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The Cluster ImmunoSensation is very proud to report the scientific and structural progress that has been made in the second year of funding by the German Research Foundation, DFG. Our Cluster is in the midst of a process of superb, dynamic development and has continued its excellent scientific performance. This great success would not have been possible without the tremendous support of the DFG, the University of Bonn and the other two participating institutions, the German Center of Neurodegenerative Diseases, DZNE, and the Max-Planck-associated center of advanced european studies and research, caesar.

The steering committee of the Cluster is a dedicated group of scientists who contribute to the advancement of the Cluster in organizational and scientific issues from their different angles of expertise. The retreat of this steering committee to the Amalfi coast of Southern Italy in May 2014 was the perfect occasion to enjoy scientific exchange and friendship (see page 102). There can be no excellent science without excellent scientific management: the team of the Cluster coordination office has grown and can now provide optimal support for the numerous events activities within the Cluster (see page 90). At the heart of the Cluster are its many highly motivated young scientists. 14 students were newly recruited into the ImmunoSensation graduate program, the International Immunology Training Program, IITB (see page 106). Besides the opportunity to participate in the outstanding scientific research within the Cluster, this graduate program offers training and education in scientific techniques as well as soft skills, such as scientific presentation and writing.

Our Cluster is now regarded as one of the - if not the - leading center of immunology in Germany. In 2014, ImmunoSensation had the honor of hosting the Annual Meeting of the German Society of Immunology (DGfI) in Bonn (see page 91). We are grateful to the German Society of Immunology for the fantastic venue, the World Conference Center with the former Plenary Chamber of the Deutsche Bundestag, where the political decision was made to unify East and West Germany, and all the wonderful surrounding facilities located on the banks of the river Rhine. This 2014 meeting had the highest attendance of all annual meetings of the German Society of Immunology, and it was a wonderful forum for lively discussions and a bustling and dynamic exchange of new ideas and concepts in immunology. One highlight of the meeting was a whole session dedicated to the research focuses within ImmunoSensation. About our research and the meeting as a whole, we received extremely positive feedback, which was both highly motivating and rewarding for the Cluster in Bonn.

Great input and advice also came from our International Scientific Advisory Board, who were invited to our Cluster Science Days in November 2014 (see page 92). It was the first time that members of the Scientific Advisory Board could dedicate two full days to meeting the scientists of the Cluster and to learning about our scientific projects and structural and strategic plans. The general structure of the work programs A to E was endorsed by the Advisory Board.

The steering committee of the Cluster were also grateful to receive a number of recommendations regarding scientific techniques and instruments as well as structural issues such as gender equality and the promotion of female careers.
The Advisory Board also noted that two female scientists of the Cluster had successfully advanced their career within ImmunoSensation advancing from post-doctoral stage as Cluster-funded junior research group leaders to full W2 professorships in 2014 (Andrea Ablasser, EPFL in Lausanne; and Linda Diehl, UKE in Hamburg).

In addition to furthering the careers of young scientists, the Cluster ImmunoSensation has continued its outstanding performance in scientific terms. Out of more than 360 papers which have been published by Cluster members in 2014, almost one hundred are featured in journals which boast impact factors of 8 or higher (see page 125). Once again, the most outstanding results of the Cluster are visible in top scientific forums, such as the communities addressed by Nature, Cell, Nature Immunology and Immunity. Our publications also include a fair number of important and well-received reviews. All of these papers clearly reflect the comprehensive scope of our initiative. They document how our interests and ambitions range from the discovery of new molecular receptors and the corresponding ligands of the immune sensory system to the local implementation of these principles in specific organs. Moreover, we are interested in the interactions of the immune sensory system with other systems, such as the nervous system, and its overall systemic integration. Finally, one of our most important mid to long-term goals is, of course, the elucidation of molecular principles of disease and specifically of the mechanisms that lead to sterile inflammatory diseases or the contribution of sterile inflammatory processes to other diseases. In this annual report, you find detailed information on a selected number of publications from our research areas A to E in 2014. We would particularly like to draw your attention to the following exciting new discoveries made by our scientists in 2014.

The group of Eicke Latz discovered that the inflammasome machinery also acts as an immune sensory principle outside of cells (Franklin et al., Nature Immunology, 2014) (see page 17). The authors of this paper focus on so-called “ASC specks”. ASC specks are signalosomes which were thought to be solely responsible for the intracellular processing of information from inflammasome sensors (such as NLRPs) and relaying this information to caspases (the cell-death inducing enzymes). Strikingly, the researchers could show that, after activation, ASC specks are released from cells and accumulate in the extracellular space. These “specks” were not only found in experimental systems but could also be detected in patients with inflammatory airway pathologies. Extracellular inflammasomes may therefore be part of a novel cell-to-cell immuno-sensory communication system.

While the work above refers to signal transfer downstream of immune sensing receptors, the groups of Hartmann and Schlee, in an international collaboration with Caetano Reis e Sousa from Cancer Research UK, identified 5'-diphosphate RNA as a new natural ligand for the RNA immune sensor RIG-I (Goubau, Schlee et al., Nature 2014) (see page 20). Using sophisticated biochemical methods and nucleic acid chemistry, this work now provides definite evidence on how mammalian reoviruses (e.g. the gastroenteritis virus Rotavirus) are detected by our immune system. Since 5'-diphosphate RNA does not exist in our own RNA repertoire, this form of RNA is now one of the few nucleic acid structures known to date that represents a pathogen-specific molecular pattern.

Another important part of the Cluster is interested in finding out how immune cells are programmed to function properly during development or by their...
environment. Joachim Schultze (Xia et al., Immunity 2014) and his lab used a sensitive and comprehensive toolset including genomic analyses and bioinformatics to unravel the functional polarity of macrophages (see page 41). Macrophages are an important cellular component of the chronic inflammatory processes which underlie diseases such as atherosclerosis, diabetes, obesity, Alzheimer’s disease and cancer. According to the previous paradigm, macrophages were grouped into two major classes, namely those that accelerate inflammation and those that tame immune responses, respectively. However, this new paper by the Schultze lab clearly showed that macrophages are able to assume several functional identities which are imprinted by the environment into their transcriptional networks and epigenomes. Local sub-specialization of myeloid cells is also the topic of Christian Kurts’s and Daniel Engels’s study on the functions of “sentinel” and “helper” macrophages in the recruitment of neutrophils into the infected uroepithelium (Schion et al., Cell, 2014) (see page 42).

Looking back at some of the most impressive developments of our field in recent years, and at the advent of immune check-point control as a therapeutic principle in particular, we are now certain that the immune system plays a pivotal role in the etiology of cancer – and in fighting tumors. The group of Thomas Tüting has a longstanding interest in finding out how the immune system may be mobilized against melanoma. In the course of a multidisciplinary endeavor – involving many groups of the Cluster with expertise ranging from cancer biology/medicine to vascular physiology to basic mechanisms of cell motility – he and his co-workers could show that activation of the innate immune system and particularly of neutrophil granulocytes has a strong impact on the metastatic potential of melanomas (see page 48). Importantly, innate immune activation in this context is induced by UV irradiation (Bald et al., Nature 2014).

To use Thomas Tüting’s own words, this means that UV strikes twice: high energy irradiation is not only responsible for the outset of the cancer, i.e. DNA damage, but also for the development of benign tumors into dangerous ones, and this occurs via the immune system.

Finally, another central objective of the Cluster is to contribute to advances in clinical medicine and foster translation from basic research to clinical development. In 2014, the biotech start-up Rigontec GmbH was founded and is now financed by a strong international consortium of private investors. Rigontec GmbH is located on the campus of the Medical Faculty in Bonn and has developed first in class RIG-I ligands for the treatment of cancer and viral infection.

Overall, there is a great sense of scientific community in Bonn that extends beyond the individual scientists or groups and beyond institutional and national borders. It is this great atmosphere in Bonn that makes science in the ImmunoSensation Cluster so vibrant, dynamic and enjoyable, and it is with confidence that we look forward to witnessing the future impact of the Cluster on science and medicine.

Prof. Gunther Hartmann (Speaker) and Prof. Waldemar Kolanus (Vice speaker)
Introduction

The innate immune system has evolved several classes of signaling receptors that recognize foreign material from pathogenic microbes as well as altered host substances that appear during cell stress or tissue damage. Hence, innate immune signaling receptors can sense both microbial infections as well as damage to the host. During infections, tissue damage can be inflicted by the activity of the microbe itself or as a consequence of the activity of immune cells that aim to kill the pathogen. Additionally, tissue damage can also occur under sterile conditions such as after trauma or during metabolic derangements.

Activation of innate immune signaling pathways primarily leads to transcriptional programs culminating in the production of pro-inflammatory cytokines, interferons and chemokines. Inflammasome activation leads to a proteolytic cascade which activates the biologically inactive pro-forms of IL-1β family cytokines (including IL-1β and IL-18) as well as inducing the release of these activated cytokines (Fig. 1).

Another class of receptors is involved in cell migration and motility. In particular the directed navigation of cells in chemical gradients – a process called chemotaxis – is paramount for immune cells to locate pathogens or microbes. Chemotactic navigation is a fundamental biological process that is important not only for immune cells, but also for neuronal path finding, metastasis, and many other cells or microorganisms. The chemical nature of chemoattractants is quite diverse, ranging from small molecules to larger structures.
from gases (CO₂) to steroids or proteins. Chemoreceptors that bind the chemoattractant ligand fall into different classes of membrane receptors. One important class of chemoreceptors that register various semiochemicals are guanylyl cyclases (GC). In many cells, the chemoattractant signaling pathways are not known. But even in a well-known and intensively studied model system – chemotaxis of sperm towards the egg – the underlying biophysical principles how a signaling pathway governs cell motility are only vaguely known. One aim is to develop kinetic and photonic techniques allowing to delineate the sequence of signaling events and how these events are transduced into directed movements.

Immune Sensing
Receptors and Modulators

Figure 2

Inflammation is transferred from cell-to-cell via release of ASC specks.

Activation of the inflammasome is accompanied by rapid formation of the ASC speck, a micrometer-sized perinuclear structure consisting of multimers of the ASC adaptor protein. This supramolecular structure acts as a platform for caspase-1 activity. The ASC speck is often referred to as an aggregate and shares certain features with aggresomes and prion proteins.

A new study carried out in the Institute of Innate Immunity in Bonn in collaboration with institutes from the US and Australia identified a new mechanism by which inflammation is propagated from cell to cell. The research team, led by Dr. Bernardo Franklin and Prof. Dr. Eicke Latz, has found that cells can propagate inflammation by releasing their ASC specks, which remain bioactive outside the cells and continue to produce mature IL-1β cytokines extracellularly. Strikingly, extracellular ASC specks were found to remain in tissues for longer periods and eventually undergo phagocytosis by surrounding immune cells (such as macrophages and dendritic cells). Ingested ASC specks from the extracellular space caused lysosomal damage in the phagocytic cells which, in turn, activated cell-intrinsic inflammasomes, continuing and disseminating inflammation (Fig. 2).

The authors showed that extracellular ASC specks accumulate in the lungs of human and mice with chronic obstructive pulmonary disease resulting from cigarette smoke. Furthermore, patients
with autoimmune disorders possess antibodies that were able to bind to ASC specks, suggesting that these antibodies are formed during exposure of cells to extracellular ASC specks during disease (Summary Fig. 3).

Altogether, this study has revealed a novel form of intercellular communication and a novel function of the inflammasome. The extracellular inflammasome has great potential both as a biomarker and as a new target for therapeutic antibodies.

by E Latz

Reference publication


How does a chemoreceptor encode a continuous stream of chemoattractant molecules?

The chemoreceptor GC in sperm of marine invertebrates serves two functions: It binds the chemoattractant peptide via an extracellular domain and activates the synthesis of cGMP, an intracellular messenger; cGMP eventually gives rise to brief Ca\(^{2+}\) pulses that steer the cell up the gradient (Fig. 4). The receptor binds the ligand with exquisitely high sensitivity (subnanomolar range). Because sperm sample the chemoattractant about every second, the lifetime of the ligand-receptor complex is significantly longer than the sampling time. Therefore, a mechanism of receptor inactivation is required. Moreover, the sensitivity to detect a relative change in ligand dc/dc depends on the receptor density. The packing of the GC receptor on the flagellum is extremely dense (300,000 GC molecules/flagellum or about 9000 GC molecules/µm\(^2\)). This exquisite density endows sperm with absolute sensitivity, i.e. sperm can detect single molecules of the chemoattractant.

The GC receptor is six-fold phosphorylated at rest. Upon stimulation six phosphates are removed with a half-time of 150 ms; this rapid inactivation endows sperm with the ability to sample the chemoattractant with a frequency of at least 1 Hz. In the single-molecule regime, an exponential distribution of the lifetime of the active receptor would produce "molecule noise" and impair sensitivity. The stepwise inactivation by six dephosphorylation events would result in narrow lifetime control. Similar mechanisms might operate in immune cells during chemoattractive navigation.

by UB Kaupp

Reference publication
Antiviral immunity via RIG-I-mediated recognition of RNA bearing 5’-diphosphates

Immunorecognition of viral RNA – RIG-I and MDA5 share the job

RNA viruses are the causative agents for influenza, influenza infections, such as Rhinovirus, Enterovirus and Coronavirus, measles, many common diseases of the gastrointestinal tract, such as Norovirus and Reovirus, and viral hemorrhagic fevers, including dengue fever, yellow fever, Lassa virus and Ebola. RNA receptors of the innate immune system are crucial to activating humoral and cellular antiviral defense mechanisms (Fig. 5). The Toll-like receptors TLR 3, 7 and 8 can recognize RNA mislocalized to the endosome but are predominantly expressed in specialized immune cells. In contrast, cytosolic recognition of viral replication is a widespread mechanism which is also active in somatic cells. As shown in animal models, the innate immune response to most invading RNA viruses (Fig. 6) results from the cytosolic recognition of viral RNA by the DExD/H-box family helicases receptors RIG-I (Retinoic acid Inducible Gene I) and MDA5 (Melanoma Differentiation-Associated protein 5). Both receptors are broadly expressed and part of a highly conserved pathway, and, to discriminate between viral and self-RNA, they must rely on structures or modifications that are indicative of pathogenic RNA – a process that also harbors the danger of “self-recognition”.

MDA5 recognizes long (>300bp) double-stranded RNA (dsRNA) (Kato, Takeuchi et al., 2008) and mounts an immune response to positive strand RNA ([+])ssRNA viruses (Fig. 6). MDA5 sensing is of particular importance for the detection of ([+])ssRNA viruses equipped with methods of evading recognition by RIG-I, such as Norovirus, a common cause of viral gastroenteritis (Schlee M, 2013). As we have previously shown, RIG-I can sense much shorter dsRNA ligands (>19 bp dsRNA) if these are equipped with a 5’ triphosphate (Schlee M, Roth A et al., 2009). The recognition of this PAMP is indispensable for the immune response to most ([+])ssRNA and ([−])ssRNA viruses (Schlee M, 2013) (Fig. 6).
RIG-I is composed of two N-terminal Caspase Activation and Recruitment Domains (CARDs), which mediate type I IFN induction, a central ATPase/helicase domain, and a C-terminal domain (CTD) critical for RNA binding (Cui S, Eisen- acher K et al., 2008). The interaction of short blunt ppp-dsRNA (class I ligands) with the RIG-I-CTD at the molecular level is well understood: In collaboration with the lab of Dinshaw Patel (Sloan Kettering Cancer Center, New York), our lab was one of the first to succeed in crystalizing the complex of the RIG-I-CTD with its ligand ppp-dsRNA. The co-crystal of the CTD and ppp-dsRNA provided important insight into the ligand requirements for RIG-I binding (Fig. 7): The CTD interacts via a basic binding cleft with ppp-dsRNA via 7 critical amino acids: F853, which stacks with the 5’terminal base pair, K858, H847, K861, and K888, which participates in 5’ alpha and/or beta-phosphate binding, K907, which demonstrates internucleotide phosphate binding, and H830 and Cys829 that participate in hydrogen bonds to the ribose 2’-OH of the 5’terminal nucleotides (Wang Y, Ludwig J et al., 2010) (reviewed in Kolakofsky D, Kowalinski E et al., 2012). In addition, some studies have described the activation of RIG-I as independent of 5’ppp if the dsRNA stretch extends 200-300 bp (class II ligand) (Kato H, Takeuchi O et al., 2010; Peisley A, Wu B et al., 2012). In contrast, some reports have described the activation of RIG-I by one single segment encodes 1–3 viral mRNAs (Fig. 7). The virus genome differs from mRNA, tRNA or ribosomal RNA (rRNA) in its modifications and structure: tRNA and rRNA are highly modified (e.g. 2’O-methylation), and tRNA has a 5’monophosphate. Although mRNA is also triphosphorylated, the vertebrate 5’cap structure nonetheless prevents recognition by RIG-I. Additionally, mRNA exists as ssRNA, while replication of viral RNA inevitably leads to the occurrence of dsRNA during replication: (+)ssRNA viruses (e.g. Dev, YFV) generate replicative dsRNA intermediates and dsRNA viruses have dsRNA genomes (e.g. Reovirus) (Fig. 6). Although avoiding long dsRNA structure formation during replication via protein coating of their genomes, (-) ssRNA viruses, such as Influenza and Arenavirus, possess self-complementary genomic ends forming a base-paired panhandle structure activating RIG-I (Fig. 6). Methods of avoiding RIG-I activation include the incorporation of a protein (VpG) at the 5’e end of their genome, or the enzymatic removal of 5’triphosphorylated nucleotides (Schliee M, 2013) (Fig. 6).

RIG-I recognizes 5’ppp-RNA of Reovirus dsRNA genomes

In addition to recognition of the dsRNA products generated during RNA virus replication, RIG-I can also directly detect dsRNA viral genomes. Reoviridae are segmented dsRNA viruses which can cause Rotavirus, a widespread illness of the gastrointestinal tract. The whole genome comprises 10–12 segments which are categorized corresponding to their size: L (large), M (medium) and S (small). The length of the segments ranges from about 1 to 3.9 kbp, whereas one single segment encodes 1–3 proteins. In the featured study, we have shown that direct sensing of these genomic dsRNA segments allows for Reovirus recognition by RIG-I and MDA5 in vivo (Goubau D, Schtiee M et al., 2014). Our findings are in line with previous reports that blocking Reovirus transcription with the guanosine analog ribavirin had no effect on the activation of the IFN pathway (Holm GH, Zurney J et al., 2007) during Reovirus infection. Although this excluded a contribution of de novo viral RNA transcripts to type I IFN induction, a central ATPase/helicase domain, and a C-terminal domain (CTD) critical for RNA binding (Cui S, Eisen- acher K et al., 2008). The interaction of short blunt ppp-dsRNA (class I ligands) with the RIG-I-CTD at the molecular level is well understood: In collaboration with the lab of Dinshaw Patel (Sloan Kettering Cancer Center, New York), our lab was one of the first to succeed in crystalizing the complex of the RIG-I-CTD with its ligand ppp-dsRNA. The co-crystal of the CTD and ppp-dsRNA provided important insight into the ligand requirements for RIG-I binding (Fig. 7): The CTD interacts via a basic binding cleft with ppp-dsRNA via 7 critical amino acids: F853, which stacks with the 5’terminal base pair, K858, H847, K861, and K888, which participates in 5’ alpha and/or beta-phosphate binding, K907, which demonstrates internucleotide phosphate binding, and H830 and Cys829 that participate in hydrogen bonds to the ribose 2’-OH of the 5’terminal nucleotides (Wang Y, Ludwig J et al., 2010) (reviewed in Kolakofsky D, Kowalinski E et al., 2012). In addition, some studies have described the activation of RIG-I as independent of 5’ppp if the dsRNA stretch extends 200-300 bp (class II ligand) (Kato H, Takeuchi O et al., 2010; Peisley A, Wu B et al., 2012). In contrast, some reports have described the activation of RIG-I by one single segment encodes 1–3 viral mRNAs (Fig. 7). The virus genome differs from mRNA, tRNA or ribosomal RNA (rRNA) in its modifications and structure: tRNA and rRNA are highly modified (e.g. 2’O-methylation), and tRNA has a 5’monophosphate. Although mRNA is also triphosphorylated, the vertebrate 5’cap structure nonetheless prevents recognition by RIG-I. Additionally, mRNA exists as ssRNA, while replication of viral RNA inevitably leads to the occurrence of dsRNA during replication: (+)ssRNA viruses (e.g. Dev, YFV) generate replicative dsRNA intermediates and dsRNA viruses have dsRNA genomes (e.g. Reovirus) (Fig. 6). Although avoiding long dsRNA structure formation during replication via protein coating of their genomes, (-) ssRNA viruses, such as Influenza and Arenavirus, possess self-complementary genomic ends forming a base-paired panhandle structure activating RIG-I (Fig. 6). Methods of avoiding RIG-I activation include the incorporation of a protein (VpG) at the 5’e end of their genome, or the enzymatic removal of 5’triphosphorylated nucleotides (Schliee M, 2013) (Fig. 6).
to a seminal work by Chow and Shatkin. Reovirus genomic dsRNA consists of a hybrid between a (+)RNA strand with 5’cap structure and a (-)RNA strand with a 5’ diphosphate end (5’pp) (Chow NL and Shatkin AJ 1975). The 5’pp is most probably the result of an incomplete capping procedure that includes removal of the gamma-phosphate from the 5’pp by a virus-encoded 5’triphosphatase. Since the original RNA strands are either capped (5’pp) or contain a 5’pp, neither were considered capable of RIG-I stimulation according to the standard paradigm. One explanation could have been that the Reovirus genome segments, as very long dsRNAs, represent class II RIG-I ligands that are recognized in a 5’-modification independent manner. Alternatively, RIG-I recognition could have been occurrence of a small amount of 5’ppp at the (+) or (-)RNA strand because of incomplete 5’processing or 5’ppp at one of the ten genomic segments as a consequence of alternative RNA processing for single genomic segments. In the featured study, using modern mass spec methods and developing a new method protocol to selectively digest 5’pp but not 5’ppp dsRNA, we were able to confirm the identity of the 5’end structure as proposed by Chow and Shatkin for each single genomic segment. Indeed, removal of the 5’diphosphate from genomic Reovirus RNA with alkaline phosphatase abolished stimulatory activity completely. To confirm immunostimulatory capacity of pp-dsRNA, we tested the RIG-I stimulating activity of short (24mer) 5’pp-pdsRNA, which was chemically synthesized using a modified protocol of a method developed in Gunther Hartmann's lab (Goldbeck, Tuschi et al., 2014). Intriguingly, 5’pp-pdsRNA stimulated human monocytes and murine MDAs-5’-RIG-I+ cells, demonstrating that 5’pp-pdsRNA also represents a considerable RIG-I ligand (Goubau D, Schlee M et al., 2014).

RIG-I activation by 5’pp-pdsRNA is also in line with our previous work (Wang Y, Ludwig J et al., 2010) (Fig. 6). Whereas mutation of single αβ-phosphate binding residues (K688, K655, K861) in the CTD considerably impaired or completely abolished RIG-I activation, combined mutation of gamma-phosphate binding residues only dampened RIG-I stimulation at very low ligand concentrations, suggesting only a minor contribution of gamma-phosphate binding to RIG-I activation.

Indeed, both free 5’ppp-RNA and 5’pp-RNA are 5’RNA modifications that are usually not present in the cytosol of cells. Thus, they represent virus genome-associated structures, and recognition of both modifications makes sense for a targeted innate immune response. As demonstrated by the RIG-I CTD crystal structure, the RIG-I binding pocket is adapted to recognize both 5’ppp- and 5’pp-RNA containing endogenous 5’ppp containing RNAs since these are masked by further modifications (e.g. mRNA cap1 structure). Our identification of this novel pathogenic RIG-I ligand has furthered our understanding of RIG-I ligand interaction with important consequences for the sensing of viral pathogens.

by M Schlee

Reference publication


Other references


Picture
Dr. Martin Schlee

Immune Sensing, Receptors and Modulators
Introduction

Local control of immunity is required both to cope with specialized pathogens which attempt to break barriers via their preferred entry routes and to maintain organ integrity, whether at homeostasis or during sterile inflammation. For some organ systems, such as the central nervous system, the importance of such local immune surveillance cannot be underestimated. For example, if activation of immunity in the brain were similar to analogous immune reactions in the skin, this would have dramatic consequences for the host. Clearly, these tissues have vastly different potentials for repair and strongly divergent requirements for tissue integrity as a basis for proper organ function. Thus, the conditions for an optimal immune response, i.e. for matching out the appropriate mechanisms of immunity and tolerance, may differ vastly between organs.

In the liver, the local regulation of immune responses is mainly governed by tolerogenic liver-resident antigen presenting cells and by bone marrow-derived professional antigen presenting cells, such as dendritic cells that are skewed in their functional capacity by the tolerogenic hepatic microenvironment. Among the liver-resident antigen presenting cell populations, liver sinusoidal endothelial cells (LSEC) are of particular importance. These cells are endowed with an extraordinary scavenger activity that supports their capacity for cross-presentation of endocytosed antigens on MHC class I molecules to CD8 T cells. In two of the new papers featured below, Percy Knolle and his colleagues, in collaboration with labs of Joachim Schultze and Wolfgang Kastenmüller, shed new light on the regulatory interactions of immune cells in the liver.

The first publication focuses on the functional adaptation of CD8 T cell responses to the local microenvironment in the liver, a process which has remained poorly understood for some time. Here, Knolle and colleagues were able to find a novel mechanism of T cell priming in the liver which is not dependent on classical innate stimulation. Instead, LSEC prime CD8 T cells in a cytokine-dependent manner. Furthermore, this liver priming leads to the generation of stable memory T cells with a distinct transcriptional profile.

A second featured article describes a new role for trogocytosis, i.e. the transfer of MHC I containing membranes from antigen presenting cells to T cells in hepatic immune surveillance.

