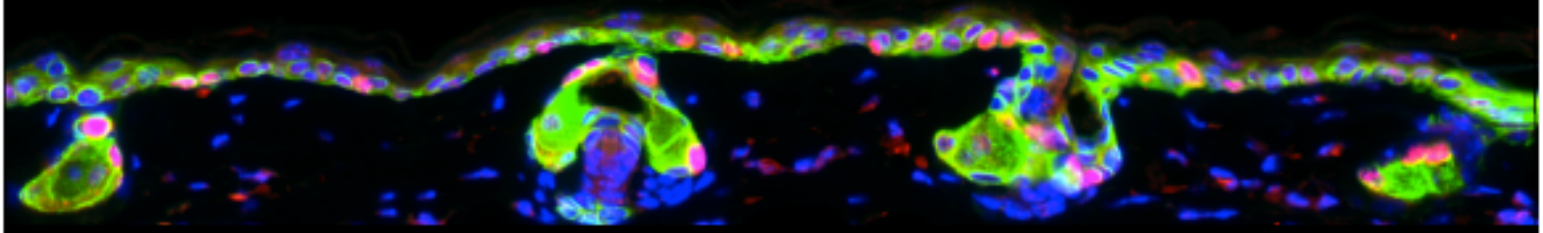
4th International PhD Workshop on Inflammation and Immunity

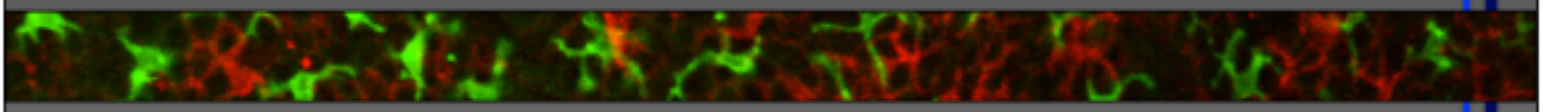
Under my skin –
Advances in Immunology



November 15th – 16th 2012

Kliniken am Südgarten, General Hospital Vienna, Währinger Gürtel 18-20

Program and Abstracts



Organized by the students of the IAI-PhD program of the MUW

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PHD-PROGRAM INFLAMMATION AND IMMUNITY

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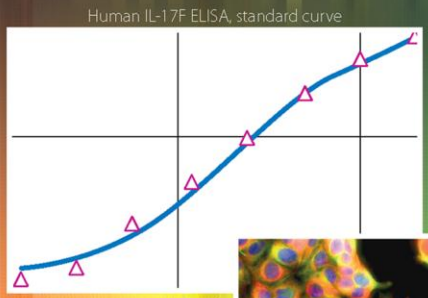

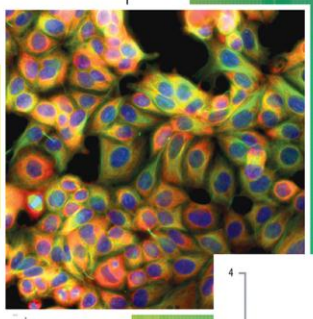

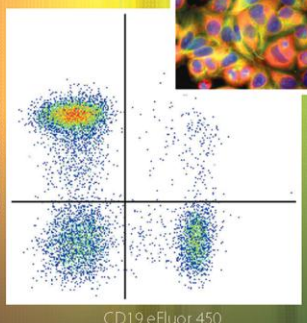

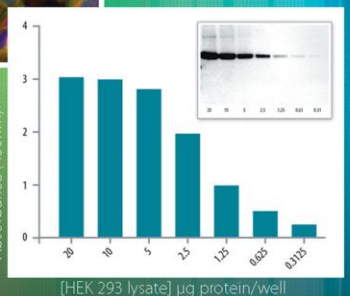

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Special thanks to

Maria Sibilia

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PHD-PROGRAM
INFLAMMATION AND IMMUNITY

The PhD and MD/PhD Program Inflammation and Immunity (IAI) aims at revealing novel mechanisms controlling the development and function of immune cells in health and disease and train excellent young researchers with a new qualification profile in basic, translational and clinical research. The IAI PhD program is closely linked to two Special Research Programs (SFB-F18 and SFB-F23) funded by the Austrian Science Fund (FWF) and several Austrian (GEN-AU, CDL) and European (NoE, RTN, Strep) networks.

Our overall scientific objective is to understand the detailed events and molecular mechanisms associated with inflammatory and immunological diseases. Genes, molecules, isolated cells and tissues as well as whole organisms are all being exploited as model systems. Thereby mouse immunologists closely interact with human immunologists and establish a close interaction between basic and clinical science. The program provides synergistic expertise in the fields of molecular biology, cell biology, mouse genetics, immunology, allergology, infectiology and immunopharmacology, also at the translational level. The major critical advantage of working in this interactive network will be the transfer of molecular observations made in vitro to the clinical treatment of immune and inflammatory diseases in patients. Access to patient material will be provided by the clinical research groups present within the IAI program. This interface between basic and clinical research is of particular importance for the success of the IAI PhD program.

The IAI PhD Program concentrates its research efforts in the following four areas:

- Basic aspects of Immunity
- Inflammatory diseases
- Infectiology and Vaccinology
- Allergy and Hypersensitivity

Our scientific goals is implemented by a state-of-the art career development plan which includes comprehensive educational training in the field of IAI, special lectures on career awareness, collaborative programs with international universities and research institutions, exchange of research tools and technologies, teaching and special scientific workshops. This offers IAI PhD students all the prerequisites for a future successful career in academia, industry or any field of health care.

http://www.meduniwien.ac.at/phd-iai/

e-mail: phd-iai@meduniwien.ac.at

Greetings from the IAI students

The international PhD program „Inflammation and Immunity“ (IAI) was established in 2007 as a part of doctoral programs offered at the Medical University of Vienna. During the past 5 years it has grown considerably and is now consisting of 27 students in 12 laboratories at the Medical University of Vienna as well as at the University of Veterinary Medicine, Vienna. The fields incorporated into the program range from basic research in the areas of immunology and cancer to applied aspects of dermatology, allergology, and virology.

