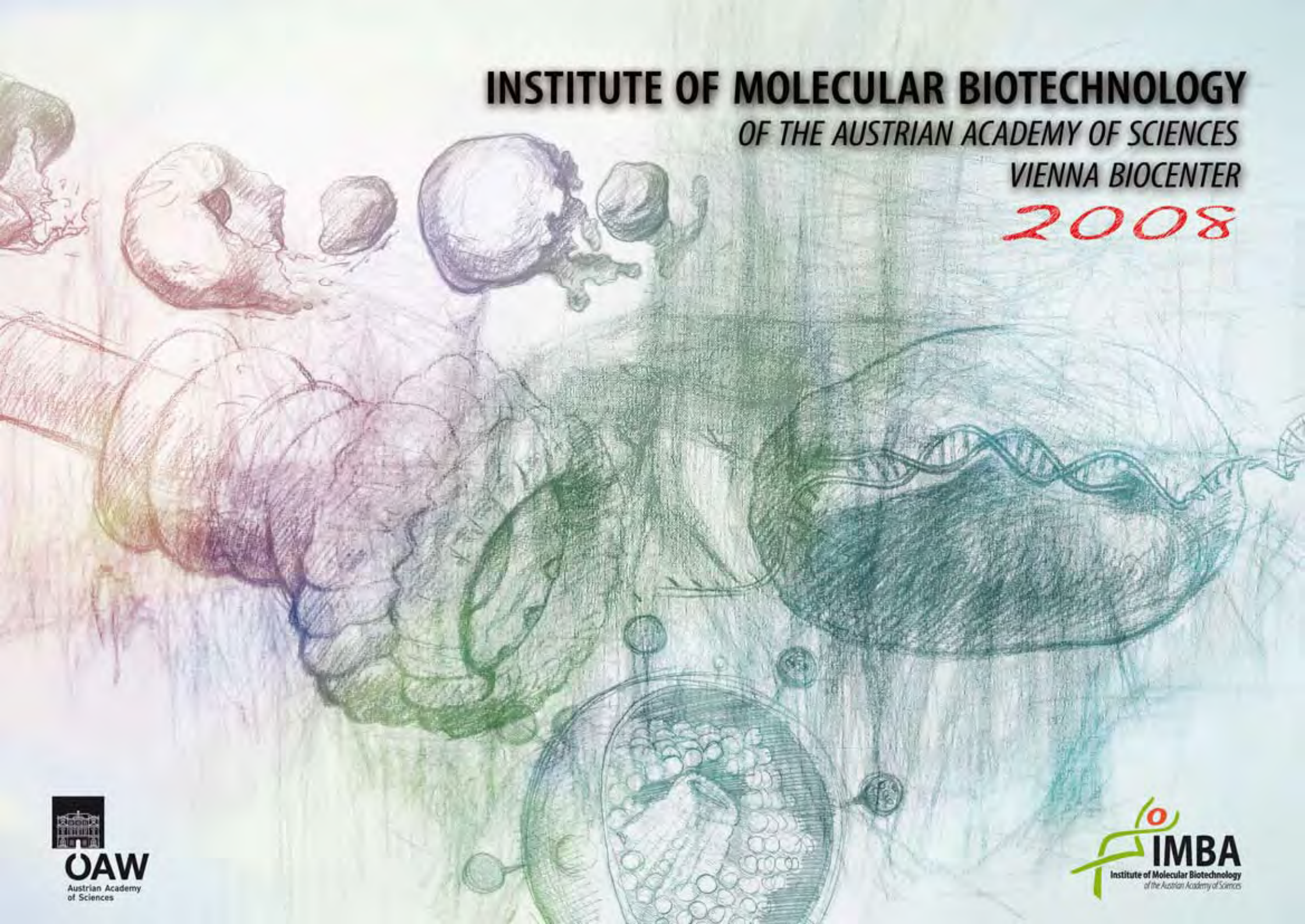
INSTITUTE OF MOLECULAR BIOTECHNOLOGY

OF THE AUSTRIAN ACADEMY OF SCIENCES

VIENNA BIOCENTER

2008



ÖAW
Austrian Academy of Sciences

IMBA
Institute of Molecular Biotechnology
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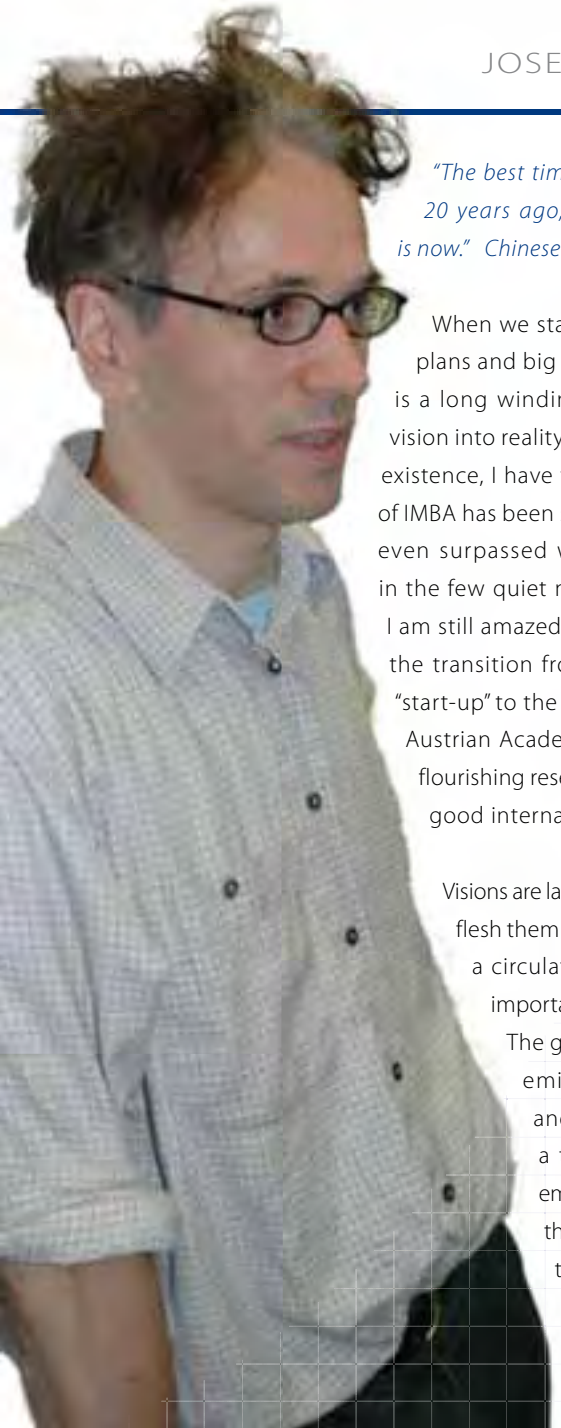


JOSEF PENNINGER *Managing Director/Science*

"The best time to start something is 20 years ago, the second best time is now." Chinese Proverb.

When we started IMBA we had big plans and big hopes. However, there is a long winding road to translate a vision into reality. After nearly 5 years of existence, I have to say that the growth of IMBA has been simply astounding and even surpassed what I had hoped for in the few quiet moments of reflection. I am still amazed how rapidly we made the transition from a small, promising "start-up" to the largest institute of the Austrian Academy of Sciences with a flourishing research culture and a very good international reputation.

Visions are largely lifeless until people flesh them out with muscle, brains, a circulatory system and, most importantly courage and heart. The growth of IMBA and our eminence within Austria and around the world is a testament to all IMBA employees and of course all the people working under the IMBA-IMP umbrella. I am truly privileged to be able to work with all of you! Together we are much stronger, we have many more eyes to see and many more hearts to weather the storms and move into the future.

Although we may well have learned to fly, there remains plenty to be done in the future. Firstly we have decided that IMBA will focus on three major topics; stem cells, modeling of human diseases, and RNA biology. These topics are based on our already existing strengths and the vision that good science not only entails intellectual beauty but also bears responsibility for improving the state of our world. Our faculty is outstanding, and I am very happy to welcome Julius Brennecke to IMBA as a new principle investigator. Julius will work on small RNAs, in particular Piwi RNA, where he has already made major breakthroughs. As a next step we plan to make a strong push into stem cell biology to develop a new centre of excellence in this critical technology.

In early October we had our prime academic event, the Annual Recess, to showcase the scientific progress of all IMBA groups. We again had a joint event with our partner IMP and we hope that these joint events will continue in the foreseeable future. We are very fortunate that Gary Ruvkun, Susan Lindquist and Fiona Watt have joined Eric Kandel, Günter Blobel, Ken Chien, and Tony Hyman to complete our scientific advisory board, the scientific and structural input of our SAB being essential for the future development of IMBA. The work of our SAB was and remains outstanding, and is certainly one of the reasons why we have already been able to receive an international standing within the short time period of our existence.

I would like to thank Steve McKnight and Titia de Lange, SAB members of our partner IMP, who also helped IMBA during the times of our inception and will now move on to other pastures. Finally, I would like to wish Erwin Wagner, Thomas Jenuwein, and Ludger Klein from our extended IMBA-IMP family all the best and great success in their scientific and personal lives. Their contributions to our campus and scientific excellence in Austria have been enormous, and will continue to shine for many years to come; may the gods of science look down upon them with a smile.

