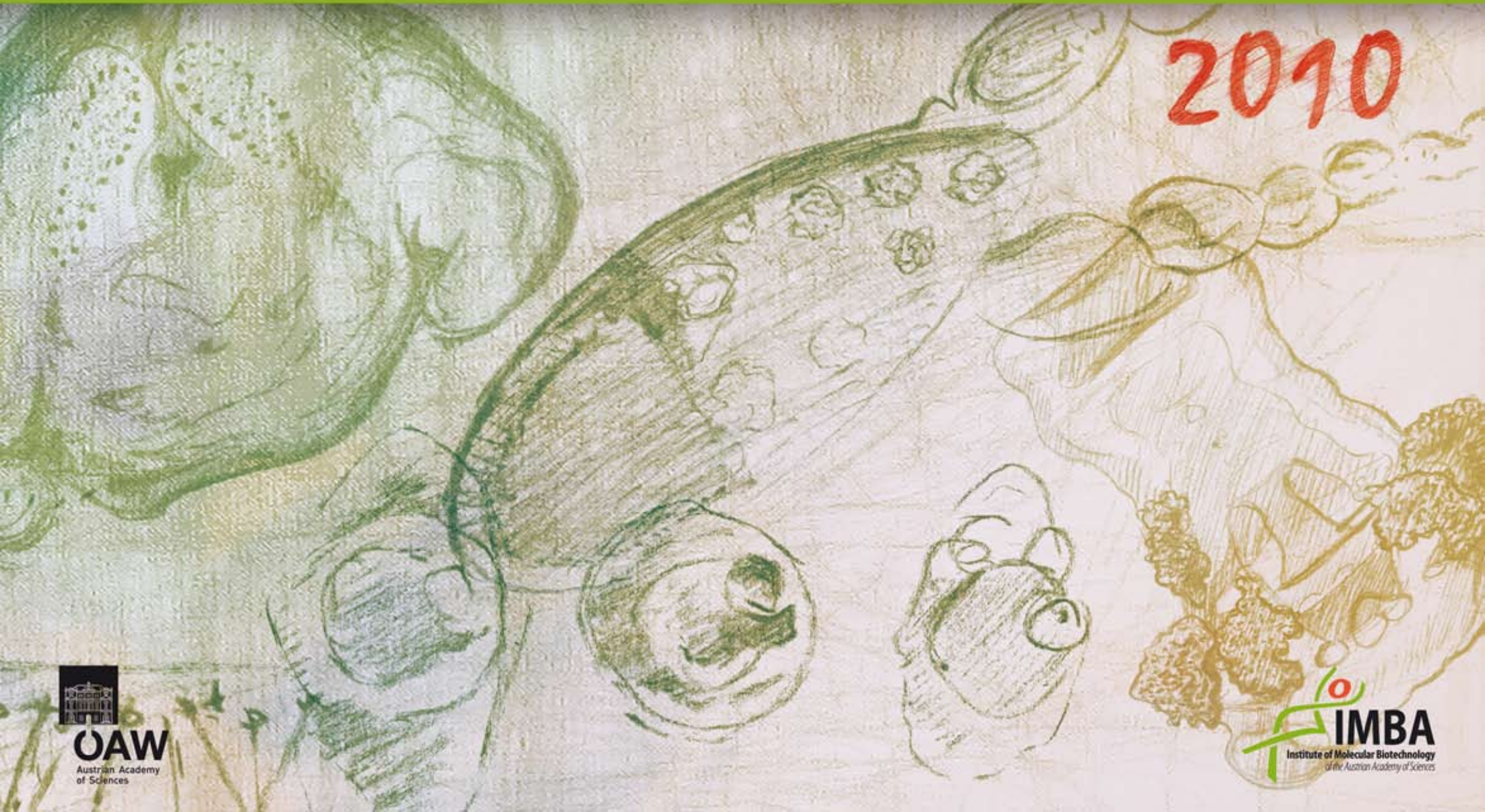
INSTITUTE OF MOLECULAR BIOTECHNOLOGY

OF THE AUSTRIAN ACADEMY OF SCIENCES

VIENNA BIOCENTER



CONTENTS

MICHAEL KREBS
Managing Director/Finance and Administration

JOSEF PENNINGER
Managing Director/Science

JÜRGEN KNOBLICH
Deputy Director/Science

When IMBA was founded in 2004, this was an experiment with a more than uncertain outcome. Would it be possible to repeat the success of the Boehringer Ingelheim funded IMP, this time using public money and integrating the new institute into the existing funding structure for science in Austria. Now, six years later, I guess no one would disagree that this has been a thorough and profound success.

IMBA has matured into an independent institution that has shaped its own profile. It has become home to some of the most successful scientists in the country and has managed to recruit six groupleaders who have established independent research groups in multiple areas of biology ranging from structural biology to epigenetics and RNA biology. Two of them were able to secure prestigious research grants from the ERC and last year, Julius Brennecke received the "Premio Leonardo da Vinci", an award given by the Rotary Club.

The rules of this success are simple: IMBA hires the best scientists and gives them the utmost degree of freedom. We provide a playground for scientists where curiosity is the sole driving force and bureaucratic obstacles are kept to a minimum. Positions at IMBA come with a package that allows the establishment of a research group so that scientists can start working immediately instead of fighting for their first grant.

One cornerstone of our philosophy is the free access to scientific infrastructure including microscopy, mass spectrometry, mouse house or DNA sequencing. The small size of our research community allows interaction with the services on a daily basis. Scientists working in the core facilities are very close to research groups to participate in the success of the projects they contribute to and enjoy sufficient freedom to adjust their service to the needs of the scientists on an individual basis.

The generous support that IMBA provides to its faculty requires constant monitoring of scientific success. Each year, our scientific advisory board visits the institute to provide feedback to each research group. The recess, which is jointly held with the neighboring IMP, not only monitors scientific progress of the institute but is also an important community event where groups interact and discuss their science. Every five years, research groups are evaluated and their resources are readjusted based on the outcome of this evaluation. During the last year, a total of three groups were evaluated and we are happy that feedback was very positive in all cases.

The past year has probably been the most successful one in the history of IMBA. Two of the senior groups are now funded by a prestigious ERC advanced grant. A series of high profile publications in the area of molecular medicine have demonstrated how functional genomics in invertebrate model organisms can identify key players in human diseases including cancer, cardiovascular disease, obesity, or chronic pain. This type of science, which reaches across multiple disciplines and model systems is only possible through an infrastructure that allows research groups to go beyond their traditional expertise in a particular animal model. We are very happy that several of our younger groups have reported results that have caught the attention of a broad community. This is particularly true in the area of RNA biology where spectacular new findings have shed new light on a role of small RNAs in DNA elimination or in defending the genome against parasitic transposons.

While we hope to continue upon this success, we are particularly excited about the year ahead of us which will be a turning point in the short history of the institute in many ways: The Austrian Academy of Sciences and the Austrian government have generously allowed us to build on our success and significantly expand the number of research groups in the institute both on the junior and on the senior level. New recruitments are vital for maintaining the dynamic and vibrant atmosphere of the institute and will be made around our existing strengths in molecular medicine, stem cell biology and RNA biology. The Campus Support Facility will become operational in January 2011. This common service infrastructure will serve all institutes and biotech companies at the Campus Vienna Biocenter bringing together the various scientific institutes and ensuring that they work towards a common goal. We welcome Andreas Tiran as the new director of this institution, which will complement the existing scientific services at the IMP, IMBA and GMI. This also allows us to establish new facilities for second-generation sequencing, mouse phenotyping and cell-based screening. At the same time, we remain committed to our own core facilities, which cover those areas where the need for flexibility and daily interaction limits the size of the community that can be served. Free access to those services is and will be a cornerstone of our success.

We would like to express our gratitude to all who contributed to the success of IMBA over the past years. We are particularly grateful to all the heads of our scientific services and everyone working in the service units whose enthusiasm contributes tremendously to the success of our institute. We also would like to thank everyone working in our administration for their constant efforts which make our lives at IMBA so comfortable and for being patient and flexible with the often very spontaneous needs of the scientific community. And finally, thanks to all scientists working at IMBA who make this a fun place to work in and an institute where going to work in the morning is something to look forward to.

RESEARCH HIGHLIGHTS

2010 has been one of the most successful years for IMBA so far. One indicator for this is the large number of highly visible research articles IMBA scientists have published during this year. A series of publications from the Penninger lab has used the genome-wide transgenic Drosophila RNAi library to identify disease-relevant genes in fruit flies and characterize their mammalian homologs to shed some light on human disease relevant processes. The group of Vic Small has used 3D electron microscopy to analyze the organization of the actin cytoskeleton in migrating cells and came up with conclusions that may fundamentally change our view on how the cytoskeleton works. In addition, two of the younger groupleaders have reported their first scientific breakthroughs. Kazufumi Mochizuki discovered a mechanism that translocates the machinery for RNA interference into the cell nucleus where it mediates the elimination of particular DNA fragments. Julius Brennecke identified components of the biosynthesis pathway for piRNAs, a group of small RNA molecules that protect the genome against transposable DNA elements.

A global in vivo Drosophila RNAi screen identifies NOT3 as a conserved regulator of heart function.

The human genome project was a major advance allowing for molecular foot hold towards an understanding of human diseases. The real question now is "what do these genes do, and how do they participate in human disease?" To this end we focused on heart disease. Heart diseases are the most common causes of morbidity and death in humans. Using cardiac-specific RNAi-silencing in Drosophila, we knocked down 7061 evolutionarily conserved genes under conditions of stress. We present a first global roadmap of pathways playing conserved roles in the cardiovascular system. One critical pathway identified was the CCR4-Not complex implicated in transcriptional and posttranscriptional regulatory mechanisms. Silencing of CCR4-Not components in adult Drosophila resulted in myofibrillar disarray and dilated cardiomyopathy. Heterozygous not3 knockout mice showed spontaneous impairment of cardiac contractility and increased susceptibility to heart failure. These heart defects were reversed via inhibition of HDACs, suggesting a mechanistic link to epigenetic chromatin remodeling. In humans, we show that a common NOT3 SNP correlates with altered cardiac QT intervals, a known cause of potentially lethal ventricular tachyarrhythmias. Thus, our functional genome-wide screen in Drosophila can identify candidates that directly translate into conserved mammalian genes involved in heart function.

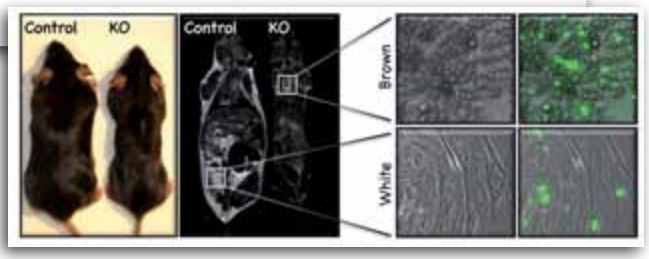
Neely, GG., Kuba, K., Cammarato, A., Isobe, K., Amann, S., Zhang, L., Murata, M., Elmén, L., Gupta, V., Arora, S., Sarangi, R., Dan, D., Fujisawa, S., Usami, T., Xia, CP., Keene, AC., Alayari, NN., Yamakawa, H., Elling, U., Berger, C., Novatchkova, M., Koglgruber, R., Fukuda, K., Nishina, H., Isobe, M., Pospisilik, JA., Imai, Y., Pfeufer, A., Hicks, AA., Pramstaller, PP., Subramaniam, S., Kimura, A., Ocorr, K., Bodmer, R., Penninger, JM. (2010). A global in vivo Drosophila RNAi screen identifies NOT3 as a conserved regulator of heart function. Cell. 141(1):142-53

Figure: A Global Network of Heart Function. The systems network includes data from the significantly enriched Drosophila KEGG and mouse and human KEGG and C2 data sets. Pathways and gene sets from the same biological processes were grouped into common functional categories. Orange nodes represent statistically enriched functional categories of pathways, red nodes represent direct primary fly RNAi hits, green nodes represent their first degree binding partners, and blue nodes indicate genes that were scored as developmentally lethal in our Drosophila heart screen. Lines indicate associations of the genes to the appropriate functional category.

Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate.

Using a novel high throughput method we were able to interrogate over 10,000 genes (75%) for their ability to influence fat levels in living adult Drosophila. As most of these genes have mouse and human homologues, the findings are providing a platform of new potential therapeutic targets for testing and development in mammals. One of the top hits was the hedgehog signaling pathway. Switching to a mammalian model, and now in collaboration with Harry Esterbauer at the MUW, we produced hedgehog mutant mice. Intriguingly, these Ap2SufuKO mice have virtually no fat tissue. They are the first completely healthy lipoatrophic model generated to date and carry important implications towards our understanding of metabolic regulation as well as towards therapeutic management of human lipodystrophies. One unique aspect of "hedgehog" control of fat biology is selectivity to block development of white, but not brown fat. In the accompanying figure, the hedgehog pathway in white and brown fat stem cells was genetically activated (green). The white fat stem cells never give up their fibroblast-like appearance whereas the brown cells differentiate fully, with a full compliment of grape-like lipid droplet clusters. As brown fat is often considered "good fat", and white considered "bad fat", the work identifies hedgehog as one of the first promoters of "good" fat development.

Pospisilik, JA., Schramek, D., Schnidar, H., Cronin, SJ., Nehme, NT., Zhang, X., Knauf, C., Cani, PD., Aumayr, K., Todoric, J., Bayer, M., Haschemi, A., Puviindran, V., Tar, K., Orthofer, M., Neely, GG., Dietzl, G., Manoukian, A., Funovics, M., Prager, G., Wagner, O., Ferrandon, D., Aberger, F., Hui, CC., Esterbauer, H., Penninger, JM. (2010). Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate. Cell. 140(1):148-60

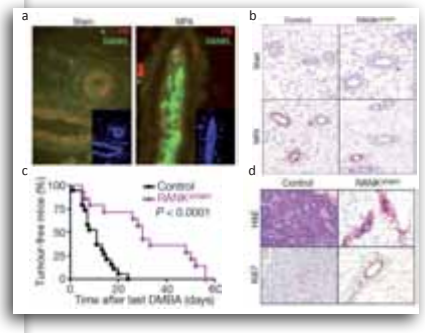


Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer

Progestins, used in contraceptives and hormone replacement therapy, have been epidemiographically linked to breast cancer. We have now found a mechanistic basis for this association and could show in a mouse model that synthetic progestins can promote mammary tumour formation by inducing the osteoclast differentiation factor RANKL, which acts on mammary epithelial cells through the RANKL receptor RANK. This then triggers uncontrolled proliferation and protection against DNA damage-induced cell death of mammary epithelial cells. Moreover, we could show a crucial role of the RANKL/RANK system in normal stem cell proliferation and expansion during pregnancy as well as in self renewal of tumor-inducing cancer stem cells. These findings were also confirmed by Gonzalez-Suarez et al., who published in a back-to-back paper that inhibition of RANKL reduces tumorigenesis in the same hormone-induced as well as in other mouse mammary gland tumour models, indicating that an anti-RANKL therapy might also proof effective in human trials. Denosumab, a monoclonal anti-RANKL Ab, has already proofen to be effective in treating bone loss in post-menopausal osteoporosis and in cancer patients with skeletal-related symptoms and could therefore be now easily tested in breast cancer patients.

Schramek, D., Leibbrandt, A., Sigl, V., Kenner, L., Pospisilik, JA., Lee, HJ., Hanada, R., Joshi, PA., Aliprantis, A., Glimcher, L., Pasparakis, M., Khokha, R., Ormandy, CJ., Widschwendter, M., Schett, G., Penninger, JM. (2010). Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature. 468(7320):98-102

Figure: The progesterone derivative MPA triggers in vivo RANKL expression and the proliferation of mammary epithelial cells as well as mammary tumorigenesis through RANK. a, Induction of RANKL expression by MPA. Nulliparouswild-type females were implanted subcutaneously with slow-release MPA pellets or treated with sham surgery. In situ immunostainingof progesterone receptor (PR, red) and RANKL (green) in mammary epithelial cells after treatment with MPA for 3 days. b, Epithelial proliferation in mammary glands of control, littermates and RANKmamfemales 3 days after sham treatment and MPA implantation. Proliferation was determined by in situ Ki67 immunostaining. c, Onset of palpable mammary tumoursin MMTV-Cre rankfloxed/ females (RANKmam) (n514) and age-matched littermate control females (n519) treated with MPA pellets and the carcinogen DMBA. d,Representative histological sections with typical invasive adenocarcinomas in the control females and normal acinarmorphology RANKmamfemales on day 7 after the final DMBA treatment. Haematoxylin/eosin (H&E)-stained sections and immunostainingforthe proliferation marker Ki67 are shown. Original magnifications x20.

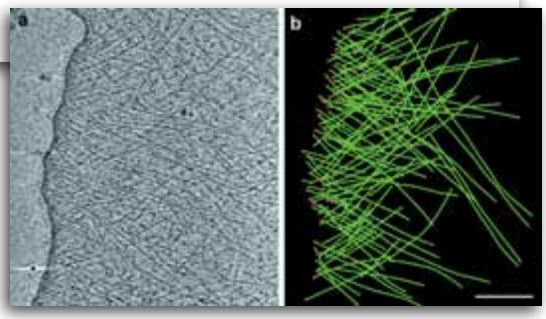


Electron tomography reveals unbranched networks of actin filaments in lamellipodia.

Cells migrate using the polymerization of actin filaments arranged in a network to push the membrane at their front edge, forming thin sheets of cytoplasm termed lamellipodia. In the textbook model, actin filaments in lamellipodia branch from their sides, forming dendritic-ljke arrays. Using the new technique of electron tomography we recently obtained the first 3D images of lamellipodia in cells vitreously frozen from the living state. Our findings reveal that actin filaments are linear and un-branched in lamellipodia and provide new details of the pushing machinery. The results show the importance of using appropriate methods of preparation and imaging in electron microscopy and provide a new basis for understanding the primary step in cell migration.

Urban, E., Jacob, S., Nemethova, M., Resch, GP., Small, JV. (2010). Electron tomography reveals unbranched networks of actin filaments in lamellipodia. Nat Cell Biol. 12(5):429-35

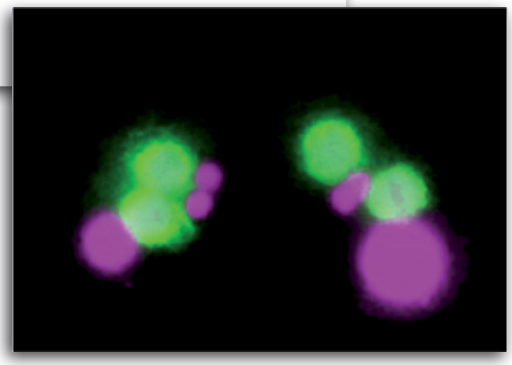
Figure: The lamellipodium of vitreously frozen goldfish fibroblast is composed of overlapping un-branched filaments. a, Cryo-electron tomogram section (4.8nm thick) of the lamellipodium showing actin filaments penetrating to the leading membrane b, Projection of the 3D model generated by tracking actin filaments (green) through the tomogram, red points mark filament plus ends. The filament ends (red points) are distributed over the surface of the network at the tip and in a zone about 400nm wide behind the tip. Bar, 200nm.



The Tetrahymena argonaute-binding protein Giw1p directs a mature argonaute-siRNA complex to the nucleus.

Although evidence from various eukaryotes has indicated that RNAi-related mechanisms play important roles in the nucleus, it is poorly understood how RNAi machinery is transported into the nucleus. The ciliated protozoan Tetrahymena provides an extreme example of a nuclear-acting RNAi machinery: the Argonaute protein Twi1p is sequentially localized in the parental and newly developed macronuclei and plays an essential role in programmed DNA elimination, which is evolutionary related to small RNA-directed heterochromatin formation in other eukaryotes. In this manuscript, we show: 1) the nuclear localization of Twi1p requires the endoribonuclease (Slicer)-activity of Twi1p; 2) the Slicer-activity plays a key role in the removal of one of two strands (passenger strand) of Twi1p-associated siRNAs; 3) the novel Twi1p-binding protein Giw1p is essential for nuclear localization of Twi1p; 4) the Slicer-activity is essential for the interaction between Giw1p and Twi1p. These results suggest that Giw1p senses the state of Twi1p-associated siRNAs and selectively transports the mature Twi1p-siRNA complex into the nucleus. This is the first report describing that 1) localization of an Argonaute protein is regulated according to state of its bound siRNAs; 2) the existence of a protein sensor of the state of Argonaute-associated siRNAs.

Noto, T., Kurth, HM., Kataoka, K., Aronica, L., DeSouza, LV., Siu, KW., Pearlman, RE., Gorovsky, MA., Mochizuki, K. (2010). The Tetrahymena argonaute-binding protein Giw1p directs a mature argonaute-siRNA complex to the nucleus. Cell. 140(5):692-703

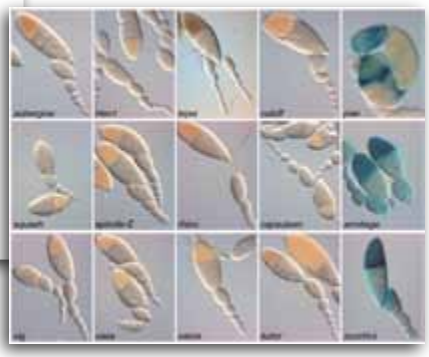


An in vivo RNAi assay identifies major genetic and cellular requirements for primary piRNA biogenesis in Drosophila

Transposons are mobile genetic elements that threaten the genome's integrity of nearly every organism due to their mutagenic character. In the animal gonad, transposons are selectively silenced via the piRNA pathway, a specialized small RNA silencing pathway centered on PIWI proteins and their bound piRNAs. In stark contrast to other small RNA silencing pathways such as the siRNA pathway or the microRNA pathway, we entirely lack insight into biogenesis of piRNAs and the silencing mode of PIWI family proteins. We therefore established an RNAi assay that allows testing any gene of interest for its involvement in the piRNA pathway within a single genetic cross. Using this assay, we identified three key players acting in the biogenesis of piRNAs. These are the two RNA helicases Armitage and Yb and the putative nuclease Zucchini. While these three proteins are promising entry points towards a mechanistic understanding of piRNA biogenesis, the established RNAi assay will allow the conduction of a genome wide screen in conjunction with the VDRC RNAi library established at IMP/IMBA.

Olivieri, D., Sykora, MM., Sachidanandam, R., Mechtler, K., Brennecke, J. (2010). An in vivo RNAi assay identifies major genetic and cellular requirements for primary piRNA biogenesis in Drosophila. EMBO J. 29(19):3301-17

Figure: Comprehensive analysis of the involvement of piRNA pathway members in the somatic pathway. Shown are ß-Gal stainings as readout for gypsy-silencing for genetically identified piRNA pathway genes using gypsy-lacZ and tj-GAL4 in a restrictive flamenco background.



JULIUS BRENNECKE GROUP

The piRNA Pathway in the *Drosophila* Germline – Guardian of the Genome

www.imba.oeaw.ac.at/research/julius-brennecke

Throughout the eukaryotic lineage, small RNA silencing pathways protect the genome from the deleterious influence of selfish genetic elements such as transposons. In animals, an elaborate small RNA pathway centered on PIWI proteins and their interacting piRNAs silences transposons within the germline. Recent studies have disclosed a fascinating conceptual framework for this pathway, which is preserved in organisms ranging from sponges to mammals. Our group is interested in understanding the molecular and genetic makeup of this pathway and in elucidating its biological functions.

Silencing selfish genetic elements

Essentially, all analyzed genomes contain selfish genetic elements such as transposons. Their devastating impact on the host is illustrated by the phenomenon of "hybrid dysgenesis" in *Drosophila melanogaster*: Intercrosses between laboratory strain females and wild caught males result in progeny with severe sterility. This is caused by the activity of a single transposon, which is present in wild populations, but absent in stocks that have been kept in laboratories for ~100 years. Several dozens of different transposons populate the *Drosophila* genome. Their transposition strategies vary widely, illustrating the need for a generic silencing system.

The piRNA pathway – a small RNA-based genome immune system

The piRNA pathway is a striking example of the highly sophisticated solutions devised by Nature to tackle a serious threat. In essence, the piRNA pathway acts as an RNA-based genome immune system. It has an inheritable genetic component and an acute response system, which enable it to combat specifically active transposons. Briefly, the transcription of discrete loci within heterochromatin (termed piRNA clusters) provides a template from which primary piRNAs are produced. These loci contain vast collections of immobile and broken copies of transposons, which are or have been active in a population. If a primary piRNA encounters a target (active transposon), cleavage of the transposon RNA by the piRNA complex leads to the synthesis of a novel and complementary piRNA. This piRNA, in turn, guides the production of more antisense piRNAs derived from the piRNA cluster transcript. Thus, piRNA clusters act not only as a genetically inherited memory component but also as relay stations to boost the production of silencing competent piRNAs.

Our recent studies have provided a framework for this pathway, largely founded on bioinformatics-based analysis of piRNA populations. We also demonstrated that two distinct piRNA pathways act within the ovary: one in the germline lineage and one in the surrounding somatic follicle cells. However, the molecular details and the proteins acting at various steps in this pathway are either unknown or only poorly understood. We study this pathway in *Drosophila*, where we can combine genetics, biochemistry, cell biology and bioinformatics to unravel the phenomenon in efficient ways. Moreover, roughly 35 years of genetic studies on transposons and host strategies to silence them provide us with a wide range of observations, which we can now connect to this pathway.

We are mainly interested in the following aspects:

1. Identifying and characterizing novel piRNA pathway members: Using sophisticated *in vivo* RNAi systems, we initiated a genome-wide screen for the identification of novel piRNA pathway genes in *Drosophila*. A pilot screen has already led to the identification of three essential factors involved in primary piRNA biogenesis. We established efficient RNAi systems for *Drosophila* germline cells as well, and initiated targeted mini-screens to probe the more elaborate makeup of the germline piRNA pathway.

2. Systems level analysis of gene/transposon expression in wild-type and piRNA pathway mutants: No systematic analysis of transposon activity, transposition frequency and patterns has been performed thus far in flies lacking the piRNA pathway. Using highly specific RNAi conditions, we will probe the genome-wide consequences of deficiencies in somatic and germline piRNA pathways. We are utilizing deep sequencing technologies to gain insight into these issues.

3. Understanding the enigmatic piRNA clusters: piRNA clusters are typically located at telomeres or at the border between euchromatin and heterochromatin. Their transcripts are believed to traverse large (up to several hundreds of kb) heterochromatic regions. We are interested in the regulation and processing of piRNA clusters. Using sophisticated genetic techniques, we will determine how the cell is able to distinguish these transcripts from other RNAs in the cell.

JULIUS BRENNECKE

julius.brennecke@imba.oeaw.ac.at

Julius studied Biology at the University of Heidelberg and obtained his PhD degree from the EMBL in 2004. His major interest is in understanding the molecular events that govern Drosophila development. During his PhD he developed a strong interest in small RNA silencing pathways and worked on microRNAs in Drosophila development. During his postdoctoral work at Cold Spring Harbor Laboratories, he worked on a novel class of small RNAs in the fly germline, the Piwi interacting RNAs (piRNAs). He started his independent research group in Vienna in 2009.

Publication highlights:

Brennecke, J., Aravin, AA., Stark, A., Dus, M., Kellis, M., Sachidanandam, R., Hannon, GJ. (2007). Discrete small RNA-generating loci as master regulators of transposon activity in Drosophila. Cell. 128(6):1089-103

Brennecke, J., Malone, CD., Aravin, AA., Sachidanandam, R., Stark, A., Hannon, GJ. (2008). An epigenetic role for maternally inherited piRNAs in transposon silencing. Science. 322(5906):1387-92

Malone, CD., Brennecke, J., Dus, M., Stark, A., McCombie, WR., Sachidanandam, R., Hannon, GJ. (2009). Specialized piRNA pathways act in germline and somatic tissues of the Drosophila ovary. Cell. 137(3):522-35

GROUP LEADER :
BRENNECKE, JULIUS

POSTDOCS:
SENTI KIRSTEN, MOHN FABIO

PHD STUDENTS:
DONERTAS DERYA, OLIVIERI DANIEL, HANDLER DOMINIK, SIENSKI GRZEGORZ

DIPLOMA STUDENT:
SCHMID CHRISTOPHER

FLY TECHNICIAN:
MEIXNER KATHARINA

Figure 1

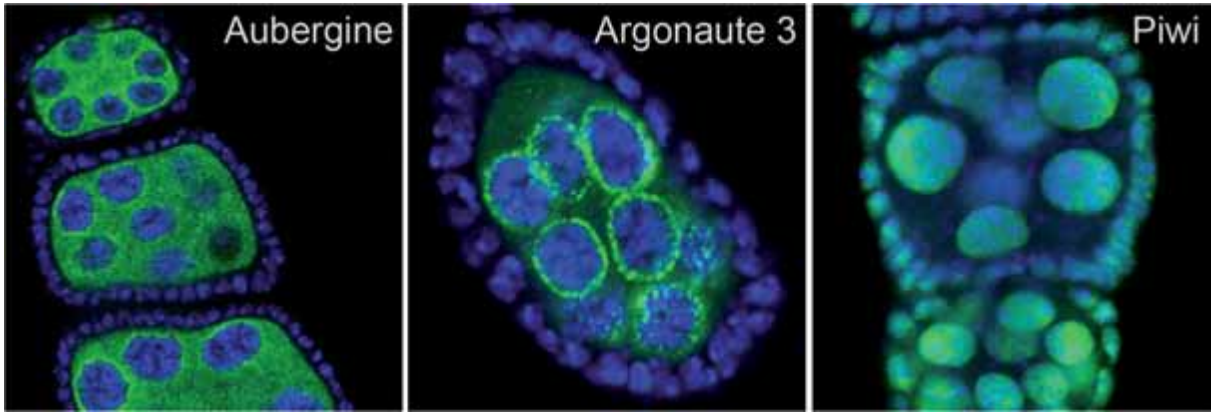


Figure 2

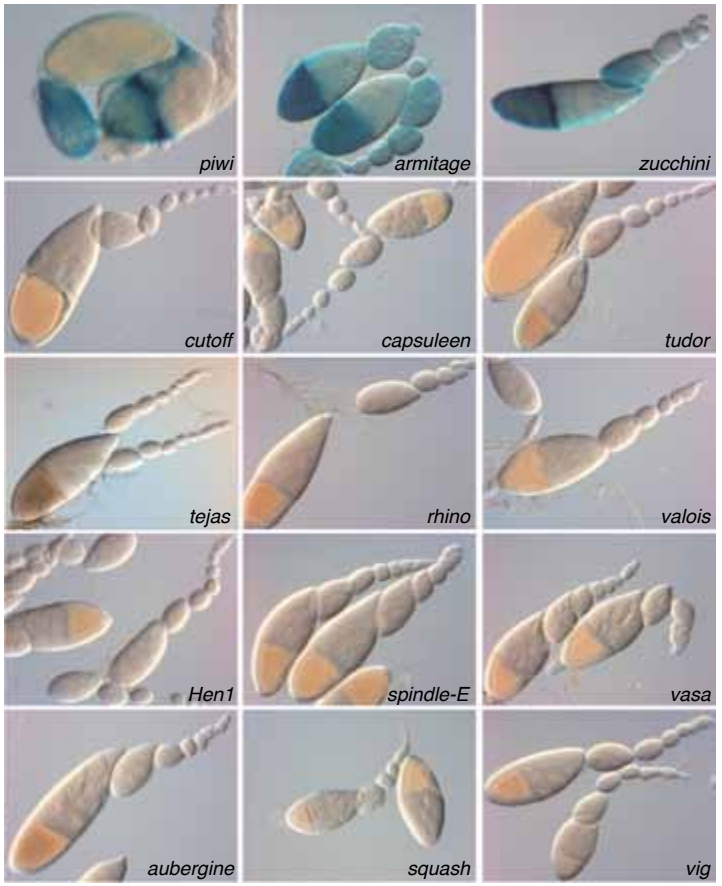


Figure 1: Immunofluorescence analysis of the three Argonaute proteins acting in the piRNA pathway (Aubergine, AGO3, Piwi). Note the developing egg chambers surrounded by the follicular epithelium (DNA in blue, Argonaute proteins in green). Only Piwi is expressed in follicular cells, whereas AGO3 and Aubergine are exclusively found in germline cells.