The annual IAI workshop, which is held for the 4th time, gives us a unique opportunity to come together, to improve our organizing as well as scientific skills and to bring to you a chance to get an overview of cutting edge research in immunology.

The first two workshops were focused on inflammation (2009) and immunoregulation (2010). Last year, we tried to broaden our scopes providing an opportunity for scientists and doctors to benefit from each other’s expertise – Brothers in Arms: From basic research to clinical application (2011).

This year, with “Under my skin – Advances in Immunology” we seek to offer a platform to discuss the state of the art in the fields of host pathogen interactions, allergy and tolerance, cancer immunology and immune cell development.

We warmly welcome you to our workshop here in Vienna and wish you a scientifically inspiring time!

On behalf of the organizing committee

Greetings from the Rector of the Medical University – Wolfgang Schütz

Dear Colleagues,

The Medical University of Vienna is one of the world's most renowned medical schools. Around 7,500 students are currently studying the diploma course in human or dental medicine. One important element of learning at the Medical University of Vienna is the PhD course delivered in English.

The excellent quality of this postgraduate education, which complies with the most rigorous of standards, has earned the PhD courses at the MedUni Vienna tremendous international acclaim. This is also highlighted by the high proportion of PhD students who are from outside Austria, accounting for 38 per cent of the students on these courses.

One of the key areas of research at the MedUni Vienna is allergology, immunology and infectious diseases. The 4th international PhD workshop entitled "Under my skin – Advances in Immunology" is therefore the ideal complement to this research.

I wish the event every success, and would like to thank the people who have organised it and worked behind the scenes for their tremendous commitment. I hope that everyone who participates will have the opportunity to enjoy stimulating debate and gain new experiences.

Wolfgang Schütz, Rector Medical University of Vienna

Greetings from the Head of the IAI Program – Maria Sibilia

Welcome to the 4th International Workshop of the Doctoral Program Inflammation and Immunity (IAI)"Under my skin – Advances in Immunology"

In 2007 we started with the Austrian Science Fund (FWF) sponsored Doctoral Program “Inflammation and Immunity” (IAI) after going through a multistep evaluation and hearing process. In 2010 we successfully passed the first evaluation and could increase the number of participating faculty members / PIs from eight to eleven. The IAI program runs as an educational excellence platform in basic medical research at the Medical University of Vienna (MUW) which as a major European Center of biomedical research and education provides the infrastructure for students from all over the world. Meanwhile 34 students from 12 countries have been accepted into the international IAI PhD program after passing a competitive selection procedure. They are conducting their research in the laboratories of the 11 faculty members that are part of the IAI PhD program. Our aim is to strengthen the research interactions and to extend our collaborative network beyond laboratory wallsand different research disciplines, as well as language gaps and cultural differences. Each year the IAI PhD students organize an international workshop which should contribute to facilitate our endeavors.

The topics chosen by our students for the 4th workshop are medically extremely important to accelerate the process from basic discoveries to new therapeutic strategies for the cure of many disorders such as cancer, allergy, and infections. The students have invited internationally well-known experts and world leading scientists in the field and we are looking forward to an active exchange of opinions, stimulating discussions and exciting scientific interactions for the next two days.

In the name of all faculty members I would like to thank the students for putting together such an exciting program and to all the speakers for accepting the invitation and traveling to Vienna to make this event possible. I wish all the IAI students and all participants of the workshop two exciting days.

Finally, we would like to express our gratitude towards the Austrian Science Fund (FWF) and the MUW for financing and supporting our PhD program and to all companies for co-sponsoring this workshop.

Maria Sibilia (IAI PhD program coordinator)

and all PIs of the program: Barbara Bohle (MUW), Robert Eferl (MUW), Wilfried Ellmeier (MUW), Franz X. Heinz (MUW), Mathias Müller (VetMed), Veronika Sexl (VetMed), Georg Stingl (MUW), Johannes Stöckl (MUW), Herbert Strobl (MUW), Rudi Valenta (MUW).

„Under my skin“ – Advances in Immunology

Thursday, November 15th, 2012

08:30 – 09:00 Registration

09:00 – 09:15 **Welcome**.

09:15 – 10:15 **Human tumorvirus infection and immune control in vivo**
Christian Münz (Opening lecture)

SESSION I: Host Pathogen Interactions

10:15 – 11:00 **Molecular Mediators of the Human Antiviral Response**
Curt M. Horvath

11:00 – 11:15 *Student talk:* Julia Schwaiger - Specificity of CD4+ T-cells after tick-borne encephalitis virus infection and vaccination

11:15 – 11:45 *Coffee break*

11:45 – 12:30 **Rotavirus and Vaccines: host range, pathogenesis & innate Immunity -- a ménage a trois**
Harry B. Greenberg

12:30– 14:00 *Lunch break*

14:00 – 15:00 Poster Session

SESSION II: Allergy and Tolerance

15:00 – 15:45 **Mechanisms of immune tolerance to allergens**
Mübeccel Akdis

15:45 – 16:00 *Student talk:* Eva Wollmann – Natural tolerance to peanut in African allergic patients

16:00 – 16:30 *Coffee break*

16:30 – 17:15 **Tolerance autoimmunity, thresh holds and biological clocks**
Ed Palmer

17:15 – 17:30 *Student talk:* Elisabeth Glitzner – The role of Langerhans cells in Psoriasis

Friday, November 16th, 2012

08:30 – 09:15 Registration

SESSION III: Cancer Immunology

09:15 – 10:00 **Put to the acid test: immune cells in the tumor environment**
Marina Kreutz