With gratitude I would like to acknowledge all the people and funding agencies who have supported us; foremost the Austrian Academy of Sciences (ÖAW) and the Austrian Ministry of Sciences, the Austrian Science Foundation (FWF), Genome Austria (GEN-AU), the European Union FP6 and FP7 programmes and the European Research Council (ERC). Half of the very competitive Junior and Advanced ERC grants in Life Sciences that went to Austria were awarded to IMBA researchers, a great testament that we are moving in the right direction. I am grateful to our supervisory board and our "Leitungsgremium" who have continued to carefully and with poise maneuver IMBA through both times of tranquility and times of turmoil. I would like to thank Prince Max Liechtenstein, Erich Streissler and Ludwig Scharinger for their donations to IMBA and their commitment to basic research as a key to future human prosperity. Finally, I would like to thank with all my heart Michael Krebs and Jürgen Knoblich, who always keep my feet on the ground and without whom IMBA would have remained just a vague dream.

I always liked the analogy of building an institute with building a cathedral; one wall of IMBA is already standing and being admired, but we now have to finish the entire building, and I will do everything in my power to make this happen.

MICHAEL KREBS *Managing Director/Finance and Administration*

Five years after hiring our first Group Leader, IMBA – with currently 150 employees and a research budget of around € 15 million - has become the largest institution of the Austrian Academy of Sciences and one of the most prominent and exciting places for functional genomics research in Europe. In this context, we would like to thank all our employees, our shareholder, the Ministry of Science and Research, the funding organizations of the City of Vienna, the Austrian Science Fund (FWF), and the EU, our cooperation partner Boehringer Ingelheim and the IMP as well as all the other people who have been involved in our success story for their valuable contributions.

A major milestone in 2008 was the approval of our "Vision 2020" concept to establish a shared technology and service infrastructure at the Campus Vienna Biocenter (VBC). This program will be funded by the City of Vienna and the Ministry of Science and Research with a total amount of around € 50 million over a period of 10 years. In 2009, a separate legal entity will be set-up to run new infrastructures and technologies such as mouse phenotyping, in-vivo imaging, large scale RNAi screening, etc. The concept is a joint initiative from all VBC members and will bring a new spirit of collaboration onto our campus.

In view of the growing size and coordination requirements of the scientific services, IMP and IMBA management recently agreed on some fundamental organizational changes. It was decided to implement the new position of a Manager of Scientific Services (MSS) who will bear the responsibility for the shared services at the IMP-IMBA Research Centre. We are very happy that Peter Steinlein has accepted our offer for this very important management position. We also congratulate Karin Aumayr on her promotion as new head of our biooptics facility to replace Peter Steinlein who has done a great job setting up and operating that service for the last 10 years.

The implementation of the new SAP system has been a major project in 2008, involving many resources from different departments. Like any other organization that goes through such a major system migration process, we are still struggling with some bottlenecks, especially in the ordering and the reporting process. However, the switch to SAP has been an important step in the modernization of our IT infrastructure. Additional IT investments have been committed to significantly increase the capacity of our file and e-mail server and to improve accessibility to these servers. We thank all of you for your patience and continuous support of Werner Kubina and his team during the transition period.

Over the last year some major steps have been taken to enhance our administrative services. In the Human Resources Department for example, we created the new position of a recruitment and personnel development manager in order to better coordinate recruiting activities at the IMP and IMBA, and establish career development programs for our people. The controlling competence in the Accounting Department was also strengthened, to extract the most benefit from the new possibilities the SAP system offers us in terms of integrated planning and management reporting. Last but not least, we added another position in the Fundraising Department to extend our existing contacts with potential donors.

Thanks to the high commitment and very professional approach of Sabina Tandari and her team, IMBA already managed to generate some initial donations in 2008 along with some great opportunities for the future.

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 collaboration is known under the name of "IMP-IMBA Research Center".

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 PR agency, a non-profit scientific society and the Vienna Open Lab.

More than 1000 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 150 scientists and administrative staff.

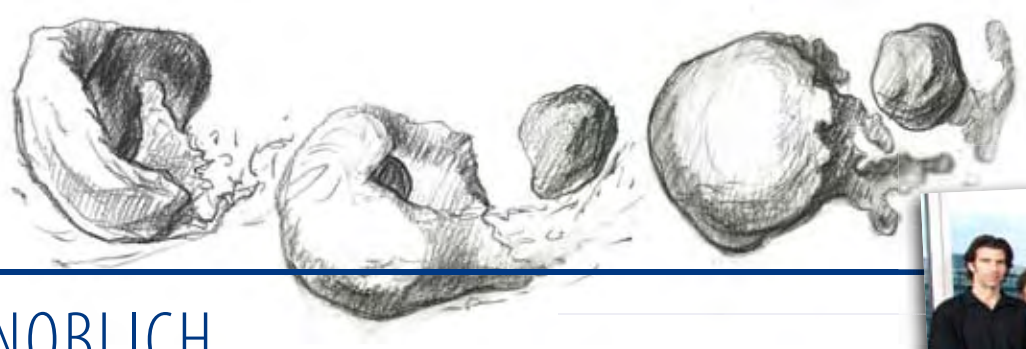
Graduate students join the IMBA through the Vienna Biocenter International PhD Program, run jointly with the Max F. Perutz Laboratories (MFPL), the Institute of Molecular Pathology (IMP) and the Gregor Mendel Institute of Molecular Plant Biology (GMI). A call for applications goes out twice a year, with 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, two day-care facilities are available in the immediate neighborhood. 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 creer opportunities at IMBA is available at:
www.imba.oeaw.ac.at/career



JÜRGEN KNOBLICH

Asymmetric cell division and proliferation control in neural stem cells

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Stem cells are essential for tissue maintenance and repair in our body. Although each stem cell has unique tissue specific properties, one feature is common among all stem cells: Stem cells have the unique ability to generate identical copies of themselves but at the same time can also give rise to more differentiated progeny that eventually replace cells in the target tissue. How one cell can generate two daughter cells of such dramatically different properties and how defects in this asymmetry can contribute to tumour formation, are the questions we are trying to resolve.

During *Drosophila* development, thousands of neurons arise from stem cell-like precursors called neuroblasts. Neuroblasts undergo repeated rounds of asymmetric cell division during which they form a large and a small daughter cell (Fig. 1A). While the small daughter cell divides only once more into two differentiating neurons, the large cell continues to grow and proliferate in a stem cell-like manner. Why are the two daughter cells so different in their cell growth and proliferation properties?

Stem Cell Tumours in *Drosophila*

The answer is that neuroblasts are capable of segregating key regulatory proteins into one of their two daughter cells during mitosis (Fig. 1B, C). One of them is the tumour suppressor Brat (Brain tumour). We found Brat by mass-spectometry in a search for proteins regulating fly brain development (Fig. 2A). When neuroblasts divide, Brat localises into a crescent overlying one of the two spindle poles, so that it is inherited by only one of the two daughter cells (Fig. 1B). In the absence of Brat, cell growth and proliferation are no longer restricted to only one cell. As a consequence, both cells proliferate leading to an expansion of the neuroblast pool and the formation of a brain tumour that fills the whole body and kills the fly (Fig. 2B). Thus, Brat is an important regulator of proliferation in *Drosophila* neural stem cells.

Brat is a member of a conserved protein family that is characterised by a similar domain structure (Fig. 2A). Our results indicate that regulation of stem cell proliferation seems to be a common task of this protein family. We found that the Brat-like protein Mei-P26 regulates proliferation in stem cells of the *Drosophila* ovary. Ovarian stem cells depend on a signal coming from the surrounding stem cell niche. After division, one daughter cell looses niche contact and no longer receives the signal. After a few transit amplifying divisions, this cell upregulates Mei-P26. Like Brat, Mei-P26 inhibits cell growth and proliferation so that this cell will exit the mitotic cycle and undergo differentiation. In the absence of Mei-P26, all cells proliferate leading to the formation of an ovarian tumour. Thus, control of stem cell proliferation seems to be a common function of Brat-like proteins.

Regulation of micro RNAs

How do Brat and Mei-P26 regulate proliferation? Using mass-spectrometry, we found the protein Argonaute-1 to be a common binding partner of Brat and Mei-P26. Argonaute-1 is well known for its key function in the micro RNA pathway. Argonaute is part of the RNA-induced silencing complex (RISC) that uses short double stranded RNA molecules to inhibit gene activity. Our genetic experiments show that Mei-P26 inhibits the activity of a large number of micro RNAs. In the ovarian stem cells, these micro RNAs are active, but when Mei-P26 is upregulated, their activity is compromised. Since micro RNAs are required for ovarian stem cell self renewal, this allows

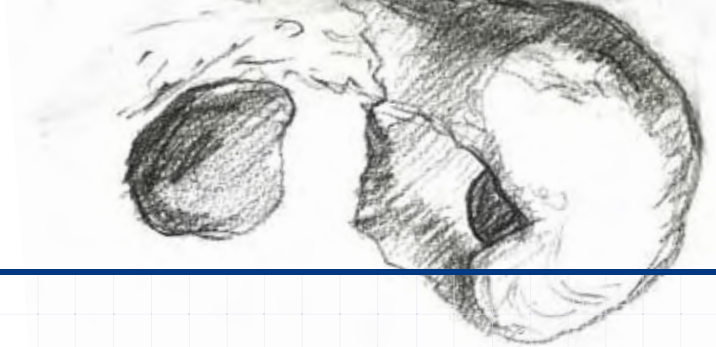
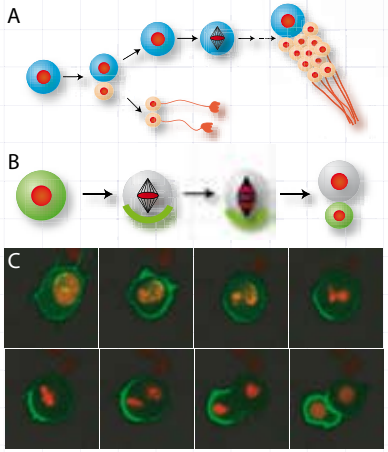


Figure 1



differentiation and ensures proper cell cycle control during *Drosophila* oogenesis. Thus, Brat/Mei-P26 proteins might use the micro RNA pathway to control stem cell proliferation.