Figure 2: An *in vivo* RNAi assay identifies Piwi, Armitage and Zucchini as essential components of the somatic piRNA pathway. This figure shows beta-Galactosidase staining of ovarioles, in which the indicated genes were knocked down in somatic follicle cells by RNAi and which express a lacZ sensor for the somatic piRNA pathway (see Olivieri et al. 2010 for details).


cutaff
capsuleen
tejas

JÜRGEN KNOBLICH GROUP

Control of self renewal and asymmetric division in stem cell lineages

www.imba.oeaw.ac.at/research/juergen-knoblich

Stem cells achieve the remarkable task of generating identical copies of themselves while simultaneously giving rise to more lineage-restricted cells that eventually undergo terminal differentiation. How cells can create two daughter cells of such dramatically different properties and how defects in this asymmetry can contribute to tumor formation, are the questions we are trying to resolve.

We are using both the fruitfly *Drosophila melanogaster* and mice to understand mechanisms related to stem cell biology. In the *Drosophila* brain, neural stem cells known as neuroblasts undergo repeated rounds of asymmetric cell division (Figure 1A). While one daughter cell continues to divide in a stem-cell-like manner, the other cell divides only once into two differentiating neurons. What makes the two daughter cells so different and how do the mechanisms we identify in *Drosophila* compare to what is happening in mammalian brains?

Stem Cell Tumors in *Drosophila*

During each neuroblast division, the cell fate determinants Numb, Prospero and Brat segregate into the smaller basal daughter cell where they prevent self-renewal and induce differentiation (Figure 1B). This occurs because the protein kinase aPKC localizes to the opposite apical side and removes the determinants by phosphorylating their membrane localization domains. At the same time, aPKC associates with microtubule binding proteins to ensure that the mitotic spindle is set up in apical-basal orientation. As a result, only the basal daughter cell inherits the determinants.
In the absence of Brat, Numb or Prospero, differentiation is impaired and both daughter cells retain the ability to self-renew. As a consequence, stem cell numbers grow exponentially and the overgrowing stem cells eventually develop into gigantic lethal brain tumors (Figure 1C). Understanding how defects in asymmetric cell division cause the formation of stem-cell-derived tumors is one of the key questions we are currently investigating.

Genome-wide analysis of biological processes

During the last few years, we have performed genome-wide RNAi screens to identify a large number of genes controlling asymmetric cell division and self-renewal in various tissues. For this purpose we use the VDRC RNAi library, a collection of more than twenty thousand transgenic *Drosophila* RNAi lines that can be induced in a tissue-specific manner. We have used the collection to analyze neural stem and progenitor cells in both the central and peripheral nervous systems of the fly. Our screens have assigned loss-of-function phenotypes to more than 20% of all protein coding *Drosophila* genes. As each of our phenotypes is precisely quantified, we can use the results for extensive bioinformatics-based analysis. For instance, we can perform hierarchical clustering to group genes by their potential cellular function and integrate our data with pre-existing protein-protein and genetic interaction data to generate functionally annotated networks for specific biological processes (Figure 2).

As a result, we have discovered 23 new global regulators of the Notch signaling pathway. Computer analysis of the resulting interaction network for the Notch pathway has enabled us to identify nuclear pore and nuclear import complexes as well as the COP9 signalosome as rate-limiting components. For neural stem cells, our analysis has revealed remarkable roles for alternative splicing, chromatin remodeling, and transcriptional elongation in the control of self-renewal. By combining phenotypic data with gene expression analysis, we try to decode the circuits that regulate self-renewal in *Drosophila* neural stem cells. Our goal is to describe how the circuits are reprogrammed when one of the two daughter cells is driven towards terminal differentiation, and to understand how defects in this reprogramming event lead to the formation of a lethal stem-cell-derived brain tumor.

Asymmetric cell division in mouse stem cells

Can we transfer our results from *Drosophila* to mammalian and ultimately to human stem cells as well? To analyze the relevance of our data for mammalian biology, we have focused on the mouse brain. The mouse forebrain develops from a limited number of progenitors, which first expand by symmetric division and then switch to an asymmetric division mode in which they generate one progenitor and one or more differentiating neurons. Many of the genes that control neuroblasts act in this system as well. To characterize the newly identified candidates from our fly screens, we use *in utero* electroporation (Figure 3). This technology, by which DNA constructs are co-introduced with GFP by high voltage electricity, enables us to perform lineage tracing and study gain or loss of function phenotypes in a single experiment. We have identified phenotypes for several mouse homologs that suggest a remarkable conservation of the molecular machinery governing asymmetric cell division. Ultimately, we hope that these experiments will enhance our understanding as to how vertebrate stem cells control proliferation and differentiation and how these processes are deregulated in tumor development.

JÜRGEN KNOBLICH

juergen.knoblich@imba.oeaw.ac.at

Juergen Knoblich did his PhD in the laboratory of Christian Lehner at the Friedrich Miescher Institute of the Max Planck Society in Tübingen. After a postdoctoral period in the laboratory of Yuh Nung Jan at UCSF, San Francisco, he joined the IMP in 1997 as a junior group-leader. In 2004, he moved to IMBA where he is now senior scientist and deputy director. His laboratory uses both Drosophila and mice to study how self renewal is controlled in neural stem cells and how defects in this process can lead to tumor formation.

Publication highlights:

Wirtz-Peitz, F., Nishimura, T., and Knoblich, J.A. (2008). Linking cell cycle to asymmetric division: Aurora-A phosphorylates the Par complex to regulate Numb localization, Cell, 135, 161-173.

Schwamborn, J.C. Berezikov, E., and Knoblich, J.A. (2009). The Brat homolog TRIM32 Prevents Self-renewal in Neural Progenitors by Degrading c-Myc and Activating Micro-RNAs, Cell, 136, 913-925.

Mummery-Widmer, J.L., Yamazaki, M., Stoeger, T., Novatchkova, M., Chen, D., Dietzl, G., Dickson, B.J., and Knoblich, J.A. (2009) Genome-wide analysis of Drosophila external sensory organ development by transgenic RNAi, Nature, 458, 987-992.

SENIOR SCIENTIST & DEPUTY DIRECTOR/SCIENCE:
JÜRGEN KNOBLICH

POSTDOCS:
CHRISTIAN BERGER, RYAN CONDER, NINA CORSINI, CHRISTOPHER ESK, CATARINA HOMEM, MADELINE LANCASTER, MARIA PIA POSTIGLIONE, ILKA REICHARDT, YUNLI XIE, TETSUO YASUGI

PHD STUDENTS:
ELIF EROGLU, ANJA FISCHER, SPYROS GOULAS, HEIKE HARZER, ONUR KAYA, FEDERICO MAURI, MARKO REPIC, CONSTANCE RICHTER, VIVIEN ROLLAND, JONAS STEINMANN

RESEARCH ASSOCIATE / LAB MANAGER:
ELKE KLEINER

RESEARCH ASSISTANT:
ANGELA MARIA PEER

SCIENTIFIC PROGRAMMER:
PEDRO SERRANO-DROZDOWSKYJ

Figure 1

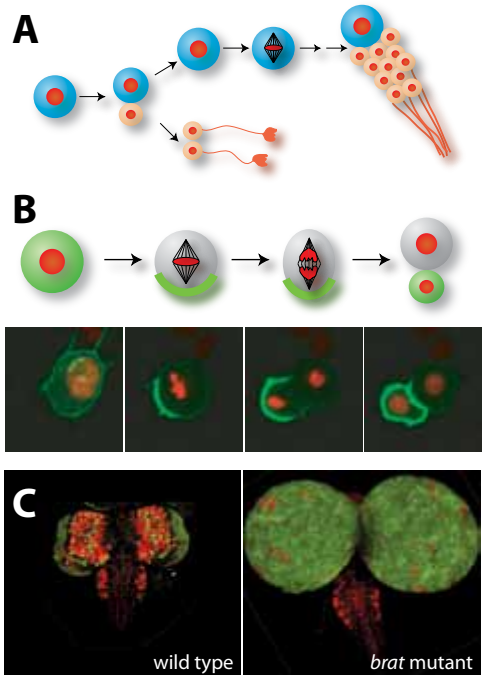


Figure 2

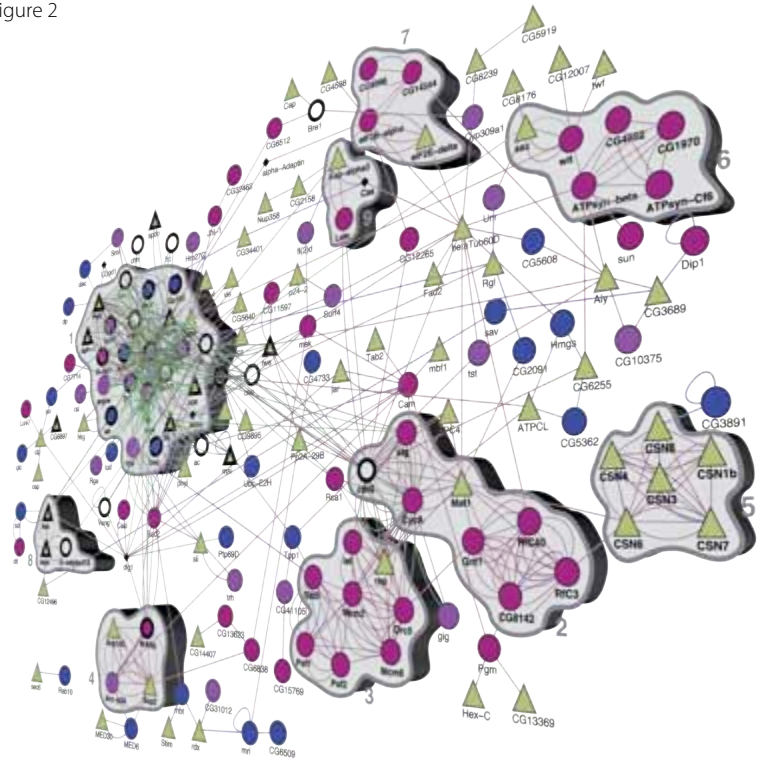


Figure 3

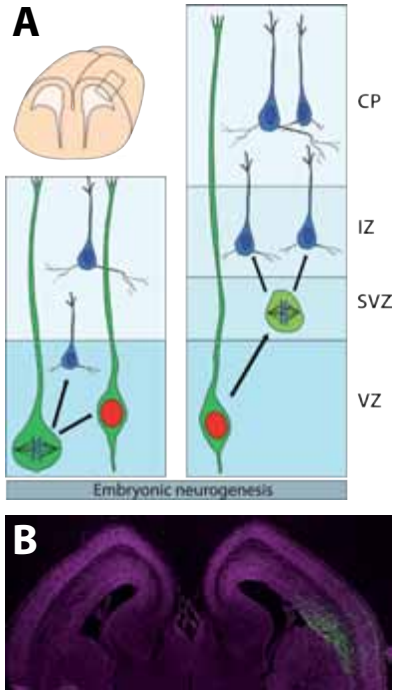


Figure 1: How cells divide asymmetrically. A. Drosophila neuroblasts divide asymmetrically in a stem cell-like fashion.crescent **B**. During each neuroblast division, Brat, Prospero and Numb (green) are inherited by only one of the two daughter cells. A schematic view of the process is shown at the top. The lower half shows stills from a time-lapse movie of Histone-RFP (red, to visualize chromatin) and Pon-GFP (green, to visualize the Numb protein). C. Larval brain from a wild-type (left) and *brat* mutant animal. Neuroblasts are green, and differentiating neurons red. Brat brains show a dramatic over-proliferation of neuroblasts.

Figure 2: Genome-wide analysis of biological processes in a whole organism. Functionally validated interaction network of the Notch signaling pathway assembled from genome-wide analysis of the development of external sensory organs in Drosophila. The network shows genes that cause phenotypes in external sensory organs and have previously been shown to interact biochemically or genetically. The encircled groups are protein complexes identified by a clustering algorithm.

Figure 3: Progenitor cell proliferation in the mouse brain. a. Neurons in the mammalian brain (blue) arise from progenitor cells (green, nucleus in red) in the ventricular zone (VZ). Progenitors either generate one neuron and one progenitor (left side) or one progenitor and one basal progenitor (light green) which resides in the subventricular zone (SVZ). IZ: intermediate zone, CP: cortical plate. **b**. Cross-section through the developing mouse neocortex (DNA in magenta). GFP (green) was introduced by in utero electroporation specifically into dividing progenitor cells. For this, DNA was injected into the lateral ventricles and electroporated using a short pulse of high voltage electricity applied to the living mouse brain. *In utero* electroporation allows us to monitor progenitor lineages while simultaneously knocking down or overexpressing interesting genes.


CSN6
CSN2
RIC3
CG8142
CG13369

THOMAS MARLOVITS GROUP

Molecular Machines

www.imba.oeaw.ac.at/research/thomas-marlovits

Membrane-associated processes are a fundamental characteristic of all living cells. They ensure that the cells are able to effectively communicate with, and adapt to, their environment. The cells achieve this by either physically translocating molecules to the opposite site of a membrane or by receiving, transmitting, and amplifying incoming signals. Our laboratory is interested in understanding the molecular mechanism underlying such processes. Specifically, we focus on machineries capable of translocating bacterial toxins into eukaryotic cells.

Microbial Pathogenesis

One of the most exciting discoveries in the last few years is that supramolecular assemblies are one of the key elements involved in the infection of eukaryotic cells by bacterial pathogens. These systems give rise to intimate contact between cells, deliver specific toxins - which are collectively known as effectors proteins - into host cells, and possess the remarkable ability to modulate diverse regulatory networks. In particular, many Gram-negative pathogens such as *Salmonella*, *Yersinia*, *Pseudomonas*, or *Shigella* utilize the type III secretion system (TTSS) to initiate infection in eukaryotic cells. TTSS is a multicomponent system comprising more than 20 different proteins. A mere fraction of these assemble into the so-called needle complex, which is the most prominent core structure of the system. It is a membrane-associated complex with > 3.5 MDa, and is composed of a set of soluble and membrane proteins. Although it is essential for microbial infection in many animal as well as plant pathogens, the assembly of the needle complex and how the needle complex identifies and triggers efficient translocation of substrates are still poorly understood. Using *Salmonella typhiumurium*, we are investigating the molecular mechanisms and structural framework required to translocate effector proteins specifically and safely into eukaryotic cells.

Recent crystallographic analyses of individually separate domains, which are predicted to be located within the plasma, revealed a common structural motif organized in repeating modules. Attempts have been made to "dock" these protein domains into the needle complex structure, which resulted in several mutually incompatible locations. We have used a combination of methods including bacterial genetics, biochemistry, mass spectrometry and cryo electron microscopy/single particle analysis to experimentally determine the position of specific protein domains within the needle complex. In addition, we have identified specific sites of interaction among components of the needle complex, which are critical for stable assembly and the subsequent functional complex. Jointly, this analysis provides the first experimentally validated topographic map of different components of the needle complex of the *S. typhimurium* TTSS (Figures 1 and 2) (Schraidt et al., 2010)

Our topological analysis revealed that additional proteins must be present. These constitute the cup/socket structure which is located in the center of the needle complex (export apparatus). Using mass spectrometry, we were able to identify five additional candidate proteins that co-fractionate in marginal quantities with purified needle complexes. Subsequent structural analysis revealed the absence of the cup/socket, suggesting that one or more of these proteins is required to build up the cup/socket (Figure 3A). We were also able to show that these proteins nucleate the coordinated assembly of the needle complex (Wagner et al., 2010)

Efficient effector protein translocation is known to occur only after host cell contact. Therefore, it is conceivable that the extracellular filament is a key player in the transmission of this information, probably due to small conformational changes throughout the filament. This hypothesis is supported by mutations found in the homologous *Shigella* needle filament, which convert the system into a constitutively "on" state. If this is true, it would be justifiable to presume that the filament is provided with a certain degree of structural heterogeneity in order to accommodate the required conformational plasticity for signal transmission. Therefore, we analyzed the structure of the needle filament by cryo electron microscopy (Figure 3B) and discovered that the structure is, indeed, highly variable (Galkin et al., 2010).

Although the design of the TTSS appears to be conceptually simple, many questions remain unanswered: How dynamic is the entire assembly process? How are substrates recognized by the needle complex? What is the molecular mechanism of protein translocation? We have begun to address some of these questions. By understanding the molecular mechanism of TTSS-mediated protein transport, we hope to provide a basis for the development of novel therapeutic strategies that will either inhibit its activity or modify the system for targeted drug delivery.

THOMAS MARLOVITS

thomas.marlovits@imba.oeaw.ac.at

Thomas is intrigued by the architecture of macromolecules and wants to understand how they perform fundamental biological processes. He obtained a PhD in biochemistry from the University of Vienna, did his postdoctoral studies at the Max-Planck-Institute of Biophysics (Germany) and Yale University (USA). In 2005 he started his independent research group as a joint IMP/IMBA group leader and opened the first cryo electron microscopy laboratory in Austria.

Publication highlights:

Schraidt, O., Lefebre, MD., Brunner, MJ., Schmied, WH., Schmidt, A., Radics, J., Mechtler, K., Galán, JE., Marlovits, TC. (2010). Topology and organization of the Salmonella typhimurium type III secretion needle complex components. PLoS Pathog. 6(4):e1000824

Marlovits TC, Kubori T, Lara-Tejero M, Thomas D, Unger VM, Galán JE. (2006) Assembly of the inner rod determines needle length in the type III secretion injectisome. Nature. 441:637-40.

Marlovits TC, Kubori T, Sukhan A, Thomas DR, Galán JE, Unger VM. (2004) Structural insights into the assembly of the type III secretion needle complex. Science. 306:1040-2.

JOINT IMP/IMBA GROUP LEADER:
THOMAS C MARLOVITS

PHD STUDENTS:
MATTHIAS BRUNNER, AGATA KOSAREWICZ, LISA KÖNIGSMAIER, JULIA RADICS, JESUS FERNANDEZ RODRIGUEZ, OLIVER SCHRAIDT

DIPLOMA STUDENTS:
JOANNA RADEK, WOLFGANG SCHMIED

SUMMER STUDENT:
KIMBERLY MCMANUS (MIT - BOSTON, USA)

LAB MANAGER / RESEARCH ASSISTANT:
WOLFGANG WEBER

Figure 1

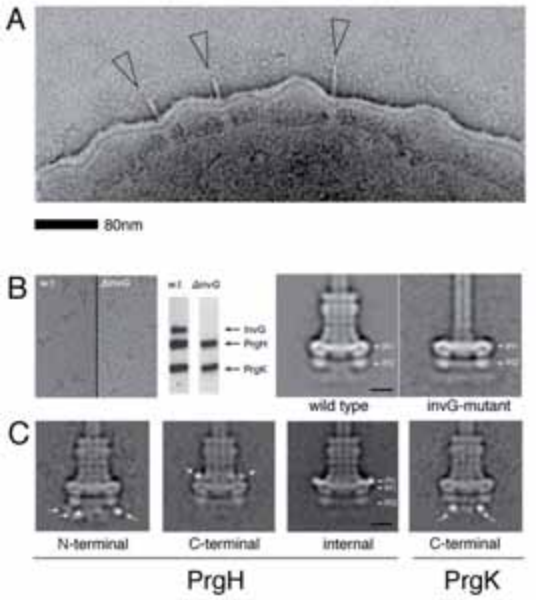


Figure 2

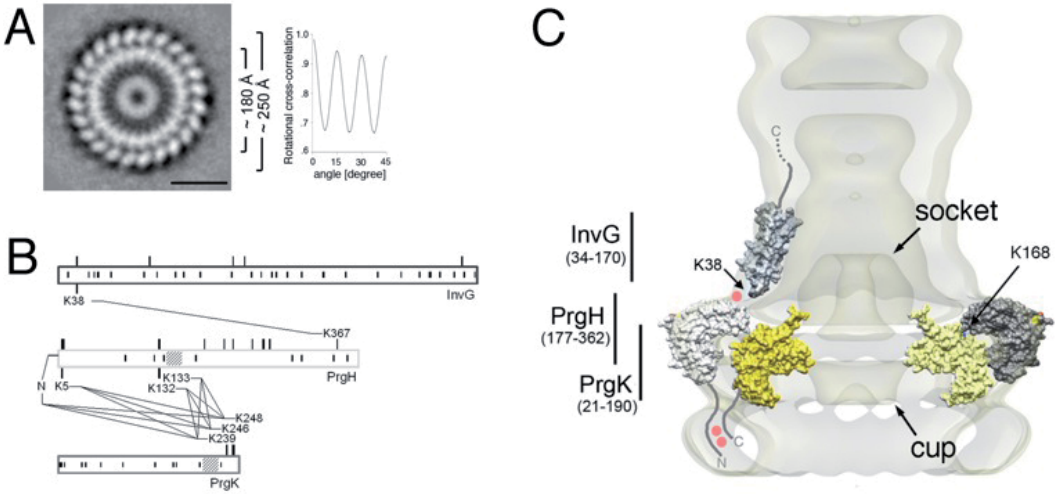


Figure 3

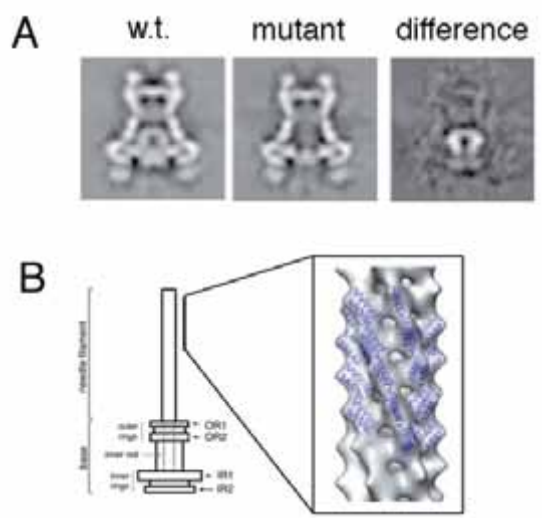
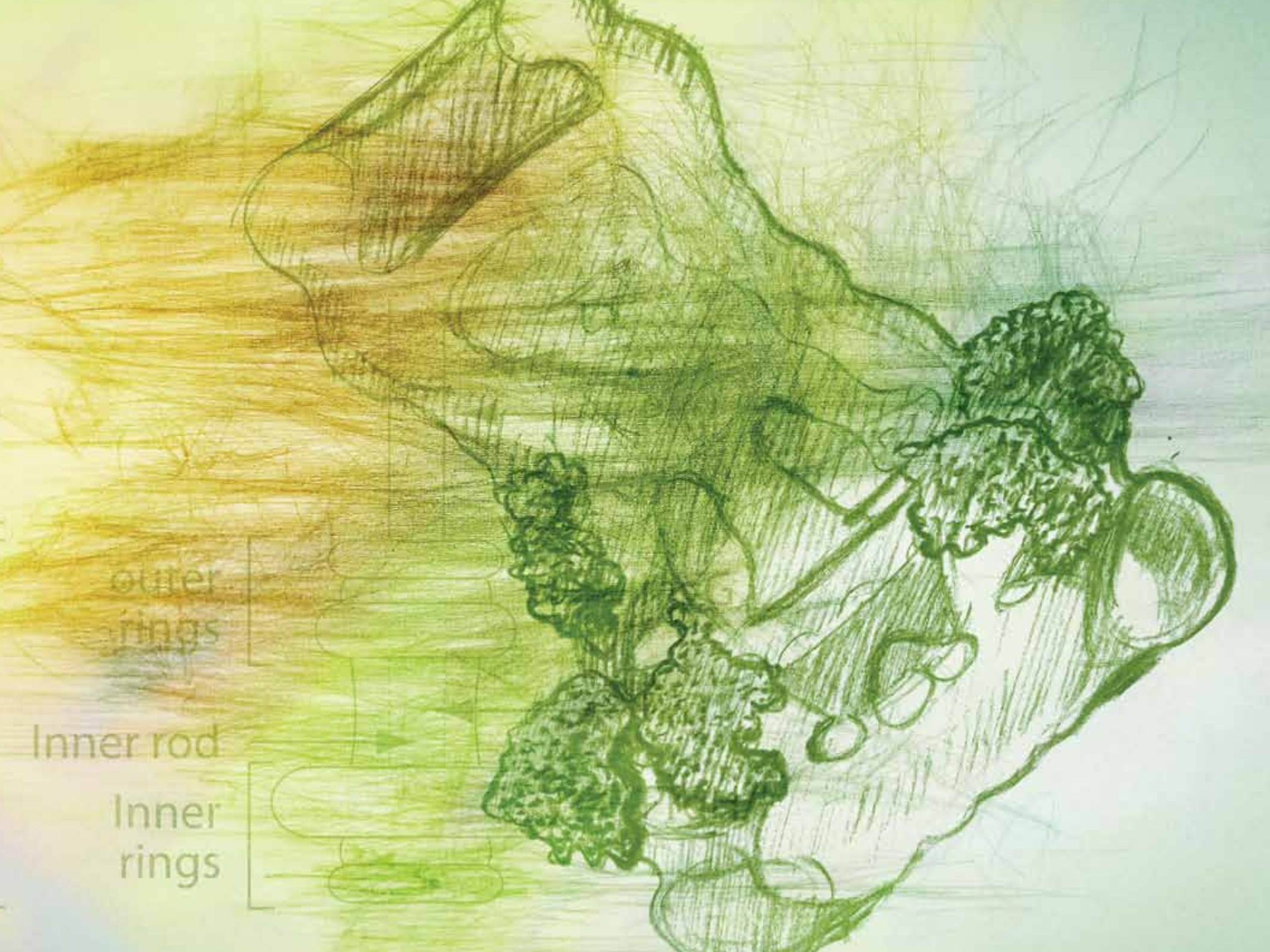


Figure 1: The needle complex is the core structure of the type III secretion system. (A) Needle-like structures (approx. 50 nm) that extend into the extracellular environment are visible on the surface of osmotically shocked S. typhimurium. (B) Isolated complexes from wild-type and a invG mutant strain are structurally different. (C) Isolated needle complexes harboring poly-histidine tags at various positions in PrgH or PrgK can be specifically labeled using nanogold.

Figure 2: Organization of PrgH, PrgK and InvG within the needle complex (A) End view class average derived from single particle analysis from negatively stained electron microscopy images of sub-structures of the inner rings. The sub-structures were obtained by selective disassembly of needle complexes isolated from a mutant strain encoding for a C-terminally, four amino acid truncated PrgH. Rotational cross-correlation analysis revealed that the maximum of the cross-correlation peak is repeatedly obtained every 15°, demonstrating that the larger concentric rings of the inner ring structure exhibit 24-fold symmetry. (B) Proximity of specific domains of the base proteins, InvG, PrgH, and PrgK within the needle complex. The block diagrams shows the three major base proteins, InvG, PrgH, and PrgK, and covalent cross-links of peptides obtained from chemically derivatized needle complexes at primary amino groups. (C) Topographic model of the needle complex: Localization of domains of InvG, PrgH, and PrgH within the base of the needle complex. The N-terminal domain of InvG (blue-grey) reaches far down into the neck region and is in close contact with the C-terminal domain of PrgH (white and grey). Sites of interaction found by cross-linking and mass spectrometry are labeled as red dots. The N-terminal domain of PrgH is pointing to the cytoplasmic side of the complex, and interacts with the C-terminal domain of PrgK. For both, no high-resolution structure is available as of now. The N-terminal domain of PrgK is located within the complex and is therefore packed into its position by PrgH from the side and InvG from the top.

Figure 3: Sub-structures of the needle complex. (A) Structural analysis of complexes from strains lacking the export apparatus proteins (SpaSPQR, InvA) reveal marked differences in the central portion of the complex (socket/cup) compared to the wild type. (B) The needle filament protein PrgI is the building block of the extracellular needle filament.


outer rings
Inner rod
Inner rings

JAVIER MARTINEZ GROUP

Novel enzymes and mechanisms to process RNA molecules

www.imba.oeaw.ac.at/research/javier-martinez

Short interfering RNAs, or siRNAs, became stellar players in modern biology by allowing loss of function experiments in mammalian cells. Our laboratory has rather adopted siRNAs as stable, surrogate substrates to identify so far elusive enzymes that phosphorylate and ligate RNA molecules in mammalian cells. This innovative approach has been successful: We have identified Clp1 as the first human 5'-RNA kinase and also revealed and characterized Nol9, a Clp1 homologue involved in ribosomal RNA processing. Using 3' phosphorylated siRNAs and monitoring inter-strand ligation we have recently purified the long sought human tRNA-ligase. In addition, we continue our search for the elusive activity that ligates the Xbp1-mRNA during the Unfolded Protein Response.

Nol9, a novel polynucleotide 5'- kinase in the nucleolus of human cells:

An enormous amount of energy is channeled into the biogenesis of ribosomal RNAs (rRNAs). In a multistep process, mature rRNAs are generated from a long polycistronic precursor. Recent advances in large scale mass spectrometry and high throughput screens revealed a plethora of ribosomal and non-ribosomal proteins to be involved in rRNA processing, yet detailed studies on their individual roles are missing and important enzymatic activities remain elusive.
Our laboratory previously identified Clp1, an RNA 5'-kinase that phosphorylates tRNA exons and siRNAs *in vitro*. Bioinformatics analysis revealed a family of proteins closely related to Clp1, the "Grc3/Nol9 family", that contains Walker A and Walker B motifs, both implicated in ATP/GTP binding. Interestingly, human Nol9 was previously detected in proteomic analyses of the nucleolus. Temperature sensitive mutants of Grc3, the yeast homolog of Nol9, showed an rRNA processing defect in a global screen for non-coding RNA processing, however the role of Grc3 has so far not been clarified.

