2013). NLRP3 is activated in Alzheimer‘s disease and contributes to pathology in APP/PS1 mice. Nature, 493(7434), 674-678.
3. Bossaller L, Rathinam VA, Bonegio R, Chiang PI, Busto P, Wespiser AR, Caffrey DR, Li QZ, Mohan C, Fitzgerald KA, **Latz E*** and Marshak-Rothstein A*. (2013). Overexpression of membrane-bound fas ligand (CD95L) exacerbates autoimmune disease and renal pathology in pristane-induced lupus. Journal of Immunology, 191(5), 2104-2114.
4. Bossaller L, Chiang PI, Schmidt-Lauber C, Ganesan S, Kaiser WJ, Rathinam VA, Mocarski ES, Subramanian D, Green DR, Silverman N, Fitzgerald KA, Marshak-Rothstein A and **Latz E**. (2012). Cutting Edge: FAS (CD95) Mediates Noncanonical IL-1beta and IL-18 Maturation via Caspase-8 in an RIP3-Independent Manner. Journal of Immunology, 189(12), 5508-5512.
5. Duewell P*, Kono H*, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nunez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V* and **Latz E***. (2010). NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature, 464(7293), 1357-1361.
6. Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, **Latz E*** and Fitzgerald KA*. (2009). AIM2 recognizes cytosolic dsDNA and forms a caspase-1- activating inflammasome with ASC. Nature, 458(7237), 514-518.
7. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, Fernandes- Alnemri T, Wu J, Monks BG, Fitzgerald KA, Hornung V* and **Latz E***. (2009). Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol, 183(2), 787-791.
8. Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, Fitzgerald KA* and **Latz E***. (2008). Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol, 9(8), 847-856.
9. **Latz E**, Verma A, Visintin A, Gong M, Sirois CM, Klein DC, Monks BG, McKnight CJ, Lamphier MS, Duprex WP, Espevik T and Golenbock DT. (2007). Ligand-induced conformational changes allosterically activate Toll-like receptor 9. Nat Immunol, 8(7),772-779.
10. **Latz E**, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, Lien E, Nilsen NJ, Espevik T and Golenbock DT. (2004). TLR9 signals after translocating from the ER to CpG DNA in the lysosome. Nat Immunol, 5(2), 190-198.

* These authors contributed equally

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Research Expertise

Neuroinflammation, mechanisms of inflammatory neurodegeneration, microglia-neuron interaction, stem cell-derived microglia

Education / Training

Technical University Munich, Germany Neuroimmunology Habilitation, 1998
University of Hagen, Germany Business Business Administration, 1994
University of Würzburg, and University of Munich (LMU), Germany, Medicine M.D., Thesis, 1991

Appointments / Positions Held

2004 - present
Head of the Neural Regeneration Group, University of Bonn, Germany
2001 - 2004
Head of the Neuroimmunology Group European Neuroscience Institute Göttingen, University Göttingen
1995 - 2001
Group leader, Department of Neuroimmunology Max-Planck-Institute of Neurobiology, Martinsried
1992 - 1994
Research fellow, Department of Neuroimmunology Max-Planck-Institute of Psychiatry, Martinsried
1990 - 1992
Medical Internship, Department of Neurology, University Ulm, Germany

Honors / Awards

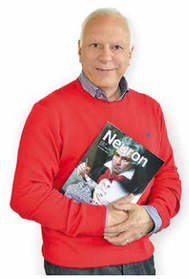
2010
PCT-Patent (WO2010/125110) entitled ‚Method for obtaining human microglial precursor cells from pluripotent stem cells'; with the following inventors Neumann, Roy, Brüstle, Peitz; international publication on 4. Nov 2010.
2005 - 2010
Co-coordinator of the EU Integrated Project NeuroproMiSe
2002 - 2009
Managing Board member of the Institute of MS Research
2003 - 2008
Editorial Board member of ‚Stem Cells'
2007
DANA-Foundation-Award, Neuroimmunology-Program
1996
PCR-Award Boehringer Mannheim
1992
Research scholarship (German science foundation)

10 Most Relevant Publications for Prof. Harald Neumann

1. Claude J, Linnartz-Gerlach B, Kudin AP, Kunz WS and **Neumann H.** (2013). Microglial CD33-related Siglec-E inhibits neurotoxicity by preventing the phagocytosis associated oxidative burst. J. Neurosci. 33(46):18270-6.
2. Zhang B*, Gaiteri C*, Bodea LG*, Wang Z, McElwee J, Podtelezhnikov AA, Zhang C, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, **Neumann H**, Zhu J, Emilsson V. (2013). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell. 2013 Apr 25;153(3):707-20.
3. Wang Y, **Neumann H**. 2010. Alleviation of neurotoxicity by microglial human Siglec-11. J. Neurosci 30: 3482-8.
4. Beutner C, Roy K, Linnartz B, Nappoli I, **Neumann H.** 2010. Generation of microglial cells from mouse embryonic stem cells. Nature Protocols: 5:1481-94.
5. Takahashi K, Prinz M, Stagi M, Chechneva O, **Neumann H.** 2007. TREM2-transduced myeloid precursors mediate nervous tissue debris clearance and facilitate recovery in an animal model of multiple sclerosis. PLoS Med 4: e124.
6. Stagi M, Gorlovoy P, Larionov S, Takahashi K, **Neumann H.** 2006. Unloading kinesin transported cargoes from the tubulin track via the inflammatory c-Jun N-terminal kinase pathway. FASEB J 20: 2573-5.
7. Takahashi K, Rochford CD, **Neumann H. 2005**. Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. J Exp Med 201: 647-57.
8. Stagi M, Dittrich PS, Frank N, Iliev AI, Schwille P, **Neumann H.** 2005. Breakdown of axonal synaptic vesicle precursor transport by microglial nitric oxide. J Neurosci 25: 352-62.
9. **Neumann H**, Schweigreiter R, Yamashita T, Rosenkranz K, Wekerle H, Barde YA. 2002. Tumor necrosis factor inhibits neurite outgrowth and branching of hippocampal neurons by a rho-dependent mechanism. J Neurosci 22: 854-62.
10. Medana I, Martinic MA, Wekerle H, **Neumann H.** 2001. Transection of major histocompatibility complex class I-induced neurites by cytotoxic T lymphocytes. Am J Pathol 159: 809-15.