Proliferation control in *Drosophila* and mouse stem cells

To identify the genes that regulate stem cell proliferation, we use a combination of genome-wide screens in *Drosophila* and transient transgenic mouse techniques. We have used a library of transgenic flies expressing hairpin RNAi constructs for essentially every gene in the fly genome (generated by Barry Dickson) to screen for genes affecting asymmetric cell division in the *Drosophila* peripheral and central nervous systems and have identified a number of new genes affecting these important biological processes. Most of the genes are conserved and to characterise their mammalian homologues, we use in utero electroporation into the mouse brain. For this, DNA is injected into the ventricle of the developing brain and electroporated specifically into the dividing progenitor cells that line the ventricular surface of the brain. By using RNAi and overexpression constructs together with GFP markers, we can study the gain and loss of function effect of candidate genes on the proliferation and differentiation pattern of mouse neural progenitor cells. So far, these experiments have revealed a striking functional conservation of Brat-like proteins in regulating stem cell proliferation. Ultimately, we will transfer our knowledge to adult stem cells to understand how stem cells control proliferation and lineage in our body and how these processes are deregulated in tumour development.

Figure 2

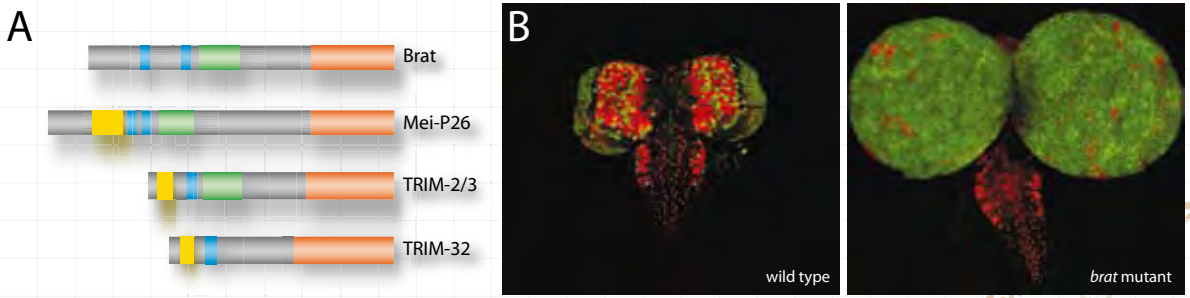
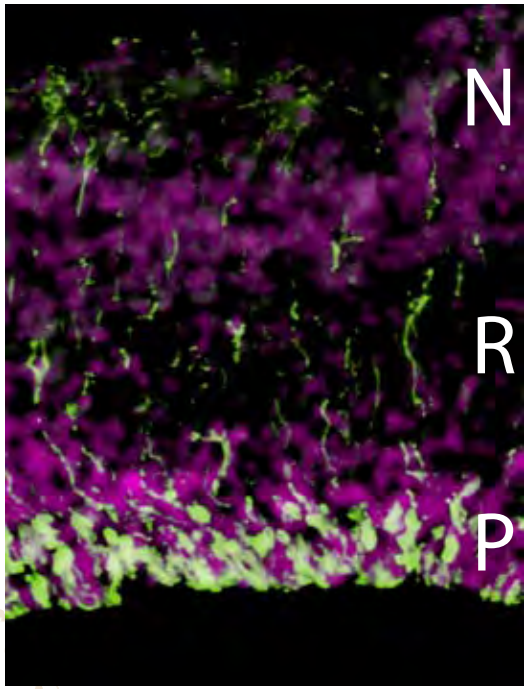


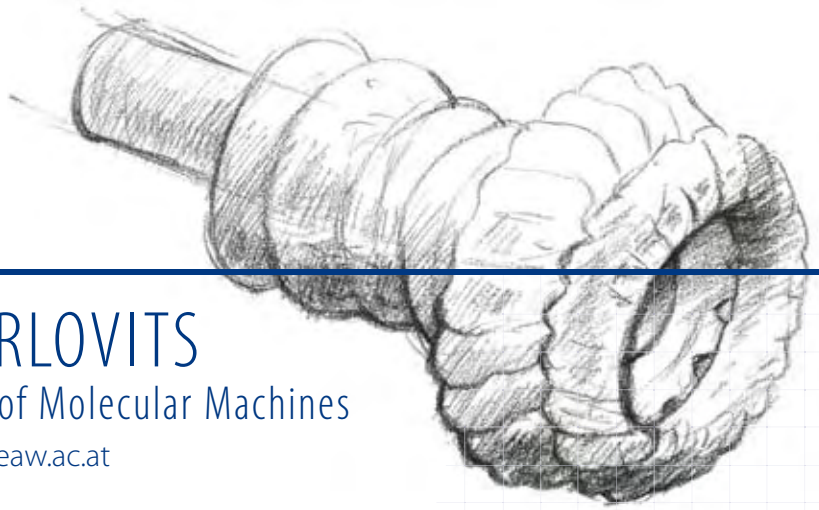
Figure 1: How cells divide asymmetrically
A. Drosophila neuroblasts divide asymmetrically in a stem cell-like fashion. crescent **B.** During each neuroblast division, Brat (green) localises into a cortical crescent and is inherited by only one of the two daughter cells. **C.** Live imaging of asymmetric cell division. Stills from a movie (available on our website) of asymmetric cell division in the Drosophila peripheral nervous system. Histone-RFP (red, to visualise chromatin) and Pon-GFP (green, to visualise asymmetric protein segregation) are recorded.

Figure 2: Stem cell-derived tumour formation in Drosophila. A. The Brat protein family. NHL domains are red, Coiled coil motifs green, B-boxes (Zn finger like motifs) blue and Ring fingers yellow. **B.** Larval brain from a wild type (left) and brat mutant animal. Neuroblasts are green, differentiating neurons are red. Brat brains show a dramatic overproliferation of neuroblasts.

Figure 3: Analysis of progenitor cell proliferation in the mouse brain. Cross-section through the developing mouse neocortex (DNA in magenta) on day 15 of embryonic development. GFP (green) was introduced by in utero electroporation specifically into dividing progenitor cells one day before fixation. Cell bodies (P) and characteristic radial glia processes (R) of transfected progenitors as well as the neurons that have developed from them (N) are visible.

Figure 3





THOMAS MARLOVITS

Design and Function of Molecular Machines

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Molecular machines are essential to maintain life at a cellular level. We are aiming to understand the fundamental molecular design, assembly processes, and mechanistic details of such higher-ordered structures.

Host-Pathogen-Interaction

Gram negative pathogens, like *Salmonella*, *Yersinia*, or *Shigella*, use the type III secretion system (TTSS) to initiate infection in eukaryotic cells. The TTSS is a complex macromolecular system that serves as a structural platform to make physical contact between the host cells and pathogens and mediates the unidirectional transport of bacterial toxins (effector proteins) into eukaryotic cells (Figure 1A, 1B). These systems are essential for a successful infection resulting in well known clinical symptoms ranging from mild headaches and diarrhoea to even life-threatening diseases such as typhoid fever or bubonic plaque.

The Molecular Design

Made up of more than twenty proteins, TTSSs assemble into large "molecular nanomachines" composed of a set of soluble as well as membrane proteins. All of the structural components as well as other proteins involved in the step-wise assembly process (Figure 1C) and function are encoded on specific pathogenicity islands.

The most prominent substructure of the TTSS is known as the "needle complex", a cylindrical, needle-shaped and membrane-embedded organelle protruding from the bacterial envelope (Figure 1E). The needle complex is believed to serve as a conduit for the safe transport of virulence factors from the bacterial cytoplasm through a number of natural barriers into eukaryotic cells. In *Salmonella typhimurium*, which serves as our model for bacterial delivery systems, this complex is formed by multiple copies of only five proteins: PrgH, PrgK, and InvG build up the membrane-associated base-structure, PrgJ, the inner rod, and PrgI, the needle filament extending into the extracellular environment (Figure 1).

In order to investigate the molecular mechanism of type III secretion, we first set out to determine structural components of the TTSS (Figure 2A). We were challenged by the megadalton size of the complex, its natural composition (membrane and soluble proteins), and the limited availability. Nevertheless, we were able to purify sufficient amounts of the entire 'needle complex' and its precursor, the 'base', by a combination of detergent extraction and size separation by velocity gradient centrifugation. A detailed structural analysis by three-dimensional electron cryo-microscopy and single particle analysis finally revealed that several rotational symmetries or oligomeric states are present in the population of the 'needle complex' and the 'base'. Whether all of these complexes have a physiological role remains an open question.

