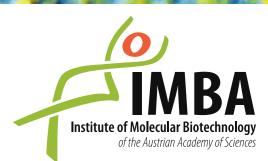
INSTITUTE OF MOLECULAR BIOTECHNOLOGY OF THE AUSTRIAN ACADEMY OF SCIENCES VIENNA BIOCENTER 2004







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IMBA and IMP operate in partnership as a joint initiative of the Austrian Academy of Sciences and Boehringer Ingelheim. IMBA is a member of the Campus Vienna Biocenter.

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This is the first Annual Report of IMBA and it is time to look back at our beginning. It has been an interesting ride. Much has been accomplished. Much needs to be done.

IMBA was founded as a subsidiary of the Austrian Academy of Sciences with support from the Federal Government and the City of Vienna. IMBA has good and close ties with our partners, the Research Institute of Molecular Pathology (IMP) and Boehringer Ingelheim. IMP and IMBA share infrastructure to strengthen the already world-class services at the IMP and to allow IMBA investigators to have rapid access to such services. The contract that guarantees equal access of researchers from IMBA and IMP to the services has been signed. We are grateful to everyone at the IMP, in particular to the members of the service departments, for their generous and cooperative spirit in this endeavor. We view this service agreement as a significant milestone in the establishment of IMBA, and the cornerstone of our future cooperation with the IMP.

When I arrived 18 months ago from Canada our partner, the IMP, gave us space to set up shop. Thus, IMBA was physically born. We were very fortunate to welcome Barry Dickson and Jürgen Knoblich, two former IMP members as the first Senior Scientists. Barry Dickson's group works on neurobiology and Jürgen Knoblich's group on stem cells and cell polarity genes. Javier Martinez joined us from the Rockefeller University as a junior scientist. His group works on the mechanism of RNAi. We are also privileged that Victor Small decided to join IMBA and bring to us his great expertise in cell migration and imaging. Last but not least, I won over Michael Krebs as co-director of IMBA who became responsible for budgeting, financing, and business development allowing me to focus on research. Many people including members of our search committee and Scientific Advisory Board have been involved in these recruitments. I am indebted to you all.

On a personal note I have to say that we indeed have splendid partners at all levels of the IMP and at the Academy of Sciences. My particular thanks go to Kim Nasmyth, IMP, Andreas Barner, Boehringer Ingelheim, Werner Welzig, the past and present Presidium of the Austrian Academy of Sciences, the Board of Directors, and Scientific Advisory Board for their help and support in sometimes difficult times. Without them, IMBA would not exist. All IMBA members have best intentions and will try everything to make this cooperation work and to contribute to the success of our sister institution.

To paraphrase John F. Kennedy: We are building IMBA, not because it is easy, but because it is hard. The challenge is one that we are willing to accept, one we are unwilling to postpone, and one we intend to win. The future will be indeed exciting. We had a great beginning.



Josef Penninger December 2004

2004 has been the first year of full operations for IMBA and a year of great achievements and tremendous growth. Since 2003, IMBA has built up a research workforce of over 80 scientists working in six independent research groups and almost 20 people in scientific and administrative support functions.

This unbelievable growth has only been possible because IMBA could rely on its strong research partnership with the Research Institute of Molecular Pathology (IMP) - one of the most prominent scientific institutes for basic research in Europe. Based on an agreement to a shared service concept, IMBA has been provided access to one of the crown jewels of the IMP: their world-class scientific services. We are very pleased to be able to build our institute on that high level of experience right from the beginning. Equally, we hope to be able to contribute to this high service quality and to generate synergies that are of mutual benefit to both institutes.

One of the major challenges in 2004 has been the construction of our new research building at the "Campus Vienna Biocenter". For the time being, the work is well in progress and will be terminated as expected by the end of 2005. The new research facility will offer a state-of-the-art infrastructure for up to 200 researchers, thus creating a very competitive environment in the molecular biology research landscape in Austria. In this context, we thank our public sponsors such as the City of Vienna, the Ministry of Science, Education, and Culture (BMBWK) as well as the National Foundation for their substantial financial contributions.

In 2004, IMBA operated with a research budget of around \notin 10 m, thereof \notin 7.5 m came from financial commitments of the Austrian government and the Austrian Academy of Sciences. In addition to this, IMBA scientists raised more than \notin 2.5 m in research grants from the Austrian Science Fund (FWF), GENAU, the Austrian National Bank, and from the 6th Framework Programme of the EU. To get the institute off the ground, IMBA will mostly rely on public funding in the near future. However, we are highly committed to exploit new sources for financing the future growth of the institute through private sponsorship activities and the commercialization of our research.

One of the reasons why I joined IMBA was its strong commitment to world-class science and its dedication to translating the basic discoveries into novel approaches to human medicine. In this context, we are very excited to initiate a unique platform for drug target discovery based on a Drosophila RNAi Screening Library that has been developed by Barry Dickson and his research group. Through partnerships with the pharmaceutical industry and academic institutions, IMBA expects to gain a very high visibility and reputation within the scientific community.

Thank you to everybody at IMBA for your exceptional commitment and your tolerance and patience with the bottlenecks and problems we have been facing in the process of implementing the IMBA infrastructure from the scratch. Also, thank you to all the IMP members for hosting us and for the continuous support in setting-up the institute and managing the past headcount growth.

The management team is committed to shape IMBA into one of the leading Centers of Excellence in Molecular Biology in Europe; your dedication and engagement is the basis for delivering on this promise.

bm:bwk

















Michael Krebs December 2004



Your career at IMBA

The establishment of any institution depends on the expertise and commitment of its employees. At IMBA, we believe our success stems from our highly skilled scientists who are dedicated to make a difference in molecular biology research. We are a young and rapidly growing team that is committed to provide its people with the best working environment that encourages creativity, enthusiasm, fun and collaboration among the scientific groups. Our new research facility at the Campus Vienna Biocenter and world-class scientific services shared with the IMP offer a state-of-the-art infrastructure for up to 200 researchers, representing an attractive new Center of Excellence in biomolecular research in Europe.

We offer a variety of attractive positions at all levels of research training and career. Currently, IMBA consists of 6 research groups that include 26 Postdoctoral Fellows, 27 PhD Students, 22 Technical Assistants and 3 Diploma Students representing 23 different nationalities. Graduate students join IMBA through the Vienna Biocenter International PhD Program. The doctoral degree is awarded by the University of Vienna. Selection of PhD students takes place twice a year. Information about the PhD program at the Vienna Biocenter is available at: www.univie.ac.at/vbc/PhD.

Applicants for scientific positions are evaluated by IMBA Scientific Search Committee consisting of internationally renowned scientists: Prof. Anton Berns (Netherlands Cancer Institute, Amsterdam, The Netherlands), Prof. Meinrad Busslinger (IMP, Vienna, Austria), Prof. Kim Nasmyth (IMP, Vienna, Austria), Prof. Jeff Schatz (Swiss Science and Technology Council, Basel, Switzerland), Prof. Peter Schuster (Austrian Academy of Sciences, Vienna, Austria) and Prof. Jim Woodgett (Ontario Cancer Institute, Ontario, Canada). Positions available at IMBA are advertised at: www.imba.oeaw.ac.at/positions.







An extensive seminar program brings internationally renowned scientists to IMBA at least once a week. Information about the seminar speakers is available at: *www.imba.oeaw.ac.at/news*.

Our personnel department and assistants support new team members in their relocation efforts and in settling down in Vienna. Since we are aware that moving is an important factor to spouses and kids, we are also committed to help family members of our colleagues to get acquainted with Vienna.





Assembly and function of neural circuits

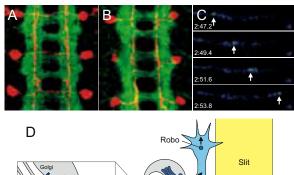
All animals are born with a set of instincts, or innate behaviours. Selection has favoured the evolution of genetic programmes that "hard-wire" these behaviours into the nervous system. We seek to unravel these programmes - to understand how genes direct the assembly of neural circuits, and how these circuits generate complex behaviours.

Assembly

Neural circuits are formed as individual neurons send out axons and dendrites to find, recognize, and connect with their appropriate target cells. We are using *Drosophila* genetics to investigate the molecular mechanisms that direct circuit assembly. We focus on two systems: the ventral nerve cord of the embryo, and the olfactory system of the adult.

In bilaterally symmetric nervous systems, such as our own and the fly's, many axons must decide whether or not to grow across the midline. Our recent work has revealed how this decision is controlled in Drosophila (Figure 1). Crossing and non-crossing axons differ in their sensitivity to the midline repellent Slit. Both crossing and non-crossing neurons express the Slit receptor Robo. In non-crossing neurons, Robo accumulates at the tip of the axon, making it sensitive to the repulsive activity of Slit. Crossing neurons express an intracellular sorting receptor called Comm, which diverts newly synthesized Robo from the Golgi to endosomes and lysosomes for degradation. This prevents Robo from reaching the axon tip, and so the axon is insensitive to Slit and able to grow across the midline. Another guidance cue, Netrin, acts as a short-range attractive cue to help some of these axons grow across the midline. Whether or not they cross, many axons turn to grow anteriorly or posteriorly alongside the midline. These axons follow pathways at specific distances from the midline. The choice of these pathways is controlled in part by the combinatorial expression of three different Robo receptors, possibly also in response to the Slit signal from the midline.

Our sense of smell, and the fly's, depends on the precise wiring of olfactory neurons in the nose (or the antenna) to targets in the brain. In



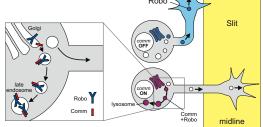


Figure 1: Crossing the midline. In the Drosophila CNS, some axons (red in A) but not others (B) cross the midline. This decision is controlled by Comm, which regulates the trafficking of Robo (C, D). Panel C shows a series of images from a movie in which a Robo-GFP vesicle (red) moves towards the tip (right) of an axon in a living embryo. There is no Comm in this neuron. In neurons in which Comm is expressed, no Robo-GFP can be seen moving down the axon.

Drosophila, each of the ~1300 olfactory receptor neurons (ORNs) in the antenna expresses one of ~60 odorant receptors. ORN axons project to the antennal lobe, a "raspberry-like" structure in the brain consisting



Barry Dickson / Senior Scientist

Mattias Alenius¹ / Postdoc Doris Chen / Postdoc Carlos Ribeiro² / Postdoc Frank Schnorrer³ / Postdoc László Tirián² / Postdoc Eleftheria Vrontou / Postdoc Alexander Widmer⁴ / Postdoc Satoko Suzuki⁵ / Postdoc Takashi Suzuki^{5,6} / Postdoc Marko Brankatschk / PhD Student Africa Couto / PhD Student Ebru Demir / PhD Student Georg Dietzl / PhD Student Giorgio Gilestro / PhD Student Amina Kurtovic / PhD Student Duda Kvitsiani / PhD Student Shay Rotkopf / PhD Student Nilay Yapici / PhD Student Dominik Muggenhumer / Diploma Student Krystyna Keleman / Research Associate Angela Graf / Technician Erika Viragh / Technician

Fellowships: 1 Marie Curie, 2 EMBO, 3 HFSP, 4 SNF, 5 JSPS, 6 Max Plank

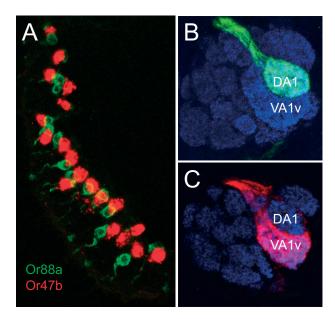


Figure 2: Olfactory wiring. (A) ORNs in the antenna expressing either of two different odorant receptors, Or88a (green) or Or47b (red). (B and C) ORNs that express the same odorant receptor project to the same glomerulus in the antennal lobe in the brain. The blue staining shows all the glomeruli in the antennal lobe. Red and green staining labels the axons of the same ORNs shown in A, which converge on glomeruli called DA1 and VA1v respectively.

