

**Institute of Immunology**  
**MEDICAL UNIVERSITY OF VIENNA**

**RESERACH REPORT 2005**

## INTRODUCTION

The main goal of the Institute of Immunology is to strive towards a better understanding of the immune system through concentrated research and to provide knowledge to students as well as to promote professional education. Elucidating the molecular basis of immune cell development and function is aimed at increasing insight into the principles of immune reactivity. This will form the basis for the development of new strategies for therapeutic interventions as well as for decisive diagnostic procedures. Among the various types of human immune cells, the phagocyte family of innate immune cells, in particular DC, and T lymphocytes, the central players of adaptive immunity, are primary targets of the research. Disease states most thoroughly investigated by Institute members are malignancies of the haematopoietic system, infectious and chronic inflammatory processes, transplantation-related disease problems and primary immunodeficiencies. The study of both fundamental immunological problems and issues of practical clinical relevance shall complement each other in order to unravel still existing secrets of immune homeostasis.

2004 has been a dramatic year in several respects. First we had to regret the loss of Walter Knapp, who served as Chairman of the Institute for more than 15 years and has contributed tremendously to the success and reputation of our institution as well as to the advancement of the discipline in Austria and abroad. This reasearch report of the current research groups of the Institute is particularly devoted to the commemoration of Prof. Knapp and shall indicate the achievements of the Institute under his leadership. We herewith also wish to express our gratitude for his tireless help and motivation to advance our progress in the field.

Another far-reaching event has been the reorganization of the Medical University of Vienna, which brought about the formation of new organization units. Here we have put our efforts to enable the formation of a Center with a strong immunological focus and, therefore, have joined the Clinical Institute of Hygiene and Medical Microbiology headed by Prof. Manfred Rotter. As has been done very successfully in the past, the research activities of our institution are realized by the ambitious efforts of the individual independent research groups that for the most part are funded by highly competitive grants. Trough the establishment of larger units we expect that common research interests and intensified mutual stimulation will further high quality scientific research.

## Professor WALTER KNAPP (1944- 2004)

It was with much sadness that we received the news of the passing of the Chairman of the Institute of Immunology, our mentor and teacher, Professor Walter Knapp, who was taken from us on August 30<sup>th</sup> 2004. Our sincere compassion goes to his wife and three children, who have lost this extraordinary man.



Professor Walter Knapp was an exceptional person whose professional life was characterized by enormous activity. He can be regarded as one of the pioneers of modern immunology. He came to Vienna at the end of the sixties and started as assistant to Professor Carl Steffen at the newly founded Institute of Immunology. These early days of immunology in Vienna were characterized by highly ambitious research. Discussion rounds and numerous courses in basic and applied immunology were initiated in order to promote the progression of the discipline. Immunology has been integrated into the main lectures of various courses and also the Medical Specialization in Immunology has been instituted. Professor Knapp contributed to all of these achievements as one of the major driving forces. He managed to establish the discipline as one of the most successful within the Medical Faculty of the University of Vienna.

Professor Knapp acquired the fundamental knowledge about immunofluorescence technology in The Netherlands, which served him so effectively when he started to introduce the monoclonal antibody technology in Vienna. His engagement in this field finally led to the establishment of the CD nomenclature, which will always be connected with his name. His research activities were devoted to the functional characterization of immune cell receptors. He also focused from the beginning of his career on cells of the innate arm of the immune system and thus also contributed crucially to the elucidation of the central importance of dendritic cells in immunity. Professor Knapp was able to foresee key developments and technologies in immunology and thus was always one step ahead of the others in the field. He was also among the first to realize the potential of monoclonal antibodies for diagnostic and therapeutic purposes which is well reflected by his status as key figure in leukemia typing.

Professor Knapp was Vice-President of the Austrian Science Fund, President of the Austrian Society of Allergology and Immunology, Member of the Austrian Academy of Sciences, President of the European Federation of Immunological Societies, Honorary Member of many scientific societies and has received numerous national and international awards. We all will miss him enormously, but his legacy is huge – his work, his excellence and most of all our memories of his straightness, his loyalty and his infectious humor he showered upon those around him.

Gerhard Zlabinger

## HUMAN LEUCOCYTE DIFFERENTIATION ANTIGENS

### *Reflections and Outlook*

Relatively soon after Ceasar Milstein and Georg Köhler had published their pioneering studies on "*Continuous cultures of fused cells secreting antibody of predefined specificity. Nature, 1975, 256 (5517): 495–497*", my late mentor Walter Knapp started to show great interest in establishing these methods at our institute. In the beginning his working group consisted only of one post doc position and one technician. So Walter Knapp undertook this high-risk project in conferring a thesis to me in 1978, on producing monoclonal antibodies to human leukocyte differentiation antigens, which resulted in our participation at the first HLDA workshop held in Paris in 1982.

At this initial meeting only fifteen agreed molecular entities were listed, but it created an internationally agreed basis for the nomenclature of leukocyte molecules. This CD nomenclature is based on the grouping of antibodies with a similar reaction pattern designated as "Clusters of Differentiation", CDs. Already at that time, we were able to contribute three monoclonal antibodies, VILA1 (WS Code B10), VIMD5 (WS Code M5), which helped to define the CD10 and CD15. The third antibody VIMD2 was unique, not until it has helped to define CD93, in combination with a second monoclonal antibody of our laboratory.

So far the wide range of characterised molecules from CD1 to CD339, has been derived from eight HLDA Workshops. From the very beginning many of our monoclonal antibodies were used to define new molecules, e.g. CD27, CD65, CD65s, CD92, CD93, CD97. The last 8th HLDA Workshop was a four year international project, culminating in the 8th HLDA Conference held in Adelaide, December 12 -16, 2004. It involved several hundred laboratories around the world and our „tissue culture unit“ was represented with a number of antibodies, three of which defined the new clusters CD274, CD276, and CDw328. Remarkably, the definition of CD276 (B7-H3) is exclusively due to the three monoclonal antibodies, submitted by our laboratory.

At present, we have raised 135 different monoclonal antibodies that describe a total of 63 CDs. In addition, we possess even more monoclonal antibodies that are specific for molecules, which have not yet been clustered.

To bridge the gap between scientific research and the organisation and the maintenance of well established monoclonal antibodies, is the big challenge at present. What has begun as „hobby“ of Walter Knapp, being deeply inspired by Köhler and Milstein's report on „Continuous culture of fused cells“, and especially the final sentence „.....Such cultures could be valuable for medical and industrial use“, is now indispensable at our institute in the fields of scientific research, differential diagnosis, monitoring and treatment of diseases.

HLDA MEETINGS were held in Paris 1982, Boston 1984, Oxford 1986, **Vienna** 1989 (Organization Walter Knapp, Inst. of Immunology, Vienna), Boston 1993, Kobe 1996, Harrogate 2000, and Adelaide 2004.