Prof. Pierluigi Nicotera, MD

German Centre for Neurodegenerative Diseases (DZNE)



German Centre for Neurodegenrative Diseases (DZNE), Scientific Director
E-Mail: pierluigi.nicotera@dzne.de

Research Expertise

Prof. Nicotera's main research focus is on molecular mechanisms of cell death and neurodegeneration.

Education / Training

University of Pavia, Medical School, Italy, Cardiology Consultant, 1987
Karolinska Institute, Stockholm, Biochemical Toxicology PhD, 1986
University of Pavia, Medical School, Italy, Medicine MD, 1982

Appointments / Positions Held

April 2009 - present
Scientific Director & Chairman of the Executive Board vGerman Centre for Neurodegenerative Diseases (DZNE), Bonn, Germany
2002 - 2009
Director of the British Medical Research Council Toxicology Unit and Honorary Professor of Neuroscience (Dept. of Cell Physiology & Pharmacology), University of Leicester
2005 - 2008
Teaching Professor of Toxicology, Faculty of Pharmacy University of Siena, Italy
1996 - 2002
Foreign Adjunct Professor in Toxicology, Karolinska Institute, Stockholm, Sweden
1995 - 2000
C4 Professor of Molecular Toxicology, University of Konstanz, Germany
1989 - 1994
Senior University Lecturer, Karolinska Institute, Stockholm, Sweden
1992
Docent in Molecular Toxicology, Karolinska Institute, Stockholm, Sweden
1986 - 1989
Research assistant Professor, Department of Karolinska Institute, Stockholm, Toxicology, Sweden

Honors / Awards

2013
The Chancellor's Award Lecture in Neuroscience at LSU Neuroscience Center of Excellence, New Orleans, USA
2012
Honorary Citizenship and Key to the City of New Orleans
2010
The Cardano Prize University of Pavia and Rotary Club Pavia
2003
The Chancellor's Award Lecture in Neuroscience at LSU Neuroscience Center of Excellence, New Orleans, USA
2002
"Molecular switches in neuronal cell death" Lecture at the 37th Nobel Conference on Apoptosis, Stockholm
1999
The Jacob Hooisma Honorary Lecture at the 7th Meeting of the International Neurotoxicology Association, Leicester
1995
The EUROTOX Award Lecture, 1st G. Zbinden Memorial Lecture Award, Prague
1992
"Nuclear Calcium Signalling" Lecture at the 20th Nobel Conference on Calcium Signalling, Saltsjöbaden, Sweden
1992
The International Life Science Institute Research Foundation U.S.A. (ILSI), award

10 Most Relevant Publications for Prof. Pierluigi Nicotera

1. Ziviani E, Lippi G, Bano D, Munarriz E, Guiducci S, Zoli M, Young KW, **Nicotera P.** 2011. Ryanodine receptor-2 upregulation and nicotine-mediated plasticity. EMBO J 30(1): 194-204.
2. Regad T, Bellodi C, **Nicotera P**, Salomoni P. 2009. The tumor suppressor Pml regulates cell fate in the developing neocortex. Nat Neurosci 12: 132-40.
3. Berliocchi L, Fava E, Leist M, Horvat V, Dinsdale D, Read D, **Nicotera P**. 2005. Botulinum neurotoxin C initiates two different programs for neurite degeneration and neuronal apoptosis. J Cell Biol 168: 607-18.
4. Bano D, Young KW, Guerin CJ, Lefeuvre R, Rothwell NJ, Naldini L, Rizzuto R, Carafoli E, **Nicotera P**. 2005. Cleavage of the plasma membrane Na+/Ca2+ exchanger in excitotoxicity. Cell 120: 275-85.
5. Orrenius S, Zhivotovsky B, **Nicotera P**. 2003. Regulation of cell death: the calcium- apoptosis link. Nat Rev Mol Cell Biol 4: 552-6.
6. Schierle GS, Hansson O, Leist M, **Nicotera P,** Widner H, Brundin P. 1999. Caspase inhibition reduces apoptosis and increases survival of nigral transplants. Nat Med 5: 97-100.
7. Leist M, Single B, Castoldi AF, Kuhnle S, **Nicotera P**. 1997. Intracellular adenosine triphosphate (ATP) concentration: a switch in the decision between apoptosis and necrosis. J Exp Med 185: 1481-6.
8. Bonfoco E, Krainc D, Ankarcrona M, **Nicotera P**, Lipton SA. 1995. Apoptosis and necrosis: two distinct events induced, respectively, by mild and intense insults with N-methyl-D- aspartate or nitric oxide/superoxide in cortical cell cultures. Proc Natl Acad Sci U S A 92: 7162-6.
9. Ankarcrona M, Dypbukt JM, Bonfoco E, Zhivotovsky B, Orrenius S, Lipton SA, **Nicotera P**. 1995. Glutamate-induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. Neuron 15: 961-73.
10. Juntti-Berggren L, Larsson O, Rorsman P, Ammala C, Bokvist K, Wahlander K, **Nicotera P**, Dypbukt J, Orrenius S, Hallberg A, et al. 1993. Increased activity of L-type Ca2+ channels exposed to serum from patients with type I diabetes. Science 261: 86-90.

Prof. Markus M. Nöthen, MD

Institute of Human Genetics

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Human Genetics, Director

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Research Expertise

The identification of the genetic causes of inherited diseases, and a special focus on genetically complex and multifactorial phenotypes.