We have discovered that the non-ribosomal protein Nol9 is a polynucleotide 5'-kinase that sediments primarily with the pre-60S ribosomal particles in HeLa nuclear extracts. Depletion of Nol9 imposes a severe block in the processing of the 32S precursor (Figure 1A) and consequently affects ribosome biogenesis (Figure 1B). The polynucleotide kinase activity of Nol9 is particularly required for efficient generation of the 5.8S and 28S rRNAs from the 32S precursor. Upon Nol9 knock down, we also observe a specific maturation defect at the 5' end of the predominant 5.8S short form rRNA (5.8SS), possibly due to the Nol9 requirement for 5'>3' exonucleolytic trimming. In contrast, the endonuclease-dependent generation of the 5'-extended, minor 5.8S long form rRNA (5.8SL) is largely unaffected. In Figure 2 we outline a model for the function of Nol9 in rRNA processing.

In the future we plan to identify RNA substrates and interacting proteins, potentially the still missing rRNA endonucleases that process ribosomal RNA precursors. Together with Toshikatsu Hanada (Josef Penninger's Laboratory) we are generating a Nol9 conditional knockout mouse. Preliminary experiments deleting Nol9 in mouse embryonic fibroblasts recapitulate the Nol9-RNAi phenotype observed in HeLa cells.

JAVIER MARTINEZ

javier.martinez@imba.oeaw.ac.at

Javier Martinez obtained his PhD from the University of Buenos Aires, Argentina. Javier joined the RNA silencing field as a Post-Doctoral Fellow in the laboratory of Thomas Tuschl, revealing the protein and RNA composition of the RNA-induced silencing complex, or RISC. As a Junior Group Leader at IMBA, Javier explored the assembly of RISC and how secondary structures in target RNAs modulate its cleavage activity. The finding of the human RNA-kinase hClp1 opened a new direction in his laboratory, towards aspects of RNA metabolism, including tRNA splicing, ribosomal RNA processing, mRNA 3' end formation and mRNA splicing during the Unfolded Protein Response. Since 2006, Javier organizes the "Microsymposium on small RNAs", a free-attendance meeting fully sponsored by companies and scientific societies with a strong focus on young group leaders.

Publication highlights:

Katrin Heindl and Javier Martinez. Nol9 is a novel polynucleotide 5'-kinase involved in ribosomal RNA processing. EMBO Journal, Epub 2010 Nov 9

Priscilla Braglia, Katrin Heindl, Alexander Schleiffer, Javier Martinez† and Nick J. Proudfoot†. Role of the RNA/DNA kinase Grc3 in transcription termination by RNA polymerase I. EMBO Reports, 2010 Oct;11(10):758-64. Epub 2010 Sep 3. ; †co-corresponding authors.

GROUP LEADER:
JAVIER MARTINEZ

POSTDOCS:
CHRISTOPH GEBESHUBER, ANNE NIELSEN, STEFAN WEITZER

PHD-STUDENTS:
SABRINA BANDINI, KATRIN HEINDL, JOHANNES POPOW, ARIELA REISS

RESEARCH ASSISTANT:
JUTTA DAMMANN

RESEARCH TECHNICAN:
BARBARA MAIR

Figure 1

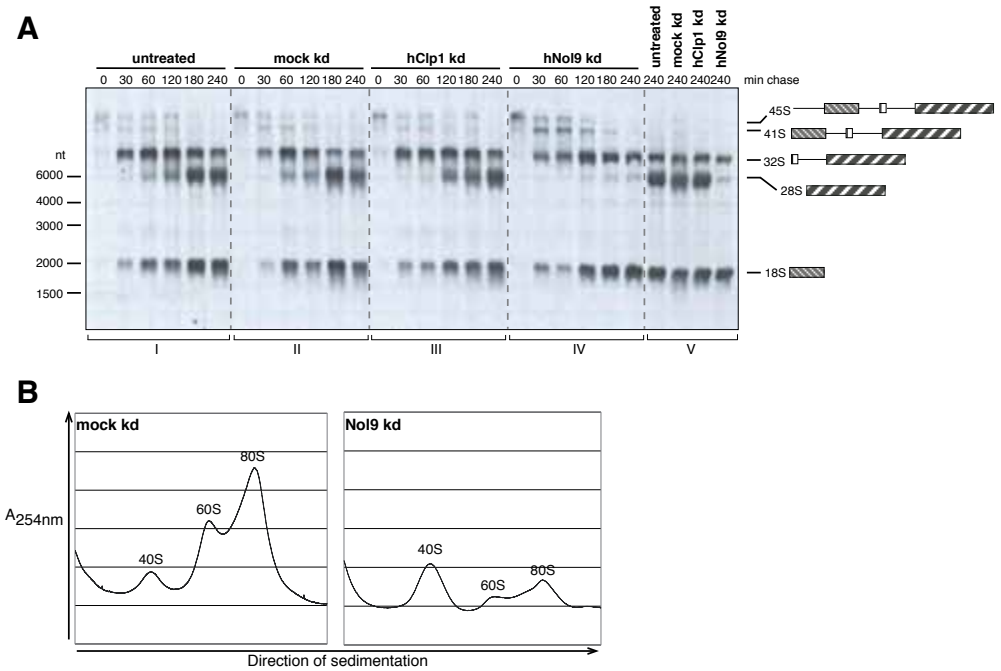


Figure 2

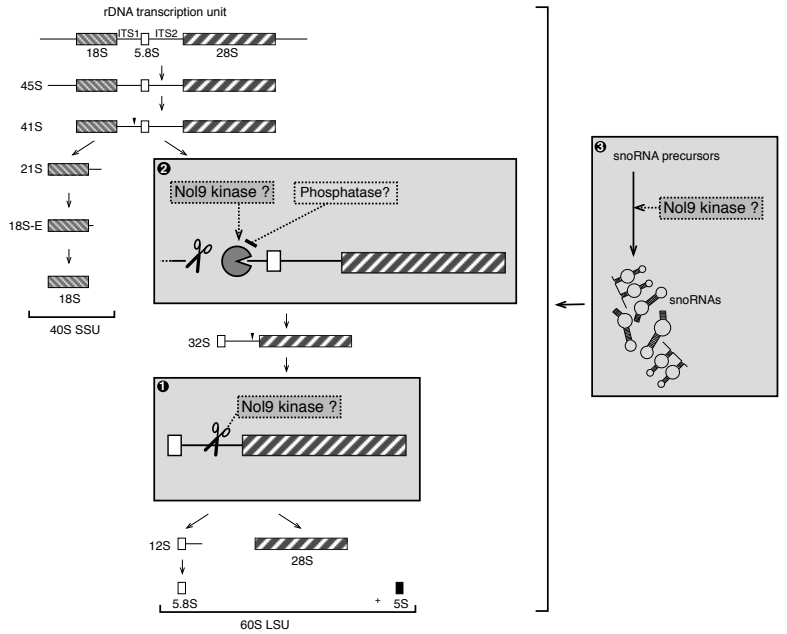


Figure 1: Depletion of Nol9 impairs ribosomal RNA processing and leads to a severe decrease in 60S and 80S ribosomes. (**A**) Metabolic labeling of untreated (panel I) or mock transfected HeLa cells (panel II), or HeLa cells transfected with siRNAs targeting Clp1 (panel III) or Nol9 (panel IV). Cells were starved in methionine-free medium followed by addition of ^{3}H-methyl-methionine and chased in non-radioactive medium for the indicated time periods. Panel V is shown to compare all four backgrounds after chasing for 240 min. (**B**) Ribosome profiles were obtained from HeLa cells transfected with a mock control or siRNAs against Nol9. Cytoplasmic extracts were separated on a 10-45% sucrose density gradient. UV absorption along the gradient was measured.

Figure 2: Possible roles of the polynucleotide kinase Nol9 in rRNA processing. (1) Nol9 might act directly on the endonuclease cleaving within ITS2. (2) Nol9 together with an elusive phosphatase activity might regulate 50 end formation of 32S RNA by an exonuclease. (3) Nol9 might be required for snoRNA processing. Scissors indicate endonucleolytic cleavage sites, the 'pacman' represents the exonuclease. RNAs are depicted in 50430 orientation.


in vivo
in vitro
in situ
in silico
MICROSYMPOSIUM on
SMALL RNAs

KAZUFUMI MOCHIZUKI GROUP

Programmed DNA elimination in Tetrahymena

www.imba.oeaw.ac.at/research/kazufumi-mochizuki

The onion's genome is 12 times larger than the human one. Does this mean onions are more complicated and more intelligent than we are? Perhaps yes, but this presumably means onions possess more "junk" DNA than do humans. If some DNA are useless, why do onions not dispense with them? The underlying raison d'être is still controversially discussed. Several creatures actually do throw away such DNA during their development. By studying a DNA elimination event, we are trying to determine how our cells regulate junk DNA and how junk DNA regulates our genomes.

Evolutionary link between DNA elimination, heterochromatin formation, RNA interference and transposon silencing

Junk DNA contains numerous transposable elements that are able to move from one genome position to another and are therefore potentially harmful to the integrity of genomes. On the other hand, many junk DNAs are not really junk but perform important functions by way of proper chromosome segregation, recombination, and gene expression. Several organisms dispense with junk DNAs during the development of their somatic lineage. This developmentally programmed DNA elimination event presumably reflects two aspects of junk DNA: its harmfulness by the actions of transposons, and its usefulness in maintaining genome integrity in the germline lineage. The ciliated protozoan *Tetrahymena* (Figure 1) possesses a somatic macronucleus (Mac) and a germline micronucleus (Mic) in each cell. Mac is polyploid and transcriptionally active, whereas Mic is diploid and transcriptionally inert during vegetative growth. In the sexual process of conjugation, Mic gives rise to a new Mac and a Mic, and the parental Mac is destroyed. During the development of the new Mac, ~6000 Internal Eliminated Sequences (IESs) are removed (DNA elimination), and the remaining Mac-destined sequences are re-ligated. Most IESs are moderately repeated in the Mic and many of them are related to transposable elements (Figure 1). Heterochromatin formation is involved in the IES elimination process (Figure 2). In *Tetrahymena*, heterochromatin components, including histone H3 methylated on lysine 9 (H3K9me) and on lysine 27 (H3K27me), and the chromodomain protein Pdd1p are specifically associated with eliminated IES sequences and are essential for DNA elimination. A mechanism related to RNA interference (RNAi) is also essential for DNA elimination (Figure 2). Small (~28-29 nt) RNAs are produced by the Dicer protein Dcl1p and associate with the Argonaute protein Twi1p. Dcl1p and Twi1p are required for accumulation and/or targeting of H3K9me/H3K27me/Pdd1p as well as for DNA elimination. Thus, heterochromatin formation occurs downstream of the RNAi-related mechanism in the DNA elimination pathway. As recent studies in animals and plants have shown that transposable elements are silenced by a heterochromatin and/or RNAi-related mechanism, transposon silencing by RNAi-directed formation of heterochromatin has probably arisen in an ancestral eukaryote. Therefore, further study of the programmed DNA elimination process in *Tetrahymena* should yield basic and important data about transposon silencing by RNAi-directed formation of heterochromatin in eukaryotes.

Molecular scissors for DNA elimination

In contrast to the evolutionary conservation of RNAi-directed formation of heterochromatin in transposon silencing, the DNA excision process is unique in some limited eukaryotic lineages; including ciliates. It has long been thought that a transposase-like endonuclease activity is involved in DNA elimination while the enzyme responsible for this activity had remained unknown. We recently identified a PiggyBac transposase-like enzyme (Tpb2p) which is essential for DNA elimination in vivo. Because recombinantly expressed Tpb2p can produce double-strand breaks in vitro (Figure 3), we believe Tpb2p is the enzyme catalyzing DNA elimination. This discovery enables us to analyze how heterochromatin serves as a binding platform to recruit the DNA excision machinery, how specificity of the boundary of DNA elimination is determined, and how DNA elimination is linked to the subsequent DNA repair process. *TPB2* appears to have gone through a domestication process to become a host gene and be maintained in the macronucleus. Although several domesticated transposon-derived proteins are known to be involved in host genome regulation in other eukaryotes, their evolutionary histories are not clear. Studies of Tpb2p may show how a transposon can be domesticated to regulate a eukaryotic genome.

KAZUFUMI MOCHIZUKI

kazufumi.mochizuki@imba.oeaw.ac.at

Kazufumi Mochizuki obtained his Ph.D. from the Graduate University for Advanced Studies (Hayama, Japan) in 2000. He joined Professoer Martin A. Gorovsky laboratory at the University of Rochester as a post-doctroal research fellow in 2001. From 2006, he is a junior group leader in IMBA. His research interests are in the regulation of chromatin structure by non-coding RNAs.

Publication highlights:

Noto, T., Kurth, H.M., Kataoka, K. Aronica, L., Desouza, L.V., Siu, K.W., Pearlman, R.E., Gorovsky, M.A., and Mochizuki, K. (2010) The Tetrahymena Argonaute-binding protein Giw1p directs a mature Argonaute-siRNA complex to the nucleus. Cell,140, 692-703

Aronica, L., Bednenko, J., Noto, T., Desouza, L.V., Siu, K.W., Loidl, J., Pearlman, R.E., Gorovsky, M.A., and Mochizuki, K. (2008) Study of an RNA helicase implicates small RNA-noncoding RNA interactions in programmed DNA elimination in Tetrahymena. Genes Dev. 22, 2228-2241.

Mochizuki, K., Fine, N. A., Fujisawa, T., and Gorovsky, M. A. (2002) Analysis of a piwi-related gene implicates small RNAs in genome rearrangement in Tetrahymena. Cell 110, 689-699..

GROUP LEADER:
KAZUFUMI MOCHIZUIKI

POSTDOCS:
KENSUKE KATAOKA, HENRIETTE KURTH

PHD STUDENTS:
LUCIA ARONICA[1], URSULA SCHÖBERL, ALEXANDER VOGT, SOPHIE WÖHRER

TECHNICAL ASSISTANTS:
CLARA JANA LUI BUSCH[2], TOMOKO NOTO.

[1] UNTIL FEBRUARY
[2] UNTIL MARCH

Figure 1

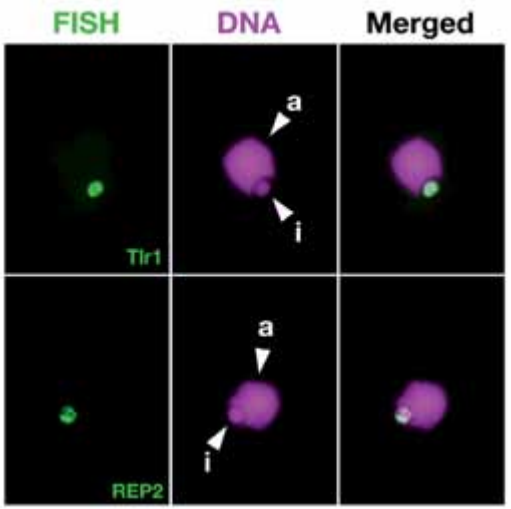


Figure 1: Transposons are eliminated from the macronucleus The unicellular eukaryote *Tetrahymena thermophila* has two different nuclei (stained purple): a small micronucleus (i) and a larger macronucleus (a). Two types of transposable elements, namely *Tlr1* (top) and REP2 (bottom), are found only in the micronucleus by fluorescent in situ hybridization (FISH, green).

Figure 2

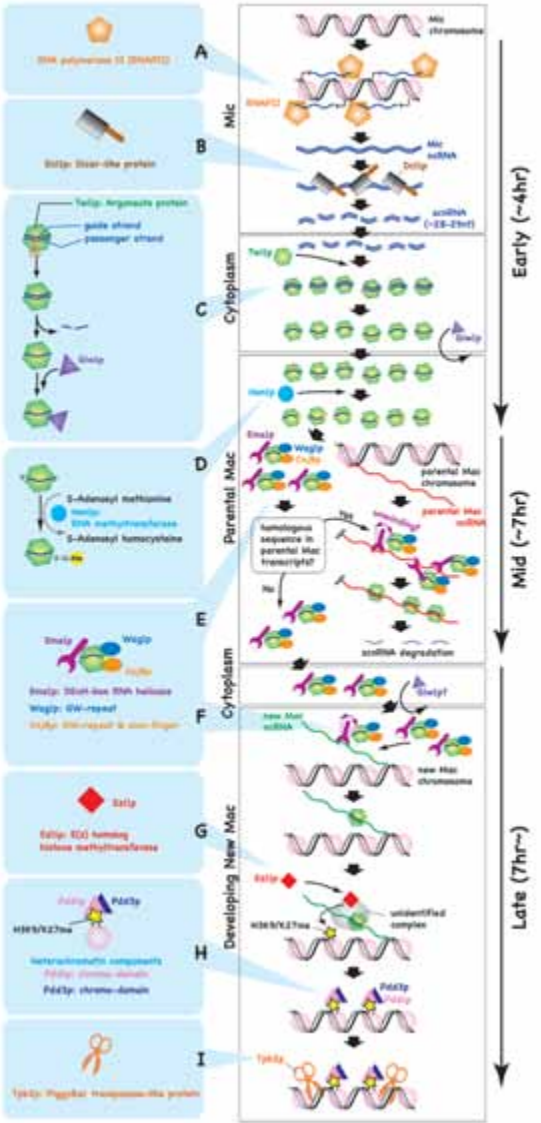


Figure 2: A model for RNA-directed DNA rearrangement in Tetrahymena (A) Promiscuous bi-directional transcription of the micronuclear (Mic) genome by RNA polymerase II produces long double-stranded non-coding (nc) RNA. (B) The Dicer-like protein Dcl1p processes the ncRNA to short (~28-29nt) RNAs, named scnRNAs, in Mic. (C) scnRNA forms a complex with the Argonaute protein Twi1p. The endoribonuclease (Slicer) activity of Twi1p cuts and removes one of two strands of scnRNA. Giw1p then transports Twi1p to the parental macronucleus (Mac). (D) The RNA methyltransferase Hen1p 2′-O-methylates scnRNA and this modification stabilizes scnRNA. (E, F) The RNA helicase Ema1p facilitates interaction between the Twi1p-scnRNA complex and nascent Mac ncRNA. This interaction induces scnRNA degradation in the parental Mac and recruits the histone methyltransferase Ezl1p in the new Mac. (G) Ezl1p catalyzes methylations of histone H3 at lys9 and lys27. (H) The chromodomain proteins Pdd1p and Pdd3p bind to the methylated histone H3 and establish heterochromatin structure. (I) The Piggybac transposase-like protein Tpb2p, which possesses endonucleotidase activity and is required for DNA elimination, is most likely involved in the final DNA excision process.

Figure 3

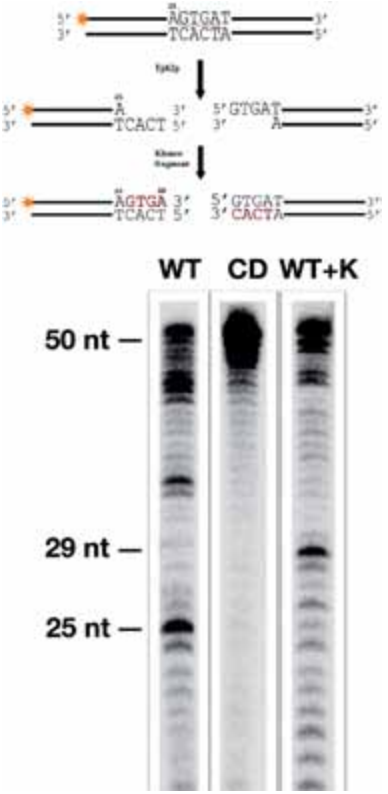
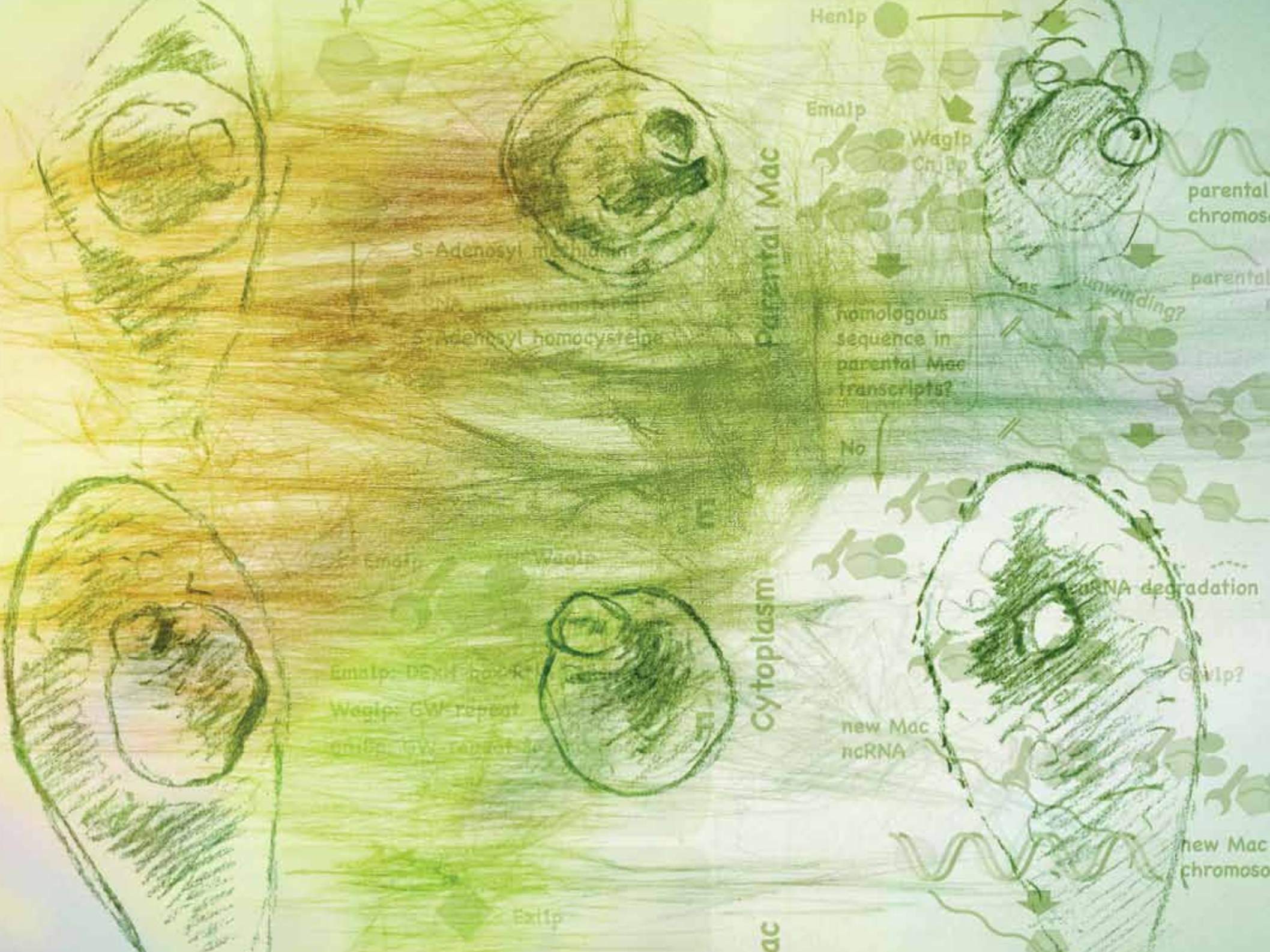


Figure 3: A piggy-Bac transposase-like protein, Tpb2p, cleaves the R-element recognition motif Wild-type (WT) and a catalytically dead mutant (CD) Tpb2p were expressed in *Escherichia coli* and incubated with 50 bp DNA substrates which had AGTGAT sequence identified at a boundary of an IES at their 25th position. An aliquot of the product from wild-type Tpb2p was also treated with Klenow fragment (WT+K).


Parental Mac
Cytoplasm
Hen1p
Ema1p
Wag1p
Cnj1p
parental
chromoso
S-Adenosyl
S-Adenosyl homocysteine
homologous
sequence in
parental Mac
transcripts?
Yes
unwinding?
No
ncRNA degradation
new Mac
ncRNA
new Mac
chromoso
Exi1p

JOSEF PENNINGER GROUP

Genetic dissection of disease mechanisms

www.imba.oeaw.ac.at/research/josef-penninger

A plethora of genes have been correlated with human diseases. Genetic animal models proved to be extremely valuable in elucidating the essential functions of genes in normal physiology as well as the pathogenesis of disease. Using gene-targeted mice, my group attempts to model human disease and genetically dissect disease mechanisms.

Drosophila whole-genome screen reveals Hedgehog signaling as a key regulator of the fate of brown/white adipose cells

Over 1 billion people are estimated to be overweight, thus being at risk for diabetes, cardiovascular disease and cancer. We performed a systems-level genetic dissection of obesity regulation using genome-wide RNAi screening in adult *Drosophila*. Candidate obesity genes were classified functionally, using muscle-, oenocyte-, fat body- and neuron-specific drivers. Of the several known and novel candidate genes revealed by these investigations, hedgehog signaling scored as the most prominent fat-body-specific obesity pathway. To translate these findings into mammals, we generated adipose-tissue-specific Sufu mutant mice to specifically activate the hedgehog pathway in adipose tissue. Interestingly, these aP2-SufuKO mice displayed near total loss of white, but not brown, adipose tissue compartments (Figure 1). Mechanistically, activation of hedgehog signaling blocked differentiation of white adipocytes incompletely and irreversibly through direct dysregulation of early adipogenic factors. These investigations disclosed a novel role for hedgehog signaling in white/brown adipocyte determination, and link in vivo RNAi-based scanning of the Drosophila genome to regulation of adipocyte cell fate in mammals (Pospisilik et al. Cell, 2010).

A global *in vivo Drosophila* RNAi screen identifies NOT3 as a conserved regulator of heart function

Heart disease is the most common cause of morbidity and death in humans. Using heart-specific RNAi silencing in *Drosophila*, we knocked-down 7061 evolutionary conserved genes under conditions of stress. This enabled us to develop a first global road map of pathways that might play conserved roles in the cardiovascular system. One critical pathway we identified was the CCR4-Not complex implicated in transcriptional and post-transcriptional regulatory mechanisms. Silencing of CCR4-Not components in adult *Drosophila* resulted in myofibrillar disarray and dilated cardiomyopathy. Heterozygous *not3* knockout mice showed spontaneous impairment of cardiac contractility and greater susceptibility to heart failure. These heart defects were reversed via inhibition of HDACs, suggesting a mechanistic link to epigenetic chromatin remodeling. In humans, we showed that a common *NOT3* SNP correlates with altered cardiac QT intervals, which is a known cause of lethal arrhythmias (Figure 2). Thus, functional genome-wide screens in *Drosophila* can identify candidates that directly translate into conserved mammalian genes involved in cardiac function (Neely et al. Cell 2010).

Osteoclast differentiation factors RANKL/RANK control the development of progestin-driven mammary cancer

Breast cancer is one of the most common cancers in humans and is anticipated to affect one of every eight women in the US and Europe. The Women's Health Initiative (WHI) and the Million Women Study have shown that hormone replacement therapy (HRT) is associated with an increased risk of incident and fatal breast cancer. In particular, synthetic progesterone derivatives (progestins) such as medroxyprogesterone acetate (MPA), used by millions of women as HRT and in contraceptives, markedly increase the risk of developing breast cancer. Receptor Activator of NF-κB Ligand (RANKL, also known as ODF, TRANCE, OPGL, TNFSF11) and its receptor RANK (TRANCE-R, TNFRSF11A) are essential for the development and activation of osteoclasts. Our group has also reported that RANKL/RANK controls lymph node organogenesis (Kong et al., Nature), central thermoregulation (Hanada et al., Nature), and the formation of a lactating mammary gland during pregnancy (Fata et al., Cell). Both RANKL and RANK expression have been observed in primary breast cancers in humans and breast cancer cell lines. We and others have proposed that the RANKL/RANK system may regulate bone metastases of epithelial tumors (Jones et al., Nature). Given the facts that the inhibition of RANKL is now approved for potentially millions of patients to prevent bone loss, the genetically defined role of RANKL/RANK in mammary epithelial proliferation in pregnancy, and the regulation of the RANKL/RANK system by sex hormones, we speculated that RANKL/RANK might play a role in the development of primary hormone-driven mammary cancer.

We have now been able to show that *in vivo* administration of MPA triggers massive induction of RANKL in epithelial cells of the mammary gland. Genetic inactivation of the RANKL receptor RANK in mammary gland epithelial cells ($RANK^{\Delta mam}$) prevents MPA-induced epithelial proliferation, impairs expansion of the $CD49f^{hi}$ stem cell-enriched population, and protects these cells to apoptosis induced by damage to DNA. Importantly, RANK deletion in the mammary epithelium markedly reduces the occurrence of, and delays the onset of, MPA-driven mammary cancer (Figure 3). These data show that RANKL/RANK control the incidence and onset of progestin-driven breast cancer (Schramek et al., Nature 2010). Our results were directly confirmed in a back-to-back publication by Bill Dougall's group (Gonzalez-Suarez et al. Nature 2010). Since our results show that the RANKL/RANK system is an important molecular link between progestins and epithelial carcinogenesis, RANKL inhibition should be considered as a novel approach to prevent and/or treat breast cancer.

JOSEF PENNINGER

josef.penninger@imba.oeaw.ac.at

Josef Penninger received an MD's degree from the University in Innsbruck in 1990 and then moved to the Ontario Cancer Institute and University of Toronto where he still holds adjunct Full Professorships in Immunology and Medical Biophysics. In 2003, Josef came back to Europe to become the founding director of IMBA. Josef has published more than 350 scientific papers, is a recipient of the first round of Advanced ERC grants, and he currently holds a Full Professorship of Genetics at the University of Vienna.