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Asymmetric cell division in Drosophila

While most cells divide into two identical daughter cells, some cell divisions are asymmetric and give rise to two different daughter cells. To achieve this, cell fate determinants localize asymmetrically during mitosis and segregate into only one of the two daughter cells. Asymmetric cell divisions are best understood in insects and in worms, yet they contribute to the development of the mammalian brain as well.

Numb belongs to a group of proteins that act as segregating determinants during the development of the *Drosophila* nervous system. Numb is a membrane-associated protein. It localizes asymmetrically during mitosis and segregates into one of the two daughter cells, thus establishing its fate to differentiate into a cell type different from its sister's (Figure 1). When Numb is absent (*numb* mutants) or overexpressed, both daughter cells become identical. Numb is conserved in vertebrates. It seems to play a similar role in asymmetric cell divisions that take place during the mouse brain development. Our goal is to understand how Numb and other cell fate determinants localize asymmetrically in the parental cells, and how they influence the fate of one of the daughters. Asymmetric localization of Numb, and of several other cell fate determinants, requires the conserved Par-protein complex. This complex contains the protein kinase aPKC and two PDZ domain proteins, Par-3 and Par-6. Before mitosis, the Par-complex localizes to the cell cortex at the site opposite to where Numb will accumulate. Using preparative immunoprecipitation and mass spectrometry, we identified an additional component of the Par-protein complex, the cytoskeletal protein Lgl (Figure 2A). Lgl is active at one side of the cell where it allows the recruitment of cell fate determinants to the cell cortex. At the other side of the cell, Lgl is phosphorylated by aPKC. Phosphorylation inactivates Lgl and blocks its association with the cortical actin cytoskeleton. Deletion analysis revealed that the C-terminus of Lgl associates with

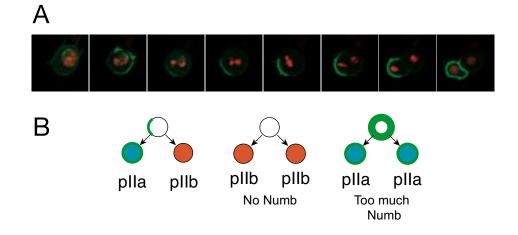


Figure 1: How cells divide asymmetrically. (A) Stills from a movie of a neural precursor cell (SOP) undergoing asymmetric cell division in a Drosophila pupa. Neural precursors are visible as they specifically express an RFP fusion to histone (in red, to visualize DNA) and a GFP fusion to Pon (Partner of Numb, green). Pon is a Numb-binding partner that colocalizes with Numb thus enabling its indirect visualization. (B) In wild-type animals, the two daughter cells of an asymmetric cell division assume different fate. However, in numb mutants or when Numb is overexpressed, both daughter cells become identical.



Jürgen Knoblich / Senior Scientist

Jörg Betschinger¹ / Postdoc Gregory Emery² / Postdoc Mihaela Zigman / Postdoc Sheetal Bhalerao / PhD Student Sarah Bowman³ / PhD Student Ciara Gallagher / PhD Student Andrea Hutterer / PhD Student Bernd Mayer / PhD Student Jennifer Mummery / PhD Student Frederik Wirtz-Peitz³ / PhD Student Eva Hörmanseder / Diploma Student Bernhard Hampölz / Technician Elke Kleiner / Technician Yangning Zhang / Technician

Fellowships: 1FWF, 2Swiss Nat. Fonds, 3BI

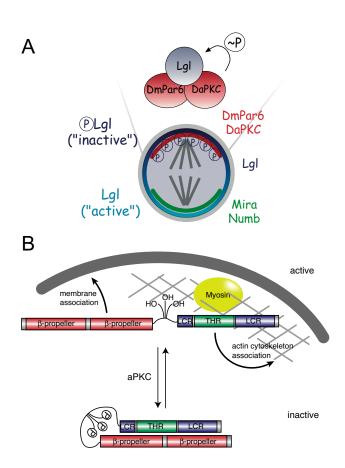


Figure 2: How Lgl directs asymmetric cell division. (A) In neural precursor cells, the Par-protein complex localizes asymmetrically and phosphorylates the cytoskeletal protein Lgl on one side of the cell. Phosphorylation inactivates Lgl. On the opposite side, however, non-phosphorylated Lgl is active and allows localization of cell fate determinants to the cell cortex. (B) In the active form, the C-terminus of Lgl interacts with myosin. Upon phosphorylation, however, the N-terminus binds to the C-terminus abolishing its interaction with myosin. In consequence, Lgl becomes inactive and translocates into the cytosol.

cytoplasmic myosin II. Upon phosphorylation, the N-terminus of Lgl binds to the C-terminus thus blocking myosin interaction (Figure 2B). Hence, Lgl activity is regulated by phosphorylation-induced auto-inhibition. We are using mass spectrometry to identify binding partners of the various functional domains of the Lgl to gain a better understanding of how this protein mediates the localization of cell fate determinants to the cell cortex.

How does Numb establish a particular cell fate? Genetic experiments revealed that Numb represses the activity of the transmembrane receptor Notch. In asymmetric cell divisions, Notch and its ligand Delta are present in both daughter cells. However, Notch is active only in one cell. In the other cell, Notch activity is abolished by Numb-induced endocytosis of Notch and/ or of other members of the Notch pathway. Numb triggers this reaction by binding to α -Adaptin, a protein involved in receptor-mediated endocytosis. In a genetic screen for mutations that cause a phenotype similar to numb, we identified alleles of α -adaptin that specifically disrupted this interaction and displayed defects in the development of the nervous system, consistent with Numb loosing its ability to suppress Notch. Like Numb, α -Adaptin is asymmetrically localized during asymmetric cell division. Numb may therefore act by polarizing the key components of the endocytic machinery. We are currently investigating the subcellular distribution of the major endocytic compartments and analyzing whether other endocytic proteins show an asymmetric distribution as well.

The key components of the asymmetric cell division machinery are conserved in vertebrates. Mouse Numb segregates asymmetrically during mouse brain development. The Par-complex is involved in mammalian cell polarity and, like in *Drosophila*, acts by phosphorylating the Lgl homolog. We have just begun to analyze mammalian homologues of genes involved in asymmetric cell division in *Drosophila*: We are examining their subcellular distribution, and have begun to generate knock-out mouse strains to study their respective mutant phenotypes. These experiments should provide insight into how asymmetric cell divisions contribute to mammalian development and what role they play in stem cells. Ultimately, we hope to understand to what extent asymmetric cell divisions contribute to the development of our own body.

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Mechanism of RNA interference in human cells

Scientists have recently been gifted with RNA interference (RNAi), a magic bullet to silence their favorite gene. Curiously, although RNAi is widely used, its mechanism is largely unknown. We employ refined biochemical tools to identify siRNA-binding proteins in cytoplasmic and nuclear extracts and to study the mechanism by which RISC, the RNA-induced silencing complex, recognizes and cleaves complementary mRNAs.

RNA interference (RNAi) is a post-transcriptional gene silencing mechanism triggered by double-stranded RNA. The use of RNAi as a tool to silence gene expression has spread worldwide from the pioneer work done in Thomas Tuschl's laboratory: short interfering RNA duplexes (siRNAs), consisting of 19 base-pairs and 2-nt overhangs at the 3' end, when transfected into mammalian cells, guide degradation of homologous mRNAs with exquisite specificity. This degradation generates a knock-down phenotype, i.e. the partial or total disappearance of the targeted protein. However, research towards the elucidation of the molecular mechanism of RNAi has not followed the same pace. The main question of how do siRNAs achieve the degradation of complementary mRNAs remains unanswered. Our laboratory is taking a biochemical approach to reveal the nature of the RNAi machinery components.

RNAi biochemistry: Purification of the RISC complex

In order to elucidate the mechanism of RNAi in human cells, we developed an *in vitro* system that utilizes HeLa cell cytoplasmic extracts. We set out to isolate the RNA-induced silencing complex (RISC) by affinity purification using siRNA duplexes containing biotinylated photocleavable linkers on each strand. Upon incubation with HeLa cell cytoplasmic extracts, biotinylated siRNAs were captured with Streptavidin, rigorously washed, released by UV irradiation and finally recovered. The affinity-purified RISC is a 130 kDa ribonucleoprotein complex containing a single-stranded siRNA and two members of the Argonaute protein family, eIF2C1 or Argonaute 1 and eIF2C2 or Argonaute 2. Greg Hannon's laboratory recently revealed that Argonaute 2 is the actual endonuclease of RISC.

Structural and chemical features of RISC-guided RNA cleavage.

To investigate how RISC cleaves a complementary RNA, we labeled a 21-nt long RNA substrate at the scissile phosphodiester bond. Upon RISC-guided cleavage, the radiolabeled phosphate was present as a

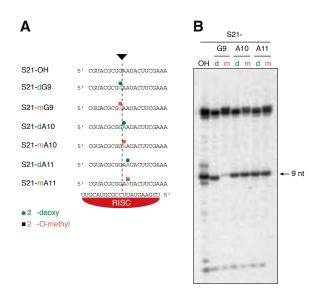


Figure 1: Cleavage analysis of modified substrate RNAs. (A) Sequence and position of 2'-deoxy (S21-d) and 2'-O-methyl (S21-m) modified substrates. (B) Cleavage reactions loaded into a 15% denaturing polyacrylamide gel. Substrate RNAs were labeled at the 5' end. The arrow indicates the 5'-labeled cleavage products.



Javier Martinez

Javier Martinez / Group Leader

Stefan Weitzer / Postdoc Philipp Leuschner / PhD Student Gregor Obernosterer / Diploma Student 5'-phosphate at the 12-nt 3' cleavage product, indicative of a hydrolytic reaction in which cleavage products carry 3'-hydroxyl and 5'-phosphate termini. To further study the chemistry of the cleavage reaction, we synthesized short RNAs containing modifications at the 2' position of the ribose, such as deoxy or 0-methyl groups. The presence of a deoxy group at the cleavage position (and nearby) did not affect the RISC activity indicating that the 2'-hydroxyl group is not essential for the cleavage (Figure 1). However, the activity was completely abolished by placing the 2'-0-methyl group at the cleavage position (G9). These results suggest that the methyl group might cause steric interference, possibly with positioning of an essential divalent metal ion required for catalysis of the cleavage reaction.

Recent reports describe off-target effects of RNAi, i.e. the "unwanted" degradation of RNAs showing extensive but not full complementarity to the siRNA duplex. We have demonstrated that RISC is able to cleave an RNA substrate as short as 15 nucleotides (Figure 2) suggesting that such extent of complementarity is sufficient for cleavage to occur. This observation should help to better design siRNAs in order to avoid off- targeting.

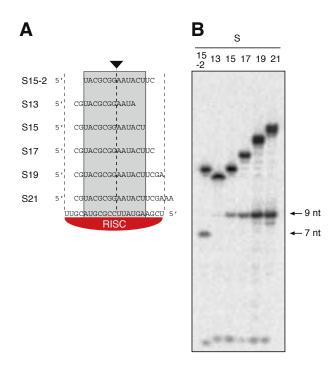
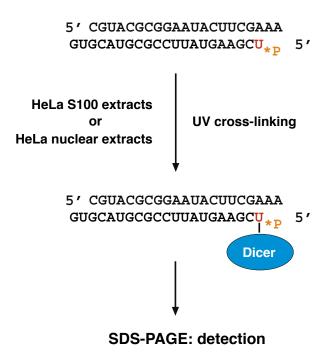


Figure 2: RISC cleaves substrates as short as 15 nucleotides. (A) Sequences of the truncated substrates (S). The 13-nt core sequence required for the RISC-guided cleavage is shaded. (B) Cleavage reactions loaded into a 15% denaturing polyacrylamide gel. Substrate RNAs were labeled at the 5' end. Arrows indicate the size of the 5'-labeled cleavage products.