Education / Training

University of Bonn, Germany, Human Genetics, Habilitation, 1996
University of Bonn, Germany, Human Genetics, Medical Board Qualification, 1995
University of Würzburg, Germany, Internal Medicine, Medical thesis, 1992, University of Würzburg, Germany, Clinical Medicine, MD, 1989

Appointments / Positions Held

2008 - present
Director and Chair, Institute of Human Genetics, University of Bonn, Germany
2006 - present
Vice Dean for Research, Medical Faculty, University of Bonn, Germany
2004 - present
Alfried Krupp von Bohlen und Halbach Professor in Genetic Medicine, University of Bonn, Germany
2004 - present
Head, Department of Genomics, Life & Brain Center, University of Bonn, Germany
2001 - 2004
Head of Department and Chair of Medical Genetics, University of Antwerp, Belgium
1999 - 2001
Assistant Medical Director, Institute of Human Genetics University of Bonn, Germany
1996 - 2001
Assistant Professor, Institute of Human Genetics, University of Bonn, Germany
1991 - 1996
Postdoctoral Fellow, Institute of Human Genetics, University of Bonn, Germany
1990 - 1991
Internship, Institute of Human Genetics, University of Bonn, Germany

Honors / Awards

2013 - present: Scientific Advisory Board of the Leipzig Research Center for Civilization Diseases (LIFE) (Member)
2013 - present: Scientific Advisory Board of the Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology (IKP) and the Robert Bosch Hospital (RBK) (Member)
2012 - present: International Advisory Board of iPSYCH (Lundbeck Foundation) (Chair)
2011 - present: European Society of Human Genetics (Elected Member of the Board)
2010 - 2012: Project Committee of the National Genome Research Network (Spokesman)
2010 - present: Scientific Advisory Board of the Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics, Cardiff, UK (Member)
2010 - present: German Academy of Sciences Leopoldina (National Academy of Sciences)
2009 - present: Hermann Emminghausen-Prize
2008 - 2013: Project Committee of the National Genome Research Network (Elected member)
2007 - present: Institute of Science and Ethics, Bonn (Member of the Scientific Advisory Board)
National Foundation for Legasthenia and Dyscalculia (Member of the Medical Advisory Board)
2006 - present: National Alopecia Areata Foundation (Member of the Medical Advisory Board) Task Force on Genetics, World Federation of Societies of Biological Psychiatry
2005 - present: International Society of Psychiatric Genetics (Elected Member of the Board)

10 Most Relevant Publications for Prof. Markus M. Nöthen

1. Mühleisen TW, Leber M, Schulze TG, Strohmaier J, Degenhardt F,…,Forstner AJ, Schumacher J,…, Herms S, Hoffmann P,…,Propping P, Becker T, Rietschel M, **Nöthen MM**, Cichon S. 2014. Genome-wide association study reveals two new risk loci for bipolar disorder. Nature Communications doi: 10.1038/ncomms4339.
2. Cross-Disorder Group of the Psychiatric Genomics Consortium, … , **Nöthen MM**, … , Wray N. 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 45:984-994.
3. Ludwig KU, Mangold E, Herms S, Nowak S, Reutter H,…, **Nöthen MM**. 2012. Genome-wide meta-analyses of nonsyndromic cleft lip with or without cleft palate identify six new risk loci. Nat Genet 44:968-971.
4. Cichon S, Mühleisen TW, Degenhardt FA, Mattheisen M,..., Schumacher J, Maier W, Propping P, Rietschel M, **Nöthen MM***. 2011. Genome-wide association study identifies genetic variation in neurocan as a susceptibility actor for bipolar disorder. Am J Hum Genet 88:372-81.
5. Stefansson H, Ophoff RA, Steinberg S,..., **Nöthen MM**, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA*. 2009. Common variants conferring risk of schizophrenia. Nature 460: 744-7.
6. Birnbaum S, Ludwig KU,..., **Nöthen MM**, Mangold E*. 2009. Key susceptibility locus for nonsyndromic cleft lip with or without cleft palate on chromosome 8q24. Nat Genet 41: 473-7.
7. Stefansson H, Rujescu D, Cichon S,..., **Nöthen MM**, Peltonen L, Collier DA, St Clair D, Stefansson K*. 2008. Large recurrent microdeletions associated with schizophrenia. Nature 455: 232-6.
8. Pasternack SM, von Kügelgen I, Aboud KA, Lee YA, Rüschendorf F, Voss K, Hillmer AM, Molderings GJ, Franz T, Ramirez A, Nürnberg P, **Nöthen MM**, Betz RC. 2008. G protein- coupled receptor P2Y5 and its ligand LPA are involved in maintenance of human hair growth. Nat Genet 40: 329-34.
9. Hillmer AM, Brockschmidt FF, Hanneken S, Eigelshoven S, Steffens M, Flaquer A, Herms S, Becker T, Kortum AK, Nyholt DR, Zhao ZZ, Montgomery GW, Martin NG, Mühleisen TW, Alblas MA, Moebus S, Jöckel KH, Bröcker-Preuss M, Erbel R, Reinartz R, Betz RC, Cichon S, Propping P, Baur MP, Wienker TF, Kruse R, **Nöthen MM**. 2008. Susceptibility variants for male-pattern baldness on chromosome 20p11. Nat Genet 40: 1279-81.
10. Cichon S, Martin L, Hennies HC, Müller F, Van Driessche K, Karpushova A, Stevens W, Colombo R, Renné T, Drouet C, Bork K, **Nöthen MM**. 2006. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. Am J Hum Genet 79: 1098-104.

* Publications with more than 10 authors have been shortened

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E-Mail: natalija.novak@ukb.uni-bonn.de

Research Expertise

Pathophysiology of atopic dermatitis including genetic changes, regulation of the surface expression of the high affinity receptor for IgE on dendritic cells, role of IgE receptor bearing Langerhans cells and inflammatory dendritic epidermal cells, predictive factors for atopy in cord-blood, development and characterization of new therapeutic strategies for atopic dermatitis, role of dendritic cells in the oral and nasal mucosa.