Otto Majdic

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Laboratory „Development and Activation of Immune Cells“



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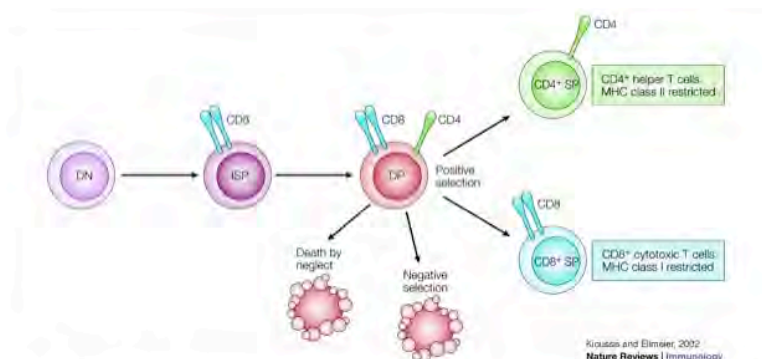
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My long-term research interest is to understand molecular mechanisms that regulate the development and activation of cells of the immune system. Ongoing research in my laboratory focuses on studies to understand gene regulation at the transcriptional level during T cell development and to obtain insight into regulatory mechanisms that determine chromatin (epigenetic) modifications and to link them with cell fate specification. Furthermore we are studying the various roles of Tec family kinases in signal transduction pathways in different cell lineages of the immune system. By using a variety of techniques, including RNAi approaches, retroviral-mediated gene transduction into DN thymocytes or bone marrow stem cells, and mouse molecular genetic tools, we expect a better understanding of fundamental biological processes, and on the long-term run also medical-relevant insight into the immune system.

### Molecular Mechanisms of T Cell Development

One question we are interested in is how the development of CD4<sup>+</sup> or CD8<sup>+</sup> T cells from immature CD4 and CD8 expressing double-positive precursor in the thymus is regulated. Not only is our T cell repertoire formed during this important developmental transition, but also T helper or cytotoxic T cell fate decisions

are made. Therefore, at the same developmental stage signal transduction events are induced by TCR-MHC interaction and lineage-specific transcriptional programs must be initiated. By performing DNA microarray analysis combined with retroviral-mediated gene transduction approaches we aim to identify key regulatory genes that regulated the DP to SP transition during T cell development.



The majority of thymus-derived TCR $\alpha\beta$ -positive T cells express either the CD4 or the CD8 coreceptor molecules. CD4-expressing cells almost always have a helper phenotype, and express TCRs specific for MHC class II, whereas CD8<sup>+</sup> T cells have a cytotoxic phenotype and are MHC class I restricted. These single-positive (SP) cells develop in the thymus from a common double-positive (DP) progenitor cell, that expresses both CD4 and CD8.

Wilfried Ellmeier

### Epigenetic and Transcriptional Regulation of CD8 Expression during T Cell Development

The transcriptional regulation of CD4 and CD8 is tightly linked to the functional program of the developing T cell. It is conceivable that factors regulating CD4 and CD8 expression are also involved in directing DP thymocytes towards the helper or cytotoxic lineage. We therefore aim to understand how CD8 is transcriptionally regulated and to identify cis-regulatory elements and trans-acting factors.

Multiple developmental stage-specific CD8 cis-regulatory elements have been identified. We have recently shown that deletion of two of these elements in the mouse germline leads to variegated expression of CD8 in DP thymocytes and epigenetic alterations at the CD8 locus, suggesting that they may serve as recruitment sites for factors that initiate chromatin remodeling during the DN to DP transition. Currently we are working on the identification and characterization of those trans-acting factors.

### Tec Family Kinases and Signalling Pathways in Immune Cells

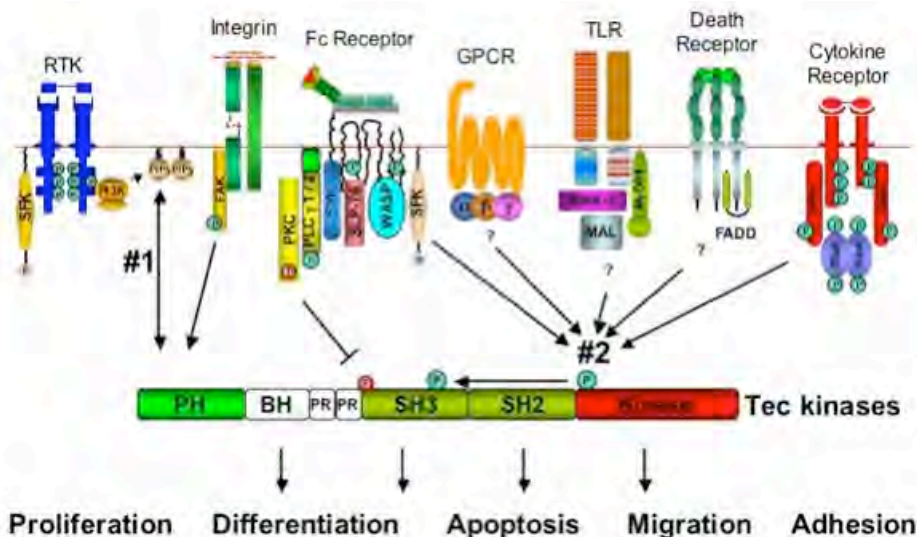
Members of the Tec family (Tec, Btk, Itk, Rlk and Bmx) of non-receptor protein tyrosine-kinases (PTKs) are expressed in various hematopoietic cells. Mutations in Btk (Bruton's tyrosine kinase) are the cause of X-linked agammaglobulinemia (XLA) in humans.

We have recently generated Tec-deficient mice and could show that B cell development requires Tec function in the absence of Btk. In ongoing experiments we are now investigating the role of the Tec family kinases Tec and Itk in CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes.

To shed light on the role of Tec kinases in myeloid cells, we have recently started to analyze the function of primary mast cells, neutrophils and macrophages lacking multiple Tec kinase family members. It is very likely that mice lacking more than one Tec kinase family member display more severe myeloid impairments and - even more important - will help us to uncover novel, so far unidentified functions of Tec kinases in these cells.

### Molecular Characterization of Dendritic Cell Differentiation

Dendritic cells (DC) are bone marrow-derived leukocytes and are the most potent antigen-presenting cells. Based on the expression of several cell surface molecules and also their different functional abilities, several subclasses can be defined. However, the molecular mechanisms and the identity of genes that regulated their development from hematopoietic progenitors and their functional maturation are largely unknown. Therefore, we employ several experimental strategies to identify the "key" molecular players involved in the development and function of DC.



A variety of extracellular signals in addition to TCR and BCR stimulation are known to activate Tec family kinases. #1 and #2 indicate the consecutive steps of Tec family kinase activation: recruitment to the membrane via PH domain-mediated binding to PIP<sub>3</sub> (#1), and phosphorylation by Src family kinases (SFK) followed by autophosphorylation of a tyrosine residue within the SH3 domain (#2). Negative feedback regulation of Btk via PKC is indicated as well. Dependent on the cell type and the presence of other signals, several downstream pathways may be induced. This will lead to different biological outcomes that can include cell proliferation, differentiation, apoptosis, cell migration and adhesion. Figure is taken from Schmidt et al., 2004, *Int Arch Allergy Immunol.*134, 65-78.