We have recently begun to build a siRNA-protein interaction map, using HeLa cell cytoplasmic and nuclear extracts, and radiolabeled siRNA duplexes containing 4-thio-uridines at specific positions (Figure 3). Upon UV irradiation, proteins in close proximity to the modified uridines become covalently bound to the siRNA, and thus radiolabeled. Denaturing polyacrylamide gel electrophoresis allows detection of those radiolabeled proteins, while identification is achieved by immunoprecipitation. In cytoplasmic extracts, we are able to cross-link Dicer, the RNase III endonuclease that processes dsRNAs into siRNAs, to both 3' overhangs of a siRNA duplex. Argonaute 2



Immunoprecipitation: identification

Figure 3: Building a siRNA-protein interaction map. Identification of Dicer by cross-linking using a single 4-thio-uridine (depicted in red) is shown as an example.

becomes cross-linked to the center of the siRNA duplex in a time-dependent manner. Future experiments will focus on the identification of other siRNA binding proteins and enzymes in the RNAi pathway, like helicase/s involved in the unwinding of siRNA duplexes – a process that leads to the formation of RISC – and later in the release of the target RNA upon cleavage by RISC. In addition, it will become challenging to identify nuclear siRNA binding proteins, since siRNAs have recently been found to play a role in heterochromatin formation.

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Molecular control of T cell activation

Efficient immunity requires both activation of T cells and generation of cytokines. T cell activation involves two signals: A signal via the peptide-specific TCR and a signal via a co-stimulatory receptor. Failure to activate the second signal results in T cell unresponsiveness. Thus, lack of immunity to many tumours or chronic infections can be ascribed to the fact that so affected cells cannot provide a second signal for T cell activation. By contrast, deregulated activation can trigger autoimmunity. What are the molecular mechanisms controlling T cell activation in normal physiology and in disease?

The E3 ubiquitin ligase Cbl-b, autoimmunity, and T cell tolerance

The three mammalian Cbl-family proteins, c-Cbl, Cbl-b, and Cbl-3 are RING-finger containing E3 ubiquitin ligases that control degradation, localization, receptor recycling, and protein-protein interaction of multiple signalling molecules. Genetic inactivation of c-Cbl in mice causes altered thymocyte selection whereas inactivation of Cbl-3 shows no apparent phenotype. Cbl-b mutation leads to spontaneous autoimmunity and exacerbates autoimmunity in arthritis and diabetes models. Our results provided the first molecular link between protein ubiquitination and autoimmunity.

How does Cbl-b control autoimmunity and T cell activation? Our data showed that loss of Cbl-b causes TCR-mediated T cell activation in the absence of CD28 co-stimulation and "forces" T cells to use a second signal *via* CD28 to form immune synapses (Figure 1). Antigen specific immuno-tolerance limits the expansion of self-reactive T cells involved in autoimmune diseases. A dominant "tolerogenic" factor that represses activation of anergic T cells remains unknown. Does Cbl-b also control T cell tolerance? We have shown that Cbl-b is selectively up-regulated in T cells exposed to tolerizing antigens. Loss of Cbl-b in mice prevents induction of T cell tolerance both *in vitro* and *in vivo*. Importantly, re-challenging of Cbl-b mutant mice with tolerizing antigens causes massive lethality. It was found that loss of Cbl-b rescues the reduced calcium mobilization by anergic T cells, which is attributed to Cbl-b-mediated regulation of PLC γ -1 phosphorylation. However, yet

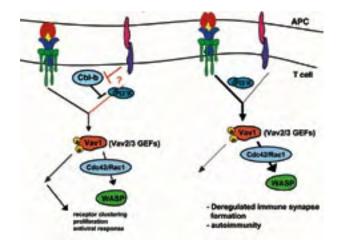


Figure 1: Proposed Cbl-b regulated signaling pathways in T cells. (See e.g. Bachmaier et al. Nature; Krawczyk et al. Immunity; Jeon et al. Immunity).

unexplored mechanisms of Cbl-b action must exist as our results point to a critical role that Cbl-b plays in the regulation of peripheral tolerance and clonal anergy of T cells. Whether Cbl-b can trigger the immune response to weak antigens such as those present in malaria vaccines, or to tumor antigens, is currently the focus of our investigation.



Josef Penninger / Senior Scientist and Director

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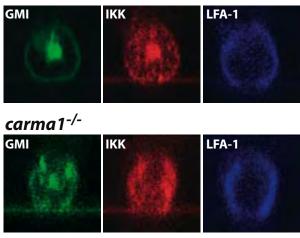


Figure 2: Carma1 is essential for recruitment of IKK into cSMACs at T cell-APC conjugates. Localization of GM-1 associated lipid rafts (green), IKKa/b (red) and LFA-1 (blue) at the immune synapse interface is also shown. IKKs localize to the immune synapse but IKK molecules are excluded from lipid rafts in cSMACs in carma1-/- T cells (see e.g. Hara et al. J. Exp. Med.).

Carma1 in T cell activation

T cell activation depends on the contact between T cell receptors (TCRs) and agonistic peptides displayed by major histocompatibility complex (MHC) expressed on antigen presenting cells (APCs). TCR-mediated stimulation results in the assembly of antigen receptors, signaling molecules and lipid rafts into superamolecular activation clusters (SMACs) at the interface between T cells and APCs. Based on the structural similarity to neural synapses, SMACs are also referred to as immune synapses. Deficiencies of proteins such as the exchange factor Vav1 that affect immune synapse formation result in impaired T cell activation (Figure 1).

MAGUK (membrane–associated gunanylate kinase)-family proteins have been shown to control the polarity of membrane domains at epithelial cell junctions and to function in the formation and/or organization of the immune synapses in lymphocytes. Carma1/CARD11/Bimp3 is a caspase recruitment domain (CARD)-containing MAGUK family protein that is abundantly expressed in lymphoid tissues. Using gene targeting, we have recently demonstrated that Carma1 plays an essential role in antigen receptor-induced NF- κ B and JNK activation, and that loss of Carma1 abrogates T cell proliferation and cytokine production. We showed that Carma1 acts downstream of immune synapse formation and PKC activation, controls entry of IKK into lipid raft aggregates and, most importantly, into the central SMAC areas at the immune synapse (Figure 2). Carma1-regulated recruitment of both IKK and Bcl10 into lipid rafts is, however, differently regulated (Figure 3). Taken together, our data established the molecular hierarchy by which components of NF- κ B activation pathway become recruited to the immune synapse, identified the molecular mechanism by which the adapter protein Carma1 couples antigen receptor signaling to IKK and NF- κ B activation in T cells, and provided the first genetic evidence of a new class of molecular scaffold essential for the selective recruitment of defined signaling machinery, i.e. IKK, into specific regions of immune synapses. To further dissect the signaling hierarchies of TCR-mediated immune synapse formation essential for effective T cell activation we have begun to analyze a novel Carma1 binding partner that also binds to other CARD-containing proteins and a cytoskeletal protein that associates with PKC Θ .

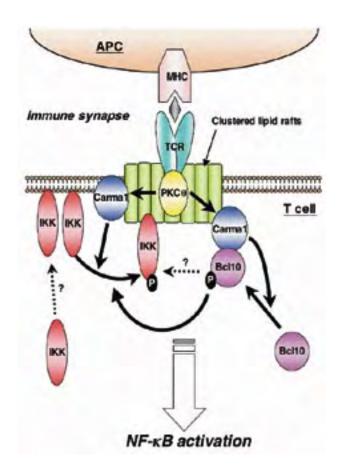


Figure 3: Model of the role of Carma1 in the NF-KB pathway. Carma1 acts downstream of immune synapse formation and downstream of PKCs and is essential for IKK and Bcl-10 recruitment into lipid rafts at the immune synapse. Since IKK, but not Bcl-10, still form supramolecular clusters in card11-/- T cells, a molecule other than Carma1 or Bcl10 might be involved in this initial IKK redistribution. Moreover, recruitment of Bcl-10 and IKK to membranes appears to be independently regulated. It is possible that recruitment of Bcl-10 through Carma1 is important for entry of IKK into the cSMAC (see e.g. Hara et al. Immunity and J. Exp. Med.).

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Mechanisms underlying cell motility and guidance

The migration of cells is essential to life, as a primary feature of developmental and repair processes. It also contributes to disease states, such as in the dissemination of malignant cells during metastasis. We address questions of how the process of cell motility is driven and controlled.

Guiding the way with microtubules

One area of our research programme addresses the question of how a cell polarises to move in a given direction. We now know that cell motility relies on the dynamic formation and reorganisation of actin filaments that form the "actin cytoskeleton". But in many cells, polarisation requires the "microtubule cytoskeleton" and our investigations are aimed at revealing how microtubules exert their influence on the turnover of the actin cytoskeleton to confer this polarisation. The dependence on microtubules for polarisation generally parallels the degree of anchorage of a cell with the substrate, namely with the extent of formation of "focal adhesions". Our recent work has provided evidence for the involvement of microtubules in focal adhesion turnover. Thus, we have shown that the growing ends of microtubules specifically target focal adhesions and that multiple targeting events lead to focal adhesion disassembly, or their release from the substrate. Focal adhesion formation requires the development of tension in the actin cytoskeleton, and results with tension inhibitors provides support for the idea that microtubules destabilise adhesions by delivering a factor(s) that promotes relaxation locally at the targeted adhesion sites. More recently, we applied the technique of total internal reflection fluorescence (TIRF) to living cells and have shown that microtubules approach focal adhesions in a range of nanometres, consistent with an exchange of molecular signals between the two.

The idea that interactions of microtubules with the "cell cortex" are involved in morphogenetic processes has been substantiated in studies of diverse biological systems, from yeast to eukaryotes. A striking development in the field is the realization that microtubules accumulate at their growing tips a complex of protein components that appears

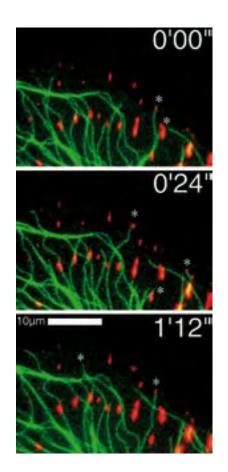


Figure 1: Microtubules target focal adhesions. Video sequences of a fibroblast transfected with eGFP-tubulin (green; microtubules) and Ds-Red zyxin (red; focal adhesions) showing events of targeting of focal adhesions by microtubules (*).



/ic Small

Vic Small / Senior Scientist

Irina Kaverina / Staff Scientist Elisabetta Caspani / Scientific Assistant Stefanie Benesch / Postdoc Stephan Koestler / PhD Student Guenter Resch / PhD Student Sonia Auinger / Technician Jana Tashkova / Technician

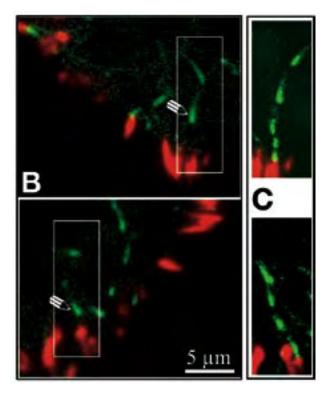


Figure 2: Microtubule tips target focal adhesions in the nanometre range. Total Internal Reflection Fluorescence Microscopy (TIRF) of a cell transfected with Ds-Red zyxin (focal adhesions) and eGFP CLIP-170 (a microtubule tip component). (C) shows accumulated video frames of regions boxed in (B). In this imaging mode, a fluorescence signal is obtained only from structures situated within around 150nm of the substrate. The images show that microtubule tips target focal adhesions within this range.

to influence microtubule dynamics and mediate cortical interactions. In budding yeast, for example, the proper orientation of the mitotic spindle requires the guidance of microtubules along actin cables into the bud tip through cooperation of the microtubule tip protein Bim1 and a myosin V (Myo2) mediated by the adaptor protein Kar9. Our future studies are directed at defining the means of guidance of microtubules into adhesion sites in vertebrate cells and the nature of the signalling events, focusing attention on the molecular complexes that accumulate at microtubule tips and in focal adhesions. These studies will exploit the TIRF method for analysing microtubule-cortical interactions.