10:00 – 10:15 *Student talk:* Sriram Srivatsa - Role of EGFR in inflammation induced colorectal cancer

10:15 – 10:45 *Coffee break*

10:45 – 11:30 **TNF receptor signalling in skin homeostasis and inflammation**
Manolis Pasparakis

11:30 – 11:45 *Student talk:* Nicole Amberg - The role of EGFR signaling in hair follicle morphogenesis

11:45 – 12:00 *Student talk:* Karin Hock - Recipient age facilitates bone marrow induced chimerism

12:00 – 13:30 *Lunch break*

SESSION IV: Immune cell development

13:30 – 14:15 **Genetic autoimmune diseases as model to study regulatory T cells**
Rosa Bacchetta

14:15 – 15:00 **Insights from experimental model of atopic dermatitis**
Michiko Oyoshi

15:00 – 15:30 *Coffee break*

15:30 – 15:45 *Student talk:* Thomas Bauer - Identification of Axl as a downstream effector of TGF-b1 during Langerhans cell differentiation and epidermal homeostasis

15:45 – 16:45 **Biology of Macrophages**
Frederic Geissmann (Closing lecture)

16:45 – 17:00 **Closing remarks**

HUMAN TUMORVIRUS INFECTION AND IMMUNE CONTROL IN VIVO

Christian Münz

Viral Immunobiology, Institute of Experimental Immunology, University of Zürich, Switzerland (christian.muenz@uzh.ch)

The human oncogenic Epstein Barr virus (EBV) infects only humans. Therefore, in order to study EBV infection and its immune control in vivo, we explore mice with reconstituted human immune system components (huNSG mice) to characterize viral determinants and human immune responses that protect from virus mediated tumorigenesis.

Along these lines we have identified a virally encoded tumor suppressor gene that limits lymphoma generation upon infection, probably in order to protect the virus host from infection induced mortality and morbidity. EBV deficient in this EBNA3B gene caused virus induced B cell lymphomas in huNSG mice due to both more robust transformation and decreased production of the chemokine CXCL10, which otherwise attracts protective lymphocytes into the tumor microenvironment.

Confirming the clinical relevance of our findings, we were able to identify viral variants with loss of EBNA3B expression in three cases of EBV associated diffuse large B cell lymphomas. A second determinant of EBV infection that predisposes for virus induced tumorigenesis is the course of primary infection. Symptomatic infection, called infectious mononucleosis, elevates the risk to develop certain EBV associated tumors, primarily Hodgkin's lymphoma. In huNSG mice we could demonstrate that depletion of natural killer (NK) cells, which control lytic, infectious virus producing EBV infection, leads to increased EBV titers and tumor formation. In contrast, infection with recombinant EBV that is no longer able to switch into lytic replication due to loss of the immediate early transactivator BZLF-1, is unaffected by NK cell depletion.

Thus, both viral determinants and innate immune responses during primary EBV infection influence tumorigenesis of EBV in vivo.

PUT TO THE ACID TEST: IMMUNE CELLS IN THE TUMOR ENVIRONMENT

Marina Kreutz

Department of Haematology and Oncology,
University Hospital Regensburg,93053 Regensburg, Germany

The function of tumor-infiltrating immune cells is depressed and several tumor-derived factors have been implicated as potential mediators including cytokines and tumor metabolites. A characteristic feature of tumor sites is local acidosis, which is attributed to the accelerated glycolysis of tumor cells, a phenomenon known as “Warburg effect”. Tumor cells upregulate glucose transporters and lactate dehydrogenase and produce high levels of lactate. Lactate is exported in co-transport with protons by monocarboxylate transporters and this lowers the pH in the tumor environment. We studied the effect of such an acidic environment on the differentiation and activation of immune cells. Lactic acid modulated both the differentiation of human monocytes to dendritic cells and the activation of monocytes and T cells. In human monocytes, lactic acid inhibited the LPS-stimulated cytokine response. TNF secretion was suppressed at a concentration as low as 5 mM lactic acid, whereas higher concentrations were needed to suppress IL-6 or IL-10 production. Similar results were obtained for CD8+ T cells. Proliferation, cytokine production (IL-2 and IFN-gamma) and cytotoxic activity were strongly diminished after a 24h culture period with 5-20 mM lactic acid. Further analysis revealed,that monocytes and T cells take up lactate, which results in an inhibition of the glycolytic flux. This indicates that an impairment of energy supply could be one reason for the immunosuppressive effects of lactate on immune cells. A recovery period of 24 h in medium without lactic acid restored cytokine production of T cells demonstrating that the suppressed phenotype is not stable. Therefore a therapeutic rescue of T cells from lactic acid-mediated suppression seems conceivable. To test whether inhibition of lactate production could rescue immune cell function, we used lactate-producing multicellular tumor spheroids. Human monocytes and T cells infiltrated these melanoma spheroids and the co-incubation resulted in a decreased cytokine secretion. An inhibitor of lactate production partially prevented the suppressive effect of lactic acid on infiltrating monocytes and T cells. Furthermore we generated stable murine melanoma cell lines with low lactate secretion by means of Ldh-A short hairpin RNA technology. Tumor incidence and tumor growth of clones with low lactate secretion was significantly diminished in comparison to the control clones with high lactate secretion. We conclude, that lactic acid is an important modulator of immune cell function and may contribute, together with other factors, to immune escape mechanisms in the tumor environment. Therefore, targeting glycolysis in tumor cells could restore immune cell activation and immune response against tumor cells.

This work is supported by DFG Kr1418/7-1.