## WINFRIED PICKL

Laboratory „Cellular Immunology and Immune Hematology“



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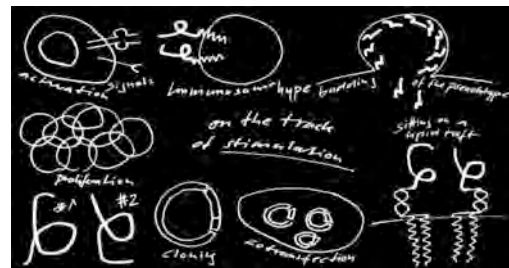
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Professional antigen presenting cells (pAPC) are capable of inducing primary immune responses against infectious agents and tumor antigens. In order to do so, they express a special set of cell surface molecules, which enable them to bind to and to activate naive T lymphocytes in an antigen-specific manner. Still, numerous tumor-associated or viral antigens fail to initiate a protective/curative T cell response for reasons that are not yet understood completely. The further understanding of how to direct the process of T lymphocyte stimulation in a predictable way shall help to induce immune responses proficient to fight infectious diseases and cancer.

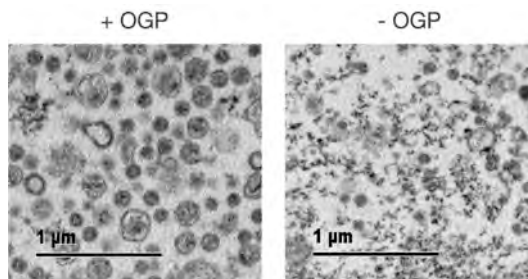
### Artificial antigen presenting platforms

The growing list of dendritic cell subtypes as well as the co-expression of activating and inhibitory receptors on one and the same cell type makes their functional capabilities sometimes hard to predict and their use problematic. Both basic and applied research shall profit from a reductionist system for antigen presentation and T lymphocyte activation based on a natural assembly system. Immunosomes fulfill those requirements, they result from the co-expression of viral core proteins

in human HEK-293 cells. Lipid modification sequences attached to the immune receptor molecules target them to lipid rafts of the plasma membrane, the site of virus budding.



Scheme for immunosome production



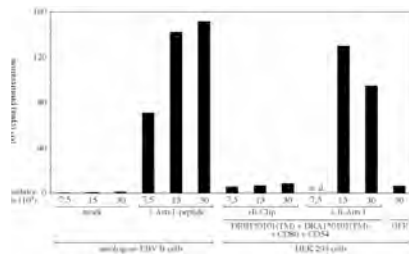
Visualization of immunosomes by EM

together with molecules relevant in antigen presentation and T lymphocyte activation

We have found that immunosomes induce accessory cell independent T cell proliferation and antigen-specific CTL responses *in vitro*. T cell activation by immunosomes is co-stimulation dependent and enhanced by co-expressed adhesion-molecules. Concentration, purification as well as long-term storage protocols have been developed by now. Antigen-specific immunosomes are being developed in several *in vivo* models at present.

### Anergosomes to influence allergen specific immune responses

T lymphocytes play a central role in the pathogenesis of allergic disease and modulation of T lymphocyte function can ameliorate symptoms. In order to elicit a curative response in type I allergy, we target allergen specific T lymphocytes by delivering to them preformed 'packets of information' with an energizing potential. Instead of using whole antigen-presenting cells, we explore the usefulness of pseudotyped microvesicles (i.e. 'anergosomes') as surrogate antigen presenting platforms. With an invariant chain-based antigen delivery system relying on exchangeable CLIP we have created artificial antigen presenting cells which are able to drive allergen-specific T lymphocytes, recognizing *Artemisia vulgaris* (*Art v1*), towards vigorous proliferation.



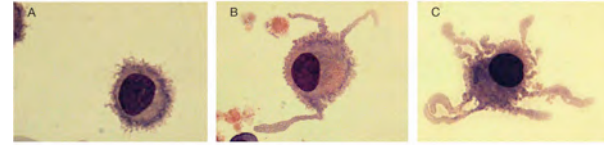
Activation of *Art v1* specific T cell clones with artificial APCs. Autologous EBV Blasts pulsed with specific peptide are compared to artificial APCs loaded internally via modified li-chains.

T cell activation was found to be co-stimulation and adhesion dependent. Most importantly, similar levels of T cell activation can be achieved with transmembrane as compared to GPI-anchored HLA Class II heterodimers used in our system. Currently, we work on the development of an efficient procedure for the export of the above mentioned molecules to enveloped virus particles.

### "Better vaccines": Virus particles pseudotyped with functionally active cytokines

The above-described technology of changing the molecular repertoire of enveloped virus particles might also have practical implications leading to the creation of 'better vaccines'. As a proof of principle we have developed a procedure for the targeting of functionally active cytokine molecules to the membrane-surface of enveloped viruses without the need to (genetically) modify viral proteins themselves. In contrast to previous attempts we have tried to lay the ground for a more universal concept, which shall be suitable for the phylogenetically diverse collection of envelop-

-ed viruses. Human IL-4, used as a model cytokine, is targeted to enveloped viruses with high efficiency and remains functionally active as demonstrated by differentiation of monocytes to dendritic cells, and T-lymphocyte co-activation.

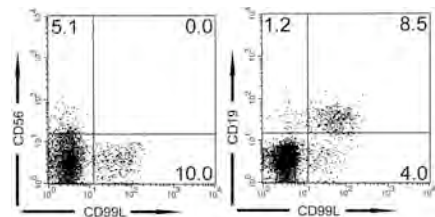


Wright staining of DC generated with hIL-4::GPI expressed on virus particles. Supplementation: A) soluble GM-CSF; B) hIL4::GPI + soluble GM-CSF; 3) soluble IL-4 + soluble GM-CSF.

Our studies shall open the opportunity to create more immunogenic viral strains for vaccination and might contribute to the establishment of platforms for the propagation and/or activation of various progenitor or immune effector cells.

### Characterization of novel co-stimulatory molecules and immunophenotyping of leukemias

Together with Peter Steinberger we are setting up a functional genetic screening system for the characterization of novel co-stimulatory molecules for T lymphocyte activation. The system relies on BW5137 cells expressing a surrogate TCR/CD3-complex ligand (OKT3 scFv). Signal 2 - is introduced into BW cells by retroviral transfection of cDNAs derived from leukocytes.