Pushing forward

The first stage of cell movement involves the protrusion of a thin layer of cytoplasm, termed the lamellipodium, which is driven by the polymerisation of actin. The lamellipodium, together with integrated bundles, called filopodia, serve, in turn to initiate adhesion with the substrate. Understanding the structural basis of motility requires a knowledge of the organisation of the actin networks that make up the protrusive lamellipodia of migrating cells. Divided opinions about the mode of generation and assembly of actin filament networks in lamellipodia have however arisen through discrepancies in results obtained by different preparative techniques used for electron microscopy. To help resolve current controversies we have initiated the applicaton of cryo-electron microscopy for investigations of cytoskeleton architecture. In parallel studies we are developing techniques for the correlation of the motile activity of the living cell in the light microscope, with the ultrastructure in the EM. Future aims include the characterization of actin reorganizations leading to adhesion formation and defining the relative functional roles of lamellipodia and filopodia.

Additional information may be obtained from our website: http://cellix.imba.oeaw.ac.at/Videotour/video_tour_1.html

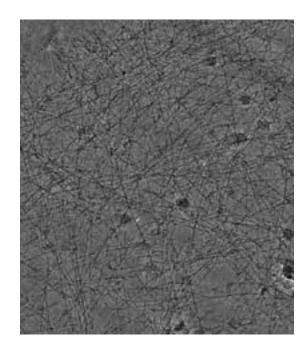


Figure 3: Cryo-EM image of the actin network in the lamellipodium of a fibroblast cytoskeleton.

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Drosophila RNAi group

In Drosophila, RNAi can be triggered in vivo from transgenes that produce "hairpin" RNAs. With this approach, it is possible to perturb the function of almost any gene in any cell or tissue at any time. We are constructing a genome-wide library of such transgenes, to enable systematic surveys of gene function in vivo.

The sequencing of the complete genomes of humans and several model organisms has revealed the entire set of genes that direct all the complex biological processes underlying their development and physiology. The major challenge now is to assign functions to each of these genes – this is the goal of functional genomics. The success of functional genomics relies on a set of reagents and procedures for systematically perturbing the function of each and every gene in an organism's genome. Significant new insights into complex multicellular processes will require that such gene perturbation studies be performed in the intact, living organism. A further requirement, necessitated by the pleiotropy of gene function, is that gene perturbation be restricted as far as possible to the tissues or cells of interest.

Genome-wide, tissue-specific gene perturbation studies are currently feasible in only a single multicellular organism: *Drosophila melano-gaster*. RNAi can be triggered in *Drosophila* by the spatially and temporally controlled expression of an RNAi transgene, which produces a potent and tissue-specific RNAi effect (Figure 1). In the *Drosophila* RNAi group, we are constructing a library of transgenic RNAi strains, comprising over 20,000 lines – 1 or 2 lines for each of the 13,681 genes in the *Drosophila* genome. This library should be completed during 2005.

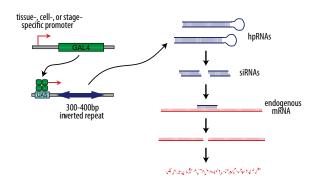


Figure 1: Transgenic RNAi in Drosophila. The generic GAL4/UAS system is used to drive the expression of a hairpin RNA (hpRNAs). These double-stranded RNAs are processed by Dicer into siRNAs, which direct sequence-specific degradation of the target mRNA. From preliminary tests, we estimate that over 70% of the lines are effective. And by testing RNAi lines for genes for which classical loss-of-function mutations are available, we know that the effect is both potent and specific (Figure 2).

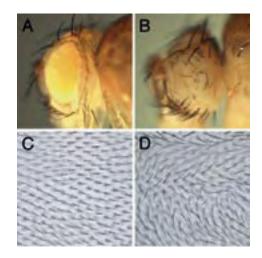


Figure 2: RNAi phenotypes. (A) Control with GAL4 driver only. (B) GAL4 driver + UAS-eyRNAi, targeting the eyeless gene. The eye is missing, as in the eyeless mutant. (C) Wing hairs in a wild type fly all point in the same direction. (D) GAL4 driver + UAS-fmiRNAi, targeting flamingo, a gene required for planar cell polarity. The wing hairs are misorientated, as in the flamingo mutant.

We will exploit this library in academic research at IMBA, and strive to make it available to the academic research community worldwide. For commercial exploitation, the library will be licenced to the newlyfounded Ludwig Boltzmann Institute of Functional Genomics, which will be housed within the IMBA building and commence operation during 2005.

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Caterina Sturtzel² / Technical Assistant Kuan-Chung Su² / Technical Assistant Marlene Vinzenz² / Technical Assistant

¹ FWF, ² part-time, ³ EU Project FLYSNP



Biooptics Department

Biooptics Department

The services offered by our department to the researchers at the IMP and IMBA cover flow cytometry and cell sorting, a wide variety of microscopic techniques, image analysis and processing as well as cDNA-microarray production and analysis.

Flow cytometry

Microarrays

This year, in response to increasing demands for multicolor flow cytometric analyses, a new FACSCanto flow cytometer was installed allowing acquisition of data from cells simultaneously labelled with up to six different fluorochromes.

Microscopy and image analysis

The major accomplishment of the microscopy unit in 2004 was the establishments of a variety of 4D-technologies that utilize laser scanning and spinning disk confocal microcopy, wide-field fluorescence microscopy and deconvolution technology. As the number of users and the amount of generated images steadily increases, an institute-wide database system for image management is currently being implemented.

This year we were able to dramatically improve the quality of our cDNA-microarrays by reengineering almost all of the steps of the array

production. The generation and purification of the PCR-products is now highly automated, and, by changing the buffer conditions the printing of arrays is independent of environmental conditions such as temperature and humidity. The improved quality of the arrays allows faster and more reliable analysis of the data. An additional benefit of the reengineering is an approx. 50% reduction of the costs *per* array.

Together with the group of Thomas Jenuwein at the IMP, we are building up the infrastructure and technology to generate a high-resolution epigenetic map of the mouse chromosome 17 using the ChIP-on-chip technology. So far we have produced microarrays enabling us to map the non-repetitive sequences with an average resolution of approximately 15kb. Next year we plan to increase the resolution to 5kb. To refine our methodology we are yet optimizing array production, sample preparation and downstream analysis. In addition, in order to visualize the data, a web-based epigenome-browser is being developed in collaboration with Insilico Software, Vienna. The browser will be inter-connected with other tools and databases available in our department.

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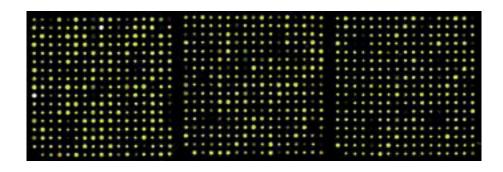


Figure: Example of a ChIP-on-chip experiment. First generation genomic array is hybridized with input DNA (red) and anti-Trimethyl-H3-K4 (green) from mouse embryo fibroblasts. (Data provided by Joast Martens, Group Jenuwein, IMP).

Peter Steinlein / Staff Scientist

Sebastian Carotta¹ / Postdoc Volker Leidl / Software Architect Karin Paiha / Microscopy and Imaging Pawel Pasierbek² / Microscopy and Imaging Martin Radolf / Microarrays Gabriele Stengl / Flow Cytometry

¹until August 2004 ²since September 2004



Service Department

The Service Department offers a variety of high quality and rapid services to the IMP and IMBA scientists. The majority of our efforts involve DNA sequencing and preparation of various media and solutions.

Sequencing and DNA isolation

Using two ABI 3100 Genetic Analyzer capillary sequencers, and, since June, an additional ABI 3730 DNA Analyzer, we sequenced approximately 41'000 samples in the first 9 months of this year (see figure). This is a substantial increase as compared with 2003. The increase has been caused not only by the acquisition of "new customers" from IMBA but also by generally higher number of requests and "genetic screens" as compared with the previous years. The average read-length on both capillary sequencers, the 3100 Genetic Analyzer equipped with the 80 cm capillaries, and the 3730 DNA Analyzer equipped with the 50 cm capillaries, is comparable (700-900 bases) for standard DNA samples. However, the 3730 DNA Analyzer is more sensitive and requires smaller amounts of expensive reagents, and of DNA. For both platforms we employ the same easy and fast clean-up protocol with Sephadex columns on a 96-well microtiter plate.

Production of antibodies

Our department is also responsible for the production and isolation of continuously increasing amounts and varieties of monoclonal antibodies in hybridomas, and for organizing the antibody production in rabbits with an outside company.

Preparation of solutions and media

Our Media Kitchen prepares substantial quantities of reagent quality solutions and media for cell culture, *D. melanogaster* (approximately 500'000 bottles and tubes per year) and *C. elegans*. We also prepare many selected reagents such as DNA molecular weight markers, enzymes, a variety of transformation-competent *E.coli* strains, and maintain a stock of cloning vectors, primers and other cloning reagents.

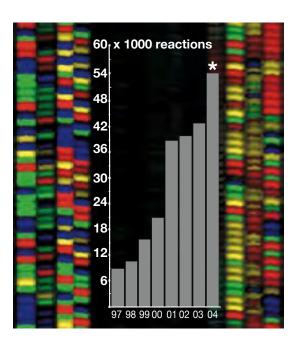


Figure: A sequencing run on an ABI 377 PRISM and number of reactions analyzed on ABI 377 (1997 - 2001), on ABI 3100 (2001 - 2004) and on ABI 3730 (since June 2004) done with dye deoxy terminators (v3.1) in the years 1997 to 2004 (scale 0 to 60'000). *calculated from January 2004 to September 2004 data

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Service Department

Gotthold Schaffner / Scientist

Ivan Botto / Technician Markus Hohl / Technician Shahryar Taghybeeglu / Technician Gabriele Botto / Technician Media Kitchen Franziska Stransky / Technician Fly Food Preparation Ulrike Windholz / Technician Media Kitchen Oliver Botto / Part-time Help Fly Food Preparation Anna Windholz / Part-time Help Fly Food Preparation

Protein Chemistry Facility

Protein Chemistry Facility

The IMP-IMBA Protein Chemistry Facility performs a large variety of mass spectrometry experiments, including identification of proteins by peptide sequencing and characterization of post-translational modifications such as phosphorylation. In addition, we develop new methods for quantification of post-translational modifications. Finally, our facility specializes in peptide synthesis and antibody purification.

Shotgun 2D Proteomics

Tandem mass spectrometry (MS/MS) experiments generate short stretches of sequence information but in most cases only a small fraction of all generated peptides can be recovered and analyzed. To overcome this problem we developed a "shotgun" approach: Protein complexes are purified by immunoprecipitation and digested by different enzymes, the generated peptides are separated by multi-dimensional liquid chromatography and analyzed by MS/MS. By combining the high sensitivity and the resolution of nanoscale multi-dimensional liquid chromatography with the precise structural specificity of MS/MS spectral data the sites and types of modifications are identified in large portions of the sequence of the protein complexes. This approach is particularly important for analyzing the structure of multi-subunit protein complexes. In addition we designed a web-based program called "Mascot Protein Extractor" (see figure) for rapid merging and comparing of seguence search engine results from multiple LC-MS/MS peptide analysis (http://extractor.imp.univie.ac.at).



Figure: Mascot Extractor-software for merging and comparing mass spectrometry data.

Post-translational modifications

Protein phosphorylation is the most important reversible post-translational modification. Thus, analysis of phosphorylated proteins and identification of the phosphorylation sites helps us to understand their biological functions. Our group develops strategies to improve the sensitivity and selectivity of phosphorylation analysis techniques such as:

- Immobilized metal affinity chromatography (IMAC)
- Beta-Elimination of the phosphate group and Michael addition with 2-aminoethanethiol
- Neutral loss and precursor ion scan with our new QTRAP 4000 mass spectrometer.