IKK/NF-KB SIGNALLING IN SKIN INFLAMMATION

Manolis Pasparakis, PhD

Institute for Genetics, University of Cologne, 50674 Cologne, Germany

Intracellular signal transduction pathways activated downstream of pattern recognition receptors and cytokine receptors play a critical role for the regulation of immune and inflammatory responses.

The NF-κB pathway is one of the most important signalling cascades activated by cytokine and innate immune receptors. NF-κB regulates cellular responses to infection, injury and other stressful conditions requiring rapid reprogramming of gene expression. NF-κB activation has been implicated in the pathogenesis of many diseases, particularly chronic inflammatory conditions and cancer. NF-κB activation is mediated by the IκB kinase (IKK), which consists of two catalytic subunits, IKK1(IKKα) and IKK2(IKKβ), and a regulatory subunit named NF-κB Essential Modulator (NEMO) or IKKγ. *In vivo* studies in genetic mouse models provided experimental evidence for the fundamental functions of NF-κBsignalling in inflammation.

Using tissue specific ablation of IKK subunits we have studied the role of NF-κB for the maintenance of immune homeostasis in epithelial surfaces. Epidermis-specific blockade of NF-κBsignalling by keratinocyte-restricted knockout of IKK2 caused strong inflammatory skin lesions resembling human psoriasis. The development in skin inflammation in this mouse model was prevented by genetic deficiency in TNFR1, demonstrating that TNF plays a crucial role in the induction of inflammatory skin lesions upon keratinocyte-specific NF-κB inhibition.

Our current experiments investigate the mechanisms by which NF-κB signalling acts in keratinocytes to regulate skin homeostasis and prevent the pathogenesis of chronic skin inflammation. The results of our most recent studies will be discussed.

MECHANISMS OF IMMUNE TOLERANCE TO ALLERGENS

Mübeccel Akdis, MD, PhD

Swiss Institute of Allergy and Asthma Research (SIAF),
University of Zurich, Davos, CH-7270, Switzerland

The pivotal role of Treg cells in inducing and maintaining immune tolerance has been demonstrated during the last 15 years, where their adoptive transfer was shown to prevent or cure several T-cell mediated disease models, including asthmatic lung inflammation, autoimmune diseases and allograft rejection. In addition, subsets of CD8+ T cells, γδ T cells, DC, IL-10-producing B cells, NK cells and resident tissue cells, which may promote the generation of Treg cells, may contribute to suppressive and regulatory events.

Regulatory B cells expressing IL-10 suppress immune responses and the lack or loss of regulatory B cells leads to exacerbated symptoms in experimental autoimmune encephalitis, chronic colitis, contact hypersensitivity, collagen-induced arthritis and non-obese diabetic mouse models. Another B cell-related immune regulatory response restricted to humans is induction of non-inflammatory IgG4 antibodies, which is characteristic for high dose antigen tolerance models. Several molecules including CD25 and PD-L1 were upregulated in IL-10-producing B cells. Br1 cells potently suppressed antigen-specific CD4+ T cell proliferation whereas other B cells did not.

Furthermore we demonstrate that human Br1 cells show selectively increased production of IgG4. B cells specific for the major bee venom allergen phospholipase A2 that were isolated from beekeepers had increased expression of IL-10 and IgG4. Human Br1 cells may regulate humoral and cellular immunological tolerance through suppression of T cells responses and production of anti-inflammatory IgG4 antibodies.

INSIGHTS FROM EXPERIMENTAL MODELS OF ATOPIC DERMATITIS

Michiko Oyoshi PhD

Children's Hospital Boston, Department of Pediatrics,
Immunology/Karp10007E, 1 Blackfan Circle, Boston, MA 02115

Atopic dermatitis (AD) is a common pruritic inflammatory skin disease often associated with a family and/or personal history of allergy. The prevalence of the disease is on the rise all over the world, particularly in the developed countries.

The hallmark of AD is skin barrier dysfunction that results in dry itchy skin. Itching causes scratching that inflicts mechanical injury followed by allergic sensitization to environmental antigens and allergic skin inflammation. We have established a mouse model of AD that displays many features of human AD. In this model, repeated epicutaneous (EC) sensitization of tape-stripped skin with ovalbumin (OVA) results in a Th2 dominated systemic immune response and the development of allergic skin inflammation characterized by dermal infiltration of $CD4^+$ T cells and eosinophils, increased local expression of Th2/Th17 cytokines, fibrosis, and collagen deposition. Oral challenge of EC sensitized mice with OVA developed systemic anaphylaxis as evidenced by decreased body temperature. We will also discuss, based on information from the mouse model of AD, the contributions of neutrophils and leukotrienes to the pathogenesis of AD.

Our studies provide a mouse model to study human atopic march, suggesting that the skin may be an important route of sensitization to antigen in AD and in the development of allergic diseases such as food allergy.

AUTOIMMUNE GENETIC DISEASES AS MODELS TO STUDY REGULATORY T CELLS

Rosa Bacchetta, MD

Telethon Institute for Gene Therapy,
San Raffaele Scientific Institute, Milan, Italy

Immune regulation results from a finely tuned network of distinct mechanisms operating throughout life and balancing the need to clear infections and prevent self-aggression. Primary Immunodeficiencies (PIDs) are “experiments of nature” where the ability to fight against pathogens is deeply impaired, and the study of patients with PIDs has been instrumental to identify and characterize key components and mechanisms that govern development and function of the human immune system. Similarly to the impairment of immune defence to pathogens, specific genetic defects can lead to altered immune regulation and break of immunological tolerance. In these monogenic diseases autoimmune symptoms may easily prevail over infections.