CD99L expression on PB B-lymphocytes

Apart from detecting novel co-stimulatory molecules, we have also studied established ones and we have successfully defined a functional ligand for CD99 on human peripheral blood B-lymphocytes recently. Engagement of CD99L by CD99-Ig leads to co-stimulation of preactivated B lymphocytes, and depends on an as yet undefined serum-factor. The detailed study of immune receptors enables us to further develop immunophenotyping protocols on the European level within EGIL (European Group for the Immunophenotyping of Leukemias)

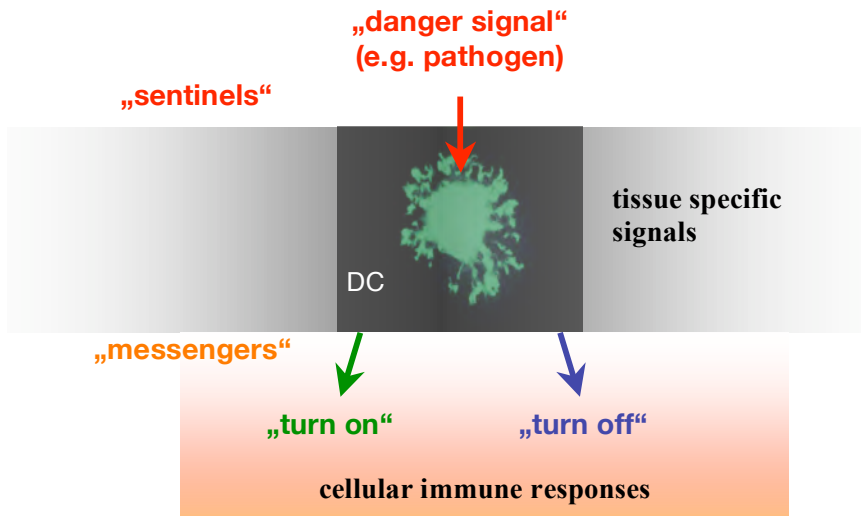
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Dendritic cells (DC) represent the interface between the universe of foreign and tissue-specific antigens and T lymphocytes and are therefore key regulators of cellular immunity. Our research group has longstanding interests and experience in the molecular and functional analysis of human DC. It is our goal to learn how DC differentiation and function can be manipulated by exogenous and endogenous signals and to characterize novel and functional relevant receptors on DC and T cells via which adaptive immunity can be tuned.

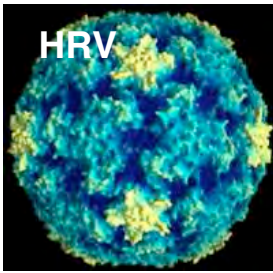


**J. Stöckl and O. Majdic**

**Regulation of DC function through endogenous and exogenous signals**

Danger signals arising from acute infection and inflammation are recognized as potent stimuli which up-regulate the T cell stimulatory capacity of DC. In contrast to that, little is known about regulatory signals for DC. We could demonstrate that oxidized phospholipids (oxPLs), which are generated during infections, apoptosis and tissue damage, interfere with DC activation preventing their maturation. OxPLs blocked TLR-3 and TLR-4-mediated induction of the costimulatory molecules

CD40, CD80, CD83, and CD86, the cytokines IL-12 and TNF, as well as lymphocyte stimulatory capacity. CD40 and TLR-2-mediated cytokine production was also inhibited, while upregulation of costimulatory molecules via these receptors was not affected by oxPLs. Thus, formation of oxPLs during the course of an inflammatory response may represent a negative feedback loop preventing excessive and sustained immune reactions through regulating DC maturation.

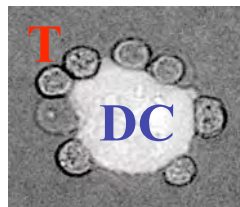


Human rhinovirus (HRV), the major cause of the common cold, is another potent modulator of DC function discovered by us. We could demonstrate that HRV-14, a member of the major group HRV family, can efficiently

inhibit the accessory function of DC. We observed that HRV-14-treated DC (R-DC) lose their T cell stimulatory capacity and induce a promiscuous and deep anergic state in co-cultured T cells in spite of high levels of MHC-molecules as well as co-stimulatory molecules e.g. B7.1 (CD80) and B7.2 (CD86) and independent of inhibitory soluble factors such as IL-10. In contrast, expression of inhibitory B7-H1 molecules was upregulated and R-DC *de novo* expressed Siglec-1 (CD169). Most importantly, blocking of B7-H1 and Siglec-1 on R-DC with specific mAbs against both receptors reverted the inhibitory phenotype. Thus, inhibitory signals delivered from R-DC to T cells via B7-H1 and Siglec-1 were critical for the induction of anergy. These observations suggest that an altered accessory molecule repertoire on DC upon interaction with HRV downmodulates adaptive immune responses during the viral infection.

### Molecular interactions at the DC - T cell interphase

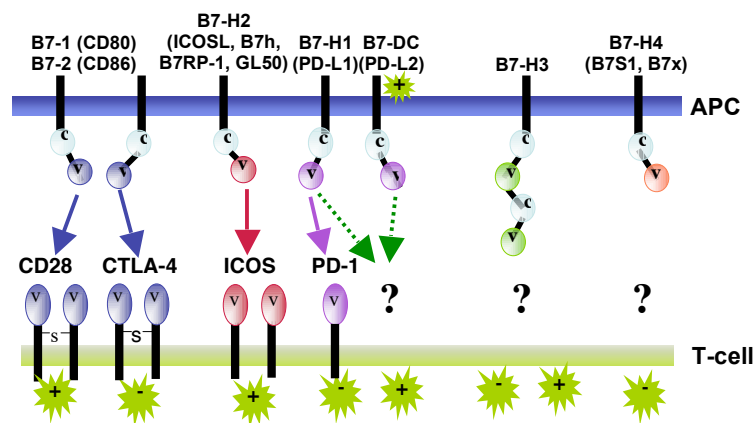
There are several known receptor structures on DC that play a critical role in the stimulatory function in particular members of the B7-family such as B7.1 (CD80) and B7.2 (CD86).



For a novel member of this accessory molecule family, B7-H1 (PD-1 ligand), we could recently demonstrate critical immuno-regulatory function on DC. Targeting of B7-H1 with our mAb DF272 prevented the induction as well as the maintenance of IL-10/DC-triggered anergy in T cells. Thus, B7-H1 appears to be a prime target in diseases where it is desired to stimulate immunity (cancer) or to modulate immune responses (allergy).

Moreover, we have described B7-family member B7-H3 as a molecule that differs from the other B7-homologs in having 4 instead of 2-3 Ig domains and furthermore found out that human B7-H3 does not costimulate cytokine production and proliferation of T cells.