Publication highlights:

Neely, GG., Kuba, K., Cammarato, A., Isobe, K., Amann, S., Zhang, L., Murata, M., Elmén, L., Gupta, V., Arora, S., Sarangi, R., Dan, D., Fujisawa, S., Usami, T., Xia, CP., Keene, AC., Alayari, NN., Yamakawa, H., Elling, U., Berger, C., Novatchkova, M., Koglgruber, R., Fukuda, K., Nishina, H., Isobe, M., Pospisilik, JA., Imai, Y., Pfeufer, A., Hicks, AA., Pramstaller, PP., Subramaniam, S., Kimura, A., Ocorr, K., Bodmer, R., Penninger, JM. (2010). A global in vivo Drosophila RNAi screen identifies NOT3 as a conserved regulator of heart function. Cell. 141(1):142-53

Pospisilik, JA., Schramek, D., Schnidar, H., Cronin, SJ., Nehme, NT., Zhang, X., Knauf, C., Cani, PD., Aumayr, K., Todoric, J., Bayer, M., Haschemi, A., Puviindran, V., Tar, K., Orthofer, M., Neely, GG., Dietzl, G., Manoukian, A., Funovics, M., Prager, G., Wagner, O., Ferrandon, D., Aberger, F., Hui, CC., Esterbauer, H., Penninger, JM. (2010). Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate. Cell. 140(1):148-60

Schramek, D., Leibbrandt, A., Sigl, V., Kenner, L., Pospisilik, JA., Lee, HJ., Hanada, R., Joshi, PA., Aliprantis, A., Glimcher, L., Pasparakis, M., Khokha, R., Ormandy, CJ., Widschwendter, M., Schett, G., Penninger, JM. (2010). Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature. 468(7320):98-102

SENIOR SCIENTIST & MANAGING DIRECTOR SCIENCE:
JOSEF PENNINGER

POSTDOCS: ULRICH ELLING, REIKO HANADA, TOSHIKATSU HANADA, TATSUO HASHIMOTO, VANJA NAGY, GREGORY NEELY, ROBERTO NITSCH, THOMAS PERLOT, SHUAN RAO, KARIM REZAUL, DANIEL SCHRAMEK, JEAN TRICHEREAU, JIAN LIANG ZHANG, TAMARA ZORANOVIC

PHD STUDENTS: MICHAEL ORTHOFER, MAGDALENA PAOLINO, BLANKA PRANJIC, VERENA SIGL

RESEARCH ASSISTANT: RUBINA KOGLGRUBER

RESEARCH ASSOSIATE: IVONA KOZIERADZKI

TECHNICAL ASSISTANT: MARIE-THERES TAZREITER

Figure 1

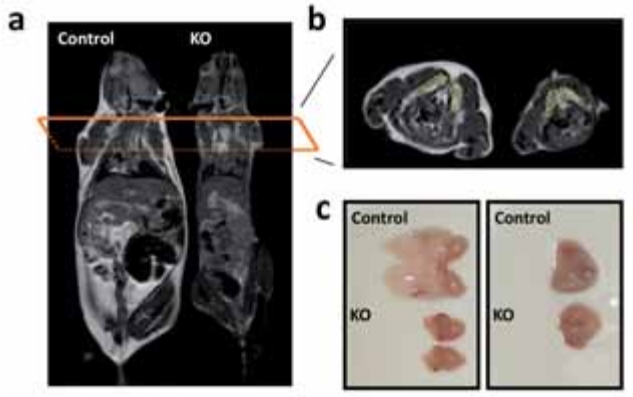


Figure 2

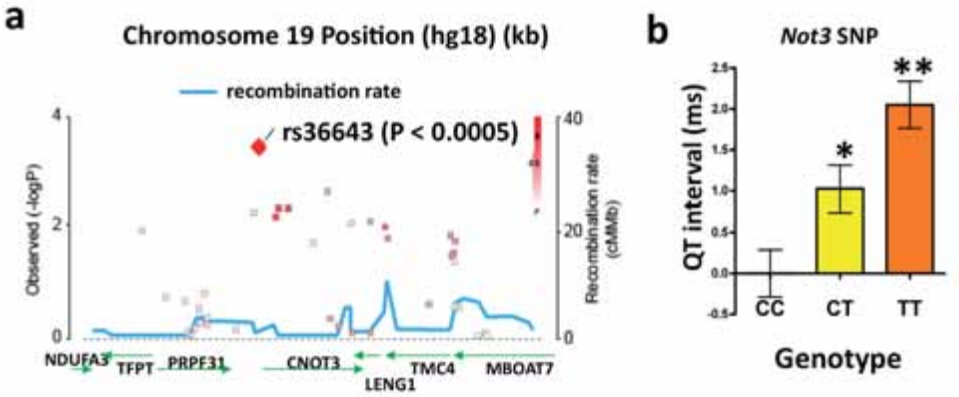


Figure 3

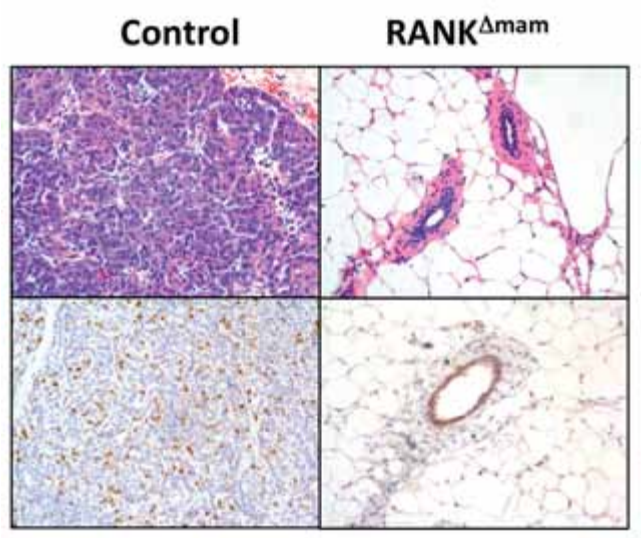
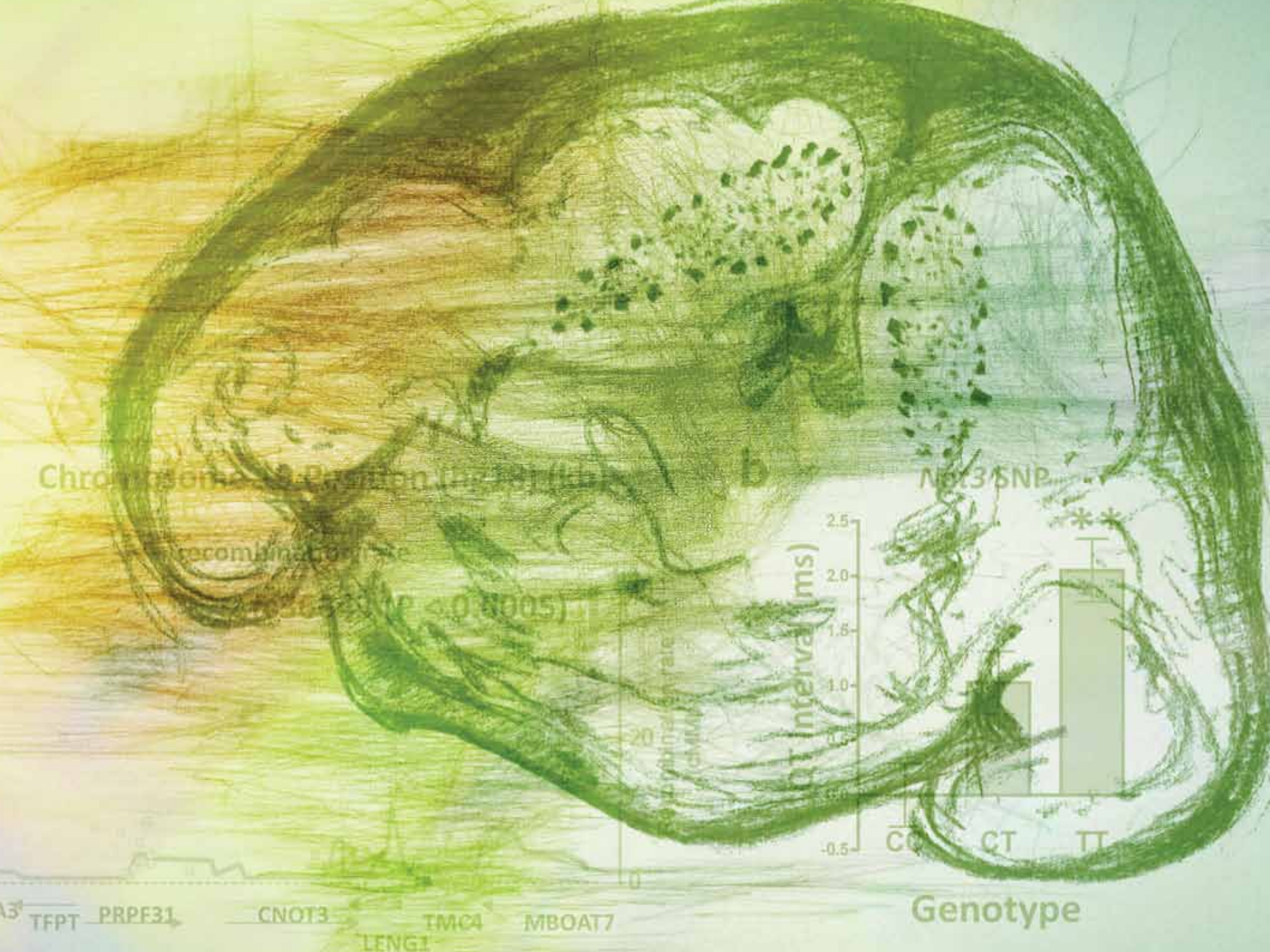


Figure 1: ***aP2-Sufu*** **mice display a marked reduction in white adipose tissue, but have normal brown adipose tissue** (**a**) NMR imaging of an aP2-SufuKO mouse and a Sufu-expressing littermate control. (**b**) Cross-section of the same mice at the level of the scapulae show unaltered brown adipose depots (interrupted yellow lines). (**c**) Tissue dissection of white adipose tissue (left panel) and brown adipose tissue (right panel) revealed fully developed brown adipose depots despite severely compromised white adipose tissue depots in aP2-SufuKO mice.

Figure 2: **Not3 is a conserved regulator of cardiac function.** (**a**) Regional visualization of the association signal between common variants in the NOT3 region and the adjusted QT interval (QTc). SNP rs36643 in the 5' region of NOT3 (-969bp from the transcription start and -924 from the TATA box) showed a significant regional association (p=0.000366). (**b**) Association between the T allele of SNP rs36643 and a prolongation of QTc. * P< 0.0005 from linear regression with inverse variance weighting using an additive genetic model.

Figure 3: **RANK controls the incidence and onset of progestin-driven mammary cancer** Representative histological sections with typical invasive adenocarcinomas in control females on day 7 after the final DMBA treatment. $RANK^{\Delta mam}$ females reveal normal acinar morphology. It should be noted that eventually all $RANK^{\Delta mam}$ females developed tumors in this model system. H&E-stained sections (top panels) and immunostaining for the proliferation marker Ki67 (bottom panels). 20-fold magnification.


b
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
CT
TT
Genotype
TFPT
PRPF31
CNOT3
TMC4
MBOAT7
LENG1

LEONIE RINGROSE GROUP

Epigenetic regulation by the Polycomb and Trithorax group proteins

www.imba.oeaw.ac.at/research/leonie-ringrose

A single stem cell, with a single genomic DNA sequence, can give rise to an extraordinary diversity of cell identities and functions. The highly conserved Polycomb (PcG) and Trithorax (TrxG) group proteins constitute an epigenetic "cellular memory" system that is essential for maintaining the correct identity of both stem cells and differentiated cells. We aim to understand how this dynamic system can ensure both flexibility and stability of cell identities.

Polycomb/Trithorax Response elements in flies and mammals

The PcG and TrxG proteins act through Polycomb/Trithorax response elements (PRE/TREs). PRE/TREs are switchable bi-stable regulatory DNA elements that can preserve a memory of the activated or silenced state of their associated genes over several cell generations. We have previously developed an algorithm to predict fly PRE/TREs, and have examined the evolution of PRE/TRE elements across several *Drosophila* species, showing that PRE/TRE evolution is extraordinarily dynamic. This year we have demonstrated an essential role in PRE/TRE switching for individual motifs that were predicted computationally, and have shown that different PRE/TREs quantitatively modulate the output of their adjacent enhancer, showing for the first time that PRE/TREs from different genes and from different species have intrinsically different properties. Elucidating the molecular mechanisms by which PRE/TRE sequence contributes to gene activation, silencing and switching will be important tasks for the future.

In contrast to fly PRE/TREs, the corresponding mammalian elements have so far proved highly elusive. During the past year we have established reporter assays and training data sets for experimental and bioinformatic analysis of mammalian PRE/TREs. In future we hope to combine the expertise learned from the fly, with computational and experimental analysis in the mouse, to begin to tackle the question of what makes a mammalian PRE/TRE.

Noncoding RNAs in PRE/TRE regulation

Our recent work in both fly and mouse has identified several novel long noncoding RNAs that are transcribed from Polycomb regulatory sites, and suggests an essential role for these RNAs in PRE/TRE regulation during development and differentiation. In the fly, we have shown that the *vestigial* PRE/TRE undergoes a developmental switch, in which embryonic transcription of one PRE/TRE strand is associated with *vestigial* gene activation in specific cells, whereas larval transcription of the other strand is linked to gene repression (Figure 1). In the mouse, analysis of purified cell populations from different stages of neural differentiation reveals sites of intergenic noncoding transcription in each cell type that precisely co-localize with PcG binding sites in the same or other cell types. Both of these studies have in common that they document a remarkable plasticity of transcription of these noncoding RNAs during development and differentiation. Our future work will address the molecular mechanisms by which selected transcripts act on PcG/TrxG regulation in specific cell types and at specific developmental stages (Figure 2).

Quantitative live imaging and mathematical modeling

We have established an "*in vivo* biochemistry" approach to perform quantitative analysis of PcG and TrxG protein dynamics in living *Drosophila* in defined cell types that undergo mitosis and differentiation. This analysis shows fundamental differences in the chromatin binding properties of these proteins between stem cells and differentiated cells, and between different proteins (Figure 3). This is the first study of an epigenetic system to quantify numbers of molecules and their kinetic constants during defined differentiation events *in vivo*. We have used the quantitative measurements to construct mathematical models that have identified parameters of the system that can explain the observed changes in chromatin binding plasticity upon mitosis and differentiation. In future we aim to elucidate the molecular mechanisms underlying these changes, and to determine their contribution to the establishment and maintenance of different cell identities.

LEONIE RINGROSE

leonie.ringrose@imba.oeaw.ac.at

I have always been fascinated by DNA - protein interactions. How do these molecules work together in the complex environment of the cell with such exquisite specificity? For my PhD, I worked on the FLP and Cre recombinases, and found that quantitative experiments combined with mathematical modelling gave insights that I could not imagine just by drawing things on paper. I was hooked, and since then I have taken this principle into the field of epigenetic regulation by the Polycomb and Trithorax group proteins. We aim to understand the behaviour, design and evolution of the DNA and protein components of this system in quantitative terms.

Publication highlights:

Comparative kinetic analysis of FLP and cre recombinases: mathematical models for DNA binding and recombination. Ringrose L, Lounnas V, Ehrlich L, Buchholz F, Wade R, Stewart AF. J Mol Biol. 1998 Nov 27;284(2):363-84.

Genome-wide prediction of Polycomb/Trithorax response elements in Drosophila melanogaster. Ringrose L, Rehmsmeier M, Dura JM, Paro R. Dev Cell. 2003 Nov;5(5):759-71.

Evolutionary plasticity of polycomb/trithorax response elements in Drosophila species. Hauenschild A, Ringrose L, Altmutter C, Paro R, Rehmsmeier M. PLoS Biol. 2008 Oct 28;6(10):e261.

GROUP LEADER:
LEONIE RINGROSE

POSTDOCS:
ROBERT HEINEN, BETÜL HEKIMOGLU-BALKAN [1], ADELHEID LEMPRADL [2]

PHD STUDENTS:
JOAO FONSECA, HELENA OKULSKI, FRANK RUGE, PHILIPP STEFFEN, JOHANNA TRUPKE [3]

TECHNICAL ASSISTANTS:
CHRISTINA ALTMUTTER, MICHEL BAFFOE-BONNIE OWUSU, EVA DWORSCHAK

[1] PHD STUDENT UNTIL OCTOBER, POST DOC SINCE OCTOBER
[2] POST DOC UNTIL APRIL
[3] PHD STUDENT SINCE OCTOBER)

Figure 1

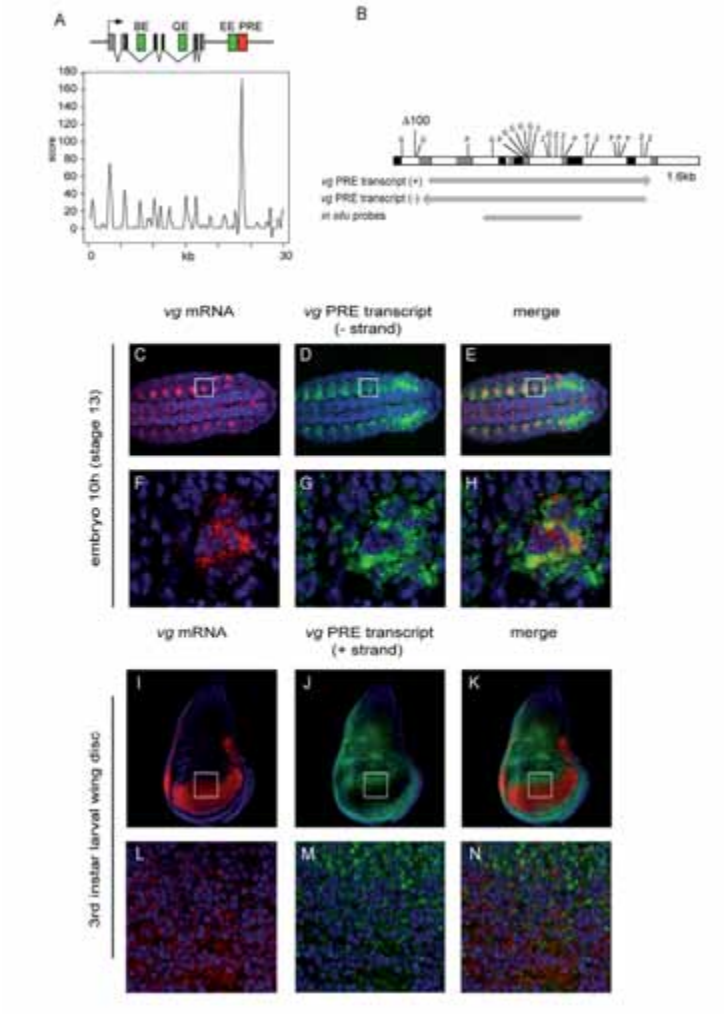


Figure 2

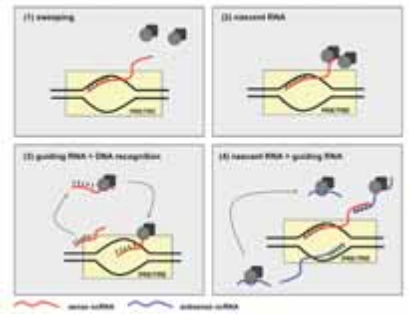


Figure 3

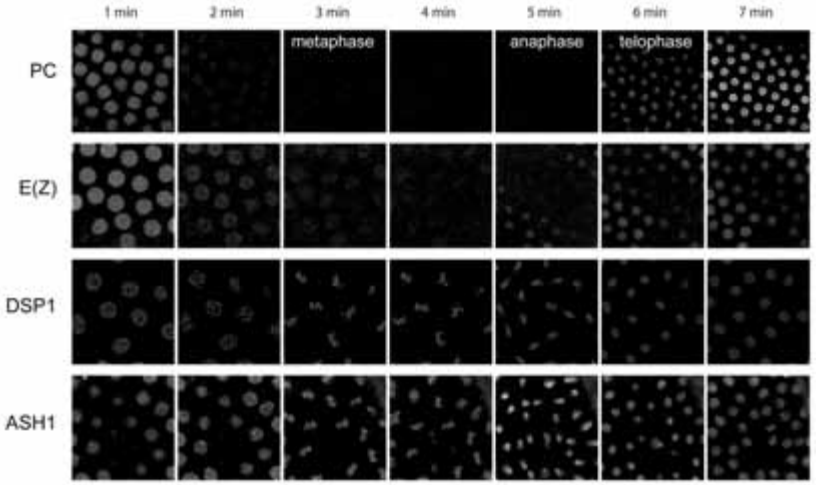
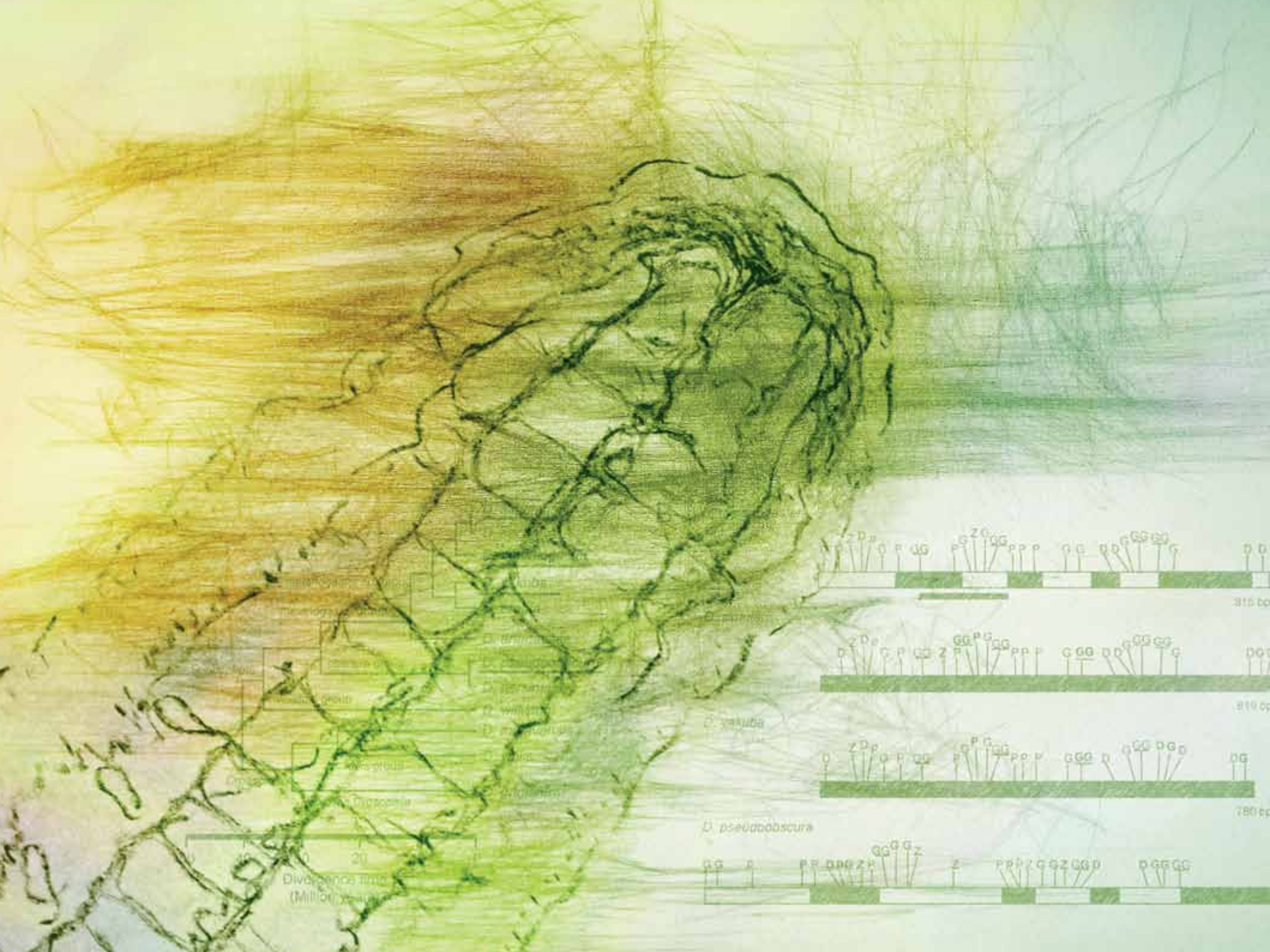


Figure 1: non coding transcription from the *vestigial* PRE/TRE undergoes a developmental switch. (A) (top) *vestigial* locus showing enhancers in green (BE, QE, larval wing enhancers; EE, embryonic enhancer), PRE/TRE in red. (bottom) PRE/TRE prediction score plot. (B) 1.6kb centered on highest scoring region in (A) showing functional PRE/TRE motifs and conservation with D.pseudoobscura orthologous sequence (dark grey, >90% identical; light grey, > 70% identical). C- H. The minus strand of the PRE/TRE colocalises with the vg mRNA in late embryogenesis in the pioneer muscle cells (identifiable by fused nuclei in zoom, G). The PRE/TRE is expressed in all muscle precursors and remains in mature embryonic body wall muscles (D, G and not shown). The vg mRNA is expressed in the central nervous system (C) and the first muscle pioneers (zoom, F), and later in all body wall muscles (not shown). I-N. In larval tissues the plus strand of the PRE/TRE is expressed and the minus strand is no longer detectable (not shown). The plus strand is detected in a spatial pattern that is reciprocal to that of the vg mRNA. (Lempradl et al., in revision)

Figure 2: Models for non-coding RNA in PcG/TrxG regulation and recruitment. (From Hekimoglu, B., and Ringrose, L. Non-coding RNAs in Polycomb/Trithorax regulation. RNA Biol. 2009, 6(2).) The PRE/TRE is shown as a melted DNA. Non-coding transcripts from the top ("sense") strand are shown in red; those from the antisense strand are shown in blue. The protein complexes may be either PcG or TrxG complexes. (A) Sweeping. The act of transcription removes chromatin bound complexes from DNA. (B) Nascent RNA. PcG or TrxG complexes bind to the nascent RNA and/or to single stranded DNA that is being transcribed. (C) RNA-DNA recognition. The non-coding RNA is bound by PcG or TrxG complexes independently of chromatin, and is recruited back to a DNA site of complementary sequence by DNA-RNA pairing. (D) RNA-RNA recognition. A single strand of the non-coding RNA binds to proteins and guides them to a nascent RNA transcribed from the opposite strand.

Figure 3: PcG and TrxG proteins interact differently with mitotic chromatin. (A) GFP fusions to each of the proteins shown (left) were imaged in living embryos. PC : Polycomb; E(Z) Enhancer of Zeste, a PcG protein; DSP1: a DNA binding protein; ASH1, a TrxG protein. Stills from movies of a single mitotic division in preblastoderm embryos are shown. Each protein has a characteristic dissociation behaviour, notably DSP1 and ASH1 stay bound to chromatin throughout mitosis. (From Steffen et al., in preparation).


D. yakuba
D. pseudoobscura

VIC SMALL GROUP

Pushing cells and pathogens with actin

www.imba.oeaw.ac.at/research/vic-small

An integral feature of life is movement. Cells move by utilizing actin filaments to push and our aim is to unravel the secrets of this pushing mechanism.

Introduction

Organ development, wound repair and immune defense all rely on the movement of single cells or cell groups. And in metastasis, renegade cells that escape from primary tumors disperse by migration to propagate in multiple sites elsewhere. Discovering how cells move is therefore important for understanding normal and pathological processes, with perspectives of bringing unwanted events under control.

In order to move, eukaryotic cells have developed subtle variations in strategy, all based on remodelling the actin cytoskeleton. Net translocation is achieved by protrusion at the cell front, followed by retraction at the rear. Protrusion is effected by lamellipodia, thin sheets of cytoplasm composed of networks of actin filaments and filopodia, finger-like rods of bundled actin filaments (Fig. 1). Various complexes are involved in regulating the polymer state of actin, in coupling actin filaments to membranes and in cross-linking actin filaments into functional arrays. Our goal is to define the structural organization of actin arrays involved in protrusion as well as the roles of specific complexes that orchestrate the construction processes. In this mission we are using electron tomography in combination with live cell imaging in the fluorescence microscope to relate structure to function.

Various pathogens, like *Listeria* and *Rickettsia*, as well as vaccinia virus, hijack the actin machinery of infected cells to move from one cell to another. They achieve this by using surface receptors to activate the polymerization of actin, generating a comet tail of filaments with the pathogen riding at the head. To contribute to an understanding of pathogen motility we aim to resolve the structural organization of the actin comet tails.

Pushing in lamellipodia: the elusive branch

According to a currently accepted model, actin filaments form branched, dendritic arrays in lamellipodia, with the ubiquitous Arp2/3 complex at the branch points (Fig. 2). This model is supported by the results of experiments showing that the Arp2/3 complex induces branched arrays of actin filaments *in vitro*, when activated by a member of the WASP family of nucleation promoting factors. Our recent studies by electron tomography (Urban et al., 2010) demonstrated however, that actin filaments in protruding lamellipodia do not form dendritic arrays, contrary to current dogma. Instead, we found that actin networks in lamellipodia are formed from overlapping filaments (Fig.3). We also observed filament pairs in lamellipodia and showed these could serve as precursors of filopodia bundles (Fig.3). Although branched arrays of actin filaments are not observed in established lamellipodia, we cannot exclude the possibility that branching is required for lamellipodia initiation. We are now investigating this possibility using an intracellular wound-healing assay, whereby a small hole is produced in thin, peripheral areas of cytoplasm by a microneedle and repair takes place by lamellipodia formation at the periphery of the hole. Correlated live cell imaging and electron tomography are being used to capture the structural changes during the first seconds of lamellipodia initiation.

Baculovirus and mimetic models of motility

In collaboration with Marie France Carlier and Christophe Le Clainche (CNRS, Paris), we have been analyzing mimetic models of actin driven motility, in which plastic beads are pushed *in vitro* by a comet tail of actin filaments. The observed movement mimics that of *Listeria* in infected cells. With plastic beads as small as 200nm, it has however been difficult to resolve the structure of the comet tail by electron tomography. With the more recent demonstration that baculovirus (50x200nm in size) is propelled in cytoplasm by actin (Ohkawa et al., J. Cell Biol. 190:187-195, 2010) we have turned our attention to analyzing the structure of tails formed behind this virus, both *in vitro* and in infected cells *in vivo*. Our preliminary findings show that baculovirus is pushed by short - a few hundred nm long - actin filaments in a fish-bone like array. Filament tracking is now being used to establish the 3D geometry of the pushing machinery and whether or not actin filaments associate in branched, end-to-side interactions in the core of the comet tail.

VIC SMALL

vic.small@imba.oeaw.ac.at

Since I first peered onto an EM screen as a Ph.D. student I have been captivated by the inner complexity of cell architecture. After contributing, in the 1970's to the discovery and characterization of the cytoskeleton my interests focused on the structural basis of cell movement and guidance. The three early publications listed below were among those that started things off.

Publication highlights:

Urban, E., Jacob, S., Nemethova, M., Resch, GP., Small, JV. (2010). Electron tomography reveals unbranched networks of actin filaments in lamellipodia. Nat Cell Biol. 12(5):429-35

Small, J.V. (1981). Organization of actin in the leading edge of cultured cells: Influence of osmium tetroxide and dehydration on the ultrastructure of actin meshworks. J. Cell Biol. 91, 695-705.

Small, J.V., Isenberg, G. and Celis, J.E. (1978). Polarity of actin at the leading edge of cultured cells. Nature 272, 638-639.