Apart from its role during infections, local immune regulation can also have an important influence on the development of other diseases. Within the skin, the immune system plays an important role in the development of malignant tumors. The skin environment can both inhibit and promote skin tumor growth. In a joint effort of several scientists from within ImmunoSensation and led by Thomas Tüting from Department of Dermatology and Allergy of the University of Bonn, a novel mechanism for UV–light mediated melanoma progression was recently discovered (see page 48). It has been known for quite a long time that UV light is a strong skin carcinogen. It induces mutations in melanocytes, and these frequently escape from DNA repair mechanisms and are therefore prone to initiate tumors. However, it has now become apparent that UV light can “strike twice” and also plays an important additional role in melanoma progression and in the metastatic spread of these tumor cells. To delineate between these two processes, tumor initiation and progression were uncoupled.
in an experimental mouse model of melanoma. Using this model, the researchers could reveal that continuous exposure of the tumor-bearing animals to UV light led to inflammation, and that this, in turn, stimulated the metastatic dissemination of melanoma cells along blood vessels via directed motility. Thus, this newly discovered mechanism of local inflammation has provided a novel approach for developing new therapies for malignant melanoma.

**Novel mechanisms of immune control in the liver**

In our publication in Cell Reports “IL-6 trans-signaling-dependent rapid development of cytotoxic CD8 T cell function”, by Böttcher et al., we have reported the first discovery of a direct T cell adjuvant. In addition to T cell receptor stimulation, local cross-presentation of antigen by LSECs delivers a hitherto unrecognized signal via IL-6 trans-signaling and thereby initiates a unique transcriptional profile leading to the differentiation of LSEC-primed T cells into central memory-like T cells. Since CD8 T cells do not express IL-6R, Böttcher et al. have demonstrated that such stimulated T cells rapidly but transiently upregulate granzyme B expression before acquiring a quiescent state. These results provide evidence of a novel adjuvant-like effect of IL-6 trans-signaling in initiating long-lasting and protective T cell responses that are delivered by non-immune cells to T cells within non-lymphoid tissues such as the liver. Further research will focus on elucidating the mechanisms that determine the transcriptional profile of IL-6 trans-signaling in T cell differentiation. Since IL-6 trans-signaling in combination with cross-presentation by LSEC does not require inflammatory signaling via TLRs or NLRs, we will investigate whether innate immune stimuli as a consequence of immune sensing further enhance local T cell activation (Fig. 1).

In a further publication “Transfer of MHC class I molecules among liver sinusoidal cells facilitates hepatic immune surveillance” by Schölzel et al. in the Journal of Hepatology, we reported that tropoptyosis of MHC class I molecules confers cross-presentation capacity to cells. Within the liver sinusoid, several cell populations are located in close physical proximity, i.e. LSECs, stellate cells, Kupffer cells and hepatocytes. Using transgenic mice with cell-type specific expression of MHC class I molecules, we observed that MHC class I molecules that were selectively expressed in hepatocytes, LSECs or stellate cells were transferred together with other cell membrane constituents to neighboring cells. Beyond the recently reported phenomenon of “cross-dressing”, where peptide-load- ed MHC class I molecules were transferred among immune cell populations, we found that transferred MHC class I molecules allowed the recipient cells to engage in cross-presentation only if they were intrinsically capable of cross-pre- sentation. However, MHC class I molecule transfer allowed LSECs to recruit additional MHC molecules for cross-presentation, which may mediate these cells to circumvent viral immune escape that targets MHC class I gene expression, such as herpes virus family members. Our data reveal important insights into the local regulation of immune responses in the liver and how these mechanisms cooperate to protect the host from infectious microorganisms.

**UV-induced inflammation and the metastatic spread of melanoma cells**

Human skin is constantly exposed to mild UV irradiation, yet prolonged exposure to sunlight leads to acute inflammation, commonly known as sunburn or erytherma. It is well known that the DNA-damaging effect of UV irradiation is a key factor in the initiation of melanoma. However, in the recent work of Böld et al. published in Nature, the group of Thomas Tüting could show that the UV-induced inflammatory response also strongly enhances the metastatic progression of melanoma through a phenomenon called angiotropism. They demonstrated that in an inflammatory microenvironment melanoma cells migrate along the abluminal surface of blood vessels, allowing the spread of tumor cells with an increased number of lung metastases. The genetic and clinical implications of these findings are summarized in Research Area E of this annual report.

In close cooperation with the groups of Waldemar Kolanus, Wolfgang Kastenmüller, Bernd Fleischmann, Irmgard Förster and Michael Hölzel, the group of Thomas Tüting also investigated the molecular mechanism how the UV-induced inflammatory response enhances angiotropism of the tumor cells. In this work, it could be shown that the UV-induced increase in angiogenesis and lung metastases is dependent on Toll-like receptor (TLR)4 and the signal adaptor MyD88 but not the adaptor TRIF. In MyD88-de-

**Reference publications**


efficient mice, the infiltration of neutrophils into the inflamed skin after two erythematous doses of UV was nearly abolished, and UV-induced acanthosis, a reactive thickening of the epidermis, was substantially reduced. With the help of conditional MyD88 knock-in mice provided by Heike Weighardt, it could be proven that TLR signaling in neutrophils is essential for skin inflammation after UV irradiation.

MyD88-LSL mice carry a loxp-flanked stop cassette in the first intron of the myd88 gene so that transcription is blocked unless the cells undergo Cre-mediated recombination of the mutant myd88 gene. Thus, exclusive expression of MyD88 in myeloid cells was achieved by crossing MyD88LSL mice with LysMcCre mice (MyD88MYEL). For keratinocyte-specific MyD88 expression (MyD88KOC), K5Cre mice were utilized for comparison. As LysMcCre-mediated deletion affects neutrophils as well as macrophages, clodronate liposomes were also used to exclude a role for macrophages in the induction of the inflammatory response.

Furthermore, high mobility group box 1 (HMGB1) released by epidermal keratinocytes after severe cell stress could be identified as the TLR4 ligand mainly responsible for stimulation and recruitment of neutrophils into the skin after UV irradiation. Thus, sensing of the UV-induced stress factor HMGB1 initiates neutrophil inflammation which is further amplified by the release of pro-inflammatory cytokines and chemokines. Strikingly, using a model of serial melanoma skin transplants into MyD88-/- versus MyD88MYEL mice or in the presence of pharmacological inhibitors of HMGB1, the HMGB1/TLR4 axis was proven to have a central role in the angiotropic spreading of melanoma cells and development of lung metastases.

Yet how could the inflammation-dependent spread of melanoma cells be explained mechanistically? One important and plausible possibility was the direct induction of melanoma cell migration towards blood vessels and/or their surrounding tissues. To this end, cell migration analyses were conducted by Thomas Quast and Tobias Bald with the aim of elucidating the pathomechanisms exerted by this cell type.

Here, we were initially confronted with the baffling finding that melanoma cells are highly inert and essentially immobile on most of the extracellular adhesion ligands and matrices employed. In stark contrast, however, melanoma cells from humans and mice were observed to be selective-ly motile on endothelial cells in vitro and their random migration on luminal surfaces of endothelia could be enhanced even further by the presence of TNF-alpha.

To investigate melanoma cell migration in a complex tissue environment, an ex vivo assay with mouse ear slices was then adapted to use with melanoma cells (Fig. 2). Using two-photon microscopy provided by Wolfgang Kastenmüller, it was subsequently shown, that melanoma cells effectively migrate into ear slices and that they are predominantly found there in close association with blood vessels. These data strongly suggest, that direct angiotropic migration which is enhanced by inflammatory mediators such as TNF contributes to inflammation-induced metastatic spread in melanoma.

Global gene expression analysis by the group of Michael Hözel revealed that inflammatory signals like TNF-alpha re-activate migratory programs and genes known to play a role in neural crest progenitor migration during embryonic development. Hence, this work interconnects the local sensing of tissue damage by UV-irradiation and the resulting neutrophilic inflammation with a phenotypic switch of melanoma cells that is characterized by increased metastatic potential. During embryonic development, neural crest progenitors ultimately giving rise to the melanocytes in the skin migrate together with expanding blood vessels to their final destination. In that sense inflammation triggers an inverse switch and melanoma cells re-engage endothelial cell interactions that may not only promote local dissemination, but also facilitate access to the bloodstream and hematogenous dissemination. Our collaborative work also emphasizes the reciprocal interactions between melanoma, endothelial and immune cells fostered by pro-inflammatory conditions e.g. triggered by UV light sunburns or ulcerations that may provide novel therapeutic opportunities.

by I Förster and W Kolanus

Reference publication


Figure 2 Ex vivo ear tissue invasion assay with murine melanoma cells. EGFP expressing HCmel12 melanoma cells (green) were seeded on the ventral side of inflamed ear tissue explants from UV-irradiated mice. HCmel112 cells were allowed to adhere and invade the ear tissue for 16 hours. Ears were fixed and immunohistochemistry was performed using an Alexa594-conjugated secondary antibody (red). Images were acquired with an inverted LSM5Live confocal laser-scanning microscope (Carl Zeiss). Volume-rendered 3D reconstruction on the z-series, was performed using Imaris software (Bitplane).
Introduction

A common theme of the three projects in this section is the realization that many vital signaling pathways are not limited to any one specific biological process, but are utilized at multiple times and in different tissues to modulate distinct physiological events. The research groups of Hoch, Pankratz and Zimmer, and indeed throughout Area C, use different model organisms and approaches to address how the immune system interacts with metabolic and nervous systems to maintain organismal homeostasis.

The featured projects illustrate this by investigating key signaling systems in metabolic and neural contexts, and then extending this to study how they function in immune sensing.

The study by Mass et al., from the lab of Michael Hoch together with Dagmar Wachten, deals with the Cystein-Rich with EGF-Like Domains (Creld) family of conserved proteins, found in both mammals and insects, which are involved in calcium signaling. They show that a member of this family, Creld1, is a positive regulator of the calcineurin/NFAT signaling in mice: the ER-localized Creld1 protein interacts with calcineurin to control the activity of the NFAT transcription factor. Knocking out Creld1 activity results in defects in heart development. The calcineurin/NFAT signaling system is already known to be important for immune cell function. Thus, with the demonstration that Creld1 is an essential regulator of calcineurin/NFAT activity, current work is now aimed at studying the role of Creld1 in T cells and macrophages.

In the publication by Schoofs et al., from the lab of Michael Pankratz, a Drosophila model was used to study the role of neuromodulators in regulating feeding and locomotion, behaviors that are highly dependent on the metabolic as well as on the immune state of an organism, e.g. many sick animals decrease their feeding behavior. Using genetic tools to manipulate specific neurons in the brain, the group identified conserved neuropeptides involved in feeding and locomotion. One of these is a homolog of the mammalian Neuromedin U (NMU) that interconnects chemosensory organs with endocrine circuits. The neuromedins are also involved in immune signaling, and current research is focused on defining the function of neuromedin homologs in the sensing of bacterial infection.

The third study from Schmöle et al., from the group of Andreas Zimmer investigated the role of the endocannabinoid system in a murine model of Alzheimer’s disease. The endocannabinoids signal through two G-protein-coupled receptors, CB1 and CB2. Whereas CB1 is expressed in the central nervous system, the CB2 receptor is found mostly in immune cells. The group studied the role of CB2 in microglia activation in vitro and in a mouse model of Alzheimer’s disease. They showed that microglia derived from mice lacking CB2 are less responsive to pro-inflammatory signals. Furthermore, in an Alzheimer’s model, the CB2 mutants showed less infiltration of macrophages in the brain. This clearly demonstrates a role for CB2 in the neuroinflammation associated with Alzheimer’s disease.

Altogether, these studies provide inroads to studying how important signaling molecules utilized in metabolic and neural processes can interact with the immune system to bring about appropriate behavioral and physiological responses.
Chemosensory and neuroendocrine pathways that modulate feeding and locomotion: relevance for immune sensing by the CNS

There is increasing evidence that the nervous system can sense pathogenic bacteria and mount an appropriate physiological and behavioral response. For example, bacterial products can directly interact with sensory neurons, resulting in the secretion of neuropeptides or neurotransmitters that modulate immune response (Steinberg et al., 2014). We are using Drosophila as a model organism to study the neural mechanisms that underlie chemosensation of bacteria and the neuroendocrine signaling pathways that modulate immune response at physiological and behavioral levels.

In our recent work (Schoofs et al., 2014a), we characterized two factors in the central nervous system (CNS) that oppositely regulate feeding: the neuropeptide hugin, a homolog of mammalian neuropeptide U (NMU), and serotonin. Activation of hugin-producing neurons in the brain suppresses feeding, and these animals move away from a food source (Fig. 1). This response resembles a behavior common to many animals that have been infected with pathogenic bacteria. It has also been shown that NMU has a similar effect on feeding and locomotion in the mouse: increased NMU signaling leads to the suppression of food intake and increased locomotor activity. The hugin neuropeptide circuit interconnects two areas of the Drosophila brain which are analogous to the vertebrate brain stem and hypothalamicus and receive direct inputs from the chemosensory neurons in the periphery. Furthermore, the receptor for the neuropeptide is expressed in the insulin-producing cells as well as in cells that express the Drosophila homolog of corticotropin-releasing hormone. The hugin/NMU circuitry may represent an ancient neuroendocrine system that regulates basic functions, such as feeding, locomotion and stress response.

Serotonin has an effect opposite to that of hugin neuropeptide: activation of central serotoninergic neurons increase motor activity related to feeding as well as aggression (Schoofs et al., 2014a; Alekseyenko et al., 2014). Interestingly, a subpopulation of these neurons have axons that leave the brain and project into the enteric nervous system, innervating the gut and key endocrine organs. This direct neuronal connection between the brain and the gut has similarities to the vagus nerve (Schoofs et al., 2014b).

Altogether, the central hugin/NMU and serotonin systems comprise a neuro-modulatory network that acts in opposing manners to regulate feeding behavior. It is known from vertebrate studies that both components are also involved in feeding as well as immune regulation. In this context, Drosophila infected with pathogenic bacteria show alterations in feeding and locomotive behaviors. Our current findings provide a basis for the further investigation of how the hugin neuropeptide, serotonin and other neurotransmitters may be involved in sensing bacterial infection and modulating the immune response.

by MJ Pankratz

Reference publication

Other references
Cannabinoid receptor 2 deficiency results in reduced neuroinflammation in an Alzheimer’s disease mouse model

Several studies have indicated that the endocannabinoid system (ECS) plays an important role in neuroinflammation (Di Marzo V. et al., 2015; Maccafone M. et al., 2015). The ECS is a retrograde messenger system, consisting of lipid signaling molecules that bind to at least two G-protein-coupled receptors, CB1 and CB2. In contrast to CB1, CB2 is primarily expressed on immune cells, such as B cells, T cells, macrophages, dendritic cells, and microglia (Di Marzo V. et al., 2015; Maccafone M. et al., 2015).

In our study, we examined the role of CB2 in microglia activation in vitro and analyzed the neuroinflammatory process in a transgenic mouse model of Alzheimer’s disease (AD) (APP/PS1 mice). Neuropathological hallmarks of AD include extracellular amyloid-β (Aβ) plaque deposition and intracellular neurofibrillary tangles accompanied by neuroinflammation characterized by astrocytosis and microglial cell activation. Since this process subsequently results in cognitive impairment, the contribution of the ECS to AD is of great interest.

We demonstrated that microglia harvested from mice lacking the CB2 receptor (CB2-/-) were less responsive to pro-inflammatory stimuli than CB2+/- microglia, based on the expression of the cell-surface markers iCAM and CD40 and the release of chemokines and cytokines CCL2, IL-6, and TNFα. As these in vitro data already suggested a crucial role for CB2 in microglia activation, we subsequently studied the influence of CB2 on AD-associated neuroinflammation in vivo by generating APP/PS1*CB2-/- mice. Aged APP/PS1*CB2-/- mice had reduced levels of microglia and infiltrating macrophages. Moreover, they showed lower expression levels of pro-inflammatory chemokines and cytokines TNFα and CCL2 in the brain, as well as diminished concentrations of soluble Aβ 40/42 (Fig. 2). In the chosen paradigm, we could not detect significant changes in the acquisition phase of the Morris Water maze test; therefore, we conclude that the observed reduction in neuroinflammation was not sufficient to rescue cognitive impairments. Nonetheless, our data clearly suggest a role for CB2 in Alzheimer’s disease-associated neuroinflammation.

Reference publication


Other references


Murine Creld1 controls cardiac development through activation of calcineurin/NFATc1 signaling

The genes coding for the Cysteine-rich with EGF-like domains (Creld) protein family were discovered many years ago, occurring in mammals and even insects (Rupp PA. et al., 2002). However, the precise role of the proteins remained elusive. We could demonstrate in collaboration with Dr. Dagmar Wachten (Research Center caesar, Bonn) that murine Creld1 encodes a new regulator of calcineurin/NFATc1 signaling essential for embryonic heart valve development (Mass E. et al., 2014). Calcineurin is a heteromeric Ca2+-dependent serine/threonine phosphatase that is activated when intracellular Ca2+-levels increase. It dephosphorylates cytoplasmic NFAT transcription factors, which subsequently undergo nuclear translocation and regulate numerous biological processes including cardiac development and immune cell activation.

Our study identifies the Cysteine-Rich with EGF-Like Domains 1 (Creld1) gene as an essential positive regulator of calcineurin/NFAT signaling. Creld1 is a highly conserved transmembrane protein containing a WE domain, two EGF-like and two Ca2+-binding EGF-like domains. We showed that increased expression of mCreld1 in various human and murine cell lines is sufficient to cause NFATc1 dephosphorylation and its translocation to the nucleus. This requires the WE domain, which is unique for the Creld protein family and does not involve a change of intracellular Ca2+-fluxes. Rather, ER-localization of Creld1 interacts with the regulatory subunit of calcineurin, CNB and thereby controls the phosphatase activity of the catalytic calcineurin subunit, CnA.

To analyze the function of mCreld1 in vivo, we generated a murine Creld1KO model. We found that homozygous Creld1KO mice are embryonic lethal at E11.5 and show severe heart-venteal defects. Murine heart-venteal morphogenesis requires the calcineurin/NFAT-dependent proliferation of endocardial cells. We demonstrate that loss of mCreld1 abolishes endocardial cell proliferation because NFATc1 fails to translocate to the nucleus, and, thereby, the expression of the NFATc1 target genes DSCR1 and NFATc1 are severely reduced. In humans, mutations in CRELD1 are associated with atrioventricular septum defects (AVSD). We have introduced two different CRELD1 point mutations found in human patients with AVSD into the murine Creld1 protein and revealed that both mutations strongly impair the calcineurin-dependent NFATc1 translocation. Collectively, our study identified Creld1 as an essential regulator of calcineurin/NFAT1 activation, in the cells of the adaptive as well as the innate immune systems, NFAT belongs to the key modulators regulating the development, activation, proliferation,
survival, and differentiation. Until now, elevated cytoplasmic calcium-levels have been proposed to be the main upstream activator of calcineurin and, therefore, of NFAT in many cell types, including T cells, B cells, dendritic cells, and macrophages (Fric J. et al., 2012). In macrophages, NFAT members are not activated under physiological conditions; however, under pathologic conditions, e.g. inflammatory gut diseases, the activation of the calcineurin/NFAT signaling pathway leads to excessive pro-inflammatory cytokine production and to the establishment of chronic inflammatory processes (Zanoni I. and Granucci F., 2012).

We currently explore the role of Creld1 in T cells and macrophages using a conditional Creld1 allele and various CRE driver lines in immune cells.

by M Hoch

Reference publication


Other publications


Introduction

Immune sensing pathways provide complex information, and their integration into a coordinated immune responses is one of the most important aspects of immunity. Such integration occurs both at the intracellular and the cellular level. The two subsections of area D deal with both aspects of signal integration. In each of them, several breakthroughs have been made, and two of them are described in detail in the following:

Signal integration on transcriptional level

Signal-specific functional cellular programs are induced by function-specific gene transcription events. Particular innate immune cells, equipped with a large number of different sensing receptors, can react to a myriad of external signals. Functional plasticity of the myeloid cell compartment, particularly macrophages, can be linked to the cells’ ability to specifically react to a diverse spectrum of input signals. During the last few decades, investigators have favored a polarizing system to describe macrophage activation. However, this rather rigid model did not correspond to many more recent observations made by researchers in the field. Using a systems approach, the Schultze group could resolve the discrepancy between this old dogma and our current knowledge of macrophage biology. In a seminal paper, they present a new model of macrophage activation (Xue J. et al., Immunity. 2014). Compiling what is currently the largest transcriptome dataset on human macrophage activation and applying mathematical modeling, they could definitively demonstrate that macrophages compute input signals on the transcriptional level and that the net effect is a rather input-specific functional cellular program. These findings were also instrumental for a new nomenclature suggested by Schulze, Murray, Wynn and other experts of macrophage biology (Murray P. et al., Immunity. 2014).

Transcriptome-based network analysis reveals a spectrum model of human macrophage activation.

Macrophages are important cells of the innate immune system. They can be found in every tissue and, unsurprisingly, they have been linked to many major diseases including infections, obesity, diabetes, atherosclerosis, cancer and neurodegeneration. Tissue macrophages are derived from the yolk sac, but they are replaced in parenchymal tissue over time to a varying degree by monocyte-derived macrophages that originate from the hematopoietic system. Activation of macrophages in response to stress signals either derived from pathogens (Pathogen-associated molecular pattern molecules (PAMPs)) or damaged tissue (Damage-associated molecular pattern molecules (DAMPs)) leads to changes in their cellular function. Traditionally, the cellular response of macrophages has been divided into anti- and pro-inflammatory responses, with the postulation of a rather simplistic model of so-called M1 (pro-inflammatory) or M2 (anti-inflammatory) macrophages. Unsurprisingly, attempts to use this simple dichotomy in context of many diseases has not been straightforward, since such a polar model does not reflect the complexity of inflammatory processes.

To overcome this dogma in the field, Professor Schultze and his team, in collaboration with Professor Latz, compiled the largest transcriptome dataset of human macrophage activation comprising 28 distinct stimuli. Using advanced bioinformatics approaches, they investigated whether macrophage activation could be better
explained by a polar model or a multi-dimensional one. Their analyses clearly demonstrated that macrophage activation is a multi-dimensional process. In fact, macrophages demonstrate a complex integration of various input signals thereby activating an entire network of transcriptional and epigenetic regulators that guide gene expression, which, in turn, leads to the induction of specific cellular functions.

These novel findings open new avenues for the study of macrophage activation in context of sterile inflammation and other important diseases (Fig. 1). Using their multi-dimensional model, Schultze and his colleagues could already demonstrate that alveolar macrophages in patients with chronic obstructive pulmonary disease are characterized by a loss of immune functions, a distinction which could not have been revealed if the old polar model of macrophage activation had been applied. Thus, this paradigm shift is of great importance in the context of disease, where macrophages integrate particularly complex tissue-specific and stress-derived signals. Here, a multi-dimensional approach will allow for both the elucidation of complex pathologies and the identification of novel targets for therapeutic interventions. This groundbreaking work was published in the journal “Immunity” and has already been recognized as one of the highest-scored articles of this journal.

by JL Schultze

Reference publication


Signal integration on the cellular level

At the cellular level, Daniel Engel, Christian Kurts, and colleagues discovered how three different innate immune cell types cross-talk with each other to integrate sensory input into functional responses during bacterial infections (Schiwon M, et al., Cell. 2014). It has long been recognized that neutrophils, tissue macrophages and monocyte-derived macrophages from the circulation must act in concert in response to infections. However, the exact interplay, exchange of information and integration of cellular functions is still an important area of research. The scientists identified the different signals exchanged by the different cell types and their functional consequences and discovered what can be considered the innate equivalent of immunological “help”.

Crosstalk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium

The immune system uses powerful weapons to combat pathogens which must be tightly regulated to avoid collateral tissue damage and immune-mediated disease. One goal of area D of the ImmunoSensitivitiy Cluster of Excellence is the identification of immunoregulatory mechanisms that control the response of the immune system and prevent unwanted tissue injury. The Cluster scientists Daniel Engel and Christine Kurts, in cooperation with an international team of scientists in Hamburg, Würzburg, Aachen, Leuven, Yale and Heidelberg, have discovered a “helper” macrophage subset that regulates the most important immune effector cell against bacterial infections, neutrophil granulocytes, known simply as “neutrophils”. The scientists studied the immune response against urinary tract infections, one of the most common infections worldwide. These are caused by distinct subspecies of *E. coli* bacteria that enter the bladder through the urethra, especially in women because of anatomical reasons. Because the bacteria often cannot be completely eliminated, urinary tract infections can become chronic. They then may relapse, for example, in stressful situations and cause sepsis. Although these can be treated with antibiotics, they are very painful, and may even inflict irreparable tissue damage, ascend to the kidney or promote the development of bladder cancer. Thus, it is of great interest to better understand the body’s defense mechanisms against urinary tract infections.

It has been known for quite some time that neutrophils play a critical role in infection. These effector cells normally circulate in the blood and rapidly enter infected tissues to combat invading bacteria, primarily by phagocytosis or releasing toxins. It is also known that macrophages can regulate neutrophils, although it is not clear how they do so. The Cluster scientists have found that two distinct types of macrophages need to exchange information in a tightly coordinated manner in order to regulate the neutrophils. One macrophage type is present in all tissues and acts as a tissue-specific sentinel macrophage. As their name suggests, these macrophages invade, sentinel macrophages alert the host by secreting chemokines that attract neutrophils into the infected organ. In addition, the sentinel macrophages attract another macrophage type from the circulation with a previously unknown regulatory helper function. These cells also sense the infection and confirm the need to fully activate the neutrophils (Fig. 2). This process is facilitated by the secretion of the chemokine CXCL2, which allows the neutrophils to produce the metalloproteinase MMP9. MMP9, in turn, allows neutrophils to enter the infected epithelial tissue, the “front lines” of the infection. This communication between the two types of macrophages can be interpreted as the sentinel macrophage’s “requesting a second opinion” on whether the infection is dangerous enough before the neutrophils are fully unleashed, and this mechanism guarantees that these potent immune cells are only activated if absolutely necessary.