Our analysis revealed a new structural component, the inner rod, which is located in the centre of the needle complex. It extends the secretion path from the base into the needle filament, and also serves as an anchor to stably connect the needle filament with the base (Figure 1E). During assembly the inner rod and the needle filament are added as new structural components to the base. As a consequence, it must undergo large conformational rearrangements, which demonstrates the flexible but also stable property of the base (Figure 1 and 2). While functionally, this dynamic behaviour is a crucial event during the assembly phase, in which the secretion machine

Figure 1

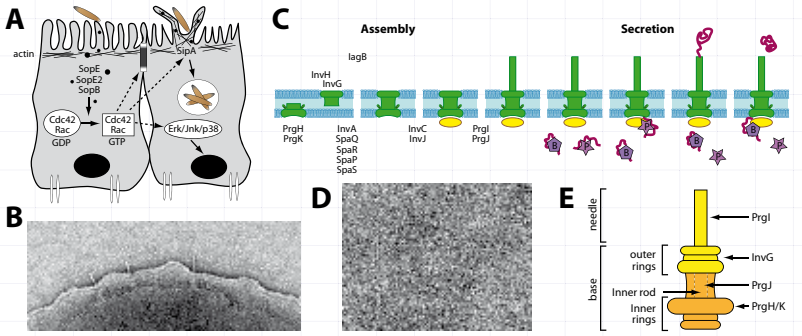


Figure 2

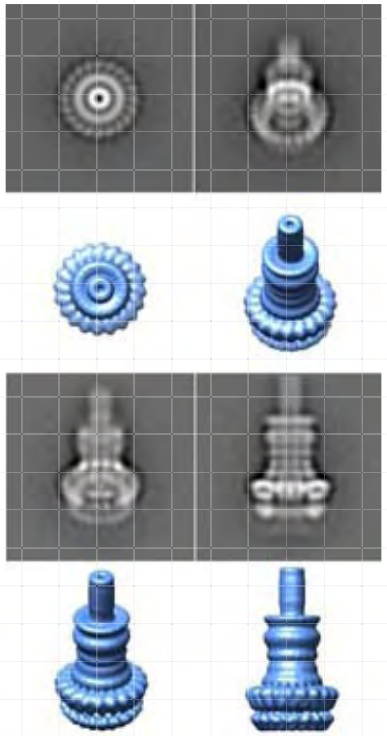
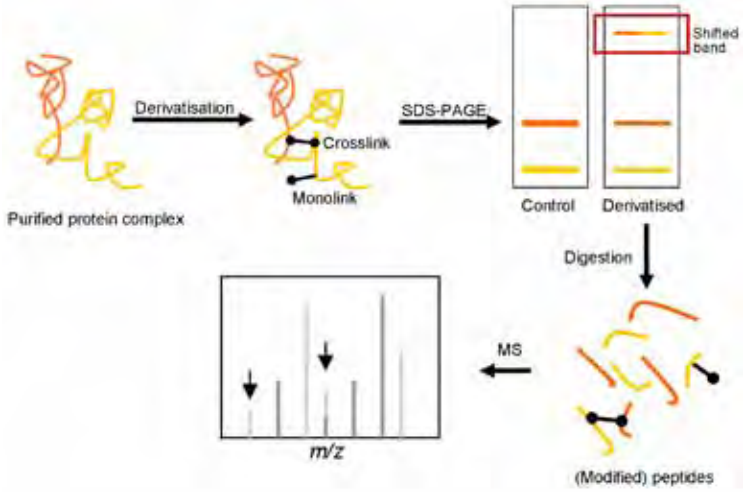


Figure 1: **The type III secretion system.** (A) The type III secretion system is essential to deliver virulence factors such as SopE or SopB into eukaryotic cells. (B) (E) Needle-like structures (appr. 50 nm) that extend into the extracellular environment are visible on the surface of osmotically shocked *S. typhimurium* and can be released after detergent treatment (D). (C) Formation of intermediate substructures during assembly. Once the growth of the needle filament is terminated the type III secretion system changes substrate specificity and delivers effector proteins (reprogramming phase). (E) Schematic representation of the Salmonella needle complex and its components. PrgH, PrgK, and InvG make up the membrane-embedded base structure, whereas PrgI forms the helical filament protruding into the extracellular environment. The inner rod anchors the filament into the base.

Figure 2: **The structure of the needle complex.** Surface renderings and projections of the ~30 nm wide needle complex obtained from three-dimensional image reconstruction from vitrified needle complexes.

Figure 3: **Mass spectrometry of derivatized complexes.** Isolated complexes are chemically derivatized and analysed by SDS-PAGE and mass spectrometry. The determination of crosslinked peptides of shifted bands indicate positions near or identical to the interaction epitopes within a complex.

Figure 3



is reprogrammed to become competent for the secretion of virulence factors, structurally, it underlines the importance of specific interaction epitopes critical for assembly into a functional unit. To this end we have established a method that uses high-resolution mass spectrometry of chemically derivatized complexes, to determine interaction sites and consequently topological information about individual proteins within larger macromolecular complexes (Figure 3).

Although the design of the TTSS appears to be conceptually simple, structural characterisation of the needle complex is at an early stage, leaving many questions unanswered:

What nucleates the assembly of the TTSS? How are the individual proteins organised in the TTSS? How dynamic is the entire assembly process? How does the export machinery interface with the needle complex? What determines the substrate specificity for protein secretion? We have begun to address some of these questions, and we hope that by understanding the molecular mechanism of TTSS-mediated protein transport we may provide the basis for the development of novel therapeutic strategies to either inhibit its activity or modify the system for targeted drug delivery.

JAVIER MARTINEZ

RNA Silencing and Processing in Mammalian Cells

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The discovery of RNA silencing phenomena has made a tremendous, dual impact on biology. On one side, it has "created" RNAi, bringing genetics to mammalian cells. In parallel, it has uncovered microRNAs (miRNAs), a class of small RNAs that tune the expression of a large portion of the genome. Our laboratory uses biochemistry to reveal novel enzymatic and non-enzymatic factors in RNA silencing and global RNA metabolism. Within RNA silencing, we focus on the control of miRNA expression at the post-transcriptional level and the role of miRNAs in metastasis and synaptic plasticity. Our interest in RNA metabolism stems from the identification of the first and likely multifunctional (si) RNA kinase hClp1, which led us to revisit and further study the processes of tRNA splicing and mRNA 3' end formation in mammalian cells.

Controlling miRNA expression at the post-transcriptional level:

Starting from large volumes of HeLa cytoplasmic extracts, we used classical chromatography and affinity-purification techniques to isolate an inhibitory protein that prevents the cleavage of the ~70 nt, miRNA-138-2 precursor into the mature, 23-24 nt miRNA-138 by the RNase-III enzyme Dicer. After concatenating eight purification steps, mass spectrometry analysis revealed the presence of very few proteins in the fraction containing the highest inhibitory activity. We are currently validating these candidates. Finding the inhibitory factor will allow us to a) investigate the expression of the inhibitor in different tissues and developmental stages, b) generate a conditional knockout mouse to remove the inhibitor from tissues in which it is expressed, and express it where it is absent, and c) study its potential role in controlling the expression of other miRNAs.

Revealing the cellular functions of the RNA-kinase hClp1:

We have previously reported the identification of human Clp1 (hClp1) as an RNA-kinase that phosphorylates the tRNA 3' exon during tRNA splicing. hClp1 is also part of the mRNA 3' end formation complex, with a still enigmatic function. We have developed a method to enrich and identify endogenous substrates of Clp1. The experiment entails a comparison between 5' *de novo* phosphorylated RNAs in wild type mouse embryonic fibroblast cells (MEFs) and RNAs present in MEF cells engineered to encode a kinase-inactive version of hClp1. We will perform deep sequencing to reveal the identity of Clp1-phosphorylated RNAs and assign Clp1 to specific RNA metabolic pathways.

Searching for the elusive ligase activity in the tRNA splicing pathway:

Two pathways seem to coexist in human cells to splice pre-tRNA molecules. They differ in the source of the phosphate group that remains at the splice-junction after ligation of tRNA 5' and 3' exons. tRNA-ligase activities have been extensively described in cell extracts, however the encoding genes remained unidentified. We have

