Come Together to Bridge the Gap

Inflammation - Immunology - Neurobiology - Vascular Biology

IAI-CCHD PhD Symposium 2015

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Universität Zürich; Zürich, Switzerland

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Karolinska Institutet; Stockholm, Sweden

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Spemann Graduate School of Biology and Medicine; Freiburg, Germany

Rafael Fernandez Chacon
Instituto de Biomedicina de Sevilla; Seville, Spain

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Cold Spring Harbor Laboratory; Cold Spring Harbor, NY, United States

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Polly Matzinger
National Institute of Health; Bethesda, MA, United States

Anura Rambukkana
MRC Centre for Regenerative Medicine; Edinburgh, United Kingdom

Filip Swirski
Harvard Medical School; Boston, MA, United States

Ari Waisman
Johannes Gutenberg Universitätsmedizin; Mainz, Germany

Steve P. Watson
University of Birmingham; Birmingham, United Kingdom

Info and free registration at
www.meduniwien.ac.at/phd-cchd/
www.meduniwien.ac.at/phdiai/form.htm

Hörsaalzentrum am Südgarten
General Hospital of Vienna
Währingergürtel 18-20, 1090 Vienna
“Come together-to Bridge the Gap”
2nd Joint IAI-CCHD Symposium

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CELL COMMUNICATION IN HEALTH AND DISEASE

PHD-PROGRAM
INFLAMMATION AND IMMUNITY

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“Come together-to Bridge the Gap”
2nd Joint IAI-CCHD Symposium

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Dear Participants at the PhD Joint Symposium,

the MedUni Vienna is one of the most highly renowned medical schools in the world and is the largest medical training centre in the German-speaking countries by student numbers.

We have around 7,500 students on degree courses in Human or Dental Medicine. Our English-language PhD course is key to the education offered by the Medical University of Vienna. Over 1,300 early-career researchers are studying for a doctorate or a PhD here. The PhD students are directly involved in our research teams and even as they study they are laying the foundations for their personal specialties. When they graduate, they will already be able to point to several publications, often in top journals.

The high quality and top standards of this postgraduate education have won the Medical University of Vienna’s PhD courses huge international respect, and boosted Vienna’s status as an outstanding research centre. This is underlined by our high percentage of international PhD students – over 30 per cent come from outside Austria.

The motto of today’s symposium, which was arranged by PhD students on the Inflammation, Immunology, Neurobiology and Vascular Biology doctoral courses, is “Come Together to Bridge the Gap”, emphasising the students’ strongly collaborative and cohesive approach.

Once again, this shows how highly motivated our PhD students are to participate and to get their own outstanding events up and running, which can only be to the benefit of our university’s reputation.

I would like to thank the organisers for their dedication and wish your event every success; may you and all the participants enjoy fruitful discussions and new experiences at MedUni Vienna.

Wolfgang Schütz,

Rector of MedUni Vienna
The doctoral training course 'Cell Communication in Health and Disease' (CCHD) has been implemented at the Medical University of Vienna (MUV) in September 2006. Hence, it is more than eight years that this organizational backbone exists. Now, early in 2015, a total of 63 student members have joined this program and 27 thereof have graduated. The major aim of CCHD is to guarantee multidisciplinarity in the education of PhD students in clinically relevant research topics. The research projects stem from one of four scientific themes that deal with organ independent ubiquitous regulatory systems (neurobiology, vascular biology, immunology, and inflammation research). Although these research themes appear heterogeneous, they all focus on the communication within or between cells in either health or various disease states. Thus, CCHD students learn in an interdisciplinary manner how to abstract from their own thesis projects into the other research themes and to thereby bridge the gap. CCHD being in its ninth year gives us the opportunity to have our Eighth International Workshop of Cell Communication in Health and Disease. As in the previous year, this meeting is organized by the current student members of CCHD in collaboration with the student members of the program Inflammation and Immunity (IAI).

In accordance with scientific multidisciplinarity as major asset of CCHD, this workshop brings together experts in the four CCHD research topics with the aim of bridging the gap. The speakers and the members of IAI and CCHD come together to provide an exciting scientific meeting with a program spanning from myocardial infarction to the development of lymphocytes and antigen presenting cells, from mechanisms of neurodegeneration to those of metabolic disease, and from the immunologic danger model to wiring within neuronal circuits. I would like to thank all the students for putting together this impressive program and our guests for accepting the students’ invitations in order to share their results and expertise with us. I look forward to enlightening seminars and stimulating discussions and I do hope that not only the student members of CCHD and IAI, but also all other participants will keep this workshop in mind as memorable event.

Stefan Boehm

Coordinator of CCHD
“Come together-to Bridge the Gap”
2nd Joint IAI-CCHD Symposium

Greetings from the Head of the IAI PhD Program – Maria Sibilia

As head of the Inflammation and Immunity (IAI) PhD Program I welcome you to this year’s Symposium “Come together – to Bridge the Gap” here in Vienna, which is for the 2nd time a Joint PhD Symposium of our PhD Program and the “Cell Communication in Health and Disease” (CCHD) PhD Program.

The IAI PhD Program is a PhD program for molecular biology at the Medical University of Vienna that offers an excellent training opportunity for graduate students in the field of basic, translational and clinical research. We encourage our students to think freely as well as work independently in a stimulating environment.

Vienna as Austria’s capital represents a long research tradition in a colorful, very diverse cultural environment and we strive to integrate these influences into our program.

The research topics for the 2nd Joint IAI-CCHD PhD Symposium “Come together – to Bridge the Gap” mainly focus on Immunology and Inflammation and additionally covers the fields of Vascular Biology and Neurobiology. Here at the Medical University of Vienna it is our goal to combine the basic discoveries of all these diverse fields to keep improving therapeutic strategies against cancer, allergies and infections.

Our students are entrusted with planning the Symposium, which teaches them the soft skills needed to organize, and plan events as well as establishing a scientific network. As every year we have invited well renowned scientists to present their work from very different scientific fields.

In the name of all faculty members I would like to thank our students for putting together such an exciting program, just as much as I would like to thank all speakers for accepting our invitation and for traveling to Vienna to make this event possible. I truly wish all participants of this year’s IAI-CCHD Symposium three very exciting days.

Finally I would like to express my deepest gratitude towards the Austrian Science Fund (FWF) and the Medical University of Vienna for their continued support of our PhD program as well as all the sponsors and exhibitors that support this Symposium.
Greetings from the IAI and CCHD students

Dear Participants,

it is our great pleasure to welcome you here in Vienna to our 2\textsuperscript{nd} Joint IAI-CCHD PhD Symposium “\textit{Come together - to Bridge the Gap}”.

Last year the students of the PhD programs ‘Cell Communication in Health and Disease’ (CCHD) and ‘Inflammation and Immunity’ (IAI) initially organized a Joint Symposium, and seeing the great success of which, we decided to join forces once again this year.

We are proud to welcome 15 renowned experts from all over the world that will participate in our 2\textsuperscript{nd} Joint IAI-CCHD Symposium and agreed to introduce us into their latest scientific discoveries out of their very exciting fields of INFLAMMATION, IMMUNITY, NEUROBILOGY and VASCULAR BIOLOGY.

It is our aim to present you with a short insight into every respective field without forgetting that all of these topics are connected with one another in a biological system; hence this year’s Symposium is entitled “\textit{Come together - to Bridge the Gap}”.

We encourage all our participants to indeed come together for a stimulating scientific experience, to take this opportunity to meet our international experts and to engage in inspired discussions about these fascinating subjects.

We hope you will enjoy this year’s exciting program on both a scientific as well as on a social level and are looking forward to answering all questions concerning this meeting.

Please feel free to share your thoughts and opinions about our Symposium so that we have the chance to further improve.

Have a great stay in Vienna and with the kindest regards,

The Organizing Committee
"Come together to Bridge the Gap"
2\textsuperscript{nd} Joint IAI-CCHD Symposium

**Program of the Joint IAI-CCHD Symposium**

9\textsuperscript{th}-11\textsuperscript{th} February 2015

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<td>Wolfgang Schütz (<em>Rector of the Medical University of Vienna</em>)</td>
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<td>Maria Sibilia (<em>Coordinator of IAI PhD Program</em>)</td>
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**Vascular Biology Session I**

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<tr>
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<td>Filip Swirski</td>
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<td>Aniko V. Fejes (CCHD)</td>
<td>Effect of <em>Helicobacter pylori</em> on platelet activation</td>
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<td>Steve P. Watson</td>
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<tr>
<td>13:15-14:15</td>
<td>Andreas Diefenbach</td>
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<td>14:15-14:30</td>
<td>Barbara Maier (CCHD)</td>
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<td>14:30-15:30</td>
<td>Mathias Heikenwärder</td>
<td>Metabolic activation of intrahepatic CD8\textsuperscript{+} T cells and NKT cells causes non-alcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes.</td>
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**Immunology Session III**

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<td>Sophia Karagiannis</td>
<td>Could humoral immunity inform antibody therapeutic strategies for cancer?</td>
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<td>17:00-17:15</td>
<td>Eva Wollmann (IAI)</td>
<td>Natural clinical tolerance to peanut in African patients is caused by poor allergenic activity of peanut IgE</td>
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<td>Polly Matzinger</td>
<td>The interplay between danger signal and autoimmunity</td>
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## Program of the Joint IAI-CCHD Symposium

### 9th-11th February 2015

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<td>Mathias Parrini (IAI)</td>
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<td>Anna Moskovskich (CCHD)</td>
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<td>Solute Carriers: Proteins at the Interface of Host Metabolism and Viral Life Cycle</td>
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<td>Yenan Bryceson</td>
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<td>Lymphocyte cytotoxicity illuminated by human primary immunodeficiency syndromes</td>
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<td>14:30-14:45</td>
<td>Sriram Srivatsa (IAI)</td>
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<td>Florent Ginhoux</td>
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<td>17:30-18:30</td>
<td>Anura Rambukkana</td>
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<td>From Bacterial Infection to Stem cells: New insights into Pathogenesis and Tissue Repair</td>
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**Chair:** Veronika Sexl (IAI), Johannes Stöckl (IAI)

**Chair:** Wilfried Ellmeier (IAI), Barbara Bohle (IAI)

**Chair:** Herbert Strobl (IAI), Sylvia Knapp (CCHD)
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<td>Bernd Bodenmiller</td>
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<td>Analysis of single cell states in health and disease by CyTOF mass cytometry</td>
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<td>11:00-11:15</td>
<td>Nora Zulehner (IAI)</td>
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<td>Characterization of the allergic T-cell response to Dauc 1, the Bet v 1 homologous protein in carrot</td>
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<td>11:15-11:30</td>
<td>Nicole Amberg (IAI)</td>
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<td>The role of EGFR signaling in skin stem cells</td>
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**Neurobiology**

| 11:30-12:30  | Tibor Harkany                                |
|              | Molecular determinants of cannabis sensitivity in the fetal cerebral cortex |
| 12:30-13:30  | Lunch                                       |
| 13:30-14:30  | Rafael Fernandez Chacon                     |
|              | Synaptic and extrasynaptic functions of a molecular cochaperone |
| 14:30-14:45  | Ameya Kasture (CCHD)                        |
|              | What is the somatodendritic serotonin transporter good for? |
| 14:45-15:00  | Tugrul Özdemir (CCHD)                       |
|              | Firing Patterns of Distinct Types of Principle Cells in the Medial Prefrontal Cortex during Working Memory and Rule Switching Task |
| 15:00-16:00  | Adam Kepecs                                 |
|              | From cell-types to cognition: mapping behavioral repertoire of identified neuron types |
| 16:00-16:15  | Closing Remarks                             |
|              | Stefan Böhm (Coordinator of CCHD PhD Program) |
Overview:

INV1. Analysis of single cell states in health and disease by CyTOF mass cytometry (B. Bodenmiller)

INV2. Lymphocyte cytotoxicity illuminated by human primary immunodeficiency syndromes (Y. Bryceson)

INV3. Innate Mechanisms of Metabolic Homeostasis (A. Chawla)

INV4. Transcriptional control of ILC fate decisions (A. Diefenbach)

INV5. Synaptic and extrasynaptic functions of a molecular co-chaperone (R. Fernandez Chacon)

INV6. Dendritic cell and macrophage ontogeny (F. Ginhoux)

INV7. Molecular determinants of cannabis sensitivity in the fetal cerebral cortex (T. Harkány)

INV8. Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes non-alcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes. (M. Heikenwälder)

INV9. Could humoral immunity inform antibody therapeutic strategies for cancer? (S. Karagiannis)