The “chemical messenger” sent between the two types of macrophages is the cytokine TNF-α. This molecule is of great clinical interest both because it is already known to play a central role in several immune-mediated diseases. Drugs that block TNF-α have been shown to be highly effective in the treatment of rheumatoid arthritis and patients with inflammatory bowel disease. However, it has also been observed that the relapse bacterial infec-

Integration of Immune Sensory System Input on the Cellular and Subcellular Level

*Figure 1* Multi-dimensional model of macrophage activation. Mono-cytoid-derived macrophages but also tissue macrophages receive a myriad of tissue-associated and stress-derived signals that they integrate at the transcriptional level. Integration of these signals leads to input-specific functional cellular programs that comprise the wide functional spectrum of these important immune cells. Based on this model, we also postulate that macrophage plasticity can be explained by these transcriptional mechanisms of signal integration. Molecular mechanisms at the epigenetic and transcriptional level that could explain macrophage plasticity require further investigation (see also Xue et al., *Immunity* 2014).
Subcellular Level

the Cellular and System Input on Immune Sensory Integration of a neutrophil response. Sentinel macrophages produce the chemokine CXCL2 [4], which induces the secretion of MMP-9. This attracts helper macrophages. These indicate the secretion of TNF-α, leading to the recruitment in Th17-mediated glomerulonephritis but not in bacterial pyelonephritis.

The experiments were performed by Marzena Schiwon and by Christiane Weisheit in the Cluster junior research group led by Daniel Engel and in the Institute of Experimental Immunology led by Christian Kurts. As this mechanism is fundamentally important to our general understanding of the antibacterial immune response, it was accepted by the leading journal “Cell” for publication. This discovery could provide the basis for the development of new treatment strategies against bacterial infections.

by C Kurts

Reference publication


Other references


(Inteil senior authorship)
Research Area E: Consequences of Immune Sensing for Sterile Inflammation in Vivo

Inflammation comprises a set of responses primarily tailored to eliminate microbial pathogens and to restore the integrity of the host. Phagocytic cells such as macrophages, neutrophils or microglia employ their phagocytic capacity and direct antimicrobial effector mechanisms to eliminate pathogens. These cells deliver cytokines and chemokines which recruit other immune cells to the site of inflammation. This inflammatory reaction not only helps to eliminate the pathogen, but also initiates the repair of damaged tissue. Sterile inflammation occurs in the absence of microbial stimuli but resembles an infectious process in many aspects. While inflammation usually is a transient and self-limiting process, it can also present as an overshooting and chronic inflammatory response, leading to tissue destruction and organ damage. The same immune sensing receptors that are operational in microbial infection also drive sterile inflammation upon sensing of endogenous damage-associated molecules.

In many diseases, inflammation is inappropriate in terms of type, magnitude or duration. In part E of the Cluster research program, we primarily focus on sterile inflammation. Many sterile inflammatory conditions are caused by chemophysical damage or by overproduction and tissue deposition of endogenous molecules, commonly referred to as damage-associated molecular patterns (DAMPs). On the other hand, selected pathogen or damage-associated molecular patterns can be employed to elicit a specific set of immune responses which allows the elimination of diseased cells, such as tumor cells.

Here, we highlight three recent advances representing the broad spectrum of work in this area of research performed by Cluster groups in 2014. In the first two sections of this chapter, Cluster members Thomas Tüting and Michael Hölzel elucidate the differential roles played by sterile inflammation in the tumoral immune response. In the first section, they report the surprising finding that physicochemical damage by UV light contributes to melanoma progression not only by inducing genetic alterations but also by inducing an inflammatory response which drives tumor cell migration along the vasculature thereby promoting tumor metastasis. They identify TLR4 as the immune receptor responsible for sensing the DAMP HMGB1 released by keratinocytes. In the second section, they demonstrate that type-I interferon signaling instead participates synergistically in the anti-tumoral immune response. Triggering type-I interferon via nucleic acid sensing receptors did not drive metastasis but rather acted synergistically with PD1 inhibition to reject the tumor. The third section of this chapter focuses on the role of sterile inflammation in Alzheimer’s disease. The group of Michael Heneka has identified CXCR3 as a critical immune molecule involved in the Alzheimer pathogenesis. Elimination of CXCR3 function restored the phagocytic capacity of glial cells and thereby reduced plaque formation and disease. Thus, all three projects not only provide new mechanistic insight to inflammatory pathogenesis of disease, they also provide well-defined therapeutic targets: TLR4 blockade to reduce melanoma metastasis; the activation of nucleic acid sensing receptors to trigger anti-tumor immune responses, and the blockade of CXCR3 in Alzheimer’s disease.
Consequences of Immune Sensing for Sterile Inflammation in Vivo

The sun strikes twice

Ultraviolet radiation (UV) is a major risk factor for malignant melanoma, which is the most aggressive type of skin cancer and originates from the pigment producing melanocytes in the epidermis. Tanning is an adaptive mechanism in response to sunlight exposure to protect the skin from future sun exposure and avoid sunburns. It is well established that UV-light causes genomic aberrations, and recent large-scale tumor exome sequencing studies have revealed that UV-exposed melanomas have an extraordinarily high number of mutations. Undoubtedly, these genomic aberrations are critical for the malignant transformation of melanocytes, but the inflammatory consequences of repetitive sunburns have been largely overlooked. Epidemiological data suggest that there may be years to decades between the incipient malignant transformation of melanocytes and the clinical appearance of a malignant melanoma. Hence, it is a likely scenario that a growing melanoma is repetitively exposed to intense UV-light in persons who expose themselves to excessive sun tanning.

Using genetically engineered murine melanoma models, we simulated this epidemiologically relevant context by repeatedly exposing the skin of melanoma-bearing mice to UV-light after the melanoma developed spontaneously without UV-exposure. Surprisingly, we found that UV-exposure did not accelerate tumor growth but instead increased the frequency of distant metastases. We dissected the cascade of events and demonstrated that UV-induced inflammation in the skin favored the migratory and metastatic potential of the melanoma cells. Importantly, the pronounced inflammatory response in the skin was dominated and amplified by neutrophils, and we addressed the mechanism of their recruitment upon UV-irradiation. As we expected innate immune sensory pathways to be crucial, we UV-irradiated mice with deletions of different Toll-like receptors (TLRs) and found that TLR4 was essential to initiating the neutrophilic inflammation in response to UV.

We also found that UV-damaged keratinocytes in the epidermis release the nuclear protein HMGB1, a well-known ligand for TLR4. Indeed, pharmacological agents blocking HMGB1 or TLR4 abrogated neutrophil recruitment to the skin of UV-treated mice resulting in reduced distant metastasis. In summary, our work links UV-irradiation of the skin to innate immune sensing cascades and thus the increased metastatic potential of melanoma cells. In that sense, we have proposed the concept that “the sun strikes twice” in melanomagenesis, initially by inducing oncogenic mutations and subsequently by causing disease-exacerbating inflammation (Fig. 1). This emphasizes the importance of avoiding excessive sun tanning and the appropriate use of sun screen.

Of note, neutrophilic infiltrates are typical for ulcerated high-risk melanomas. Since our work provides a mechanistic link between neutrophils, ulceration and an increased propensity for metastatic spread, strategies counteracting these inflammatory signaling cascades and TLR4, in particular, may prove to be promising adjuvant strategies in this context. For some time, interferon-alpha was the standard of care for adjuvant treatment of high-risk melanomas, yet meta-analysis of large cohorts revealed that only patients with ulcerated melanomas benefited from this treatment. Since interferon-alpha is known to block neutrophil recruitment, our study provides a mechanistic explanation for this clinical observation. Systemic interferon-alpha treatment is accompanied by severe and dose-limiting side effects. Thus, TLR4-directed adjuvant strategies would allow for an alternative and possibly less toxic approach to preventing metastatic spread in ulcerated melanomas.

Conclusions of Immune Sensing for Sterile Inflammation in Vivo

Reference publication

Increasing benefit from PD-1 checkpoint inhibition in melanoma

Currently, immunotherapy is revolutionizing the systemic treatment of cancer. Antibodies targeting the PD-1 receptor on cytotoxic T cells or its ligand PD-L1 on tumor cells and antigen-presenting cells have achieved remarkable response rates and importantly also durable remissions in a substantial number of patients. The basis of this clinical success is the local reactivation of anti-tumoral immunity in the tumor tissue, and it is currently believed that this spatial restriction may explain why the autoimmune side effects of drugs targeting the PD-1 axis are less severe than with antibodies targeting CTLA-4, another activation immunotherapeutic approach which preceded PD-1-directed therapies into the clinic. Although malignant melanoma has emerged as a paradigmatic disease for cancer immunotherapy, PD-1 therapy is also highly effective in the treatment of lung, renal, and gastric cancer, Hodgkin lymphoma and several other tumor entities.

However, not all patients respond to PD-1 antibodies, and overcoming this primary insensitivity is now one of the key questions to address in pre-clinical and clinical research. In the case of melanoma, several clinical studies have suggested that the presence of T cells prior to therapy positively predicts responsiveness to anti-PD-1 since this also correlates with an activated type I interferon system (Fig. 2). Therefore, immune-cell poor melanomas comprise a subgroup of patients that are unlikely to benefit from PD-1 checkpoint inhibitors.

The groups of Thomas Tüting and Michael Hölzel performed a thorough histological and bioinformatic cross-species comparison of mouse and human metastatic melanomas, and they found that melanomas originating in their genetically engineered Hgf-Cdk4R24C mouse model recapitulate the immune-cell poor phenotype of PD-1 unresponsive and poor outcome human melanomas.

Indeed, application of PD-1 antibodies to melanoma-bearing Hgf-Cdk4R24C mice had no effect on tumor growth confirming the concept of primary PD-1 unresponsiveness. Therefore, they established a combinatorial protocol using PD-1 antibodies together with intra-tumoral injection of the immune stimulatory nucleic acid poly(I:C) that activates the innate immune and type I interferon system through MDA-5 (Fig. 3). Treatment with poly(I:C) alone achieved immune cell recruitment and tumor control, but, importantly, this response could now be strongly enhanced by the co-application of PD-1 antibody. Tumors treated with poly(I:C) showed an activated type I interferon system and up-regulation of PD-L1, which is known to be induced by interferons. Using transplantable melanomas and a variety of knockout mice, they demonstrated that the efficacy of this combinatorial immunotherapy strictly relies on the type I interferon system in the host mice as coordinated by dendritic, myeloid, natural killer, and T cells.

In summary, their pre-clinical work identifies innate immune sensing of immune stimulatory nucleic acids as a rational strategy for the treatment of immune-cell poor melanomas in combination with PD-1 checkpoint blockade. As anti-PD-1 demonstrates broad activity across multiple cancer entities, this approach may apply to other cancer subgroups that lack spontaneous immune cell infiltrates and PD-1 responsiveness. The work emphasizes the need for pharmacological agents like poly(I:C), RIG-I ligands or STING agonists that all activate the type I interferon system in a targeted manner. It underscores the potential of innate immune sense of poly(I:C) to unleash the antitumor capability of PD-1 therapy.

In conclusion, their pre-clinical work identifies innate immune sensing of immune stimulatory nucleic acids as a rational strategy for the treatment of immune-cell poor melanomas in combination with PD-1 checkpoint blockade. As anti-PD-1 demonstrates broad activity across multiple cancer entities, this approach may apply to other cancer subgroups that lack spontaneous immune cell infiltrates and PD-1 responsiveness. The work emphasizes the need for pharmacological agents like poly(I:C), RIG-I ligands or STING agonists that all activate the type I interferon system in a targeted manner. It underscores the potential of innate immune sense of poly(I:C) to unleash the antitumor capability of PD-1 therapy.
CXCR3 promotes plaque formation and behavioral deficits in an Alzheimer’s disease model

Dementia is one of the major causes of disability and dependency among older people worldwide. Alzheimer’s disease (AD) is the most common form of dementia, accounting for up to 70% of all sporadic, late-onset cases. There is a growing consensus in the scientific community that disease-modifying treatments that start before the onset of clinical dementia are needed. AD is a neurodegenerative brain disorder characterized by the formation of β-amyloid plaques, predominantly in hippocampal and cortical regions. Periplaque activation of microglia and astrocytes and the induction of proinflammatory molecules suggest a pathogenic role for inflammation in this disease.

Chemokines are important modulators of neuroinflammation and neurodegeneration. High levels of the chemokine CXCL10 are found in the brains of AD patients and in AD animal models suggesting a pathogenic role for this chemokine and its receptor CXCR3. Recent studies addressing the role of CXCR3 in neurological diseases revealed potent but diverse functions for CXCR3.

To elucidate the role of CXCR3 in an animal model of AD, we used transgenic mouse co-expressing APPs and PS1ΔE9 mutations (APP/PS1). This transgenic mouse model displays several pathological characteristics of AD including the progressive accumulation of cerebral amyloid plaques accompanied by the clustering of reactive microglia and astrocytes around amyloid plaques and cognitive impairment. We crossed APP/PS1 mice with CXCR3-deficient mice and compared the course of AD-like changes in CXCR3-competent and CXCR3-deficient APP/PS1 mice. We found that plaque burden and Aβ levels were strongly reduced in CXCR3-deficient APP/PS1 mice compared to APP/PS1 mice (Fig. 4). Analysis of microglial phagocytosis in vitro and in vivo demonstrated that CXCR3 deficiency increased the microglial uptake of Aβ. Applying a CXCR3-antagonist, we were able to increase microglial Aβ phagocytosis, which went along with reduced TNF-α secretion. In addition, morphological activation and plaque-associated microglia was diminished in APP/PS1/CXCR3−/− mice. CXCR3-deficiency lead to reduced levels of proinflammatory cytokines in APP/PS1 brain tissue. Furthermore, behavioral deficits observed in APP/PS1 mice were attenuated by the loss of CXCR3. We conclude that the direct and indirect induction of CXCL10 by Aβ and the subsequent activation of the CXCR3 chemokine system are able to modulate the activation state of glial cells and thereby modulating the course of an AD-like pathology in the APP/PS1 model. CXCR3 activation reduces the phagocytic competence of microglia for Aβ, which ultimately promotes plaque formation and behavioral impairment in this model. CXCR3 has a key role in the progression of the AD-like disease in APP/PS1 mice and is thus an interesting, novel therapeutic target in AD.

Consequences of Immune Sensing for Sterile Inflammation in Vivo


Reference publication

M Müller and MT Heneka

Figure 4 Detection of AD-like plaques in APP/PS1 mice, which are either CXCR3-competent or CXCR3-deficient demonstrates a striking plaque reduction in CXCR3-deficient APP/PS1 mice (A). In CXCR3-deficient APP/PS1 mice, microglial cells are less activated and less clustered around amyloid plaques (B). The phagocytosis of Aβ by microglial cells is much more pronounced in CXCR3-deficient microglia compared to CXCR3 competent microglia. The reduced Aβ phagocytosis of wild type microglia can be enhanced by blocking CXCR3 with receptor-specific antagonists.
The LIMES Zebrafish Lab

The LIMES Zebrafish Lab was set up in 2011 as a base for the establishment of Knock-Out and Knock-In models using TALEN and Crispr-Cas9-based approaches and subsequent phenotypic analysis. The Zebrafish Lab offers a unique opportunity to unravel novel gene functions and to study the pathology and therapy of human diseases. The husbandry currently holds 230 tanks, accommodating up to 4000 fish, and is equipped with a state-of-the-art, computer-controlled husbandry system manufactured by Tecniplast. Beside the aquarium room, which is a restricted area, the Zebrafish Lab space includes a needle puller, suitable for the production of capillary needles for the injection of zebrafish embryos, two microinjection systems and two incubators for raising young zebrafish (see Fig. 1 and 2).

About zebrafish as a genetic model system

Zebrafish (Danio rerio) is a member of the Cyprinidae (carp) family and originates from native zebrafish populations found in the paddy fields and shallow waters of India, Pakistan, Nepal, Bangladesh and Burma. Adult fish grow up to 5 cm in length and live for five years. Zebrafish are easy to maintain and have a short generation time (approximately 3-4 months). Though humans obviously look very different from fish, there are remarkable biological and genetic similarities, which
make zebrafish a potent model system for biomedical research. As a vertebrate model system, the zebrafish has several essential advantages when compared to Drosophila and the mouse, which allow for straightforward gene function analysis:

- Most importantly, zebrafish embryos develop ex utero, are optically fairly transparent and have a high regenerative capacity. Thus, dynamic developmental processes can be visualized easily by fluorescent confocal microscopy or even brightfield live video microscopy (Fig. 3).

- High fecundity (one female gives rise to 100 embryos per week) is prerequisite for high throughput and chemical screening.

- Fluorescent reporter lines enable the dynamic visualization of physiological processes in vivo. For the imaging of adult zebrafish, several optically transparent mutant strains are available, e.g. the casper mutant.

- The genetic networks controlling major biological processes like lipid metabolism are conserved in zebrafish. For 70% of the known disease-associated genes in humans there is an ortholog in the zebrafish genome.

- Compared to mouse breeding, zebrafish husbandry and projects are more cost effective.

Based on its remarkable evolutionary conservation, the genetic tools available and its plasticity, the zebrafish model is suitable for the establishment of human disease models for cancer, cardiovascular and immune system diseases, diabetes, neurodegeneration and many others.

by M Hoch
Recent advances in targeted genome editing technologies have opened new avenues in life science research. The advent of designer nucleases now allows the highly efficient, flexible and specific induction of DNA double-strand breaks (DSB) in eukaryotic genomes. DSBs trigger two distinct repair pathways that can both be exploited to specifically modify gene architecture. While the process of homologous recombination (HR) accurately repairs DSBs using the sister chromatid as a template, non-homologous end joining (NHEJ) repair is an error-prone end-joining mismatch repair pathway that frequently leads to genetic alterations. Providing a donor construct with appropriate homology arms as a template, the pathway of DSB-triggered HR can be used to site-specifically introduce heterologous genetic material into cells. At the same time, NHEJ-mediated repair often results in InDel events that can disrupt the reading frame of a coding exon and such lead to a functional knockout if an early and critical exon was targeted (Fig. 1). Needless to say, the ability to knockout genes in human cells constitutes a phenomenal progress, given the fact that a number of interesting candidate genes are not or only in part homologous between the human and the murine system, the latter being the classical model organism for knockout studies.

Given their high on-target activity and ease of use, designer nucleases based on the CRISPR/Cas9 technology have established themselves as the method of choice for a wide array of genome engineering applications. Clustered regularly interspaced short palindromic repeats (CRISPR) in conjunction with CRISPR-associated proteins (Cas) provide an adaptive immune system to bacteria and archaea targeting foreign genetic material. Cas9, which is a member of the type II CRISPR-Cas system, requires a so-called single guide RNA molecule (sgRNA) to be directed against its target sequence to operate as a sequence-specific endonuclease. The specificity of the sgRNA can be changed and as such re-directed to target virtually any genomic sequence, subsequently introducing double-strand breaks (DSB) at high efficiency and user-defined specificity.

At the Institute of Molecular Medicine, the Hornung laboratory has developed a high throughput assembly method for the synthesis of sgRNA constructs for the CRISPR/Cas9 system. Using this approach, a large, arrayed sgRNA library that currently covers approximately 93% of the human protein-coding genome has been constructed. Next to this resource, the group has developed a semi-automated workflow to generate knockout cell lines using targeted genome engineering at high throughput (Fig. 2). In brief, to disrupt the reading frame of a gene of interest, the following steps are taken: A designer nuclease is transiently expressed in the cell line of choice using transfection or electroporation. Subsequently, cells expressing high levels of the designer nuclease are enriched using fluorescence-activated cell sorting or antibiotic selection. This cell population is used to generate monoclonal cell lines by limiting dilution cloning. Thus obtained cell clones are then subjected to targeted deep sequencing to identify cell lines with the genetic lesion of interest (e.g. all-allelic frame shift mutations in critical exons). To this end, a custom-written software tool (www.outknocker.org) that allows the rapid and simple analysis of deep sequencing data for targeted insertions or deletion events has been devised. Cell clones with the desired genotype are then expanded and then subjected to functional assays. Using this knockout pipeline, genes involved in innate immune sensing and signaling cascades can be studied in the context of infectious and sterile inflammatory conditions.

by V Hornung
Technical Platforms: Bioinformatics

The establishment of the Bioinformatics Core

The Cluster has identified bioinformatics as an area of expertise that is of increasing importance for much of its research. Thus, ImmunoSensation has aimed to further improve its existing bioinformatics expertise and to establish a core structure which can be of optimal use for the Cluster overall. Three positions for bioinformaticians were advertised, and suitable candidates were hired after several rounds of Skype and personal interviews. The three new positions are in the groups of Joachim Schultz, Volkmar Gieselmann and Markus Nöthen. Regular meetings have been held to build up a joint core facility covering a broad spectrum of bioinformatics expertise in order to optimally support scientific groups within the Cluster.

The established bioinformatics expertise centers around three areas:

1. Mining genomic information

Numerous pathways are known to play important roles in an innate immune context, and genetic variation contributes to the individual immune response. In order to evaluate whether rare and/or common genetic variation is present among candidate genes and whether these variants have a functional effect that may subsequently have an impact on cell function and/or phenotype, an elaborate analysis pipeline based on integrative modeling of multiple genomic data (Fig. 1) was established.

Here, all rare and common genetic variants within each candidate gene and its regulatory regions are identified and ranked according to the following criteria:

(i) Associated molecular activity of common genetic variants can be retrieved by correlating genetic variants with an intermediate phenotypic trait e.g. gene expression, DNA methylation or protein levels (quantitative trait loci, QTL). Investigated expression QTL (eQTLs) include variants located in the regulatory region of the candidate gene and variants influencing the expression of the candidate gene itself. Since QTLs are tissue and context specific, data sets from various cell types and tissues are examined to cover a broader range of QTL functionality. This includes blood and brain tissue as well as immune eQTLs (iQTLs, (Kim et al., 2014)). In contrast to eQTLs under baseline conditions, iQTLs provide an interesting approach with regards to innate immunity as they map eQTLs in monocytes under stimulation with lipopolysaccharide (LPS).

(ii) Genetic variants associated with different complex diseases and diverse molecular phenotypes have been investigated in genome-wide association studies and documented in the Catalog of Published GWAS Studies (Welter et al., 2014). Determining associated phenotypes may therefore reveal a comprehensive function for each candidate gene. Identification of these associations is conducted for the candidate genes, variants which have a functional effect on the gene, variants in the regulatory region, and genes where these variants have a functional effect.

(iii) Functional consequences of rare variants are explored via ExAC, an aggregation of exome-sequencing data. Here, the accumulation of variants with defined functional annotations provides an estimate of the general consequences variations in the gene may have, i.e. low frequencies of frameshift or stop mutations in a candidate gene may indicate a central role of the gene.

Additionally, larger structural variation such as copy number variants (CNVs) within candidate genes and their contribution to disease phenotypes are investigated in DECIPHER (http://decipher.sanger.ac.uk), a database for the interpretation of genomic variants. Variations in the candidate gene region are subsequently reviewed for immune-relevant phenotypes, e.g. recurrent infections, and analysis of the type of genomic variant and its consequences, e.g. loss/gain of function, enables insight into the physiological nature of candidate genes as well as their contribution to disease pathogenesis.

References:


Bioinformatics
Technical platform for genomics and bioinformatics
the investigators of the ImmunoSensation "core workflow for protein quantification standards for proteomic data analysis. A procedures, there are few community-wide modern statistical analysis in quantitation facility has broadened its focus to include avand for dynamic immune responses. Numerous projects of Cluster members have utilized the protein analysis capabilities at the core facility. These range from single protein characterization and proteome profiling to isotope-based proteome quantification.

2. Data mining, analyzing, visualizing and interpreting functional genomic data
In addition to genetic variance, a myriad of exogenous signals drive the responses of innate immune cells. Transcription, epigenetic changes, and regulation by miRNAs and RNA-binding proteins are at the heart of the cellular responses of innate immune cells. To assess regulation on a genome-wide scale, the LIMES platform for genomics and bioinformatics provides the respective technologies and analytical capacities to support projects within the ImmunoSensation Cluster of Excellence. While the use of microarrays to assess gene transcription is now coming to an end, RNA-sequencing (RNA-Seq) has become the workhorse of functional genomics. Different RNA-Seq methods are provided to investigators within the ImmunoSensation Cluster of Excellence by the platform. Furthermore, histone modifications assessed by Chromatin immunoprecipitation sequencing (ChIP-Seq) and analysis of open chromatin by Assay for Transposable-Accessible Chromatin Sequencing (ATAC-Seq) are also available. For all these technologies, the respective analytical pipelines were established and are now offered to investigators within the ImmunoSensation Cluster of Excellence.

In addition to workflows for different sequencing technologies, the bioinformatics team has also developed novel network approaches to describe and visualize changes in transcriptional regulation. Moreover, network visualization provides completely new insights into transcriptional regulation and facilitates data interpretation. Numerous projects are ongoing in a collaborative effort between the investigators of the ImmunoSensation Cluster of Excellence and the LIMES platform for genomics and bioinformatics with some of the projects already leading to publications in 2014.

References
Most if not all of life science research depends on the availability and access to research materials and resources, such as collections of plasmids, cell lines and animal strains, advanced technologies, databases, sophisticated instrumentation and the expertise for their proper operation. This interdisciplinary approach is essential to addressing current topics in life science which require collaborations that do not stop at technical, scientific or at institutional boundaries. In order to collect, coordinate and catalogue these resources, the ImmunoSensation Cluster of Excellence has decided to offer its expertise and instrumentation collectively as an Office of Shared Resources. This Office will act as a central access point for resources that are shared on a scientific basis (cooperation), on a financial basis (usage of instruments and equipment) or within Core Facilities/Units (Fig. 1).

Although a great deal of information about the shared resources and technical platforms provided by Cluster members is already available, centralizing access to this information will standardize the information available and streamline access thus facilitating research.

Thus, at the beginning of 2014, the Shared Resources Core Unit (SRCU) was started by the Cluster Coordination Office. The SRCU offers Cluster members three main services areas – Information Services, Materials Repository and Materials Production (Fig. 2).