Education / Training

University of Bonn, Germany, Medicine, MD., 1998

Appointments / Positions Held

2008 - present
Full Professor of Dermatology and Allergy, University of Bonn, Germany
2009
Board, Andrology, University of Bonn, Germany
2006 - 2007
Visiting scientist, Heisenberg-Fellowship, Swiss Institute of Allergy and Asthma Research, Davos, Switzerland
2004
Board, Allergy, University of Bonn, Germany
2003
Assistant Professor, Dermatology and Allergy, University of Bonn, Germany
Assistant to Medical Director, Dermatology, University of Bonn, Germany
Board, Dermatology, University of Bonn, Germany

Honors / Awards

2008 Phadia International Award on Allergy Research, Phadia
2007 Heisenberg-Professorship, German Research Council
2006 Heisenberg-Fellowship, German Research Council
Travel Award EAACI Vienna, Austria
2005 Heinz Maier-Leibnitz Award, German Research Council
Research Award Atopische Dermatitis, Dermatologikum Hamburg
Young Investigator Travel Award, ISAD Meeting Acachand
2004
Karl-Hansen Memorial Award, German Society for Allergology and Immunology (DGAKI)
2003
Fujisawa "Young Investigator Achievements Award in Atopic Dermatitis Research"
Award, Herbert-Reeck-Society
Honourable Mention Diploma Pharmacia Research Foundation
Travel Award EAACI Meeting, Davos, Switzerland
Erich-Hoffmann Memorial Award
2002
Herbert-Herxheimer Award, German Society for Allergology and Immunology (DGAKI)
2002
BONFOR Award

10 Most Relevant Publications for Prof. Natalija Novak

1. Yu CF, Peng WM, Oldenburg J, Hoch J, Bieber T, Limmer A, Hartmann G, Barchet W, Eis-Hubinger AM, **Novak N**. 2010. Human plasmacytoid dendritic cells support Th17 cell effector function in response to TLR7 ligation. J Immunol 184: 1159-67.
2. Allam JP, Würtzen PA, Reinartz M, Winter J, Vrtala S, Chen KW, Valenta R, Wenghoefer M, Appel T, Gros E, Niederhagen B, Bieber T, Lund K, **Novak N**. 2010. Phl p 3 resorption in human oral mucosa leads to dose-dependent and time-dependent allergen binding by oral mucosal Langerhans cells, attenuates their maturation, and enhances their migratory and TGF-β1 and IL-10 producing properties. J Allergy Clin Immunol 126: 638-45.
3. Gros E, Bussmann C, Bieber T, Forster I, **Novak N**. 2009. Expression of chemokines and chemokine receptors in lesional and nonlesional upper skin of patients with atopic dermatitis. J Allergy Clin Immunol 124: 753-60 e1.
4. Esparza-Gordillo J, Weidinger S, Folster-Holst R, Bauerfeind A, Ruschendorf F, Patone G, Rohde K, Marenholz I, Schulz F, Kerscher T, Hubner N, Wahn U, Schreiber S, Franke A, Vogler R, Heath S, Baurecht H, **Novak N**, Rodriguez E, Illig T, Lee-Kirsch MA, Ciechanowicz A, Kurek M, Piskackova T, Macek M, Lee YA, Ruether A. 2009. A common variant on chromosome 11q13 is associated with atopic dermatitis. Nat Genet 41: 596-601.
5. Kwiek B, Peng WM, Allam JP, Langner A, Bieber T, **Novak N**. 2008. Tacrolimus and TGF-beta act synergistically on the generation of Langerhans cells. J Allergy Clin Immunol 122: 126-32, 32 e1.
6. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, Klopp N, Wagenpfeil S, Zhao Y, Liao H, Lee SP, Palmer CN, Jenneck C, Maintz L, Hagemann T, Behrendt H, Ring J, Nothen MM, McLean WH, **Novak N**. 2006. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. J Allergy Clin Immunol 118: 214-9.
7. **Novak N**, Valenta R, Bohle B, Laffer S, Haberstok J, Kraft S, Bieber T. 2004. FcepsilonRI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. J Allergy Clin Immunol 113: 949-57.
8. **Novak N**, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R, Kochan J, Bieber T. 2004. Characterization of FcepsilonRI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. J Allergy Clin Immunol 114: 364-70.
9. **Novak N**, Tepel C, Koch S, Brix K, Bieber T, Kraft S. 2003. Evidence for a differential expression of the FcepsilonRIgamma chain in dendritic cells of atopic and nonatopic donors. J Clin Invest 111: 1047-56.
10. **Novak N**, Bieber T, Katoh N. 2001. Engagement of Fc epsilon RI on human monocytes induces the production of IL-10 and prevents their differentiation in dendritic cells. J Immunol 167: 797-804.

Prof. Michael J. Pankratz, PhD

Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
Life and Medical Sciences Institute (LIMES),
Department of Molecular Brain Physiology and Behavior, Director

E-Mail: pankratz@uni-bonn.de

Research Expertise

Prof. Pankratz is an expert on the genetics of nutrient control, feeding behavior, gustation and neuroendocrine circuits in drosophila.

Education / Training

University of California, Los Angeles USA, Biochemistry PhD, 1986
Johns Hopkins University, USA, Biology BA, 1980

Appointments / Positions Held

2008 - present
Full Professorship, Molecular Brain Physiology, University of Bonn
2001 - 2007
Senior Group Leader, Genetics, Karlsruhe, Institute of Technology
2001
Habilitation, Genetics, Karlsruhe University
1997 - 2001
Group Leader, Institute of Genetics, Karlsruhe, Institute of Technology
1993 - 1997
Staff Scientist, Institute of Biophysical Chemistry, Max Planck Institute
1988 - 1992
Postdoctoral Fellow, Institute for Genetics and Microbiology, University of Munich
1987 - 1988
Postdoctoral Fellow, Institute for Developmental Biology Max Planck Institute

Honors / Awards

2003 - 2005
Member of the Scientific Advisory Board “Network of Molecular Nutrition Research“, State of Baden-Wurttemberg, Germany
2000 - 2001
Consultant for Aventis