INV10. Neural circuits behind cognition: behavioral algorithms and neural mechanisms of confidence judgments (A. Kepecs)

INV11. Separate neutrophil subsets identified by leukocyte dynamics and changes in functionality: studies performed in LPS challenged individuals (L. Koenderman)
INV12. The interplay between danger signal and autoimmunity  
   (P. Matzinger)  
INV13. From Bacterial Infection to Stem cells: New insights into Pathogenesis and Tissue Repair (A. Rambukkana)  
INV14. Innate response activator B cells in acute and chronic inflammation  
   (F. Swirski)  
INV15. Transcriptional and cytokine regulation of Th17 cells (Ari Waisman)  
INV16. The role of the Podoplanin-CLEC-2 pathway in platelets in development and thromboinflammation (S. P. Watson)
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Bernd Bodenmiller
University of Zürich

INV1. Analysis of single cell states in health and disease by CyTOF mass cytometry

Tissues and tumors are complex assemblies of multiple cell types that interact and communicate with each other to achieve physiological states. In cancer, many aspects of tumor development to metastasis depend on these cell interactions in unique microenvironments. Especially signaling networks, forming the core of cellular decision making, are shaped by cell interactions. To study and understand the decision making in the microenvironments, single cell analysis technologies are needed that allow to measure cell type, signaling network state and other cellular processes with spatial resolution. Mass cytometry is a recent single cell analysis approach that enables to measure up to 100 molecules simultaneously using isotopically pure rare earth metals as reporters. Previously, only cells in suspension could be analyzed using mass cytometry, and thus essential information on cell location and cell-to-cell interactions was lost. We have now coupled immunocytochemical and immunohistochemical methods with high-resolution laser ablation to mass cytometry. The approach enables the simultaneous imaging of up to 100 proteins and phosphorylation sites at a sub-cellular resolution. We used the imaging mass cytometry to study the signaling networks activated during the epithelial-mesenchymal transition (EMT), a process driving the formation of metastasis, within their native microenvironment in multiple breast cancer tumors. Imaging mass cytometry revealed an unexpected complexity of cell-to-cell interactions and cellular (EMT) states in the analyzed tumors. The approach also allowed to accurately classify patients based on the visualized single cell marker expression and cell interactions. Imaging mass cytometry will enable the analysis into how cellular assemblies generate phenotypes in health and disease and will support the transition of medicine towards individualized molecularly targeted therapies.

1999-2001: Vordiplom (Biochemistry), University of Bayreuth
2001-2004: Diplom (Biochemistry), ETH Zurich
2004-2008: Ph.D. Systems Biology (ETH Zurich, Lab of Ruedi Aebersold)
2008-2009: Postdoc (ETH Zurich, Lab of Ruedi Aebersold)
2009-2012: Postdoc (Stanford University, Lab of Garry P. Nolan)
2013- Assistant Professor University of Zurich
INV2. Lymphocyte cytotoxicity illuminated by human primary immunodeficiency syndromes

Cytotoxic lymphocytes, including CD8+ cytotoxic T cells (CTL) and natural killer (NK) cells, can recognize and eradicate infected as well as transformed cells. Target cell killing is mediated through directed release of perforin-containing secretory lysosomes. Congenital defects in lymphocyte cytotoxicity are associated with early-onset, potentially fatal primary immunodeficiency syndromes characterized by hyperinflammatory conditions. Through studies of patients with suspected primary immunodeficiencies, our lab is gaining understanding of the molecular mechanisms underlying cytotoxic lymphocyte development, differentiation, and effector function. Providing novel insights to secretory lysosome release, we have identified non-coding mutations that regulate expression of protein isoforms required for secretory lysosome exocytosis. Moreover, other cell biological studies have uncovered a role for recycling endosome fusion in facilitating secretory lysosome exocytosis. This seminar will highlight recent advances in our knowledge of lymphocyte cytotoxicity and discuss implications for human health.

Yenan received his Masters degree from the University of Oslo, Norway in 2000, and his PhD from Karolinska Institutet in 2008 after working in the lab of Eric Long at the National Institutes of Health, Rockville, MD, USA and receiving support from the National Institutes of Health, Karolinska Institutet Graduate Partnership Program. He is Assistant Professor. His laboratory is located within the Center for Infectious Medicine at Karolinska University Hospital Huddinge.

(Source: http://ki.se/en/medh/yenan-bryceson-group)
INV3. Innate Mechanisms of Metabolic Homeostasis

Macrophages take residence in nearly all tissues, where they function as sensors and integrators of environmental and metabolic stress. In metabolic tissues, tissue resident macrophages sense their local and systemic environment to coordinate parenchymal cell metabolism. Here, we present evidence that the innate immune system also regulates acclimatization to environmental cold. Previous work has demonstrated that prolonged cold exposure induces the growth of uncoupling protein 1⁺ brown adipocytes in the subcutaneous white adipose tissue of mice, termed “beige” fat, to provide a defense against cold and obesity. Although a cold environment is the physiologic stimulus for inducing beige fat mass in mice and humans, the events that lead from the sensing of cold to the development of beige fat had remained poorly understood. We have identified the efferent circuits that regulate the development of thermogenic beige fat. These circuits consist of type 2 innate immune cells and signals, including type 2 innate lymphoid cells (ILC2s), eosinophils, alternatively activated macrophages, and the type 2 cytokines IL-33, IL-4 and IL-13. We found that type 2 immunity sequentially regulates the expansion, commitment, and differentiation of adipocyte precursors into functional beige adipocytes. The mechanisms by which these type 2 innate circuits regulate the biogenesis of thermogenic beige fat, and its implications for the treatment of obesity will be presented at this meeting.

Ajay Chawla graduated with an MD and a PhD in Physiology from the University of Pennsylvania, Philadelphia, in 1996. He then joined the laboratory of Ronald M. Evans at the Salk Institute, San Diego, CA, where his postdoctoral research focused on the regulation of lipid metabolism in macrophages. He was an assistant professor at Stanford University from 2003-2010, until he was appointed to his current position as Associate Professor of Physiology and Medicine at the University of California, San Francisco. His research focus spans from the transcriptional control of innate immune activation to immune determinants of tissue regeneration.
INV4. Transcriptional control of ILC fate decisions

Innate lymphoid cells (ILCs) are a recently discovered family of innate lymphocytes that are substantially represented at mucosal surfaces and have been implicated in the protection of epithelial barriers. Various types of ILCs can be discriminated based on the expression of distinct transcription factors controlling the expression of a distinct set of cytokine genes endowing the various ILC subsets with a specific range of effector functions. Currently, three groups of ILCs are being recognized. Group 1 ILCs (ILC1s) are a diverse group of ILCs comprised of natural killer (NK) cells and other, poorly defined subsets of ILCs. It is believed that the ILC1 fate decision is controlled by the T-box transcription factor T-bet endowing ILC1s with the capability to produce large amounts of IFN-γ. ILC2s express high levels of GATA-3, produce IL-5 and IL-13 and have been involved in immunity to helminth infections and in the pathogenesis of allergic diseases. Group 3 ILCs developmentally depend on the transcription factor RORγt and produce the cytokines IL-22, IL-17A and IL-17F. ILC3s are believed to be involved in the protection against intestinal bacterial infections and, if inappropriately stimulated, can be important drivers of inflammatory disorders. The transcriptional programs and effector cytokines of the various ILC subsets strikingly resemble those of the various T helper cell effector fates suggesting that such transcriptional circuitry already formed in the evolutionary older innate immune system. The various ILC subsets are developmentally related as all ILC lineages depend on the transcriptional regulator Id2 (inhibitor of DNA binding 2) that interferes with E2 protein-controlled gene expression. This raises the important issue if ILCs may derive from a common ILC progenitor (CILP). Identification of such a progenitor would allow to identify the molecular signals required for the specification of the various ILC lineages. I will discuss progress towards our understanding of the molecular programs regulating ILC fate decisions and our current models of transcriptional stability and plasticity of ILC fates. Finally, I will discuss an unprecedented role of ILC3s in the protection against mucosal virus infections.

Andreas Diefenbach received his medical training at the Imperial College London and the University of Erlangen-Nuremberg, obtaining his MD in 1996 and his PhD in Medicine (“summa cum laude”) in 1997. He was a postdoctoral fellow at the University of California, Berkeley and held professorships at New York University Medical Center and at the University of Freiburg. In 2013 he was appointed full professor for Medical Microbiology and Hygiene at the University of Mainz. His research interests include infection biology, development and function of innate immune cells as well as tumor immunology.
INV5. Synaptic and extrasynaptic functions of a molecular co-chaperone

Nerve terminals are able to maintain the continuous release of neurotransmitters during extended periods of time at locations far away from the cell soma. For example, presynaptic terminals from tonic motorneurons receive from 300,000 to 500,000 action potentials per day (Hennig and Lomo, Nature 1985) imposing on SNARE complexes a heavy-duty cycling of protein folding and unfolding reactions. Cysteine String Protein alpha (CSP-alpha) is a synaptic vesicle protein that, together with Hsc-70 and SGT (small glutamine-rich protein), forms a chaperone complex essential to maintain a functional pool of SNAP25 and to promote SNARE complex assembly (Chandra et al., Cell 2005; Sharma et al. Nat. Cell Biol. 2011). Interestingly knock-out mice lacking CSP-alpha suffer from early lethality due to presynaptic degeneration (Fernández-Chacón et.al., Neuron 2004). We have recently found that motorneurons require CSPalpha to maintain the readily releasable vesicular pool and synaptic vesicle recycling (Rozas., et al., Neuron 2012). Interestingly, in central neurons, we have shown that CSP-alpha prevents activity-dependent degeneration of GABAergic synapses in high firing rate parvalbumin-positive neurons, indicating that high-neural activity increases synapse vulnerability and CSP-alpha is essential to maintain presynaptic function under a physiologically high-activity regime (García-Junco-Clemente et al., JNeurosci. 2010). In my talk I will discuss recent findings that uncover unexpected functions of CSP-alpha beyond the nerve terminals.
INV6. Dendritic cell and macrophage ontogeny

Dendritic cells (DCs), monocytes and macrophages play crucial and distinct roles in tissue homeostasis and immunity, but also contribute to a broad spectrum of pathologies and are thus attractive therapeutic targets. Potential intervention strategies aiming at manipulation of these cells will require in-depth insights of their origins and the mechanisms that govern their homeostasis. DCs and monocytes arise from common bone marrow (BM) precursor named macrophage-dendritic cell precursors (MDP), branching into exclusively DC- or monocyte-committed progenitors named common dendritic cell progenitors (CDPs) or common monocyte progenitor (cMoPs) respectively. CDPs give rise to plasmacytoid DC and migratory DC precursors termed pre-DCs. Pre-DCs seed tissues where they differentiate into the two major functionally specialized DC lineages, CD8α⁺/CD103⁺ DCs and CD11b⁺ DCs. Recent evidence from our laboratory and others have showed that monocytes do not substantially contribute to all tissue macrophage populations in steady state and inflammatory conditions. Rather certain tissue macrophages in mice are derived from embryonic precursors, are seeded before birth and maintain themselves in adults by self-renewal. In addition, we now provided evidence that commitment to CD8α⁺/CD103⁺ DC or CD11b⁺ DC subsets is imprinted early in the BM. Combining single cell sequencing with conventional transcriptomic analysis and intra-femoral transfer, we identified for the first time DC subset-specific precursors in the BM as well as previously unknown molecular checkpoints for DC lineage commitment as early as the CDP stage. These new insights into the origins of DCs, monocytes and macrophages should aid the rational design of therapies aimed at harnessing the functions of these cells in homeostasis and inflammation and will allow efficient targeting and manipulation during health and disease.