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) and Immune-dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) Syndrome are unique model of PID primarily characterized by loss of tolerance to self. APECED is due to mutation of *AIRE* gene a transcription factors with a key functional role during thymic clonal deletion of autoreactive T cells. IPEX syndrome is a life-threatening disease in which mutations in *Forkhead box P3* (*FOXP3*) lead to dysfunction of CD4+CD25+ nTreg cells. Indeed, FOXP3 is essential for Treg cell function, and altered regulation by mutated (mut) Treg cells is the primary cause of the disease. However, many patients with symptoms resembling IPEX (IPEX-like) do not have *FOXP3* mutations. Some of them are affected by mutation of the IL2-receptor alpha gene, also an essential molecule for the correct function of Treg cells and for immune homeostasis. In other patients, regulatory T cells are functional but their number is not sufficient to maintain peripheral tolerance, for reasons that still need to be clarified. In addition, there is a large number of patients with early onset polyautoimmunity of unknown origin in which the number and the function of Treg cells have never been investigated.

In depth investigations of the pathogenesis of these diseases have significantly contributed, in recent years, to a better understanding of the immune regulatory mechanisms and have provided indications for new therapeutic strategies to reestablish tolerance.

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TOLERANCE AUTOIMMUNITY, THRESH HOLDS AND BIOLOGICAL CLOCKS

Ed Palmer, MD, PhD

Department of Biomedicine,
University Hospital Basel, Hebelstrasse 20, CH - 4031 Basel

T lineage cells are capable of differentially responding to self-antigens of varying affinity. The lecture will present the basics of T cell receptor / ligand binding, signal initiation and the development of an "appropriate" cellular response. These experimental observations will be discussed in the context of T cell tolerance and autoimmunity.

MOLECULAR MEDIATORS OF THE HUMAN ANTIVIRAL RESPONSE

Curt M. Horvath, PhD

Northwestern University, Pancoe Pavilion, Rooms 4401/4301,
2200 Campus Drive Evanston , IL 60208-3500

Virus infection or stimulation virus replication intermediates like double-stranded RNA (dsRNA), initiate biosynthesis of interferon (IFN). The IFN signaling systems produce a broadly effective innate antiviral response that restricts the replication of diverse viruses. Most of the antiviral activity is the result of transcriptional programs initiated by dsRNA or IFN that activate antiviral gene expression. In mammalian cells dsRNA can activate signaling by RIG-I, MDA5, and LGP2 receptors to activate IFN biosynthesis, and IFN signaling activates the ISGF3 transcription factor complex, composed of STAT1, STAT2, and IRF9 to stimulate antiviral gene expression.

The functions of these antiviral transcription factors have been investigated, and several classes of co-activating cellular machinery have been uncovered, including histone modifying enzymes and the pol II mediator complex. Identification of these cofactors has provided insights into the mechanisms of antiviral signaling. The importance of the IFN antiviral system is underscored by the numerous examples of animal viruses that have evolved strategies to destroy elements of this system. One family of RNA viruses, the Paramyxoviridae, not only inhibit IFN biosynthesis by disrupting dsRNA signaling by MDA5 and LGP2, but also directly target STAT proteins to evade IFN induced antiviral responses. The diverse mechanisms of IFN evasion include ubiquitylation and proteasomal degradation, cytoplasmic sequestration of signaling factors, and inhibition of nuclear translocation.

These mechanisms evolved to target antiviral responses, and therefore these virus systems provide unique insights into successful host targeting strategies that may have therapeutic value in control of cancer, inflammation, and other diseases characterized by hyperactive cellular signal transduction.

ROTAVIRUS AND VACCINES: HOST RANGE, PATHOGENESIS & INNATE IMMUNITY-- A MÉNAGE A TROIS"

Harry B Greenberg MD

Departments of Medicine and Microbiology and Immunology, Stanford University

Rotaviruses are the single most important cause of severe infantile gastroenteritis all over the world. Rotaviruses replication in the GI tract is highly species specific and this specificity forms the basis for attenuation of several rotavirus vaccines. We have quantified the replication capacity of a library of murine (EW) x simian (RRV) reassortants in suckling mice.

We showed that the high replication capacity of EW is absolutely dependent on the presence of EW gene 5, encoding NSP1, a multifunctional protein that interferes with interferon signaling. Further analysis and the role of additional genes, including VP4, the cell binding protein, on host range will be discussed. To further evaluate the effects of NSP1s on host range restriction we challenged STAT1 KO mice with selected reassortants. Replication of all reassortants and parental strains increased in STAT1 KO mice, but the increase was significantly greater simian RV and reassortants with simian NSP1 (> 800X) than for murine or reassortants with murine NSP1 (<50 X). Given the importance of innate immunity in regulating host range restriction, we next undertook a series of bulk and single cell experiments to study IFN signaling in the mouse intestine.

We compared early antiviral innate immunity to homologous murine RV in bulk intestinal tissues, fractionated intestinal cell types, and in single absorptive villous intestinal epithelial cells (IECs). To resolve the signaling pathways involved, we infected genetic knockout mice deficient in interferon responses ($IFNAgR^{-/-}$ and $STAT\text{-}1^{-/-}$) with murine and simian rotavirus. Despite its high replication potential, murine RV robustly activated type I interferons (IFN) and several antiviral genes in 'bulk' intestinal cell analysis. Induction of type I IFNs was relatively replication-insensitive since the simian RV also efficiently activated host innate responses but replicated poorly. The induction of IFN mostly occurred in intestinal hematopoietic cells and required signaling through type I/II IFN receptors and STAT1. In contrast, microfluidics-based single cell multiplex RT-PCR allowed analysis of RV-infected and -bystander absorptive villous IECs. EW replication took place in discrete IEC subsets differing in their basal levels of type I IFN transcription and resulted in IRF3-dependent and -augmented transcription, but not in increased NF-kB activity or the transcription of type I IFNs. Several antiviral responses in uninfected bystander IECs were also identified and were presumably the result of IFN secretion from immune cells.