10 Most Relevant Publications for Prof. Michael Pankratz

1. Schoofs A, Hückesfeld S, Schlegel P, Miroschnikow A, Peters M, Zeymer M, Spieß R, Chiang AS, **Pankratz MJ**. 2014. Selection of motor programs for suppressing food intake and inducing locomotion in the Drosophila brain. PLoS Biol, in press.
2. Bader R, Sarraf-Zadeh L, Peters M, Moderau N, Stocker H, Köhler K, **Pankratz MJ***, Hafen E. 2013. The IGFBP7 homolog Imp-L2 promotes insulin signaling in distinct neurons of the Drosophila brain. J Cell Science 126, 2571-2576.
3. Bülow M, Aebersold R, **Pankratz MJ***, Jünger M. 2010. The Drosophila FoxA Ortholog Fork Head Regulates Growth and Gene Expression Downstream of Target of Rapamycin. PLoS One 5(12): e15171.
4. Min KJ, Yamamoto R, Buch S, **Pankratz MJ**, Tatar M. 2008. Drosophila lifespan control by dietary restriction independent of insulin-like signaling. Aging Cell 7: 199-206.
5. Buch S, Melcher C, Bauer M, Katzenberger J, **Pankratz MJ**. 2008. Opposing effects of dietary protein and sugar regulate a transcriptional target of Drosophila insulin-like peptide signaling. Cell Metab 7: 321-32.
6. Melcher C, Bader R, **Pankratz MJ**. 2007. Amino acids, taste circuits, and feeding behavior in Drosophila: towards understanding the psychology of feeding in flies and man. J Endocrinol 192: 467-72.
7. Bader R, Colomb J, Pankratz B, Schrock A, Stocker RF, **Pankratz MJ**. 2007. Genetic dissection of neural circuit anatomy underlying feeding behavior in Drosophila: distinct classes of hugin-expressing neurons. J Comp Neurol 502: 848-56.
8. Melcher C, Bader R, Walther S, Simakov O, **Pankratz MJ**. 2006. Neuromedin U and its putative Drosophila homolog hugin. PLoS Biol 4: e68.
9. Bauer M, Katzenberger JD, Hamm AC, Bonaus M, Zinke I, Jaekel J, **Pankratz MJ**. 2006. Purine and folate metabolism as a potential target of sex-specific nutrient allocation in Drosophila and its implication for lifespan-reproduction tradeoff. Physiol Genomics 25: 393-404.
10. Melcher C, **Pankratz MJ**. 2005. Candidate gustatory interneurons modulating feeding behavior in the Drosophila brain. PLoS Biol 3: e305.

* Corresponding author

Prof. Joachim L. Schultze, MD

Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
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Genomics & Immunoregulation, Director

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Research Expertise

Prof. Schultze’s current central expertise is at the interphase of immunoregulation and genomics, with a focus on transcriptional and epigenetic control of cell activation and immunoregulation, particularly in macrophages and regulatory T cells.

Education / Training

University of Freiburg, Medicine Fellow, 1992 - 1993
University of Freiburg, Medicine, M.D., 1991
University of Freiburg, Medicine, State examination, 1991

Appointments / Positions Held

2007 - present
W3 Professorship, Genomics & Immunoregulation, University of Bonn
2002 - 2007
C3 Professorship, Tumor Immunology, University of Cologne
1997 - 2002
Instructor in Medicine, Adult Oncology, Daner-Farber Cancer Institute, MA, USA
1996 - 1997
Instructor in Medicine, Hematologic Malignancies, Daner-Farber Cancer Institute, MA, USA
1995 - 1996
Research Associate, Hematology, Daner-Farber Cancer Institute, MA, USA
1993 - 1995
Research Fellow, Hematology, Daner-Farber Cancer Institute, MA, USA

Honors / Awards

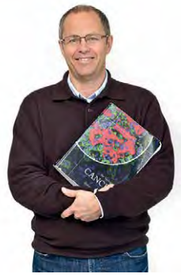
2012 - present Vice Dean for Research, Faculty for Mathematics and Natural Sciences, University of Bonn
2010 Patent: A method for lung cancer early detection and prognosis. Zander T, Schultze JL, Wolf J, Staratschek-Jox A, Debey-Pascher S, Eggle D, Boffetta P, Linseisen J.
2009 Patent: Anticancer Agent. Hoch M, Schultze JL, Loer B.
2009 Patent: Novel Marker Genes for regulatory T cells from human blood. Schultze JL, Beyer MD, Warner N, Hingorani R.
2002 Sofja-Kovalevskaja Award of the Alexander von Humboldt-Foundation
2000 Senior Investigator Award of the Multiple Myeloma Research Foundation
1999 Translational Research Award of the Leukemia & Lymphoma Society
1998 Special Fellowship Award of the Leukemia & Lymphoma Society
1997 Fellowship Award of the Lymphoma Research Foundation of America
1997 Travel Award Annual Meeting of the American Society of Hematology
1997 Leukemia Clinical Research Award (Deutsche Gesellschaft für Hämatologie und Onkologie)