Florent Ginhoux started his PhD in the Immunology Team of GENETHON, Evry and obtained his PhD in 2004 from the University Pierre et Marie CURIE, Paris VI. As a postdoctoral fellow, Florent Ginhoux joined the Laboratory of Miriam Merad in the Mount Sinai School of Medicine (MSSM), New York where he studied the ontogeny and the homeostasis of dendritic cell populations, with a strong focus on Langerhans cells. In 2008 he became an Assistant Professor in the Department of Gene and Cell Medicine, MSSM and member of the Immunology Institute of MSSM. He joined the Singapore Immunology Network (SIgN) in May 2009 where he currently is a Senior Principal Investigator focusing on the origin and differentiation of dendritic cells and macrophages.
INV7. Molecular determinants of cannabis sensitivity in the fetal cerebral cortex

Endocannabinoids have emerged as modulators of neuronal development. Increasing amount of evidence supports the hypothesis that a continuum of endocannabinoid actions overarches the differentiation and postnatal modulation of many cortical synapses. My laboratory has dissected the molecular and cell biology of endocannabinoid signaling by focusing on successive stages of cortical development, including the definition of the anatomical blueprint of endocannabinoid signaling networks, characterizing their roles in neurogenesis, cell migration, and axonal growth and guidance, and highlighting molecular hubs for endocannabinoid signal diversification and upstream control. These studies allowed us to test the hypothesis whether delta-9-tetrahydrocannabinol (THC), the major psychoactive component from Cannabis sativa, can trigger a cannabinoid receptor-driven molecular cascade to impact neuronal specification, imparting permanent structural deficits. This question is timely considering the rapidly changing landscape of cannabis legislation, and increased cannabis consumption for recreational and medical purposes. Repeated THC exposure erroneously times CB1 cannabinoid receptor activation to rewire the fetal cortical circuitry. I suggest that THC primarily binds CB1 cannabinoid receptors and down-regulates endocannabinoid production. Upon interrogating the THC-sensitive neuronal proteome we identified Superior Cervical Ganglion 10 (SCG10)/stathmin-2, a microtubule-binding protein in axons, as a substrate of altered neuronal connectivity. We found SCG10 reduced in both experimental models and in the hippocampus and cortical plate of mid-gestational (week 18-22) human fetuses exposed in utero to cannabis. THC-induced CB1 cannabinoid receptor activation was shown to recruit c-Jun N-terminal kinases to phosphorylate SCG10, promoting its rapid degradation within motile axons and microtubule stabilization in situ. I will support the notion that THC can permanently modify the cortical circuitry by showing impaired long-term synaptic plasticity at both excitatory and inhibitory cortical synapses in adult mice prenatally exposed to THC. Overall, our results define key sites of neuronal vulnerability to plant-derived cannabinoids in the developing cerebral cortex, and highlight the maintenance of cytoskeletal dynamics as a molecular target for cannabis whose imbalance can limit the computational power of neuronal circuitries in affected offspring.

Tibor Harkány received his M.Sc. from the University of Szeged, Hungary, in 1995, followed by a Ph.D. in medical sciences from Semmelweis University, Hungary. He now jointly holds the positions of Head of the Department of Molecular Neurosciences, Center for Brain Research at the Medical University of Vienna, Austria, and Professor of Neurobiology at the Karolinska Institute, Sweden. His laboratory implicated endocannabinoids in axon guidance and identified molecular substrates of Δ9-tetrahydrocannabinol action in developing neurons. Current research addresses how disrupted endocannabinoid signalling during brain development primes for delayed neuropsychiatric illness.
INV8. Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes non-alcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes.

Overweight and metabolic syndrome (e.g. abdominal obesity, insulin resistance) are reaching pandemic dimensions in industrialized countries and strongly increase in developed countries. Non-alcoholic fatty liver disease (NAFLD) is the most frequent liver disease world-wide with 90 million patients in the USA and approximately 40 million patients in Europe and is the clinical manifestation of a high caloric and sedentary life style. A significant number of NAFLD patients develop non-alcoholic steatohepatitis (NASH), fibrosis and consequently hepatocellular carcinoma (HCC). With 800,000 deaths/year HCC is the 2nd most common cause of cancer-related mortality. Overweight and metabolic syndrome have become the major etiology of HCC in industrialized countries (slowly overtaking Hepatitis B, C virus infections as etiologies) making NASH-driven HCC the most rapidly increasing cancer in the USA with utmost clinical importance. At the same time efficacious therapies for NASH or HCC are lacking. The exact mechanisms of NASH and subsequent HCC development have remained unknown. We have recently established a mouse model of NASH-driven HCC recapitulating human pathology. Analyzing human patient samples as well as our mouse model we could show that interactions between immune cells and hepatocytes control NASH and subsequent HCC development, providing novel targets for treatment.

Mathias Heikenwälder obtained his PhD in 2004 from the University Hospital Zurich (USZ)/ETH Zurich where he studied immunological aspects of prion pathogenesis. After his postdoctoral fellowship with Prof. Dr. Aguzzi, he was given the opportunity to establish his own research group at the USZ/ETH with a focus on chronic hepatitis and liver cancer, chronic inflammation, cell death and autoimmunity. Since 2010 he is a Helmholtz Young Investigators group leader at the Helmholtz Zentrum München and W2 Professor at the Technische Universität München in Munich, Germany.
INV9. Could humoral immunity inform antibody therapeutic strategies for cancer?

Studying the interactions between cancer cells with B cells and their antibodies may inform novel treatments. Despite enhanced frequencies of tumour-reactive B cell and antibody responses in patients, Th2-biased inflammation in tumours, driven by IL-10, can modulate B cells to express IgG4 a less effective antibody isotype. IgG4 antibodies poorly activate immune effector cells against cancer and can interfere with the Fc-mediated effector functions of otherwise cytotoxic IgG1 by blocking their interactions with effector cells. Such suppressive forces may restrict activation of effector cells and reduce the therapeutic impact of IgG1 antibodies, supporting the design of antibodies less prone to blockade. Although human immunity functions through nine antibody isotypes, antibody therapies developed for cancer employ IgG class antibodies, with IgG1 being the most commonly used. However, application of IgG antibodies may be restricted by inhibitory Fc receptors or by antibodies such as IgG4 in tumours. Antibodies engineered with IgE Fc regions targeting tumour antigens may confer superior anti-tumour efficacy compared to IgGs. IgEs participate in the human allergic responses, but also contribute to defenses against parasitic infections. Attributes of IgE, such as immune surveillance functions in tissues, high affinity for cognate receptors on frequently tumour-resident effector cells and lack of Fcε inhibitory receptors may translate into immune activation and protection against tumours. The pathway to translation of IgE antibodies will be discussed, focusing on functional model systems interrogated to elucidate potency and mechanisms of action.

Sophia Karagiannis is a translational tumour immunologist specialising in B cell and antibody immunity and in designing antibody therapies for cancer. She received BA and MS degrees in Biochemistry at Rutgers University, USA, and a PhD in B cell and IgE Immunology at King’s College London (SERC and SmithKline Beecham-funded scholarships). She developed immunotherapeutics for inflammatory diseases and cancer in academic and biotechnology environments in London and Cambridge. She was appointed as NIHR/BRC Senior Research Fellow in 2007 and as Senior Lecturer at King’s College London in 2013. The Karagiannis laboratory focus antibody immunotherapies, including antibodies with IgE class Fc regions, for solid tumours and elucidating their immune activatory properties through functional assay and disease-relevant model system design. Dissecting patient-derived antibodies and B cell responses inform antibody discovery, target and biomarker identification, to derive stratified medicine approaches. The group are developing an antibody pipeline and working towards a first-in-man Phase I clinical trial of an IgE antibody. Karagiannis is senior/corresponding author of >20 peer-reviewed manuscripts and senior author of a published patent. She is a co-founder of the International Task Force on AllergoOncology since 2008 and Task Force secretary for the European Academy of Allergy and Clinical Immunology (EAACI) since 2014.
INV10. Neural circuits behind cognition: behavioral algorithms and neural mechanisms of confidence judgments

Decision confidence is a forecast about the correctness of one’s decision. It is often regarded as a higher-order function of the brain requiring a capacity for metacognition that may be unique to humans. If confidence manifests itself to us as a feeling, how can then one identify it amongst the brain’s electrical signals in an animal?

We tackle this issue by using mathematical models to gain traction on the problem of confidence, allowing us to identify neural correlates and mechanisms. I will begin with a statistical theory that enables us to establish that human self-reports of confidence are based on a computation of statistical confidence. Next, I will discuss computational algorithms that can be used to estimate confidence and decision tasks that we developed to behaviorally read out this estimate in humans and rats. Finally, I will discuss the neural basis of decision confidence and specifically the role of the orbitofrontal cortex and the function of specific projection neuron types.

POSITIONS
2013–present Associate Professor, Cold Spring Harbor Laboratory, NY
2010–present Adjunct Assistant, Associate Professor, SUNY Stony Brook University
2007–2013 Assistant Professor, Cold Spring Harbor Laboratory, NY

EDUCATION AND TRAINING
Ph.D., Neuroscience, Brandeis University, Waltham, MA, 1997-2002
EU Advanced Course in Computational Neuroscience, Crete, Greece, 1996
INV11. Separate neutrophil subsets identified by leukocyte dynamics and changes in functionality: studies performed in LPS challenged individuals

Neutrophils are considered to be a homogenous population of short-lived end-stage effector cells of the innate immune response. These cells are well equipped to move towards microorganisms, recognize and neutralize them by phagocytosis and intracellular killing. This rather simple concept has recently been challenged by multiple studies describing: 1. much longer lifespans of these cells in blood compared to the textbook lifespan of 7-9 hrs and 2. T-cell suppression by a distinct subset of neutrophils also referred to as myeloid-derived suppressor cells. New and unpublished data also show clear compartmentalization in neutrophil subsets with respect to killing of microorganisms. These new paradigms will be discussed with the conclusion that the neutrophil compartment in man consists of multiple functional subsets that are visible in blood only during (acute) inflammatory conditions.


Leo Koenderman is a full professor at the Department of Respiratory Medicine, University Medical Center (UMC) Utrecht, the Netherlands. He obtained his PhD in 1990 at the Central Laboratory of the Netherlands’ Red Cross Blood Transfusion Service in Amsterdam, characterizing signal transduction in human granulocytes. He then joined the UMC as a postdoctoral research fellow and has been leading his own research group since 1993. Leo Koenderman has had a longstanding interest in human neutrophils. His scientific work has contributed greatly to our current understanding of neutrophil biology and function during immune responses.
INV12. The interplay between danger signal and autoimmunity

When faced with a potential threat, the immune system must answer two main questions. 1) shall I respond, and 2) (if the answer to #1 is “yes”) what kind of response should I make. The self-non-self model of immunity suggested that the immune system answers the first question affirmatively if the potential threat is “foreign”. Janeway’s “Infectious non-self” model suggested that the threat should be an evolutionarily distant one, and the Danger model suggests that the immune system responds to things that do damage, whether they are foreign or not. Neither the self-nonself model nor the infectious-non-self model can explain the phenomenon of autoimmunity. I will give a brief overview of the danger model and how it explains why transplants are rejected while fetuses and tumors are usually not, and then show how the danger model gives us a new view of autoimmune disease.

Polly Matzinger finished her PhD in 1979 at the University of California, San Diego. She then became a NIH overseas fellow at the Cambridge University. She then went on to Basel to work at the Institute for Immunology till 1989. Currently, she is a researcher at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda MD. Polly is an expert on T cell tolerance and memory. She was the first to propose that antigen presenting cells react to “danger signals”. Building up a theory many students will have been challenged in their studies of the immune system. Apart from science Poly enjoys Jazz music and is a dog trainer.
INV13. From Bacterial Infection to Stem cells: New insights into Pathogenesis and Tissue Repair

How lineage committed tissue cells can change their cell fate is a fundamental question in biology, and has a potential for developing effective therapeutic strategies for tissue repair and modifications as well as new level of understanding of disease pathogenesis. Such insights are particularly attractive for regeneration of the damaged or diseased nervous system and better understanding of early phases of neurodegenerative diseases. Our research centers a unique neurotropic bacterial infection model that naturally causes similar host cell reprogramming events for bacterial advantage. Many years of our studies on the cell biology of Mycobacterium leprae (ML) infection, the causative organism of human leprosy, which is a chronic neurodegenerative diseases, led to the recent discovery that ML hijacks the notable plasticity of its preferred niche Schwann cells, the glial cells of the peripheral nervous system (PNS) and reprogram these lineage committed glial cells to progenitor/stem-like cells by changing gene expression. Although ML appears to use this sophisticated bacterial strategy for its own advantage, spreading infection to other tissues without detecting from host immune responses, the biology behind this infection-driven natural reprogramming provides new information into general mechanisms of cell fate reversal and change. By taking advantage of this bacterial ingenuity of ML as a model our ongoing research dissects the molecular basis of this natural reprogramming and cell fate change using in vitro and in vivo model systems with molecular biological, biochemical, genetic and imaging technologies. Our long-term goals of these efforts are to apply this new knowledge for developing new strategies for nervous system repair and to better understanding of neurodegenerative diseases.