A particularly interesting accessory molecule at the DC-T cell interphase discovered by us is CD63 (LAMP-3). We detected with our new mAb 11C9 that CD63 is expressed on activated T cells and functions as potent costimulatory molecule. CD63-mediated costimulation of T cells is characterized by pronounced induction of proliferation, strong IL-2 production and, compared to CD28, enhanced T cell responsiveness to restimulation. Particularly in this latter quality CD63 clearly surpasses several other CD28-independent costimulatory pathways described before. CD63 thus represents an activation-induced reinforcing element, whose triggering promotes sustained and efficient T cell activation and expansion



## HERBERT STROBL

Laboratory „Molecular Biology of Hematopoietic Stem Cells and Dendritic Cells“



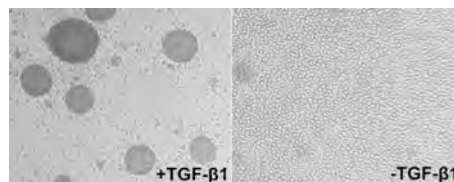
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We use human CD34<sup>+</sup> hematopoietic progenitor/stem cells purified from umbilical cord blood as a main model cell population for our studies. We have identified cytokine stimuli for the selective expansion or lineage differentiation of CD34<sup>+</sup> cells. Furthermore, we have established methods for efficient gene modification of these cells using retroviral vectors. In ongoing projects we analyze molecular mechanisms underlying progenitor cell expansion versus differentiation along various myelomonocytic and dendritic cell sublineage pathways, and explore the specific properties of defined DC subsets generated from CD34 cells (in particular of epithelial Langerhans-type (LC) or interstitial-type DCs). Furthermore we are characterizing intracellular signals involved in triggering activation/maturation of postmitotic immature DCs, and use functional genetic cDNA library screens for identifying novel key regulators of hematopoietic stem cells and DCs. These projects aim for the development of novel concepts in immuno- and stem cell therapy of cancer and immune disorders.

### CD34<sup>+</sup> model cells

Hematopoietic stem cells (HSC) and lineage committed progenitors of various hematopoietic/immune cell lineages are included within a small fraction of bone marrow or blood cells identified by the expression of the surface molecule CD34. In all our projects we use CD34<sup>+</sup> cells from umbilical cord blood as a basic model system to study aspects in stem cell and dendritic cell biology. Previous work of our group demonstrated for the first time clinically applicable serum-free ex vivo culture conditions for generating dendritic cells. We showed that in vitro stimulation of cultured CD34<sup>+</sup> cells with the cytokine TGF- $\beta$ 1 induces lineage commitment of progenitors toward a subset of dendritic cells (DCs) known as epidermal Langerhans cells (LCs).



*CD34 pos. cells are induced to differentiate into Langerhans-type DCs. We found that these cells require TGF- $\beta$ 1 for differentiation in clinically approved serum-free medium. LCs are easily recognized by their typical cluster growth morphology.*

Based on these findings we subsequently demonstrated conditions for generating large numbers of immature LC-type DCs in serum-free cultures. These patented

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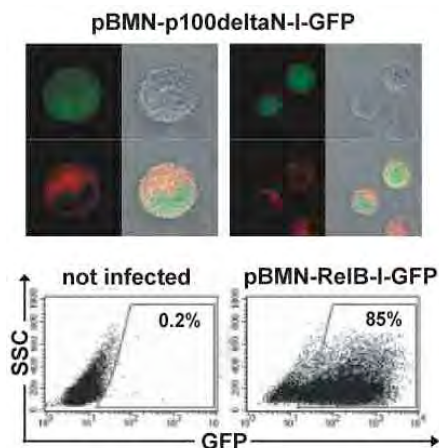
growth conditions have become a standard for basic and clinically oriented studies of LCs.

### Dendritic cells

In vivo, LCs are known as the prototype DCs residing in epithelia of various organs. LCs lose their immature features once isolated from tissues. Our in vitro model allows to generate immature LCs resembling LCs in vivo. Therefore, novel aspects in DC biology can be studied towards a view to the therapeutic use of these cells. (1) What are the molecular events that triggers induction of LC maturation, a process key to the induction of T cell responses? (2) Which T cell responses are specifically induced by LCs versus other DC types? (3) Are TGF- $\beta$ 1-dependent LCs a potentially tolerizing DC subset that differs from other defined DC subsets in tolerance or immunity induction to certain candidate antigens? (4) What are the mechanisms downstream of TGF- $\beta$ 1 that induce LC lineage commitment, and LC:T cell regulation. (5) How can we upscale LC production from CD34<sup>+</sup> cells under clinically applicable conditions (e.g. pre-expand LC progenitors in vitro in defined growth media)?

### Gene transfer in stem cells and DCs

As basic tools for our studies we have established efficient retroviral gene transduction procedures that allow us to simultaneously express up to 3 candidate signaling proteins in primary cells generated from CD34<sup>+</sup> cells using both constitutive and conditional (tetracycline-inducible) gene expression systems.

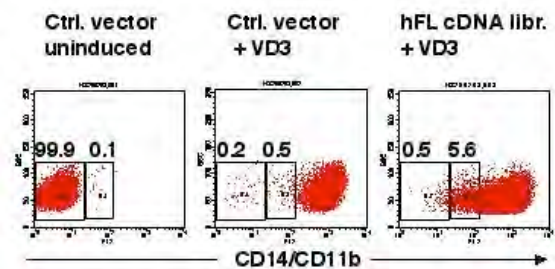


Gene transduction of human DCs. Examples show representative flow cytometry and immunofluorescence microscopy analyses of gene transduced DCs. FACS diagrams show DCs transduced with RelB-IRES-GFP; micros-

copy shows DCs transduced with the RelB inhibitor p100 $\Delta$ N. p100 $\Delta$ N captures the transcription factor RelB in the cytoplasm and thus prevents nuclear localization of endogenous RelB (green: GFP; red: anti-RelB-PE staining). RelB gain or loss of function in human DCs can thus be analyzed using functional read-outs (Platzer, Blood, 2004)

### Functional genetic screens

We have successfully applied functional genetic retroviral cDNA library screens to identify molecules that inhibit monopoiesis or downregulate CD40 ligand induced DC maturation of model cell lines.



Functional genetic identification of molecules that block monocytic cell differentiation of hematopoietic progenitors. A homogenous U937 monocytic cell clone expressing the ecotropic murine MMLV receptor was transduced with ecotropic virions carrying individual cDNAs from a human fetal liver library (at conditions which favor 1 or 0 integrations/cell). Those cells that remain refractory to monocyte induction by vitamin D3 after repeated FACS and/or MACS sorting are expanded in single cell cultures. Retroviral inserts of candidate clones are then PCR amplified, cloned into a retroviral vector backbone containing an IRES site followed by GFP as FACS detectable marker and are then validated in the U937 assay system followed by testing in primary CD34<sup>+</sup> differentiation models.

### Immunophenotyping

Our model of primary hematopoietic stem cell differentiation allows to phenotypically characterize progenitors and lineage committed progeny and has provided a basis for introducing novel marker molecules for clinical leukemia diagnosis. We are currently initiating a European multicenter study (within the European group of immunologic leukemia classification, EGIL) for improved intracellular flow cytometric classification of monoblastic and plasmacytoid DC leukemias, which are difficult to classify using current methods.

## GERHARD ZLABINGER

Laboratory „Autoimmunity and Transplantation Immunology“



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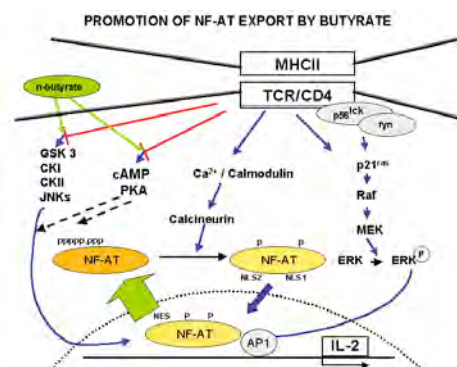
Understanding the immunologic mechanisms nature has developed to defeat potentially harmful invaders and to spare host tissue and elucidation of the principles to maintain the balance between these mutually non exclusive actions is a central concern in modern immunology. Both the knowledge about triggering appropriate reactions in case of imminent threat for the host and the insight into the highly complex regulatory mechanisms operating to sustain the integrity of an individual are of central importance to exploit effective strategies for interference in case of disturbed or unwanted immune reactivity as operative in allergy, autoimmunity, malignancy or transplantation.