Small, J.V. and Sobieszek, A. (1977). Studies on the function and composition of the 10 nm (100 A) filaments of vertebrate smooth muscle. J. Cell Sci. 23, 243-268.

SENIOR SCIENTIST:
VIC SMALL

POSTDOCS:
EDIT URBAN, ZHENGRUI XI

DIPLOMA STUDENT:
JAN MUELLER

RESEARCH ASSOCIATE:
SONJA JACOB, MARIA NEMETHOVA

RESEARCH ASSISTANT:
MARLENE VINZENZ

Figure 1

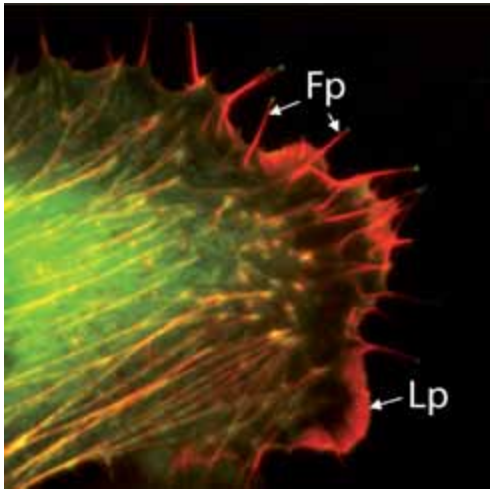


Figure 2

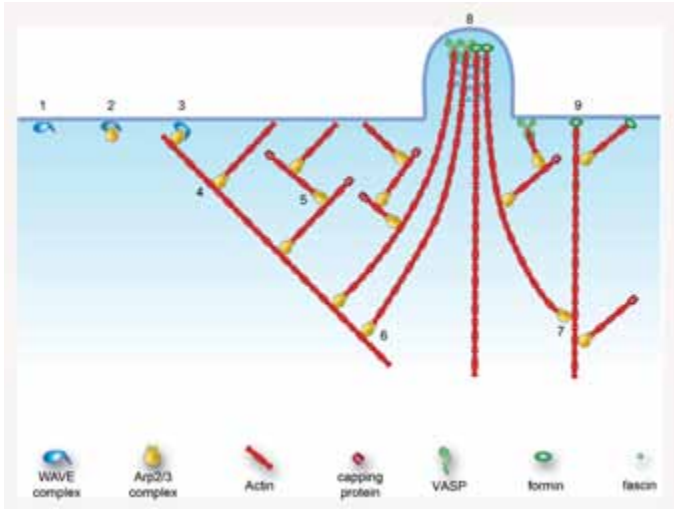


Figure 3

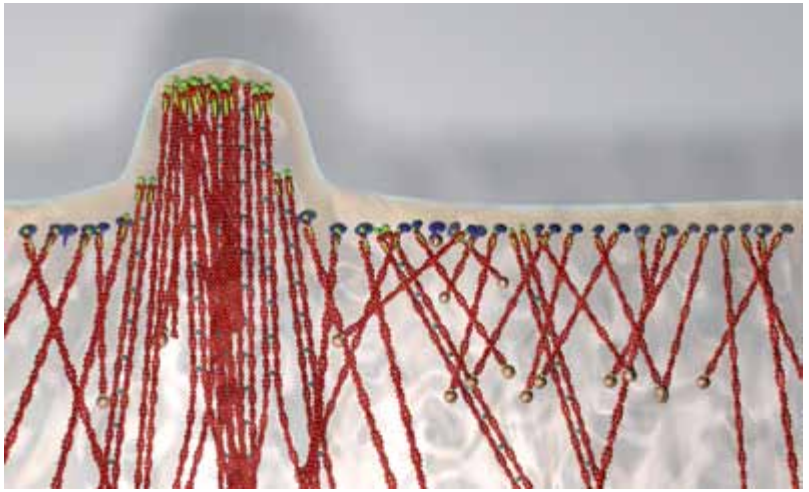


Figure 1: Lamellipodia and filopodia in a migrating fibroblast. Image shows a frame from a video sequence of a living cell that was expressing actin tagged with RFP (red) and the protein VASP tagged with GFP (green). Lp, lamellipodium; Fp, filopodium.

Figure 2: The currently accepted "Dendritic nucleation/array treadmilling model of lamellipodia protrusion". Actin filaments in protruding lamellipodia are nucleated by activation of the Arp2/3 complex situated on the side of a pre-existing filament, to form a branched array. For further details see Small (2010).

Figure 3: The alternative, "Tethered nucleation/elongation model of actin network formation in lamellipodia", based on our studies (Urban et al., 2010). Filaments in protruding lamellipodia are nucleated at the membrane by the Arp2/3 complex, without branch formation. For further details see Small (2010).

Figure 1

STEM CELL CENTER - MOUSE GENE TARGETING

austromouse@imp.ac.at

The main objective of the Stem Cell Center – Mouse Gene Targeting is to provide state-of-the-art technologies for the manipulation of the mouse genome. By combining homologous recombination, site-specific recombination, and transgenesis using mouse embryonic stem (ES) cells, ideal human disease models can be engineered. Our most recent addition is the establishment of mouse and human induced pluripotent stem (iPS) cell technology.

ES cells and gene targeting

The several missions of the ES cell core facility include the production of quality-controlled ES cell lines with mutations introduced by homologous recombination, the creation and handling of quality-controlled ES cell lines, and enhancing knowledge of mouse genetics, ES cell culture and manipulation. Targeted ES cells can be used to generate germline ES cell-mouse chimeras that can be bred to generate mouse lines or for *in vitro* assays. In addition, highly germline-competent ES cells derived from inbred strains, which are preferentially used in biomedical research, would greatly facilitate the generation of targeted mutations in appropriate genetic backgrounds, such as FVB/N and C57BL6/N ES cell lines. This provides essential tools for the analysis of mutations, especially when the phenotype is embryonic lethal in the early stages of development. We also develop *in vivo* inducible gene targeting systems and try to generate new transgenic recombinase mouse models.

Gene targeting tool box

We maintain a shared "gene targeting tool box" in addition to providing expertise, cell lines, efficient exchange of information, and stem cell assays. The collection includes Cre and Flp recombinase-expressing transgenic lines and activity-reporter lines, which are essential for the generation and characterization of conditional, inducible, and/or tissue-specific mutant mice. The unit also maintains a collection of "ES and vectors tools", reagents, feeders (neomycin resistant or neo/hygro/puro resistant), cell lines, and plasmid vectors.

Generation of induced pluripotent stem cells

Our most recent addition is expertise and skills in mouse and human iPS cell technology. The ability to create patient-specific pluripotent stem cells, and study those cells in the lab could be a great advantage to study human diseases. Currently we are establishing assays to evaluate the characteristics of mouse and human iPS cells for further research. The feasibility of the concept will be proven by using mutant mice to demonstrate how reprogramming, repair of genetic diseases via homologous recombination, tissue-specific differentiation and gene therapy can be developed.

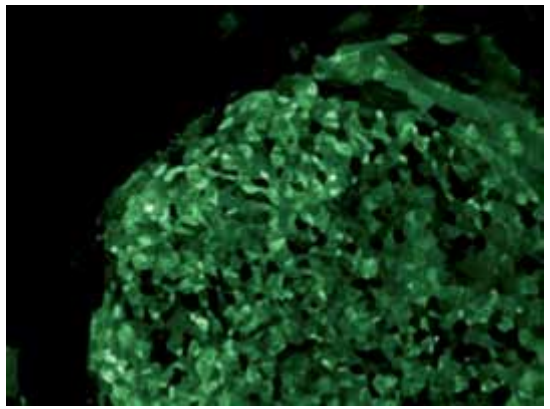
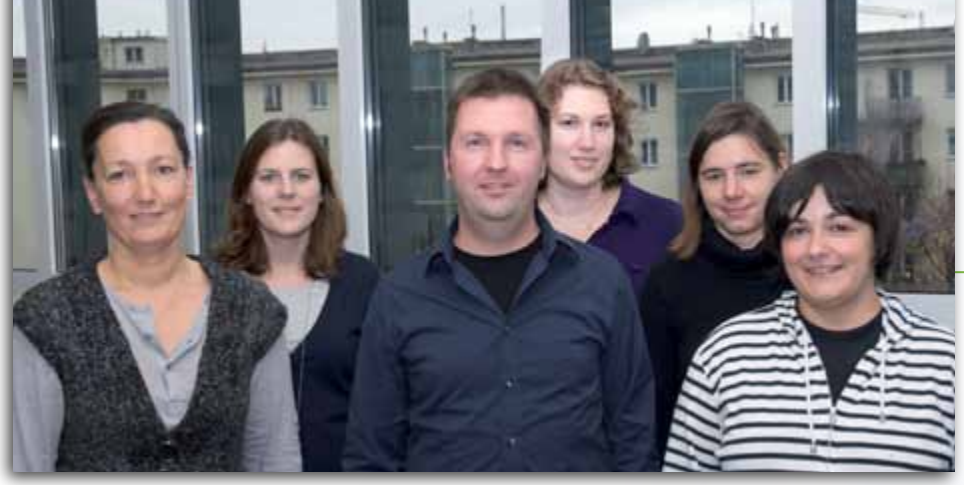


Figure 2

Figure 1: *www.austromouse.at*
Figure 2: Human iPS cells generated from adult dermal fibroblasts express the embryonic cell surface marker Tra-1-81.



FLY HOUSE

Peter Duchek
peter.duchek@imba.oeaw.ac.at

HEAD OF FACILITY:
PETER DUCHEK

TECHNICAL ASSISTANTS:
SABINE BRYNDA[1], EVA DWORSCHAK,
SARA FARINA LOPEZ, CHRISTINE MARCHER[2],
KATHARINA MEIXNER, IVICA SOWEMIMO[3],
CLAUDIA VALENTA

[1]UNTIL SEPTEMBER
[2]SINCE JUNE
[3]SINCE SEPTEMBER

The Fly House provides research support for the growing number of scientists at IMBA working with the fruitfly Drosophila melanogaster as a genetic model system. Our service includes the generation of transgenic fly lines, gene targeting via homologous recombination to generate knock-out or knock-in mutants, large-scale in vivo RNAi screens, and the maintenance of stock collections.

Embryo injections

One of the cornerstones of the Fly House is the generation of transgenic fly lines. We routinely inject DNA constructs into a range of commonly used host strains, including various landing site stocks for phiC31-mediated targeted integration, and subsequently perform crosses to establish mapped and balanced transgenic stocks.

Gene targeting

Although the use of homologous recombination to generate defined mutations is a well-established technique in several genetic model organisms, gene targeting in Drosophila has only recently been developed. Given the need to confirm the RNAi knock-down phenotypes with classical loss-of-function alleles or to tag genes at their endogenous locus, we have set up a Drosophila gene targeting service at the institute. Currently we use an ends-out strategy of homologous recombination to create defined deletions or add tag sequences to genes.

Research support

The first genome-wide collection of inducible RNAi lines, available through the Vienna Drosophila RNAi Center (VDRC), has revolutionized loss-of-function genetic screens in Drosophila. It is now possible to systematically investigate the function of each gene in a tissue of interest. We support scientists conducting large-scale in vivo RNAi screens as well as subsequent follow up experiments to validate their hits.

Fly stock maintenance and plasmid collection

In addition to maintaining lab stock collections, we keep various commonly used fly stocks such as balancers and virginizer lines. We also have a growing plasmid collection consisting mainly of vectors used for targeted integration or homologous recombination. These tools are being improved on an ongoing basis.

VIENNA DROSOPHILA RNAI CENTER (VDRC)

Krystina Kelemann

kelemann@imp.ac.at, office@vdrc.at

STAFF SCIENTIST/HEAD OF THE VDRC:
KRYSTYNA KELEMAN

RNAI LIBRARY MAINTENANCE AND DEVELOPMENT
REINHARD KLUG

SOFTWARE DEVELOPER:
SELEN IREZ ALACAPTAN

ADMINISTRATION:
BARBARA MÜLLNER[1]

TECHNICAL ASSISTANTS:

KRISTINA BELOGRADOVA, LUIZA DESZCZ [1], MICHAELA ECKMANN, MICHAELA FELLNER, ANDREAS GANSCH, ANGELA GRAF [1], LASZLO HUNOR, AMINA KADUM, RAINER KECK [1], IRINA KOLAROV, SONJA LANG, FLORENCE MAXWELL, BARBARA MÜLLNER, IRENE PENZENAUER, ELENA POPOWICH, ALISHER TASHPULATOV, SANDOR URMOSI – INCZE, JUDITH UTNER [1], STEFANIE WANDL, SVETLANA ZORINYANTS, RENÉ ZÖRNIG [2]

[1] 50%, [2] 80%

Genome-wide RNAi

We have generated two independent genome-wide transgenic RNAi libraries for Drosophila, allowing researchers to systematically study gene functions in specific tissues at specific developmental stages. The VDRC maintains and further develops these libraries, and distributes RNAi lines to Drosophila researchers world-wide.

RNAi can be effectively triggered in Drosophila by spatially and temporally controlled expression of a dsRNA from a transgene that contains a long inverted repeat under control of a genetic promoter the GAL4-responsive element (Figure1). The initial creation of a genome-wide transgenic RNAi library [1] has revolutionized Drosophila genetics. The VDRC, maintains, further develops and distributes this library.

Recently, we have embarked on the construction of a new RNAi library (the KK library) that exploits site-specific transgene integration and to overcome some of the problems associated with random insertion of the P element transgenes of the original collection (GD library). In the new KK library, all RNAi transgenes are targeted to the VIE-260b site, selected on the basis of its low basal expression and high levels of GAL4-induced expression.

An additional attractive feature of our new collection is that it targets a different gene fragments than our first library. We have completed 10,000 RNAi lines, which were made available to researchers world-wide in March last year.

Since the VDRC opened two and a half years ago, we have already delivered over 340,000 lines to more than 1,500 registered users world-wide. This has been made possible in part through core funding provided by the city of Vienna and the federal government, with the rest of the costs covered by user fees. The VDRC also provides such support for researchers in house, having delivered over 200,000 lines to IMBA and IMP groups.

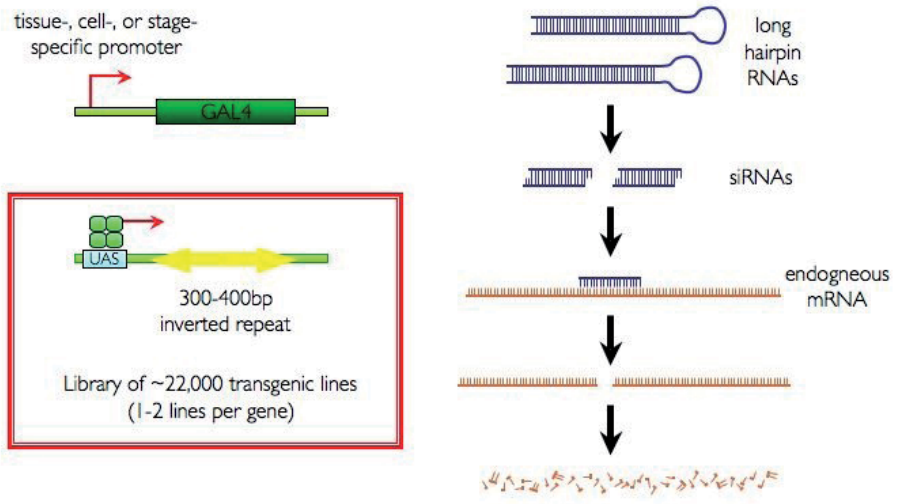


Figure: RNAi in Drosophila

RESEARCH SUPPORT

PROTEIN CHEMISTRY

karl.mechtler@imp.ac.at

Studying the Abundance and Functions of Protein Arginine Phosphorylation

The discovery of arginine phosphorylation as a post-translational modification of proteins in bacteria, which performs an important function in stress adaptation of cells, demonstrates that this acid labile post-translational modification is now accessible to investigation by proteomic methods. To detect this modification and also elucidate its function in bacteria and mammalian cells types, we established specific methods which improve the stability of the modification through sample preparation, including specific enrichment techniques and reliable methods for detection by LC-MS/MS, and permit improved data analysis by the use of a probability-based scoring algorithm.

Methodological Advances in LC-MS/MS

LC-MS/MS (liquid chromatography-tandem mass spectrometry) experiments in expression-based proteomics aim for extremely high numbers of identified proteins which, however, is actually achieved only by two-dimensional LC-MS/MS. Given the fact that 2D-LC-MS/MS is very time-consuming, we investigate and design methods to increase the numbers of peptides and proteins identified in a single LC-MS/MS experiment. We succeeded in raising this number to about 2,500 proteins, based on approximately 14,000 peptides, which is sufficient to analyze samples of moderate complexity.

Measuring Protein Complexes with Mass Spectrometry

Proteins assemble into macromolecular protein complexes that regulate fundamental cellular processes such as cell cycle progression and mitosis. Using our previously described EtEP strategy to generate an equimolar set of internal reference peptides, we are determining protein complex stoichiometries and protein copy numbers per cell using selected reaction monitoring (SRM)- based absolute quantification.

Applying this workflow to affinity-purified cohesin complexes, we determined the stoichiometries of the four core cohesin subunits throughout the cell cycle. Furthermore, using isoform-specific reference peptides, we determined the relative abundance of the two populations of cohesin complexes in human somatic cells (Figure).

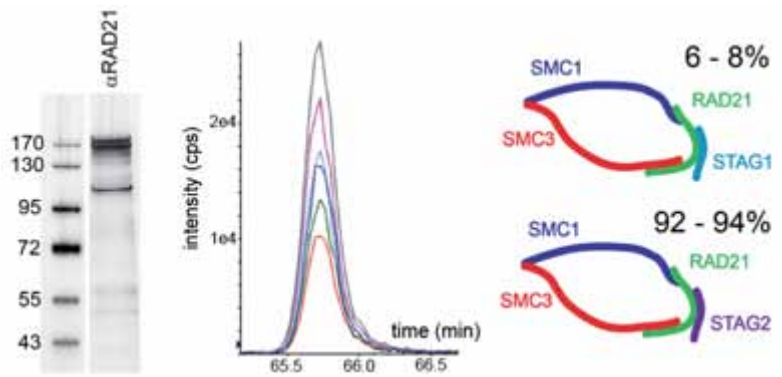


Figure: Absolute quantification of cohesin populations by SRM. (Holzmann et al., JPR, 2010)

Head of Facility:
Mechtler Karl

Postdocs:
Holzmann Johann, Köcher Thomas, Jordanova Rositsa, Jüschke Christoph[1];

PhD Student:
Broch Trentini Debora

Bachelor Student:
Taus Thomas

Technical Assistent:
Fuchs Johannes, Hudecz Otto, Krssakova Gabriela, Madalinski Mathias, Mazanek Michael[3], Opravil Susanne[2], Roitinger Elisabeth, Schutzbier Michael, Steinmacher Ines

[1] joint appointment with Jürgen Knoblich, IMBA
[2] joint appointment with Stefan Westerman, IMP
[3] maternity leave

BIOOPTICS

aumayr@imp.ac.at

Head of BioOptics:
Karin Aumayr

Microscopy:
Pawel Pasierbek, Gabriele Stengl

Flow Cytometry/Image Analysis:
Thomas Lendl, Gerald Schmauss

The services offered by the BioOptics Facility to researchers at IMP, IMBA and GMI cover analytical flow cytometry and cell sorting, as well as a large variety of microscopy techniques, image processing and analysis.

Flow Cytometry

We provide instrumentation, education and expertise for all flow cytometry requiring experiments, and offer high-speed cell sorting, as well as advanced and general flow cytometry analysis. Users are given guidance and support with the planning of experiments and implementation of new fluorophore combinations. They are trained in the use of hardware and software for all of the three available state-of-the-art flow cytometers, as well as in data processing and analysis. Two cell sorters are operated by the staff of the facility. Four cell populations can be sorted simultaneously in bulk, or single cell sorting can be performed.

Microscopy

The BioOptics Facility currently manages more than twenty microcopy systems, including wide-field microscopy, confocal laser scanning microscopy (CLSM), two-photon (2P) microscopy, total internal reflection (TIRF) microscopy techniques, and an automated slide scanner for samples with or without fluorescence. Most of the systems are motorized - thus providing automation for higher throughput - and are suitable for fixed samples as well as live cell experiments. The facility provides assisted use and training on instrumentation and consultation concerning all microscopy-related subjects, including project planning, staining, microscope selection, etc.

Image Processing and Analysis

Five state-of-the-art computer workstations are available at the BioOptics Facility, operating most of the common commercial image processing and visualization software. A server solution with a Web-based interface has been set up to enable deconvolution of microscopy images. The server permits efficient, multi-user, parallel, batch deconvolution that can easily be started from the individual scientist's computer. Users are trained in the use of specific software, depending on their demands. Several image analysis algorithms are available, such as object tracking and tracing, determination of measurement parameters like intensity, distance, area, volume and co-localization. Customized classification and measuring algorithms are developed at the facility for advanced image analysis and automated object recognition.

For more information please visit http://cores.imp.ac.at/biooptics/

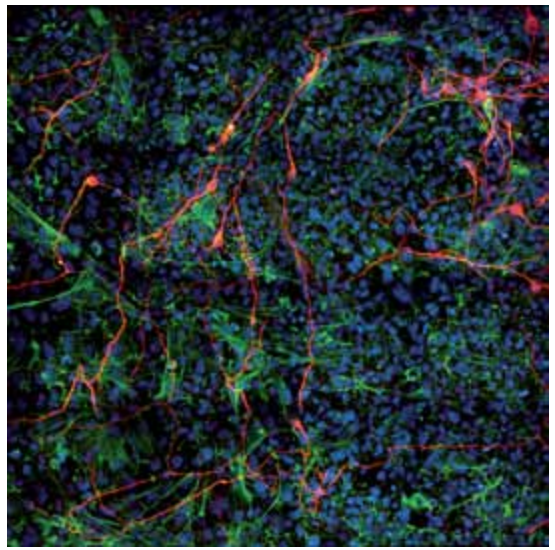


Figure: In vitro differentiation of a murine embryonic stem cell line established by multiple rounds of FACS sorting. Differentiation was induced by embryoid body formation and retinoic acid treatment. Stitched image of 5x5 fields of view (FOV) acquired with the spinning disk (SD) confocal microscope. Blue: DAPI, green: phalloidine, red: TuJ1(neuron specific beta tubulin)

ELECTRON MICROSCOPY

guenter.resch@imba.oeaw.ac.at

Head of Electron Microscopy Facility: Guenter Resch

Technical Assistants: Marlene Brandstetter, Nicole Fellner

Trainee: Veronika Wonesch

The Electron Microscopy Facility provides a wide range of preparation techniques for tissues, cells, and purified molecules for transmission electron microscopy, as well as facilities for microscopy, data management and image processing. Access to scanning electron microscopy is provided via external collaboration.

Preparation of Specimens

Know-how, training and instrumentation for a wide variety of preparation techniques for visualization of ultrastructure in tissues or cells and of biomolecules by transmission electron microscopy (TEM) are being offered by the Electron Microscopy Facility to researchers at IMBA, IMP and GMI. Techniques routinely used at the facility include the production of support films, negative staining, rotary shadowing of sprayed molecules, chemical fixation, immersion freezing, high pressure freezing, freeze substitution, embedding in epoxy- and acrylic resins, and ultrathin sectioning of resin-embedded or frozen samples.

New instrumentation for specimen preparation is also being developed. The Leica EM GP immersion freezer, developed jointly by the EM Facility and Leica Microsystems, is commercially available from 2010 onward.

Microscopy

The Facility is equipped with two instruments: The FEI Morgagni is a robust and easy-to-use 100 kV TEM, equipped with an 11-megapixel CCD camera. It is tailored to meet routine requirements at the Facility's multiuser environment. Advanced applications run on the FEI TF30 Polara. This 300 kV TEM, unique in Austria and equipped with the most advanced imaging systems, was funded by a Vienna Spot of Excellence grant and became fully operational at the beginning of 2008. It is primarily used for cryo-TEM of molecules and cells, electron tomography, and electron energy loss spectroscopy.

Software Development and Image Processing

To support users with data management, a Web-based project-oriented database system named MIMAS was developed by, and is being run at, the Facility. Electron micrographs from both microscopes, including meta data, can be stored on and accessed from this database on a user-restricted basis. Furthermore, software solutions for automated image acquisition and for status monitoring of the microscope were developed on the Polara. Workstations and training are provided for image processing of EM data, especially those obtained by electron tomography.

More and up-to-date information about the work of the EM Facility can be found at *http://cores.imp.ac.at/em*.

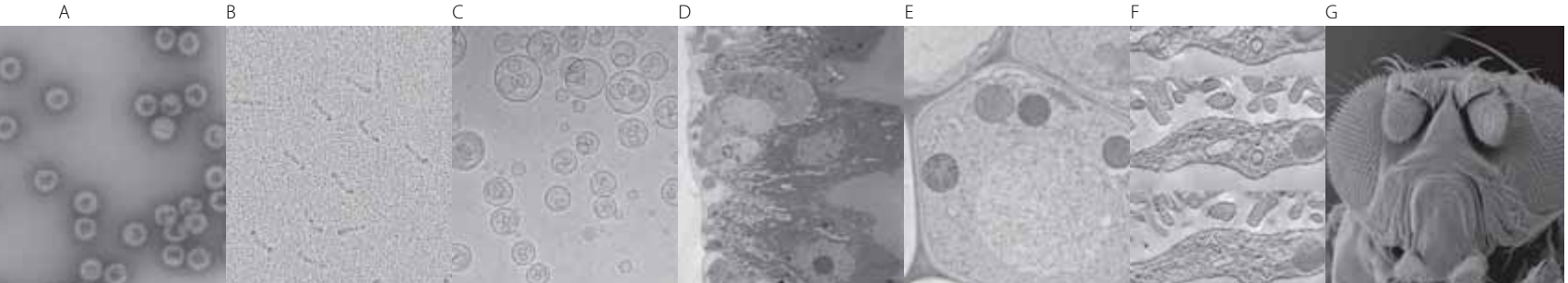
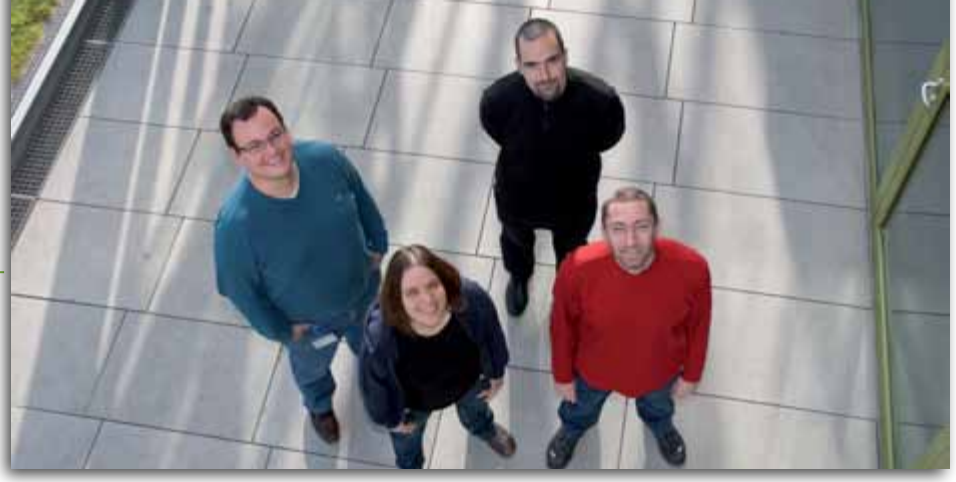


Figure:

A: Negatively stained rotavirus-like particles (Cornelia Gänger, Ringrose Group)
B: Glycerol sprayed and rotary shadowed α-actinin molecules.
C: DPPC liposomes visualized by cryo electron microscopy.
D: Drosophila melanogaster intestine also showing stem cells from a chemically fixed specimen (sample: Ryan Conder, Knoblich Group).
E: Cells from high pressure frozen Arabidopsis thaliana root (sample: Matzke Group, GMI).
F: z-Sections from a three-dimensional reconstruction by electron tomography showing the endothelial lining in a blood vessel.
G: Scanning electron micrograph of Drosophila melanogaster.



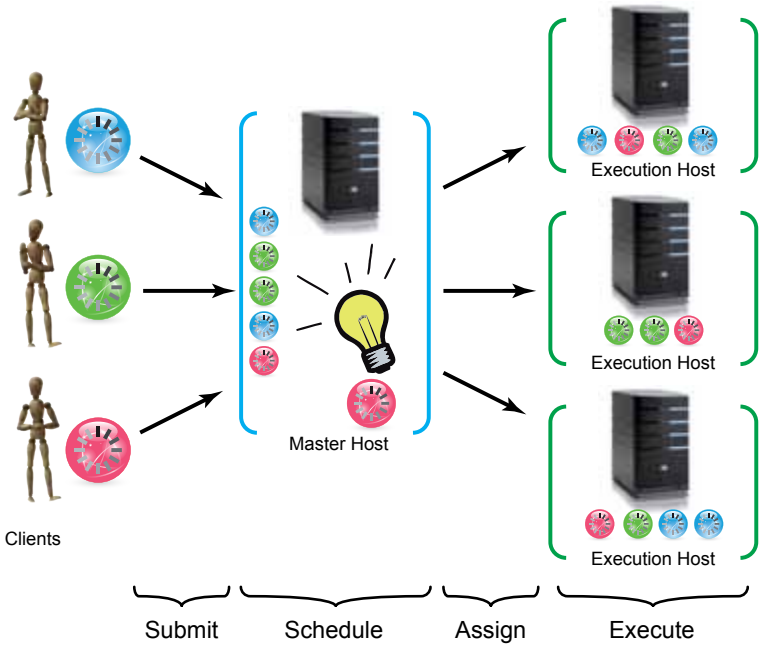
BIOINFORMATICS

bioinfo.grp@imp.ac.at

Computational Biologist:
Thomas Burkard, Maria Novatchkova, Alexander Schleiffer

Software Engineer:
Wolfgang Lugmayr

The Bioinformatics unit assists research groups in molecular-biology-related fields by providing sequence analysis services, scientific data mining, hardware and software infrastructure, and training in bioinformatics.



Sequence analysis

The main expertise of the IMP-IMBA Bioinformatics unit lies in the field of sequence analysis. Typical tasks include functional and structural characterization of proteins and genomic regions using methods such as pattern matching, complexity analysis and homology searches. As conclusions in bioinformatics are achieved by synthesizing the results of multiple algorithms, we maintain and develop a set of specialized software tools to support this type of meta-analysis.
Web access is being provided for widely used scientific applications related to protein motif analysis, similarity searching (BLAST, PSI-BLAST, FASTA), whole-genome viewing (GBrowse), transcription factor analysis (Transfac), and various sequence manipulation and exploration tasks (EMBOSS).