Post-translational modifications of histones, e.g. methylation, can modulate transcription according to the 'histone code' hypothesis. Mass spectrometry (MS) has proven a valuable tool to identify and quantify changes in histone methylation patterns. In quantitative MS, it is essential to correct for different efficiencies of ionization and detection of differentially modified peptides. These efficiencies are measured using isotopically labeled synthetic peptides as external standards. The labeled peptides are excellent tools for proteomics and are used in applications ranging from absolute quantification of protein abundance and modifications to determination of complex stoichiometry.

Peptides and antibodies

We synthesize about 150 peptides *per* year, including an increasing number of branched peptides containing acetylated, phosphorylated or methylated amino acid residues and isotopically labeled peptides for protein quantification. The affinity purification of antibodies is performed under mild conditions.

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Karl Mechtler / Head of Facility

Elisabeth Roitinger / Postdoc Nedim Mujezinovic / PhD Student Richard Imre / Technician Gabriela Krssakova / Technician Mathias Madalinski / Technician Goran Mitulovic / Technician Michael Schutzbier / Technician Ines Steinmacher / Technician Christoph Stingl / Technician Sebastian Schmittner / Summer Student Reinhard Wohlfart / Summer Student



Animal House

The animal house group provides husbandry of animals and services for the various research groups at the IMP and IMBA.

Mouse Service

The Mouse Service Department was set up at the beginning of 1998 to cope with the increasing demand for mouse studies and generation of transgenics. The Mouse Service Department services are shared by the IMP and IMBA.

Husbandry

The husbandry is divided into three main areas containing the following species: mice, chicken and *Xenopus*. The largest area is the mouse section, where more than 10 000 mice are kept. These comprise breeding colonies, stock, and experimental animals including many transgenic and knock-out mouse lines. To provide a constant supply of mice for the various projects, 20 standard strains are routinely bred in-house.

Animal house services

Veterinary services, such as monitoring of the facility's health-status (sentinel-program etc.), experimental procedures in animals such as collection of blood, implantation of tumor cells and administration of substances by iv, ip or sc injections. All procedures are performed to a high standard under appropriate anaesthetic regimes and in conjunction with the necessary project licenses.

Animal procurement, such as ordering of mice from external breeding companies, organizing and handling of approximately 50 incoming and outgoing mouse-shipments per year.

Administration of regulatory affairs in accordance with the Austrian laboratory animal law, which include record-keeping and updating of laboratory animal statistics, and specific documentation of laboratory animal experiments.

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The main duties of this service unit are the injection of ES cells into blastocysts [also tetraploid] and of DNA into the pronucleus of fertilized mouse eggs. This service also provides for the transfer of 'clean' embryos into our animal house, the freezing of embryos for the preservation of specified mouse strains and the teaching of basic embryological techniques to the IMP and IMBA staff. *In vitro* fertilization experiments (IVF) are performed and the mouse strain database is kept up-to-date. About 30 different ES cell clones and several DNA constructs are being successfully injected *per* year. The activities of this department are overseen by an Animal User Committee, which meets bimonthly to set priorities and to coordinate the duties. At present, it is chaired by Erwin F. Wagner.

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Animal House

Andreas Bichl / Head, Veterinarian Erwin F. Wagner / Scientific Coordinator Norma Howells / Consultant Mijo Dezic / Technician Katja Flahndorfer-Stepanek / Technician Sabine Häckl / Technician Sabine Jungwirth / Technician Erika Kiligan / Technician Milan Lazic / Technician Elisabeth Pölzlbauer / Technician Esther Rauscher / Technician Alexandra Stepanek / Technician

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Mouse Service Department

Hans-Christian Theussl / Technician

Awards and honours

Joerg Betschinger

Received the award from the Austrian Society for Biochemistry and Molecular Biology for his PhD thesis (September 2004).

Barry Dickson

Elected EMBO Member (October 2004).

Karl Mechtler

Received a science prize of the federal state of Lower Austria for his research in protein chemistry (September 2004).

Josef Penninger

Elected Austrian Scientist of the Year 2003 (January 2004).

Honorary Professor, University of Vienna (February 2004).

Kennedy Visiting Professor, London (March 2004).

Elected to the Deutsche Akademie der Naturforscher Leopoldina as Full Member (October 2004).

Austria04' Award (October 2004).

The Koy Lecture, Trinity College, Toronto (October 2004).

The Harold Copp Lecture, Vancouver (October 2004).

Honorary Professor, Peking Union Medical College (December 2004).

Member of the New York Academy of Sciences (December 2004).





MANAGEMENT

Josef PENNINGER Gerhard SCHADLER Michael KREBS

MANAGEMENT ASSISTANTS

Antje SCHILLINGER - DE ZWAAN Denise KLOSS Managing Assistant Administrative Secretary

Managing Director (Science)

Managing Director (Business)

Managing Director (New Building Development)



The administrative and other service groups provide our researchers with the necessary support in the respective areas and consist of IMP and IMBA members which jointly offer their services to both institutes.

GENERAL ADMINISTRATION

Engelbert BERGER Birgit GRUBER Larissa KAHR Werner LEITNER Sabine SVOBODA Brigitte WEISER Anita SOMMER Eva-Maria RUDLOF Renate BICHLER Robert LASETZKY Head of Controlling (IMP) Secretary (part-time; IMP) Grants Manager (IMP) Head of Personnel Department (IMP) Personnel Officer (part-time; IMP) Chief Accountant (IMP) Assistant Accountant (IMBA) Secretary (part-time; IMP) Travel Agent (IMP; until March) General Assistant / Driver (IMP)

PUBLIC RELATIONS

Heidemarie HURTL

Public Relations Officer (part-time; IMP)



PURCHASE DEPARTMENT

Friedrich KUNTNER Kashinath MITRA Angela GANGLBERGER Brigitte LENZ Nikolaus KUNTNER Head of Purchase Department (IMP) Store Manager (IMP) Secretary (IMP) Secretary (IMBA) Warehouseman (part-time; IMBA)





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LIBRARY

Susanne VRBA Wolfgang GÖSCHL Chief Librarian (part-time; IMP) Assistant Librarian (part-time; IMP)



BIOINFORMATICS SERVICE

(provided by the IMP group of Frank Eisenhaber)

IT SERVICE DEPARTMENT

Andreas RIEPL Werner KUBINA Herlind WURTH IT System Manager (IMP) IT System Manager (IMP) IT System Manager (IMBA)

WASHING KITCHEN

Nuray KILIC Erika KLEIN Renate STIX Renate WÖHRER

CAFETERIA

Michael ENZBERGER Markus GIGLER Helga MEHOFER Sabine SMALCL Güler CICOS Selma YILDIRIM Laboratory Technician (IMP) Laboratory Technician (IMP) Laboratory Technician (IMP) Laboratory Technician (IMP)

Chef de Cuisine (IMP) Junior Chef (IMP) Buffet (IMP) Buffet (part-time; IMP) Washing up (part-time; IMPA) Washing up (part-time, IMBA)







Hannes TKADLETZ Jola GLOTZER Graphics Service (IMP) Web Maestra (part-time; IMP)

TECHNICAL DEPARTMENT

Alexander CHLUP Martin COLOMBINI Nadir AYKUT Christian DAVID Vladimir KOLCAR David KUMMERER Gerhard MÜLLER Martin ROJDL Grete KOCINA Chief Engineer (IMP) Mechanical Workshop (IMP) House Maintenance (IMP) House Maintenance (IMP) House Maintenance (IMPA) Technical Maintenance (IMPA) House Maintenance (IMBA) Receptionist (part-time; IMP)



ation and other services

Publications (since IMBA's incorporation)

GROUP DICKSON

(2003)

Dickson, B. J. (2003). Development. Wiring the brain with insulin. Science 300, 440-1.

Senti, K. A., Usui, T., Boucke, K., Greber, U., Uemura, T., and Dickson, B. J. (2003). Flamingo regulates R8 axon-axon and axon-target interactions in the Drosophila visual system. Curr. Biol. 13, 828-32.

(2004)

Dickson, B. J., and Walsh, C. A. (2004). Development: Editorial Overview. Curr. Op. Neurobiol. 14, 1-5.

Lundstrom, A., Gallio, M., Englund, C., Steneberg, P., Hemphala, J., Aspenstrom, P., Keleman, K., Falileeva, L., Dickson, B. J., and Samakovlis, C. (2004). Vilse, a conserved Rac/Cdc42 GAP mediating Robo repulsion in tracheal cells and axons. Genes Dev. 18, 2161-71.

Ryder, E., Blows, F., Ashburner, M., Bautista-Llacer, R., Coulson, D., Drummond, J., Webster, J., Gubb, D., Gunton, N., Johnson, G., O'Kane, C. J., Huen, D., Sharma, P., Asztalos, Z., Baisch, H., Schulze, J., Kube, M., Kittlaus, K., Reuter, G., Maroy, P., Szidonya, J., Rasmuson-Lestander, A., Ekstrom, K., Dickson, B., Hugentobler, C., Stocker, H., Hafen, E., Lepesant, J. A., Pflugfelder, G., Heisenberg, M., Mechler, B., Serras, F., Corominas, M., Schneuwly, S., Preat, T., Roote, J., and Russell, S. (2004). The DrosDel collection: A set of P-element insertions for generating custom chromosomal aberrations in Drosophila melanogaster. Genetics 167: 797-813.

Schnorrer, F., and Dickson, B. J. (2004). Axon guidance: morphogens show the way. Curr. Biol. 14, R19-21.

Schnorrer, F., and Dickson, B. J. (2004). Muscle Building: Mechanisms of Myotube Guidance and Attachment Site Selection. Develop. Cell 7, 9-20.

GROUP KNOBLICH

(2004)

Betschinger, J., and Knoblich, J. A. (2004). Dare to Be Different: Asymmetric Cell Division in Drosophila, C. elegans and Vertebrates. Curr. Biol. 14, R674-85.

Betschinger, J., and Knoblich, J. A. (2005). Phosphorylation induced auto-inhibition regulates the cytoskeletal protein Lethal (2) giant larvae. Curr. Biol., in press.

Hampoelz, B., and Knoblich, J. A. (2004). Heterotrimeric G-Proteins: New tricks for an old dog. Cell 119, 453-6.

Hutterer, A., Betschinger, J., Petronczki, M., and Knoblich, J. A. (2004). Sequential roles of Cdc42, Par-6, aPKC, and Lgl in the establishment of epithelial polarity during Drosophila embryogenesis. Dev. Cell 6, 845-54.

Zarnescu, D. C., Jin, P., Betschinger, J., Nakamoto, M., Wang, Y., Dockendorff, T. C., Feng, Y., Jongens, T. A., Sisson, J. C., Knoblich, J. A., Warren, S. W., and Moses, K. (2005). Fragile X protein functions with Lgl and the PAR complex in flies and mice. Dev. Cell 8, 43–52.

GROUP MARTINEZ

(2004)

Martinez, J., and Tuschl, T. (2004). RISC is a 5' phosphomonoester-producing RNA endonuclease. Genes Dev. 18, 975-80.

GROUP PENNINGER

(2002)

Cheng, H.-Y. M., and Penninger, J. M. (2002). Transcriptional mechanisms underlying neuropathic pain: DREAM, transcription factors and future pain management? Exp. Rev. Neurotherapeutics 2, 677-89.

Cheng, H. Y., Pitcher, G. M., Laviolette, S. R., Whishaw, I. Q., Tong, K. I., Kockeritz, L. K., Wada, T., Joza, N. A., Crackower, M., Goncalves, J., Sarosi, I., Woodgett, J. R., Oliveira-dos-Santos, A. J., Ikura, M., van der Kooy, D., Salter, M. W., and Penninger, J. M. (2002). DREAM is a critical transcriptional repressor for pain modulation. Cell 108, 31-43.