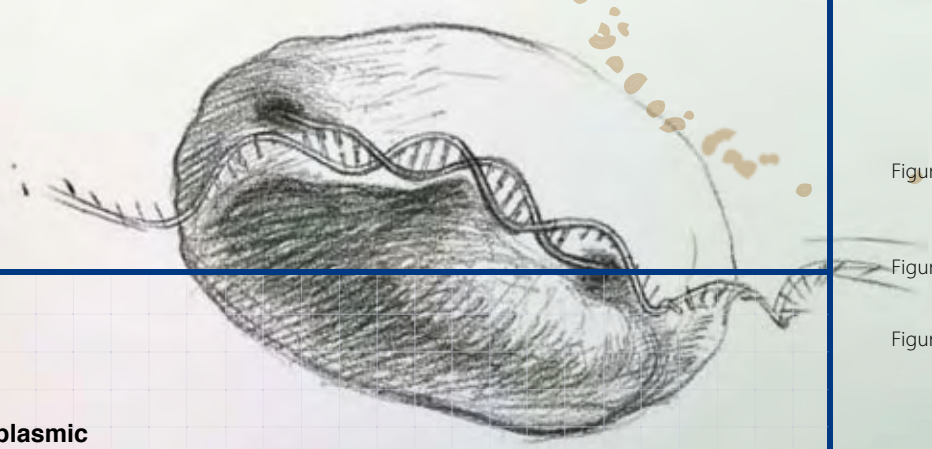


Figure 1

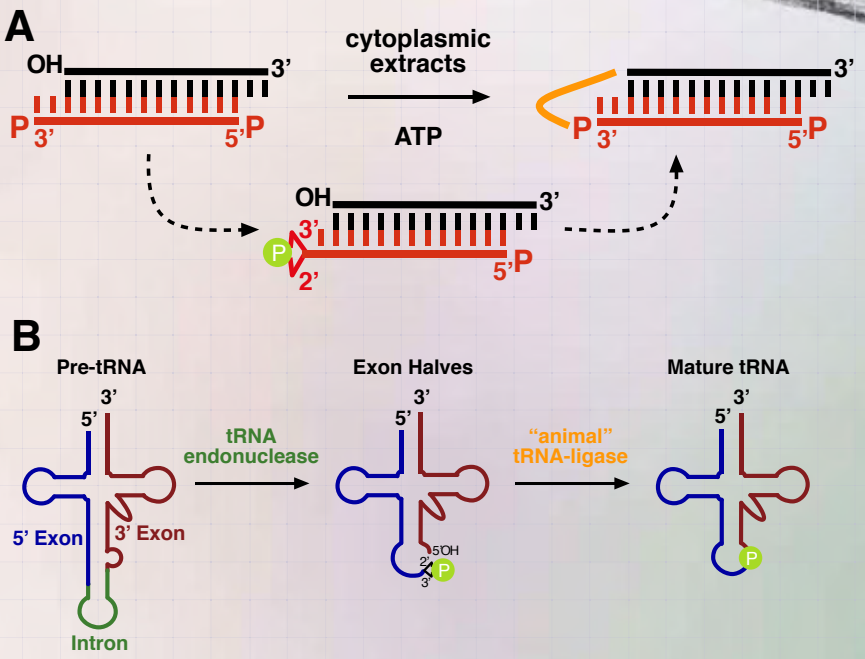
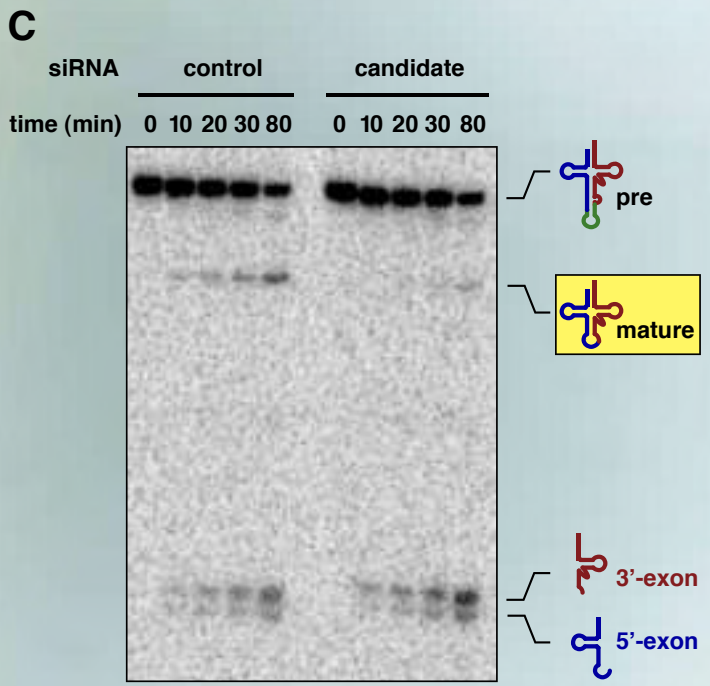


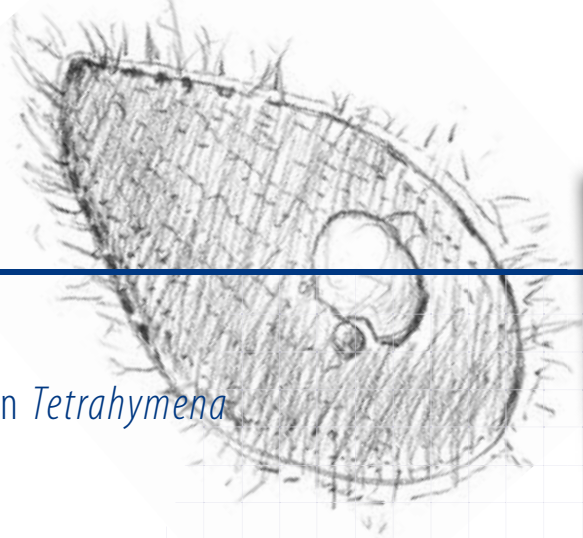
Figure 1A: siRNA duplexes displaying 3' phosphate and 5' hydroxyl termini become ligated (in orange) upon incubation with cytoplasmic extracts and ATP. The reaction most probably occurs through a 2' – 3' cyclic phosphate intermediate.

Figure 1B: The "animal" tRNA splicing pathway in human cells. The phosphate at the phosphodiester bond (in light green) originates from the 2' – 3' cyclic phosphate.

Figure 1C: HeLa cells were treated with siRNAs against the candidate gene for the siRNA-ligase activity (Fig. 1A). Extracts prepared from these cells were unable to process pre-tRNAs into mature tRNAs. Therefore, the same polypeptide seems to exert both siRNA-ligase and tRNA-ligase activities.



observed that siRNAs displaying a 3' phosphate and a 5' hydroxyl group undergo ligation in HeLa cell extracts (Fig. 1A). This reaction resembles the ligation of 5' and 3' exons in the "animal" tRNA splicing pathway (Fig. 1B). We have purified a factor with siRNA-ligase activity from large amounts of HeLa cytoplasmic extracts and identified a candidate factor. Strikingly, RNAi-mediated knock-down of this factor impairs not only the ligation of 3' phosphorylated siRNAs but also abolishes tRNA maturation, making it a strong candidate for the elusive tRNA ligase activity (Fig. 1C).



KAZUFUMI MOCHIZUKI

Small RNA-directed DNA elimination in *Tetrahymena*

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Transposable elements are molecular parasites that are able to move from one genome position to another. Our cells have a mechanism to silence these potentially harmful elements: locking transposable elements into a closed form of chromatin, called heterochromatin. Chemically, both transposable elements and the other parts of the genome are just stretches of DNA. So how can cells distinguish junk from precious DNA? Several pieces of evidence suggest that tiny RNAs, ~20–30 nucleotides in length, act as security guards to identify transposable elements. Our group studies how these short RNAs lock transposable elements into heterochromatins using the tiny-hairy protozoan Tetrahymena as a model.

Small RNA-directed DNA elimination

The ciliated protozoan *Tetrahymena* (Figure 1) has a macronucleus (Mac) and a 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 forms both new Mac and 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 sequences are re-ligated. IESs are mostly moderately repeated in Mic and many of them are related to transposable elements. Heterochromatin is involved in IES elimination. In *Tetrahymena*, heterochromatin components, methylated histone H3 on lysine 9 (H3K9me), H3K27me and the chromodomain protein Pdd1p, are specifically associated with eliminated IES sequences and are essential for DNA elimination. We previously demonstrated that small (~28 nt) scan (scn) RNAs are also involved in DNA elimination. scnRNAs 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 and for DNA elimination. Thus, heterochromatin formation occurs downstream of the RNAi-related mechanism in the DNA elimination pathway.

RNA helicase Ema1p and non-coding RNA

Complementarity between IESs and scnRNAs likely underlies the heterochromatin formation and the IES elimination process in *Tetrahymena*. However, the mechanism by which scnRNAs identify IES sequences is not well understood. scnRNAs are complexed with the Argonaute protein Twi1p. We have demonstrated that a Twi1p-associated putative RNA helicase Ema1p is required for the interaction between Twi1p and chromatin. This requirement explains the phenotypes of *EMA1* KO strains, including loss of selective down-regulation of scnRNAs homologous to Mac-destined sequences, loss of H3K9 and K27 methylations in the developing new Macs, and failure to eliminate DNA. We have further demonstrated that Twi1p interacts with non-coding transcripts derived from parental and developing macronuclei and that this interaction is greatly reduced in the absence of Ema1p. These results indicate that Ema1p probably functions in DNA elimination by stimulating base-pairing interactions between scnRNAs and non-coding transcripts in both parental and developing Macs (Figure 2). A small RNA–nascent RNA interaction in heterochromatin formation has also been proposed in fission yeast. Therefore, RNA–RNA interaction may regulate heterochromatin formation in a wide variety of eukaryotes.

Figure 1

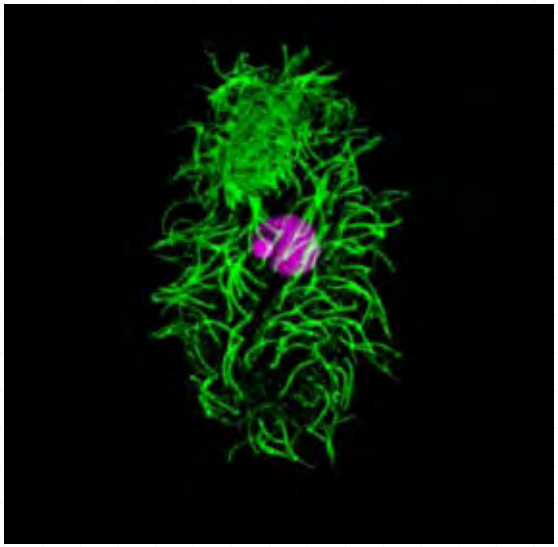


Figure 1: ***Tetrahymena thermophila.*** *Tetrahymena* is a unicellular eukaryote. It has many cilia on its cell surface (green = anti-alpha-tubulin staining). *Tetrahymena* has two different nuclei stained purple, a smaller micronucleus (Mic) and a larger macronucleus (Mac).