Large-scale data analysis

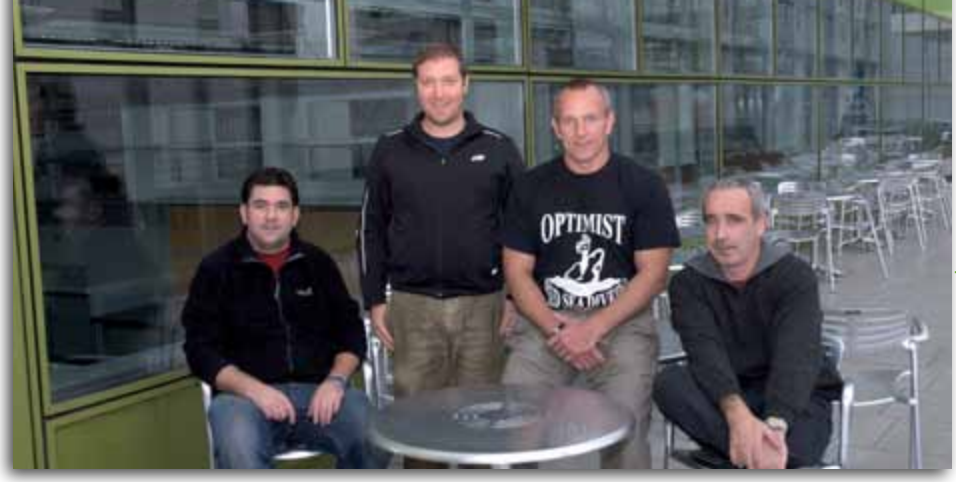
Additional demands arise from the investigation of large functional genomics or high-throughput biological datasets. We engage in custom software and database development, and design computational and mathematical solutions that can cope with the higher load and memory requirements. To perform complex sequence analysis tasks, we also maintain the IMP ANNOTATOR, which is a user-friendly web application and a high-throughput protein annotation system.
For heterogeneous computational tasks, the main computing cluster has been updated to a state-of-the-art processing system using batch and parallel computing environments. The cluster is managed by the Sun Grid Engine (SGE) software, which provides policy-based workload management for a large number of jobs and nodes.

Software installed and maintained on the bioinformatics cluster includes tools for statistical computing (e.g. R, Bioconductor), motif discovery and analysis (e.g. AlignAce, MDscan, MEME, Weeder), structural biology (e.g. VMD, pyMOL, NAMD), a wide range of sequence analysis, assembly, mapping and classification tasks (e.g. RNAhybrid, phylip, HMMer), and others.

Training

We provide hands-on training courses on the ANNOTATOR. Attendees of the course learn the basic principles and limitations of sequence analysis and data integration.

Figure: The IMP/IMBA high-performance computing (HPC) cluster. Users may submit jobs on dedicated clients to the Sun Gridengine (SGE) master, which is responsible for running the jobs on the cluster nodes.



GENOMICS

genomics@imp.ac.at

Engineers:
Martin Radolf, Harald Scheuch, Andreas Sommer

Technical Assistant (part-time):
Markus Sonntagbauer

A new high-throughput technology, the BeadXpress Reader (Illumina), was established in 2010. Using VeraCode® holographic microbead technology, we are able to perform SNP genotyping, gene expression, and protein-based assays.

We routinely hybridized more than 200 microarrays on self-spotted cDNA arrays containing RIKEN 3 clones. Over 22,500 genes per array were analyzed and processed using an internally programmed, fully automated analysis software tool. We offer Spotfire from the summer of 2009 onward.

As an additional platform we offer hybridization on Agilent arrays. Currently we use the 4x44K and 8x44K designs for different model organisms. With Agilent, we can also offer microarrays to analyze DNA methylation, microRNAs, and custom-made microarrays.

A further noteworthy aspect of our work at the genomics department is the use of robotics in the lab. We are currently working with a Tecan TeMO provided with 96 channels, and two Biotek Precison XS for 8-channel and single pipetting. In early 2010 we purchased a XIRIL 100 which helps in automated genomic DNA isolation of mouse tails and single fly. The second main task of this robot is automated plasmid mini-preparation. Given the increasing demand and complexity of liquid handling processes, we decided to establish another robot platform: an Agilent Bravo robot was purchased in October 2010. Its main task will be automated in situ hybridization for fly embryos.

The demand for next-generation sequencing continued to grow in 2010: more than 600 samples were processed this year. We acquired a third paired-end module, which increased flexibility and throughput by permitting paired-end runs on all three existing genome analyzers. The read length for standard paired-end runs was increased to 76 base pairs and the maximal offered read length to 100 base pairs. As in the last year, constant upgrades led to higher sequencing yields: more than 25 million raw reads per lane were consistently achieved. In order to deal with next year's workload, a Hi-Seq 2000 (Illumina's most advanced sequencing instrument) was purchased and is currently being installed.

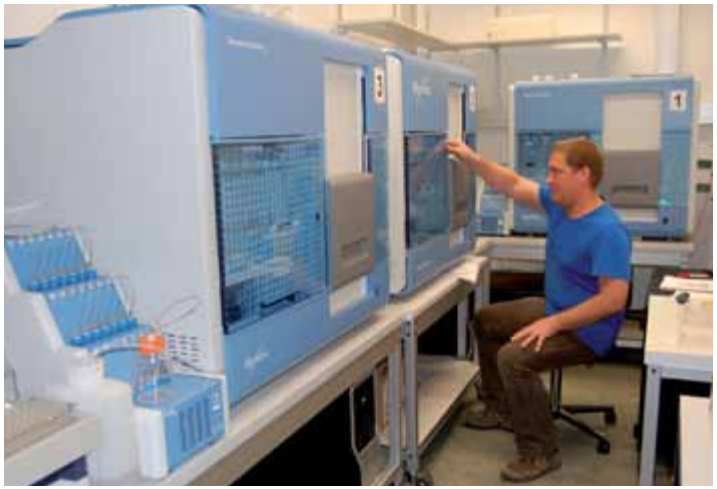


Figure: Illumina Genome Analyzer II

HISTOLOGY

vukoslav.komnenovic@imba.oeaw.ac.at

Head of Facility:
Vukoslav Komnenovic

Technical Assistant:
Mihaela Zeba

The Histology Service Department offers state-of-the art sectioning, histology and immuno-histochemistry services to all IMBA and IMP scientists. In addition, we offer training and support for researchers in new technologies.

Histology Services

The histology services include the embedding of tissues, assistance with the sectioning of paraffin and cryo-preserved tissues, and preparation of slides for standard H&E stains, as well as specialized stainings such as PAS, Alcian blue, Cab, Gomeri, MayGruenwald-Giemsa and van Kossa stains for human, mouse, *Xenopus* and *Drosophila* studies. With these services, we are able to offer support to get quick results.

Sectioning of Paraffin and Frozen Tissues

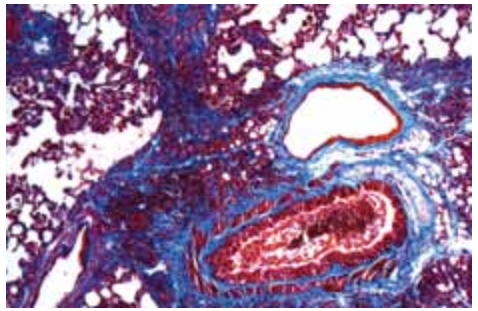
In our group we have developed a high throughput method to cut paraffin and frozen tissues. Using this method, we could increase the quality and also the quantity of services.

Immunohistochemistry

The Histology Service Department also provides automated preparation and processing facilities for standardized immuno-histochemistry, in situ hybridization, FISH analysis, DNA microarray and tissues microarray applications. Various antibodies have been characterized for optimized in situ signaling studies. Standard antibodies such as apc, cd (several markers), l-ad, gfp, gfap, c-fos, c-jun, junB, fra1,2, jun-D, ki67, smad3, brdu, egf, egfr, H3K9me tri meth, H4K20me3 tri meth, cl. caspase3, caspase7, procatepsiK are available.

In addition, the Histology Service Department administrates legal regulatory affairs such as the record-keeping and documentation of experiments in accordance with the Austrian Histolaboratories guidelines (*www.mta-labor.info*).

1



2

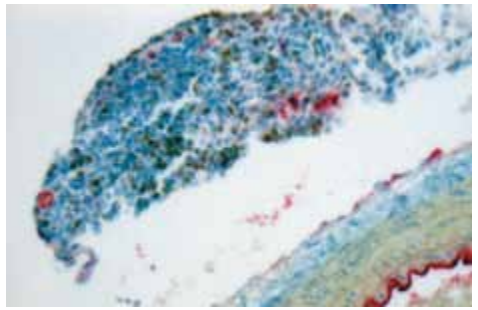
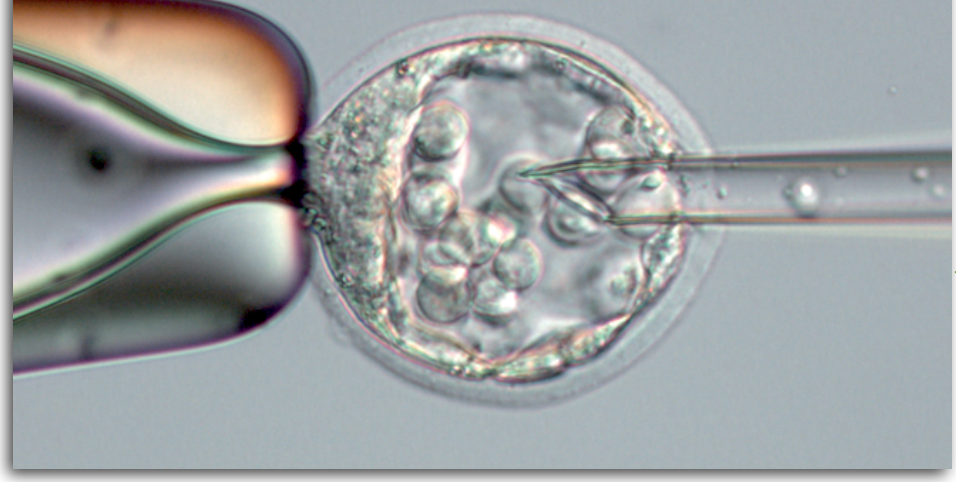


Figure 1: *Trichrom blue staining. The picture shows 4 different signals, light blue for Lung fibrosis, red for Mast cells and Neutrophils, pink for Myeloiud cells and dark blue for the Nuclei.*

Figure 2: *Double Staining with Ki67 and von Willebrand Factor. Ki67 turnes out to be brown whereas vWF shows a red signal. The counter staining was done with Hematoxylin (blue).*



1

COMPARATIVE MEDICINE

animal@imp.ac.at

TRANSGENIC SERVICE

transgenic@imp.ac.at

Comparative Medicine

Scientific work at the IMP and IMBA depends to a high degree on the use of model organisms. IMP and IMBA acknowledge and accept responsibility for the care and use of those animals according to the highest ethical standards. The institute ensures that all employees dealing with the animals understand their individual and collective responsibilities for compliance with Austrian laboratory animal law as well as all relevant regulations and rules concerning laboratory animal husbandries. In accordance with this institutional policy the animal house group - trained and highly qualified animal attendants - provides husbandry of animals and services for the various research groups.

Husbandry:

The largest area of the animal house is the mouse section, which comprises 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, commonly used standard strains are routinely bred in-house.

Comparative Medicine 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. 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 incoming and outgoing mouse-shipments per year. Administration of regulatory affairs in accordance with the Austrian laboratory animal law, which includes record-keeping and updating of laboratory animal statistics, specific documentation of laboratory animal experiments.

Transgenic Service

The Transgenic Service Department was set up at the beginning of 1998 to cope with the increasing demand for mouse studies and the generation of transgenic mice. Both IMP and IMBA avail themselves of the services of the Transgenic Service Department.

The main duties of this service unit are the injection of ES cells into blastocysts [also tetraploid and 8-cell] and of DNA into the pronucleus of fertilized mouse eggs. This service also provides for the transfer of 'clean' embryos to our animal house, as well as the freezing of embryos for preservation of specified mouse strains and for teaching basic embryological techniques to the staff of IMP and IMBA. Many different ES cell clones and DNA/BAC constructs are being injected every year. The activities of this department are overseen by an Animal User Committee, which meets on a regular basis to set priorities and coordinate tasks. The committee is currently chaired by Meinrad Busslinger.

2

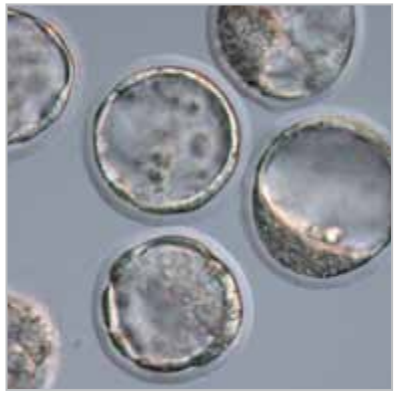


Figure 1: Injection of embryonic stem cells into mouse blastocyst.

Figure 2: Mouse blastocysts.

SERVICE DEPARTMENT

gotthold.schaffner@imp.ac.at

Head of Facility:
Gotthold Schaffner

Technicians:
Ivan Botto, Markus Hohl, Shahryar Taghybeeglu

Technicians, Media Kitchen:
Christa Detz-Jaderny, Dagmar Faustenhammer, Ulrike Windholz

Technicians, Fly Food Preparation:
Christine Giesel, Franziska Stransky

Freelancers, Fly Food Preparation:
Oliver Botto, Thomas Haydn, Anna Windholz

The Service Department offers IMP, IMBA and GMI scientists a wide range of rapid and high-quality services. Our efforts primarily consist of DNA sequencing, fly food production, and the preparation of various media and solutions.

Our Media Kitchen and Fly Food staff prepare substantial quantities of reagent quality solutions and media for cell culture, flies (more than 1'700'000 tubes and bottles per year) and other organisms. The Fly Food facilities are located in the IMP building, which is provided with sufficient daylight and space to create better and more convenient working conditions for preparing fly food and storing the goods we need.
We also prepare several selected reagents such as DNA molecular weight markers, enzymes, and a variety of transformation-competent E. coli strains. We maintain a stock of cloning vectors, sequencing primers and other reagents.

Production of antibodies

A part of our working hours are devoted to the production and isolation of many different monoclonal antibodies in hybridomas in collaboration with IMP group members, and the organization of antibody production in rabbits in collaboration with an external company.

Sequencing and DNA isolation

The 48-capillary ABI 3730 DNA Genetic Analyzer is the only workhorse, but clearly at its limit. An additional sequencer will be needed as soon as possible to keep the return time within reasonable limits. We sequenced approximately 100'000 samples during the first ten months of this year. This implies a substantially higher demand due to screening projects, the new fly library, as well as new groups at IMBA, IMP, GMI and, last but not least, SUMMER STUDENTS.

The quality and concentration of DNA samples, even when prepared by sophisticated Qiagen kits such as Midi-, Maxi- or Minipreps, is still a problem. The same is true for incorrect primer sets or insufficiently documented plasmid constructs from external sources.

Sequencing is performed faster and more easily than analyzing the samples by restriction digests or running them on an agarose gel!
The clean-up 96-well microtiter plates are no longer filled manually but with a BioTek benchtop minirobot with an optimized Sephadex G50 superfine slurry.

The centrifugation conditions have also been optimized. Occasionally, we still see "dye blobs" in cases of poor quality or with low yield DNA from standard procedures. The greater proportion of contaminants as compared to PCR products obviously plays a major role.

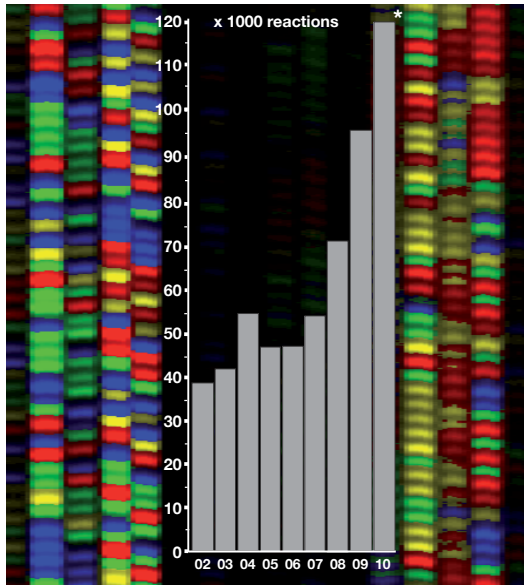


Figure: A sequencing run on an ABI 377 PRISM and numbers of reactions analyzed on ABI 3100 (from 2002 onward) and ABI 3730 (from June 2004 onward) with dye deoxy terminators (v3.0 from 2002 onward) from 2002 to 2010 (scale 0 to 96,000).
*calculated from data collected between January 2010 and September 2010

MAX PERUTZ LIBRARY

library@imp.ac.at

Head Librarian: Karlo Pavlovic

The Max Perutz Library is a specialized reference library located at the Campus Vienna Biocenter. Its mission is to develop and maintain collections and services that support research at the various institutes.

The main task of the library is to provide comprehensive scientific literature pertaining to the areas of research pursued at the institutes. The Max Perutz Library holds more than 3500 titles in print. These are partly available in the library's premises itself, being labeled and shelved according to a specific classification system. A part of the titles are shelved in the group laboratories and offices. All book holdings can be searched for systematically in the online catalog, where each item is described in respect of its location and lending status. Special book collections are available online on the platform of the relevant publishers.
Several bibliographic and full-text databases can be searched for relevant literature on a given topic. This also applies to literature on methods and protocols, including Springer Protocols, Current Protocols, Cold Spring Harbor Protocols and the recently licensed Journal of Visualized Experiments. A document delivery option is offered for the literature not licensed by the library.

Study environment

The reading room serves as a quiet and well-equipped place for reading, writing or just relaxing. Twenty-four study desks and a cozy lounge as well as two public computers, wireless LAN and a printing facility are provided.

Teaching

The library offers special individually oriented training on literature search tools such as catalogs and bibliographic databases for all library users. This ranges from a comprehensive hands-on course on Pubmed searching to a specific consultation concerning a single challenge in retrieving literature. Assistance is also provided for a variety of client- and web-based literature management tools, such as Endnote or Mendeley.

Users

The core user group consists of affiliates of the Research Institute of Molecular Pathology (IMP), the Institute of Molecular Biotechnology (IMBA), and the Gregor Mendel Institute of Molecular Plant Biology (GMI). External users from the Max F. Perutz Laboratories (MFPL), the FH Campus Vienna and other readers from the Vienna Biocenter are welcome to visit the library premises.

Publications

BRENNECKE

Olivieri, D., Sykora, MM., Sachidanandam, R., Mechtler, K., Brennecke, J. (2010). An in vivo RNAi assay identifies major genetic and cellular requirements for primary piRNA biogenesis in Drosophila. EMBO J. 29(19):3301-17

Senti, KA., Brennecke, J. (2010). The piRNA pathway: a fly's perspective on the guardian of the genome. Trends Genet. 26(12):499-509

KNOBLICH

Khazaei, MR., Bunk, EC., Hillje, AL., Jahn, HM., Riegler, EM., Knoblich, JA., Young, P., Schwamborn, JC. (2010). The E3-ubiquitin ligase TRIM2 regulates neuronal polarization. J Neurochem. In press.

Knoblich, JA. (2010). Asymmetric cell division: recent developments and their implications for tumour biology. Nat Rev Mol Cell Biol. 11(12):849-60

Mummery-Widmer, JL., Yamazaki, M., Stoeger, T., Novatchkova, M., Bhalerao, S., Chen, D., Dietzl, G., Dickson, BJ., Knoblich, JA. (2009). Genome-wide analysis of Notch signalling in Drosophila by transgenic RNAi. Nature. 458(7241):987-92

Neumüller, R.A. and Knoblich, J.A. (2009). Dividing cellular asymmetry: asymmetric cell division and its implications for stem cells and cancer. Genes Dev 23, 2675-2699.

Schwamborn, JC., Berezikov, E., Knoblich, JA. (2009). The TRIM-NHL protein TRIM32 activates microRNAs and prevents self-renewal in mouse neural progenitors. Cell. 136(5):913-25

MARLOVITS

Galkin, VE., Schmied, WH., Schraidt, O., Marlovits, TC., Egelman, EH. (2010). The structure of the Salmonella typhimurium type III secretion system needle shows divergence from the flagellar system. J Mol Biol. 396(5):1392-7

Khan, AG., Pickl-Herk, A., Gajdzik, L., Marlovits, TC., Fuchs, R., Blaas, D. (2010). Human rhinovirus 14 enters rhabdomyosarcoma cells expressing icam-1 by a clathrin-, caveolin-, and flotillin-independent pathway. J Virol. 84(8):3984-92

Marlovits, TC., Stebbins, CE. (2010). Type III secretion systems shape up as they ship out. Curr Opin Microbiol. 13(1):47-52

Schraidt, O., Lefebre, MD., Brunner, MJ., Schmied, WH., Schmidt, A., Radics, J., Mechtler, K., Galán, JE., Marlovits, TC. (2010). Topology and organization of the Salmonella typhimurium type III secretion needle complex components. PLoS Pathog. 6(4):e1000824

Wagner, S., Königsmaier, L., Lara-Tejero, M., Lefebre, M., Marlovits, TC., Galán, JE. (2010). Organization and coordinated assembly of the type III secretion export apparatus. Proc Natl Acad Sci U S A. 107(41):17745-50

MARTINEZ

Katrin Heindl and Javier Martinez. Nol9 is a novel polynucleotide 5'-kinase involved in ribosomal RNA processing. EMBO Journal, Epub 2010 Nov 9

Priscilla Braglia, Katrin Heindl, Alexander Schleiffer, Javier Martinez† and Nick J. Proudfoot†. Role of the RNA/DNA kinase Grc3 in transcription termination by RNA polymerase I. EMBO Reports, 2010 Oct;11(10):758-64. Epub 2010 Sep 3. ; †co-corresponding authors.

Johannes Popow, Markus Englert,* Stefan Weitzer, Alexander Schleiffer, Beata Mierzwa, Karl Mechtler, Simon Trowitzsch, Cindy Will, Reinhard Lührmann, Dieter Söll† and Javier Martinez†. HSPC117/C22ORF28 is the catalytic subunit of the human tRNA ligase. Science, *co-first authors; †co-corresponding authors. In press.*

MOCHIZUKI

Busch, CJ., Vogt, A., Mochizuki, K. (2010). Establishment of a Cre/loxP recombination system for N-terminal epitope tagging of genes in Tetrahymena. BMC Microbiol. 10:191

Cheng, CY., Vogt, A., Mochizuki, K., Yao, MC. (2010). A domesticated piggyBac transposase plays key roles in heterochromatin dynamics and DNA cleavage during programmed DNA deletion in Tetrahymena thermophila. Mol Biol Cell. 21(10):1753-62

Kataoka, K. and Mochizuki, K. (2010) Programmed DNA elimination in Tetrahymena: a small RNA-mediated genome surveillance mechanism. in ncRNA Networks, Collins, L. ed. Landes Bioscience, In press.

Kataoka, K., Schoeberl, UE., Mochizuki, K. (2010). Modules for C-terminal epitope tagging of Tetrahymena genes. J Microbiol Methods. 82(3):342-6

Lukaszewicz, A., Howard-Till, RA., Novatchkova, M., Mochizuki, K., Loidl, J. (2010). MRE11 and COM1/SAE2 are required for double-strand break repair and efficient chromosome pairing during meiosis of the protist Tetrahymena. Chromosoma. 119(5):505-18

Mochizuki, K. (2010) DNA rearrangements directed by non-coding RNAs in ciliates. Wiley Interdisciplinary Reviews: RNA, Wilusz, J. ed. John Wiley & Sons, DOI: 10.1002/wrna.34.

Mochizuki, K. (2010). RNA-directed epigenetic regulation of DNA rearrangements. Essays Biochem. 48(1):89-100

Noto, T., Kurth, HM., Kataoka, K., Aronica, L., DeSouza, LV., Siu, KW., Pearlman, RE., Gorovsky, MA., Mochizuki, K. (2010). The Tetrahymena argonaute-binding protein Giw1p directs a mature argonaute-siRNA complex to the nucleus. Cell. 140(5):692-703

PENNINGER

Awad, AE., Kandalam, V., Chakrabarti, S., Wang, X., Penninger, JM., Davidge, ST., Oudit, GY., Kassiri, Z. (2010). Tumor necrosis factor induces matrix metalloproteinases in cardiomyocytes and cardiofibroblasts differentially via superoxide production in a PI3Kgamma-dependent manner. Am J Physiol Cell Physiol. 298(3):C679-92

Blaas, L., Kornfeld, JW., Schramek, D., Musteanu, M., Zollner, G., Gumhold, J., van Zijl, F., Schneller, D., Esterbauer, H., Egger, G., Mair, M., Kenner, L., Mikulits, W., Eferl, R., Moriggl, R., Penninger, J., Trauner, M., Casanova, E. (2010). Disruption of the growth hormone--signal transducer and activator of transcription 5--insulinlike growth factor 1 axis severely aggravates liver fibrosis in a mouse model of cholestasis. Hepatology. 51(4):1319-26

Charlier, E., Condé, C., Zhang, J., Deneubourg, L., Di Valentin, E., Rahmouni, S., Chariot, A., Agostinis, P., Pang, PC., Haslam, SM., Dell, A., Penninger, J., Erneux, C., Piette, J., Gloire, G. (2010). SHIP-1 inhibits CD95/APO-1/Fas-induced apoptosis in primary T lymphocytes and T leukemic cells by promoting CD95 glycosylation independently of its phosphatase activity. Leukemia. 24(4):821-32

Del Toro, R., Prahst, C., Mathivet, T., Siegfried, G., Kaminker, JS., Larrivee, B., Breant, C., Duarte, A., Takakura, N., Fukamizu, A., Penninger, J., Eichmann, A. (2010). Identification and functional analysis of endothelial tip cell-enriched genes. Blood. 116(19):4025-33

Dobnig, H., Penninger, J., Leibbrandt, A., Resch, H., and M. Woltz. (2010). Denosumab – postemnopausale Osteoporose. Arzneimittel Profil. 3-11.

Fleuren, ED., O'Toole, S., Millar, EK., McNeil, C., Lopez-Knowles, E., Boulghourjian, A., Croucher, DR., Schramek, D., Brummer, T., Penninger, JM., Sutherland, RL., Daly, RJ. (2010). Overexpression of the oncogenic signal transducer Gab2 occurs early in breast cancer development. Int J Cancer. 127(6):1486-92

Guo, D., Kassiri, Z., Basu, R., Chow, FL., Kandalam, V., Damilano, F., Liang, W., Izumo, S., Hirsch, E., Penninger, JM., Backx, PH., Oudit, GY. (2010). Loss of PI3K{gamma} Enhances cAMP-Dependent MMP Remodeling of the Myocardial N-Cadherin Adhesion Complexes and Extracellular Matrix in Response to Early Biomechanical Stress. Circ Res. 107(10):1275-89

Hanada, R., Hanada, T., Penninger, JM. (2010). Physiology and pathophysiology of the RANKL/RANK system. Biol Chem. 391(12):1365-70

Hanada, R., Hanada, T. and J. M. Penninger. (2010). RANKL/RANK - beyond bones. J. Mol. Med. In press.

Hanada, R., and J. M. Penninger. (2010). Central control of fever and female body temperature by RANKL/RANK. Experimental Med. 28, 930-906.

Haubner, BJ., Neely, GG., Voelkl, JG., Damilano, F., Kuba, K., Imai, Y., Komnenovic, V., Mayr, A., Pachinger, O., Hirsch, E., Penninger, JM., Metzler, B. (2010). PI3Kgamma

protects from myocardial ischemia and reperfusion injury through a kinase-independent pathway. PLoS One. 5(2):e9350

Heindl-Erdmann, C., Axmann, R., Kreitz, S., Zwerina, J., Penninger, J., Schett, G., Brune, K., Hess, A. (2010). Combining functional magnetic resonance imaging with mouse genomics: new options in pain research. Neuroreport. 21(1):29-33

Imai, Y., Kuba, K., Ohto-Nakanishi, T., Penninger, JM. (2010). Angiotensin-converting enzyme 2 (ACE2) in disease pathogenesis. Circ J. 74(3):405-10

Jin, R., Yu, S., Song, Z., Quillin, JW., Deasis, DP., Penninger, JM., Nanda, A., Granger, DN., Li, G. (2010). Phosphoinositide 3-kinase-gamma expression is upregulated in brain microglia and contributes to ischemia-induced microglial activation in acute experimental stroke. Biochem Biophys Res Commun. 399(3):458-64

Klaiber, M., Kruse, M., Völker, K., Schröter, J., Feil, R., Freichel, M., Gerling, A., Feil, S., Dietrich, A., Londoño, JE., Baba, HA., Abramowitz, J., Birnbaumer, L., Penninger, JM., Pongs, O., Kuhn, M. (2010). Novel insights into the mechanisms mediating the local antihypertrophic effects of cardiac atrial natriuretic peptide: role of cGMP-dependent protein kinase and RGS2. Basic Res Cardiol. 105(5):583-95

Kuba, K., Imai, Y., Ohto-Nakanishi, T., Penninger, JM. (2010). Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther. 128(1):119-28

Leibbrandt, A., Penninger, JM. (2010). Novel Functions of RANK(L) Signaling in the Immune System. Adv Exp Med Biol. 658:77-94

Leibbrandt, A., and Penninger, J. M. (2010). Beyond bones – functions of RANKL and RANK in the immune system. Proceedings of the TNF meeting 2009. In press.