Crackower, M. A., Oudit, G. Y., Kozieradzki, I., Sarao, R., Sun, H., Sasaki, T., Hirsch, E., Suzuki, A., Shioi, T., Irie-Sasaki, J., Sah, R., Cheng, H. Y., Rybin, V. O., Lembo, G., Fratta, L., Oliveira-dos-Santos, A. J., Benovic, J. L., Kahn, C. R., Izumo, S., Steinberg, S. F., Wymann, M. P., Backx, P. H., and Penninger, J. M. (2002). Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. Cell 110, 737-49.

Crackower, M. A., Sarao, R., Oudit, G. Y., Yagil, C., Kozieradzki, I., Scanga, S. E., Oliveira-dos-Santos, A. J., da Costa, J., Zhang, L., Pei, Y., Scholey, J., Ferrario, C. M., Manoukian, A. S., Chappell, M. C., Backx, P. H., Yagil, Y., and Penninger, J. M. (2002). Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 417, 822-8.

Eriksson, U., Danilczyk, U., and Penninger, J. M. (2002). Just the beginning: novel functions for Angiotensin-converting enzymes. Curr. Biol. 12, R745-52.

Griffiths, E. K., and Penninger, J. M. (2002). Communication between the TCR and integrins: role of the molecular adapter ADAP/Fyb/Slap. Curr. Opin. Immunol. 14, 317-22.

Griffiths, E. K., and Penninger, J. M. (2002). ADAP-ting TCR signaling to integrins. Sci. STKE 2002, RE3.

Ito, N., Yokomizo, T., Sasaki, T., Kurosu, H., Penninger, J., Kanaho, Y., Katada, T., Hanaoka, K., and Shimizu, T. (2002). Requirement of Phosphatidylinositol 3-Kinase Activation and Calcium Influx for Leukotriene B4-induced Enzyme Release. J. Biol. Chem. 277, 44898-904.

Jones, D. H., Kong, Y. Y., and Penninger, J. M. (2002). Role of RANKL and RANK in bone loss and arthritis. Ann. Rheum. Dis. 61 Suppl. 2, ii32-9.

Joza, N., Kroemer, G., and Penninger, J. M. (2002). Genetic analysis of the mammalian cell death machinery. Trends Genet. 18, 142-9.

Kim, H. J., Yoon, M. J., Lee, J., Penninger, J. M., and Kong, Y. Y. (2002). Osteoprotegerin ligand induces beta-casein gene expression through the transcription factor CCAAT/enhancer-binding protein beta. J. Biol. Chem. 277, 5339-44. Krawczyk, C., Oliveira-dos-Santos, A., Sasaki, T., Griffiths, E., Ohashi, P. S., Snapper, S., Alt, F., and Penninger, J. M. (2002). Vav1 controls integrin clustering and MHC/peptide-specific cell adhesion to antigen-presenting cells. Immunity 16, 331-43.

Kurrer, M. O., Kopf, M., Penninger, J., and Eriksson, U. (2002). Cytokines that regulate autoimmune myocarditis. Swiss Med. Wkly 132, 408-13.

Mate, M. J., Ortiz-Lombardia, M., Boitel, B., Haouz, A., Tello, D., Susin, S. A., Penninger, J., Kroemer, G., and Alzari, P. M. (2002). The crystal structure of the mouse apoptosis-inducing factor AIF. Nat. Struct. Biol. 9, 442-6.

Matsumoto, G., Tsunematsu, S., Tsukinoki, K., Ohmi, Y., Iwamiya, M., Oliveira-dos-Santos, A., Tone, D., Shindo, J., and Penninger, J. M. (2002). Essential role of the adhesion receptor LFA-1 for T cell-dependent fulminant hepatitis. J. Immunol. 169, 7087-96.

Opavsky, M. A., Martino, T., Rabinovitch, M., Penninger, J., Richardson, C., Petric, M., Trinidad, C., Butcher, L., Chan, J., and Liu, P. P. (2002). Enhanced ERK-1/2 activation in mice susceptible to coxsackievirus-induced myocarditis. J. Clin. Invest. 109, 1561-9.

Penninger, J. M., and Bachmaier, K. Infections and the immune response to cardiac antigens. (2002). Book Chapter. "Epitope recognition since Landsteiner's discovery – 100 years since the discovery of human blood groups". Editors: M. Eibl, W. R. Mayr, G. J. Thorbecke. pp: 103-17.

Roumier, T., Vieira, H. L., Castedo, M., Ferri, K. F., Boya, P., Andreau, K., Druillennec, S., Joza, N., Penninger, J. M., Roques, B., and Kroemer, G. (2002). The C-terminal moiety of HIV-1 Vpr induces cell death via a caspase-independent mitochondrial pathway. Cell Death Differ. 9, 1212-9.

Sasaki, T., Sasaki-Irie, J., and Penninger, J. M. (2002). The potential role of CD45 as a drug target. Curr. Topics Med. Chem., 131, 495-501.

Sasaki, T., Suzuki, A., Sasaki, J., and Penninger, J. M. (2002). Phosphoinositide 3-kinases in immunity: lessons from knockout mice. J. Biochem. (Tokyo) 131, 495-501.

Suzuki, N., Suzuki, S., Duncan, G. S., Millar, D. G., Wada, T., Mirtsos, C., Takada, H., Wakeham, A., Itie, A., Li, S., Penninger, J. M., Wesche, H., Ohashi, P. S., Mak, T. W., and Yeh, W. C. (2002). Severe impairment of interleukin-1 and Toll-like receptor signalling in mice lacking IRAK-4. Nature 416, 750-6.

Tani-Ishii, N., Penninger, J. M., Matsumoto, G., Teranaka, T., and Umemoto, T. (2002). The role of LFA-1 in osteoclast development induced by co-cultures of mouse bone marrow cells and MC3T3-G2/PA6 cells. J. Periodontal Res. 37, 184-91.

Theill, L. E., Boyle, W. J., and Penninger, J. M. (2002). RANK-L and RANK: T cells, bone loss, and mammalian evolution. Annu. Rev. Immunol. 20, 795-823.

Watanabe, T., Nakagawa, K., Ohata, S., Kitagawa, D., Nishitai, G., Seo, J., Tanemura, S., Shimizu, N., Kishimoto, H., Wada, T., Aoki, J., Arai, H., Iwatsubo, T., Mochita, M., Satake, M., Ito, Y., Matsuyama, T., Mak, T., Penninger, J., Nishina, H., and Katada, T. (2002). SEK1/MKK4-Mediated SAPK/JNK Signaling Participates in Embryonic Hepatoblast Proliferation via a Pathway Different from NF-kappaB-Induced Anti-Apoptosis. Dev. Biol. 50, 332-47.

(2003)

Brosnihan, K. B., Neves, L. A., Joyner, J., Averill, D. B., Chappell, M. C., Sarao, R., Penninger, J., and Ferrario, C. M. (2003). Enhanced renal immunocytochemical expression of ANG-(1-7) and ACE2 during pregnancy. Hypertension 42, 749-53. Cheng, H. Y., and Penninger, J. M. (2003). When the DREAM is gone: from basic science to future prospectives in pain management and beyond. Expert Opin. Ther. Targets 7, 249-63.

Crackower, M. A., Kolas, N. K., Noguchi, J., Sarao, R., Kikuchi, K., Kaneko, H., Kobayashi, E., Kawai, Y., Kozieradzki, I., Landers, R., Mo, R., Hui, C. C., Nieves, E., Cohen, P. E., Osborne, L. R., Wada, T., Kunieda, T., Moens, P. B., and Penninger, J. M. (2003). Essential role of Fkbp6 in male fertility and homologous chromosome pairing in meiosis. Science 300, 1291-5.

Danilczyk, U., Eriksson, U., Crackower, M. A., and Penninger, J. M. (2003). A story of two ACEs. J. Mol. Med. 81, 227-34.

Eriksson, U., Kurrer, M. O., Sonderegger, I., Iezzi, G., Tafuri, A., Hunziker, L., Suzuki, S., Bachmaier, K., Bingisser, R. M., Penninger, J. M., and Kopf, M. (2003). Activation of dendritic cells through the interleukin 1 receptor 1 is critical for the induction of autoimmune myocarditis. J. Exp. Med. 197, 323-31.

Eriksson, U., Ricci, R., Hunziker, L., Kurrer, M. O., Oudit, G. Y., Watts, T. H., Sonderegger, I., Bachmaier, K., Kopf, M., and Penninger, J. M. (2003). Dendritic cellinduced autoimmune heart failure requires cooperation between adaptive and innate immunity. Nat. Med. 9, 1484-90.

Giuriato, S., Pesesse, X., Bodin, S., Sasaki, T., Viala, C., Marion, E., Penninger, J., Schurmans, S., Erneux, C., and Payrastre, B. (2003). SH2 domain containing inositol 5-phosphatases 1 and 2 in blood platelets: interaction and respective role in the control of phosphatidylinositol 3,4,5-trisphosphate level. Biochem. J. 376, 199-207.

Gonzalez-Espinosa, C., Odom, S., Olivera, A., Hobson, J. P., Martinez, M. E., Oliveira-Dos-Santos, A., Barra, L., Spiegel, S., Penninger, J. M., and Rivera, J. (2003). Preferential Signaling and Induction of Allergy-promoting Lymphokines Upon Weak Stimulation of the High Affinity IgE Receptor on Mast Cells. J. Exp. Med. 197, 1453-65.

Griffiths, E. K., Sanchez, O., Mill, P., Krawczyk, C., Hojilla, C. V., Rubin, E., Nau, M. M., Khokha, R., Lipkowitz, S., Hui, C. C., and Penninger, J. M. (2003). Cbl-3-Deficient Mice Exhibit Normal Epithelial Development. Mol. Cell Biol. 23, 7708-18.

Hara, H., Wada, T., Bakal, C., Kozieradzki, I., Suzuki, S., Suzuki, N., Nghiem, M., Griffiths, E. K., Krawczyk, C., Bauer, B., D'Acquisto, F., Ghosh, S., Yeh, W. C., Baier, G., Rottapel, R., and Penninger, J. M. (2003). The MAGUK family protein CARD11 is essential for lymphocyte activation. Immunity 18, 763-75.

Heximer, S. P., Knutsen, R. H., Sun, X., Kaltenbronn, K. M., Rhee, M. H., Peng, N., Oliveira-dos-Santos, A., Penninger, J. M., Muslin, A. J., Steinberg, T. H., Wyss, J. M., Mecham, R. P., and Blumer, K. J. (2003). Hypertension and prolonged vasoconstrictor signaling in RGS2-deficient mice. J. Clin. Invest. 111, 445-52.

Irie-Sasaki, J., Sasaki, T., and Penninger, J. M. (2003). CD45 Regulated Signaling Pathways. Curr. Top. Med. Chem. 3, 783-96.

Jun, J. E., Wilson, L. E., Vinuesa, C. G., Lesage, S., Blery, M., Miosge, L. A., Cook, M. C., Kucharska, E. M., Hara, H., Penninger, J. M., Domashenz, H., Hong, N. A., Glynne, R. J., Nelms, K. A., and Goodnow, C. C. (2003). Identifying the MAGUK protein Carma-1 as a central regulator of humoral immune responses and atopy by genome-wide mouse mutagenesis. Immunity 18, 751-62.

Kim, C., Marchal, C. C., Penninger, J., and Dinauer, M. C. (2003). The Hemopoietic Rho/Rac Guanine Nucleotide Exchange Factor Vav1 Regulates N-Formyl-Methionyl-Leucyl-Phenylalanine-Activated Neutrophil Functions. J. Immunol. 171, 4425-30. Kishimoto, H., Nakagawa, K., Watanabe, T., Kitagawa, D., Momose, H., Seo, J., Nishitai, G., Shimizu, N., Ohata, S., Tanemura, S., Asaka, S., Goto, T., Fukushi, H., Yoshida, H., Suzuki, A., Sasaki, T., Wada, T., Penninger, J. M., Nishina, H., and Katada, T. (2003). Different properties of SEK1 and MKK7 in dual phosphorylation of stress-induced activated protein kinase SAPK/JNK in embryonic stem cells. J. Biol. Chem. 278, 16595-601.