Figure 2

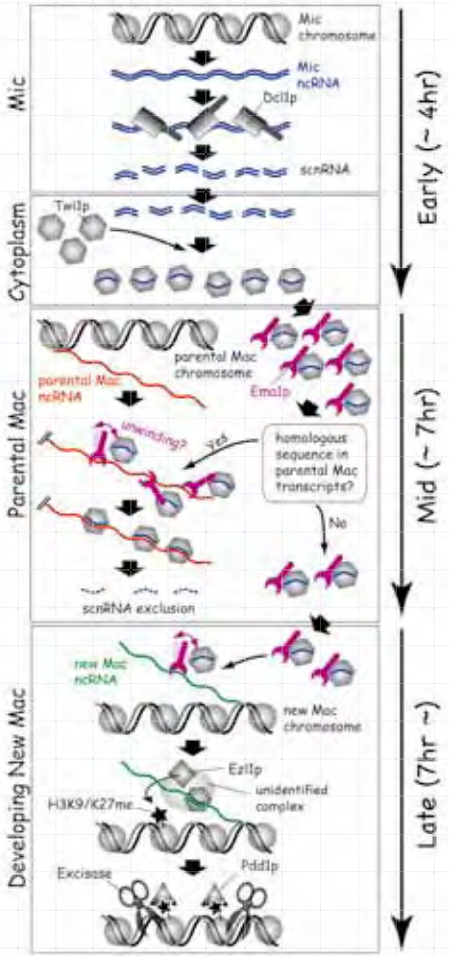


Figure 2: **Proposed roles of Ema1p and non-coding RNA.** In the early stages of conjugation, bidirectional ncRNA transcription (blue wavy lines) occurs in the Mic and the transcripts are processed to scnRNAs by Dcl1p. The scnRNAs are then transferred to the cytoplasm where they form a complex with Twi1p. Then, the scnRNA-Twi1p complex localises in the parental Mac in the mid stages of conjugation. In parallel, ncRNAs are made from parental Mac (red wavy lines). We propose that interactions between scnRNAs and the parental Mac ncRNAs induce degradation of scnRNAs. Ema1p (drawn in purple) likely functions in this selective elimination of scnRNAs by unwinding the parental Mac ncRNAs to enhance the scnRNA–ncRNA interaction. Next, the remaining IES-specific scnRNAs localise to the developing new Mac in the late stages of conjugation. The interaction between scnRNA and new Mac ncRNAs (green wavy lines) recruits a complex containing the histone methyltransferase Ezl1p to induce H3K9/K27me. Again, we propose that Ema1p is involved in the homology dependent methylation of H3K9/27 by enhancing the interaction between scnRNAs and their complementary nascent new Mac ncRNAs. Then, H3K9/27me attracts Pdd1p to establish heterochromatin, which serves as a platform to attract an unidentified endonuclease Excisase that cuts out the IES and rejoins the flanking sequences (Aronica et al., Genes & Dev. 2008).

2´-O-methylation stabilises scnRNAs

In some eukaryotes, 3′-terminal 2´-O-methylation stabilises small RNAs but its biological significance remains unclear. We have demonstrated that scnRNAs are 2´-O-methylated at their 3´ ends. We have also found that the RNA methyltransferase Hen1p is responsible for scnRNA 2´-O-methylation. In the absence of Hen1p, the length and abundance of scnRNAs are gradually reduced as conjugation proceeds (Figure 3). Consequently, DNA elimination and the production of sexual progeny are affected in *HEN1* knockout strains. Hen1p-mediated 2´-O-methylation therefore stabilises scnRNA and ensures DNA elimination in *Tetrahymena*. This study clearly showed that 3′-terminal 2´-O-methylation on a specific class of small RNAs regulates the function of a specific RNAi pathway.

Figure 3

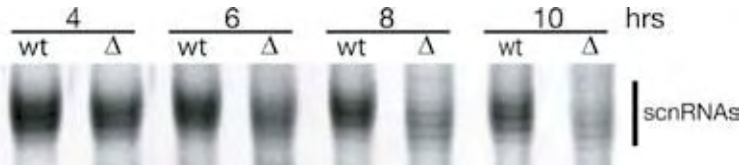
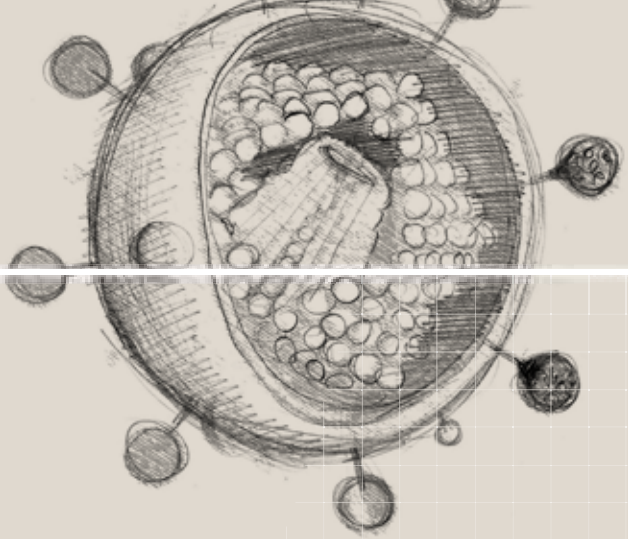


Figure 3: **HEN1-mediated 2´-O-methylation stabilises scnRNAs in *Tetrahymena*.** Total RNA from wild-type (wt) and *HEN1* knockout (Δ*HEN1*, Δ) strains was extracted at the indicated time points of conjugation, run on a sequencing gel, and stained with a nucleic acid-specific fluorescent dye. scnRNAs in Δ*HEN1* cells became shorter and less abundant as conjugation proceeded compared to wt scnRNAs at the same time points.



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Modelling of human diseases

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With the advent of human genetics, a plethora of genes have been correlated with human diseases. Genetic animal models have proven to be extremely valuable for elucidating the essential functions of genes in normal physiology and the pathogenesis of disease. Using gene-targeted mice my group is attempting to model human disease and to genetically dissect disease mechanisms.

Oxphos defects in mice and the development of diabetes and obesity

Type-2 diabetes and obesity represent the largest and fastest growing epidemic in the world and affect hundreds of millions of people. The pathological mechanisms underlying insulin resistance in diabetes and obesity are poorly understood. It has been proposed that defective mitochondrial Oxphos plays a causal role in the development of diabetes and obesity. However, the causative or compensatory nature of these mitochondrial deficiencies remained an enigma.

To investigate the relationship between Oxphos and insulin resistance at the genetic level, we generated a novel mouse model with a muscle- and liver-specific primary Oxphos deficit that faithfully mimics that of insulin resistant human subjects. Against all expectations, full metabolic analyses revealed improved glucose tolerance, enhanced insulin sensitivity, and a general up-regulation of the glucose uptake machinery. These mice displayed virtually complete resistance to obesity and diabetes even under the pressures of a high fat diet (Figure 1). Similar to the muscle- and liver-specific Oxphos deficiency, a generalised Oxphos deficit did not predispose towards insulin resistance and again protected against the development of diabetes and obesity. The predominant hypothesis predicts that primary Oxphos defects initiate insulin resistance. However, our data clearly show that a primary genetic Oxphos defect results in an increase in insulin sensitivity and prevents the onset of diabetes and obesity. These findings carry profound implications for the understanding of basic metabolism and the development of future therapies towards insulin resistance, diabetes, and obesity (Pospisilik et al., Cell 2007).

The role of oxidative stress and TLR4 in acute lung injury

Most patients who died of SARS developed the acute respiratory distress syndrome (ARDS) – the most severe form of acute lung injury (ALI). ARDS was also the cause of death in millions of people during the Spanish Influenza pandemic. Recently, H5N1 avian influenza virus infections have spread through the world prompting the fear that H5N1 might cause a major world-wide lethal pandemic. The high lethality of H5N1 or SARS infections as well as their economic and social impact makes it paramount to explore novel disease mechanisms and common therapeutic targets of ARDS. The same clinical syndrome of ALI is observed in sepsis, gastric acid aspiration, or pulmonary infections with anthrax in multiple species ranging from birds, rodents, tigers, and primates to humans.

To identify genes that control the severity of ALI, we previously developed an "intensive care unit" for mice that allows us to model ALI (Imai et al., Nature 2005; Kuba et al., Nature Med. 2005). Intriguingly, in congenic and knock-out experiments, innate TLR4-TRIF-TRAF6-NFκB immune signaling was identified as a key disease pathway that controls the severity of ALI (Figure 3). Mechanistically, chemical as well as viral lung pathogens trigger the oxidative stress machinery resulting

Figure 1

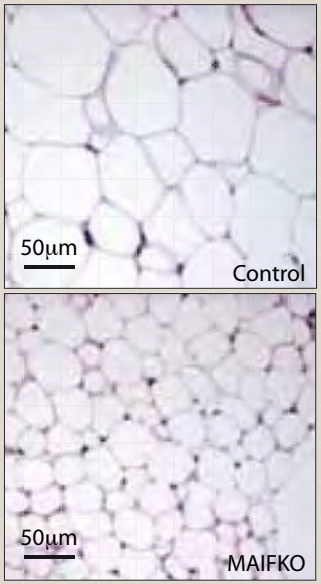
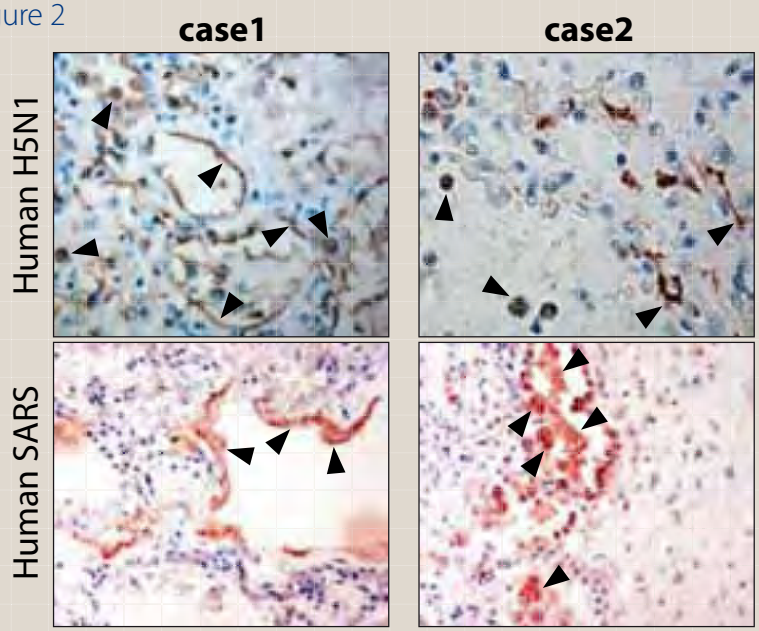