Resolution of 'averaged' intestinal innate immune responses among various cell types and their analysis in single IECs thus revealed unexpected heterogeneity in both the induction and subversion of early host antiviral immunity for a pathogenic mucosal virus.

THE ROLE OF EGFR SIGNALING IN HAIR FOLLICLE STEM CELLS AND HAIR FOLLICLE MAINTENANCE

Amberg N[1], Lichtenberger B[1], Holcmann M[1], Sotiropoulou P[2], Blanpain C[2], Sibilia M[1]

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The skin has important functions in several biological processes like environmental barrier, tissue regeneration, and wound repair. During these processes stem cells from the interfollicular epidermis and the hair follicle bulge 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.

In order to study the role of EGFR signalling in hair follicle development, we analyzed mice lacking the EGFR in two distinct mouse models. $EGFR^{\Delta ep}$ mice lack the EGFR in basal keratinocytes and the outer root sheath (ORS) of the hair follicle, whereas in $EGFR^{\Delta LGR5}$ mice EGFR can be deleted in stem cells of the lower bulge and the secondary hair germ.Lack of EGFR in $EGFR^{\Delta ep}$ mice resulted in a delay of hair follicle morphogenesis, which further lead to degradation of the hair follicles. Moreover, morphogenesis appeared to be defective, as hair from $EGFR^{\Delta ep}$ mice did not show inner root sheath layers or cuticle and cortex layers of the hair shaft. This was also reflected by the inability of proper hair type formation. Single hair analysis from $EGFR^{\Delta ep}$mice revealed that the 4 different hair types (Awl, Guard, Zig-zag and Auchene) were not formed and instead hair showed curled or waved morphology. Additionally, the main hair follicle bulge stem cell marker CD34 was almost completely absent from hair of $EGFR^{\Delta ep}$ mice. Nevertheless we detected expression of hair follicle stem cell transcription factors Lhx2 and Sox9 in the lower hair follicle parts. Upon BrdU pulse chase experiments, EGFR-deficient skin showed reduced numbers of label retaining cells in the hair follicle at postnatal day 80 (P80), as well as reduced numbers of $LGR5^{+}$ stem cells in the bulge and secondary hair germ region. In mouse hair follicles cells in the bulge are believed to have stem cell activity. Upon deletion of the EGFR soon after birth in $EGFR^{\Delta LGR5}$ mice we observed that the coat of these mice appeared matt with irregular hair outgrowth and waved Awl and Guard hair as well as irregularly angled Zig-zag and Auchene hair at P80.

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, dependent on cell identity.

THE ROLE OF DENDRITIC CELLS IN PSORIASIS

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Psoriasis is a frequent, chronic, debilitating autoinflammatory disease of the skin. In this condition, the skin is affected by disorganization of the epidermis, resulting in loss of stratification as well as thickening and dedifferentiation of the corneal layer.

Based on these observations an intrinsic defect of the keratinocyte layer has been proposed to be the primary event in disease initiation. Within psoriatic lesions, Langerhans cell (LC) numbers are often reduced compared to noninvolved skin, whereas plasmacytoid dendritic cell (pDC) numbers are increased.

Recently, it has been reported that mice harboring an inducible deletion of the AP-1 transcription factors c-jun and junB in the basal layer of the epidermis (jun/junBΔep) develop a psoriasis-like phenotype resembling human disease. Upon initiation of disease in jun/junBΔep mice, LC number in the epidermis was increased, however, as lesions progressed, LC numbers decreased. To study LC function in psoriasis, we crossed jun/junBΔep mice to Langerin-DTREGFP mice that can be inducibly depleted of Langerin+ cells by application of diphtheria toxin (DT). With this technique, we were able to deplete Langerin+ cells efficiently and consistently over an extended time period. Additionally, we were able to selectively deplete Langerhans cells and Langerin+ dermal DC, respectively by using bone marrow chimeric mice.

The advent of another DT-based depletion strategy using BDCA2-DTR mice enables us to furthermore selectively deplete pDC from jun/junBΔep mice. These studies will provide important insights into the function of LC and pDC in psoriasis.

RECIPIENT AGE FACILITATES BONE MARROW TRANSPLANTATION-BASED TOLERANCE INDUCTION

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Tolerance induction through bone marrow transplantation (mixed chimerism) holds promise for clinical translation but is commonly only investigated in young recipients. Senescence is paralleled by substantial modifications of the immune system including increased frequencies of memory T cells (Tmem) which are in general considered a substantial barrier to tolerance induction.Young (2mth; 20 g) and old (12mth; 25 g) recipients (C57BL/6) were treated with 5 different BMT protocols. In each protocol recipients were transplanted with un-separated Balb/c BM cells adjusted to body weight ($1x10^3$/kg, i.e. young $20x10^6$/mouse; old $25x10^6$/mouse). 3 Gy total body irradiation (TBI) and an induction treatment of costimulation blockade (CB: anti-CD154 mAb and CTLA4Ig) or T cell depletion (TCD: anti-CD4 and anti-CD8), 1 Gy and CB or rapamycin and without irradiation and rapamycin. Lymphocyte subsets and cytokine production were compared between young and old naïve mice and multi-lineage chimerism was assessed by flow cytometry. Old mice contained significantly higher frequencies of CD4 ($p<0.001$) and CD8 ($p<0.001$) memory T cells ($CD44^{high}CD62L^{low}$), early activated CD4 T cells ($CD4^+CD69^+$; $p<0.001$) and comparable amounts of CD4, CD8 and regulatory T cells (Tregs; $CD4^+CD25^+FoxP3^+$, p=n.s. vs. young animals). Moreover, older CD4 T cells released significantly more IFN-γ ($p<0.05$) and IL-6 ($p<0.05$) after polyclonal stimulation but not after allogeneic stimulation. While rates of successful chimeras were comparable in the non-myeloablative TBI (3 Gy) together with CB (7/8 old vs. 11/11 young), in the TCD protocol the chimerism levels achieved were significantly higher in old than in young recipients in all tested lineages (e. g. donor B-cell chimerism: 56.33% old vs. 18.17% young; $p<0.0001$; and donor MAC-1-cell chimerism: 79.82% old vs. 39.10% young; $p<0.05$; 8 weeks post BMT). Under minimal conditioning (1 Gy) together with CB most recipients became chimeric (7/10 old vs. 6/6 young). 1 Gy irradiation in combination with rapamycin led to chimerism in only 2 out of 6 old recipient mice compared to none of the young recipients and none became chimeric without irradiation and rapamycin. Notably, the frequency of Tregs derived from the spleen of old BMT recipients was significantly increased. BM engraftment and chimerism can be successfully achieved in old recipients under reduced intensity conditions. Those results support the clinical relevance of the chimerism strategy for tolerance induction for a wide group of potential patients.