A longstanding interest of my research group concentrates on studies about both naturally occurring ways of immunomodulation as reflected by microbial evasion strategies and experimental approaches to purposefully interfere with particular signalling events operating at crucial stages of immune activation.

### Bacterial Immunomodulation

Beyond its function as an essential nutrient for a large part of the gastrointestinal tract, the fermentation product butyrate created by the resident colonic microflora has been identified as a molecule that exerts a variety of immunomodulatory effects. While it has been recognized that this simple molecule influences a tremendous array of cellular functions in several cell types, the picture emerges that this short-chain fatty acid (SCFA) critically serves to mediate information between commensal bacteria and the host mucosal compartment. Interestingly, the epithelial cell antigen-presentation machinery is modulated and we have shown that pro-inflammatory cytokine production and sensitivity are both dampened by this bacterial metabolite, especially in professional antigen-presenting cells such as monocytes and dendritic cells (DC). Moreover, T cells are affected by butyrate in their early T-cell

receptor-triggered signalling pathways by a sophisticated mechanism involving an increased export of the transcription factor NF-AT that results in cessation of the production of cellular growth factors such as IL-2 .



Gerhard Zlabinger

As a molecular target for the anti-inflammatory effects of butyrate also the transcription factor NF- $\kappa$ B has been identified, which does not transactivate essential mediators of an inflammatory response such as IL-8, IL-12, TNF- $\alpha$ . Similarly, the NF- $\kappa$ B-dependent process of DC maturation is prevented by the SCFA. The detailed mechanisms of the interference of butyrate with NF- $\kappa$ B, however, remains largely unknown. Rather, a complex scenario of transcription factor inhibition might be envisioned, since recent data indicate that histone acetylating/deacetylating enzymes directly interact with NF- $\kappa$ B subunits to regulate transcription and thus could be affected by butyrate or its metabolites.

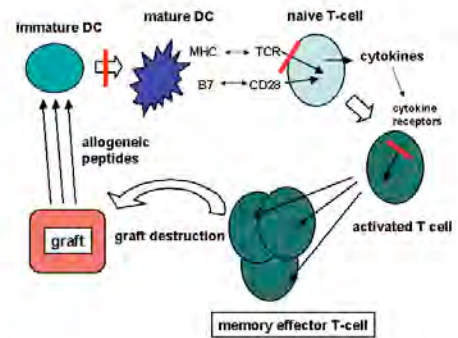
### Immunomodulation through interference with cell signaling

Recently, Janus kinase 3 (JAK3) has been identified as a molecule that plays a critical role in cell signalling specifically within the immune system. Genetic absence or ablation of this tyrosine kinase is associated with defective T-cell immunity resulting in severe-combined immunodeficiency (SCID) without apparent changes in other organ systems. Furthermore, pharmacological inhibition significantly prolongs allograft survival in several experimental models of organ transplantation.

Studying the influence on early T-cell signalling events, we detected a profound inhibition of IL-2 secretion when JAK3 activation was selectively prevented. Moreover, the production of other early-induced cytokines such as IFN-g or IL-10 was similarly prevented by the disruption of JAK3 activity assessed by gene protection assays. Using a Jurkat cell line stably transfected with an IL-2 promoter luciferase gene construct we found that JAK3 inhibition efficiently prevented IL-2 gene transcription linked to a complete failure of NF-AT and AP-1 transactivation. Further analysis of critical upstream signalling events showed defective PLC-g1 phosphorylation and diminished Ca<sup>2+</sup>-mobilization. We further observed a complete failure of JAK3-inhibited cells to undergo homoaggregation, a b2-integrin-dependent event.

Furthermore, our group demonstrated that monocyte-derived DC cannot mature upon CD40 activation in the presence of a JAK3-inhibitor. The resulting impaired immunostimulatory function of JAK3-inhibitor treated DC led to allogeneic T-cell hyporesponsiveness suggesting a further immunomodulatory mode of JAK3-inhibitors.

SITES OF INTERFERENCE WITH JAK3 IN ALLORAECTIVITY



Therefore, the PTK JAK3 would be an ideal candidate molecule to achieve tailored immunosuppression due to its importance for proper T-cell activation and its immune-cell restricted expression. It may be envisioned that a combination of drugs that selectively target myeloid cells as part of the innate arm of the immune system as well as highly selective T-cell inhibitors such as JAK3-inhibitors might have great impact in future immunosuppressive protocols.

In another attempt, we generated tolerogenic DC by activating immature DC in the presence of NF- $\kappa$ B inhibition. Such treatment blocked DC maturation in terms of costimulatory molecule expression, cytokine production and capacity to support T cell proliferation. Importantly, a state of allogeneic tolerance is even induced when such differentiated DC are used as priming APC irrespective of concomitant calcineurin inhibitor therapy. Given the therapeutic potential of DC to induce tolerance in general, these findings suggest that immunization strategies using allogeneic myeloid DC that are characterized by a maturation blockade might be potentially useful in the control of allograft rejection.

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## AWARDS

- START Prize of the FWF and BMWK 2000 (Herbert STROBL)
- START Prize of the FWF and BMWK 2001 (Wilfried ELLMEIER)
- Aventis Prize 2002 (Johannes STÖCKL)
- Poster Award 2003 of the Austrian Society for Allergology and Immunology (Stefanie KIRCHBERGER)
- Poster Award 2003 of the Austrian Society for Allergology and Immunology (Hans KÜNG)
- Poster Award 2004 of the Austrian Society for Allergology and Immunology (Katharina PFISTERSHAMMER)
- Award for the Best Habilitation 2004 (Wilfried ELLMEIER)
- Aventis Habilitation Prize 2004 (Johannes STÖCKL)
- Novartis 2004 Award for Biology (Wilfried ELLMEIER)

## CURRENT GRANTS

### **Austrian Academy of Sciences, CeMM 20030**

*Winfried Pickl*

Towards a better definition of the immunological synapse: Further development of a highly modular, plasma membrane-derived microvesicle-based antigen presentation platform in combination with a functional genomics approach to characterize novel co-stimulatory molecules/factors

### **EU 6<sup>th</sup> Framework Program, LSHC-CT-2004-503216, Leukemia Net**

*Herbert Strobl*

EGIL classification of acute leukemias, diagnostic platform (work package 10)