Meixner, A., Karreth, F., Kenner, L., Penninger, JM., Wagner, EF. (2010). Jun and JunD-dependent functions in cell proliferation and stress response. Cell Death Differ. 17(9):1409-19

Molyneux, SD., Di Grappa, MA., Beristain, AG., McKee, TD., Wai, DH., Paderova, J., Kashyap, M., Hu, P., Maiuri, T., Narala, SR., Stambolic, V., Squire, J., Penninger, J., Sanchez, O., Triche, TJ., Wood, GA., Kirschner, LS., Khokha, R. (2010). Prkar1a is an osteosarcoma tumor suppressor that defines a molecular subclass in mice. J Clin Invest. 120(9):3310-25

Neely, GG., Hess, A., Costigan, M., Keene, AC., Goulas, S., Langeslag, M., Griffin, RS., Belfer, I., Dai, F., Smith, SB., Diatchenko, L., Gupta, V., Xia, CP., Amann, S., Kreitz, S., Heindl-Erdmann, C., Wolz, S., Ly, CV., Arora, S., Sarangi, R., Dan, D., Novatchkova, M., Rosenzweig, M., Gibson, DG., Truong, D., Schramek, D., Zoranovic, T., Cronin, SJ., Angjeli, B., Brune, K., Dietzl, G., Maixner, W., Meixner, A., Thomas, W., Pospisilik, JA., Alenius, M., Kress, M., Subramaniam, S., Garrity, PA., Bellen, HJ., Woolf, CJ., Penninger, JM. (2010). A Genome-wide Drosophila Screen for Heat Nociception Identifies α2δ3 as an Evolutionarily Conserved Pain Gene. Cell. 143(4):628-38

Neely, GG., Kuba, K., Cammarato, A., Isobe, K., Amann, S., Zhang, L., Murata, M., Elmén, L., Gupta, V., Arora, S., Sarangi, R., Dan, D., Fujisawa, S., Usami, T., Xia, CP., Keene, AC., Alayari, NN., Yamakawa, H., Elling, U., Berger, C., Novatchkova, M., Koglgruber, R., Fukuda, K., Nishina, H., Isobe, M., Pospisilik, JA., Imai, Y., Pfeufer, A., Hicks, AA., Pramstaller, PP., Subramaniam, S., Kimura, A., Ocorr, K., Bodmer, R., Penninger, JM. (2010). A global in vivo Drosophila RNAi screen identifies NOT3 as a conserved regulator of heart function. Cell. 141(1):142-53

Oh, SY., Park, JU., Zheng, T., Kim, YK., Wu, F., Cho, SH., Barber, D., Penninger, J., Zhu, Z. (2010). Cbl-b regulates airway mucosal tolerance to aeroallergen. Clin Exp Allergy. In press.

Oudit, GY., Liu, GC., Zhong, J., Basu, R., Chow, FL., Zhou, J., Loibner, H., Janzek, E., Schuster, M., Penninger, JM., Herzenberg, AM., Kassiri, Z., Scholey, JW. (2010). Human recombinant ACE2 reduces the progression of diabetic nephropathy. Diabetes. 59(2):529-38

Paolino, M., Penninger, JM. (2010). Cbl-b in T-cell activation. Semin Immunopathol. 32(2):137-48

Pospisilik, JA., Schramek, D., Schnidar, H., Cronin, SJ., Nehme, NT., Zhang, X., Knauf, C., Cani, PD., Aumayr, K., Todoric, J., Bayer, M., Haschemi, A., Puviindran, V., Tar, K., Orthofer, M., Neely, GG., Dietzl, G., Manoukian, A., Funovics, M., Prager, G., Wagner, O., Ferrandon, D., Aberger, F., Hui, CC., Esterbauer, H., Penninger, JM. (2010). Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate. Cell. 140(1):148-60

Saade, M., Irla, M., Yammine, M., Boulanger, N., Victorero, G., Vincentelli, R., Penninger, JM., Holländer, GA., Chauvet, S., Nguyen, C. (2010). Spatial (Tbata) expression in mature medullary thymic epithelial cells. Eur J Immunol. 40(2):530-8

Schramek, D., Leibbrandt, A., Sigl, V., Kenner, L., Pospisilik, JA., Lee, HJ., Hanada, R., Joshi, PA., Aliprantis, A., Glimcher, L., Pasparakis, M., Khokha, R., Ormandy, CJ., Widschwendter, M., Schett, G., Penninger, JM. (2010). Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature. 468(7320):98-102

Seo, J., Asaoka, Y., Nagai, Y., Hirayama, J., Yamasaki, T., Namae, M., Ohata, S., Shimizu, N., Negishi, T., Kitagawa, D., Kondoh, H., Furutani-Seiki, M., Penninger, JM., Katada, T., Nishina, H. (2010). Negative regulation of wnt11 expression by Jnk signaling during zebrafish gastrulation. J Cell Biochem. 110(4):1022-37

Treml, B., Neu, N., Kleinsasser, A., Gritsch, C., Finsterwalder, T., Geiger, R., Schuster, M., Janzek, E., Loibner, H., Penninger, J., Loeckinger, A. (2010). Recombinant angiotensin-converting enzyme 2 improves pulmonary blood flow and oxygenation in lipopolysaccharide-induced lung injury in piglets. Crit Care Med. 38(2):596-601

Wysocki, J., Ye, M., Rodriguez, E., González-Pacheco, FR., Barrios, C., Evora, K., Schuster, M., Loibner, H., Brosnihan, KB., Ferrario, CM., Penninger, JM., Batlle, D. (2010). Targeting the degradation of angiotensin II with recombinant angiotensin-converting enzyme 2: prevention of angiotensin II-dependent hypertension. Hypertension. 55(1):90-8

Xu, H., Su, Z., Wu, J., Yang, M., Penninger, JM., Martin, CM., Kvietys, PR., Rui, T. (2010). The alarmin cytokine, high mobility group box 1, is produced by viable cardiomyocytes and mediates the lipopolysaccharide-induced myocardial dysfunction via a TLR4/phosphatidylinositol 3-kinase gamma pathway. J Immunol. 184(3):1492-8

Zhao, M., Penninger, J., and R. R. Isseroff. (2010). Electrical activation of wound healing pathways. In press.

Zhong, J., Basu, R., Guo, D., Chow, FL., Byrns, S., Schuster, M., Loibner, H., Wang, XH., Penninger, JM., Kassiri, Z., Oudit, GY. (2010). Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. Circulation. 122(7):717-28, 18 p following 728

Zhong, JC., Ye, JY., Jin, HY., Yu, X., Yu, HM., Zhu, DL., Gao, PJ., Huang, DY., Shuster, M., Loibner, H., Guo, JM., Yu, XY., Xiao, BX., Gong, ZH., Penninger, JM., Oudit, GY. (2010). Telmisartan attenuates aortic hypertrophy in hypertensive rats by the modulation of ACE2 and profilin-1 expression. Regul Pept. In press.

SMALL

Resch, GP., Urban, E., Jacob, S. (2010). The actin cytoskeleton in whole mount preparations and sections. Methods Cell Biol. 96:529-64

Small, JV. (2010). Dicing with dogma: de-branching the lamellipodium. Trends Cell Biol. 20(11):628-33

Small, J.V. and Rottner, K.R. (2010). Elementary Cellular Processes Driven by Actin Assembly: Lamellipodia and Filopodia. In "Actin-based Motility" Ed by M.F. Carlier, Springer Science, in press.

Small, J.V. (2010). Cell migration. Encyclopedia of Biological Chemistry, 2nd Edn, Elsevier Inc. in press.

Urban, E., Jacob, S., Nemethova, M., Resch, GP., Small, JV. (2010). Electron tomography reveals unbranched networks of actin filaments in lamellipodia. Nat Cell Biol. 12(5):429-35

PUBLICATIONS

STEM CELL CENTER – MOUSE GENE TARGETING

Meixner A, Karreth F, Kenner L, Penninger JM, Wagner EF. Jun and JunD-dependent functions in cell proliferation and stress response. Cell Death Differ. 2010 Sep;17(9):1409-19.

Neely GG, Hess A, Costigan M, Keene AC, Goulas S, Langeslag M, Griffin RS, Belfer I, Dai F, Smith SB, Diatchenko L, Gupta V, Xia CP, Amann S, Kreitz S, Heindl-Erdmann C, Wolz S, Ly CV, Arora S, Sarangi R, Dan D, Novatchkova M, Rosenzweig M, Gibson DG, Truong D, Schramek D, Zoranovic T, Cronin SJ, Angjeli B, Brune K, Dietzl G, Maixner W, Meixner A, Thomas W, Pospisilik JA, Alenius M, Kress M, Subramaniam S, Garrity PA, Bellen HJ, Woolf CJ, Penninger JM. A Genome-wide Drosophila Screen for Heat Nociception Identifies α2δ3 as an Evolutionarily Conserved Pain Gene Cell. 2010 Nov 12;143(4):628-38.

KELEMAN

Schnorrer, F., Schönbauer, C., Langer, CC., Dietzl, G., Novatchkova, M., Schernhuber, K., Fellner, M., Azaryan, A., Radolf, M., Stark, A., Keleman, K., Dickson, BJ. (2010). Systematic genetic analysis of muscle morphogenesis and function in Drosophila. Nature. 464(7286):287-91

BIOOPTICS

Baumann CL, Aspalter IM, Sharif O, Pichlmair A, Blüml S, Grebien F, Bruckner M, Pasierbek P, Aumayr K, Planyavsky M, Bennett KL, Colinge J, Knapp S, Superti-Furga G. (2010) CD14 is a co-receptor of Toll-like receptors 7 and 9. J Exp Med. 2010 Nov 22;207(12):2689-701

Baudrimont A, Penkner A, Woglar A, Machacek T, Wegrostek C, Gloggnitzer J, Fridkin A, Klein F, Gruenbaum Y, Pasierbek P, Jantsch V (2010) Leptotene/zygotene chromosome movement via the SUN/KASH protein bridge in C. elegans. PLoS Genet 6(11): e1001219

Penkner AM, Fridkin A, Gloggnitzer J, Baudrimont A, Machacek T, Woglar A, Csaszar E, Pasierbek P, Ammerer G, Gruenbaum Y, Jantsch V. (2009) Meiotic chromosome homology search involves modifications of the nuclear envelope protein Matefin/SUN-1. Cell. 2009 Nov 25;139(5):920-33. Epub 2009 Nov 12.
Hoelbl, A., Schuster, C., Kovacic, B., Zhu, B., Wickre, M., Hoelzl, MA., Fajmann, S., Grebien, F., Warsch, W., Stengl, G., Hennighausen, L., Poli, V., Beug, H., Moriggl, R., Sexl, V. (2010). Stat5 is indispensable for the maintenance of bcr/abl-positive leukaemia. EMBO Mol Med. 2(3):98-110

Pospisilik, JA., Schramek, D., Schnidar, H., Cronin, SJ., Nehme, NT., Zhang, X., Knauf, C., Cani, PD., Aumayr, K., Todoric, J., Bayer, M., Haschemi, A., Puviindran, V., Tar, K., Orthofer, M., Neely, GG., Dietzl, G., Manoukian, A., Funovics, M., Prager, G., Wagner, O., Ferrandon, D., Aberger, F., Hui, CC., Esterbauer, H., Penninger, JM. (2010). Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate. Cell. 140(1):148-60

ELECTRON MICROSCOPY

Urban, E., Jacob, S., Nemethova, M., Resch, G. P., Small, J. V. (2010): Electron tomography reveals unbranched networks of actin filaments in lamellipodia. Nat Cell Biol 12(5): 429-435.

Resch, G. P., Urban, E., Jacob, S. (2010): The Actin Cytoskeleton in Whole Mount Preparations and Sections. Meth Cell Biol 98: 529-564.

BIOINFORMATICS

Braglia, P., Heindl, K., Schleiffer, A., Martinez, J., Proudfoot, NJ. (2010). Role of the RNA/DNA kinase Grc3 in transcription termination by RNA polymerase I. EMBO Rep. 11(10):758-64.

Hutchins, JR., Toyoda, Y., Hegemann, B., Poser, I., Hériché, JK., Sykora, MM., Augsburg, M., Hudecz, O., Buschhorn, BA., Bulkescher, J., Conrad, C., Comartin, D., Schleiffer, A., Sarov, M., Pozniakovsky, A., Slabicki, MM., Schloissnig, S., Steinmacher, I., Leuschner, M., Ssykor, A., Lawo, S., Pelletier, L., Stark, H., Nasmyth, K., Ellenberg, J., Durbin, R., Buchholz, F., Mechtler, K., Hyman, AA., Peters, JM. (2010). Systematic analysis of human protein complexes identifies chromosome segregation proteins. Science. 328(5978):593-9.

Leeb, M., Pasini, D., Novatchkova, M., Jaritz, M., Helin, K., Wutz, A. (2010). Polycomb complexes act redundantly to repress genomic repeats and genes.. Genes Dev. 24(3):265-76.

Lukaszewicz, A., Howard-Till, RA., Novatchkova, M., Mochizuki, K., Loidl, J. (2010). MRE11 and COM1/SAE2 are required for double-strand break repair and efficient chromosome pairing during meiosis of the protist Tetrahymena.. Chromosoma. 119(5):505-18.

Malin, S., McManus, S., Cobaleda, C., Novatchkova, M., Delogu, A., Bouillet, P., Strasser, A., Busslinger, M. (2010). Role of STAT5 in controlling cell survival and immunoglobulin gene recombination during pro-B cell development.. Nat Immunol. 11(2):171-9.

Marth, K., Novatchkova, M., Focke-Tejkl, M., Jenisch, S., Jäger, S., Kabelitz, D., Valenta, R. (2010). Tracing antigen signatures in the human IgE repertoire.. Mol Immunol. 47(14):2323-9.

Neely, GG., Hess, A., Costigan, M., Keene, AC., Goulas, S., Langeslag, M., Griffin, RS., Belfer, I., Dai, F., Smith, SB., Diatchenko, L., Gupta, V., Xia, CP., Amann, S., Kreitz, S., Heindl-Erdmann, C., Wolz, S., Ly, CV., Arora, S., Sarangi, R., Dan, D., Novatchkova, M., Rosenzweig, M., Gibson, DG., Truong, D., Schramek, D., Zoranovic, T., Cronin, SJ., Angjeli, B., Brune, K., Dietzl, G., Maixner, W., Meixner, A., Thomas, W., Pospisilik, JA., Alenius, M., Kress, M., Subramaniam, S., Garrity, PA., Bellen, HJ., Woolf, CJ., Penninger, JM. (2010). A Genome-wide Drosophila Screen for Heat Nociception Identifies α2δ3 as an Evolutionarily Conserved Pain Gene. Cell. 143(4):628-38.

Neely, GG., Kuba, K., Cammarato, A., Isobe, K., Amann, S., Zhang, L., Murata, M., Elmén, L., Gupta, V., Arora, S., Sarangi, R., Dan, D., Fujisawa, S., Usami, T., Xia, CP., Keene, AC., Alayari, NN., Yamakawa, H., Elling, U., Berger, C., Novatchkova, M., Koglgruber, R., Fukuda, K., Nishina, H., Isobe, M., Pospisilik, JA., Imai, Y., Pfeufer, A., Hicks, AA., Pramstaller, PP., Subramaniam, S., Kimura, A., Ocorr, K., Bodmer, R., Penninger, JM. (2010). A global in vivo Drosophila RNAi screen identifies NOT3 as a conserved regulator of heart function. Cell. 141(1):142-53.

Nishiyama, T., Ladurner, R., Schmitz, J., Kreidl, E., Schleiffer, A., Bhaskara, V., Bando, M., Shirahige, K., Hyman, AA., Mechtler, K., Peters, JM. (2010). Sororin mediates sister chromatid cohesion by antagonizing wapl. Cell. 143(5):737-49

Rumpf, C., Cipak, L., Novatchkova, M., Li, Z., Polakova, S., Dudas, A., Kovacikova, I., Miadokova, E., Ammerer, G., Gregan, J. (2010). High-throughput knockout screen in Schizosaccharomyces pombe identifies a novel gene required for efficient homolog disjunction during meiosis I. Cell Cycle. 9(9):1802-8.

Rumpf, C., Cipak, L., Schleiffer, A., Pidoux, A., Mechtler, K., Tolić-Nørrelykke, IM., Gregan, J. (2010). Laser microsurgery provides evidence for merotelic kinetochore attachments in fission yeast cells lacking Pcs1 or Clr4. Cell Cycle. 9(19):3997-4004.

Schnorrer, F., Schönbauer, C., Langer, CC., Dietzl, G., Novatchkova, M., Schernhuber, K., Fellner, M., Azaryan, A., Radolf, M., Stark, A., Keleman, K., Dickson, BJ. (2010). Systematic genetic analysis of muscle morphogenesis and function in Drosophila. Nature. 464(7286):287-91.

GENOMICS

Schnorrer, F., Schönbauer, C., Langer, CC., Dietzl, G., Novatchkova, M., Schernhuber, K., Fellner, M., Azaryan, A., Radolf, M., Stark, A., Keleman, K., Dickson, BJ. (2010). Systematic genetic analysis of muscle morphogenesis and function in Drosophila. Nature. 464(7286):287-91.

PROTEIN CHEMISTRY

Alpert, AJ., Petritis, K., Kangas, L., Smith, RD., Mechtler, K., Mitulović, G., Mohammed, S., Heck, AJ. (2010). Peptide orientation affects selectivity in ion-exchange chromatography. Anal Chem. 82(12):5253-9.

Haider, S., Wagner, M., Schmid, MC., Sixt, BS., Christian, JG., Häcker, G., Pichler, P., Mechtler, K., Müller, A., Baranyi, C., Toenshoff, ER., Montanaro, J., Horn, M. (2010). Raman microspectroscopy reveals long-term extracellular activity of Chlamydiae.. Mol Microbiol. 77(3):687-700.

Heinz E, Pichler P, Heinz C, Op den Camp HJ, Toenshoff ER, Ammerer G, Mechtler K, Wagner M, Horn M. Proteomic analysis of the outer membrane of Protochlamydia amoebophila elementary bodies. Proteomics. 2010 Oct 14. [Epub ahead of print]

Holzmann, J., Fuchs, J., Pichler, P., Peters, JM., Mechtler, K. (2010). Lesson from the Stoichiometry Determination of the Cohesin Complex: A Short Protease Mediated Elution Increases the Recovery from Cross-Linked Antibody-Conjugated Beads. J Proteome Res. Nov, 18 [Epub ahead of print]

Holzmann J, Pichler P, Madalinski M, Kurzbauer R, Mechtler K. Stoichiometry determination of the MP1-p14 complex using a novel and cost-efficient method to produce an equimolar mixture of standard peptides. Anal Chem. 2009 Dec 15;81(24):10254-61.

Hutchins, JR., Toyoda, Y., Hegemann, B., Poser, I., Hériché, JK., Sykora, MM., Augsburg, M., Hudecz, O., Buschhorn, BA., Bulkescher, J., Conrad, C., Comartin, D., Schleiffer, A., Sarov, M., Pozniakovsky, A., Slabicki, MM., Schloissnig, S., Steinmacher, I., Leuschner, M., Ssykor, A., Lawo, S., Pelletier, L., Stark, H., Nasmyth, K., Ellenberg, J., Durbin, R., Buchholz, F., Mechtler, K., Hyman, AA., Peters, JM. (2010). Systematic analysis of human protein complexes identifies chromosome segregation proteins. Science. 328(5978):593-9

Katis, VL., Lipp, JJ., Imre, R., Bogdanova, A., Okaz, E., Habermann, B., Mechtler, K., Nasmyth, K., Zachariae, W. (2010). Rec8 phosphorylation by casein kinase 1 and Cdc7-Dbf4 kinase regulates cohesin cleavage by separase during meiosis.. Dev Cell. 18(3):397-409.

Leitner, A., Sturm, M., Hudecz, O., Mazanek, M., Smått, JH., Lindén, M., Lindner, W., Mechtler, K. (2010). Probing the phosphoproteome of HeLa cells using nanocast metal oxide microspheres for phosphopeptide enrichment. Anal Chem. 82(7):2726-33.

Mach-Aigner, AR., Grosstessner-Hain, K., Pocas-Fonseca, MJ., Mechtler, K., Mach, RL. (2010). From an electrophoretic mobility shift assay to isolated transcription factors: a fast genomic-proteomic approach. BMC Genomics. 11(1):644.

Mazanek, M., Roitinger, E., Hudecz, O., Hutchins, JR., Hegemann, B., Mitulović, G., Taus, T., Stingl, C., Peters, JM., Mechtler, K. (2010). A new acid mix enhances phosphopeptide enrichment on titanium- and zirconium dioxide for mapping of phosphorylation sites on protein complexes. J Chromatogr B Analyt Technol Biomed Life Sci. 878(5-6):515-24

Morandell, S., Grosstessner-Hain, K., Roitinger, E., Hudecz, O., Lindhorst, T., Teis, D., Wrulich, OA., Mazanek, M., Taus, T., Ueberall, F., Mechtler, K., Huber, LA. (2010). QIKS--Quantitative identification of kinase substrates. Proteomics. 10(10):2015-25.

Mujezinovic, N., Schneider, G., Wildpaner, M., Mechtler, K., Eisenhaber, F. (2010). Reducing the haystack to find the needle: improved protein identification after fast elimination of non-interpretable peptide MS/MS spectra and noise reduction. BMC Genomics. 11 Suppl 1:S13.

Nishiyama, T., Ladurner, R., Schmitz, J., Kreidl, E., Schleiffer, A., Bhaskara, V., Bando, M., Shirahige, K., Hyman, AA., Mechtler, K., Peters, JM. (2010). Sororin mediates sister chromatid cohesion by antagonizing wapl. Cell. 143(5):737-49

Olivieri, D., Sykora, MM., Sachidanandam, R., Mechtler, K., Brennecke, J. (2010). An in vivo RNAi assay identifies major genetic and cellular requirements for primary piRNA biogenesis in Drosophila.. EMBO J. 29(19):3301-17.

Owald, D., Fouquet, W., Schmidt, M., Wichmann, C., Mertel, S., Depner, H., Christiansen, F., Zube, C., Quentin, C., Körner, J., Urlaub, H., Mechtler, K., Sigrist, SJ. (2010). A Syd-1 homologue regulates pre- and postsynaptic maturation in Drosophila.. J Cell Biol. 188(4):565-79.

Pichler, P., Köcher, T., Holzmann, J., Mazanek, M., Taus, T., Ammerer, G., Mechtler, K. (2010). Peptide labeling with isobaric tags yields higher identification rates using iTRAQ 4-plex compared to TMT 6-plex and iTRAQ 8-plex on LTQ Orbitrap.. Anal Chem. 82(15):6549-58.

Rumpf, C., Cipak, L., Dudas, A., Benko, Z., Pozgajova, M., Riedel, CG., Ammerer, G., Mechtler, K., Gregan, J. (2010). Casein kinase 1 is required for efficient removal of Rec8 during meiosis I. Cell Cycle. 9(13).

Rumpf, C., Cipak, L., Schleiffer, A., Pidoux, A., Mechtler, K., Tolić-Nørrelykke, IM., Gregan, J. (2010). Laser microsurgery provides evidence for merotelic kinetochore attachments in fission yeast cells lacking Pcs1 or Clr4. Cell Cycle. 9(19):3997-4004.

Schmitz, MH., Held, M., Janssens, V., Hutchins, JR., Hudecz, O., Ivanova, E., Goris, J., Trinkle-Mulcahy, L., Lamond, AI., Poser, I., Hyman, AA., Mechtler, K., Peters, JM., Gerlich, DW. (2010). Live-cell imaging RNAi screen identifies PP2A-B55alpha and importin-beta1 as key mitotic exit regulators in human cells. Nat Cell Biol. 12(9):886-93

Schraidt, O., Lefebre, MD., Brunner, MJ., Schmied, WH., Schmidt, A., Radics, J., Mechtler, K., Galán, JE., Marlovits, TC. (2010). Topology and organization of the Salmonella typhimurium type III secretion needle complex components. PLoS Pathog. 6(4):e1000824

Stasyk, T., Holzmann, J., Stumberger, S., Ebner, HL., Hess, MW., Bonn, GK., Mechtler, K., Huber, LA. (2010). Proteomic analysis of endosomes from genetically modified p14/MP1 mouse embryonic fibroblasts.. Proteomics. 10(22):4117-27.

Köcher T., Pichler P., Swart., R., Mechtler K. Quality control in LC-MS/MS. Proteomics. (2010). In press

Köcher T., Pichler P.,Mazanek M., Swart., R., Mechtler K. Mascot search results depend on the m/z range of MS/MS spectra: analysis and potential applications. Anal. Bioanal. Chem. (2010).

HISTOLOGY

Haubner, BJ., Neely, GG., Voelkl, JG., Damilano, F., Kuba, K., Imai, Y., Komnenovic, V., Mayr, A., Pachinger, O., Hirsch, E., Penninger, JM., Metzler, B. (2010). PI3Kgamma protects from myocardial ischemia and reperfusion injury through a kinase-independent pathway. PLoS One. 5(2):e9350.

Hnisz, D., Majer, O., Frohner, IE., Komnenovic, V., Kuchler, K. (2010). The Set3/Hos2 histone deacetylase complex attenuates cAMP/PKA signaling to regulate morphogenesis and virulence of Candida albicans.. PLoS Pathog. 6(5):e1000889.

TRANSGENIC SERVICE

Radner, FP., Streith, IE., Schoiswohl, G., Schweiger, M., Kumari, M., Eichmann, TO., Rechberger, G., Koefeler, HC., Eder, S., Schauer, S., Theussl, HC., Preiss-Landl, K., Lass, A., Zimmermann, R., Hoefler, G., Zechner, R., Haemmerle, G. (2010). Growth retardation, impaired triacylglycerol catabolism, hepatic steatosis, and lethal skin barrier defect in mice lacking comparative gene identification-58 (CGI-58). J Biol Chem. 285(10):7300-11.

Awards & Honors 2010

Julius Brennecke:

- *"Starting Independent Researcher Grants" by the European Research Council ERC*
- *START Prize, Vienna, Austria*
- *Premio Leonardo da Vinci, Vienna, Austria*

Jesus Fernandez Rodriguez:

- *Best Poster Prize & Best Selected Talk at "Analysis and Engineering of Biomolecular Systems"*

Jürgen Knoblich:

- *"Advanced Investigator Grant" by the European Research Council ERC*
- *Elected to the Austrian Academy of Sciences as Corresponding Member*

Vukoslav Komnenovic:

- *Publication Prize of the German Speaking Mycological Society (DMykG)*

Henriette Kurth:

- *Nature Structural Molecular Biology Poster Prize, The 15th annual meeting of the RNA Society, Seattle*
- *VBC PhD Award*

Karl Mechtler:

- *"Outstanding Scientist Technology Award" by the Association of Biomolecular Resource Facilities*

Fabio Mohn:

- *Prize for best PhD thesis by FMI Basel*

Daniel Schramek:

- *VBC PhD Award*

Marlene Vinzenz:

- *Best Poster Prize at the International meeting of the German society for cell biology "Actin Dynamics", Jena*

SEMINAR SPEAKERS

JANUARY

07.01.10 Stanley A. Plotkin
Sanofi Pasteur
Correlates of Immunity After Vaccination

12.01.10 Scott W. Lowe
Cold Spring Harbor Laboratory
Dissecting tumor suppressor gene networks in vivo

18.01.10 Hongjuan Dong
Institute of Chemical Technologies and Analytics, Vienna
Intact cell mass spectrometry of mycotoxin-producing fungi Fusarium for differentiation and identification

21.01.10 Ron Hay
University of Dundee
Role of SUMO modification in ubiquitin mediated proteolysis

FEBRUARY

11.02.10 Reinhard Luehrmann
Max Planck Institute for Biophysical Chemistry
Assembly, structural dynamics and function of the spliceosome

16.02.10 Sui Huang
University of Calgary
Systems Biology of Cell fate decision: Transcriptome fluctuations and the Epigenetic Landscape

25.02.10 Andrew Murray
Harvard University
A manipulative approach to understanding chromosome behavior in mitosis and meiosis

MARCH

11.03.10 Cathie Martin
John Innes Centre, Department of Metabolic Biology
Engineering phenylpropanoid metabolism for healthy foods

16.03.10 Oliver Hobert
Columbia University
Making and breaking neurons in the nematode C.elegans

18.03.10 George Coupland
Max Planck Institute for Plant Breeding
Seasonal flowering in annual and perennial plants

23.03.10 Christoph Klein
Medizinische Hochschule Hannover
Novel monogenic defects of the immune system - from genetic diagnosis to gene therapy

23.03.10 Paul Nurse
Rockefeller University
Controlling the fission yeast cell cycle

24.03.10 Karl-Peter Hopfner
Gene Center, University of Munich
Mechanism of signaling and repair of DNA double-strand breaks

30.03.10 Duncan Odom
Cambridge Research Institute (CRI)
Five vertebrate ChIP-seq reveals the evolutionary dynamics of transcription

APRIL

01.04.10 Joachim Lingner
Swiss Institute for Experimental Cancer Research
Telomeres and telomerase: RNA-dependent machines at chromosome ends

06.04.10 Len Pennacchio
DOE Joint Genome Institute
Large-Scale Identification of Tissue-Specific Enhancers In Vivo

08.04.10 Detlef Weigel
Max Planck Institute for Developmental Biology
Next-generation genetics in plants: Evolutionary tradeoffs, immunity and speciation

12.04.10 Carolin Kutzki
Thermo Fisher Scientific
Protein Interactions – The way proteins are communicating

MAY

06.05.10 Paul Anderson
Harvard Medical School
Polysomes, P-bodies and Stress Granules: Spatial Control of mRNA Translation/Decay

11.05.10 Detlev Arendt
EMBL
Evolution of brains and eyes in animals: a cell type perspective

18.05.10 Mathias Mueller
University Halle
Collision-Induced Dissociative Chemical Cross-Linkers for Protein Structure Characterization

18.05.10 Mike Snyder
Stanford University
Personal and Nonpersonnel genomes: their analysis and variation

25.05.10 Kerstin Schmitz
DKFZ, Heidelberg
Non coding RNA regulates the epigenetic state of ribosomal RNA genes

25.05.10 Jussi Taipale
University of Helsinki
Systems biology of growth control and cancer

JUNE

10.06.10 Alfred Wittinghofer
Max Planck Institute of Molecular Physiology
G protein signaling and diseases

11.06.10 Mike Levine
University of California
Whole-genome analysis of transcriptional precision in the Drosophila embryo

15.06.10 Kevin White
University of Chicago
Mining transcriptional networks in flies and humans for cancer biomarkers

17.06.10 Jeffrey Gerst
Weizmann Institute of Science
mRNA trafficking: An entire genome in transit?

23.06.10 Charlie Boone
University of Toronto
The Genetic Landscape of a Cell

JULY

01.07.10 Matthias Hentze
EMBL Heidelberg
Control of protein synthesis by miRNAs and regulatory proteins

15.07.10 Arturo Casadevall
Albert Einstein College of Medicine
Rethinking antibody-mediated immunity

20.07.10 Eric Davidson
Caltech
Genomic Control System for development: The sea urchin embryo gene regulatory network

29.07.10 Ian Krantz
The Children's Hospital of Philadelphia
Developmental Repercussions of Cohesin

AUGUST

02.08.10 Matthias Wabl
University of California San Francisco
Retroelements causing autoimmunity

SEPTEMBER

02.09.10 Frank McCormick
UCSF
Cancer therapy based on the Ras/MAPK pathway

09.09.10 Hiroshi Takayanagi
Tokyo Medical and Dental University
RANKL and osteimmunology

16.09.10 Sheena Josselyn
University of Toronto
Continuing the search for the engram

23.09.10 Christian Haering
EMBL, Heidelberg
How does condensin pack mitotic chromosomes?

23.09.10 Bill Kelly
Emory University
Trans-Generational Epigenetic Regulation of the Germ Line in C. elegans

24.09.10 Wallace Y Langdon
University of Western Australia
The role of c-Cbl in myeloid malignancies

30.09.10 Peter Baumann
Stowers Institute for Medical Research
Telomerase Biogenesis and Function

OCTOBER

01.10.10 Rama Khokha
University Health Network, Toronto
RANKL Signaling in the Regulation of Stem Cells and Cancer

01.10.10 Irmgard Sinning
Biochemistry Center, Heidelberg University
Novel insights into SRP-mediated protein targeting

14.10.10 Alexey Khodjakov
Wadsworth Center
Keeping centriole duplication under control

NOVEMBER

04.11.10 Arshad Desai
Ludwig Institute for Cancer Research
Segregating the Genome During Cell Division

15.11.10 Poul Sorensen
University of British Columbia
The role of the Hect1 ubiquitin ligase HACE1 in cancer

17.11.10 Mark Stitt
Max Planck Institute for Molecular Plant Physiology
Balancing Metabolism and Growth with the Carbon Supply in Arabidopsis; Sensing, Budgets and Clocks

22.11.10 Benoît Zuber
MRC Laboratory of Molecular Biology
The structure of acetylcholine receptor clusters at the neuromuscular junction

DECEMBER

02.12.10 Matthias Merkenschläger
MRC Imperial College London
Non-canonical cohesin functions in T cell differentiation

15.12.10 Denise Kandel and Eric Kandel
Columbia University
There is Life After the Nobel Prize: A Molecular Approach to the Epidemiological Gateway Hypothesis of Drug Abuse

Scientific Advisory Board

Prof. Eric R. Kandel
Columbia University, New York, USA

Prof. Günter Blobel
Rockefeller University New York, USA

Prof. Anthony Hyman
Max Plank Institute of Molecular Cell Biology and Genetics, Dresden, Germany

Prof. Kenneth Chien
Cardiovascular Research Center, Massachusetts, USA

Prof. Susan Lindquist
Whitehead Institute for Biomedical Research, Cambridge, MA, USA

Prof. Fiona Watt
Wellcome Trust Centre for Stem Cell Research, Cambridge, UK

Prof. Gary Ruvkun
Department of Genetics/ Harvard Medical School, Boston, USA

REPRESENTATIVES OF THE AUSTRIAN ACADEMY OF SCIENCES

Prof. Helmut Denk
Chairman of the Section for Mathematics and the Natural Sciences; President of the Austrian Academy of Sciences, Vienna, Austria

Prof. Georg Stingl
Dermatology Department, University Hospital, Vienna; Secretary of the Austrian Academy of Sciences, Vienna, Austria

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

Supervisory Board

Prof. Erich Streissler
Department of Economics, University of Vienna, Austria (chairman)

Mag. Gottfried Schellmann
Müller-Koch & Schellmann Steuerberatungs GmbH, Austria

Prof. Josef Smolen
Department of Rheumatology, Internal Medicine III, University of Vienna, Austria

Prof. Georg Wick
Division of Experimental Pathophysiology & Immunology, Dept. Biocenter, Innsbruck Medical University, Austria

Prof. Josef Aicher
Institut für Handels- und Wirtschafts- recht, University of Vienna, Austria (deputy chairman)

Prof. Oskar Grün
Institute of Supply Management, Vienna University of Economics and Business Administration, Austria

Prof. Bernhard Keppler
Department of Inorganic Chemistry, University of Vienna, Austria

The Supervisory Board of IMBA serves as advisor to and monitors the actions of the management team on a regular basis. It consists of persons with a strong background in academic science and medicine, legal and tax affairs, auditing and other areas of business administration.