SPECIFICITY OF CD4$^+$ T-CELLS AFTER TICK-BORNE ENCEPHALITIS VIRUS INFECTION AND VACCINATION

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Tick-borne encephalitis (TBE) virus is a major human pathogen in Europe and Asia. The virion contains three structural proteins: E (envelope), prM/M (membrane) and C (capsid). Neutralizing and protective antibodies are directed against the E protein which covers the viral surface and mediates virus entry. Production of such antibodies is strongly dependent on the helper function of antigen-specific CD4$^+$ T-cells presumed to be specific for epitopes in E, prM/M and C. The extent, specificity and individual variability of CD4$^+$ T-cell responses after TBE virus infection and vaccination and their relationship to the magnitude of antibody responses, however, are presently unknown.

A highly sensitive IL-2 ELISpot assay using libraries of overlapping peptides from E, prM/M and C was developed to determine the TBE virus-specific CD4$^+$ T-cell response in CD8 depleted peripheral blood mononuclear cell samples from infected and vaccinated people.

Our results demonstrate that the CD4$^+$ T-cell responses in both groups are directed primarily against peptides of C and E and to a much lesser extent to prM/M. Although the magnitude of the response is significantly higher after TBE vaccination compared to TBE virus infection, the relative contribution of the single protein specificities to the total response is similar in these two groups. Analysis of the fine-specificity using single peptides shows that there is individual variation in the epitope specificity and in the magnitude of the CD4$^+$ T-cell response. Despite this individual variation 6 immunodominant regions were identified both in vaccinated and infected individuals which mapped to domain III of the TBE E protein and helix 2 and 4 of the C protein. In addition, we identified specific reactivities that were characteristic of infected and vaccinated people, respectively.

ROLE OF EGFR IN INFLAMMATION INDUCED COLORECTAL CANCERS

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Colorectal cancer (CRC) is one of the major causes of mortality in the western world. Inflammatory bowel diseases such as Ulcerative Colitis, Crohn's disease are associated with an increased risk of CRC suggesting that immune system activation contributes to tumour promotion.

The Epidermal Growth Factor Receptor (EGFR), a member of the tyrosine kinase receptor super family, is known to be overexpressed in CRC, but its molecular functions in this disease are not fully known. This project employs a transgenic murine colitis associated cancer model, wherein *Egfr* expression is specifically abrogated in the intestines of these mice using the Cre-loxP system. Azoxymethane (genotoxic carcinogen) is administered to these mice, to produce random genetic alterations, followed by Dextran Sulphate Sodium in drinking water which causes chronic inflammation in distal and intermediate colon. Both treatments mimic the environment for induction of colorectal tumours. The project aims at establishing a concrete role of *Egfr* in colon carcinogenesis.

Our current observations show no difference in tumour incidence in mice lacking *Egfr* in intestinal epithelial cells ($Egfr^{\Delta IEC}$) compared to controls ($Egfr^{f/f}$). Molecular analysis show higher inflammatory markers in $Egfr^{\Delta IEC}$mice. Interestingly tumour incidence is reduced in mice lacking *Egfr* in the myeloid cell lineage. Furthermore, in other intestinal tumour model, mice which are WT heterozygous for the *Min* allele of Adenomatosis Polyposis Coli gene *Apc* and spontaneously develop polyps in the gut, the loss of *Egfr* leads to significant reduction in life span likely because of higher tumour incidence. These observations suggest a tissue specific protective role of *Egfr* that is contrary to the current belief that *Egfr* is a tumour promoter.

Further molecular investigations currently underway will reveal the mechanisms leading to the observed phenotypes.

IDENTIFICATION OF AXL AS A DOWNSTREAM EFFECTOR OF TGF-B1 DURING LANGERHANS CELL DIFFERENTIATION AND EPIDERMAL HOMEOSTASIS

Thomas Bauer[1, 2], Anna Zagórska[3], Jennifer Jurkin[1], Nighat Yasmin[1], René Köffel[1, 2], Susanne Richter[1], Bernhard Gesslbauer[1], Greg Lemke[3, 4] and Herbert Strobl[1, 2]

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Transforming growth factor- β1 (TGF-β1) is a fundamental regulator of immune cell development and function. In this study, we investigated the effects of TGF-β1 on the differentiation of human Langerhans cells (LCs), and identified Axl as a key TGF-β1 effector.

Axl belongs to the TAM (Tyro3, Axl and Mer) receptor tyrosine kinase (RTK) family, whose members function as inhibitors of innate inflammatory responses in dendritic cells (DCs) and are essential to the prevention of lupus-like autoimmunity. We found that Axl expression is induced by TGF-β1 during LC differentiation, and that LC precursors acquire Axl early during differentiation. We also describe prominent steady-state expression as well as inflammation-induced activation of Axl in human epidermal keratinocytes and LCs. TGF-β1-induced Axl enhances apoptotic cell (AC) uptake and blocks pro-inflammatory cytokine production. The anti-inflammatory role of Axl in the skin is reflected in a marked impairment of the LC network preceding spontaneous skin inflammation in mutant mice that lack all three TAM receptors.