10 Most Relevant Publications for Prof. Joachim L. Schultze

1. Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H, Nino-Castro A, Mallmann MR, Labzin L, Theis H, Kraut M, Beyer M, Latz E, Freeman TC, Ulas T, **Schultze JL**. Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. Immunity. 2014 Feb 20;40 (2):274-88. doi: 10.1016/j.immuni.2014.01.006. Epub 2014 Feb 13.
2. Sommer D, Peters A, Wirtz T, Mai M, Ackermann J, Thabet Y, Schmidt J, Weighardt H, Wunderlich FT, Degen J, **Schultze JL**, Beyer M. Efficient genome engineering by targeted homologous recombination in mouse embryos using transcription activator-like effector nucleases. Nat Commun. 2014 Jan 13; 5:3045. doi: 10.1038/ncomms4045.
3. De Nardo D, Labzin LI, Kono H, Seki R, Schmidt SV, Beyer M, Xu D, Zimmer S, Lahrmann C, Schildberg FA, Vogelhuber J, Kraut M, Ulas T, Kerksiek A, Krebs W, Bode N, Grebe A, Fitzgerald ML, Hernandez NJ, Williams BR, Knolle P, Kneilling M, Röcken M, Lütjohann D, Wright SD, **Schultze JL**, Latz E. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol. 2014 Feb;15(2):152-60. doi: 10.1038/ni.2784. Epub 2013 Dec 8.
4. Beyer M, Thabet Y, Mueller R-U, Sadlon T, Classen S, Lahl K, Basu S, Zhou X, Bailey-Bucktrout SL, Krebs W, Schoenfeld EA, Boettcher J, Golovina T, Mayer CT, Hofmann A, Sommer D, Debey-Pascher S, Endl E, Limmer A, Hippen KL, Blazar BR, Balderas R, Quast T, Waha A, Mayer G, Famulok M, Knolle PA, Wichenhauser C, Kolanus W, Schermer B, Bluestone JA, Barry SC, Sparwasser T, Riley JL, **Schultze JL**. 2011. Repression of genome organizer SATB1 in regulatory T cells is required for suppressive function and inhibition of effector differentiation. Nat Immunol. 12: 898-907.
5. Becker T, Loch G, Beyer M, Zinke I, Aschenbrenner AC, Carrera P, Inhester T, **Schultze JL**, Hoch M. 2010. FOXO-dependent regulation of innate immune homeostasis. Nature 463: 369-73.
6. Beyer M, Karbach J, Mallmann MR, Zander T, Eggle D, Classen S, Debey-Pascher S, Famulok M, Jager E, **Schultze JL**. 2009. Cancer vaccine enhanced, non-tumor-reactive CD8(+) T cells exhibit a distinct molecular program associated with „division arrest anergy“. Cancer Res 69: 4346-54.
7. Chemnitz JM, Eggle D, Driesen J, Classen S, Riley JL, Debey-Pascher S, Beyer M, Popov A, Zander T, **Schultze JL**. RNA fingerprints provide direct evidence for the inhibitory role of TGFbeta and PD-1 on CD4+ T cells in Hodgkin lymphoma. Blood. 2007 Nov 1;110(9):3226-33. Epub 2007 Jul 20.
8. Popov A, Abdullah Z, Wickenhauser C, Saric T, Driesen J, Hanisch FG, Domann E, Raven EL, Dehus O, Hermann C, Eggle D, Debey S, Chakraborty T, Krönke M, Utermöhlen O, **Schultze JL**. Indoleamine 2,3-dioxygenase-expressing dendritic cells form suppurative granulomas following Listeria monocytogenes infection. J Clin Invest. 2006 Dec;116(12):3160-70. Epub 2006 Nov 16.
9. Beyer M, Kochanek M, Giese T, Endl E, Weihrauch MR, Knolle PA, Classen S, **Schultze JL**. 2006. In vivo peripheral expansion of naive CD4+CD25high FoxP3+ regulatory T cells in patients with multiple myeloma. Blood 107: 3940-9.
10. Trojan A, **Schultze JL**, Witzens M, Vonderheide RH, Ladetto M, Donovan JW, Gribben JG. 2000. Immunoglobulin framework-derived peptides function as cytotoxic T-cell epitopes commonly expressed in B-cell malignancies. Nat Med 6: 667-72.

Prof. Thomas Tüting, MD

Department of Dermatology and Allergy



Rheinische Friedrich-Wilhelms-Universität Bonn
Department of Dermatology and Allergy

E-Mail: thomas.tueting@ukb.uni-bonn.de

Research Expertise

Role of UV irradiation and the immune system in the pathogenesis of melanoma; mechanisms of melanoma metastasis and therapy resistance; preclinical and clinical evaluation of approaches combining immunotherapies and other treatment modalities for melanoma; development of novel genetic mouse models to study inflammation-induced phenotypic plasticity and reciprocal interactions between melanoma, immune and endothelial cells in the perivascular niche.

Education / Training

University of Frankfurt, Germany, M.D., Thesis, 2000
University of Mainz, Germany, Dermatology and Allergic Diseases, Board Certification, 1998
University of Frankfurt School of Medicine, Medicine, M.D., 1987

Appointments / Positions Held

2001 - present
Associate Professor and Laboratory Head, Experimental Dermatology, University of Bonn, Germany
2001 - present
Clinical work, General and Oncologic Dermatology, University of Bonn, Germany
1998 - 2001
Clinical and Scientific Work, Department of Dermatology, University of Mainz, Germany
1995 - 1997
Research Fellow in Tumor Immunology and Gene Therapy, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
1991 - 1995
Residency in Dermatology and Allergic Diseases, Department of Dermatology, Military Hospital Koblenz and University of Mainz, Germany
1988 - 1991
Drafted as Airforce Medical Officer, Fighter- Bomber Wing 33, Cochem, Germany

Honors / Awards

2009
Steigleder prize of the AG Dermatological Histology
2006
Translational Research prize of the AG Dermatological Research
2000
Research Award of the Erich Hoffmann Society, Bonn