Figure 2



in ROS generation, TLR4 upregulation, and the local production of oxidized phospholipids (OxPLs). OxPLs can directly trigger ALI *in vivo*, dependent on TLR4 expression. Pulmonary challenge with an inactivated H5N1 avian influenza virus rapidly induces lung injury *in vivo* with OxPL formation. Loss of TLR4 and TRIF expression protected mice from ALI in response to inactivated H5N1 viruses. Importantly, deletion of ncf1, which controls ROS production, improves the severity of H5N1-mediated lung injury. Finally, chemical injury, infections of humans with H5N1 avian influenza or SARS-coronavirus (Figure 2), and infections of different species with anthrax, monkey pox virus, or Yersinia pestis, result in the formation of OxPLs in the lung.

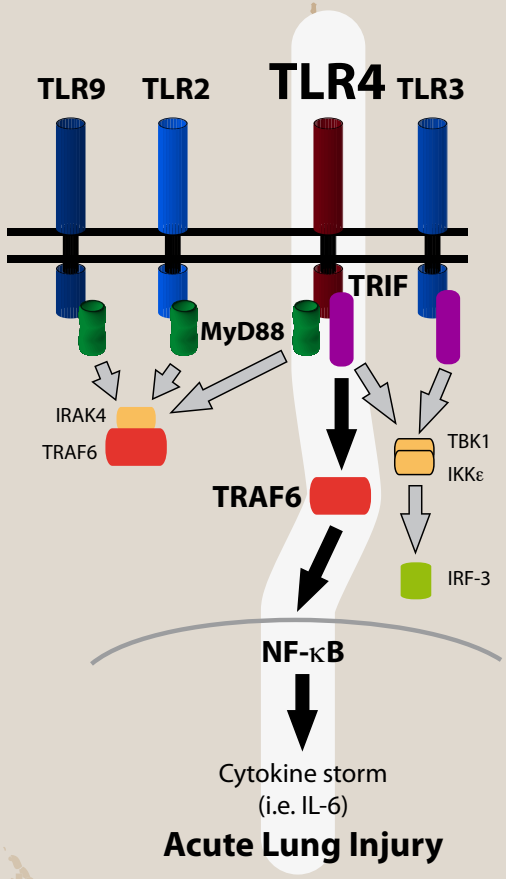
Our data show that the acute onset of severe lung injury caused by different pathogens critically depends on activation of the oxidative stress machinery that couples to innate immunity (Imai et al., Cell, 2008).

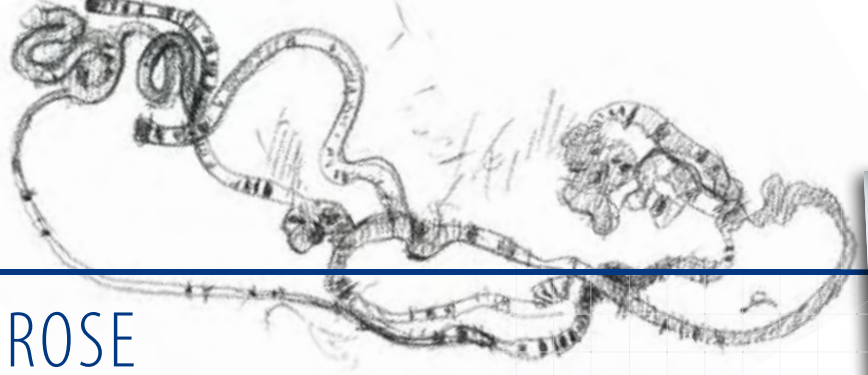
Figure 1: Loss of AIF in muscle (MAIFKO) results in reduced development of adiposity when mice were fed a high fat diet from 3 to 8 weeks of age. Deletion of loxP flanked exon 7 of the *Aif* allele by Mck-driven transgenic cre recombinase resulted in muscle specific AIF deletion termed MAIFKO. H&E staining of white adipose tissue is shown. (Pospisilik et al., Cell 2007)

Figure 2: Immunohistochemistry of CxPLs in lungs from two different patients infected with H5N1 avian influenza virus (upper panels), and two different patients infected with SARS-coronavirus (lower panels). (Imai et al., Cell 2008).

Figure 3: Schematic diagram depicting the role of TLR4, TRIF, TRAF6, and defined cytokines in acute lung injury. The scheme is based on our genetic dissection of lung injury pathways. (Imai et al., Cell 2008)

Figure 3





LEONIE RINGROSE

Epigenetic regulation by the Polycomb and Trithorax group proteins

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How do different cell types remember their identities over many cell generations? Part of the answer lies in the Polycomb and Trithorax groups of proteins. We aim to understand this epigenetic regulatory system on both the molecular and the genomic levels, in terms of the design, function and evolution of its components.

The Polycomb (PcG) and Trithorax (TrxG) groups of proteins work antagonistically on the same target genes, to maintain repressed (PcG) or active (TrxG) transcription states. Both groups of proteins work as large complexes that can modify nearby chromatin. In flies and vertebrates the PcG and TrxG operate on several hundred developmentally important genes, which they recognise through specialised DNA elements called PRE/TREs (Polycomb/Trithorax Response elements, Figure 1A).

How does PRE/RTRE regulation change during mitosis and differentiation?

The PcG are essential for maintaining the correct identities of both stem cells and differentiated cells. How does this regulatory system maintain a stable memory of transcriptional states, but nevertheless allow for change? To answer these questions we use experimental systems in which we can observe and manipulate mitosis and differentiation.

Paradoxically, although the silenced and activated states perpetuated by the PcG and TrxG are stable over many cell generations, the proteins themselves associate with their targets as dynamic complexes, in constant flux between bound and free pools (Figure 1A, B). To study this dynamic behaviour in the context of cell differentiation, we use live imaging of GFP-tagged PcG and TrxG proteins in developing tissues of living *Drosophila* (Figure 1C to H). We combine quantitative measurements with mathematical modelling (Figure 1B). In this way, we hope to understand in quantitative terms, how a system in constant flux can ensure both stability and flexibility.

In addition, we are using the developing *Drosophila* eye as a model system in which to study specific PRE/TREs. The PcG and TrxG are essential for correct eye development (Figure 2A, B). A key target gene of the PcG and TrxG in this tissue is the eyes absent gene, a master regulator of eye cell identity. We have generated transgenic reporter flies with which we examine the dynamic regulation of the eyes absent PRE/TRE during mitosis and differentiation in the developing eye (Figure 2C, D).

In mammals, defined cell differentiation systems enable genomic scale analysis of protein binding and transcription upon cell fate transitions. We are using *in vitro* differentiation of mouse ES cells into neural progenitors and neurons, in combination with high resolution tiling arrays, to document transitions in PcG and TrxG binding, chromatin modifications and gene transcription upon differentiation (Figure 3).

What makes a PRE/TRE?

Fly PRE/TREs are complex combinatorial DNA elements with a flexible design. The sequence requirements for PRE/TRE function in flies are not fully understood. To throw light on this question, we collaborate with bioinformaticians (Marc Rehmsmeier, University of Bielefeld/GMI Vienna). We have examined the evolution of these elements across several *Drosophila* species, showing that PRE/TRE evolution is extraordinarily dynamic. By showing that the evolution of PRE/TREs goes far beyond the gradual

Figure 1

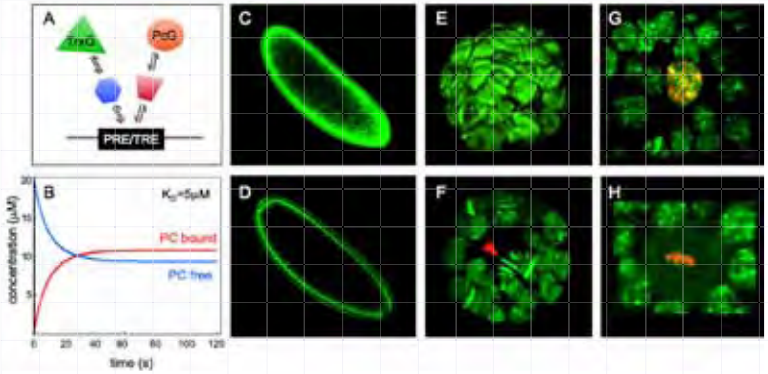
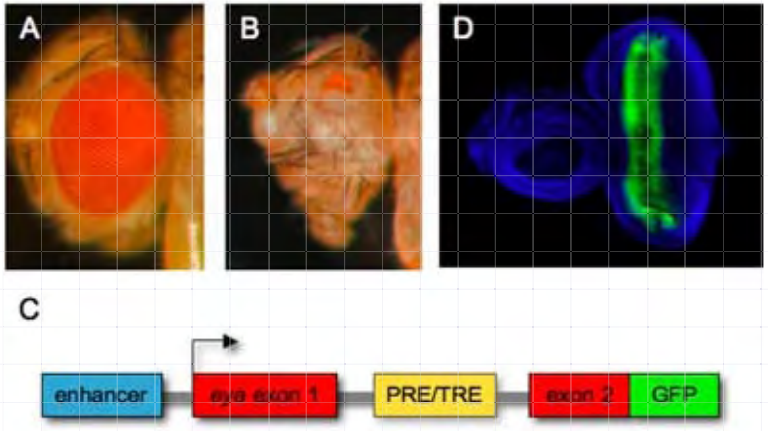


Figure 2



adaptation of pre-existing elements, this study documents a novel dimension of cis-regulatory evolution, and brings us closer to understanding the essential sequence requirements for PRE/TRE function. In mammals, we know still less about what makes a PRE/TRE. We are using reporter assays in mouse ES cells in combination with computational analysis to address the sequence requirements for mammalian PRE/TRE function.