### **FWF and BMWK - START Program Y156**

*Herbert Strobl*

Functional genomics analysis of human dendritic cell development

### **FWF and BMWK - START Program Y163**

*Wilfried Ellmeier*

Mechanisms of lymphocyte development and activation

### **FWF, SFB F23**

*Wilfried Ellmeier*

Mechanisms of establishment and maintenance of immunological tolerance

Subproject SFB 2301: Scientific Coordination

Subproject SFB 2305: Signaling requirements in T cells for the induction and the maintenance of T cell tolerance

### **FWF, SFB F23 Projekt F2304**

*Herbert Strobl*

TGF- $\beta$ 1-polarized epithelial Langerhans cells-a candidate tolerogenic DC subset

### **FWF, SFB F23 Project F2307**

*Johannes Stöckl*

Regulatory T cells induced by human rhinoviruses

### **FWF P16708-B13**

*Wilfried Ellmeier*

Analysis of the epigenetic and transcriptional regulation of CD8a and CD8b gene expression during T cell development

**FWF B17669-B13**

*Peter Steinberger*

Role of B7-H3 during T-cell activation – identification of receptor structures involved

**FWF P-15634 B08**

*Winfried Pickl*

Influencing the allergen-specific immune response at the level of antigen presentation: Anergosomes for allergen-specific anergisation

**K-Plus Program BM:BWK; BM:VIT, Biomolecular Therapeutics, BMT005**

*Otto Majdic, Johannes Stöckl*

Identification of immune-regulatory targets structures on dendritic cells

**K-Plus Program BM:BWK; BM:VIT, Biomolecular Therapeutics, BMT005**

*Wilfried Ellmeier*

Molecular analysis of dendritic cell function

**Österr. Nationalbank Jubiläumsfonds ONB 10530**

*Wilfried Ellmeier*

Molecular analysis of the function of a C2H2 Zinc-finger containing DNA binding molecule during T cell development

**Österr. Nationalbank Jubiläumsfonds ONB10795**

*Peter Steinberger*

Heat shock protein receptor structures – targets for immunotherapeutic interventions

**Österr. Nationalbank Jubiläumsfonds ONB10294**

*Herbert Strobl*

Genetic Screening System for Identifying Molecules which Downregulate the Immune Response by Inhibiting Dendritic Cell Signaling Processes

**St. Anna Kinderspital Project**

*Peter Steinberger*

Identification of DC-antigens recognized by antibodies in graft vs. host sera by retroviral expression cloning.

**WWTF Project, LS200**

*Johannes Stöckl*

Modulation of DC function by oxidized phospholipids: a novel way to control adaptive immune responses

## TEACHING

Teaching and continued professional education is the fundamental issue in preparing people adequately for their professional life. To raise the interests for a particular discipline and to impart the necessary knowledge in order to acquire the competence to deal with the imposed challenges properly is the essential milestone in every kind of education.

Among the multiple teaching activities the primary task of the Institute of Immunology is to instruct students both about the fundamentals in immunology at the beginning of their studies and to confront them also with more specialized subject matters of the discipline during advanced stages. Students are supervised during their diploma work as well as when preparing their Ph.D. thesis, which enables them to get a proper insight into the field and into the actual challenges in research and science. In addition to the training activities in studies like medicine or natural sciences members of the Institute are engaged in teaching courses for other areas of the health care sector as well.

Besides the engagement in actual teaching and education the Institute is also active in the advancement of study programmes by developing selected parts of the study of medicine. Furthermore, attempts are made in preparing novel devices to provide teaching material in a modern and attractive way like web-based interactive learning tools.

Regarding professional education our institution is engaged in training physicians for specialization in immunology, which is a distinct speciality among the laboratory medicine specialities. In this respect it is of real concern to us that there is continuous advancement and thus we further develop regulations for training as well as for the subject-specific examinations. These activities are also directed to set up training programmes at the European level and to prepare the ground for harmonization of education.

## PROGRESS REPORTS

On a regular basis young scientists of the Institute are presenting their work in progress to all colleagues. These biweekly reports are chaired by two colleagues of the other research groups and are always followed by intensive discussions.

To improve presentation skills all speakers get professional training. Veronika Maierhofer, responsible for PR and documentation, has undergone a special education in Communication and Presentation Techniques. Thus, every speaker has the opportunity to obtain individual feedback to his presentation.



*Progress Reports*

## **DIPLOMA and Ph.D. THESES**

### ***Wilfried Ellmeier***

#### ***Diploma Theses***

- Molekulare Charakterisierung des CD8 Enhancers E8III. (Johanna TINHOFER, 2003)
- Identification and characterization of transcription factors binding to a CD8 enhancer (Arnulf HERTWECK, 2004)
- The role of Tec family kinases in CD8+ T cells (Benjamin VIGL)
- Molecular analysis of T cell development (Ahmed EL-GAZZAR)
- Genetic analysis of mast cell function (Eva ECKELHART)

#### ***Ph.D. Theses***

- Identification of a transcription factor that mediates epigenetic regulation of CD8 gene expression (Ivan BILIC)
- Molecular and functional characterization of the CD8 enhancer E8III (Collin FEIK)
- Molecular analysis of CD8 gene expression (Peter KINROSS)
- Functional analysis of dendritic cells (Christina KÖSTERS)
- Molecular analysis of T cell development, Tec family kinases in myeloid cells (Martin MELCHER)
- Loss of function approaches to study CD8 enhancer binding factors (Shinya SAKAGUCHI)
- Tec family kinases in myeloid cells (Bernd UNGER)

### ***Winfried Pickl***

#### ***Diploma Theses***

- Definition of human counterparts of viral core proteins capable of inducing membrane-budding and vesicle secretion (Alina NEUNKIRCHNER)
- Development of a functional genomic screening system for novel costimulatory molecules (Klaus SCHMETTERER)
- GPI-Membranverankerung von humanen Zytokinen und kostimulatorischen Molekülen auf Immunosomen zur Modulation von Immunantworten (Hans KÜNG, 2004)
- Characterization of a cellular ligand for CD99 (MIC2/E2). (Robert NEUMANN, 2003)

#### ***Ph.D. Theses***

- Influencing the allergen-specific immune response at the level of antigen presentation (Victoria LEB)
- Immunosomes – T cell stimulation by novel multi-purpose antigen-presenting platforms (Sophia DERDAK, 2003)
- Die Rolle von membranverankerten Zytokinen im Rahmen der artifiziellen Ag-Präsentation (Hans KÜNG)

## **Johannes Stöckl and Otto Majdic**

### **Diploma Theses**

Induction and regulation of innate, antimicrobial defense mechanisms in phagocytes  
(Berit ROSC)

Identification of a specific cell surface markers on regulatory T-cells (Christoph JINDRA)

Surface molecules involved in T cell activation (Judith LEITNER)

Use of engineered T cell stimulators to assess the functional role of accessory molecules  
(Johanna KOBER)

### **Ph.D. Theses**

Effects of oxidized phospholipids on dendritic cell-membrane protein expression (Nina GUNDACKER)

Applied immunoproteomics: investigating effects of oxidized phospholipids on dendritic cells (Elisabeth TRAXLER)

Modulation of immune cell function by human rhinoviruses (Stefanie KIRCHBERGER)