10 Most Relevant Publications for Prof. Thomas Tüting

1. Bald T, Landsberg J, Lopez-Ramos D, Renn M, Glodde N, Jansen P, Gaffal E, Steitz J, Tolba R, Kalinke U, Limmer A, Jönsson G, Hölzel M, **Tüting T.** Immune-cell poor melanomas benefit from PD-1 blockade after targeted type I IFN activation. Cancer Discovery. In press, 2014.
2. Bald T, Quast T, Landsberg J, Rogava M, Glodde N, Lopez-Ramos D, Kohlmeyer J , Riesenberg,S. van den Boorn-Konijnenberg D, Hömig-Hölzel C, Reuten R, Schadow B, Weighardt I, Wenzel D, Helfrich I, Schadendorf D, Bloch W, Bianchi ME, Koch M, Fleischmann BK, Förster I, Kastenmüller W, Kolanus W, Hölzel M, Gaffal E, **Tüting T.** Ultraviolet radiation-induced inflammation promotes angiotropism and metastasis in melanoma. Nature 507:109-13, 2014.
3. Hölzel M, Bovier A, **Tüting T.** Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? Nat Rev Cancer. 13:365-76, 2013.
4. Gaffal E, Cron M, Glodde N, Bald T, Kuner R, Zimmer A, Lutz B, **Tüting T.** Cannabinoid 1 receptors in keratinocytes modulate proinflammatory chemokine secretion and attenuate contact allergic inflammation. J. Immunol. 190:4929-36, 2013.
5. Gehrke N, Mertens C, Zillinger T, Wenzel J, Bald T, Zahn S, **Tüting T**, Hartmann G, Barchet W. Oxidative damage of DNA confers resistance to cytosolic nuclease TREX1 degradation and potentiates STING-dependent immune sensing. Immunity. 39:482-95, 2013.
6. Landsberg J, Kohlmeyer J, Renn M, Bald T, Rogava M, Cron M, Fatho M, Lennerz V, Wölfel T, Hölzel H, **Tüting T.** Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. Nature. 490:412-416, 2012.
7. Kohlmeyer J, Cron M, Landsberg J, Bald T, Renn M, Mikus S, Bondong S, Wikasari D, Gaffal E, Hartmann G, **Tüting T.** Complete regression of advanced primary and metastatic mouse melanomas following combination chemoimmunotherapy. Cancer Res 69:6265-74, 2009.
8. *Poeck H, *Besch R, *Maihoefer C, *Renn M (*gemeinsame Erstautorschaft), Tormo D, Shulga Morskaya S, Kirschnek S, Gaffal E, Landsberg J, Hellmuth J, Schmidt A, Anz D, Bscheider M, Schwerd T, Berking C, Bourquin C, Kalinke U, Kremmer E, Kato H, Akira S, Meyer R, Häcker G, Neuenhahn M, Busch D, Ruland J, Rothenfusser S, Prinz M, Hornung V, Endres S, **Tüting T**, Hartmann G. 5'-triphosphate-siRNA: turning gene silencing and Rig-I activation against melanoma. Nat Med 14: 1256-63, 2008.
9. Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino S, Starowicz K, Steuder R, Schlicker E, Cravatt B, Mechoulam R, Buettner R, Werner S, Di Marzo V, **Tüting T**, Zimmer A. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science 316: 1494-1497, 2007.
10. Tormo D, Ferrer A, Bosch P, Gaffal E, Basner-Tschakarjan E, Wenzel J, **Tüting T.** Therapeutic efficacy of antigen-specific vaccination and toll-like receptor stimulation against established transplanted and autochthonous melanoma in mice. Cancer Res 66: 5427-5435, 2006.

* These authors contributed equally

Prof. Andreas Zimmer, PhD

Institute of Molecular Psychiatry

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Molecular Psychiatry, Director

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Research Expertise

Prof. Zimmer and his groups are interested in the molecular mechanisms of neuropsychiatric disorders with a focus on addiction, pain and affective disorders, molecular biology of modulatory neurotransmitters, and the molecular biology of aging.

Education / Training

Max Planck Institute for Biophysical Chemistry, Microbiology, PhD, 1989
Justus-Liebig Universität Giessen, Biology, Diploma, 1986

Appointments / Positions Held

2006 - present
Professor of Molecular Psychiatry (W3), Director, Institute for Molecular Psychiatry, University of Bonn
2005 - 2006
Professor of Cell Biology (W3), University of Bielefeld
1999 - 2005
Professor for Molecular Neurobiology (C3), University of Bonn
1997 - 1999
Adjunct Professor, Department of Pharmacology, Georgetown University, Medical School, USA
1997 - 2000
Research Fellow, National Institute of Mental Health, USA
1995 - 1997
Visiting Research Fellow, National Institute of Mental Health, USA
1991 - 1995
Visiting Associate, National Institute of Mental Health, USA
1991 - 2000
Section Head, National Institute of Mental Health, USA
1989 - 1991
Postdoctoral researcher, DFG-Fellow, National Institute of Mental Health, USA

Honors / Awards

2000
U.S. Department of Health and Human Services Special Act or Service Award
1990 - 1992
DFG-Fellow
1987 - 1989
Max-Planck-Fellow
1989
PhD thesis awarded 'summa cum laude'