Prof. Anura Rambukkana is currently a chair of Regeneration Biology at the MRC Centre for Regenerative Medicine, Edinburgh. He relocated to the University of Edinburgh in 2010 from The Rockefeller University New York where he was a faculty member since 2000. He obtained his PhD from the University of Amsterdam, The Netherlands, and continued his first postdoctoral training in the Academic Medical Center, University of Amsterdam. He then moved to Rockefeller University for his second postdoctoral training before obtaining his faculty position there. Prof. Rambukkana is also a member of the Edinburgh Infectious Diseases (EID). He received several awards including awards from NWO Foundation in Netherlands, Heiser Foundation New York and from the World Health Organization, and four consecutive R01 grant awards from US National Institutes of Health.
INV14. Innate response activator B cells in acute and chronic inflammation

Innate response activator (IRA) B cells are a population of B-1a derived B cells that produce the growth factors GM-CSF and IL-3. In this talk, I will describe the function of IRA B cells in several inflammatory contexts. In a mouse model of sepsis, B-1a B cells recognize bacteria in the peritoneum, migrate to the spleen, and differentiate to IRA B cells. In response to lung infection, B-1a B cells migrate from the pleural space to the lung parenchyma to secrete GM-CSF-dependent, polyreactive emergency immunoglobulin-M (IgM). The function of IRA B cells depends on the growth factor they produce in the spatiotemporal context. Our data suggest that the strategic location, coupled with the capacity to produce GM-CSF and IL-3, positions IRA B cells as important mediators of innate immunity.

Selected Publications (from total of 94 as of January 2015)


INV15. Transcriptional and cytokine regulation of Th17 cells

Th17 cells are critically involved in the development of autoimmune disease, but the mechanism for that is not clear. In our lab, we use techniques of conditional gene targeting to study the function of these cells. In my talk, I will discuss the need for cytokine signaling for the development of pathogenic Th17 cells. Furthermore, I will show how the transcription factor IRF-4 (Interferon regulatory factor 4) and RORγt (RAR-related orphan receptor gamma) regulate the development of these cells. Finally, I will show how the gut microbiota is responsible for the pathogenicity of these cells.

Ari Waisman obtained his PhD from the Weizmann Institute of Science, Rehovot, Israel in 1994. He then joined the lab of L. Steinmann at the Weizmann Institute as a postdoctoral research fellow and moved on to Cologne in 2000 where he became a research associate in 2001 and an independent Group Leader in 2005. Since 2010 he is the Director of the Institute for Molecular Medicine, University Medical Center of the Johannes Gutenberg-University, Mainz. His research interests include molecular mechanisms of CNS inflammation, regulation of inflammatory T cell response and neuroimmune interaction.
INV16. The role of the Podoplanin-CLEC-2 pathway in platelets in development and thromboinflammation

The role of platelets in haemostasis was first described in 1881 by the ground-breaking research of the Italian pathologist Giulio Bizzozero. However, it is only within the last ten years that platelets have been shown to play a critical role in a wide range of processes beyond that of haemostasis or its pathological counterpart, thrombosis.

Much of this new era in platelet research stemmed from the unexpected discovery of the C-type lectin receptor, CLEC-2, on platelets as a receptor for the snake venom toxin rhodocytin and the later discovery of podoplanin (also known as gp38 and aggrus) as its endogenous ligand. Podoplanin is widely distributed on many cell types with particularly high levels on lung type 1 alveolar cells, kidney podocytes, and lymphatic endothelial cells. In addition, podoplanin is markedly up-regulated at sites of inflammation. In contrast, only platelets and activated mouse dendritic cells (DCs) express CLEC-2, with the levels on platelets far exceeding that on DCs. The absence of podoplanin from the vasculature is consistent with the minor, if any, role of CLEC-2 in haemostasis. Studies on podoplanin and CLEC-2 deficient mice have shown a critical role for the podoplanin-axis in development of the lymphatics, cerebrovasculature and in lymph nodes, while beyond development, this pathway is important in vascular integrity at sites of inflammatory challenge and in high endothelial venules, and in inflammation. In this presentation, I will give an overview of the events that led to the discovery of CLEC-2 and elucidation of its tyrosine kinase-based signalling pathway, and describe its role in the development of the cerebrovasculature and in a novel inflammation-driven pathway of thrombosis in salmonella-infected mice.

2003- : British Heart Foundation Professor in Cardiovascular Sciences University of Birmingham, UK
1998–03: British Heart Foundation Senior Research Fellow
1988–98: Royal Society University Research Fellow Department of Pharmacology, University of Oxford

Research: Platelet ITAM and ITIM receptors and their signalling pathways; The study of patients with platelet bleeding disorders. The role of platelets in development, vascular integrity and thromboinflammation
Overview:

S1. The role of EGFR signaling in skin stem cells (N. Amberg)
S2. Effect of Helicobacter pylori on platelet activation (A.V. Fejes)
S3. What is the somatodendritic serotonin transporter good for? (A. Kasture)
S4. LPS-induced disease tolerance in Gram-negative sepsis (B. Maier)
S5. Solute Carriers: Proteins at the Interface of Host Metabolism and Viral Life Cycle (A. Moskovskich)
S6. Nuclear receptor corepressor 1 (NCoR1) in T cell development and homeostasis (L. Müller)
S7. Firing Patterns of Distinct Types of Principle Cells in the Medial Prefrontal Cortex during Working Memory and Rule Switching Task (A.T. Ozdemir)
S8. STAT1 Isoforms in Transcriptional Control – Distinct Traits (M. Parrini)
S9. Role of EGFR in colitis and colorectal cancer development. (S. Srivatsa)
S10. NSAIDs not only sensitize melanoma cells to TRAIL-induced apoptosis through upregulation of DR5 but also induces TRAIL expression by innate immune cells (Vazquez Strauss)
S11. Natural clinical tolerance to peanut in african patients is caused by poor allergenic activity of peanut IgE. (E. Wollmann)
S12. Characterization of the allergic T-cell response to Dauc 1, the Bet v 1 homologous protein in carrot (N. Zulehner)
S1. "The role of EGFR signaling in skin stem cells"

Amberg N, Lichtenberger BM, Sotiropoulou P, Holcmann M, Blanpain C, Sibilia M

The skin has important functions in several biological processes like environmental barrier, tissue regeneration, hair cycling, and wound repair. During these processes stem cells of distinct parts of the pilosebaceous unit are activated to renew the epidermis or hair. The morphogenesis and the regulation of homeostatic renewal of epidermis and hair follicle require a tight regulation of several molecular signalling pathways, including the epidermal growth factor receptor (EGFR) pathway. By elucidating the detailed mechanisms of EGFR signaling in homeostatic renewal of epidermis and hair follicles we aim for a better understanding of how aberrant and/or transactivated EGFR signaling may on the one hand impair hair follicle development and on the other hand contribute to tumor formation and progression.

In order to study the role of EGFR signalling in hair follicle development, we analysed mice lacking the EGFR in two distinct mouse models:

- EGFR$^{∆ep}$ mice lack the EGFR in basal keratinocytes of the interfollicular epidermis (IFE) and the outer root sheath (ORS) of the hair follicle (HF),
- EGFR$^{LGR5}$ mice delete the EGFR only in stem cells of the ORS.

Lack of EGFR in IFE and ORS results in a delay of hair follicle morphogenesis, which further leads to defective hair layer formation and subsequent degradation of the hair follicles. Moreover, EGFR-deficient IFE shows reduced survival, impaired differentiation and a loss of barrier function. Together, this results in a severe skin inflammation, which is similar to patients receiving anti-EGFR therapies. Surprisingly, deletion of the EGFR in the ORS only does not lead to impaired hair morphogenesis.

We therefore conclude that EGFR signalling in the IFE controls expression of paracrine signals, which are important for HF development and homeostasis.
S2. Effect of Helicobacter pylori on platelet activation

A. V. Fejes¹, C. Mannhalter¹

¹ Department of Laboratory Medicine

Background. Helicobacter pylori is a Gram negative microorganism, which can be found in the gastric mucosa and the epithelial cells of the stomach in more than 50% of the human population. To maintain an intact stomach tissue, the blood flow in the gastric mucosa has to be adequate, supported by the gastric microcirculation. H. pylori in the mucosal layer may get in contact with the gastric microcirculation and may also release bacterial virulence factors into the blood. These may interact with platelets and cause platelet activation and aggregation. However, it is currently unclear whether the platelet - H.pylori contact occurs directly (between bacterial cells and platelets) or indirectly (between released virulence factors, e.g. vacuolating cytotoxin A, vacA) and platelets.

Aim. We will examine the contribution of vacA, attached to bacteria or released from them, with and without plasma proteins to platelet activation.

Materials & methods. Citrated blood from healthy donors of whom the H. pylori infection status is known was used for platelet isolation by density gradient centrifugation with OptiPrep. Washed platelets or platelet rich plasma (PRP), 10^8 cells, were incubated with 6 x 10^6 CFU/ml vacA positive (ATCC 49503) or vacA negative (ATCC 51932) live bacteria cultured on agar plates. The effect of virulence factors released from H.pylori on platelets was tested by using the supernatant of a liquid culture. Platelets were analyzed by flow cytometry from different timepoints: immediately after exposure to the H. pylori release, after 1 hour and after 3 hours. Staining of the platelets was done with anti-CD41-APC and anti-P-selectin antibodies.

Results. After 1h incubation of washed platelets with the vacA positive strain obtained from solid culture we found an average of 1.3 fold increase of P-selectin positive platelets. The number rises to 2.3 fold after 3 h of incubation. In case of PRP the P-selectin positive cell number is 2.1 fold higher after 1 h and 3.2 fold after 3 h incubation compared to time 0. Using liquid culture supernatants we got corresponding results.

Conclusion. The results indicate that vacA contributes to platelet activation. However, plasma components seem to act as enhancers. We plan to investigate which plasma proteins are involved in the platelet activation process.
S3. What is the somatodendritic serotonin transporter good for?

A. Kasture¹, M. Freissmuth¹

¹Medical University Vienna, Institute of Pharmacology, Centre of Physiology & Pharmacology

Neurotransmitter transporters belonging to solute carrier 6 (SLC6) gene are located on the presynaptic specialization (i.e. the axonal terminals), where they mediate their primary physiological function, the rapid retrieval of neurotransmitters from the synapse. Neurotransmitter transporters are also found on soma and dendrites. The functional relevance of somatodendritic neurotransmitter transporters, however, remains unclear. Neurotransmitter transporters are endowed with C termini that vary greatly in sequence. However, the C termini of these neurotransmitter transporters harbor a conserved RI/RL motif. The RI motif has been shown to interact with the endoplasmic reticulum (ER)-export machinery, most notably the COPII component SEC24; of which 4 isoforms exist, SEC24A-D. Mutation of conserved RI/RL to AA results in impaired axonal enrichment of neurotransmitter transporter. In other words, the RI-AA mutant of neurotransmitter transporters localize predominately in somatodendritic compartment, because they fail to recruit SEC24 and exit the ER in a COPII-independent manner. In the present study, I used mutant versions of serotonin transporter (SERT, SERT-607RI608-AA, SERT-R607A, and the corresponding Drosophila SERT mutants) as tools to study the functional role of somatodendritic SERT in vivo.
S4. LPS-induced disease tolerance in Gram-negative sepsis

B. Maier\textsuperscript{1,2}, R. Gawish\textsuperscript{1,2}, S. Knapp\textsuperscript{1,2}

\textsuperscript{1} Medical University of Vienna, Dept. of Medicine 1, Laboratory of Infection Biology
\textsuperscript{2} CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences

The concept of “disease tolerance” was described recently by Medzhitov et al. as a previously unrecognized host defense strategy, next to the well-studied strategies of “avoidance” and “resistance”, and involves mechanisms aiming to reduce the detrimental impact of infection on host fitness without directly influencing pathogen burden. In sepsis, which frequently leads to lethal organ failure despite antibiotic treatment, enhanced tolerance towards overshooting inflammation might be of great clinical significance as it can contribute to survival despite an ongoing infection.