MANAGEMENT

Josef PENNINGER	Managing Director/Science
Jürgen KNOBLICH	Deputy Director/Science
Michael KREBS	Managing Director/ Finance and Administration
Peter STEINLEIN	Manager Scientific Services

MANAGEMENT ASSISTANCE

Ursula KOSIR (till 04/10)	Assist. to the Scientific Director
Denise LANGER	Assist. to the Admin. Director
Sonja PAULICK	Assist. to the Deputy Scientific Director
Erika WOOD (since 03/10)	Assist. to the Scientific Director

ACCOUNTING/CONTROLLING

Brigitte WEISER	Head of Accounting/Controlling
Renate ZETL	Accounting Clerk
Anita SOMMER	Accounting Clerk
Hanna VOGL	Accounting Clerk
Gesine WALNSCH	Controller

HUMAN RESOURCES

Werner LEITNER	Personnel Officer
Daniela PILLER	Personnel Officer
Sabine STEURER	Recruiting & Development Manager

GRANTS MANAGEMENT

Tanja WINKLER	Head of Grants Management
Uta POHN	Assistant to the Grants Manager

IT SERVICE DEPARTMENT

Werner KUBINA	Head of IT-Service Dept.
Andreas RIEPL	Deputy Head of IT-Service Dept.
Benjamin ALMEIDA	IT System Manager
Christian BRANDSTÄTTER	IT System Manager
Sebastian RUF	IT System Manager
Johannes TRUSCHNIGG (since 09/10)	IT System Manager
Herlind WURTH	IT System Manager

GRAPHICS DEPARTMENT

Hannes TKADLETZ	Graphics Artist
Tibor KULCSAR	Graphics Artist

RECEPTION

Christian LAUFER	Receptionist
Christine SCALISI	Receptionist

PURCHASING DEPARTMENT / STORE

Erwin KUNZ	Head of Purchasing Dept./Store
Brigitte LENZ	Deputy Head of Purchasing Dept.
Angela GANGLBERGER	Purchasing Agent
Caroline FORMANN	Purchasing Agent
Eva SCHARNER-KÖCK	Purchasing Agent
Jürgen Gerhard RUSCHER	Store Manager
Robert BLÜMEL	Store Clerk

COMMUNICATIONS

Heidemarie HURTL	Communications Manager
Evelyn MISSBACH	Communications Manager

LIBRARY

Karlo PAVLOVIC	Chief Librarian

PRIVATE FUNDING

Sabina TANDARI	Head of Private Funding
Sylvia WEINZETTL	Fundraising Assistant
Renate OTTO (since 11/10)	Team Assistant
Antje SCHILLINGER-DE ZWAAN (till 11/10)	Team Assistant

CAFETERIA

Michael ENZBERGER	Chef de Cuisine
Taoufik BAHMOU	Chef
Wolfgang BRAUN	Chef
Joachim LINS	Pastry Chef
Katrin HUPF	Buffet
Helga MEHOFER	Buffet
Sabine SMALCL	Buffet
Hanna AHARODNIKAVA	Kitchen Assistant
Güler CICOS	Kitchen Assistant
Selma YILDIRIM	Kitchen Assistant
Semra YILDIRIM	Kitchen Assistant

FACILITY MANAGEMENT

Alexander CHLUP	Head of Facility Management
Michael KRATOCHWILLE	Deputy Head of Facility M.
Nadir AYKUT	Maintenance Technician
Christian DAVID	Maintenance Technician
Patrick GUST	Maintenance Technician
Gerhard MÜLLER	Maintenance Technician
Wolfgang RACHOLZ	Maintenance Technician
Martin ROJDL	Maintenance Technician
Alexander TRIEB	Maintenance Technician
Stefan TRINKER-GRONAU	Maintenance Technician

WORKSHOP

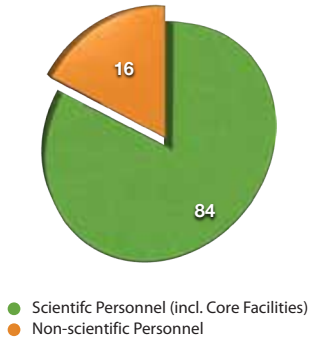
Martin COLOMBINI	Head of Workshop
David KUMMERER	Deputy Head of Workshop
Vladimir KOLCAR	Workshop Technician
Michael ZIEGLER	Workshop Technician

DISH WASHING

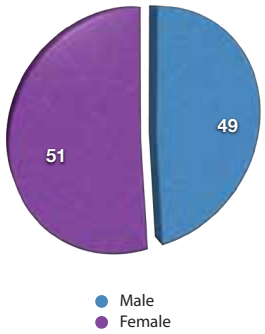
Renate WÖHRER	Head of Dish Washing
Aysel AYKUT	Technical Assistant
Sultan CAN	Technical Assistant
Vesna DJORDJEVIC	Technical Assistant
Nuray KILIC	Technical Assistant
Bettina RADICH	Technical Assistant
Renate STIX	Technical Assistant

IMBA Key Facts *(Data as of November, 2010)*

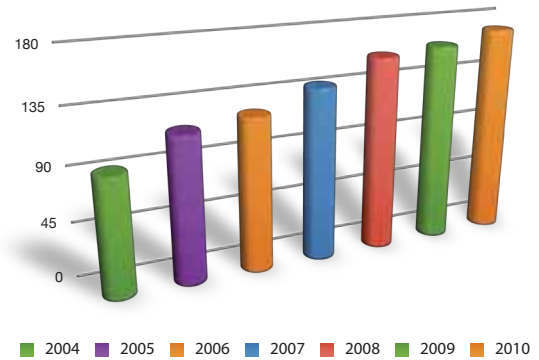
IMBA Staff (in %)



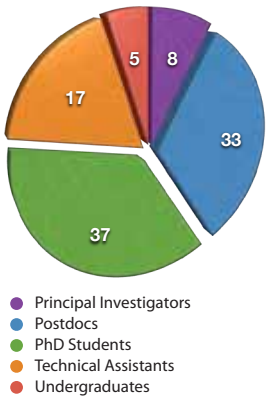
IMBA Staff - Gender Distribution (in %)



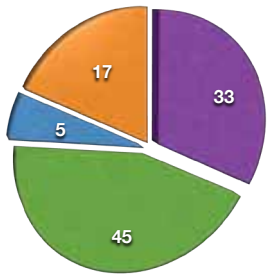
IMBA Staff - Development (Headcount)



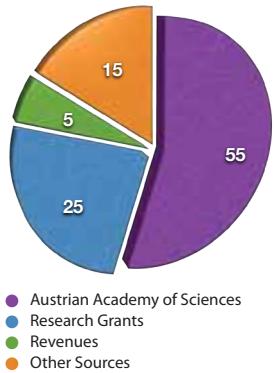
Scientific Staff - Functions (in %)



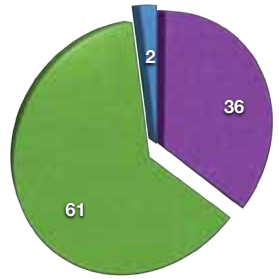
Scientific Staff - Nationalities (in %)



IMBA Budget 2010 (in %)



Public Research Grants 2010 (in %)



Sponsors & Partners

IMBA would like to thank the following funding organizations and private sponsors for their valuable financial commitment and continuing support:

Funding Partners and Public Sponsors

BMWFJ
BMWF
Boehringer Ingelheim
EMBO *
ESF
European Research Council
European Union
FEBS *
FFG
FWF
GEN-AU
HFSP
LISA
Marie Curie
ÖAW
OeNB
Stadt Wien
Wirtschaftsagentur Wien
WWTF
ZIT

** individual fellowships*

Major Private Sponsors *(in alphabetical order)*

We thank all our donors and sponsors for their valuable contribution, especially for the major donations from:

Special Thanks to DEBRA Austria

debra
Hilfe für die Schmetterlingskinder.

for their generous support of the Research Project "Development and genetic repair of induced pluripotent stem cells in RDEB".

Special Thanks to Dr. Ludwig Scharinger

Raiffeisen Landesbank Oberösterreich

IMBA and its Surroundings

The Institute of Molecular Biotechnology (IMBA) is located in Vienna, the capital of Austria. IMBA was founded in 1999 by the Austrian Academy of Sciences in cooperation with Boehringer Ingelheim, an international pharmaceutical company with its headquarters in Germany. IMBA operates in close collaboration with the Research Institute of Molecular Pathology (IMP), Boehringer's basic research center in Vienna. The two institutes are located next to each other and share large parts of their infrastructure.

The Campus Vienna Biocenter

IMBA is situated at the "Campus Vienna Biocenter" (VBC), a rapidly growing biotechnology hub located halfway between Vienna's international airport and the city center. Apart from IMBA and its partner institute IMP, the VBC is also home to the Max F. Perutz Laboratories (MFPL; University and Medical University of Vienna), the Gregor Mendel Institute of Molecular Plant Biology (GMI; Austrian Academy of Sciences), a University of Applied Sciences, several biotech companies, a non-profit scientific society and the Vienna Open Lab.

More than 1400 people from 40 different nations currently work at the Campus VBC. Campus members enjoy a scientifically and socially stimulating environment and take advantage of shared facilities such as the Max Perutz Library and the Vienna Biocenter International PhD Program. A number of events, including seminars and lectures, are open to all.

Vienna – a City of many Facets

For those whose interests stretch beyond science, Vienna also has a lot to offer. Home to about 1.7 million people, the city is the political and cultural center of the country and its gateway to the east. Once the heart of the largest European empire, Vienna draws on a rich cultural heritage which is reflected in splendid buildings and unique art collections. But Vienna is a city of many facets. Modern architecture, splendid galleries and stylish shops are as much a part of everyday life as the famous concert halls, the big museums and the nostalgic little streets. As any European capital, Vienna also offers a vibrant nightlife, with a rich selection of restaurants, cozy bars, and trendy clubs.

Apart from Vienna's focus on art and culture, it also has a long-standing tradition in science. Founded in 1365, the University of Vienna is the oldest university in the German-speaking world and the largest in Austria. With a student population of more than 120,000, Vienna offers not only the academic but also the cultural and social infrastructure that comes with student life.

And if your brain needs to be refreshed, there is always the call of nature. A day away from the lab may take you skiing to the nearby Alps, windsurfing at Lake Neusiedl or watching rare birds in the Seewinkel. Even within the borders of Vienna you can enjoy a hike through dense woods, go canoeing in a National Park, climb impressive limestone cliffs or stroll through rolling vineyards. In fact, more than 50% of Vienna's surface area is covered by vegetation.

Your Career at IMBA

IMBA offers exciting positions at all levels of your research training and career. If you consider joining IMBA, you will find first class research and state-of-the-art scientific services. As a member of one of the scientific groups, you will be part of a young, international team, using English as a working language. The atmosphere at IMBA is stimulating and focused, and a certain pioneering spirit can be felt among its staff. The brand-new state-of-the-art laboratory and office building was officially opened in 2006 and is now the inspiring home to about 160 scientists and administrative staff.

Graduate students join the IMBA through the Vienna Biocenter International PhD Program, run jointly with the Max F. Perutz Laboratories (MFPL), the Institute of Molecular Pathology (IMP) and the Gregor Mendel Institute of Molecular Plant Biology (GMI). A call for applications goes out twice a year, with contracts typically lasting 3-4 years.

IMBA's research groups are well funded to support a number of pre- and postdoctoral positions. A substantial travel budget allows scientists to take part in meetings, conferences and courses. IMBA and the IMP organize a couple of conferences, workshops and symposia every year. An intensive seminar program brings internationally renowned scientists to the institute on a regular basis.

If you come to work at IMBA, you'll obviously come in the first place for the science. We do, however, appreciate your private needs and try to make relocation as smooth as possible. For newcomers, there are several in-house apartments to bridge the time until they have found a place of their own. Our administrative staff is helpful in finding housing, and our personnel department will take care of your legal requirements including visas, registration, health insurance and family matters. For parents with young children, the campus has its own Kindergarten, offering child care from the age of three months and opening hours according to the needs of scientists. For school-age children, Vienna offers a large range of different types of schooling, from public to private, German- or foreign language-speaking, traditional or with more experimental concepts.

Many of our new employees are accompanied by spouses who are themselves looking for a qualified position in line with their training. IMBA is certainly aware of this fact and can, in some cases, help with securing a job. We also support your efforts to learn German and sponsor language courses run by one of Vienna's best language schools as well as team sports.

More information about career opportunities at IMBA is available at: *www.imba.oeaw.ac.at*

May 10

5th Microsymposium on small RNAs

The 5th Microsymposium on small RNAs brought to Vienna a powerful blend of senior and junior scientists in the field of RNA silencing. Post-Docs on their way to an independent position as well as PhD students participated in the PhD Workshop. The award for the best talk of the Workshop – a free registration to the next EMBO-meeting in Barcelona as well as a DVD and Viennese chocolates – went to Jordi Xiol from Cataluna, Spain. As usual, a large number of companies fully supported the Symposium. Their generous support makes it possible to keep the Microsymposium a registration-free meeting. Almost 300 people attended this year. The goal for the future is to keep improving, as easy and as difficult as that.

June 10

VBC PhD Retreat

The VBC PhD Retreat 2010 was held at the Hotel Kongress in Leoben from June 21 to 22. 50 PhD students from the VBC spent their time in Styria to interlink science, career perspective and simply having a good time. The 2010 PhD retreat was organized by the VBC PhD representatives Anita Kazda, Juliane Mayerhofer, Sascha Waidmann (GMI); Heike Harzer, Federico Mauri, Alexander Vogt (IMBA); Cosmas Arnold, Dominika Bienkowska (IMP); Ursula Pilat and Lanay Tierney (MFPL). During two poster sessions each student had the opportunity to present and discuss his/her project in a very relaxed atmosphere. The poster sessions were followed by presentations of Rafael Carazo Salas (The Gurdon Institute, University of Cambridge) and Ueli Grossniklaus (Institute of Plant Biology, University of Zurich). Both of these top notch researchers gave interesting insights into their sometimes more sometimes less straightforward career in science. Like the whole summer, so was also the VBC PhD Retreat 2010 marked by the FIFA world cup. Therefore everyone gathered at the local pub in the evening to watch the 2-0 win of later world champion Spain over Honduras. The retreat ended with a tour through the ancient iron mines of Erzberg. The 2011 VBC PhD retreat will be held from June 20 to 21, 2011 in "Eisenberg an der Raab".

VBC Summer Concert

It has become a nice tradition to have music as a part of the VBC's cultural program. At this year's summer concert the audience enjoyed a lively potpourri of different performances: singers, a jazz group, and a Turkish folk music group, and then of course the MolBioOrchestra - featuring students and staff from all over the campus.

August 10

The first Vienna Biocenter Summer School

This summer, the VBC organized its first ever Summer School for undergraduate students to attract the best and the brightest of the new generation of scientists. The program received more than 250 applications from all over the world. Eventually, 22 participants from 13 different countries qualified for the intensive ten-week course. The experience involved an independent research project in one of the scientific groups and a series of lectures, and was accompanied by a number of social and cultural activities in and around Vienna. On September 3, the Summer School was rounded off by a scientific mini-symposium where the participants presented the projects they had been working on for the past weeks. The event was entirely organised by the students themselves and was an impressive demonstration of the skills and knowledge they had acquired during those summer months.
www.vbcsummerschool.at

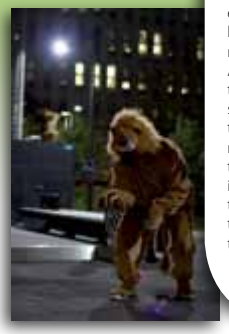
September 10

Postdoc Retreat 9th/10th September 2010

This year the annual Postdoc Retreat, themed SCIENCE IN FICTION, took us, the IMP/IMBA/GMI Postdocs, to Lake Balaton in Hungary. After a three-hour drive and a few cookies, we arrived at Club Dobogomajor, a lovely resort close to Keszthely, the former capital of the Balaton region. Things got underway quickly as the afternoon sessions were opened by Prof Charalambos Kyriacou (Affectionately, Bambos, for short) from Leicester University/UK who told us 25 years worth of amazing stories, detailing experiences from his scientific life. We learned some very valuable lessons, particularly to watch out if Bambos has a camera. Next was Chris Mooney, a science writer from the US. He gave an interesting talk about politics and science, which sparked some stimulating discourse following the talk. We concluded that at the moment, we are all extremely happy we are working in the EU and not the US. The evening discussion and dinner were spent on lake Balaton shipping around in a rather classic looking boat where we were treated to a beautiful sunset as the night began. As people relaxed and got to know each other a little better over fruit, the dropping temperatures were ignored in exchange for some brilliant conversation and even a little late night swimming for the courageous few. For the next morning session, we invited Prof Carl Djerassi, who is most famous for the invention of the birth control pill. He spent hours (yes, hours) recanting about the ethics in modern science that he extensively described in his fascinating theatrical performances and novels such as The Cantor's dilemma. Our brains full of science in fiction, we shifted the discussion to a lovely winery atop a hill that not only offered us excellent regional wines but also a gorgeous view over the lake spanned by a pretty rainbow. After a few wines and wonderful cheese, we eventually made our way back to Vienna where the night ended this very SMart experience.

A Midsummer Night's Dream

On September 6th and 7th at the Campus Vienna Biocenter, a cast of 22 performed an experimental version of Shakespeare's "A Midsummer Night's Dream". The play was directed by Brooke Morriswood (MFPL). Experimental in more ways than one - the performers were all resident scientists of the Biocenter, not actors! They were all members of the VBC's newly-formed Amateur Dramatic Club, which had also produced Peter Shaffer's "Amadeus" at the IMP lecture theatre earlier in the year. Reflecting the diversity of the campus, most of the actors were speaking English as a second language, and a majority had no previous stage experience prior to their involvement in the Club. A total of roughly 200 people braved the elements over the two nights to watch the action, which utilised multiple locations in the VBC courtyard to represent the various settings for the play's action. Thus, the Intercell patio became Duke Theseus' Court in Athens, the basketball court became the Mechanicals' workplace, and the rectangular lawn the forest outside Athens, with the audience being moved between the locales to coincide with the shifting action of the play. On the second night, the weather very nearly conspired to ruin things, with Puck (Martina Doetsch, MFPL) delivering the famous "Give me your hands, if we be friends" soliloquy in the rain. The soggy crowd obliged, first by applauding and then by helping the performers haul the set and equipment out of the downpour, and back into the labs.



Recess

From October 6-8 IMBA scientists met with members of the Scientific Advisory Board (SAB) to present their work and discuss their research. The SAB, consisting of internationally recognized scientists, were once more impressed by the scientific performance and high standards of the research presented. IMBA would like to thank all its SAB members and the representatives of the Austrian Academy of Sciences for their tremendous support.

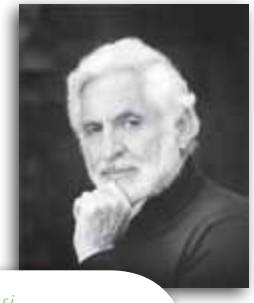
IMBA SAB members: page 56 in this booklet.

VBC PhD Symposium Nov 18-19th 2010

ORIGIN OF LIFE

VBC-PHD SYMPOSIUM "Origin of Life"

This year's PhD Symposium from November 18th to 19th was dedicated to the very old but still hotly debated topic of the Origin of Life. The aim of the Symposium was to address this timeless question by looking at a variety of different perspectives and furthermore to draw a circle from the chemical and biological origins of life over to evolution and species diversification and finally the extinction of species. About 280 registered students, 100 off-campus guests from all over Europe, and numerous journalists took part in this event. The scientific highlights were the 2009 Nobel laureate Ada Yonath presenting her ongoing work on the structure of the Ribosome, Antonio Lazcano who gave a fascinating overview about what is known about the molecular Origin of Life and what remains still elusive. Janet Siefert explained her work on microbial evolution and Lewis Dartnell introduced the amazing world of extremophiles. To close the circle, the symposium concluded with Arnold Miller and Stefan Lötters raising the question if there is a man-made sixth mass extinction approaching. Even though many questions on the origin of life have been addressed and partially answered during the symposium the puzzle of how life actually originated still remains open for further investigation.



Honorary Doctorate for Carl Djerassi

In recognition of his brilliant work in Synthetic Chemistry, Carl Djerassi ("father of the pill") received an honorary doctorate from the Technical University of Graz, Austria. Born 1923 in Vienna he spent the first few years of his life in the Captial of Bulgaria, Sofia and Vienna. He received 23 honorary doctorates and countless international awards for his research in more than 1.200 publications. The latest Austrian prize the scientist received was the bestowal of the "Ehrenring" from the Austrian Academy of Science in 2008. Carl Djerassi is since 2004 an Austrian Citizen again and a member of the IMBA Fundraising Committee.

October 10

IMBA Trip to Melk

The IMBA autumn event 2010 on October 11 took the IMBA employees on a boat trip from Krems to Melk. Even though the buses left very early everyone arrived on time. A fantastic breakfast and the beautiful surroundings of the ship MS Kaiserin Elisabeth greeted everyone. The next three hours were spent relaxing, chatting and enjoying the autumn colours of the banks of the Danube. Buses were waiting at the arrival to take everyone to Göttweig abbey. Lunch included fantastic panoramic views over the Danube Valley and a looking back and making plans for the coming year by Michael Krebs, Jürgen Knoblich and Peter Steinlein. The tour through the abbey was fascinating and according to some not nearly long enough. The crowning of the tour was an impromptu Organ Concert at the church which everyone really enjoyed. At the "Heurigen im Schreiberhaus" in Krems fantastic food and wine and a cheerful atmosphere finished off a perfect day for everyone.

November 10

"Genetics & Art - A Symbiosis"

Inspired by science topics and impressions gained in discussions with IMBA researchers, young students from the University of Applied Arts in Vienna designed a total of eighteen projects as part of a competition. The internationally renowned Austrian artist Erwin Wurm was on the jury; "Science can serve as a source of inspiration, my concern is to extend perceptions and foster interest in discovery on both sides." Four of the projects have now been realised at IMBA. The works of art are a twelve-meter high installation, three giant mandalas with plant and animal motifs, vector graphics developed from 'found' organisms and a provocative logo, which can be read in the winter garden at IMBA.

December 10

2010 National Medal of Science goes to IMBA SAB member

On November 17 US President Barack Obama presented the award to this year's recipients, one of which was Susan Lindquist, member of the IMBA Scientific Advisory Board. The National Medal of Science is an honor to individuals who have made important contributions to the advancement of knowledge in the fields of behavioral and social sciences, biology, chemistry, engineering, mathematics and physics. Susan received the award in the category of Biological Sciences "For her studies on protein folding, demonstrating that alternative protein conformations and aggregations can have profound and unexpected biological influences, facilitating insights in fields as wide-ranging as human disease, evolution, and biomaterials." IMBA would like to congratulate Susan on this occasion and wishes her continued success!

Impressum

Published by
IMP-IMBA Communications Department

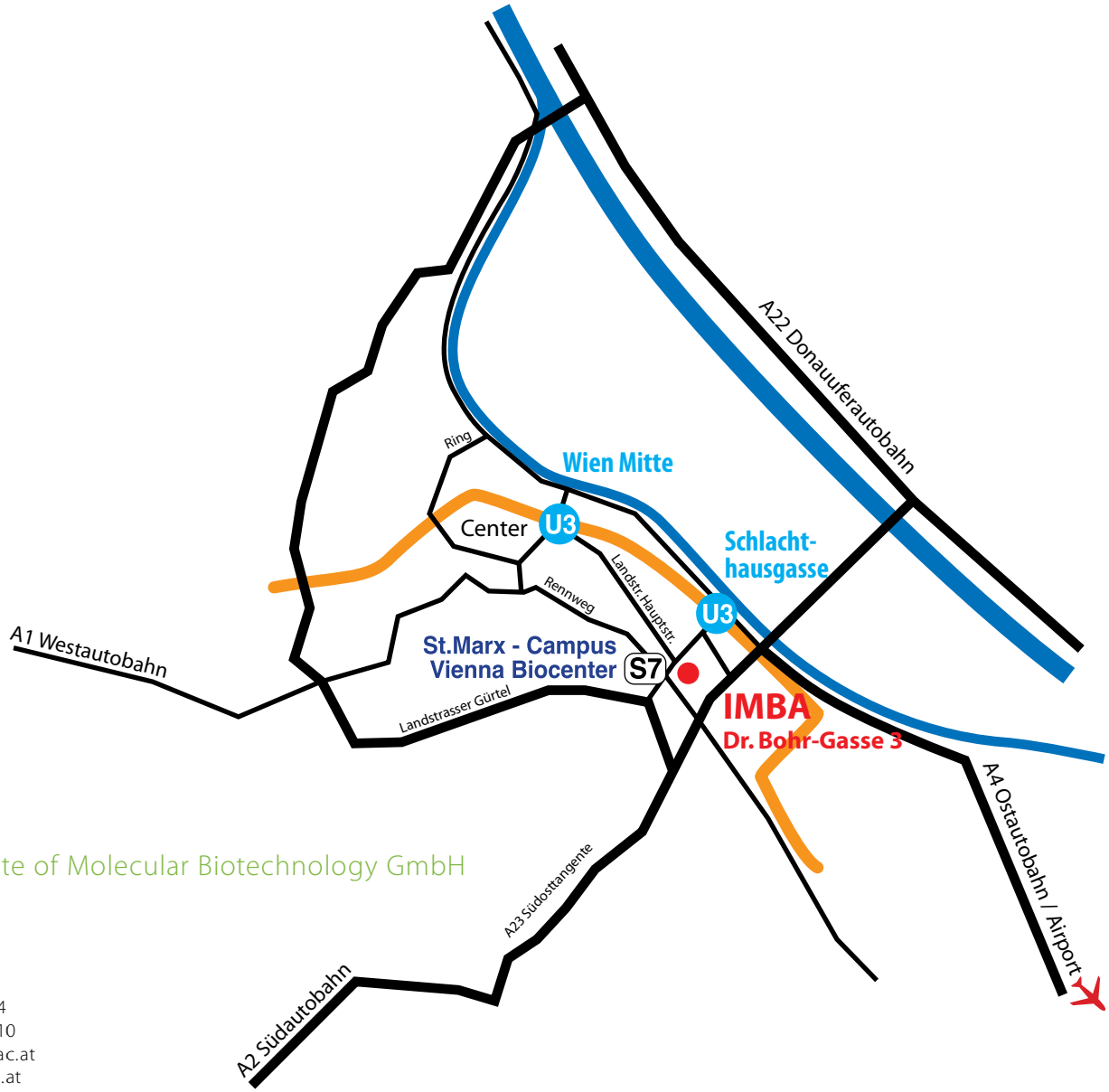
©2010 all rights by IMBA Vienna

Project Management
Evelyn Missbach

Layout & Design
IMP-IMBA Graphics Department

Pictures, Artwork & Credits
IMP/IMBA
IMP-IMBA Graphics Department
Hans Krist (pp: 2,7,11,15,19,23,26,27,31,35,60,61)
Bojan Vilagos (p: 62)
Georg Bauer (p: 62)
Karl Mayr (p: 63)
Ryan K Morris (p: 63)

Printed by
Ueberreuter Print GmbH
Industriestraße 1
A-2100 Korneuburg



IMBA - Institute of Molecular Biotechnology GmbH

Dr. Bohr-Gasse 3
1030 Vienna
Austria

Phone: +43(1)790 44
Fax: +43(1)790 44/110
office@imba.oeaw.ac.at
www.imba.oeaw.ac.at

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.