The goal of the Information Services is to collect and maintain information provided by Cluster members in a continually updated, centralized database. Primarily, this information focuses on which instrumentation Cluster members are willing to share and on what basis. This database has been already implemented within the Cluster IntraNet platform and currently includes more than 100 instruments. Each individual instrument catalogued within the IntraNet instrumentation database can be added to the category of “Shared Resources / Core Facility” or “Collaborative Infrastructures” (Fig. 3).
The SRCU offers users a professional management staff, user guidelines, access policies and a cost recovery model to ensure participating members can continue to meet the needs of the users. It will help Cluster researchers find the most appropriate means of managing their shared resources, allowing for cutting edge research and outstanding, reliable results in a time and cost-efficient manner.

Additionally, Cluster members can also use the SRCU for the “Recovery Storage” of materials. Research groups also have the possibility of depositing materials at the Core Unit to store as “back-up” samples without making them publicly available.

An extra service available on demand from the SRCU is the processing of materials requests from external, non-Cluster researchers. When a Cluster member receives requests from external researchers for any materials already deposited to the repository (on a “shared” or “recovery” basis), these requests can simply be redirected to the SRCU. The SRCU can take care of preparing and sending the requested materials all over the world, including the packaging and all required documentation, such as quality controls and the MTA. The principle investigator will only need to sign the MTA. This service will allow Cluster members to save time and resources which they can instead devote to research.

In addition, the SRCU will also offer production of high quality research materials derived from its available materials collection including:

- Cloning genes of interest from the plasmids provided or from ORFs/cDNA libraries into a variety of expression vectors and tags
- Production of viruses using standard systems (e.g. lentiviruses, retroviruses, adenovirus)
- Generation of stably transfected cell lines at the polyclonal or monoclonal stage

Finally, the Shared Resources Core Unit plans to organize teaching and training (technical seminars, lectures, lab rotations etc.) for all the techniques and methods available at the SRCU. This training will be available for any Cluster members and associated scientists (students, Postdocs, TAs etc.) who would like to learn new techniques and improve their skills. Certification of skills will also be available on request.

by A Kubarenko and E Endl

- Testing for residual virus after transduction in order to return cell lines to S1 cell culture with the corresponding documentation.
Interview with Prof. Regina C. Betz

Hair loss in translation

ImmunoSensation: Prof Betz, could you tell us a bit about your research and its connection to the Cluster?

Regina Betz: I am geneticist and one of my current focuses is on alopecia areata (AA), or patchy hair loss. The disease is auto-immune-triggered: its pathology is connected to a misguided immune response against the hair follicle that leads to hair loss with sudden onset and a recurrent course. However, there are still many unanswered questions about the pathogenesis of the disease. For example, we know that genes that are involved in T cell regulation, Treg maintenance and immune modulation play an important role but still do not know exactly how the disease is triggered and what antigens are targeted. Thus, discovering susceptibility loci is particularly important to understanding the disease. Connecting susceptibility genes to immunopathomechanisms requires a multi-disciplinary approach, and this fits well with the scope of the Cluster. Additionally, my lab also does research on a variety of monogenic skin diseases which are of particular interest to better understand the biology of the skin and hair growth.

ImmunoSensation: What made you interested in genetics and in alopecia areata?

Regina Betz: I’ve been interested in genes and chromosomes ever since I heard my first lecture on the subject at university. We had an excellent professor, Prof. Zang in Homburg. He just managed to transport his enthusiasm for the subject. After that, I knew that I wanted to do a lab rotation in genetics, and I was able to find a group at the Karolinska Institute in Stockholm. I was in such good hands there as a medical student that I went...
back to do more research with them during my practical year, and I even returned again as a research scientist.

My interest in AA, however, first came several years later while I was working as postdoc for Prof. Nöthen in Antwerp, Belgium. I had previously concentrated on monogenic hair loss disorders and wanted to broaden my “genetic horizons”. As Prof. Nöthen is an expert in genetically complex diseases, we thought AA was a particularly interesting area to do research on. And the better we understand the pathomechanism behind this autoimmune-mediated disease, the more interesting it has become.

**ImmunoSensation:**
Your recent work demonstrates a strong association between HLA-DR variants and AA. Are there HLA or other genetic associations between AA and other autoimmune diseases? Has this helped your understanding of the disease?

**Regina Betz:**
At the HLA-level and also for several other genes involved in autoimmune processes, there is a very interesting overlap of AA with other autoimmune diseases on a genetic level, for example rheumatoid arthritis (RA), Crohn’s disease and multiple sclerosis. However, these connections do not really explain everything yet. Even though an AA patient may display the same genetic variants as seen in RA, it doesn’t mean that he will develop the disease. Common comorbidities in AA patients are atopic dermatitis, asthma and thyroid disorders. There seems to be more to the picture that we just do not know yet, so there is a lot of work that still has to be done. Nonetheless, discovering these associations has still been very important for developing therapeutic approaches for AA treatment. For example, the association with CTLA4 has led to clinical trials of Abatacept for treatment of AA. Abatacept is a fusion protein containing the extracellular domain of CTLA4 and acts as a decoy receptor for CD80 and CD82, inhibiting T cell activation. This therapy is an important component in the treatment of therapy-resistant rheumatoid arthritis, and we hope that it will produce similarly promising results for AA patients.

**ImmunoSensation:**
You spent quite a bit of time abroad in less typical research destinations, meaning not the US or UK. What made you decide to go to Sweden and Belgium? What did you gain from your experience there?

**Regina Betz:**
When I was at med school, I knew I wanted to do research on genetics and to go to Sweden. So I did both, and I found a fantastic lab at the Department of Medical Genetics in Stockholm. As a post-doc, I went to Antwerp, Belgium because my PI, Markus Nöthen, accepted the position of head of the Center of Medical Genetics there. In both cases, it gave me a chance to learn a new language, both Swedish and Flemish, to gain experiences in diverse labs and to have a great time abroad. I would recommend going abroad to any researcher.

**ImmunoSensation:**
As you began your group in Bonn, you were the head of an Emmy-Noether Research Group. Now you have a Heisenberg Professorship. The DFG has clearly played an important role in your scientific career. Could you briefly comment on the programs you’ve participated in and how they helped you develop as a scientist?

**Regina Betz:**
The Emmy-Noether program was a very important step in my scientific career. It allowed me to start my own group and offered lots of support on the way: networking with other researchers, career planning, and soft skills courses. The exchange with other young scientists from other fields was also very helpful.

The Heisenberg Professorship has also been immensely important. Being in a tenure-track program has given me a long-term perspective in Bonn, and has contributed to my role as a faculty member. Another DFG institution that I have participated in is ImmunoSensation of course. Being a Cluster member has allowed me to collaborate with new partners in new fields. And I have two fantastic PhD students who are both funded by Cluster IITB scholarships.

**ImmunoSensation:**
Well, collaborating with a geneticist is definitely helpful for us immunologists, but have we really been able to help you with your research?

**Regina Betz:**
Of course, we discover new genetic associations for diseases, but these associations have to be further explored on a functional level. Geneticists are used to collaborating since we work in consortia. Since alopecia areata belongs to the autoimmune-mediated diseases, it is very helpful to collaborate with other Cluster researchers. In addition, some collaborations are both technical and immunological. For example, I am collaborating with Veit Hornung in a project using CRISPR/Cas9 in a skin cell line.

**ImmunoSensation:**
One last question, what advice would you give to aspiring young scientists?

**Regina Betz:**
Do what you enjoy and do it well. If you put all of your energy and enthusiasm into your goals, it is amazing what you can accomplish.

 interviewed by Cluster Coordination Office
Interview with PD Dr. Dagmar Wachten

New applications for optogenetics

ImmunoSensation: What is the main focus of your research and how is your work connected to the Cluster?

Dagmar Wachten: At the moment, my group is working on heart as well as sperm physiology. We are looking at congenital heart defects by introducing mutations found in human patients into the mouse system. We focus on CRELD1 in particular, which we have identified as a key regulator of heart development. My research on sperm physiology focuses on the questions: (1) how sperm swim and (2) what can go wrong during their development that keeps them from ultimately finding the egg. To do this, we have different mouse models that are infertile, and we try to understand at a molecular level what is going on. Our technical focus is on molecular imaging, and this is where the Cluster comes into play. We are working quite intensely on the development of new optogenetic tools and new genetically-encoded biosensors to study second messenger-mediated signaling pathways in different cell types, including immune cells. This imaging technique is what I brought into the Cluster, and it allows the study of a variety of signaling pathways in diverse cell types.

ImmunoSensation: Is optogenetics already used in the clinic? Could you imagine that new clinical applications or drugs could be developed using this tool?

Dagmar Wachten: It is known that cyclic AMP is really important for sperm function, and sperm that lack cyclic AMP synthesis are not able to swim. We tried to rescue this defect through the use of an optogenetic, or “light-activated”, tool. We generated a transgenic mouse model that expresses a light-activated enzyme that produces cyclic AMP in sperm upon illumination with blue light. In the dark, the sperm are swimming normally. However, when stimulated with blue light, their flagellar beat increases and they start to speed up. Because we succeeded in controlling sperm motility by light, we went one step further and crossed our transgenic mice with mice that lack cyclic AMP synthesis in sperm. These sperm are completely immotile in the dark. However, when we shine blue light on them, they become active again because the enzyme is activated by light, which leads to the production of cyclic AMP. With cyclic AMP available, the sperm can swim again and thereby regain the potential to fertilize the egg. So, just by shining blue light on the sperm, we can make them fertile again.

ImmunoSensation: Cyclic AMP has also a role in inflammasome activation. Do you also use it to study this process?

Dagmar Wachten: Yes, that’s our goal now. We are working together with the group of Eicke Latz to introduce our new optogenetic tools and genetically-encoded biosensors into immune cells. In particular, we are looking at the role of cyclic AMP and calcium in cells where the inflammasome plays an important role.

ImmunoSensation: You were involved in the Cluster application, so you have been part of it from the beginning. What did you expect from the Cluster and has it met your expectations?

Dagmar Wachten: It was really exciting at the beginning to get to know all these big shots in the field of immunology, especially because I had not been in contact with immunology before. It was a great chance to get insight into this field. The greatest advantage of being part of the Cluster was establishing new collaborations. I started projects for example with Michael Hoch and Eicke Latz, who are my main collaborators now. The collaboration with Michael Hoch already resulted in a really great publication last year (see also Research Area C). With Eicke Latz, I started new projects that have opened a completely new field of research for both of us. This means that we had to split the projects between the labs to cover all of it, but it works very nicely.
ImmunoSensation: One goal of the Excellence Initiatives was to promote interdisciplinary work and to establish new branches of research, so this seems to be a good example.

Dagmar Wachten: Yes, it has all worked out well, especially the technical exchange. For example, I use the mouse facility and a lot of equipment at the Venusberg. This is really great since we do not have everything in house. I also have access to the transgenic service in the LIMES, and they use our high-resolution microscope in return.

ImmunoSensation: Would you say this technical exchange works better between the institutions than before the Cluster started?

Dagmar Wachten: I would say it does because we have been able to offer and use technical services and equipment free of charge ever since they became part of the technical platforms. There might have been possibilities before on collaborative basis, as well, but that makes things more complicated. What makes it a lot easier now, especially for a young group leader like me, is that you know the people from the Cluster, and you do not hesitate to ask anymore. The network and interaction between the researchers has become much better since we began the Cluster.

ImmunoSensation: Do you have suggestions how to further improve Cluster networking and interactions?

Dagmar Wachten: Collaborations have to develop out of the research itself, but I think it is a good idea to have these technical platforms and a regular exchange between them. The “Handbook of Shared Resources” for example is a very good way to inform members about technical opportunities. I think it has become very important to share equipment and technical knowledge because some instruments are so incredibly expensive that you could hardly afford to buy one just for yourself. It might be a good idea to organize “tech meetings” on a regular bases, like the BFB (Bonn Forum of Biomedicine) does, to further improve interaction.

ImmunoSensation: I would also like to bring up one completely different topic. You mentioned once that you participated in the MeTra Program of the University of Bonn, which is also supported by the Cluster. Every year, we can give a couple of young researchers the opportunity to participate in MeTra. What was your impression of the program? Did it help you personally?

Dagmar Wachten: Absolutely. It did. First of all, I think it is very important to meet people that are in the same situation you are, especially if you are on the way to becoming an independent investigator and if you want to become a professor. Our group consisted of female scientists that all wanted to become a professor at some point, and the workshops that were organized were specifically designed for this purpose. It helped to strengthen our own profiles, boost our self-confidence, and encourage us to get out on the job market and apply for positions. It was really helpful, and Ms. Pottek, the organizer, gave us a lot of help with finding the right mentor and dealing with whatever problems came up along the way. The program also helped me to get financial assistance from the “Gleichstellungsbüro” (Office of Equal Opportunity) since I applied for the Maria von Linden program for my habilitation phase. They paid for two student assistants for one year. This was very helpful since I had lots of mouse work, and they took care of genotyping. This takes normally a lot of time without directly benefitting your research. I have now become a mentor in the program myself. I can really highly recommend it, and I have already motivated one of my PhD students to take part since participation is offered through the Cluster.

interviewed by Cluster Coordination Office
Interview with Dr. Annett Halle

Neuroinflammation in Alzheimer’s disease progression

Dr. Annett Halle

is affiliated at the center of advanced European studies and research (caesar), Bonn, and head of the Max Planck Research Group "Neuroimmunology"

ImmunoSensation:
Dr. Halle, what is the focus of your research?

Annett Halle:
I am interested in how the innate immune system is involved in the pathogenesis of Alzheimer’s disease. In the past years, we have begun to understand that not only peptide aggregation is important for the formation of Alzheimer’s plaques, but also that the immune system plays a pivotal role in their development. As a postdoc in the lab of Doug Golenbock in Worcester [Massachusetts, USA], I investigated how microglia, the macrophages of the brain, react to amyloid peptide. I was able to demonstrate that amyloid peptide activates the inflammasome in vitro. Afterwards, during my specialization in neuropathology in Berlin, I had the opportunity to work with mouse models of Alzheimer’s disease. I have continued this research in Bonn, and, in addition to my research on inflammasome activation, I have begun to work on methods to investigate the function of microglia in vivo. In particular, I would like to understand the interplay between Alzheimer’s disease and microglia function. Understanding and quantifying the functionality of these cells and its consequences for the disease is vital. At the root of these investigations is the question whether these cellular processes are reversible and, if so, whether their reversal would have positive or negative consequences for the progression of the illness.

ImmunoSensation:
Does that mean that you are developing a method to directly test the functional capability of the cells?

Annett Halle:
Exactly! We are currently using two-photon microscopy to directly investigate microglial motility. This can change radically in the course of the disease, and we are now working on analyzing these changes at a transcriptional level. We are especially interested in local changes and would ultimately like to investigate these at a single-cell level. We are developing this approach in collaboration with other Cluster members, Joachim Schulze and Marc Beyer.

ImmunoSensation:
What role have other researchers such as Douglas Golenbock played in your career development? Would you say that you had a mentor who particularly encouraged and inspired you?

Annett Halle:
In Doug’s lab, the atmosphere was great and there were many opportunities to pursue your research. I enjoyed the international atmosphere and the interaction between researchers. Doug is also a very generous and supportive supervisor and he gave us the space to develop our own ideas. However, when my project had progressed to a certain point, and I needed the support, he was also very actively involved.

My colleagues were also a great source of inspiration. Worcester is where I met Eicke Latz, Veit Hornung and Andrea Blasser. Although Doug greatly supported my research, I cannot say that there was one mentor who inspired me, but, rather, that I have been influenced by the many excellent scientists I have worked with.

ImmunoSensation:
You came to Bonn as the Cluster was just beginning. What influence did that have on your research?

Annett Halle:
I thought it was great to have the opportunity to meet all of these immunologists here in Bonn at once. It was also very interesting to see how the concept of the Cluster arose and developed. It was fun to be involved.

In fact, the Cluster was one of the reasons that I came to Bonn in the first place. I could watch how the Cluster was planned and then developed. The atmosphere here was and is very dynamic. And there were also several people here who I knew I enjoyed working with. From the very beginning, I also knew that there were other scientists I could collaborate with, such as Michael Heneka, whose work has a close thematic link to mine.

ImmunoSensation:
Just as you were establishing yourself as a scientist, you also decided to have two children. There are different programs that endeavor to support women in science so that they can successfully combine career and family. Did you receive enough support? Do these programs help in practice as well as in theory?

Annett Halle:
These programs cannot help with everything. There are some problems that just cannot be avoided, such as the fact that you simply have less time when you have a family than you did before. Having said that, I have received a lot of very helpful support from the Cluster and from caesar. Caesar has in-house daycare which both of my children have attended.

In general, I also have to say that my colleagues, among them Benjamin Kaupp, the director at caesar, have been very supportive and understanding, which has been very positive for me. It is also good to see that these programs have become an integral part of the Cluster and other institutions.

ImmunoSensation:
As a young PI, you are still in the process of establishing your group. Has it been difficult for you to find good students or fill positions? How do you find applicants?

Annett Halle:
Fortunately, it hasn’t been that difficult so far. Neurodegeneration and, specifically, the connection between inflammation and...
Jonathan Schmid-Burgk is a PhD student in the Institute of Molecular Medicine in the group of Prof. Veit Hornung.

Interview with Jonathan Schmid-Burgk

Expanding the genomic toolbox

Jonathan Schmid-Burgk:
We want to identify genetic components of the innate immune system to find out how information is processed in immune cells. We are focusing on the information processed within single cells, or cell intrinsic immunity. This means that the pathways that we study can be characterized on a genetic level within a cell. For this purpose, we need to manipulate a lot of different genes, which is why we first had to set up a high-throughput genome editing pipeline.

ImmunoSensation:
During your PhD you developed a semi-automated high-throughput assembly platform for TALE nuclease genes and CRISPR gRNA plasmids. If you think back to your start as a PhD Student, what are the most important technical developments since then?

Jonathan Schmid-Burgk:
I started in 2011. At that time it was really difficult to manipulate the genome of human cells and immunological research focused mainly on mouse genetics. Manipulating genes in human cell lines was already possible, theoretically speaking, since zinc finger nucleases had already been identified, but practically it was difficult to produce these nucleases. Quite soon after TALE nucleases were described in the literature for the first time, Tobias Schmidt and I started to work with this new tool and improved it for our own purposes to use it at a high throughput scale. About two years later the CRISPR-Cas9 system was described. The greatest advantage of the CRISPR/Cas9 system is that we can manipulate genes very easily and efficiently. It is quite easy to make plasmids allowing the manipulation of human genes. This has enabled us to

Alzheimer’s disease seem to be themes of great interest to young scientists. I have advertised open positions using standard channels and have received hundreds of applications. I also found a new PhD student through the IITB program. It was very helpful that the IITB had already pre-selected the best candidates for their pool. Otherwise, going through hundreds of applications can be quite time-consuming. I was able to interview several candidates that had made it through the first round and was able to quickly find a very good PhD candidate for my lab.

ImmunoSensation: Since you have a student from the IITB program, could you comment on what you see as the advantages of the program? And what could we improve?

Annett Halle:
My student has already taken part in technical training via the IITB, and she could put her new knowledge directly to use. I think the program is great for the students, in particular because students can pick the courses that are relevant for their research and are not obliged just to fill up their study plans. It is also good that the IITB students have a chance to get to know each other – especially for students here at caesar, since we are a bit isolated, geographically speaking, from the other institutes.

What I would like to see added to the program is a “thesis committee”, in order to better structure the PhD research projects and to bring in new ideas.

Interviewed by
Cluster Coordination Office
knock out genes at high throughput and to study their function in immune cells. I think it is a groundbreaking development with a lot of implications not only for research but also for medicine, which has also spurred a renewed ethical debate about genome manipulation in general.

ImmunoSensation: In what ways does it change the ethical debate?

Jonathan Schmid-Burgk: Cas9 genome editing is so efficient that it could well be used as a therapeutic approach to manipulate genes in somatic cells of human beings. But even beyond that, in April (2015) a paper was published in which genetic manipulation of human embryos was described for the first time.

Of course, several people in the field had already anticipated this development for some time, but manipulating the germ line of humanity would of course be something with serious ethical implications. It is a step that can never be reversed. Until recently, germline manipulation had been discussed as more of a theoretical problem, but since we now might have an efficient tool at hand, it brings the debate to another level. It is now up to the public to discuss the implications, and recent articles in ‘Die Zeit’ and ‘Der Spiegel’ reflect this happening.

ImmunoSensation: Like with other techniques, there are still risks and side effects. There has been off-target effects described where the Cas9 complex binds to homologous sequences and induces double strand breaks in other genes. Is this problem part of the current debate, or are there already technical solutions for this problem?

Jonathan Schmid-Burgk: There has been a lot of research on off-target effects in the last couple of years. We had a finding, which was in fact published faster by another group, that Cas9 targets with higher specificity when shorter guide RNAs are used: Normally, the sequence that determines where Cas9 will cleave is about 20 bases long, but if you shorten it to 18 bases, cleavage gets much more specific. Besides that, other groups have developed a mutated form of Cas9 that does not completely cleave the genome but only nicks it. Since it only nicks one strand, you have to use two guide RNAs that bind close to each other in the genome to generate a double strand brake, which makes the process much more specific.

ImmunoSensation: I guess it was quite exciting to work on this new technique with all the new potential?

Jonathan Schmid-Burgk: It was indeed quite exciting. Every week, new high impact papers come out with important new findings. On the other hand, that meant a lot of competition and pressure. For example, we invested a lot of time in polycrificial CRISPR screens in order to identify new genes that are involved in certain immune pathways – an unbiased approach. But in the meantime, four or five CRISPR screens have already been published, while ours is still ongoing. But it is really great to work on something when you know that, as soon as it works, it could be used by a lot of people. That is a good feeling.

ImmunoSensation: I suppose that was also one of the reasons why the platform for genomic engineering was started: It allows the sharing of this technical knowledge as well as collaborations with other researchers?

Jonathan Schmid-Burgk: That is correct, and it is also very worthwhile. I think by collaborating with other people from slightly different fields of biology, one gains a lot of experience, which in turn helps to further improve the methods for your own research.

ImmunoSensation: How important has been the technical equipment that you have had available here in Bonn? You mentioned that there are many other labs working on this topic.

Jonathan Schmid-Burgk: We need state of the art machinery, like pipetting robots and a deep sequencing machine for example. In theory it would have been possible to do the deep sequencing at an external core facility, but having our own sequencer gave us much more flexibility and direct access to the raw data, which was quite important for us.

ImmunoSensation: What do you think is the influence of the Cluster on your work? Do you think it helped you to get more insights into other fields of research?

Jonathan Schmid-Burgk: Oh yes, the Science Days, for example, were always very helpful for me to get an overview what is happening scientifically in Bonn. Thinking back to the time when the Cluster was not there, there was much less interaction, and I knew much less about the work of other groups. I think this is especially important if we want to compete with universities in the United States or with institutions like the Max Planck institutes. Their groups often work together quite closely, and I think it is really good to do it similar here in Bonn.

ImmunoSensation: You are signed up as an IITB student. Do you find the time to participate in the program and do you benefit from it?

Jonathan Schmid-Burgk: I had the pleasure of visiting the R course given by Rick Scavetta. It was really good for me, since programming has become most important for our work and I did not use R before. I think the Cluster offers great opportunities, and it is worthwhile to participate.

ImmunoSensation: As you mentioned, within your work you also developed bioinformatics tools for data analysis. Do you see it as an advantage or disadvantage that, due to collaborations, people have used them even before they were developed to a final state?

Jonathan Schmid-Burgk: I see it as an advantage every time our open source software get used and tested. There is a constant development going on, especially with the software we developed for high-throughput genome editing like OutKnocker.org. We are happy to share these tools and we can improve them based on the comments we get. The human genome project was finished in 2003, which revealed that our genome contains about 20,000 genes. I think one of the greatest challenges of our time is to assign function to these genes and to understand what every single gene product does. We now have good tools to answer these questions.

Interviewed by Cluster Coordination Office
Interview with Lucia Torres Fernandez

From basic research to tumor immunotherapy

Lucia Torres Fernandez is a PhD student in the group of Prof. Waldemar Kolanus. After finishing her diploma in Biotechnology at the Polytechnic University of Valencia (Spain), she completed a Master of Life and Medical Sciences at the LIMES Institute and now has a PhD fellowship from the IITB program.

ImmunoSensation: What attracted you to Bonn?

Lucia Torres Fernandez: I had always been interested in learning German. When I finished my studies in Spain, I decided to continue my studies in Germany to combine this interest with my further education. Germany is a country with a lot of opportunities for researchers, and therefore, I had many options. I first found out about the Master of Life and Medical Sciences offered in Bonn on the DAAD webpage. I could have done a PhD directly, since I had a diploma from Spain, but I was afraid of choosing something very specific too soon without having a broader understanding of biomedicine. That is why I decided to join the master’s program at the LIMES. For my master’s thesis I joined the lab of Professor Waldemar Kolanus, and I decided to stay for my PhD, because I really loved my project and I was very interested in continuing with this research topic.

In addition, I also enjoyed the atmosphere here in the LIMES very much. So I started my PhD in November 2014, directly after I finished my master thesis. I must admit, that when I came to Bonn, it took some time for me to settle and adapt to my new life. At the beginning it was quite hard for me to leave my family and friends in Spain and get used to a different culture and the people here, but now I have awesome friends (most of them scientists as well) and enjoy life here very much. I feel home now.

ImmunoSensation: You seem to be very enthusiastic about your project. What topic are you working on?

Lucia Torres Fernandez: I am working on a novel and very versatile stem cell regulator. On one hand, it is an RNA binding protein, which acts as microRNA repressor, but on the other hand, it has also E3 ligase functions. This factor is expressed in early stages of mammalian embryonic development but not in the adult organism – with the exception of adult stem and progenitor cells. It therefore plays an important role in embryonic development and, like many other pluripotency factors, also in tumorigenesis, since its expression is reactivated in many cancer types. It might regulate immunological functions as well, since previous studies in our lab performed by Dr. Karin Schneider show that many immunologically relevant genes are altered at transcriptional level in a conditional skin knockout mouse. The aim of my work so far is to investigate the molecular mechanisms underlying the RNA repressor module in order to understand its role in tumorigenesis and immunity.

ImmunoSensation: How was it shown that the protein is involved in certain immune functions?