Our lab has established a tolerance model in which a single, low LPS dose protects mice from sepsis-induced organ damage during Gram-negative sepsis. This protection lasts for at least five weeks following LPS application, which is remarkable since LPS effects on cells are only reported to last for several days. In thorough analyses we discovered that neutrophils as well as platelets are the main contributors to LPS-induced organ damage during sepsis. Using various cell-depletion strategies and genetically modified mouse models we believe cells of lymphoid origin to mediate organ-protective properties in this LPS-dependent model of disease tolerance. The final identification of distinct cells and potential mediators of disease tolerance might possibly allow for novel therapeutic approaches in patients suffering from sepsis.
S5. Solute Carriers: Proteins at the Interface of Host Metabolism and Viral Life Cycle

A. Moskovskich¹, C. Trefzer¹, E. Girardi¹, B. Snijder¹, R. K. Kandasamy¹ and G. Superti-Furga¹

¹ CeMM, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

Host factor requirements for many classes of viruses are yet to be unraveled. Replication of the viral genome and synthesis of viral proteins inside the host cell are associated with altered, often enhanced, cellular metabolism and increased demand for nutrients and specific molecules. With some 400 identified members in humans, the solute carrier (SLC) family represents the largest group of trans-membrane proteins dedicated to the transport of small molecules, such as amino acids, sugars, nucleotides and ions. Thus far, several members of the SLC protein family were described as being viral receptors; however, their role in other parts of the life cycle, such as viral uncoating, replication or virion assembly, remains obscure. Given the crucial physiological functions of SLCs, at the interface between metabolism and the environment, the action of these proteins may contribute importantly to the pathology of viral infection.

Herein we aim to characterize the role of host SLCs in viral replication as well as confirm their function as a new regulatory group of proteins in the antiviral immune response. Upon integration of multiple large-scale datasets from recent genome-wide screens, a group of approximately 20 SLC proteins has been identified to have a function linked to viral replication or the immune response. We will systematically inactivate the genes encoding these SLCs; we will study the protein-protein interactions of their gene products and will try to deduce the natural cargo that may be critical during the viral life-cycle. Together, this “viral transportome” may offer new insights into possible strategies to pharmacologically interfere with viral infections.
S6. Nuclear receptor corepressor 1 (NCoR1) in T cell development and homeostasis


(1) Division of Immunobiology, Institute of Immunology, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria (2) Biocenter, Division of Developmental Immunology, Innsbruck Medical University, Innsbruck, Austria (3) Laboratory of Integrative and Systems Physiology, Ecole Polytechnique Fédérale de Lausanne, Switzerland

NCoR1 (nuclear receptor corepressor 1) has been identified as a regulator of nuclear receptor mediated gene repression. Interestingly, studies with NCoR1 knockout mice revealed important functions for NCoR1 during stages of early embryonic development, such as neural cell differentiation, progression of erythrocytes and fetal thymocyte development. NCoR1 facilitates transcriptional repression through the interaction with chromatin modifying enzymes and is recruited to target gene loci via binding to transcription factors. Among them, a set of BTB zinc finger (BTB-ZF) transcription factors (e.g. PLZF, BCL6 and MAZR), which are key regulators of T cell development and function, are in a complex with NCoR1. Together, this implies important roles for NCoR1 in T cells. To study the role of NCoR1 in T cells, we have crossed Ncor1loxP mice with T cell-specific Cre deleter lines to determine the function of NCoR1 during thymocyte development and in peripheral T cells. Preliminary results indicate an essential role for NCoR1 in maintaining a proper T cell lineage developmental program and in the regulation of T cell homeostasis.
S7. Firing Patterns of Distinct Types of Principle Cells in the Medial Prefrontal Cortex during Working Memory and Rule Switching Task

Ozdemir, A. T., Michael Lagler, Lagoun S., Thomas Klausberger

1Department of Cognitive Neurobiology, Center for Brain Research, Medical University of Vienna, Austria
2MRC Anatomical Neuropharmacology Unit, Oxford University, UK

Synchronous activity of neuronal networks is a fundamental requirement for precise transmission of information to drive behavioural responses. In cerebral cortex, distinct types of neuron contribute differentially to network activity to establish a spatiotemporal division of labour. To date, despite the continuous efforts to explain cortical events through specific circuits, we still lack the basic knowledge of how many types of neuron exist and how these distinct cells are interconnected. In medial prefrontal cortex, excitatory principle cells extend axons to far distant intracortical, subcortical and subcerebral targets. Across different cortical layers, principle cells have diverse projection profiles, with unique axo-dendritic arborisations, expressing different transcription factors and ultimately serving different network operations. By using juxtacellular recording/labelling technique, tetrode and chronic silicon probes, we recorded single and large-scale multiple unit activity of the medial prefrontal cortex in freely behaving rats during a working memory and rule switching task to understand the diversity of principle cells, their interactions with interneurons and how they contribute in the local circuitry to drive highly precise working memory and cognitive flexibility.
S8. STAT1 Isoforms in Transcriptional Control – Distinct Traits

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Signal Transducer and Activator of Transcription (STAT) 1 is a key regulator of interferon (IFN) dependent gene transcription and accordingly STAT1-deficiency increases susceptibility to bacterial and viral infections in humans and mice. Alternative splicing of STAT1 results in a full-length STAT1\textalpha and a C-terminally truncated STAT1\textbeta isoform that lacks the transactivation domain. To determine the role of the individual STAT1 isoforms \textit{in vivo}, mice that lack either of the two isoforms were generated in our lab. We could show that STAT1\textbeta is not acting in a dominant negative manner but contributes to the innate immune defence against bacterial and viral infection, albeit less efficiently than STAT1\textalpha. Consistently, we found that STAT1\textalpha and STAT1\textbeta drive distinct transcriptional profiles in response to IFN\gamma: around half of STAT1-regulated genes were equally well induced by either STAT1\textalpha or STAT1\textbeta, whereas other target genes showed reduced, delayed or even no induction in the presence of STAT1\textbeta only. In the absence of STAT1\textalpha, phosphorylation and nuclear localization of STAT1\textbeta was prolonged, which correlated with an extended binding to target gene promoters. Surprisingly, this did not lead to a generally enhanced response as only a small subset of genes showed increased expression at late time points. Activated STAT1\textbeta was not resistant to phosphatases, suggesting that the impaired induction of the negative regulator suppressor of cytokine signalling (SOCS) 1 in the absence of STAT1\textalpha causes the more persistent activation of STAT1\textbeta. In contrast to IFN\gamma, IFN\alpha/\beta- and IFN\lambda-dependent immune responses were similar in the presence of either one of the STAT1 isoforms. Ongoing studies are aimed at elucidating the molecular mechanisms underlying the isoform specificity in STAT1-dependent transcriptional activation.

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S9. Role of EGFR in colitis and colorectal cancer development.

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Inflammatory bowel disease (IBD) such as Ulcerative Colitis and Crohn’s disease is one of the major causes of discomfort and poor quality of life, and in addition increases the risk of developing colitis associated cancer (CAC), which is one of the major causes of mortalities worldwide. The Epidermal Growth Factor Receptor (EGFR) is known to be overexpressed in colorectal cancer, Recent findings demonstrate that the role of EGFR as a pro-survival and tumour promoting factor is very complex in both IBD and CAC and still poorly understood. In mice IBD and CAC can be modeled by the administration of dextran sulfate sodium (DSS) alone or in combination with Azoxymethane (AOM), respectively. In the current study we will report the results obtained by analyzing IBD and CAC development in mice lacking the EGFR.

This study was supported by FWF (Austrian Science Fund) and the IAI PhD program of the Medical University of Vienna.

S10. NSAIDs not only sensitize melanoma cells to TRAIL-induced apoptosis through upregulation of DR5 but also induces TRAIL expression by innate immune cells.

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Development of resistance represents an enormous obstacle to successful tumor therapy (both targeted and immunological). The design of strategies to overcome resistance is therefore of crucial importance. We have characterized, through a flow cytometric AV/PI apoptosis assay, 3 melanoma cell lines according to their susceptibility to undergo TNF-related apoptosis ligand (TRAIL)-induced
apoptosis. Our results reflect the presence of the resistance phenomenon as we find 2 resistant melanoma cell lines (WM983 - 20% apoptosis; and 1205Lu - 15% apoptosis) and one highly susceptible one (WM793 - 60% apoptosis). Flow cytometry staining of the TRAIL receptors (TRAIL-R1/DR4, TRAIL-R2/DR5, TRAIL-R3/DcR1 and TRAIL-R4/DcR2) showed that resistant cell lines express lower levels of TRAIL-R2/DR5 compared to the susceptible cell line. However, the lower expression of TRAIL-R2/DR5 does not seem to completely explain resistance. To further identify the molecules responsible for resistance, we performed a qPCR array of 91 apoptosis-related genes and assessed the mRNA differential expression between the before mentioned resistant and susceptible melanoma cell lines. Both resistant cell lines expressed higher constitutive levels of BCL2A1 than the susceptible cell line. As it has been described that non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., diclofenac) augment apoptosis of cancer cells and thus may have a role in cancer chemoprevention, we began to study the role of NSAIDs in melanoma resistance. Interestingly, we found that when the resistant cell lines (WM983A and 1205Lu) are pretreated with diclofenac, before incubation with skTRAIL, they become sensitized and undergo apoptosis to a larger extent than when they are not pretreated (diclofenac pretreatment vs. skTRAIL only; WM983A: 71.70% vs. 27.00%; 1205Lu: 23.98% vs. 2.28% apoptotic cells, respectively). In fact, diclofenac treatment of WM983A cell line results in the upregulation of the death receptor TRAIL-R2/DR5 (at the mRNA and protein level) as well as the proapoptotic molecules caspases 5 and 10, NOXA, CYCS, CHOP and XBP1 (at the mRNA level). Surprisingly, additional experiments showed that stimulation of PBMCs with diclofenac as well as celecoxib results in the enhanced expression of TRAIL by different immune cell subpopulations (monocytes, mDCs, pDCs) in a magnitude similar to that observed with Imiquimod. These results suggest (i) that NSAIDs could be a reasonable strategy to improve susceptibility of melanoma to the cytotoxic properties of the immune system, and (ii) that the antitumoral properties of NSAIDs are not only related to their direct effects on tumor cells but also to their capacity to promote a cytotoxic effector phenotype in immune cells.
S11. Natural clinical tolerance to peanut in african patients is caused by poor allergenic activity of peanut IgE.

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Background: Peanut allergy may cause life-threatening allergic reactions. Here we investigated immunological patterns of clinical tolerance to peanut in peanut sensitized but asymptomatic patients from central Africa compared to Swedish peanut allergic vs. sensitized but asymptomatic patients.

Methods: Sera from allergic patients (n=54) from Zimbabwe with IgE to peanut but without symptoms, and sera from peanut allergic (n=25) and sensitized but asymptomatic (n=25) patients from Sweden, were analyzed for total IgE, peanut extract-specific IgE and IgG, IgG1 and IgG4 reactivity towards Ara h 1-3, 6, 8, 9 using an allergen microarray. Allergenic activity was investigated by basophil activation assays. IgE to Ara h 2 peptide epitopes was analyzed.

Results: Forty-six percent of the African and all peanut allergic Swedish patients showed IgE towards one of the highly allergenic peanut allergens (Ara h 1-3, 6, 9). However, 48% of the African patients had IgE to cross-reacting carbohydrates (CCD) with low allergenic activity and 60% of the Swedish asymptomatic patients had IgE against the PR-protein Ara h 8. Peanut IgE from both peanut asymptomatic patients groups showed very poor allergenic activity compared to IgE from peanut allergic patients. Asymptomatic patients almost completely lacked IgE to Ara h 2 peptide epitopes which were recognized by Swedish peanut allergic patients.

Conclusion: Natural clinical tolerance to peanut in the African and Swedish patients could be explained by exclusive IgE to low allergenic peanut components e.g. such as profilins, CCD and/or PR-10 proteins and by poor allergenic activity of peanut-specific IgE.
S12. Characterization of the allergic T-cell response to Dauc 1, the Bet v 1 homologous protein in carrot

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Background: A high number of birch pollen-allergic patients develop clinical symptoms to stone-fruits, hazelnuts and certain vegetables (carrot, celery) due to immunological cross-reactivity between the primary sensitizing (major birch pollen allergen) Bet v 1 and structurally related proteins in these foods. The Bet v 1-homolog in carrot is Dauc 1 but it has been reported that Dauc 1 might initiate food allergy also independently from Bet v 1. The aim of the study is to analyze the T-cell response to Dauc 1 to elucidate its sensitizing capacity.

Method: Dauc 1-specific T-cell lines (TCLs) and T-cell clones (TCCs) were generated from PBMCs of birch-pollen allergic patients with clinical symptoms to carrot. These cultures were analyzed for epitope specificity, cytokine production, cross-reactivity with Bet v 1 and expression of skin homing receptor cutaneous lymphocyte antigen (CLA) and integrin-ß7, a receptor critical for gut homing.