Nakashima, T., Wada, T., and Penninger, J. M. (2003). RANKL and RANK as novel therapeutic targets for arthritis. Curr. Opin. Rheumatol. 15, 280-7.

Oudit, G. Y., Crackower, M. A., Backx, P. H., and Penninger, J. M. (2003). The Role of ACE2 in Cardiovascular Physiology. Trends Cardiovasc. Med. 13, 93-101.

Oudit, G. Y., Crackower, M. A., Eriksson, U., Sarao, R., Kozieradzki, I., Sasaki, T., Irie-Sasaki, J., Gidrewicz, D., Rybin, V. O., Wada, T., Steinberg, S. F., Backx, P. H., and Penninger, J. M. (2003). Phosphoinositide 3-kinase gamma-deficient mice are protected from isoproterenol-induced heart failure. Circulation 108, 2147-52.

Penninger, J. M., and Kroemer, G. (2003). Mitochondria, AIF and caspases-rivaling for cell death execution. Nat. Cell Biol. 5, 97-9.

Saibil, S. D., Ohteki, T., White, F. M., Luscher, M., Zakarian, A., Elford, A., Shabanowitz, J., Nishina, H., Hugo, P., Penninger, J., Barber, B., Hunt, D. F., and Ohashi, P. S. (2003). Weak agonist self-peptides promote selection and tuning of virus-specific T cells. Eur. J. Immunol. 33, 685-96.

Schmitt, E., Parcellier, A., Gurbuxani, S., Cande, C., Hammann, A., Morales, M. C., Hunt, C. R., Dix, D. J., Kroemer, R. T., Giordanetto, F., Jaattela, M., Penninger, J. M., Pance, A., Kroemer, G., and Garrido, C. (2003). Chemosensitization by a nonapoptogenic heat shock protein 70-binding apoptosis-inducing factor mutant. Cancer Res. 63, 8233-40.

Suzuki, N., Chen, N. J., Millar, D. G., Suzuki, S., Horacek, T., Hara, H., Bouchard, D., Nakanishi, K., Penninger, J. M., Ohashi, P. S., and Yeh, W. C. (2003). IL-1 receptorassociated kinase 4 is essential for IL-18-mediated NK and Th1 cell responses. J. Immunol. 170, 4031-5.

Suzuki, N., Suzuki, S., Eriksson, U., Hara, H., Mirtosis, C., Chen, N. J., Wada, T., Bouchard, D., Hwang, I., Takeda, K., Fujita, T., Der, S., Penninger, J. M., Akira, S., Saito, T., and Yeh, W. C. (2003). IL-1R-associated kinase 4 is required for lipopolysaccharide-induced activation of APC. J. Immunol. 171, 6065-71.

(2004)

Anglesio, M. S., Evdokimova, V., Melnyk, N., Zhang, L., Fernandez, C. V., Grundy, P. E., Leach, S., Marra, M. A., Brooks-Wilson, A. R., Penninger, J., and Sorensen, H. B. (2004). Differential expression of a novel ankyrin containing E3 ubiquitin protein ligase Hace1, in sporadic Wilms' tumour versus normal kidneys. Hum. Mol. Genet. 13, 2061-74.

Cande, C., Vahsen, N., Kouranti, I., Schmitt, E., Daugas, E., Spahr, C., Luban, J., Kroemer, R. T., Giordanetto, F., Garrido, C., Penninger, J. M., and Kroemer, G. (2004). AIF and cyclophilin A cooperate in apoptosis-associated chromatinolysis. Oncogene 23, 1514-21.

Cheng, H. Y., Laviolette, S. R., Van Der Kooy, D., and Penninger, J. M. (2004). DREAM ablation selectively alters THC place aversion and analgesia but leaves intact the motivational and analgesic effects of morphine. Eur. J. Neurosci. 19, 3033-41.

Cheng, H.-Y. M., Obrietan, K., Cain, S. W., Lee, B. Y., Agostino, P. V., Joza, N. A., Harrington, M. E., Ralph, M. R., and Penninger, J. M. (2004). Dexras1 Potentiates Photic and Suppresses Non-Photic Responses of the Circadian Clock. Neuron 43, 715-28. Cheng, H.-Y. M., and Penninger, J. M. (2004). DREAMing about arthritic pain. Ann. Rheum. Dis. 3 Suppl. 2, ii72-ii75.

Danilczyk, U., Eriksson, U., Oudit, G. Y., and Penninger, J. M. (2004). Physiological roles of angiotensin-converting enzyme 2. Cell. Mol. Life Sci. 61, 2714-9.

Danilczyk, U., and Penninger, J. M. (2004). Hypertension with a grain of salt. Nature Med. 10, 1163-4.

Eriksson, U., Kopf, M., Afanasyeva, M., and Penninger, J. M. (2005). Models of autoimmune heart disease: a review of current status. Drug Discovery Today, in press.

Eriksson, U., and Penninger, J. M. (2004). Autoimmune heart failure: new understandings of pathogenesis. Int. J. Biochem. Cell Biol. 37, 27-32.

Fischer, L., Gukovskaya, A. S., Young, S. H., Gukovsky, I., Lugea, A., Buechler, P., Penninger, J. M., Friess, H., and Pandol, S. M. (2004). Phosphatidylinositol 3kinase regulates Ca2+ signaling in pancreatic acinar cells through inhibition of sarco-endoplasmic reticulum Ca2+-ATPase (SERCA). Am. J. Physiol. Gastrointest. Liver Physiol. 287, G1200-12.

Gronski, M. A., Boulter, J. M., Moskophidis, D., Nguyen, L. T., Holmberg, K., Elford, A. R., Deenick, E. K., Kim, H. O., Penninger, J. M., Odermatt, B., Gallimore, A., Gascoigne, N. R., and Ohashi, P. S. (2004). TCR affinity and negative regulation limit autoimmunity. Nat. Med. 10, 1234-9.

Gukovsky, I., Cheng, J. H., Nam, K. J., Lee, O. T., Lugea, A., Fischer, L., Penninger, J. M., Pandol, S. J., and Gukovskaya, A. S. (2004). Phosphatidylinositide 3-kinase gamma regulates key pathologic responses to cholecystokinin in pancreatic acinar cells. Gastroenterology 126, 554-66.

Hara, H., Bakal, C., Wada, T., Bouchard, D., Rottapel, R., Saito, T., and Penninger, J. M. (2004). The molecular adapter Carma1 controls entry of IKK into the central immune synapse. J. Exp. Med. 200, 1167-77.

Jeon, M.-S., Atfield, A., Venuprasad, K., Krawczyk, C., Sarao, R., Elly, C., Yang, C., Arya, S., Bachmaier, K., Su, L., Bouchard, D., Jones, R., Gronski, M., Ohashi, P., Wada, T., Bloom, D., Fathman, C. G., Liu, Y.-C., and Penninger, J. M. (2004). Essential role of the E3 ubiquitin ligase Cbl-b in T cell anergy induction. Immunity 21, 167-77.

Kong, Y.-Y., and Penninger, J. M. RANK, RANKL, and OPG. (2005). Cytokine Knockouts, in press.

Krawczyk, C. M., Jones, R. G., Atfield, A., Bachmaier, K., Arya, S., Odermatt, B., Ohashi, P. S., and Penninger, J. M. (2005). Differential control of CD28-regulated in vivo immunity by the E3 ligase Cbl-b. J. Immunol, in press.

Marra, L. E., Zhang, Z. X., Joe, B., Campbell, J., Levy, G. A., Penninger, J., and Zhang, L. (2004). IL-10 induces regulatory T cell apoptosis by up-regulation of the membrane form of TNF-alpha. J. Immunol. 172, 1028-35.

Martin-McCaffrey, L., Willard, F. S., Oliveira-dos-Santos, A. J., Natale, D. R., Snow, B. E., Kimple, R. J., Pajak, A., Watson, A. J., Dagnino, L., Penninger, J. M., Siderovski, D. P., and D'Souza. S. J. (2004). RGS14 is a mitotic spindle protein essential from the first division of the mammalian zygote. Dev. Cell. 7, 763-9.

Matsumoto, G., Kubota, E., Omi, Y., Lee, U., and Penninger, J. M. (2004). Essential role of LFA-1 in Activating Th2-Like Responses by α -Galactosylceramide-Activated NKT Cells. J. Immunol. 173, 4976-84.

Nishitai, G., Shimizu, N., Negishi, T., Kishimoto, H., Nakagawa, K., Kitagawa, D., Watanabe, T., Momose, H., Ohata, S., Tanemura, S., Asaka, S., Kubota, J., Saito, R., Yoshida, H., Mak, T. W., Wada, T., Penninger, J. M., Azuma, N., Nishina, H., and Katada, T. (2004). Stress induces mitochondria-mediated apoptosis independent of SAPK/JNK activation in embryonic stem cells. J. Biol. Chem. 279, 1621-6.

Oudit, G. Y., Sun, H., Kerfant, B.-G., Crackower, M. A., Penninger, J. M., and Backx, P. H. (2004). The role of phosphoinositide-3 kinase and PTEN in cardiovascular physiology and disease. J. Mol. Cell. Cardiol. 37, 449-71.

Perfettini, J. L., Roumier, T., Castedo, M., Larochette, N., Boya, P., Raynal, B., Lazar, V., Ciccosanti, F., Nardacci, R., Penninger, J., Piacentini, M., and Kroemer, G. (2004). NF-{kappa}B and p53 Are the Dominant Apoptosis-inducing Transcription Factors Elicited by the HIV-1 Envelope. J. Exp. Med. 199, 629-40.

Rangachari, M., and Penninger, J. M. (2004). Negative regulation of T-cell receptor signals. Curr. Opin. Pharmacology 4, 415-22.

Reif, K., Okkenhaug, K., Sasaki, T., Penninger, J M., Vanhaesebroeck, B., and Cyster, J. G. (2004). Differential Roles for Phosphoinositide 3-Kinases, p110g and p110d, in Lymphocyte Chemotaxis and Homing. J. Immunol. Cutting Edge. 173, 2236-40.

Vahsen, N., Cande, C., Briere, J. J., Benit, P., Joza, N., Larochette, N., Mastroberardino, P. G., Pequignot, M. O., Casares, N., Lazar, V., Feraud, O., Debili, N., Wissing, S., Engelhardt, S., Madeo, F., Piacentini, M., Penninger, J. M., Schagge, H., Rustin, P., and Kroemer, G. (2004). AIF deficiency compromises oxidative phosphorylation. EMBO J. 23, 4679-89.

Wada, T., Joza, N., Cheng, H. Y., Sasaki, T., Kozieradzki, I., Bachmaier, K., Katada, T., Schreiber, M., Wagner, E. F., Nishina, H., and Penninger, J. M. (2004). MKK7 couples stress signalling to G2/M cell-cycle progression and cellular senescence. Nat. Cell Biol. 6, 215-26.

Wada, T., Nishina, H., Katada, T., and Penninger, J. M. (2004). MKK7 couples stress singlaing to G2/M cell cycle progression and cellular senescence. Exper. Med. 22, 1398-400.

Wada, T., and Penninger, J. M. (2004). Stress Kinase MKK7: Savior of Cell Cycle Arrest and Cellular Senescence. Cell Cycle 3, 577-9.

Wada, T., and Penninger, J. M. (2004). Mitogen-activated protein kinases in apoptosis regulation. Oncogene 23, 2838-49.

Wang, X., Huang, G., Luo, X., Penninger, J. M., and Muallem, S. (2004). Role of RGS2 in Ca2+ oscillations and adaptation of Ca2+ signaling to reduce excitability of RGS2-/- cells. J. Biol. Chem. 279, 41642-9.

GROUP SMALL

(2003)

Gimona, M., Kaverina, I., Resch, G. P., Vignal, E., and Burgstaller, G. (2003). Calponin repeats regulate actin filament stability and formation of podosomes in smooth muscle cells. Mol. Biol. Cell. 14, 2482-91.