Lucia Torres Fernandez: When my colleague started investigating its functions, there was no clear link with the immune system, other that some proteins containing “TRIM” domains are induced by interferon and have antimicrobial activities. My colleague had a few interesting findings in the conditional knockout mouse, and that is how we gained a new perspective of this protein in immunological contexts. On the other hand, it is known that our protein can somehow act as an oncogene, having important roles in tumor formation and progression. During these processes, the immune system also plays an important role in the fight against tumor cells. However, oncogenic factors often have the ability to “trick” immune cells to keep them inactive, so that the immune system does not fight the tumor. Although I am not working on this - or at least not yet - I think it is very interesting to understand the implications of immunity in cancer development. I believe that tumor immunotherapy is the real future of cancer treatment, so that therapies like chemotherapy or radiotherapy are going to be replaced by new treatments that help the immune system to specifically fight the tumor cells in a more directed and less aggressive manner.

ImmunoSensation: You joined the IITB program. What do you think are the advantages of participating in the program?

Lucia Torres Fernandez: I think it is a big advantage for young scientists to be part of such a network where you can find people making similar experiences and having similar concerns. Other big advantages of the IITB program are the courses and workshops offered to the students in order to strengthen their skills. We scientists have to evolve together with science, so keep on learning constantly and gain new competences.

ImmunoSensation: Do you already have a plan what you want to do after your PhD? Would you like to stay in basic research or would a position in industry interest you?

Lucia Torres Fernandez: When I finish my PhD, I would first like to take some time to travel and then I would like to go for a postdoc, maybe in Spain to be back with my family. I have no interest so far in moving to industry, and I really enjoy being a researcher, so I think I will remain in academia. It would be nice to end up as a group leader at a good institute and to focus on different but related projects to gain knowledge about certain topic in a collaborative manner with my colleagues.

Interviewed by Cluster Coordination Office
Interview with Katarzyna Jobin

Conducting research on a ‘very salty organ’

Katarzyna Jobin started her PhD at the Institute for Experimental Immunology in the group of Prof. Kurts in March last year as a part of the ImmunoSensation’s graduate program. She completed her studies in Biology at the Jagiellonian University in Krakow, Poland and afterwards spent two and a half years at the University of Virginia.

Elisabeth Mettke: Can you tell us in one sentence, what your PhD project is about?

Katarzyna Jobin: It’s about the influence of sodium chloride on immune responses in kidney disease. Since the kidney is a “very salty organ”, it is quite interesting to see how the immune cells deal with it and how they are affected.

Elisabeth Mettke: Where did you work before joining the ImmunoSensation Cluster?

Katarzyna Jobin: I worked with Dr. Okusa and then Dr. Kinsey, both from the University of Virginia, USA. Their labs were studying immune responses during acute kidney injury. When I came there I was more interested in immunology than in nephrology, but these guys also made me fascinated with the kidney.

Elisabeth Mettke: What made you come to Bonn and what do you like about it?

Katarzyna Jobin: I really liked my previous lab, but, on the one hand, I was missing Europe – the architecture, the food, the culture – and, on the other hand, I wanted to move on. I felt that I needed to broaden my experience. I heard a talk by Prof. Christian Kurts, my current PI, at a conference, and I liked his presentation. Also, when I was thinking about coming back to Europe for my PhD, Prof. Christian Kurts just published a study about the dependence of kidney DCs on the fraktalkine receptor, which caught my attention once again. Last but not least, Prof. Kurts is quite a luminary in the field of nephrology, so I gave it a try, and here I am. Coming to the second part of the question: I like the broad spectrum of opportunities given me both by the Cluster and by my PI. Sometimes I feel like if I have an idea, but I don’t know how to do it, there is always a person who can help me, and there are all the resources, lab equipment and reagents, that I need. So I like the network of people and resources. What’s also nice: there are plenty of PhD students, so it’s easy to socialize and support each other. Then, Bonn is such a beautiful city, and there is plenty of good cheese, chocolate, and wine. It makes me happy whenever I think about it!

Elisabeth Mettke: What do you do when you are not in the lab?

Katarzyna Jobin: I try to relax as much as possible. I spend a lot of time with my husband. We cook a lot and, as simple as it may sound, talk a lot, and we like walking, especially along the Rhine. I also find reading quite relaxing. Being away from home, I spend quite a bit of time on Skype, as well. I also watch my favorite TV series. From time to time I try to create something pretty and paint for example. And of course I am learning German. I guess these are pretty normal things, but they make me happy.

Elisabeth Mettke: Where do you see yourself in twenty years? Do you already have plans for the future?

Katarzyna Jobin: It is very hard to answer this question, but I will try my best. I would like to stay in science as long as I can keep enjoying it. Otherwise, I would not do a good job anyway. I am planning to stay in Bonn for the next few years. Then I will see whether there will be a good opportunity to stay here for some time. However, I could also imagine going back to Poland, US or other countries. I wouldn’t mind to work for a biological company or for a research journal. Maybe I can even create my own company in Poland. You see I have some ideas, but I don’t have a concrete plan yet, I like keeping my mind open. For sure, I can say that I would like my job to be creative and science definitely is creative!

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LiMES
Life & Medical Sciences Institute
Cluster Coordination Report

44th Annual Meeting of the DGfI
2nd Cluster Science Days
Honorary Doctorate Degree
9th Night of Science
Summer Retreat
ImmunoSensation: Part of the Excellence Initiative Network
International Immunology Training Program Bonn (IITB)
Family Support & Gender Equality
Public Relations
Cluster Seminars and Seminars of Cluster Cooperation Partners 2014
Cluster Meetings 2014

Events

The Cluster Coordination Office is in charge of the implementation and financial administration of Cluster events, the coordination of the graduate program, gender and family support and public relations. Within this section, we would like to give an overview of the organized events for students and Cluster scientists.

44th Annual Meeting of the DGfI
September 17-20, 2014

The Annual Meeting of the German Society for Immunology (DGfI) with more than 900 participants and 730 submitted abstracts is one of the most important conferences for immunology in Europe. We are very pleased that two Cluster members, Prof. Gunther Hartmann and Prof. Christian Kurts, had the honor to chair this year’s annual conference.

In his opening remarks, Prof. Hartmann underlined that “The DGfI meetings gather every year a national and international delegation of renowned scientists, students and professionals from academia, industry and government organizations to present and discuss current topics of basic and translation-al immunological research in plenary sessions, symposia and workshops.” Hosting this conference in Bonn affirms the importance of Bonn as a hotbed for immunological research. The venue was the World Conference Center, in the quarter of the former German Government (“Regierungsviertel”), beautifully situated on the river Rhine.

The Cluster supported the meeting financially but also to a great extent scientifically, since multiple Cluster researchers attended the meeting and gave poster and oral presentations. It was a special highlight for the Cluster, that one session was dedicated to the research focuses within ImmunoSensation. The conference was a great opportunity for the Cluster to increase its national and international visibility what was also promoted by the information participants got at the ImmunoSensation information booth and the ImmunoSensation “immunology quiz” that took place during the meeting.
To support scientific exchange within the Cluster, the second ImmunoSensation Science Days took place on November 3 and 4 in the Biomedical Center at the University Hospital Bonn. Due to the positive feedback and high number of participating scientists in 2013, it was decided to organize it as two instead of one-day event. Like in 2013 a number of young scientist, mainly PhD students and young postdocs got the opportunity to present their data. Altogether, 114 abstracts were submitted, 21 of which were selected for short oral presentations. This year there were also poster sessions so that all students had the opportunity to present and discuss their work.

The first day of the meeting was dedicated to giving a general overview about the five different Research Areas and most of the Cluster associated groups. These presentations were held by the group leaders themselves and allowed participants to have an overview of both the general scientific scope and the scientific development of the Cluster over the last two years.

Highlights of the first day were the keynote lectures from Stephen Michael Cohen on the use of genetic models in cancer gene discovery, from Charles Dinarello on Interleukin-37 and from Tony Wyss-Coray with his presentation about “Systemic factors as modulators of neuroinflammation”.

The Cluster had the great honor that the members of its Scientific Advisory Board (SAB) of the Cluster joined the meeting, including Stephen Michael Cohen, Charles Dinarello, Tony Wyss-Coray, Douglas T Golenbock, Hidde Ploegh and Hermann Wagner. It was the first time that members of the board visited the Cluster, and the combination of talks giving a general overview of the Cluster work and the presentation of scientific highlights by the young scientists gave our invited guests the opportunity to get a broad overview of the Cluster’s work.

The SAB also met with the Cluster Steering Committee to give their initial feedback on their impressions and advice on the further development of the Cluster. In addition, Cluster scientists had the great opportunity to meet these renowned scientists during their visit. Especially for the students, it was an extraordinary chance to discuss their work during the poster sessions and “meet-the-expert” lunch session.
Prizes were awarded for the best talks and posters: four presentation prizes were available for young scientists, one for the best talk of junior group leaders and ten poster prizes.

**Prize winners: Best Talks**

The four prizes for the best talks from PhD students and young postdocs (400 €), which were selected from a jury consisting of PhD students and group leaders, were given to:

**Thomas Ebert** is a PhD student in Prof. Veit Hornung’s laboratory at the Institute for Molecular Medicine. He presented a shared project on caspase-4 mediated non-canonical inflammasome activation in human myeloid cells. 

He and his colleagues Jonathan Schmid-Burgk, Moritz M. Gaidt and Tobias Schmidt were able to show that the human monocytic cell line THP1 activates the inflammasome in response to cytosolic LPS in a TLR4-independent fashion. This response is mediated by caspase-4 and accompanied by caspase-1 activation, pyroptosis and IL-1β maturation. In addition to caspase-4, efficient IL-1β conversion upon intracellular LPS delivery relies on potassium efflux, NLRP3, ASC, and caspase-1, indicating that although caspase-4 activation alone is sufficient to induce pyroptosis, this process depends on the NLRP3 inflammasome activation to drive IL-1β maturation. This work was published in the European Journal of Immunology (PMID: 26174085, “Caspase-4 mediates non-canonical activation of the NLRP3 inflammasome in human myeloid cells”, Eur. J. Immunol. 2015).

**Anna Maria Herzner** is a PostDoc in Prof. Gunther Hartmann’s laboratory, in the group of Dr. Martin Schlee at the Institute of Clinical Chemistry and Clinical Pharmacology. She presented her work on the recognition of single-stranded DNA by the interferon-inducing innate immune receptor cGAS, which is important for the detection of retroviruses such as HIV-1. Anna-Maria was able to show that, in contrast to double-stranded DNA recognition, single-stranded DNA recognition is sequence dependent. She demonstrated that, within single-stranded DNA, short, base-paired stretches induce an interferon response only if there were guanosines among the flanking unpaired bases. Furthermore, otherwise inert, extremely short DNA duplexes (≤ 20 bp) were rendered highly stimulatory if flanked by unpaired guanosines. Thus, by the work of her and her colleagues, a novel pathogen associated molecular pattern (PAMP) was discovered. Their work is about to be published in the Journal of Immunology.

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2nd Cluster Science Days
November 03/04, 2014

Vera Jansen is currently a PostDoc in the research group of Dr. Dagmar Wachtten at the Center of Advanced European Studies and Research, caesar. She won the prize for her study about “Optogenetic manipulation of cAMP in the ciliary compartment”. Vera has completed her PhD in December 2014 in the department of Molecular Sensory Systems at the Research Center caesar under the supervision of Prof. U. B. Kaupp. During her thesis, she worked on the optogenetic control of the second messenger cAMP. Optogenetic tools are light-sensitive proteins which are used to manipulate cell function by light. To control the synthesis of cAMP by light in vivo, Vera used the bacterial photoactivated adenylate cyclase bPAC. Due to their high spatial and temporal resolution, optogenetic approaches are especially useful to study cellular signaling in small cellular compartments such as cilia or flagella. Together with Dr. Dagmar Wachtten, who leads a Minerva Research Group at caesar, Vera developed a mouse model, which uses bPAC to manipulate cAMP in sperm flagella (PMID: 25601414, “Controlling fertilization and cAMP signaling in sperm by optogenetics”, Elife, 2015 Jan 20;4). The winner of the prize for the best presentation by a junior group leader (600 €), which was selected and presented by the scientific advisory board, was Dr. Jasper van den Boom (Institute of Clinical Chemistry and Clinical Pharmacology).

Jasper van den Boom is a junior group leader in the lab of Prof. Gunther Hartmann. The project he presented concerned memory NK cell biology. Using the skin-sensitizing compound monobenzone, Jasper established that this substance induces a contact hypersensitivity (CHS) response in immunocompetent mice exclusively mediated by and fully dependent on memory NK cells. Using this memory NK cell-driven monobenzone CHS model, he and his colleagues dissected the cellular induction route of such memory NK cells and established the dependency on the NLRP3 inflammasome for their induction. The study by Jasper and his colleagues is currently under review in Immunity.

Prize winners: Best Posters
The meeting ended with poster presentations, which gave participants a great opportunity to get an overview of the scientific work within the whole Cluster. Ten presenters were awarded for their posters with 250 € prize money by the jury of PhD students and group leaders. The prize winners were announce by Prof. Waldemar Kolanus and Prof. Gunther Hartmann after the last session.

Jessica Becker is a PostDoc under the supervision of Prof. Markus Nöthen at the Institute of Human Genetics. Her study was titled: “An eight amino acid insertion in the cytoplasmic tail and two additional amino acid substitutions in the extracellular domain of HLA-DQ confer risk for idiopathic achalasia”.

Karin Schneider was a PhD student in the group of Prof. Waldemar Kolanus at the LIMES institute. (Karin will complete her PhD in molecular biomedicine in April 2015 under the supervision of Prof. Waldemar Kolanus.) Karin presented her work about a novel stem cell factor and its function in cancer development. Using a skin-specific knockout of the gene of interest, she could show for the first time that it is significantly involved in the progression and formation of tumors. In a squamous cell carcinoma model she found a striking protection of the respective knockout mice to DMBA/TPA-induced skin carcinogenesis. This new factor is important for the control of differentiation and proliferation within the tumor microenvironment and acts as an oncogene. Since the protein is barely expressed in adult tissues, but strongly upregulated in human cancers, it represents a potentially promising future target for cancer treatment.

Picture (l.t.r.) Prof. Gunther Hartmann, Thomas Ebert, Anna Maria Herzner, Karin Schneider, Vera Jansen, Prof. Waldemar Kolanus
On November 22, 2014, Prof. Charles Dinarello from the Division of Infectious Diseases in Aurora (USA) and Radboud-University Nijmegen (Netherlands) received an honorary doctorate degree by the Medical Faculty of the University of Bonn for his achievements in immunology. The Cluster nominated him for this award for his work on inflammatory cytokines. Prof. Dinarello discovered and purified interleukin-1, and this work pioneered our understanding of inflammation since it validated the role of cytokines as mediators of inflammation. His work has also provided the scientific basis for much of the research done within the Cluster, and ImmunoSensation is pleased to see his work recognized by the Medical Faculty and its dean Max Baur with this conferment.

Matthias Brückner is a PhD student under the supervision of Dr. Annett Halle at the Center of Advanced European Studies and Research, caesar. His study was titled: “Microglial dysfunction in Alzheimer’s disease”.

Felix Eppler is a PhD student under the supervision of Prof. Waldemar Kolanus at the Life & Medical Sciences Institute, LIMES. His study was titled: “Dynamin 2 is essential for integrin-clustering and regulates Rap1-activation in lymphocyte adhesion”.

Beate Henrichfreise is a Junior group leader working together with Prof. Hans-Georg Sahil at the Institute of Medical Microbiology, Immunology and Parasitology. Her study was titled: “Amyloid as a target enzyme of penicillin with dual activity in the intracellular pathogen Chlamydia pneumoniae”.

Patricia Korir is a PhD student under the supervision of Dr. Beatrix Schumak at the Institute of Medical Microbiology, Immunology and Parasitology. Her study was titled: “Macrophage-specific type I interferon signaling is involved in the immunopathology of experimental cerebral malaria”.

Paul Kern is a PhD student under the supervision of Prof. Michael Hoch at the Life & Medical Sciences Institute, LIMES. His study was titled: “Cred2 - a regulator of the unfolded protein response”.

Friederike Opitz is a PhD student under the supervision of Dr. Heike Weighardt at the Life & Medical Sciences Institute, LIMES. Her study was titled: “Analysis of the Interplay Between the Innate Immune System and Environmentally Induced Aging”.

Tobias Schmidt is a PhD student under the supervision of Prof. Veit Hornung at the Institute of Molecular Medicine. His study was titled: “Synthesis of an arrayed sgRNA library targeting the human genome”.

Kathrin Schönberg is a PhD student under the supervision of Prof. Peter Brossart at the Department of Internal Medicine III. Her study was titled: “JAK inhibition substantially affects NK cell biology in vitro and in vivo”.

Salvador Vento is a PhD student under the supervision of Prof. Natalio Garbi at the Institute of Experimental Immunology. His study was titled: “Migration of effector CTLs into the BAS during acute influenza infection is mediated by CXCR3”.

On November 22, 2014, Prof. Charles Dinarello from the Division of Infectious Diseases in Aurora (USA) and Radboud-University Nijmegen (Netherlands) received an honorary doctorate degree by the Medical Faculty of the University of Bonn for his achievements in immunology. The Cluster nominated him for this award for his work on inflammatory cytokines. Prof. Dinarello discovered and purified interleukin-1, and this work pioneered our understanding of inflammation since it validated the role of cytokines as mediators of inflammation. His work has also provided the scientific basis for much of the research done within the Cluster, and ImmunoSensation is pleased to see his work recognized by the Medical Faculty and its dean Max Baur with this conferment.
The “Night of Science”, or Wissenschaftsnacht, is a biannual event held by the University and City of Bonn in conjunction with the leading scientific and academic institutions in the greater area, i.e. caesar, German Aerospace Center, Frauenhofer Institutes, Max Planck Institutes and the local Excellence Initiatives. This event gives researchers the opportunity to present their work to interested members of the public in an interactive format, and it provides the public with the chance to learn about current questions and new advances in scientific research.

The “Ninth Night” focused on “Digital Society”, and took place at several venues in downtown Bonn. ImmunoSensation had a well-frequented booth in the “Tent of Science”, Wissenschaftszelt, at the Münsterplatz. In keeping with the theme of the event, we chose to present how advances in microscopy have assisted immunological research, with a particular focus on the role of crystalline substances in inflammation. We found this topic particularly suitable because it is one in which microscopy has played an important role and Cluster scientists have participated in pioneering research. Another reason was its particular relevance for the treatment of many widespread and debilitating illnesses.

**Why crystalline material induces inflammation**

Inappropriate immune responses to crystalline material are associated with a variety of diseases. Exogenous crystals, such as asbestos and silica, have been known to be harmful for sometime – although the precise mechanism was only recently discovered. However, the real paradigm shift came from the realization that crystalline material is also associated with the inflammation seen during Alzheimer disease, atherosclerosis and type-II diabetes and that all of these reactions, exogenous and endogenous, derive from a misguiding immune response meant to help the host defend against pathogens.

In order to explain these processes, visitors were taken on a tour of autoinflammation. They could view impressive videos of immune cells in action, including macrophages impaling themselves on crystals, and use the microscope themselves to view specimens of macrophages filled with crystals or beads.

Many of these visitors were interested in learning more about the molecular pathways associated with this process. We provided them with flyers explaining the NLRP3 inflammasome and were on hand to answer the many questions. (ASC-RFP) completely changed the image!

Friend of foe: What fits and what doesn’t?

Specifically for children, the Cluster Coordination Office prepared an “immune sensing game”, during which they could experience how the immune system works. Children were asked to put their hands in different boxes and, using only their sense of touch, figure out which items “did not fit” into the pattern presented—e.g. by discriminating between rough rocks and one smooth stone. In this way, the kids were able to test their tactile senses and relate this to how our immune system also makes use of patterns to sense what is harmful and what is harmless.

What was surprising for children (and adults!) is how difficult the game actually was. Decisions that seemed deceptively simple could go terribly wrong, because an item was chosen too rashly. The participants could go for another round, but when the immune system is mistaken, the consequence is often autoimmunity! Altogether, it was a fun way to teach children and adults about pattern recognition and immune sensing.

The Cluster and Scientific Outreach

In addition to the members of the Cluster Office, eighteen Cluster-associated scientists and students volunteered to man the exhibition in shifts, since the “Night” was open for a total of 28 hours. It was a very busy two days, and the visitors were full of questions. Many participants had an excellent general scientific background and could readily comprehend our research, yet some had never ever spoken to a scientist before. Indeed, these events provide an excellent opportunity for outreach precisely because they reach such a broad segment of society, and they provide a real chance to improve the image and awareness of scientific research among the general public. In addition, it was excellent practice for our young scientists to present research to a varied audience.

We also like to thank the scientists that provided pictures and texts for the written pamphlets, which were available in English and German on crystals and sterile inflammation with a target audience of the educated, interested non-scientists. These included simplified background information on Cluster research as well as an overview of the different portions of the exhibit.

These events are important but they require intense planning and commitment. We are very grateful to Eicke Latz and his group members Gabor Horvath and Andrea Stutz for their time and efforts with the exhibition and for managing to set up a fluorescent microscope in a tent in downtown Bonn. Furthermore, in-vivo imaging movies were created by Wolfgang Kastenmüller and members of Eicke Latz’s group demonstrating intercellular interactions as well as the phagocytosis of crystalline material. For many visitors, this was the first time they had ever thought about how the immune system works on a cellular basis, and we are grateful to our Cluster scientists who made this event possible.
In May 2014 the Cluster Steering Committee traveled to the Amalfi Coast in southern Italy for their annual retreat. It was a highly productive and enjoyable event. The Cluster scientists stayed at the Hotel Marmorata, which provided a fully equipped seminar room and offered a beautiful setting with spectacular views of the coast line. The Steering Committee also invited several newly recruited Cluster members to the meeting, and their contributions to the discussion of the scientific, structural and educational issues facing the Cluster was highly appreciated. All of the participants presented their current scientific projects and future research plans. In addition to research, the following issues were addressed during the meeting: 1. re-evaluation of the work programs A to E of the Cluster, 2. the future development of shared resources and technologies, 3. the recruitment of professors, junior research groups and the support of female academic careers, 4. the further development of the research focus immunology and infectious diseases in the Medical Faculty, 5. plans for further improving the public awareness of the Cluster and its substantial contribution to advances in medicine, 6. the design of future applications for collaborative research grants, 7. the preparation for the Cluster Science Days 2014 including questions and tasks for our international Scientific Advisory Board.

Retreats have a very important function for the development of the Cluster. During this and past retreats, the interdisciplinary group of scientists steering the Cluster who come from different institutions have a chance to get to know each other and enjoy a few days of close interaction. Retreats allow the generation of both great ideas and new friendships. In fact, the scientific concept of the Cluster was born at such a retreat. Work sessions do not usually end in the seminar rooms but continue during the joint tours and excursions in the area. This year, the group enjoyed a spectacular sailing tour along the Amalfi coast which provided plenty of opportunities to continue the discussions in smaller groups on board.
The ImmunoSensation Cluster of Excellence belongs to one of the 43 Clusters of Excellence that are currently funded by the DFG.

These Clusters represent the best research centers from different faculties and fields from mathematics to the arts. The program has allowed the development of completely new concepts for research and interdisciplinary projects to promote excellence in research. These varied infrastructures are all embedded or connected to universities and research institutes and use their organizational structures. As a result, they have many organizational tasks in common, from the organization of graduate programs or family and gender support to the appointment of new professors. Over the last years an active network among the Clusters of Excellence has developed and is used to exchange experience and support.

ImmunoSensation is an active part of this network, and CCO members joined the annual meeting of coordinators, which was organized this year in Hamburg, and the meeting for gender support, which took place in Kiel (see page 115). Beside these meetings which are organized by the coordinator network, the DFG invited all Cluster speakers and coordinators of the 43 Cluster of Excellence, 45 Graduate Schools and eleven Institutional Strategies to participate in a general discussion about the Cluster initiative in Bad Honnef. Our Cluster speaker Prof. Hartmann, vice-speaker Prof. Kolanus and Cluster manager Dr. Hömig-Hözel represented ImmunoSensation during this event.

This interaction is important to optimize organizational processes and to keep up to date on the political decisions made by the government about the future of the excellence initiative.
International Immunology Training Program Bonn (IITB)

Most of the scientists associated with the Cluster are PhD students (46%) or postdocs (28%). These young scientists come from all over the world and bring with them a great diversity of scientific backgrounds and practical knowledge. Although the Cluster benefits enormously from this broad spectrum of scientific expertise and experience, it can still be rather overwhelming for young scientists to start in a new field, and this is where the IITB program steps in. The program aims to both standardize the immunological education of young scientists as well as promoting training in specialized techniques as necessary. In addition, the IITB plays an important role by supporting scientific exchange and networking for young scientists.

IITB courses began in Summer 2014 with 105 students and young postdocs registered for the program. The course program was chosen on the basis of a survey held in October 2013 among young scientists in the Cluster to find out what kind of training they needed most. A comprehensive three-year program was then implemented to meet these interests, including technical training, soft skills, career counseling and networking.

Soft skill training
Students rarely have the opportunity to get special training to improve their communication skills during their academic studies. However, our survey among Cluster students showed they are aware of the importance of soft-skill competence and that many of them would be interested in participating in specialized courses.

In 2014, we were able to offer two courses: Scientific writing in March and Presentation Skills in September.

The Workshop “Scientific Writing” was conducted by Prof. Martin Wild from the MPI for Molecular Biomedicine/ Münster in March 2014 and focused on the clear communication of science. The focus was on using written English language, whether for presentations or publications.

Prof. Wild provided participants with the basic tools necessary to structure a story and tailor it to the reader’s interest and background. Participants also discussed how to avoid the misinterpretation of data.

In September, we offered the workshop “Presentation skills” which was conducted by Dr. Rick Scavetta from Science Craft/Berlin. It also focused on the effective and clear communication of results. The course included information on the proper presentation and design of visual aids and the correct choice of words and use of body language to clearly communicate scientific information. Students had the both intimidating and useful experience of viewing their own presentations on video, which allowed them insight into the strengths and weaknesses of their presentation skills.