Results: In 21 Dauc 1-specific TCLs several epitopes were recognized, among which the amino acid region Dauc 1_139-153 was most frequently recognized (52 %). Only 5/15 (33 %) Dauc 1-specific TCLs and 7/22 (32 %) Dauc 1-specific TCCs cross-reacted with Bet v 1. 9/15 (60 %) of Dauc 1-specific TCCs, not reactive with Bet v 1, were Th1-like, which is in contrast to Dauc 1-specific TCCs reactive with Bet v 1 (29 %). Bet v 1-non-reactive clones also expressed increased levels of integrin-ß7 compared to Bet v 1-reactive clones. The expression of CLA did not differ.

Conclusion: Dauc 1_139-153 is a dominant T-cell activating region located in the C-terminus of the protein. Th1-like cells seems to be strongly represented in the allergic T-cell response to Dauc 1, whereas this phenotype is underrepresented in the response to Bet v 1. In contrast to other Bet v 1-related food allergens, only a minority of Dauc 1-specific T-cells cross-reacted with Bet v 1 and those Bet v 1-non-reactive Dauc 1-TCCs displayed integrin-ß7 indicating that these cells have been primed in the gut. Thus Dauc 1 may be regarded as a true food allergen sensitizing by itself via the gut.
Overview:

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P2. The role of STAT1 in colitis-associated colorectal cancer (I. Crnčec)
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“Come together-to Bridge the Gap”
2nd Joint IAI-CCHD Symposium

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P14. Do Partial Releasers and Atypical Inhibitors Influence Conducting State of Human Dopamine and Serotonin Transporters? (S. Bhat)
P15. Lymphocyte-specific protein tyrosine kinase Lck in the process of T-cell-activation (C. Bonstingl)
P16. The role of H2S in autonomic nervous system (M. Dominguez Rodriguez)
P17. A monoclonal anti-EGFR antibody for a proof-of-concept study in comparative oncology (J. Fazekas)
P18. A gene-to-behaviour investigation of KCNQ ion channel families regulating membrane excitability (H. Gafar)
P19. The role of complement factor H in macrophage function (M. Kiss)
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P22. MDApos-microparticles as modulators of inflammation and thrombosis (F. Puhm)
P23. Elucidation and inhibition of the effects of osteopontin on T cells in adipose tissue inflammation (B. Wanko)
P1. STAT1 in myeloid cells is required to limit early replication and persistence of murine cytomegalovirus in vivo

Mario Biaggio(1), Caroline Lassnig(1,2), Rita Rom(1), Zsuzsanna Bago-Horvath(1,3,4), Astrid Krmpotic(5), Stipan Jonić(5), Birgit Strobl(1,2) and Mathias Müller(1,2)

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Signal transducer and activator of transcription 1 (STAT1) is a key transcription factor in interferon (IFN) type I, II and III signalling. Lack of STAT1 causes high susceptibility to viral infections in humans and mice. Cytomegalovirus (CMV) infection remains usually unnoticed in healthy individuals, while it is a common cause of congenital birth defects and can lead to life-threatening diseases in immune compromised patients. Murine CMV is frequently used as a model to study acute and persistent viral infections. The host defence with respect to natural killer (NK) cell and T cell responses against CMV infection has been extensively studied, whereas the contribution of myeloid cells is just beginning to emerge. Using conditional Stat1 knockout mice, we demonstrate that myeloid STAT1 critically contributes to the control of CMV in vivo. Stat1∆Lyz mice, which lack STAT1 in macrophages/neutrophils, showed an increased viral load in spleen and liver early after infection, despite a grossly unimpaired NK cell activation. Increased viral load correlated with increased numbers of viral genomes and increased pathology in the spleen, but not in the liver. Intriguingly, Stat1∆Lyz mice also showed a higher persistence of MCMV in the salivary glands compared to littermate controls. Preliminary experiments indicate differences in CD8⁺ and CD4⁺ T cell activation, whereas numbers and activation of macrophages and NK cells appear unaffected. Current experiments are aimed at understanding the STAT1-dependent macrophage-intrinsic and -extrinsic mechanisms that regulate host immunity against CMV.

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The transcription factor STAT1 is activated by interferon (IFN) signaling and promotes immune responses against pathogens and tumor cells. Apart from these functions in the immune system, STAT1 is considered as a tumor suppressor that integrates anti-proliferative and pro-apoptotic functions of IFNs. It can prevent expansion of neoplastic cell types by activating the transcription of genes encoding for caspases, death receptors, death ligands and iNOS. Furthermore, it negatively regulates cell cycle progression via regulation of p21\(^{\text{waf/cip1}}\), p27\(^{\text{kip1}}\), c-myc and cyclin genes. However, several studies indicated that STAT1 might also exhibit pro-tumorigenic functions. It has been shown that interleukin-12-mediated tumor regression is enhanced in STAT1\(^{-/-}\) mice. Moreover, in the absence of the closely related transcription factor STAT3, STAT1 induces expression of oncogenic FOS and EGR1 proteins in immortalized MEFs and compensatory up-regulation of STAT1 was detected in STAT3-deficient intestinal tumors of Apc\(^{\text{Min}}\) mice.

We investigated the function of STAT1 in colorectal cancer and employed mice with conditional inactivation of STAT1 in the intestinal epithelium (Stat1\(^{\Delta\text{IEC}}\)). Colorectal tumors were induced by the chemical Azoxymethane/Dextran sulfate (AOM/DSS) protocol and tumor load was assessed in male and female Stat1\(^{\Delta\text{IEC}}\) and control mice. Our studies demonstrate that STAT1 acts as a gender specific tumor suppressor in colorectal cancer of mice and humans.
P3. Systemic metabolic defects caused by epidermal EGFR-deficiency

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The epidermal growth factor receptor (EGFR) is an important regulator of epidermal function and homeostasis. Epidermal deletion of EGFR leads to severely perturbed skin differentiation and causes reduced animal growth and lethality during the first three weeks of life. The molecular cause why animals lacking EGFR in the epidermis die soon after birth is still unclear. It is known that these animals develop a severe skin inflammation and a skin barrier defect; however both of these pathological features become apparent only after mice lacking EGFR in the epidermis already show reduced growth and weight gain. In order to better understand the growth defect observed in these mice, metabolic parameters have been started to be analyzed revealing that epidermal loss of EGFR-signaling results in severely perturbed glucose metabolism and insulin levels in the blood of affected animals. Importantly, gene expression of metabolic regulators in livers of mice lacking EGFR in the epidermis indicates that glucose metabolism is deregulated already a few days after birth. In addition, the “starvation-marker” FGF-21 is highly expressed in these animals. To test whether excessive feeding protects animals with defective epidermal EGFR signaling from death, these mice were crossed in a leptin-deficient background and found that this fully rescues the lethality. Furthermore, animal growth as well as glucose and insulin levels are improved in such animals, demonstrating that the lethality caused by epidermal EGFR-deficiency stems from impaired food metabolization. We are currently searching for molecular mediators of the metabolic dysfunction of mice lacking EGFR in the epidermis.

These findings will provide new insights into the complex consequences of epidermal Egfr-deficiency, which might also be relevant for cancer patients treated with Egfr inhibitors. Furthermore, results obtained by this study will lead to a better understanding of the role of the skin in the regulation of systemic metabolism.
P4. Cell-type specific role of EGFR in liver fibrosis and cancer

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The Epidermal Growth Factor Receptor (EGFR, also known as erbB1) is a member of the erbB family of tyrosine kinases. EGFR is highly expressed in the adult liver and has been proposed to play an important role during liver development, function and regeneration. Our group has previously shown in a study of partial hepatectomy that EGFR is a critical regulator of hepatocyte proliferation in the initial phase of liver regeneration and that EGFR plays a protective role in hepatocytes. Furthermore, EGFR overexpression is found in 40-70% of human hepatocellular carcinomas (HCC). To molecularly dissect the function of EGFR during liver tumorigenesis, we employed genetically modified mice lacking EGFR in distinct cell types of the liver. We discovered that EGFR is expressed in liver macrophages/Kupffer cells and that presence of EGFR-positive liver macrophages in HCC is associated with poor survival. Moreover, EGFR was found to be expressed in hepatic stellate cells, which differentiate into myofibroblasts and contribute to liver fibrosis development, but little is known about the underlying mechanisms. We are currently investigating the role of EGFR during fibrosis development by employing genetically modified mice lacking EGFR in distinct cell types of the liver.
Identification of a microRNA that regulates inflammatory dendritic cells.

Clarice Lim

MicroRNAs are an important class of gene regulators that post-transcriptionally modulate gene expression and influence cell fate and function. While much is reported on its role in directing lymphoid cell development and activation during hematopoiesis, not much is known on how microRNAs affect dendritic cell differentiation and function. We performed an array screen for microRNAs differentially expressed by human myeloid DC subsets. miR-181a/b was among the strongest regulated miRNAs in this screen. Using methods to lentivirally knock down or over-express miR-181a/b in differentiation models of human CD34+ progenitors, we show that DC-SIGN+ dendritic cells (moDC) are positively regulated by this miRNA. DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin) is a C-type lectin pathogen binding receptor that is best known for its ability to bind HIV-gp120 with high specificity. In line with its down-regulation of DC-SIGN, moDCs which have miR-181a/b knocked-down also bind less to HIV-gp120. Although DC-SIGN is expressed on some macrophages, it marks a subset of blood dendritic cells during steady state and is relevant in diseases like Crohn’s disease, as such dendritic cells accumulate in the lymph nodes and inflamed intestinal mucosa and secrete IL-1b and TNFα. Inflammatory murine moDCs marked by the expression of DC-SIGN arise after T cell activation and accumulate in T cell areas of lymph nodes. These cells are strongly diminished in miR-181a1b1a2b2 knock out mice. Hence, we show for the first time that a microRNA can regulate the development of inflammatory moDCs marked by DC-SIGN not only in vitro but also in vivo.
P6. The role of Epidermal Growth Factor Receptor in c-Fos-dependent osteosarcoma formation

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The Epidermal Growth Factor Receptor (EGFR) is overexpressed or mutated in human carcinomas and glioblastomas, which are tumors of epithelial and glial origin, respectively. Recent studies from our laboratory using EGFR knockout mice (Egfr-/-) have also shown that EGFR plays a role in bone development and osteoblast function. In analogy, it is therefore likely that EGFR is also involved in the development of bone tumors and few publications have indeed reported EGFR overexpression in human osteosarcomas. Here we show that Egfrf/f Runx2-Cre mice (EgfrΔOb) which lack the EGFR in osteo-chondroprogenitor cells develop an increased zone of hypertrophic chondrocytes in long bones resulting in impaired bone formation. When bred to c-fos transgenic mice (H2-c-fosLTR) that develop osteosarcomas with 100% penetrance, EgfrΔOb mice show reduced tumor incidence and burden. In vitro experiments in primary bone tumor cells isolated from H2-c-fosLTR mice further indicate that EGFR inhibition leads to reduced proliferation and increased apoptosis. Taken together our data suggest an essential role of EGFR signaling during both development and progression of c-Fos-dependent osteosarcomas.
P7. Bidirectional polarization of T cell function via CD43

Madhura Modak, Petra CEJKA, Petra WAIDHOFER-SÖLLNER, Sabrina JUTZ, Otto MAJDIC, Peter STEINBERGER, Gerhard ZLABINGER, Johannes STÖCKL

CD43 is one of the abundant glycoproteins expressed on T cells. CD43 has been demonstrated to act as not only a potent co-receptor but also a negative regulator for T cell activation. To further investigate the role of CD43 in T cell activation and subsequent function, peripheral blood T cells were activated via two distinct CD43 epitopes recognized by monoclonal antibodies (mAbs) namely 6E5 and 10G7 along with TCR signaling. Both the CD43 mAbs were shown to be potent co-stimulators for T cell activation when cross-linked but they exert differential downstream effect upon ligation including differential activation of downstream signaling pathways, T cell cytokine production and also distinct effector function. T cells activated via 10G7 mAb were poorly restimulated and further acquired suppressive function compared to T cells activated either via 6E5 or via CD28. Thus, identifying a novel pathway to induce immune inhibitory T cells. Furthermore, inhibitory T cells do not directly act on responder T cells, but rather exhibit their effect via dendritic cells when added to allogenic mixed leukocyte reaction. Together our data suggests a unique role of CD43 in bidirectional polarization of T cells immunity, depending on its targeted epitope.