10 Most Relevant Publications for Prof. Andreas Zimmer

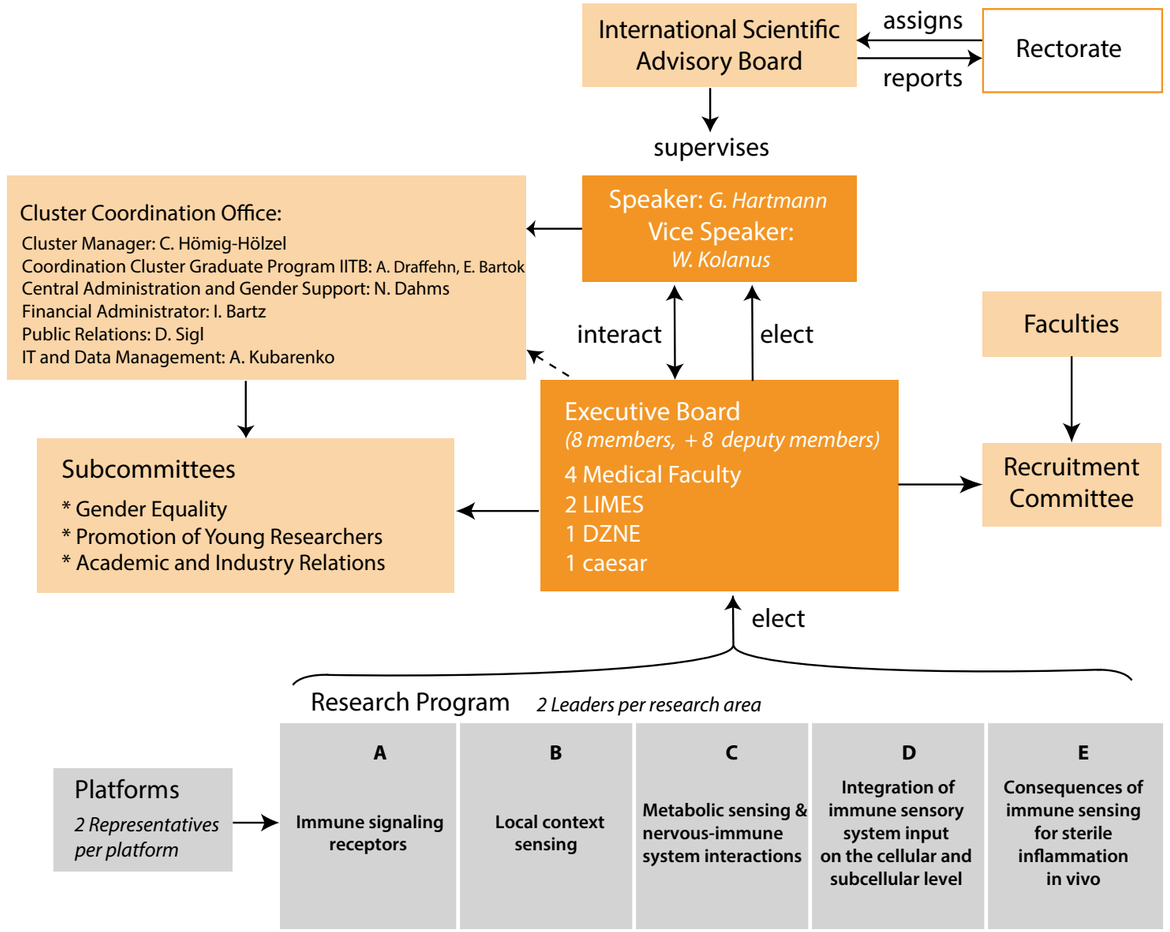
1. Albayram O, Alferink J, Pitsch J, Piyanova A, Neitzert K, Poppensieker K, Mauer D, Michel K, Legler A, Becker A, Monory K, Lutz B, **Zimmer A**, Bilkei-Gorzo A. 2011. Role of CB1 cannabinoid receptors on GABAergic neurons in brain aging. Proc Natl Acad Sci U S A, 108(27):11256-61.
2. Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, Altmann KH, Karsak M, **Zimmer A**. 2008. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci U S A 105: 9099-104.
3. Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino S, Starowicz K, Steuder R, Schlicker E, Cravatt B, Mechoulam R, Buettner R, Werner S, Di Marzo V, Tuting T*, **Zimmer A***. 2007. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science 316: 1494-7.
4. Bilkei-Gorzo A, Racz I, Valverde O, Otto M, Michel K, Sastre M, **Zimmer A**. 2005. Early age-related cognitive impairment in mice lacking cannabinoid CB1 receptors. Proc Natl Acad Sci U S A 102: 15670-5.
5. Nadeau JH, Balling R, Barsh G, Beier D, Brown SD, Bucan M, Camper S, Carlson G, Copeland N, Eppig J, Fletcher C, Frankel WN, Ganten D, Goldowitz D, Goodnow C, Guenet JL, Hicks G, Hrabe de Angelis M, Jackson I, Jacob HJ, Jenkins N, Johnson D, Justice M, Kay S, Kingsley D, Lehrach H, Magnuson T, Meisler M, Poustka A, Rinchik EM, Rossant J, Russell LB, Schimenti J, Shiroishi T, Skarnes WC, Soriano P, Stanford W, Takahashi JS, Wurst W, **Zimmer A.** 2001. Sequence interpretation. Functional annotation of mouse genome sequences. Science 291: 1251-5.
6. **Zimmer A**, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI. 1999. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci U S A 96: 5780-5.
7. Hahn H, Wojnowski L, Zimmer AM, Hall J, Miller G, **Zimmer A**. 1998. Rhabdomyosarcomas and radiation hypersensitivity in a mouse model of Gorlin syndrome. Nat Med 4: 619-22.
8. Wojnowski L, Zimmer AM, Beck TW, Hahn H, Bernal R, Rapp UR, **Zimmer A**. 1997. Endothelial apoptosis in Braf-deficient mice. Nat Genet 16: 293-7.
9. Konig M, Zimmer AM, Steiner H, Holmes PV, Crawley JN, Brownstein MJ, **Zimmer A**. 1996. Pain responses, anxiety and aggression in mice deficient in pre-proenkephalin. Nature 383: 535-8.
10. **Zimmer A**, Gruss P. 1989. Production of chimaeric mice containing embryonic stem (ES) cells carrying a homoeobox Hox 1.1 allele mutated by homologous recombination. Nature 338: 150-3.

*These authors contributed equally

Impressions

First Retreat of the ImmunoSensation Cluster of Excellence in St. Goar

Organigram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assigns
reports
Rectorate
supervises
Cluster Coordination Office:
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Coordination Cluster Graduate Program IITB: A. Draffehn, E. Bartok
Central Administration and Gender Support: N. Dahms
Financial Administrator: I. Bartz
Public Relations: D. Sigl
IT and Data Management: A. Kubarenko
Speaker: G. Hartmann
Vice Speaker:
W. Kolanus
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elect
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(8 members, + 8 deputy members)
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2 LIMES
1 DZNE
1 caesar
Recruitment Committee
Subcommittees
* Gender Equality
* Promotion of Young Researchers
* Academic and Industry Relations
elect
Research Program
2 Leaders per research area
Platforms
2 Representatives per platform
A
Immune signaling receptors
B
Local context sensing
C
Metabolic sensing & nervous-immune system interactions
D
Integration of immune sensory system input on the cellular and subcellular level
E
Consequences of immune sensing for sterile inflammation in vivo

Participating Institutions

Participating Institutions & CCO

Medical Faculty
University of Bonn
Sigmund-Freud-Straße 25
D-53127 Bonn
www.ukb.uni-bonn.de

LIMES - Life & Medical Sciences
University of Bonn
Carl-Troll-Straße 31
D-53115 Bonn
www.limes-institut-bonn.de

DZNE - German Centre for
Neurodegenerative Diseases
Ludwig-Erhard-Allee 2
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LIMES Life & Medical Sciences Institute

DZNE German Center for Neurodegenerative Diseases within the Helmholtz Association

caesar center of advanced european studies and research