Technical training
Our technical platforms participate in training courses, giving IITB participants the unique opportunity to learn state-of-the-art techniques directly from experts in the field. Our first technical workshop in cooperation with a technical platform was Proteomics-Mass Spectrometry led by Dr. Marc Sylvester from the Mass Spectrometry Service Unit of the Institute for Biochemistry and Molecular Biology in September 2014. During the three-day training, participants learned about the importance of clarity in data presentations and the advantages and disadvantages of different visualization approaches.

To increase the spectrum of courses offered, the IITB also shares workshops with the Bonn Forum of Biomedicine (BFB). In the shared course “Statistics”, participants learned how to correctly translate standard statistical models to their own work. The attendees were encouraged to bring their own data and statistical problems for discussion.

Scientific exchange and networking
Even in our digital age, scientific exchanges and networking have not lost their importance for scientific collaborations. Especially for young scientists, it can be quite difficult to build up a professional network, and we would like for IITB participants to profit from the vast networks of scientists connected to the Cluster. In 2014, we focused on our “meet-the-expert” sessions and expanding our annual meeting, Cluster Science Days.

International Immunology Training Program Bonn (IITB)

Prof. Martin Wild
Dr. Rick Scavetta
Meet-the-expert

With the help and connections of Cluster members, it is possible to invite excellent researchers to visit the Cluster in Bonn. To give our IITB members the chance to get to know invited speakers, we offered students “meet-the-expert” sessions.

While having a meal together, between ten and twelve students had the opportunity to meet these “big shots” in an informal and relaxed atmosphere.

We are very grateful that the following researchers offered to join meet-the-expert sessions after their talks in Bonn:

January 17, 2014
Dr. Sten Linnarson
Karolinska Institute, Department of Medical Biochemistry and Biophysics, Stockholm, Sweden.

February 21, 2014
Prof. Thomas Sauter
Professor of Systems Biology, Life Sciences Research Unit, University of Luxembourg, Luxembourg.

March 13, 2014
Prof. Manfred Claassen
Professor for Computational Biology, ETH Zurich, Institute of Molecular Systems Biology, Switzerland.

March 21, 2014
Prof. Stephen Turner
Department of Microbiology and Immunology, University of Melbourne, Australia.

April 25, 2014
Dr. Alex K. Shalek
Broad Institute, Cambridge, MA, USA.

May 9, 2014
Dr. Nir Yosef
Department of Electrical Engineering & Computer Science, Center for Computational Biology, University of Berkeley, USA.

May 23, 2014
Prof. Christopher Workman
Center for Biological Sequence Analysis, Kongens Lyngby, Denmark.

November 4, 2014
Prof. Douglas T. Golenbock
University of Massachusetts Medical School, Worcester, MA, USA.

November 4, 2014
Prof. Charles Dinarello
Division of Infectious Diseases, Aurora, USA.

November 4, 2014
Prof. Hermann Wagner
Technical University Munich, Germany

November 4, 2014
Prof. Tony Wyss-Coray
Stanford, CA, USA.
Cluster Science Days 2014

The Cluster Science Days are organized every year to promote networking and scientific exchange within ImmunoSensation. All Cluster-associated scientists are invited and encouraged to attend, especially students and other members of the IITB.

For them it was a great opportunity to present their data in front of a big audience. Our first Cluster Science Day in October 2013 was focused on young scientists and was a great success. For 2014, we decided to extend the meeting to two days and offer additional sessions in which the group leaders could give an overview of the research conducted in their groups. A poster session was also included in 2014, allowing a larger number of participants to present their data.

One particular highlight of the Cluster Science Day 2014 was the visit of the Scientific Advisory Board. More information can be found on pages 92-98.

Company visits and career counseling

Our student survey showed that participants were very interested in learning about career opportunities, such as visiting biotechnology companies and learning about extramural research institutes.

During our first excursion in March, a group of 13 students visited the envihab - German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt/ DLR). After a guided tour, young scientists had the chance to talk to DLR scientists and learn more about experiments at zero gravity such as during parabolic flights or in space. Of special interest were the results acquired by a DLR group on the effect of weightlessness on immune processes.

Further excursions, but also meetings with representatives of the university or DFG, are planned for the coming years.

ImmuoSensation Cluster fellowships

At the beginning of 2014, the application period for 14 ImmunoSensation Cluster fellowships was opened with the aim of recruiting students from all over the world. In July, 20 candidates from 120 applicants, were invited for telephone interviews, which were conducted by Dr. Astrid Draffehn. During these interviews, they reported on their master projects and technical background as well as their scientific interests and which groups within the Cluster they would like to join. In a second round, candidates were directly contacted by the Cluster members.

By the end of 2014, all 14 positions had been filled. Our new students are from Germany, Spain, Portugal, Greece, Poland, and Iran, and will participate in a 3-year structured PhD program. Throughout their studies, they will be guided by their supervisor and can get help and support from an additional mentor. They have the possibility to visit national and international meetings and apply for financial and organizational support to visit the labs of collaboration partners to acquire special technical expertise.

Plans for 2015

Based on the positive feedback we have had about the different workshops, we have decided to offer several of them again in 2015. In addition, we will offer more workshops for technical training in cooperation with the Cluster’s technical platforms and core facilities, including theoretical and practical training in imaging techniques, flow cytometry and genome engineering. To further promote the students’ network and especially to support the new ImmunoSensation scientists, we have planned a welcome meeting, a regular “IITB Stammtisch” and a network day for all IITB members. Other established formats, such as the Cluster Science Days, will be continued in 2015.
Family Support & Gender Equality

In Germany, the representation of women at all advanced levels of academic science has increased significantly in the last 5 years. Nonetheless, a striking discrepancy remains between the number of talented women entering the life science field and those who later on assume senior leadership positions. This problem is often compared to a “leaky pipeline”, with the loss being an enormous pool of scientific talent.

ImmuSensation would like to stop the many leaks in the pipeline by encouraging and supporting female scientists throughout their career paths. Therefore the Office of Gender Support (Nicole Dahms) coordinates programs and initiatives for women and is also an information platform for female support within the Cluster, the University of Bonn and beyond. The office is aware of the demands placed on female scientists but also conducts surveys within the Cluster to address the specific needs of male and female scientists within the Cluster. In addition, ImmuSensation’s Gender Support is involved in the recruitment of excellent female junior and senior researchers. We strongly feel that a concerted and coordinated support network for female scientists is necessary to redress the career difficulties women in science currently face and to keep talented female immunologists in research.

ImmuSensation in Numbers

In 2014, the total number of Cluster-related scientists increased form 331 to 382. Compared to last year, the number of female Cluster-associated scientists increased slightly from 47% to 48%. With the newly recruited IITB students in 2014, the number of female PhD students rose from 54% to 56%. However, at the post-doctoral level female scientists comprise 47% compared to 48% in 2013. At 12% the proportion of women at the professorial level remains unchanged. This is a solid result compared to the University of Bonn where women make up 7% at the professorial level and 10% in Molecular Biomedicine. Thus, recruiting qualified women to senior positions at the University of Bonn and within the Cluster remains a top priority for ImmuSensation. We are currently in process of filling several open positions and we have some very promising female candidates.

A measurement of the support given to young female scientists is not only their collective number but also their individual scientific output. Since this allows them to advance their careers and pursue more senior positions. An encouraging example is Dr. Andrea Ablasser. She headed a research group within the Cluster at the Institute of Clinical Chemistry & Clinical Pharmacology. As a result of her outstanding work at ImmuSensation, she was appointed tenure-track Assistant Professor in the School of Life Sciences (École Polytechnique Fédérale de Lausanne - EPFL) in 2014.

A second example for the research quality of female scientists within the Cluster is Dr. Linda Diehl, who was the head of a research group at the Institute of Molecular Medicine. In September 2014, she was appointed as W2 professor for Experimental Inflammation Research at the Institute of Experimental Immunology and Hepatology, University Hospital, Hamburg-Eppendorf.

A central goal of our Gender Support is allowing female scientists to reach their potential, and we wish Dr. Ablasser and Dr. Diehl the very best for the future.

Cooperation with the Woman in Science initiative from the LIMES Institute

The LIMES Women in Science initiative (WiS) is led by Professor Irmgard Förster. Prof. Förster was recruited as the first ImmunoSensation Cluster Professor in 2012 holding the W3 chair “Immunology and Environment” at LIMES. In addition, she is also a member of the Steering Committee of the ImmunoSensation Cluster of Excellence. The LIMES-WiS program aims to enhance the visibility of successful female scientists as role models for career development. The initiative highlights scientific presentations from excellent female scientists at all career levels and promotes inter-institutional scientific exchange. LIMES-WiS is also linked with the gender equality program of the ImmunoSensation Cluster of Excellence, and our female scientists actively participated in those events.

MeTra: Support for Career Development

The Cluster’s Young Investigator Support (coordinated by Dr. Astrid Draffen) and the Office of Gender Support hosted Ursula Mättig, equal opportunity coordinator of the University of Bonn, and Dr. Martina Pottek, coordinator of the MeTra program (mentoring and training program for young women in academia) at the University of Bonn in March 2014.

In the seminar, Mrs. Mättig provided helpful information and contacts on gender-related topics. Dr. Pottek presented the MeTra Program, which supports women in their career development at

1 Bundesbericht Wissenschaftlicher Nachwuchs 2013 www.buwin.de
2 Zwischenbericht zum Gleichstellungsplan 2013-2016 der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn
3 Statistisches Bundesamt IT-NRW und Abteilung 9.3 Controlling und Evaluation der Universität Bonn (Web 2015)
Family Support & Gender Equality

different educational levels. MeTra is part of the collaboration with the Maria-von-Linden program from the University of Bonn. In 2014, the Cluster funded the participation of two female scientists in the MeTra program. Both MeTra participants appreciated the broad range of theoretical and practical knowledge exchanged during the program and benefited from the newly gained network and experience. More about the MeTra can be read in the interview with Dr. Dagmar Wachten (Cluster member, caesar).

Workshop “Gender related communication in Life Science” by Andrea Roos

A gender-related, two-day communication workshop in Life Sciences was held in February 2014. This workshop was specifically tailored to communication issues in Life Sciences. Thus, female scientists could benefit from this individual approach addressing their everyday working situation. The feedback to the workshop was overwhelmingly positive.

“Family-friendly science is our goal” - support of childcare during working hours

Prof. Gunther Hartmann (Cluster speaker) has emphasized that “family-friendly science”, meaning the support of young parents, is essential to successful work, especially in science, since this field requires a lot of personal commitment. According to the results of the conducted survey in 2013, the Office of Gender Support offers the following programs for parents within the Cluster:

The Cluster funds regular childcare at the English-speaking nursery “Max and Mary” (Venusberg). The long opening hours and the location at the Venusberg help the scientists to improve their work-life balance. We have already received many new applications for 2015.

The Cluster cooperates with the “pmf Familienservice” which was founded in 1991 and operates in more than 30 cities all over Germany. The large number of offices ensures excellent access to childcare support. Using this service, we provide childcare for emergencies, during school holidays and also for out-of-town meetings. If the meeting is within Germany, it is even possible to take the child along and benefit from the local pmf service.

In order to assist scientists on parental leave who need to temporarily pause their laboratory work, the Cluster offers funding for hiring student assistants. This program helps to ensure that the scientist can return to their project after their parental leave. Two female scientists took advantage of this offer in 2014, and we hope parents will continue using this program.

Children and the Future of Science

To get young women interested in science, the ImmunoSensation Gender Support provides teenage girls with the possibility to get an impression of work as a scientist. In 2014, ImmunoSensation participated in the “Girls’ Day” for the first time. On March 27, eight 11-15 year-old girls visited the Cluster at the University Hospital Bonn. After a brief introduction to the Cluster and its structure, the girls met Professor Regina Betz who told them about her work and life as a Professor. Then, the girls spend the rest of the day in the laboratory and performed their own experiments under the supervision of several female Cluster scientists. Eva Bartok, Juliane Daßer, Maria Khaminet, Kerin Pelka and Andrea Stutz planned and carried out the scientific program with the girls, which focused on protein biochemistry. The girls performed Bradford protein assays, pH measurements and Ponceau stains to define the content of “mystery substances”. In addition, the girls had the opportunity to perform fluorescence microscopy using an instrument from Prof. Eicke Latz’s lab under the supervision of Dr. Gabor Horvath (Core Facility Imaging). Everyone really enjoyed the day, and ImmunoSensation looks forward to holding the Girls’ Day again in 2015.

Annual Network Meetings of the Clusters of Excellence Germany: Gender Equality

Exchange of knowledge and expertise is always a valuable tool to continually improve and evaluate one’s own actions. Therefore, the ImmunoSensation Gender Support is in close contact with Gender initiatives of other Clusters of Excellence in Germany. In regular meetings, all Gender representatives provide insights in their programs, which in turn inspire new ideas and further program topics. In 2015, we will have the privilege of hosting the meeting in Bonn.

We believe that our efforts to support female scientists are bearing fruit, but we are aware that there is still a long way to go before the pipeline stops leaking. Until then, we will be dedicated to improving the position of women in science.
Public Relations

From bench to your site!

The ImmoSensation Cluster of Excellence has an important duty not only to “produce knowledge” but also to communicate its scientific achievements to other scientists and the general public at large. However, beyond our duty to raise public awareness of our work, we are also fascinated by the immune sensory system and would like to share our enthusiasm for immunology with anyone who is interested – no matter their age or scientific background.

ImmoSensation online and on Social Media

The Internet is our most important interface with the public. Our website www.immuno-sensation.de is updated on a daily basis and provides general information on ImmoSensation as well as access to our publications and almost all information relevant to Cluster research and activities. In particular, we have started a series of podcasts with Cluster researchers. These are conducted at a “popular scientific level” to make them of interest to a broader audience.

ImmoSensation is also present on social media. Since October 2013, we use Twitter and Facebook to announce events, publications and press releases. These sites are open to anyone with a Twitter or Facebook account, and, importantly, they are interactive. Anyone has the opportunity to communicate with us directly, whether students, colleagues or just interested members of the public.

ImmoSensation “Face to Face”: Cluster Events for the General Public

We also value face-to-face interaction with the public. Our participation in events such as Bonn’s Night of Science (Bonner Wissenschaftsnacht) has allowed us to raise awareness of both immunological research of the Cluster and the Cluster as an institution. The importance of such events cannot be underestimated: for many participants this was the first time they have spoken to a “scientist”.

Here, public outreach can do a great deal more than just interest members of the public. Our participation in Bonn’s Night of Science with the Cluster scientists fielded questions ranging between “What is the resolution of your confocal microscope?” to “What is a cell?” (For more information on this event, please see the Bonn’s 9th Night of Science in the ‘Events’ Section.)

Cover story in Trillium Diagnostik: “Immunosensing – unser sechster Sinn”

Understanding the immune system as a body-wide signaling network that consists not only of immune cells but also multiple receptors on and within the cell is a key feature of our research within the Cluster. It is also called the immune sensory system, a term that is still quite new in the field and rarely used outside of research. To increase public awareness of the immune sensory system, ImmoSensation published a cover article in the journal Trillium Diagnostik entitled “Immunosensing – unser sechster Sinn: Hellwach auch wenn wir schlafen” (Immune sensing – our sixth sense: always awake even as we sleep). The article describes the interaction between cellular receptors and the innate and adaptive immune systems. In particular, it gives an overview of our current understanding of DAMP signaling and the detection intracellular viral DNA and RNA.

The journal was distributed during the Annual Meeting of the DGR in Bonn, giving us the opportunity to present the key findings of our Cluster researchers to a large group of immunologists. Trillium Diagnostik is published quarterly and highlights new developments in interdisciplinary medicine. About 12,000 copies go to subscribers from medical diagnostics and the life sciences as well as hospitals.

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since this gave us the opportunity to connect our research to recent advances in our understanding of Alzheimer’s disease, atherosclerosis, gout and type-II diabetes, providing an important connection between scientific research and relevant medical advances. During the event, the participating Cluster scientists fielded questions ranging between “What is the resolution of your confocal microscope?” to “What is a cell?” (For more information on this event, please see the Bonn’s 9th Night of Science in the ‘Events’ Section.)

Cover story in Trillium Diagnostik: “Immunosensing – unser sechster Sinn”

Understanding the immune system as a body-wide signaling network that consists not only of immune cells but also multiple receptors on and within the cell is a key feature of our research within the Cluster. It is also called the immune sensory system, a term that is still quite new in the field and rarely used outside of research. To increase public awareness of the immune sensory system, ImmoSensation published a cover article in the journal Trillium Diagnostik entitled “Immunosensing – unser sechster Sinn: Hellwach auch wenn wir schlafen” (Immune sensing – our sixth sense: always awake even as we sleep). The article describes the interaction between cellular receptors and the innate and adaptive immune systems. In particular, it gives an overview of our current understanding of DAMP signaling and the detection intracellular viral DNA and RNA.

The journal was distributed during the Annual Meeting of the DGR in Bonn, giving us the opportunity to present the key findings of our Cluster researchers to a large group of immunologists. Trillium Diagnostik is published quarterly and highlights new developments in interdisciplinary medicine. About 12,000 copies go to subscribers from medical diagnostics and the life sciences as well as hospitals.

Kinderuni (Children’s University)

The “Children’s University” is a seminar series for children aged 8 to 12 offered every semester by the University of Bonn. The series covers topics from meteorology to linguistics to ancient history, and the focus is on demonstrating the fun side of university research.

Immunology is also an important part of the curriculum. In January, Cluster member Prof. Michael Heneka from the Department of Neurology (University Hospital
Bonn) held the seminar “Of Squirrels and Immune Cells” (Von Eichhörnchen und Immunzellen: Lernen und Erinnern).

What squirrels and immune cells have in common is that they have to learn and remember: the squirrels need to find their winter stashes; immune cells have to learn and remember how to protect us from germs and to recognize them again in case of a second infection.

Children also could experience “being an immune cell” first hand. They participated in an active model of the circulatory system. Some children got a T-shirt assigning them a specific cell type: erythrocytes, endothelial cell, lymphocytes and macrophages. A viral attack was simulated by throwing black balloons into the system, and the children with the macrophage T-Shirts “ate” (phagocytosed) the viruses by putting the balloons under their T-Shirts. The game taught the basics of anti-viral defense and was a lot of fun for the participants.

Girls’ Day

ImmunoSensation also participates in the annual Girls’ Day. The event is sponsored by the Federal Ministry of Education and Research and aims to bring girls into contact with professions that are not “traditionally female”. Since women are still underrepresented in biomedical research, ImmunoSensation chose to participate in this important initiative. In January, eight girls aged 11 to 15 visited the Cluster and spent the afternoon in the laboratory with female scientists from the labs of Veit Hornung, Eicke Latz and Gunther Hartmann. (For more information, please see the “Gender Support” section of this report.)

Raising awareness of Immuno-Sensation within and without: Cluster goes Charity

ImmunoSensation also annually takes part in charity drives. In 2014, Nicole Dahms arranged our participation in two charity projects. Although, at first glance, such initiatives have little to do with immunology, they are important to help foster identification with the Cluster within its ranks, raise public awareness of our work and, most importantly, provide the needy with new shoes and school material!

The initiative “Ältere Schuhe – neues Leben” (old shoes – new life), which is supported by the University Hospital Bonn, collects old pairs of shoes, which are still wearable, and sells them to recycling companies. The proceeds go to the “Fördergemeinschaft Deutsche Kinderherzzentren e.V.”. We were able to collect more than 20 kg of shoes, which were handed over to the charity organization.

The second project which was supported by the Cluster and the University Hospital Bonn was “Mary’s Meals Deutschland e.V.” Due to the help of our Cluster members we were able to donate 16 backpacks that were filled with school material and other useful items to support children in Malawi and Liberia to visit a school.

Due to the support of the Cluster members, the charity drives were a huge success and we will continue our support for charity projects in 2015.

Future plans

At the “Night of Science” in Bonn, we were overwhelmed by how interested the general public is in our research. In addition to continuing our current public outreach, a new PR initiative is planned for 2015 in cooperation with Deutsches Museum (German Museum) and Museum König in Bonn, with plans for an exhibit on the immune sensory system.
Cluster Seminars and Seminars of Cluster Cooperation Partners 2014

Bonn Lecture Series in Neuroscience: Dendritic integration of excitatory input in subiculum hippocampal pyramidal neurons  
January 16, 2014  
Mark Harnett, PhD, Janelia Farm Research Campus, Ashburn, Virginia, USA

Bonn Lecture Series in Neuroscience: Unbiased cell type discovery by large-scale quantitative single-cell RNA-seq  
January 16, 2014  
Dr. Sten Linnarsson, Associate Professor, Karolinska Institute - Department of Medical Biochemistry and Biophysics, Stockholm, Sweden

SFB 704 Seminar: New links between inflammasome activation and cell-autonomous immunity  
February 05, 2014  
Prof. Dr. Petr Broz, University of Basel, Switzerland

Bonn Lecture Series in Neuroscience: Neural correlates of automatic processing of emotional Stimuli  
February 11, 2014  
Thomas Straube, PhD, Institute of Medical Psychology and Systems Neuroscience, University of Muenster, Germany

SFB 704 Seminar: The immunology of Salmonella infections: lessons from the mouse model  
February 21, 2014  
Prof. Dick Strugnell, Dept. of Microbiology & Immunology, Univ. of Melbourne, Australia

Bonn Lecture Series in Neuroscience: Statistical multiscale models of biological systems at single cell resolution  
March 13, 2014  
Prof. Manfred Claassen, Institute of Molecular Systems Biology, ETH Zurich, Switzerland

SFB 704 Seminar: What makes a killer? Mapping the epigenetic blueprint for virus-specific T-cell differentiation  
March 20, 2014  
Prof. Stephen Turner, Dept. of Microbiology & Immunology, University of Melbourne, Australia

Bon Lecture Series in Neuroscience: A behind scenes look at the publishing process  
March 26, 2014  
Katja Brose, PhD, Chief Editor, Neuron, Executive Editor for Neuroscience, Cell Press

Bonn Lecture Series in Neuroscience: Episodic memory encoding interferes with reward learning and decreases striatal prediction errors  
March 26, 2014  
Elliott Wimmer, PhD, Center for Experimental Medicine, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Germany

SFB 704 Seminar: The role of extracellular vesicles in NK cell regulation  
April 01, 2014  
Prof. Elke Pogge von Strandmann, Klinik I für Innere Medizin, University Hospital Cologne, Germany

SFB 704 Seminar: Surveillance of plasmacytoid dendritic cells in visceral adipose tissue  
April 08, 2014  
Dr. Susanne Stutte, Institute for Immunology, LMU Munich, Germany

April 24, 2014  
Dr. Alex K. Shalek, Broad Institute, Cambridge, USA

Bonn Lecture Series in Neuroscience: Kilohertz signaling at a central synapse  
May 07, 2014  
Prof. Stefan Hallermann, Department of Neurophysiology, University Leipzig, Germany

Bonn Lecture Series in Neuroscience: Reconstructing the Th17 differentiation network: from profiles to drug targets  
May 08, 2014  
Dr. Nir Yosef, PhD (Assistant Professor), Department of Electrical Engineering & Computer Science, Center for Computational Biology, University of Berkeley, USA

ImmunoSensation Seminar: From rare diseases to general population: The UMOD gene coding for uromodulin  
May 15, 2014  
Prof. Dr. Olivier Devuyst, University of Zurich, Zurich Center for Integrative Human Physiology (ZIHP), Switzerland

Bonn Lecture Series in Neuroscience: Systems biology approaches for determining transcriptional regulatory networks  
May 22, 2014  
Christopher Workman, Associate Professor, Center for Biological Sequence Analysis, Dept. of Systems Biology, Technical University of Denmark, Kongens Lyngby, Denmark
Cluster Seminars and Seminars of Cluster Cooperation Partners 2014

SFB 704 Seminar: Mechanisms and consequences of NFAT signaling pathway activation in innate immune cells
June 17, 2014
Prof. Francesca Granucci, Department of Biotechnology and Biosciences, University of Milano-Bicocca, Italy

ImmuNoSensation Seminar: Adaptation of Intestinal Barrier Immunity in Response to Nutrition
July 01, 2014
Dr. Christoph Wilhelm, NIH - National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Maryland, USA

SFB 704 Seminar: Global proteomics provides new insights into immunology and cancer
July 09, 2014
Dr. Philipp Mertins, The Broad Institute of MIT and Harvard, USA

SFB 704 Seminar: TCR Signal Intensity Dominantly Controls CD4+ T Cell Polarization In Vivo
July 17, 2014
Dr. Nicholas van Panhuys, Laboratory of Systems Biology, National Institutes of Health, Bethesda, USA

Seminar: Innate immune regulation of inflammasomes by extracellular ATP
July 23, 2014
Dr. Pablo Pelegrin, Murcia’s BioHealth Research Institute, Hospital Virgen de la Arrixaca, Spain

Bonn Lecture Series in Neuroscience: Activity-dependent Arc expression: mechanism, function and application
August 29, 2014
Prof. Haruhiko Bito, Department of Neurochemistry, University of Tokyo, Japan

SFB 704 Seminar: Yolky beginnings – The origin of macrophages
September 02, 2014
Dr. Christian Schulz, Division of Immunology, King’s College London, England

SFB 704 Seminar: Therapeutic Clearance of the Virally Infected Nervous System is Mediated by Nocytopathic T cell interactions with Resident Myeloid Cells
September, 25 2014
Dr. Jasmin Herz, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

SFB 704 Seminar: Unravelling Dendritic cell subset commitment – One cell at a time
September 29, 2014
Dr. Andreas Schlitzer, Florent Ginioux lab, Singapore Immunology Network

Cluster Science Days: Use of genetic models in cancer gene discovery
November 4, 2014
Prof. Stephen Michael Cohen, Department of Cellular and Molecular Medicine, Copenhagen, Denmark

Cluster Science Days: Systemic factors as modulators of neuroinflammation
November 4, 2014
Prof. Charles Dinarello, Division of Infectious Diseases, Aurora, USA

SFB 704 Seminar: Lipid signaling in immunity and sepsis
November 25, 2014
Prof. Markus Gräler, Department of Anesthesiology and Intensive Care Medicine, University Hospital Jena, Germany

Cluster Meetings 2014

Retreat ImmunoSensation Cluster of Excellence
May 25 – 28, 2014, Italy

44th Annual Meeting – German Society for Immunology (DGfI 2014)
September 17-22, 2014
World Conference Center, Bonn, Germany

Cluster Science Days 2014
November 3 & 4, 2014, University Hospital Bonn, Germany
Publications

ImmunoSensation
Publication List 2014


18. Arumugam S, Hoerauf A, Pfarr KM. Localization of a flarial phosphate permease that is up-regulated in flarial chronic filarial infection but leads to an increased microfilaremia due to an impaired splenic microfilaremia clearance. PLoS ONE 2014 Jan 1;9(5): e93072


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Common and rare variant analysis in early-onset bipolar disorder vulnerability. PLoS ONE 2014 Jan 17; e0104326


Prizes & Distinctions

Prizes and Distinctions awarded within the ImmunoSensation Cluster of Excellence 2014

2014 Prof. Anton Bovier from the Institute for Applied Mathematics of the Rheinische Friedrich-Wilhelms-Universität Bonn and Prof. Christian Kurts from the Institute of Experimental Immunology, University Hospital Bonn became member of the Selection Committee of the Heinz-Maier-Leibnitz prize

2014 Prof. Christian Kurts from the Institute of Experimental Immunology, University Hospital Bonn became an elected member of the German National Academy of Science, Leopoldina
The Leopoldina is one of the oldest academies of science and was appointed as the German National Academy of Science in 2008. It represents the German scientific community in international committees and gives advice in social and political questions.