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Cancer is one of the leading causes of death in the industrialized world. Every third diagnosed cancer is a skin cancer. Imiquimod (Imi) is an immune modifying compound used as a 5 % cream formulation (Aldara) to treat warts and basal cell carcinomas (BCC). The mechanism of action of Imi relies on the activation of Toll like receptor 7/8 (TLR7/8) expressing immune cells, prominently a subtype of dendritic cells called plasmacytoid dendritic cells (pDCs). pDCs are Type I interferon producing innate immune cells. We have recently shown that if activated they can be converted into tumor killing cells. The tumor killing ability of pDCs is independent of adaptive immunity and relies on the production of lytic molecules like Granzyme B (Gzmb) and Tumor necrosis factor related apoptosis inducing ligand (TRAIL). The production of these tumor killing molecules in pDCs as well as other pro-inflammatory molecules like tumor necrosis factor alpha (TNF-α) or Type I Interferon are controlled by a defined subset of transcription factors like interferon regulator factor 7 (IRF 7) and nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB). Another well known family of immune regulators is the AP-1 family whose role in pDCs and Imi mediated tumor clearance is poorly understood. In order to investigate the role of c-Jun in pDC development and function, we are employing mice harbouring floxed c-Jun alleles to delete c-Jun in all bone marrow (BM)-derived cells with the poly I:C inducible Mx-Cre transgenic line or in Dendritic Cells only by using the CD11c-Cre line. Our results indicate that c-Jun is dispensable for the development and maturation of pDCs. Furthermore, we could show that c-Jun is an important factor for the production of Interleukin-6 (IL-6) and Interferon beta (IFN-β) in Imi stimulated pDCs. Current studies are addressing the tumor-killing capacity of Imi-stimulated pDCs. These results will provide novel insights into how modulation of the innate immune system can be employed therapeutically to treat cancer.
P9. The soluble cytoplasmic tail of CD45 (ct-CD45) induces quiescent anergy in human T cells

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The cytoplasmic tail of CD45 (ct-CD45) is proteolytically cleaved and released upon activation of human phagocytes. The soluble ct-CD45 was found to act on T cells as an inhibitory, cytokine-like factor that reduces T cell proliferation. In this study, we aimed to elucidate the molecular mechanisms acting within T cells, upon ct-CD45 binding. Here, we demonstrate that ct-CD45 induces a novel form of anergy in human peripheral blood T cells. Ct-CD45 inhibited the function (proliferation, cytokine production) of human T cells and rendered the cells hyporesponsive to restimulation, which was reversible by exogenous IL-2 or IL-7. However, microarray analysis did not indicate induction of any classical anergy-associated genes. Instead, we found induction of Schlafen family member 12 (SLFN12) and of Krueppel-like factor 2 (KLF2). When we analyzed the expression patterns of cell cycle regulatory factors, we found inhibition in the induction of cyclin D1 while other cyclins were unaltered. In summary, ct-CD45 triggers an anergy program in T cells, which is reversible by exogenous IL-2, acting independently of classical anergy factors. From our data, the inhibition of cyclin D1 suggests a cell cycle arrest in the early G1 phase, thus making it distinct from canonical T cell anergy.
P10. The Role of Plasmacytoid Dendritic Cells in Imi Induced Skin Inflammation and Melanoma Clearance in mice

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Imiquimod (Imi) is an immune response modifier acting as an agonist of toll like receptor 7/8 (TLR7/8), a pathogen recognition receptor that recognizes single stranded RNA. Imi exerts therapeutic anti-viral and anti-tumor effects in both mice and humans. Therapeutically, Imi is applied topically as a 5% cream formulation under the trademark Aldara. Aldara has been first approved for the treatment of genital warts but is also effective against various cutaneous tumors. Previously, our group showed that Imi treatment leads to tumor clearance in a mouse model of melanoma. We showed that the anti-tumor effect of Imi is accompanied, among others, by the accumulation of plasmacytoid dendritic cells (pDCs), a dendritic cell subpopulation that expresses TLR7. We could furthermore show that Imi activated pDCs acquire tumor killing effector properties by upregulating the cytolytic molecules TRAIL and granzyme B. By employing a transgenic mouse model to specifically deplete pDCs, we demonstrated that pDCs are crucial for the tumoricidal properties of Imi. In search for the molecular pathways conferring tumor-killing activities to Imi-stimulated pDCs, we found that pDC infiltration to Imi treated skin requires the chemokine CCL2 since pDC infiltration in CCL2\textsuperscript{-/-} mice is significantly impaired. Thus, current studies are addressing the anti-tumor efficacy of Imi in CCL2\textsuperscript{-/-} mice. Albeit the important effects of Imi in tumor immune biology, we and others have shown that repeated topical application of Imi on murine skin leads to skin inflammation and is used as an established mouse model of psoriasiform dermatitis. While addressing the function of pDCs in this process, we found that pDCs exert regulatory properties during Imi induced skin inflammation. pDC depleted mice treated with Imi display increased epidermal thickening, increased levels of pro-inflammatory cytokines (e.g. IL-6, TNF\textalpha) and an altered immune infiltrate in the skin. Moreover, depletion of pDCs results in delayed resolution of Imi-mediated skin inflammation. Current studies are aimed at elucidating the mechanism by which pDCs modulate the severity of Imi mediated skin inflammation.
P11. Identification and characterization of natural adjuvants in birch pollen

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IgE-mediated allergy is a hypersensitivity reaction of the immune system to normally harmless antigens which is due to an aberrant Th2-dominated immune response. 25% of the population in industrialized countries suffer from allergic disorders and one fourth among them reacts to birch pollen (BP). The major BP allergen Bet v 1 is recognized by 95% of birch pollen-allergic patients, whereas less than 50% react to the minor allergens Bet v 2, Bet v 3, Bet v 4, Bet v 6 and Bet v 7. By expanding BP-specific T-cell clones (TCCs) from the peripheral blood of BP-allergic patients we found BP extract-specific TCCs that were not specific for any of the known allergens in BP. So far, 17 BP extract-specific TCCs could be expanded. After stimulation with BP, signature cytokines IL-4, IL-5, IL-13 (Th2) and IFN-γ (Th1) were measured in supernatants of these TCCs. 59% belonged to the Th0, 35% to the Th1 and only 1% to the Th2 subset. These findings led to the assumption that there are distinct proteins in BP which induce a Th0/1-like response rather than a Th2-like reaction. The aim of this study is to identify and characterize those proteins. BP proteins were separated with size exclusion chromatography. BP extract-specific TCCs will be tested for proliferation with the individual fractions. In parallel, the fractions will be subjected to endo-lysosomal degradation assays to draw conclusions on their immunogenicity. It has been demonstrated that proteins with higher resistance to endo-lysosomal proteolysis are more immunogenic. After identification and isolation of candidate proteins their allergenicity and immunogenicity will be analyzed in more detail. These Th0/1 subset supporting BP proteins may represent natural adjuvants which could be supplemented to vaccines for immunotherapy of BP allergy.
P12. IgM deficiency delays venous thrombus resolution

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Background: Venous thromboembolism is one of the three cardiovascular “killers” and occurs in 100/100,000 persons each year. In up to 25% of cases recurrence/non-resolution occurs, which is the cause of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension (CTEPH). The mechanisms of thrombus persistence are unclear.

Splenectomy is a risk factor for CTEPH and delays venous thrombus resolution in mice. The spleen is important for the maturation of B lymphocytes and maintenance of peritoneal B1a cells. The latter secrete IgM and have been described to have a protective effect in atherosclerosis and other vascular disorders.

Methods: Mice unable to secrete IgM (sIgM-/-) and their wildtype littermates (sIgM+/+) were used in a mouse model replicating the features of human deep vein thrombosis. Thrombi were harvested from mice 3, 7, 14 or 28 days after subtotal ligation of the inferior vena cava (IVC) and compared in terms of length, cross-sectional area, volume and weight. In addition, a group of mice was monitored by high-frequency ultrasound to assess thrombus size in vivo over a period of 28 days.

Results and conclusion: Preliminary results show a delayed thrombus resolution in sIgM-/- mice compared to sIgM+/+ littermate controls, indicated by longer thrombi at 7 and 14 days after IVC ligation. Further experiments will be necessary to confirm these findings.

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Inflammatory bowel disease (IBD) is characterized by severe inflammation of the colon and small intestine. Very early onset IBD (VEOIBD) is classified as a rare form of IBD that is observed in patients less than 5 years old and presents with a more severe phenotype. Due to the very early onset nature, environmental factors are thought to play only a limited role in the pathogenesis of the disease. Conclusively, it is highly likely to be caused by the specific genetic background of the patient. Analysis of a number of patients of both consanguineous and non-consanguineous family background revealed 65 novel variants. However, the prioritization of a causative mutation among all identified variants is difficult and limited to a “cherry-picking” approach. The aim of this project is to develop a new computational method, which will assist the selection of potential mutated candidate genes in VEOIBD with high statistical confidence. We will establish the new prioritization method based on the integration of multiple datasets like interactions, functional annotations etc. Furthermore, we will create sub-networks of causal genes, which will help us to discriminate different disease entities. The top candidate variants will be functionally validated using either patient’s primary material or genetically engineered cell lines. The combination of computational and functional studies will help us to better understand the pathogenesis of VEOIBD.
P14. Do Partial Releasers and Atypical Inhibitors Influence Conducting State of Human Dopamine and Serotonin Transporters?

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The dopamine transporter (DAT) and the serotonin transporter (SERT) belong to the SLC6 transporter family. They terminate dopaminergic and serotoninergic synaptic transmission, respectively, and replenish vesicular stores by operating in relay with the vesicular monoamine transporters. Several mutations in DAT cause misfolding of the protein and its ER retention; the phenotypical manifestation is infantile/juvenile dystonia and Parkinson’s disease. Reuptake of neurotransmitters requires the transporter to undergo a series of conformational changes during substrate translocation. This transport cycle can be inferred from an analysis of currents carried through the transporter: the peak current reflects substrate induced charge movement; the steady-state current indicates inward facing conformation visited by the transporter during the conformational cycle. Using this kinetic model, we propose to analyze a series of compounds termed partial releasers (PRs) and atypical inhibitors (AIs). These ligands have subtle differences in structure; our model posits that the rate at which they bind to transporter proteins differs from that of true substrates and inhibitors. We hypothesize that PRs and AIs bind to the transporters and arrest transport cycle by trapping the transporter in distinct intermediate conformations. This conjecture will be studied by recording currents through DAT and SERT allowing for assigning the rate-limiting step. Elucidating these transitions by electrophysiology in substrate transport cycle would provide insights into the folding trajectory of transporters during its ER export to the membrane and its effector membrane functions. This has implications in investigating the potential application of these drugs as “pharmacochaperones” that rescue SERT and DAT folding mutations that cause ER retention of the transporter. We propose to investigate pharmacochaperoning capabilities of these compounds on application by visualizing the translocation of ER trapped transporter to the cell surface (substrate uptake, confocal microscopy, glycosylation state analysis, self-surface biotinylation) and by checking restoration of normal circadian rhythm activity of sleepless fumin fly with a knock-in of mutant DAT.
P15. Lymphocyte-specific protein tyrosine kinase Lck in the process of T-cell-activation

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It is well known that lymphocyte-specific protein tyrosine kinase (Lck) plays a major role in the process of T-cell activation by antigen-presenting cells (APC). Upon activation, Lck phosphorylates the CD3 chains of the T cell antigen receptor (TCR) and in addition zeta-protein-associated protein kinase (ZAP-70), which has the power-on of several proteins most importantly PI3K and phospholipase C (PLC) as a consequence, ultimately leading to the opening of endoplasmic reticulum- and membrane-bound Ca2+ channels and thereby changing the gene expression pattern to transform T-cells into an activated state. How exactly the mechanism behind Lck and T-cell activation functions is still not entirely well-understood and therefore aim of this project. Especially in the context of how lipid-drugs such as statins and unsaturated fatty acids affect T-cell membrane composition and Lck activation this would be as interesting as relevant for cardiovascular disease treatment and tumor progression.
Hydrogen sulfide (H2S) is a toxic gas also produced in mammalian tissues where it can exert various functions. H2S has also been shown to act as endogenous neuromodulator. A recent study showed that H2S is endogenously generated and released in sympathetic ganglia and potentiates ganglionic transmission (Sha et al., 2013). We found that in radiotracer release experiments, tritium overflow triggered by either electrical fields or by depolarizing K+ concentrations was enhanced by 0.1 to 1 mM of the H2S donor NaHS in a concentration-dependent manner. In addition, we found NaHS to inhibit currents through Kv7 channels in a concentration-dependent manner, whether endogenously expressed in SCG neurons or heterologously expressed in tSA cells.