Hoogenraad, C. C., Wulf, P., Schiefermeier, N., Stepanova, T., Galjart, N., Small, J. V., Grosveld, F., de Zeeuw, C. I., and Akhmanova, A. (2003). Bicaudal D induces selective dynein-mediated microtubule minus end-directed transport. EMBO J. 22, 6004-15.

Kaverina, I., Stradal, T. E. B., and Gimona, M. (2003). Podosome formation in cultured A7r5 vascular smooth muscle cells requires Arp2/3-dependent de-novo actin polymerization at discrete microdomains. J. Cell Sci. 116, 4915-24.

Krylyshkina, O., Anderson, K. I., Kaverina, I., Upmann, I., Manstein, D. J., Small, J. V., and Toomre, D. K. (2003). Nanometer targeting of microtubules to focal adhesions. J. Cell Biol. 161, 853-9.

Nakagawa, H., Miki, H., Nozumi, M., Takenawa, T., Miyamoto, S., Wehland, J., and Small, J. V. (2003). IRSp53 is colocalised with WAVE2 at the tips of protruding lamellipodia and filopodia independently of Mena. J. Cell Sci. 116, 2577-83.

Small, J. V., and Kaverina, I. (2003). Microtubules meet substrate adhesions to arrange cell polarity. Curr. Opin. Cell Biol. 15, 40-7.

Vignal, E., and Resch, G. P. (2003). Shedding Light and Electrons on the Lamellipodium: Imaging the Motor of Crawling Cells. Biotechniques 34, 780-9.

(2004)

Prast, J., Gimona, G., and Small, J. V. (2005). Immunofluorescence microscopy of the cytoskeleton: combination with GFP tags. In "Cell Biology" 3 edn. J. E. Celis et al. Eds. Academic Press, in press.

Resch, G., and Small, J. V. (2005). Electron microscopy of the cytoskleleton; negative staining. . In "Cell Biology" 3 edn. J. E. Celis et al. Eds. Academic Press, in press.

Resch, G. P., Small, J. V., and Goldie, K. N. (2005). Electron Microscopy of Extracted Cytoskeletons: Negative Staining, Cryo-EM and Correlation with Light Microscopy. In "Cell Biology" 3 edn. J. E. Celis et al. Eds. Academic Press, in press.

Small, J. V., and Kaverina, I. (2004). Polarized cell motility: microtubules show the way. In "Cell Migration", ed. by D. Wedlich, Wiley-VCH, Weinheim, pp. 15-31.

Small, J. V., and Vignal, E. (2004). Cell Migration. In "Encyclopaedia of Biological Chemistry", ed. by W. Lennarz and M. D. Lane, Vol. 1, Elsevier Inc., pp. 356-61.

Yanagisawa, M., Kaverina, I. N., Wang, A., Fujita, Y., Reynolds, A. B., and Anastasiadis, P. Z. (2004). A novel interaction between kinesin and p120 modulates p120 localization and function. J. Biol. Chem. 279, 9512-21.

Seminar speakers

JANUARY

08.01.04	PETER STALLER (ETH Zürich)
13.01.04	MASAHIKO HARATA (Grad. School of Agric. Sci., Tohoku
	Univ., Japan)
15.01.04	NIKOLAUS PFANNER (Univ. of Freiburg, Germany)
16.01.04	RON HAY (Univ. of St. Andrews, Scotland)
20.01.04	SEBASTIAN FUGMANN (Yale School of Med.)
22.01.04	GLORIA LUCIANI (Univ. of Dundee)
22.01.04	IAIN MATTAJ (EMBL, Heidelberg)
27.01.04	JOHANNA JOYCE (UCSF)
28.01.04	MIKE VAN DEN BOSCH (Univ. of Galway, Ireland)
29.01.04	DIEGO LOAYZA (Rockefeller Univ.)

FEBRUARY

05.02.04	LUK VAN PARIJS (Center for Cancer Res., Cambridge, MA)
05.02.04	MARIA PIA POSTIGLIONE (Stazione Zoologica, Naples, Italy)
17.02.04	DANIEL TENEN (Harvard Instit. of Med., Boston)
19.02.04	GERALD H. POLLACK (Univ. of Washington, Seattle)

MARCH

04.03.04	NICK BROWN (Univ. of Cambridge)
11.03.04	SUSAN GASSER (Univ. of Geneva)
12.03.04	JOMUNA V. CHOUDHURI (Bielefeld Univ., Germany)
16.03.04	ANDREAS KUNGL (Univ. of Graz)
17.03.04	STEPHANIE BENESCH
18.03.04	PETER PARKER (Lincolns Inn Fields Lab., London)
19.03.04	KOICHI MATSUO (Keio Univ., Tokyo)
22.03.04	TADATSUGU TANIGUCHI (Univ. of Tokyo)
23.03.04	JONATHAN WEISSMANN (UCSF)
24.03.04	ROY DRISSEN (Univ. of Rotterdam)
25.03.04	HARALD VON BOEHMER (Harvard Univ.)
26.03.04	CONSTANZE BONIFER (Univ. of Leeds)
30.03.04	KATRIEN NEIRYNCK (Ghent Univ.)

APRIL

06.04.04	JOAN MASSAGUE (Memorial Sloan-Kettering Cancer Center, NY)
13.04.04	MICHAEL KIEBLER (MPI Tuebingen)
15.04.04	PHIL BEACHY (The Johns Hopkins Univ., Baltimore)
16.04.04	ALBERT SICKMANN (Rudolf-Virchow-Center for Exper. Biomed.,
	Wurzburg)
19.04.04	ULRICH CORTES (IARC, France)
20.04.04	REBECCA HEALD (Univ. of California, Berkeley)
22.04.04	MARK VAN BREUGEL (MPI Dresden)
23.04.04	ANDRE MOELLER (MPI Goettingen)
27.04.04	CHRISTOPHER BAUM (MHH Hannover)
30.04.04	PETER LENART (EMBL Heidelberg)

MAY

03.05.04	MARIANO BARBACID (CNIO, Madrid)
06.05.04	JUAN CARLOS ZÚÑIGA-PFLÜCKER (Sunnybrook & Women's
	College Health Sciences Centre, Toronto)
06.05.04	THOMAS KIEFHABER (Univ. of Basel)
11.05.04	FRANK LYKO (DKFZ, Heidelberg)
12.05.04	TOM LUEDDE (Medical Univ., Hannover)
13.05.04	COLIN STEWART (NCI-FCRDC, Maryland)
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25.05.04	JOSEPH SCHLESSINGER (Yale Univ.)
27.05.04	DAVID VIRSHUP (Univ. of Utah)
28.05.04	JOHN CONDEELIS (Albert Einstein College of Med., New York)
28.05.04	DIRK SCHUEBELER (FMI, Basel)
JUNE	

03.06.04 FRANK McKEON (Harvard Med. School) 14.06.04 GORDON KELLER (Mount Sinai School of Med., New York) 18.06.04 ELI GILBOA (Duke Univ. Med. Centre, North Carolina) (SPECIAL LECTURE IM MEMORIAM LAURA STINGL) 22.06.04 TOM ROBERTS (Harvard Med. School) GERD JÜRGENS (Univ. of Tuebingen) 24.06.04 29.06.04 I. KING JORDAN (NCBI, Bethesda) 30.06.04 ANDREA MUSACCHIO (Europ. Inst. of Oncology, Milan) JULY CORNELIS J.M. MELIEF (Leiden Univ. Med. Center, 01.07.04 The Netherlands) 05.07.04 DAVE GILBERT (SUNY Upstate Med. Univ., Syracuse, N.Y) 06.07.04 HENRY ROEHL (Sheffield Univ.)

09.07.04DOMINIQUE FERRANDON (IBMC du CNRS, Strasbourg, France)15.07.04JIM SMITH (Univ. of Cambridge, UK)16.07.04GERRY RUBIN (HHMI)26.07.04DOUGLAS HANAHAN (UCSF)29.07.04RALF ERDMANN (Inst. of Physiol. Chem., Bochum, Germany)30.07.04ANTON MEINHART (Gene Center, Univ. of Munich)

AUGUST

16.08.04	ARNDT VON HAESELER (Univ. of Duesseldorf)
19.08.04	STEFAN SCHUSTER (Friedrich Schiller Univ., Jena, Germany)

SEPTEMBER

02.09.04	YOSEF SHILOH (Tel Aviv Univ., Israel)
03.09.04	DANIEL GERLICH (EMBL Heidelberg)
06.09.04	SHIGEAKE KATO (Univ. of Tokyo)
09.09.04	DAVID SIDEROVSKI (UNC-Chapel Hill School of Med.)
09.09.04	JERRY WORKMAN (Stowers Inst. for Med. Res., Kansas City)
10.09.04	CHRIS DOE (Inst. of Neurosci./HHMI, Oregon)
15.09.04	JIMENA WEIBEZAHN (ZMBH, Heidelberg)
16.09.04	ALFRED WITTINGHOFER (MPI Dortmund)
17.09.04	JASON D. FONTENOT (Univ. of Washington, Seattle)
23.09.04	TATSUYA HIRANO (CSHL)
30.09.04	CHARLIE BOONE (Banting and Best Dept. of Med. Res., Toronto)

OCTOBER

01.10.04	YOSHINORI YAMASHITA (Dept. of Oncology, Pharm. Res. Centre of
	Kyowa Hakko Kogyo Co. Ltd.)
12.10.04	JUERG BAEHLER (The Wellcome Trust Sanger Inst., Cambridge)
18.10.04	HALLGUIR RUI (Georgetown Univ., Washington DC)
19.10.04	MARC REHMSMEIER (Univ. of Bielefeld)
20.10.04	GRAHAM ANDERSON (Dept. of Anatomy, Inst. for Biomed. Res.,
	Univ. of Birmingham)
20.10.04	LAURE STROCHLIC (Univ. of Cambridge)
22.10.04	PHILIPP SELENKO (Harvard Med. School, Boston)
22.10.04	VINCENT ARCHAMBAULT (Rockefeller Univ.)
28.10.04	HANS SCHOELER (MPI Muenster)
29.10.04	WOLFGANG FISCHLE (Lab. of Chromatin Biol., The Rockefeller
	Univ., New York)

NOVEMBER

03.11.04	JIRI FRIML (ZMBP, Univ. of Tuebingen)
04.11.04	STEFAN UHLIG (Leibniz Center for Med. and Bioscience)
08.11.04	DONALD F. HUNT (Depts. of Chem. and Path., Univ. of Virginia,
	Charlottesville, Virginia)
12.11.04	JEROEN DOBBELAERE (Inst. of Biochem., Zürich)
12.11.04	INKA PAWLITZKY (Univ. of Massachusetts, Boston)
16.11.04	TOM A. RAPOPORT (Harvard Med. School, Dept. of Cell Biol.)
18.11.04	JOHN SCOTT (Howard Hughes Med. Inst., Portland, USA)
23.11.04	TON ROLINK (Univ. of Basel)
25.11.04	ALEXANDER JOHNSON (UCSF)
26.11.04	PATRICK MATTHIAS (FMI, Basel)

DECEMBER

- 02.12.04
 JAMES MUSSER (Baylor College of Med., Texas, USA)

 03.12.04
 MATTHEW POLLI

 06.12.04
 MONIKA PRÜNSTER (Innsbruck Med. Univ.)

 10.12.04
 PETER F. AMBROS (Children's Cancer Res. Inst., St. Anna
- Kinderspital, Vienna)
- 14.12.04 KAY-UWE WAGNER (Eppley Inst. for Res. in Cancer and Allied Diseases)
- 15.12.04 MICHAEL LEITGES (MPI for Exper. Endocr., Hannover)

Seminar speakers

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In order to maintain the highest standard of research IMBA, together with the IMP, has installed a process of review and feedback: the Scientific Advisory Board (SAB), consisting of internationally recognised scientists. The Board meets yearly at IMBA, and, together with IMBA researchers, discusses the quality, the significance, and the main focus of research conducted at IMBA.

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