2014 Prof. Natalija Novak won the Allergopharma Award
Prof. Novak from the Department of Dermatology, University Hospital of Bonn won the prize for her work published in the Journal of Allergy and Clinical Immunology in 2012: “Early suppression of basophil activation during allergen-specific immunotherapy by histamine receptor 2. J Allergy Clin Immunol. 2012 Nov;130(5):1153-1158.

2014 Prof. Thomas Tüting from the Department of Dermatology received the “Deutsche Hautkrebspreis 2014”
The prize is awarded annually with financial support of the “Roche Pharma AG”.

2014 Prof. Natalija Novak won the Allergopharma Award
Prof. Novak from the Department of Dermatology, University Hospital of Bonn won the prize for her work published in the Journal of Allergy and Clinical Immunology in 2012: “Early suppression of basophil activation during allergen-specific immunotherapy by histamine receptor 2. J Allergy Clin Immunol. 2012 Nov;130(5):1153-1158.

February 7, 2014 Christian Schiffer received BFB best talk award
Christian Schiffer, PhD student in the group of Prof. U. Benjamin Kaupp, received the BFB best talk award for his presentation titled “Direct action of endocrine disrupting chemicals on human sperm”.

February 7, 2014 BFB poster awards were given to Sibylle Mitschka, Dr. Thomas Quast, Sophie Schonauer and Tobias Bald
At the BFB meeting, poster prizes were given to:

Sibylle Mitschka, PhD student in the group of Prof. Waldemar Kolanus, for her poster titled “Trim71 regulates differentiation and suppresses let-7 maturation in mES cells”

Dr. Thomas Quast, PostDoc in Prof. Waldemar Kolanus group, with his poster “Salt-Dependent Chemotaxis of Macrophages”

Sophie Schonauer, PhD student in Dr. Dagmar Wachtens group, for her poster with the title “Investigating the cross-talk between GBA1 and GBA2 in Gaucher disease”

Tobias Bald, who was PhD student in the group of Prof. Thomas Tüting, for his poster “Ultraviolet radiation-induced neutrophilic inflammation promotes angiотro-pism and metastasis in melanoma”
Prizes and Distinctions awarded within the ImmunoSensation Cluster of Excellence 2014

March 14, 2014 Dr. Andrea Ablasser received the Paul Ehrlich- und Ludwig Darmstaedter award
Cluster member Andrea Ablasser (Institute of Clinical Chemistry & Clinical Pharmacology, University Hospital Bonn) won the Paul Ehrlich- und Ludwig Darmstaedter award. Since 1952 the award is being given annually to pioneering scientists in the medical field. This recognition is only distributed to German young scientists of the biomedical domain, aged below 40. She received the price from Nobel laureate Prof. Dr. Harald zur Hausen.

June 18, 2014 Prof. Eicke Latz and Prof. Veit Hornung belonged to Thomson Reuters Highly Cited Scientists of 2014
The director of the Institute of Innate Immunity (E. Latz) and the director of the Institute of Molecular Medicine (V. Hornung) were the only Germans out of 87 globally to receive this distinction in the broad field of immunology.

July 05, 2014 Prof. Sven Burgdorf received award for excellent teaching
Prof. Sven Burgdorf from the LIMES Institute was honoured for his outstanding achievements in teaching. The faculty based on an evaluation by the students who nominated him.

July 14, 2014 Dr. Andrea Ablasser awarded from the GlaxoSmithKline foundation
Cluster member Dr. Andrea Ablasser was awarded the prize for basic research in the field of medicine from the GlaxoSmithKline foundation for her work on cytosolic DNA recognition in the Hornung group.

September 15, 2014 PhD student Alena Grebe received Young Investigator Award at 37th ELC Meeting
Alena Grebe was the joint recipient of the Joachim-Ziegenhorn-Young Investigator Award for best oral presentation for her talk titled “Cyclodextrin dissolves cholesterol crystals, mediates LXR gene expression and promotes atherosclerosis regression in mice”. Her advisor was Prof. Eicke Latz from the Institute of Innate Immunity.

October 9, 2014 Prof. Frank Bradke, has been elected as a member of the German National Academy of Science, Leopoldina
Cluster member Prof. Bradke is the head of the “Axon Growth and Regeneration” research group at the German Center for Neurodegenerative Diseases (DZNE).

October 20, 2014 Prof. Winfried Barchet – appointed for “translational immunology”
Prof. Barchet from the Institute of Clinical Chemistry and Clinical Pharmacology was appointed for a professorship at the University of Bonn with effect from October 20, 2014.

October 27, 2014 Dr. Elvira Mass (from the LIMES Institute, Prof. Hoch group) received the Bayer PhD award 2014
The Bayer Pharma AG recognizes each year outstanding PhD thesis from the LIMES Institute and the Pharmaceutical Center of Bonn. Dr. Elvira Mass received the award for her doctoral thesis: “Functional analyses of the conserved Cysteine-rich with EGF-like domains (Creld) protein family in Mus musculus”.

Prizes and Distinctions awarded within the ImmunoSensation Cluster of Excellence 2014

November 2014 Nomination of Prof. Hermona Soreq for the Rappaport Prize for Excellence in Medical Research
The Rappaport family established the prize in order to promote visionary, groundbreaking and innovative research with therapeutic ramifications that significantly promote human health.
Annual Report 2014
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## Annual Report 2014

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Annual Report 2014
ImmunoSensation Member List

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10 Most Relevant Publications for Dr. Andrea Ablasser
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Research Expertise
Structural Biology, cryo-electron microscopy, intercellular adhesion unctions, synapsis, neurodegenerative diseases.

Education / Training
University of Lausanne, Switzerland, Life science/EM Structural Biology, PhD, 2004
University of Lausanne, Switzerland, Physics, Science, 2003

Honors / Awards
2010 - present Heisenberg Professorship, Institute of Human Genetics, University of Bonn, Germany
2002 - 2004 Flemish Research Council Postdoctoral Fellowship

10 Most Relevant Publications for Dr. Ashraf Al-Amoudi

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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 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 other susceptibility genes such as the genes PTPN22, TRAF1/C5, CTLA4, MSMB, TLR1, TLR2, TLR4, TLR5, TLR6, CD18, CD24, CD43, CD58, and CD59 and others to the disease risk using candidate gene studies. By the use of genome-wide association studies, meta-analyses, immunochip and functional studies, we just recently identified HLA-DR as a key etiologic driver for AA as well as two loci outside the HLA-region: ACDL8/ESL1,21 and GARP. Future analyses and functional studies will contribute to a comprehensive understanding of AA.

Education / Training
University of Bonn, Germany, Human Genetics, Habilitation, 2009
University of Bonn, Germany, Medical Specialist, 2007
Karolinska Institute, Stockholm, Sweden University of Saarland Clinical Medicine, Medical license, 1999

Honors / Awards
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 - 2005 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

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
2009 - 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 German Translational Research Award for the advancement of basic medical research
2006 Göttingen Just-Scientific Prize of the University of the City and Ulm, Germany
2002 - 2004 Flemish Research Council Postdoctoral Fellowship
2002 - 2000 DFG Postdoctoral Fellowship

10 Most Relevant Publications for Prof. Regina Betz
Dr. Marc Beyer, MD
Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute for Applied Mathematics
E-Mail: bovier@uni-bonn.de

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 disorders in 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 applications 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
Since 2014
Group leader, University of Bonn, Germany
2008 - 2013
Senior postdoctoral research fellow, University of Bonn, Germany
2004 - 2007
Postdoctoral research fellow, University of Cologne, Germany
2002 - 2004
Medicine fellow, University of Cologne, Germany

10 Most Relevant Publications for Prof. Anton Bovier

10 Most Relevant Publications for Dr. Marc Beyer

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute for Applied Mathematics
E-Mail: bovier@uni-bonn.de

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 disorders in 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 applications 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
1989 - 1992
Research Associate, Mathematics Department
Bochum University, Germany
1985 - 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-Zürich

Honors / Awards
2014
Member of Selection Committee, Heinz-Maier-Leibnitz prize
2008
Elected Fellow, Institute of Mathematical Statistics
2005
Keck-Dean Chair, University-Leiden, NL

Plenary Speaker, Annual Meeting of the German Mathematical Association
2005
EURLAND Chair, EURLAND, Enindhoven, NL

Member of the Review Board for Mathematics of the German Research Council
2008
Member of the Review Board for Mathematics of the German Research Council
2006
Invited Speaker at the International Congress of Mathematicians, Madrid
Prof. Irmgard Förster, PhD
Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
Life and Medical Sciences Institute (LIMES),
Immunology and Environment, Director

E-Mail: irmgard.foerster@uni-bonn.de

Research Expertise

Prof. Förster has special expertise in the functional characterization of macrophages and dendritic cells using computational 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

1992 - present
W3 Professor of Immunology and Environment Life and Medical Sciences Institute (LIMES) Institute for Medical Research, Heidelberg, Germany

1995 - 2002
Visiting Scientist, Computational and Structural Biology Programme, European Molecular Biology Laboratory, Heidelberg, Germany

1998 - 2001
Research associate at the Howard Hughes Medical Institute, Dept. of Medicine, Microbiology and Immunology, University of California at San Francisco, San Francisco, USA

1995 - 1998
Research fellow in the Dept. of Biophysics, Max-Planck-Institute for Medical Research, Heidelberg, Germany

Honors / Awards

2008
Editorial Board Member. Cytokine 2001
Habilitation fellowship of the Peter and Traudl Engelhorn Stiftung, Bergisch Gladbach 1995
Long-term fellowship of the European Molecular Biology Organization (EMBO), Heidelberg 1998
Postdoctoral fellowship of the German Science Foundation (DFG) 1993

10 Most Relevant Publications for Prof. PD Matthias Geyer


10 Most Relevant Publications for PD Matthias Geyer


Rheinische Friedrich-Wilhelms-Universität Bonn
Clinical Neurosciences Unit, Director
E-Mail: michael.heneka@ukb.uni-bonn.de

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, Professional qualification (Habilitation), 2003
University of Bonn, Germany, Neurology, Specialty qualification, 2002
University of Tübingen, Germany, Medicine, MD, 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
1992 - 2004
Resident in Neurology, University of Bonn
1996 - 1999
Research Fellow, University of Tübingen
1992 - 1996
Predoctoral research fellow in the Dept. of Pharmacology, University of Cologne

Honors / Awards
2013 - present
Associate Editor Neurology, Neuroimmunology and Neuroinflammation
2013
Hans und Ilse Breuer Award for Alzheimer Research 2012 - present
Editorial Board Molecular Neurobiology

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 microbiota 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, ASfMè Institute, Wagada University, Japan
2000 - 2002
Managing Director of the LIMES Institute, Chair Molecular Developmental Biology, LIMES Institute, 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 Academy Foundation (Studienstiftung des deutschen Volkes)
2012 - present
Member of the Steering Committee of the ImmunoSensation Cluster of Excellence (Bonn) (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
2002 - 2004
Chairman of the Bonner Forum Biomedizin
2000 - 2006
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 DFG (German Academic Exchange Service)
1990
Gerhard Hess Young Investigator Award (DFG)
1989 - 1992
PhD Fellowship of the Boehringer Ingelheim Foundation (Fonds für Basisforschung in der Medizin)
1986 - 1989
PhD member of the German National Academy Foundation (Studienstiftung des deutschen Volkes)

5 Most Relevant Publications for Prof. Michael Hoch
Prof. Michael Hözel, MD
Institute of Clinical Chemistry and Clinical Pharmacology

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Medical Microbiology, Immunology and Parasitology

Prof. Achim Hörauf, MD
Institute of Medical Microbiology, Immunology and Parasitology

10 Most Relevant Publications for Prof. Michael Hölzel


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 immunity, macrophages, dendritic cells, RNA biology and genome engineering technologies.

Education / Training
University of Munich, Germany, Clinical Pharmacology MD thesis 2000 - 2003
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 of Bonn, Germany

Researcher
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
2015
Elected EMBO Member
2015
EPC Consolidator Grant
2014
Designated Highly Cited Researcher by Thomson Reuters
2013
Pettenkofer Prize of the Max von Pettenkofer Foundation
2010
GlaoSmiithKline Foundation Prize for basic medical research

2010
Paul-Martini-Prize of the Paul-Martini-Foundation
2009
ERC Starter Grant
2007
Heinrich 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 - 2002
Fellow of the German National Academic Foundation (‘Studienstiftung des deutschen Volkes’)

10 Most Relevant Publications for Prof. Veit Hornung

*These authors contributed equally

2010
GlaoSmiithKline Foundation Prize for basic medical research

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 describes and elucidates the immunological patho-mechanism 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

1998 - 2001
Visiting Research Professor, Dept. of Medicine, University of Pittsburgh, USA

1995 - 1998
Research Fellow, Department of Surgery, University of Pittsburgh, USA

1992 - 1995
Clinical Fellow, Department of Surgery, University of Bonn, Germany

1989 - 1991
Resident, Department of Surgery, University of Bonn, Germany

Honors / Awards
2006
Fellow of the American College of Surgeons (FACS) 2004
Elected Speaker of the KFO 115 2000
Ferdinand Sauerbrey 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
Prof. Wolfgang Kastenmüller, PhD
Institute of Molecular Medicine

Research Expertise
The scientific focus of his group are cellular interactions and cell communication in the context of acute infections. Central techniques are live intravital microscopy and histo-chemistry.

Education / Training
Laboratory of Systems Biology NIH/USA
Ronald N. German, PhD
2004 - 2006
Technical University of Munich, Germany, Specialization Infectious Disease

Technical University of Munich, Germany, Medicine, PhD thesis, 2003
Technical University of Munich, Germany, Medicine, MD 1995 - 1997
Universities of Regensburg, Germany, Medicine, 1995 - 1997

Appointments / Positions Held
2013
Associate Professor, University of Bonn, Germany
2008 - 2012
Postdoctoral Fellow, NH/Besthesda USA
2002 - 2006
Clinical Fellow/Post-Doc, University of Munich, Germany

Honors / Awards
2013, CIS - Best Paper Award NH
2003 Dietmar-Zumpf-Promotions Preis

10 Most Relevant Publications for Prof. Wolfgang Kastenmüller

Prof. U. Benjamin Kaupp, PhD
center of advanced european studies and research (caesar)

10 Most Relevant Publications for Prof. U. Benjamin Kaupp
Prof. Percy Knolle, MD
Institute of Molecular Immunology

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, BISF Bioscience, Corporation, Cambridge, USA

Honors / Awards
2001
Award by the Volkswagen Foundation (1.5 Million €)

10 Most Relevant Publications for Prof. Percy Knolle

Education / Training
University of Mainz, Germany, Internal Medicine Specialist, 1997
German Cancer Research Centre, Heidelberg, Applied Immunology, PhD thesis, 1990
Universities of Frankfurt, Paris, Birmingham (LM), Strasbourg, and Geneva, Medicine, MD, 1988

Appointments / Positions Held
2013 - present
Director Institute of Molecular Immunology, TU Munich
2013 - 2017
cooperator Medical Faculty, University of Bonn, Germany
2006 - 2012
Vis-à-Vis-speaker of the SFB 704, University of Bonn, Germany
2002 - 2012
Director Institute of Molecular Medicine, University of Bonn, Germany
2002
Professor of Molecular Medicine and Immunology, University of Bonn, Germany

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 to non-professional resident cell populations and their major new high 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 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. This lab also 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 CD4 T cells.

Prof. Waldemar Kolanus, PhD
Life and Medical Sciences Institute (LIMES)

2007
2004
US Patent 20040108516 - Cytohesin-PH peptides that affect the integrity of cytoskeleton
2003
US Patent 20030318641 - Targeted cytokines of HIV-infected cells by chimeric CD4 receptor bearing cells
2002
US Patent 20020176581 - Method of testing and treating HIV infection

10 Most Relevant Publications for Prof. Waldemar Kolanus

Rheinische Friedrich-Wilhelms-Universität Bonn Life and Medical Sciences Institute (LIMES)

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 adhesion of leukocytes. Recent work has led to a specific microenvironment, some of which include force-dependent slow migration of immune cells on and across barriers, versus force-independent, fast migration in the extracellular matrix.

Education / Training
University of Hannover, Medical College, PhD, 1987
University of Munich, Biology, Chemistry, Life science, examination, 1984

Appointments / Positions Held
2003 - present
Full Professorship, Molecular Immunology, University of Bonn
1999 - 2002
Associate Professor, Biochemistry, University of Munich (LMU)
1996
Habilitation in Biochemistry, Faculty of Chemistry, University of Munich (LMU)
1993
Molecular Immunology, University of Munich (LMU)

Honors / Awards
2002 - present
Post-doc Fellow, Molecular Immunology, Howard Medical School
1998 - 1990
Post-doc Fellow, Immunology, Harvard Medical School

US Patent 20040108516 - Cytohesin-PH peptides that affect the integrity of cytoskeleton
US Patent 20030318641 - Targeted cytokines of HIV-infected cells by chimeric CD4 receptor bearing cells
US Patent 20020176581 - Method of testing and treating HIV infection

US Patent 20040108516 - Cytohesin-PH peptides that affect the integrity of cytoskeleton
US Patent 20030318641 - Targeted cytokines of HIV-infected cells by chimeric CD4 receptor bearing cells
US Patent 20020176581 - Method of testing and treating HIV infection

1996
US Patent 6573362 - Cytohesin-PH peptides that affect the ability of integrins to adhere
1994
Munich Gene Center, Junior Group Leader 5-award winner, BMBF and University of Munich
Prof. Christian Kurts, MD
Institute of Experimental Immunology
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 diseases. Their main research projects focus on the molecular mechanisms of antigen cross-presentation, in particular the involvement of CD8α+ T cells, peripheral tolerance induction of T and B lymphocytes against self antigens, and the role of dendritic cells in diseases, especially in kidney disease.

Education / Training
University of Gottingen, Germany
MD Medicine, 1991

Appointments / Positions Held
2003-2006 Assistant Research Professor, UMass Medical School
2007-2011 Visiting Scientist, Department of Lipid Biochemistry, Merck Research Laboratories
2011-2016 Director of UMassNanoMed, Department of UMassMC-Northeastern Medicine
2016-2018 Professor, Institute of Innate Immunity, University of Bonn, Germany
2018-2020 Head, Center for Metabolic Inflammation, University of Bonn, Germany

Honors / Awards
2014 Highly Cited Researcher (out of 87 international immunologists)
2015 Listed in the “World’s Most Influential Scientific Minds” (Thomson Reuters)
2016 Life Scientist of the Fellow of the United States National Academy of Sciences (NAS)
2015 ERC Consolidator Grant
2011 GlaxoSmithKline Clinical Science Award
2009 Dana Foundation Award
2004 Fellow of the Clinical Immunology Societies (FOCS) Award
2001 Postdoctoral Training Grant of the German Academic Exchange Program (DAAD)
2000 PhD Thesis award “summa cum laude”
2000 Scholarship of the Japan Society for Endoscopy
2000 Award of the Japanese Society of Surgery, Tokyo National Cancer Center

10 Most Relevant Publications for Prof. Christian Kurts
Rheinische Friedrich-Wilhelms-Universität Bonn
Life and Medical Sciences Institute (LIMES)
Department of Molecular Brain Physiology and Behavior,
Director
E-Mail: pankratz@lum.de

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

10 Most Relevant Publications for Prof. Michael Pankratz


Prof. Joachim L. Schultz, MD
Life and Medical Sciences Institute (LIMES)

Rheinische Friedrich-Wilhelms-Universität Bonn
Life and Medical Sciences Institute (LIMES), Genomics & Immunoregulation, Director
E-Mail: jschultze@lum.de

Research Expertise
Professor Schultz’s current central expertise is at the interface of immunogenetics and genomics, with a focus on transcriptional and epigenetic control of cell activation and immunoregulation, particularly in macrophages and monocytes.

Education / Training
University of Freiburg, Medicine, Fellow, 1992 - 1993
University of Freiburg, Medicine, MD, 1991
University of Freiburg, Medicine, State examination, 1991
Appointments / Positions Held
2007 - present
W03 Professorship, Genomics & Immunoregulation, University of Bonn
2002 - 2007
C3 Professorship, Tumor Immunology, University of Cologne 1997 - 2002
Instructor in Medicine, Adult Oncology, Dianer-Farber Cancer Institute, MA, USA 1996 - 1997
Instructor in Medicine, Hematologic Malignancies, Dianer-Farber Cancer Institute, MA, USA 1995 - 1996
Research Associate, Hematology, Dianer-Farber Cancer Institute, MA, USA 1993 - 1995
Research Fellow, Hematology, Dianer-Farber Cancer Institute, MA, USA 1992 - 1993

Honors / Awards
2012 - present Vice Dean for Research, Faculty for Mathematics and Natural Sciences, University of Bonn
2000 Senior Investigator Award of the Multiple Myeloma Research Foundation
1999 Transitional 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 American 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. Schultz


Member of the Scientific Advisory Board “Network of Molecular Nutrition Research”, State of Baden-Württemberg, Germany
2000 - 2001
Consultant for Aventis
Prof. Thomas Tüting, MD
Department of Dermatology and Allergy

Rheinische Friedrich-Wilhelms-Universität Bonn
Institute of Molecular Psychiatry

Honors / Awards
2015
German skin cancer research prize of the German skin cancer foundation
2009
Stegleider prize of the AG Dermatologische Histologe
2006
Translational Research prize of the AG Dermatologische Research
2000
Research Award of the Erich Hoffmann Society, Bonn

10 Most Relevant Publications for Prof. Thomas Tüting

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
University of Fribourg, Germany, MD, Thesis, 2000
University of Mannheim, Germany, Dermatology and Allergic Diseases, Board Certification, 1998
University of Frankfurt School of Medicine, Medicine, MD, 1987

Appointments / Positions Held
2007 – present
Associate Professor and Laboratory Head, Experimental Dermatology, University of Bonn, Germany

Clinical work, General and Oncologic Dermatology, Clinical work, General and Oncologic Dermatology, 2001 – present
Dermatology, University of Bonn, Germany

2001 – 2006
Professor of Molecular Psychiatry (W3), Dir. Institute for Molecular Psychiatry, University of Bonn

2005 – 2006
Professor of Cell Biology (W3), University of Bielefeld

2005 – 2005
Professor for Molecular Neurobiology (C3), University of Bonn

1997 – 1999
Adjunct Professor, Department of Pharmacology, Georgetown University, Medical School, USA

1993 – 1997
Research Associate, National Institute of Mental Health, USA

Visiting Research Fellow, National Institute of Mental Health, USA

1990 – 2005
Visiting Associate, National Institute of Mental Health, USA

1989 – 1991
Postdoctoral researcher, DFG-Fellow, National Institute of Mental Health, USA

1983 – 1991
Professor of Cell Biology (W3), University of Bielefeld

1997 – 1999
Adjunct Professor, Department of Pharmacology, Georgetown University, Medical School, USA

1993 – 1997
Research Associate, National Institute of Mental Health, USA

Visiting Research Fellow, National Institute of Mental Health, USA

1990 – 2005
Visiting Associate, National Institute of Mental Health, USA

1989 – 1991
Postdoctoral researcher, DFG-Fellow, National Institute of Mental Health, USA

1983 – 1991
Professor of Cell Biology (W3), University of Bielefeld

1997 – 1999
Adjunct Professor, Department of Pharmacology, Georgetown University, Medical School, USA

1993 – 1997
Research Associate, National Institute of Mental Health, USA

Visiting Research Fellow, National Institute of Mental Health, USA

1990 – 2005
Visiting Associate, National Institute of Mental Health, USA

1989 – 1991
Postdoctoral researcher, DFG-Fellow, National Institute of Mental Health, USA

1983 – 1991
Professor of Cell Biology (W3), University of Bielefeld

1997 – 1999
Adjunct Professor, Department of Pharmacology, Georgetown University, Medical School, USA

1993 – 1997
Research Associate, National Institute of Mental Health, USA

Visiting Research Fellow, National Institute of Mental Health, USA

1990 – 2005
Visiting Associate, National Institute of Mental Health, USA

1989 – 1991
Postdoctoral researcher, DFG-Fellow, National Institute of Mental Health, USA

1983 – 1991
Professor of Cell Biology (W3), University of Bielefeld
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
D-53175 Bonn
www.dzne.de

cæsar - center of advanced european studies and research
Ludwig-Erhard-Allee 2
D-53175 Bonn
www.caesar.de

ImmunoSensation
The immune sensory system. Frontiers of excellence

Cluster Coordination Office
University Hospital Bonn
BMZI / UG / 216.3
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www.immunosensation.de
Cluster Coordination Office (CCO)

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University Hospital Bonn
Sigmund-Freud-Str. 25
D-53127 Bonn
www.immunosensation.de

Cluster Coordination Office (CCO)
2014

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Cluster Manager
Phone +49 228 287 51289
cornelia.hoemig-hoelzel@ukb.uni-bonn.de

Nicole Dahms
Central Administration & Gender Support
Phone +49 228 287 51288
immunosensation@uni-bonn.de

Dr. Astrid Draffehn
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Phone +49 228 287 51288
immunosensation@uni-bonn.de

Eva Bartok, MD
Coordination of the Cluster Graduate Program IITB
Phone +49 228 287 51150
ebartok@uni-bonn.de

Diana Sigl
Public Relations
Phone +49 228 287 51283
immunosensation@uni-bonn.de

Dr. Andriy Kubarenko
IT and Data Management
Phone +49 228 287 51290
andriy.kubarenko@ukb.uni-bonn.de

Ida Bartz
Financial Administrator
Phone +49 228 287 14733
ida.bartz@ukb.uni-bonn.de
Expertise

The Flow Cytometry Core Facility covers a broad spectrum of flow cytometric methods and applications. The multiplexed analysis of immune cell subsets has once again gained importance. 6 color experiments are now common to precisely identify and separate for example regulatory T-cells, tissue specific naive and memory T-cells, tissue primed T-cells or tumor specific T-cells for ex vivo functional analysis or adoptive transfer.