Our findings highlight the importance of constitutive Axl expression to tolerogenic barrier immunity in the epidermis, and define a mechanism by which TGF-β1 enables silent homeostatic clearing of ACs to maintain long term self-tolerance.

NATURAL TOLERANCE TO PEANUT IN AFRICAN ALLERGIC PATIENTS

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Peanut allergy is known to cause severe and life-threatening allergic reactions. To investigate allergic patients from African who show IgE reactivity to peanuts but regularly eat them without experiencing allergic reactions. We analysed sera from 54 African patients (group 1: n=37; age 0-15 years; mean 7.2 ± 4.6; group 2: n=17; >15 years mean 29.7 ±12.9) regarding IgE antibody levels to peanut allergen extracts using quantitative ImmunoCAP (Thermo Fisher, Uppsala) measurements and performed a detailed analysis of the IgE and IgG reactivity profiles towards more than 145 purified natural and recombinant allergen molecules using an allergen microarray (ThermoFisher). Also total IgE levels were assessed by ImmunoCAP and a detailed recording of patients' demographic and clinical data was performed. The allergic symptoms recorded in the allergic patients included skin-, airway- and gastrointestinal tract-related manifestations which were related to allergen sources other than peanuts. Total IgE levels of group 1 (median) are 650kU/L and 391kU/L (median) for group 2. Patients showed a broad sensitization profile to a variety of allergens with house dust mite allergens as predominating allergens. Each patient showed IgE reactivity to peanut extract in the ImmunoCAP (range 0.1kU_A/L – 200kU_A/L; median group 1: 2.3kU_A/L; median group 2: 2,7kU_A/L). Notably, 44% of the patients showed IgE reactivity towards at least one of the peanut allergens (Ara h 1, 2, 3, 6 and 9) which reportedly cause severe anaphylactic reactions. Only one of the analysed patients displayed IgE reactivity to Ara h 8 (PR-10 family) in chip analysis. Forty-eight percent of the patients showed allergen-specific IgE only towards the carbohydrate markers (MUXF3, nCup a 1, nCry j 1, nCyn d 1, nPhl p 4), but not towards the peanut allergen molecules. Interestingly, peanut allergen-specific IgG levels were elevated over IgE in the African patients and there was no correlation between allergen-specific IgE and IgG levels for Ara h 1, 2, 3, 6, 8. Only Ara h 9 allergen-specific IgE and IgG levels correlated ($r=0.54$, $p<0.01$). By contrast, significant correlations between IgE and IgG levels to the major house dust mite allergens were found. The lack of peanut symptoms maybe explained for the 48% of patients by exclusive IgE reactivity to non-allergic carbohydrate residues. Results suggest that continuous exposure to peanut (i.e., peanut ingestion) has induced elevated levels of allergen-specific IgG antibodies in the African population which seems to protect them from allergic reactions and is associated with clinical tolerance to peanuts.

INDUCTION OF IL-35 IN HUMAN T CELLS UPON CO-STIMULATION VIA CD43 AND PD-1

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ROLE OF MICRORNAS IN DENDRITIC CELL AND MACROPHAGE LINEAGE COMMITMENT

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THE ROLE OF STAT1 IN MACROPHAGES/NEUTROPHILS IN THE ANTIVIRAL RESPONSE IN VIVO

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PATHOGENIC T CELL SUBSETS IN PSORIASIS: CHARACTERIZATION OF CANDIDATE PRECURSOR POPULATIONS IN THE PERIPHERAL BLOOD

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CHARACTERIZATION OF THE ALLERGIC T-CELL RESPONSE TO DAU C 1, THE BET V 1 HOMOLOGOUS PROTEIN IN CARROT

Nora Zulehner[1], Birgit Nagl[1], Gerhard Zlabinger[2],Barbara Bohle[1]

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THE ROLE OF STAT1 IN INTESTINAL TUMORIGENESIS

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IDENTIFICATION AND CHARACTERIZATION OF MAZR INTERACTION PARTNERS

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WHY DO AFRICAN PEANUT-SENSITIZED PATIENTS NOT SHOW SEVERE ALLERGIC REACTIONS?

Eva Wollmann[1], Elopy Sibanda[2], Carl Hamsten[3], Annika Önell[4], Daniela Gallerano[1], Christian Lupinek[1], Rudolf Valenta[1], Marianne van Hage[3]

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FINE-SPECIFICITY OF THE HUMORAL IMMUNE RESPONCE TO YELLOW FEVER VACCINATION IN HUMANS"

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THE SOLUBLE CYTOPLASMIC TAIL OF CD45 (CT-CD45) INDUCES A NON-CANONICAL FORM OF ANERGY IN HUMAN T CELLS

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BTK REGULATES THE MACROPHAGE RESPONSE TO LISTERIA MONOCYTOGENESINFECTION

Afitap Derya Köprülü[1], Renate Kastner[2,6], Sebastian Wienerroither[2], Caroline Lassnig[3], Eva Maria Putz[4], Olivia Majer[5], Benjamin Reutterer[2,7], Veronika Sexl[4], Karl Kuchler[5], Mathias Müller[3], Thomas Decker[2], Wilfried Ellmeier[1]

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Registration

Registration will take place at the registration desk, which is located in the admission area at Kliniken am Südgarten of the General Hospital. Registration is open from 8:30 to 9:00 and during breaks. Admission to all scientific sessions is free.

Language

Official workshop language is English.

Congress Venue

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Lecture Hall A, Kliniken am Südgarten
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Access to the Venue

Lecture Hall A
Kliniken am Südgarten

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