### **Diploma Theses for Technicians**

Molekulare und funktionelle Charakterisierung des „13-344 Antigens“ auf dendritischen Zellen (Claudia SEEMANN, 2004)

Siglec-1 (CD 169): ein Marker für „alternde“ dendritische Zellen? (Irmgard VOGL, 2004)

## **Herbert Strobl**

### **Diploma Theses**

Transcriptional mechanisms in dendritic cell development and maturation. (Leonhard HEINZ, 2004)

The role of GATA-1 in the VD3 induced differentiation of myeloid cells (Mario KUMERZ)

### **Ph.D. Theses**

Molecular Analysis of human dendritic cell development – transcription factor RelB promotes interstitial-type dendritic cell subset differentiation (Barbara PLATZER, 2005)

Molecular mechanisms in myeloid sublineage differentiation (Sabine TASCHNER)

Molecular mechanisms of dendritic cell maturation (Almut JÖRGL)

CD40 signaling in hematopoietic cells (Florian GÖBEL)

The role of transforming growth factor beta-1 in Langerhans-type dendritic cell immunobiology (Peter REISNER)

## **Gerhard Zlabinger**

### **Diploma Theses**

Modulation of CD69 expression by the bacterial metabolite n-butyrate (Philip MATZINGER)

Impact of the complement split product C4d on inflammatory cell reactions (Jörg NEUMANN)

The role of Tamm-Horsfall glycoprotein in the generation of innate immune responses (Markus HÖLZL)

### **Diploma Theses for Technicians**

Influence of C4d on T-cell activation (Astrid PÖLZL, 2004)

Modulation of dendritic cell function by methotrexate (Herbert ROSENMEIER, 2004)

Effect of hemoxygenase 1 induction on dendritic cell maturation (Helga BERKA)

Evaluation of signaling assessment by the Luminex technology (Barbara SCHÖNY)

## DIAGNOSTICS

The activities of the Institute of Immunology in research and teaching are focused on aspects of human medicine and, therefore, it is a matter of importance to us to transfer our expertise to subjects with immediate relevance to patients. Hence, one focus of our institution is also to provide appropriate tests for the diagnosis of immune-mediated diseases. These attempts include the establishment of new testing procedures as well as further development of existing methods, which both is based on knowledge acquired in basic research.

The Institute offers diagnostic procedures for diseases, which arise as a consequence of disturbed or missing function of the immune system. Such clinical conditions include diseases caused by malignant transformation of cells of the immune system, clinical states with diminished or lacking function of the immune system or disorders associated with immune reactivity directed against components of the own body. For the diagnosis of leukemia a series of monoclonal antibodies have been developed at the Institute, which has contributed significantly also to setting international standards for the classification of these malignancies. In the field of immunodeficiencies as well as in autoimmune diseases the Institute disposes of a longstanding experience, which allows to perform these diagnostic procedures at a high quality level.

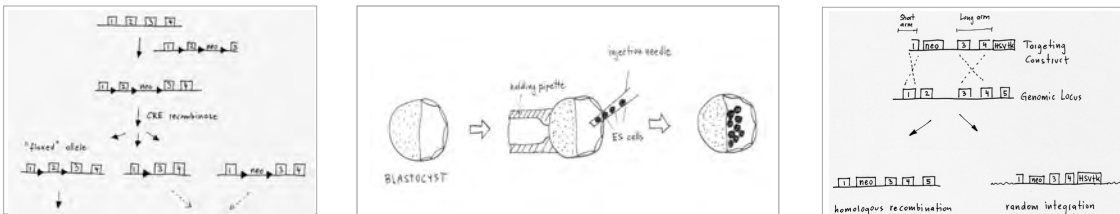
In addition to providing this service for hospitals as well as office based practitioners and specialists it is also a great concern to us to contribute to the further improvement of standardization of immunologic testing procedures.

**Diagnos**  
**tics**

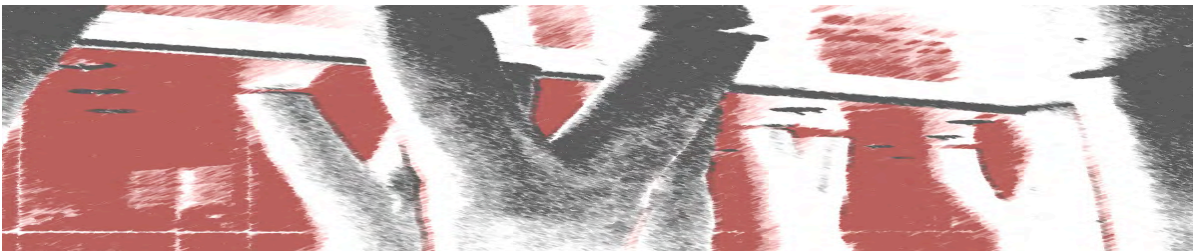


## ANIMAL LABORATORY and HYBRIDOMA GENERATION UNIT

Research groups at the Institute of Immunology use mouse models for the identification of basic processes regulating immune cell function and for the development of therapeutic strategies to manipulate the immune response. Since the analysis of gene activity and immune cell function has to be also performed in the context of an organism, we have recently established at the Institute of Immunology the technology for the generation of transgenic mice. The genetic manipulation of ES cells and their injection into blastocysts led to the successful generation of knockout mice (for details see Feik et al., J. Immunol. 174, 1513-24). Currently we are establishing the methods to perform pronuclear injection of DNA into fertilized mouse eggs.



To generate monoclonal antibodies required for the characterization of human leukocyte differentiation antigens and for the various research projects at the Institute of Immunology, we have established highly efficient protocols and procedures for the generation of hybridoma cell lines. This led to the generation of more than 300 monoclonal antibodies during the last 25 years.



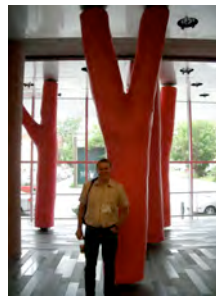
## HIGHLIGHTS and EVENTS



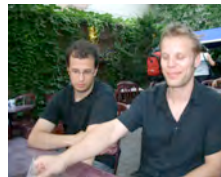
60th Birthday of Walter Knapp



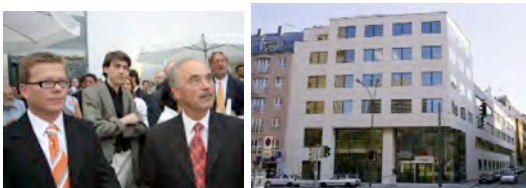
START Prize for Herbert Strobl



START Prize for Wilfried Ellmeier



World Congress of Immunology 2004 at Montreal



Opening of the Vienna Competence Center



.... action painting done by visitors



X-mas Party at the „Impressione“

Highlights and Events



*Snow and Fun at the Hochkar*



*Aventis Prize for Johannes Stöckl*



*Novartis Prize for Wilfried Ellmeier*



*JCI paper Party ☺*



*Hans Küng*



*cookies for the Magister*

**Highlights and Events**