Methods: Experiments were performed on primary cultures of rat superior cervical ganglion (SCG) or on transfected tSA cells. Neurotransmitter release was determined by measuring the outflow of radioactivity from cultures labelled with 3H noradrenaline. Electrophysiological recordings were performed by using the perforated patch-clamp technique.
P17. A monoclonal anti-EGFR antibody for a proof-of-concept study in comparative oncology

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The dog (Canis lupus familiaris) has been proposed a suitable model patient for cancer immunotherapy studies, as both the immune system and pathophysiologic processes involved in cancer are strikingly similar to those in human patients. The incidence rate of spontaneously developing mammary carcinoma in elderly dogs is even twice as high as observed in humans. Moreover, epidermal growth factor receptor (EGFR) overexpressing mammary tumors have been described in both species. In a previous study our group showed that targeting of canine EGFR on canine mammary carcinoma cells with the chimeric anti-human EGFR antibody cetuximab is leading to growth signal depletion and consequently reduction in cell viability in vitro. Thus, the aim of this study was to develop a canine version of cetuximab in the prospective of a clinical study.

The recombinant antibody Can225IgG was purified from the supernatant of CHO DUKX-B11 cells with Protein G, yielding ~20mg of pure protein per litre. Reactivity towards recombinant EGFR was proven in Western Blot and ELISA, plus highly specific binding to native canine EGFR was observed in flow cytometry and immunohistochemistry on canine mammary carcinoma cells. Furthermore, viability and proliferation of EGFR+ canine mammary cancer cells was significantly reduced upon incubation with Can225IgG. Finally, phagocytosis of canine cancer cells by isolated canine monocytes was significantly enhanced upon co-incubation with the antibody, as shown in a flow-cytometric killing assay. We propose this antibody as a possible lead compound for future diagnostic and theranostic approaches in canine cancer patients.
P18. A gene-to-behaviour investigation of KCNQ ion channel families regulating membrane excitability

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Potassium channels are the largest group of ion channels in mammals. We are interested in investigating the KCNQ family which is regulated by several distinct classes of GPCR such as purinergic or muscarinic receptors. The KCNQ family includes M-type potassium channels which are critical regulators of neuronal excitability. The differential modulation of these ion channels via GPCRs is additionally dependent on subcellular organization by scaffolding proteins. These assemblies probably depend on cellular and subcellular organisation in the context of overriding neuronal circuits. To address this issue we use the model organism \textit{Caenorhabditis elegans}. This organism’s sequenced genome shows that a family of KCNQ-like channels is present in the nematode (i.e. the KQT family). The widespread expression of these genes predicts a contribution to the circuits that control feeding behaviour, locomotion and defecation. We are currently investigating behavioural phenotypes in strains deficient in KQT genes (\textit{kqt-1}: VC1149, tm257, tm846; \textit{kqt-3}: tm542). This work will provide a platform in which we can dissect how the subcellular and cellular organization of KCNQ channels affect excitability and impact on higher function.
**P19. The role of complement factor H in macrophage function**

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Complement factor H (CFH) is the major regulator of the alternative pathway of complement activation. It is specialized to prevent host tissue damage from complement-induced proinflammatory and cytolytic effects. In addition, we recently identified CFH as a major defense protein against malondialdehyde (MDA), which is a prominent lipid peroxidation product generated on oxidized LDL particles and on the surface of dying cells. CFH can directly neutralize MDA-induced proinflammatory effects both in vitro and in vivo thereby protecting from the consequences of oxidative stress. Accumulating evidence supports that complement is activated in atherosclerotic lesions, where CFH colocalizes with MDA adducts. We hypothesize that CFH has a protective role in the pathogenesis of atherosclerosis. In order to investigate this, we first studied the effect of CFH deficiency on macrophage foam cell formation, a rate-limiting step in atherosclerosis. Thioglycollate-elicited macrophages (TG-MΦs) were incubated with MDA-modified LDL (a model of oxLDL) in the absence or presence of exogenous CFH for 24h. CFH inhibited the uptake of MDA-LDL by 70%. Next we isolated TG-MΦs from WT and CFH KO mice and incubated them with MDA-LDL for 24h in the presence of either 1% WT or CFH KO serum, respectively. CFH KO macrophages developed increased foam cell formation as compared to WT ones (31.1±3.9% vs. 7.9±1.0%, mean±SEM). Moreover, we could show that CFH produced by macrophages also prevented the uptake of MDA-LDL as we found enhanced foam cell formation in CFH KO TG-MΦs compared to WT controls (25.3±4.1% vs. 11.2±1.7%) after MDA-LDL loading for 24h in the presence of 1% CFH KO serum. Furthermore we tested whether the absence of CFH affects the phagocytic capacity of macrophages. CFH KO and WT TG-MΦs were incubated with FITC+ apoptotic RAW macrophages in the presence of either 1% CFH KO or WT serum for 1.5h and the uptake of apoptotic cells was evaluated by flow cytometry. CFH KO macrophages exhibited increased phagocytic capacity as compared to WT ones (48.2±2.1 vs. 33.1±0.6%). In summary, we found that CFH influences macrophage functions which are highly relevant to the pathogenesis of atherosclerosis.
P20. Glial-neuronal interactions in nociceptive transmission

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Amplification of synaptic strength at the first synapse in a pain pathway is a cellular model for enhanced pain sensitivity. Recent evidence suggests that solely factoring neuronal activity in terms of synaptic plasticity provides an incomplete understanding of the establishment of amplified nociceptive transmission. Although glial cells have emerged as key modulators of synaptic plasticity, so far it has not been shown whether their activation alone is sufficient to amplify synaptic strength.

We used 2′(3′)-O-(4-Benzoylebenzo|yl|adenosine 5′-triphosphate triethylammonium salt (BzATP)-induced P2X7 signalling to specifically activate glial cells in the dorsal horn and studied their effect on synaptic transmission between nociceptive C-fibres and lamina I neurons in an electrophysiological approach. Surprisingly, application of P2X7 receptor agonist BzATP induced a significant depression of synaptic transmission between C-fibres and lamina I neurons. We could show that this BzATP-induced depression was not mediated by P2X7 signalling but by adenosine acting on inhibitory A1 receptors. Activation of glial P2X7 receptors under blockade of A1 receptor signalling induced a long-term potentiation (LTP) at 60% of all C-fibre inputs recorded. The BzATP-induced potentiation was accompanied by a significant reduction of the paired pulse ratio (PPR), indicative of a presynaptic expression of LTP. This decrease of PPR could neither be observed in neurons that did not show a response to BzATP application nor under blockade of P2X7 receptors prior to BzATP application. Blockade of P2X7 receptor signalling by the specific antagonist A-438079 completely prevented the BzATP-induced potentiation, whereas blockade of A1 receptor signalling alone had no significant effect on synaptic transmission. Here, we could show for the very first time that activation of glial cells is sufficient to significantly amplify synaptic transmission at the first synapse in nociceptive pathways.
P21. How T Cells Recognize Antigen on Professional APCs; a Molecular Imaging Approach

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Antigen recognition by αβ T-helper cells (hereafter referred to as T cells) relies on their transient interaction with professional antigen presenting cells (APCs). This unique cell contact – also termed the immunological synapse – is formed through the molecular interaction of T cell antigen receptors (TCRs) on the T cell with peptide-loaded major histocompatibility complexes (pMHC) on the APC. T cells are highly selective and sensitive to antigens, and even respond to the presence of a single stimulatory pMHC. How they achieve this is not clear. After all, TCR-pMHC interactions are low in affinity, (µM range), and antigenic pMHCs are often vastly outnumbered by structurally similar, yet non-stimulatory, pMHCs. And while the thermodynamics of TCR-pMHC binding has been extensively studied in vitro, we know surprisingly little about the in vivo synaptic environment in which TCR-pMHC takes place and how it influences the recognition dynamics. The primary goals of my PhD are to characterize with the use of advanced imaging techniques the stimulatory capacity of APC plasma membranes in single-molecule detail and to study the influence of cell-intrinsic parameters on TCR-pMHC binding and TCR proximal signalling. To this end, I am currently focusing on the nanoscale, that is sub diffraction-limited, organization of endogenous and stimulatory pMHCs as well as their co-stimulatory molecules in the plasma membrane of living professional APCs. I am also tracking single pMHC molecules to assess the mobility of pMHCs within such clusters and the stability of existing pMHC clusters over time. Moreover, I will extend a Förster resonance energy transfer (FRET) - based imaging approach to quantify synaptic TCR-pMHC binding events in physiological synapses. To test the functional relevance of membrane properties in a defined manner, I plan to fine-tune pMHC clustering and mobility using artificial glass - supported lipid bilayers, which will serve as APC surrogates for T cells. Given the sensitivity and precision of single molecule imaging approaches, I expect to gain unique insights into the molecular and cell biological foundation of T-cell sensitivity and the stimulatory capacity of APCs.
Malondialdehyde (MDA) is a product of unsaturated fatty acid peroxidation. It forms covalent bonds with lysine and phosphatidylethanolamine. The resulting moieties are part of a family of oxidation-specific epitopes (OSE). Other family members are oxidized phosphatidylcholine, oxidized cardiolipin and 4-hydroxynonenal (4HNE). MDA-adducts are recognized by components of the immune system (certain natural IgM antibodies and complement factor H (CFH)) as damage-associated molecular patterns (DAMPs). Low levels of MDA-specific natural IgM are associated with increased risk for cardiovascular disease. Impaired recognition of MDA-adducts by CFH (mutant variant Y402H) increases the risk of age-related macular degeneration (AMD). MDA-adducts are found on apoptotic cells and microparticles. Microparticles (MP) are 0.1 to 1µm large membrane vesicles released from activated or dying cells. On the surface, they present phosphatidylserine and various membrane proteins that mark their cellular origin. They can transfer proteins (membrane and soluble proteins), miRNA and lipids between cells. MPs were demonstrated to act pro-thrombotic and pro-inflammatory. They stimulate IL-6 and MCP-1 release and exposure/expression of TF, E-selectin, VCAM-1 and ICAM-1 in endothelial cells. The MP mechanism of action is unknown. Given that more than 50% of MP in the circulation carry MDA-epitopes, MDA might be important in MP signalling. The aims of this project are, i) to characterize the generation of MDA\textsuperscript{pos}MP, ii) to determine the pro-inflammatory and pro-thrombotic effects of MDA\textsuperscript{pos}MP and the signalling mechanisms involved, iii) to assess whether the presence of MDA\textsuperscript{pos}MP is a risk factor in human patients with high thrombotic risk. Various cell culture models (e.g. monocytes and endothelial cells), mouse models (atherosclerosis models) will be employed. Flow-cytometry and –omics approaches (RNA sequencing, mass spectrometry) will be used to characterize MDA\textsuperscript{pos}MP content and effect. In conclusion, this study aims to provide new insights into the propagation of inflammation in the vascular system.
P23. Elucidation and inhibition of the effects of osteopontin on T cells in adipose tissue inflammation

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Obesity is known to cause a sterile low-grade inflammation in which both adipocytes and immune cells present in adipose tissue contribute to elevated levels of inflammatory cytokines. This inflammation is known to trigger insulin resistance and, consequently, type 2 diabetes and other diseases by interfering with the insulin signaling cascade. Osteopontin (OPN) is highly upregulated in obesity and plays a crucial role in obesity-associated inflammatory processes by acting as an inflammatory cytokine as well as extracellular matrix protein. OPN is implicated in the chemotaxis of T cells and has been shown to polarize T cells towards Th1 and Th17. In the onset of obesity-mediated inflammation, T cells infiltrate adipose tissue before macrophages and shift from predominant Treg and Th2 phenotype towards Th1 and are thus important for the initiation of inflammation.

Therefore, we established an assay to measure Jurkat T cell line adhesion to OPN and could block the T cell adhesion with monoclonal antibodies targeting OPN as well as sera raised against OPN-derived peptides. Furthermore, we fed OPN KO mice a high fat diet for 4 and 8 weeks. After 4 weeks of diet intervention, less T cells were present in the gonadal fat of OPN KO mice as compared to the wildtype mice. However, OPN showed only minor effects on the differentiation type of T cells in gonadal and subcutaneous fat.

In conclusion, both T cells and OPN are key-players in adipose tissue inflammation. Targeting OPN at a site which prevents OPN from acting as an adhesive and / or chemotactic factor for T cells may be the basis for a novel therapeutic approach to reduce adipose tissue inflammation.

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The title image was kindly provided by Nicole Amberg showing “Ear sheets stained for Langerin.”