The demand for a multiplexed analysis of up to 10 colors simultaneously is no longer extraordinary and strategies for the isolation of rare cell populations are frequently asked for. Beside these obvious applications of flow cytometry, the "flow cytometry" platform contributed to the analysis and separation of endosomes, operating the cytometers at their physical detection limit and encouraged the interaction of researchers from different disciplines.

Furthermore the flow cytometry platform will offer educational activities as stand-alone opportunities or as part of the existing graduate and professional programs, provide technical training, and conduct research that enables development of the next generation of state-of-the-art flow cytometry technology.

Instrumentation

- Three BD FACS Canto II digital benchtop analyzers
  The Canto is an easy-to-use benchtop analyzer, equipped with three lasers and capable of detecting up to 8 colors simultaneously. The 488nm, 635nm and 405 nm excitation wavelength and the accompanying filter settings for detection coverage of the routine applications in flow cytometry. Users are trained on the analysers and can perform their experiments without the assistance of an operator.

- LSR Fortessa digital benchtop analyser
  The LSR Fortessa is equipped with five laserlines for excitation (355nm, 405nm, 488nm, 561nm, 640nm) and 18 photomultipliers for simultaneous detection of fluorescence. Users can now take full advantage of new fluorochromes and increased sensitivity/decreased spectral overlap of PE conjugates for immunophenotyping. Moreover the configuration of the analyser enables nearly the complete spectrum of variants of fluorescent proteins, to monitor gene expression or to analyse reporter cell lines.

- BD FACS Aria digital high-speed cell sorter
  The BD FACS Aria is similar in its configuration to the LSR Fortessa. What you see on the LSR Fortessa can therefore usually be physically separated on the FACS Aria. Sterile cell sorting can be performed for single cells on all sizes of plates or microscope slides as well as sorting four populations simultaneously.

- Influx high-speed cell sorter
  The BD Influx™ cell sorter is a flexible flow cytometry platform that easily adapts to a researcher’s application or requirements. The Influx is a high speed cell sorter, with four lasers for excitation, (405nm, 488nm, 561nm, 640nm) and 16 photomultipliers to address the needs of current multicolor experiments. Four different nozzle sizes (70, 85, 100 and 130µm) allow an adequate choice for a variety of cell types and sizes and reduce shear stress, thereby increasing cell viability.
Imaging Core Facility

Director: Prof. Eicke Latz
Institute of Innate Immunity
www3.uni-bonn.de/icf
0228/287-51229
gabor.horvath@uni-bonn.de

Expertise

The Imaging Core Facility provides services for imaging microscopy techniques for live and fixed cells, and tissue sections. We also provide scientific and technical assistance for researchers to design experiments and to facilitate image acquisition and analysis.

Instruments already installed in Core Facility allow us to perform efficient measurement of fluorescence resonance energy transfer (FRET), fluorescence lifetime (FLIM) and fluorescence correlation spectroscopy (FCS) measurements. Instruments could also perform acquisitions in multi-well format.

In the nearest future in the Core Facility several new instruments will be installed. Among them are high content screening microscope and super-resolution confocal system. This will allow us to provide users with more techniques and high quality services.

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Cluster IntraNet System

Director: Prof. Gunther Hartmann
Faculty of Medicine
www3.uni-bonn.de/intra
+49 (0)228 287-51290
a.kubarenko@uni-bonn.de

Main functionality

Communication
The Message Board of the IntraNet System can be used to post messages that can be seen by all Cluster members. The Message Board can be used to post events or facilitate the search for necessary materials and reagents.

Sharing reagents
IntraNet has a "Labitems" database that helps researchers in the Cluster to share reagents. The database currently contains a list of antibodies which members of the Cluster are willing to share as well as the respective contact person information for each antibody.

Transgenic Animals
Similar to the "Labitems" category, the database will also allow users to share and search for information about the animal strains that Cluster members have and are ready to share.

Lab Equipment and Expertise

The IntraNet System can also be used as a resource for collecting information about what instruments (e.g., microscopes, flow cytometers, qPCR machines, etc.) are available within the Cluster and which scientists are responsible for them.

Publications Database

The Cluster Coordination Office is keeping a repository of all of the available publications of Cluster members. It will be possible to download full-text articles and supplementary materials (PDFs) of all these publications directly from the IntraNet database. In the publication database, it is also possible to see one of the latest impact factors (currently 2012).

People, Events and Announcements

The IntraNet System contains information about the people associated with the Cluster (regular members, PhD students, master and bachelor students etc.) within the Cluster or of general interest to Cluster-associated scientists.

Contact Information
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+49 (0)228 287-51290

ImmunoSensation has developed an IntraNet system to help Cluster members share and exchange materials and information. It is a convenient platform for managing information about Cluster people, events, resources and expertise.

The IntraNet system is also intended to facilitate communication between Cluster-associated scientists thus allowing you to rapidly find information about other Cluster members, search for and request materials and reagents. It is our intention to save you time and cut costs.

In addition to the intranet, ImmunoSensation is currently developing a Scientific Resources Management (SciReM) Core Facility. The IntraNet system will be linked to and work in close connection with the Core Facility System.

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In addition to the Leica AOBS confocal microscope line, the Zeiss instrument also has multiple filter sets for the most common fluorophores: DAPI, GFP, GPP, YFP, RFP, Cy5 and Cy7. Additionally, polarization filters can be used for imaging crystalline materials. The dual-cam system also allows for ratiometric imaging of FRET-sensors and for fast processes, like calcium-spikes. The instrument is also capable of live imaging from multi-well plates with proper temperature-, CO2- and O2-control, even in hypoxic conditions. New addition to the instrument is a full environmental chamber and the ApoTome.2 system for optical sectioning of thick samples.

The Leica SPS AOBS with SMD confocal microscope provides the strongest illumination in any confocal system due to its non-linear optics. The microscope is also completely without filters, which gives the highest flexibility for selecting the best light paths matching your fluorophores. The instrument is equipped with multi-line Argon (457, 474, 488, 497 and 514 nm), 561 nm DPSS and 633 nm HeNe lasers. Additionally, the Single Molecule Detection (SMD) unit provides pulsed laser lines at 405, 470 and 640 nm, and two Single Photon Avalanche Diode (SPAD) detectors for fluorescence lifetime (FLIM) and fluorescence correlation spectroscopy (FCS) measurements. The instrument is equipped with full environmental chamber.

Zeiss Observer.Z1 wide-field fluorescent microscope
The Zeiss microscope is an easy-to-use instrument, equipped with strong halogen-lamp and multi-line LED light-source. The instrument also has multiple filter sets for the most common fluorophores (DAPI, GFP, GPP, YFP, RFP, Cy5 and Cy7). Additionally, polarization filters can be used for imaging crystalline materials. The dual-cam system also allows for ratiometric imaging of FRET-sensors and for fast processes, like calcium-spikes. The instrument is also capable of live imaging from multi-well plates with proper temperature-, CO2- and O2-control, even in hypoxic conditions. New addition to the instrument is a full environmental chamber and the ApoTome.2 system for optical sectioning of thick samples.

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**Shared Resources**

**Light Microscopy Core Facility**

German Centre for Neurodegenerative Diseases (DZNE)

Head: Dr. Eugenio Fava

**Contact Information**

Dr. Eugenio Fava
eugenio.fava@dzne.de

Cluster members can find detailed information on the Intranet:

www.dzne.de/en/research/core-facilities.html

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**Expertise**

The DZNE Core Research Facilities & Services (CRFS) provides state-of-the-art services to scientists at the DZNE and other research organizations. Services are provided by expert staff on a fee-for-service basis.

**Instrumentation**

- Confocal Laser Scanning Microscopes (Zeiss LSM700, LSM710/LO, LSM780, Cryo/confocal/FV1000)
  - Confocal laser scanning microscopes have a pinhole in the image plane to block fluorescence light from out-of-focus layers. This results in a contrast-rich image of a thin layer of your sample often called optical section. Consecutive optical sections are commonly used for 3D reconstructions.
- Two-photon Microscopes (Zeiss LSM 7 MP, LSM 710 NLO, TRIM Scopell)
  - Two-photon microscopy uses two photons in the infrared spectral range instead of one photon in the visible spectral range to excite fluorophores. Due to less scattering of infrared light, this microscopy technique can image much deeper into the tissue than conventional “single”-photon techniques. In addition, two-photon microscopes excite fluorophores only in the plane of focus and thus provide z-resolution comparable to confocal microscopy. Two-photon-microscopes are therefore ideally suited for all kinds of photo-manipulation experiments.
- BD FACS Aria digital high-speed cell sorter
  - The BD FACS Aria cell sorter is similar in its configuration to the LSR Fortessa. What you see on the LSR Fortessa can therefore usually be physically separated on the FACS Aria. Sterile cell sorting can be performed for single cells on all sizes of plates or microscope slides as well as sorting four populations simultaneously.
- Super Resolution Light Microscope (Leica SP8/STED)
  - Depending on the technique applied super resolution light microscopes can resolve structures about 20 nm to 60 nm apart. In comparison, the best widefield fluorescence microscopes have under ideal conditions a resolution limit around 200 nm. The LMF has a microscope based on stimulated emission depletion (STED). Asphoticled arrangement of a STED laser to deplete fluorescence and a conventional excitation laser is able to create a small fluorescence spot, which is not limited by diffraction as in classical light microscopes.

The CRFS also houses Wide-field Fluorescence Microscopes, Stereology Microscopes, a Microdissection Microscope, TIRF Microscopes, Single Plane Illumination Microscope, Spinning Disk Confocal/Microscopes and Accessory equipment.

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**Light Microscopy Platform**

Molecular Immunology and Cell Biology, LIMES Institute

Director: Prof. Waldemar Kolanus

**Contact Information**

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quast@uni-bonn.de

Cluster members can find detailed information on the Intranet:

www.bonn.de/mikroimmunologie

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**Expertise**

The microscopy platform provides state-of-the-art light microscopical technologies. This comprises the localization of specific molecules/proteins as well as the analyses of dynamic processes.

We have established and developed in the past a number of analytical live cell imaging techniques in the area of cell adhesion, cell migration and immune cell activation. On the basis of this we have established numerous collaborations with other investigators to analyze immune cell migration, interaction times of T cells with dendritic cells and high-resolution intracellular protein localization.

Technologically, the platform is based on several standard as well as advanced confocal systems which allow both high-resolution and ultra-fast image acquisition. In a collaborative mode of action, the “microscopy” platform will provide a wide range of high-end imaging technologies and experimental/scientific expertise relevant to many groups.

**Instrumentation**

- **Olympus FluoviewTM FV1000 confocal laser scanning microscope**
  - This confocal laser scanning system is based on an inverted Olympus IX81 microscope and incorporates two independent, synchronized laser scanners for simultaneous laser-based stimulation and confocal observation (e.g. FRAP). The system is equipped with 405 nm diode laser, multi-line argon laser (457, 488, 515 nm) and 543/633 nm HeNe lasers. Four photomultiplier tube detectors allow the simultaneous detection of three fluorescent dyes and differential interference contrast.
- **Zeiss LSM 5 Live confocal laser scanning microscope**
  - This high-speed confocal laser scanning system is based on an inverted Zeiss Axiovert 200 microscope. The laser scanner unit uses a laser beam with a rectangular cross-section to illuminate a line in the sample, instead of a single point. The system is equipped with 405 nm diode laser, 488 nm diode laser, 532 nm diode-pumped solid-state laser and 635 nm diode laser. The system is used for the analysis of very fast dynamic processes.
- **VisiTech-Infinity 3 confocal Imaging System**
  - This system combines ultra high speed confocal imaging with 2500 adjustable pinholes to produce high resolution. The system is equipped with 488 and 532 nm solid state lasers and a high sensitivity Hamamatsu Orca R2 CCD Camera equipped with cooled photodiode for low noise performance. The Infinity system is fully integrated in the Nikon Eclipse TE 2000-E Microscope and used for ultra-fast image acquisition (e.g. analysis of intracellular calcium mobilization).
- **Nikon Eclipse TE 2000-E Inverted Research Microscope System**
  - This microscope is equipped with phase contrast and wide-field fluorescence filter cubes (DAPI, FITC, TRITC, Cy5). It is used for routine epi-fluorescence detection and video-microscopy.
Shared Resources
Mass Spectrometry Core Facility
Institute of Biochemistry and Molecular Biology
University Bonn
Director: Prof. Volkmar Gieselmann

Expertise
The mass spectrometry core facility offers services for a broad range of analyses with a focus on proteins. Techniques cover identification and characterization of proteins, detection of posttranslational modifications as well as comparative, quantitative analyses of complex proteomes.

We apply MALDI-TOF and ion trap-ESI-LC-MS instruments to measure intact protein masses, identify proteins after proteolytic digestion (e.g. from polyacrylamide gels) or analyze post translational modifications. An Orbitrap Velos hybrid mass spectrometer with high resolution and sensitivity allows analysis of complex samples such as cell lysates. This machine is also used for quantitative analyses with various stable isotope labeling strategies like SILAC and TMT.

We are currently expanding our bioinformatics tools box for characterization, visualization, and analysis of complex data sets. We will support you in utilizing your data to develop meaningful working hypotheses.

The data we provide can be very informative but also challenging, in particular the quantitative characterization of proteomes.

Therefore, early consultation with us in order to discuss the strategy, scope, and pitfalls of these experiments are essential to improve the chances for a successful mass spectrometric analysis.

Contact Information
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Cluster members can find detailed information on the Intranet: masse@uni-bonn.de

Instrumentation
- MALDI-TOF/TOF Bruker Autoflex III
  Our MALDI-TOF instrument is a versatile tool for fast analyses of proteins and peptides. Low complexity protein samples such as from 2D-gel spots can be analyzed with good mass accuracy and resolution. The TOF detector can also be used for intact protein mass measurements and fast characterization of protein preparations.
- Ion trap Bruker HCT Ultra and HCT Ultra/PTM
  These two spectrometers use electrospray ionization techniques and are usually coupled to liquid chromatography systems (micro- or nanoflow). They offer good performance for analyses of medium complex protein samples. MS/MS experiments can be performed in the ion traps for more detailed manual examination of analytes. One of the instruments offers electron transfer dissociation (ETD) for gentle fragmentation of posttransitionally modified peptides (e.g. phosphopeptides).
- Hybrid Instrument Thermo Orbitrap Velos
  The Orbitrap Velos has two detectors: a fast low resolution linear ion trap and a high resolution, high accuracy Orbitrap detector which can be used in parallel. This instrument is our workhorse for in-depth proteome analyses and whenever high resolution and sensitivity are needed.
- nanoLC systems
  Two ultra-high-performance liquid chromatography systems for nanoflow (~300 nl/min) are used for coupling with mass spectrometers. These systems perform chromatographic separations very reproducibly and assure a stable delivery of analytes to the mass spectrometers. An Advion Triversa Nanomass nanospray robot can be used for automated delivery of small sample amounts for direct infusion.
- Sample preparation devices can be provided to handle larger sets of samples with the help of a gel imaging/spot cutting device, a pipetting robot, and a pi-based peptide fractionation device.

Shared Resources
Next Generation Sequencing Core Facility
Institute of Human Genetics
Faculty of Medicine
Director: Prof. Markus Niethen

Expertise
Massive parallel sequencing, called Next Generation Sequencing (NGS), is becoming widely applied in many research projects. However, investment in / maintenance of NGS systems as well as establishing different applications is expensive and time consuming. The Next Generation Sequencing (NGS) Core Facility of the University Hospital Bonn (UMB) provides the expertise and instrumentation required to perform all aspects of this technology for biomedical research. Applications include resequencing of disease-related genomic regions, sequencing of entire exomes or genomes, transcriptomics or epigenomics. Also, NGS is indispensable for the de novo sequencing of human pathogens or resistance-related bacteria and viros, ChIP sequencing, characterization of siRNA and miRNA as well as in the area of stem cell research.

At the NGS Core Facility, our goal is to provide researchers access to state-of-the-art devices and assist them in planning their experiments and in analyzing and interpreting the results. Researchers within the UKB are encouraged to contact the NGS Core for consultation prior to sequencing projects, which will allow us to provide support in study design and therefore optimize the performance of the NGS experiments. The mission of the NGS Core Facility is to enhance the scope and quality of scientific research, and to facilitate communication amongst scientists. In addition, we provide all investigators with the scientific expertise necessary to effectively integrate NGS technology into their research projects.

Contact Information
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ngs.core@uni-bonn.de
Phone: +49 (0)228-6885420

Cluster members can find detailed information on the Intranet: ngs.core@uni-bonn.de

Instrumentation
- HiSeq 2500
  The HiSeq 2500 System is a powerful two flow cell high-throughput sequencing system that supports the broadest range of applications and study sizes. Using the latest v4 chemistry, one flow cell can generate about 500 Gb of data with 2x125 bp read length in one week, or up to 4 billion paired-end reads. This would be equivalent to sequence about 98 human transcriptomes or 96 human exomes at appropriate depth. Notably, different projects can be combined in one run on one flow cell, making the use of the system applicable to any needs and throughput.
- MiSeq
  The MiSeq is a benchtop sequencer that allows performing more focused applications such as targeted gene sequencing, metagenomics, small genome sequencing, targeted gene expression, amplicon sequencing, and HLA typing. Using the latest version of reagents (v3), up to 15 Gb of output can be generated (with 50 million paired-end reads and 2x300 bp read lengths).

Supporting devices
Prior to sequencing, samples have to be prepared according to different protocols. For quantity and quality checks as well as different steps within the protocols, different devices are required. These include Agilent’s TapeStation and BioAnalyzer, Qubit measurement kits, Diagenode Bioruptor for fragmentation and SPRI-beads based purification systems. These devices are available to the users.

Bioinformatics
NGS generates a huge amount of data which require bioinformatics solutions. At the NGS Core Facility, we provide customers with access to different software tools, such as the CLC Biomedical Genomics Workbench and Servier (Qiagen) or Cartagenia’s Bench lab NGS (Agilent), to perform their bioinformatics analyses. More complex statistical analyses can be addressed in cooperation with the bioinformatics group at the Institute of Human Genetics, or with the Institute of Medical Biometry, Informatics and Epidemiology (IMBIE).
**Intravitral Microscopy and Histocytometry**

**Institute of Experimental Medicine**
**Faculty of Medicine**
**Director: Prof. Christian Kurts**

**Expertise**
The microscopy platform provides state-of-the-art confocal and 2-photon imaging technologies. We are focussing on localisation and migrational dynamics of cells within tissues.

We have established live imaging of bone-marrow, lymph nodes, spleen, skin and liver. Based on our expertise we have established several collaborations with other investigators to analyze Lymphocyte and Leucocyte dynamics and function in situ. We are currently further developing our technologies to allow for imaging cellular effector functions. Specifically we aim to visualize signalling events live and in real time.

The second pillar of our platform is the application of high-end confocal microscopy for multi-colour fluorescent stainings (up to 7 colours). This technique the so-called Histocytometry allows fluorescence microscopy. We work with up to ten dyes and use continuous spectral detection across the complete wavelength range. LSM 710 enables confocal microscopy for a wide variety of applications. With the inverse Axio Observer from Carl Zeiss, LSM 710 offers you unrivalled confocal microscopy in cell and developmental biology. Upfront stands such as Axio Imager or Axio Examiner allow you to analyse your equipment to record neurobiological, physiological and developmental relationships to an exceptional standard.

These high-end microscopy systems are powered by several laser lines (405, 488, 496, 543, 561 and 633nm) as well as a tuneable 2-photon/laser (Chameleon) and a fixed 2-photon/ fiber laser (1055nm, Onefly). Additionally they are equipped with a spectral detector that allows for spectral unmixing and four highly sensitive GaAsP detectors (BiG) for optimal emission detection.

**Imaris software**
For optimal analysis of imaging data we provide access and guidance to Imaris software.

**Contact Information**
Prof. Wolfgang Kastenmüller
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+49 (0)228 287-11040

Cluster members can find detailed information on the Intranet: imarisinformation.net

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**Shared Resources**
**Intravitral Microscopy and Histocytometry**

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**Computational Structural Biology**

**Institute of Clinical Chemistry and Clinical Pharmacology**
**Faculty of Medicine**
**Director: Prof. Gunther Hartmann**

**Expertise**
Dr. Kubarenko has worked in the field of Computational Structural Biology for many years. His previous bioinformatic skills and expertise include:
- Homology modelling of proteins and protein-protein complexes
- function of LPS sensor lipopolysaccharide binding protein (LBP) (role of the frequent human SNP on LBP structure and function) [Immunol. 2013];
- role of posttranslational modifications in the function of death receptors (DRs) (modelling of DR glycosylation and influence on DR function and DRs cluster and signaling networks formation) [PLoS One 2011];
- intergrins and integrin-binding proteins in tumour progression and metastasis (modelling influence of SNPs in intergrins and osteopontin on their structure, function and interactions) [Cancer Gene Ther. 2011, Matrixogenesis 2012];
- sensing of hybrid DNA-RNA nucleic acid ligands by AIM2 and cGAS (modelling of protein-ligand complexes) [EMBO J. 2014].

**Drug virtual screening**
Promising small molecule inhibitors or activators can be screened using powerful virtual screening approaches with the combined use of different software solutions (Schrödinger package, PyRx/AutoDock, etc.), allowing for rapid and cost-effective analysis of a protein of interest (or set of proteins) for its silico preselection from large-scale compound libraries (>100,000 compounds) to guide smaller in vitro screenings. Modern virtual screening approaches allow for the screening of functional molecular building blocks to guide the synthesis of further putative ligands.

**Molecular Dynamics Simulation (MDS)**
MDS approach is a very powerful tool to perform energy optimization on individual proteins or protein-protein complexes after homology modelling. MDS structure optimization is an important final step in the modelling of protein-ligand structures obtained from protein-ligand docking or virtual screening.

**Main in silico research areas**
- Modelling of proteins and protein-protein complexes
- Homology modelling is a powerful method which provides structural information about whole proteins, single amino acids or small regions mutations. Dr. Kubarenko has established several novel advanced techniques and protocols that allow the modelling of proteins even when only low homology templates are available.
- Protein-ligand docking
  - De novo modelling of protein-protein complexes formation, also when no template complexes could be found for homology modelling, could be challenged by docking using different software (GRAMM, AutoDock, HADDOCK etc).
- Protein-ligand (small molecule, NA, peptide) docking
  - The interaction of small molecules or small polymeric ligands with proteins of interest could be predicted by protein-ligand docking (GRAMM, AutoDock, HADDOCK etc).

**Contact Information**
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**Intravitral Microscopy and Histocytometry**

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**Computational Structural Biology**

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**Collaborative Infrastructure**

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**Institute of Experimental Medicine**
**Faculty of Medicine**
**Director: Prof. Christian Kurts**

**Instrumentation**
- Zeiss LSM 780 upright confocal microscope
  - The sensitivity of LSM 780 is quite simply outstanding. The GaAsP detector achieves 45 percent quantum efficiency compared to 25 percent typically by conventional PMT detectors. This results in accurate details and contrast-rich images of the challenging specimens you encounter in your live cell imaging.
  - The system’s illumination and detection design allows you to simultaneously acquire up to ten dyes. You excite any common fluorophore with up to eight different lasers, detecting the signals with the 32 channel GaAsP detector. LSM 780 is so sensitive, the system even allows photon-counting.
- Zeiss LSM 710 inverted confocal microscope
  - The new illumination and detection design of LSM 710 brings complete freedom to your fluorescence microscopy. You work with up to ten dyes and use continuous spectral detection across the complete wavelength range. LSM 710 enables confocal microscopy for a wide variety of applications. With the inverse Axio Observer from Carl Zeiss, LSM 710 offers you unrivalled confocal microscopy in cell and developmental biology. Upfront stands such as Axio Imager or Axio Examiner offer you all the equipment you need to record neurobiological, physiological and developmental relationships to an exceptional standard.

**Collaborative Infrastructure**

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**Institute of Clinical Chemistry and Clinical Pharmacology**
**Faculty of Medicine**
**Director: Prof. Gunther Hartmann**

**Expertise**
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  - Promising small molecule inhibitors or activators can be screened using powerful virtual screening approaches with the combined use of different software solutions (Schrödinger package, PyRx/AutoDock, etc.), allowing for rapid and cost-effective analysis of a protein of interest (or set of proteins) for in silico preselection from large-scale compound libraries (>100,000 compounds) to guide smaller in vitro screenings. Modern virtual screening approaches allow for the screening of functional molecular building blocks to guide the synthesis of further putative ligands.
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**Contact Information**
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The cover image shows the regulation of transcription factors in human macrophages stimulated with TNF, PGE2 and P3C over time in the form of co-expression networks. Created by Kathrin Klee, Jil Sander, Jia Xue, Patrick Günther, Kevin Baßler and Dr. Thomas Ulas (See: Xue et al., 2014).