How do non-coding RNAs regulate PRE/TREs?

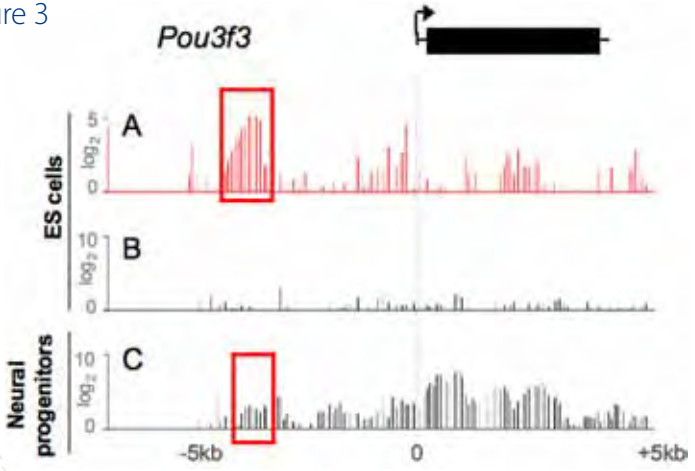
In flies, non-coding RNAs are involved in PRE/TRE regulation, but the molecular details remain obscure. We have identified novel non-coding PRE/TRE RNAs transcribed from the *Drosophila* vestigial (vg) locus. The vg gene is a master developmental regulator required to determine wing identity. Remarkably, we find that ectopic expression of the vg PRE/TRE RNA from a transgene in flies is sufficient to cause activation of the endogenous vg gene. We are now working to elucidate the molecular mechanism of this trans activation. We are also working in our mouse neural differentiation system to identify similar non-coding PRE/TRE RNAs in mammals (Figure 3).

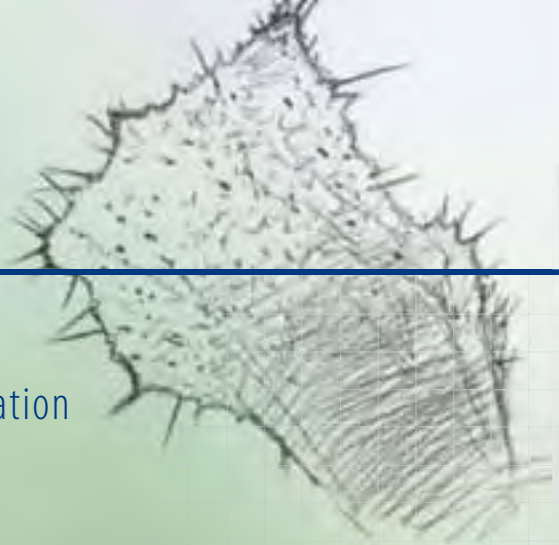
Figure 1: (A) PcG and TrxG proteins are recruited to their targets by DNA binding proteins (blue and red symbols), that recognise DNA elements called PRE/TREs. This binding is highly dynamic. (B) This system is modelled using differential equations. Quantitative parameters are determined from live imaging experiments. The plot shows a simulation of Polycomb binding to chromosomes after mitosis. (C-F) DSP1 is a DNA binding protein that recruits PcG proteins. DSP1:EGFP in (C) 1-hour-old embryo (D) 2.5-hour-old embryo, (E, F) larval salivary gland. (E) 3D reconstruction of whole salivary gland nucleus. (F) Single optical section. Individual DSP1:EGFP bound loci are visible as distinct bands (arrow). (G, H) PC:EGFP in sensory organ precursor cell (SOP). (G) Interphase. (H) Metaphase. PC:EGFP is green (all cells). Chromatin is red (SOP only).

Figure 2: (A) Wild type *Drosophila* eye. (B) Eye specific RNAi knockdown of the TrxG gene moira gives severe proliferation defects. PcG knockdown causes overgrowth and cell identity defects (not shown). (C) Transgene reporter for eyes absent (eya) regulation. The GFP reporter is fused in frame to exon 2 of the eya gene. The construct contains the upstream enhancer and the intronic PRE/TRE. (D) In situ hybridisation to GFP RNA in the eye imaginal disc of 3rd instar larva carrying the reporter construct. The reporter recapitulates the correct eya pattern in the morphogenetic furrow, in which cells are undergoing differentiation. By manipulation of the PRE/TRE sequence in the reporter, we will examine its changing role during eye cell differentiation.

Figure 3: Protein binding (red) and transcriptional profiling (black) on a single microarray platform. Monolayer differentiation of mouse ES cells to neural progenitors was followed by FACS sorting of GFP-marked precursors to obtain pure populations. (A) Chromatin IP against the PcG protein SUZ12 in ES cells shows a strong binding site upstream of the Pou3f3 gene (red box). (B) cDNA hybridisation to the same microarray platform shows that the gene is silent in ES cells. (C) Upon differentiation to neural progenitors, the gene is activated. Red boxes: non-coding transcription through the SUZ12 binding site correlates with activation of the gene.

Figure 3





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Unveiling the mechanisms of cell migration

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It moves - it's alive! In the micro-cosmos of our body tissue movement is likewise vital to life – and can contribute to death! 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 tumours find their way, 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. So what do we already know about cell movement and migration?

A primary player in cell migration is actin, a major protein in all cells that polymerises into filaments. Cells exploit two properties of actin filaments to move: the property to polymerise and push, to effect protrusion and the ability to slide with myosin II, to drive retraction. Protrusion is effected by lamellipodia, thin sheets of cytoplasm composed of networks of actin filaments and filopodia, finger-like rods of bundled actin filaments. In both lamellipodia and filopodia the actin filaments have their fast growing plus-ends directed forwards, and actin monomers are inserted at the interface of the filament plus-ends and the membrane via the activity of protein complexes that initiate and drive actin polymerisation. To understand how actin filaments push in lamellipodia, biochemical information about actin filament dynamics *in vitro* and *in vivo* must be integrated with structural details of lamellipodia structure, obtainable by electron microscopy (EM). One of our research projects deals with the development of EM procedures to resolve the three-dimensional organisation of actin filaments in protrusive zones of migrating cells.

Movement not only requires pushing, but also anchorage with the extracellular matrix and other cells to allow traction and retraction. Anchorage must be transitory and we are therefore also interested in how adhesions are assembled and disassembled during the migration process. More recent interest has also focused on the process of migration *in vivo*, using *Drosophila* as a model system. Here we have taken advantage of the RNAi fly library facility at IMBA/IMP to screen for gene products required for the migration of border cells in the *Drosophila* egg chamber.

Electron tomography of the actin nanomotor

As from March 2008 an FEI Polara 300kV EM became operational for tomography in the IMP/IMBA EM facility. Our first investigations using tomography with the new microscope showed, surprisingly, that negatively-stained cytoskeletons retain 3D integrity and deliver remarkable resolution of actin filaments, without resorting to low dose imaging (Fig.1). This finding opens the way to a two pronged approach, alongside cryo-EM tomography, to resolve actin filament architecture in protruding assemblies. We are currently focusing on collecting 3D information from lamellipodia in motile cells – keratocytes, fibroblasts and melanoma cells. This effort will include the application of recently developed techniques for correlated live cell imaging and EM tomography, which will allow us to correlate protrusion speed with the 3D architecture of the actin nanomotor. In preparation for cryo-electron tomography (cryo-ET) initials tests have shown that we can obtain vitreously frozen, unfixed cells in ice layers that are thin enough for image acquisition. Low dose cryo-ET will be pursued in the coming year, after installation of the necessary accessories on the Polara platform.

Figure 1

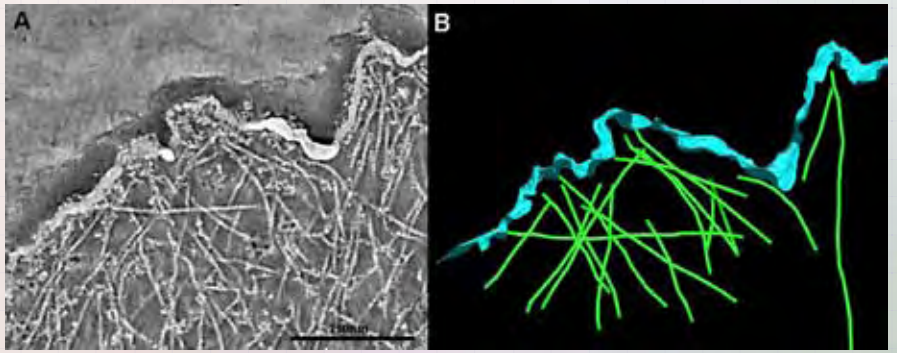


Figure 1: A, Section of an electron microscope tomogram of a region at the front of a fibroblast lamellipodium just behind the leading membrane showing the network of actin filaments. B, Three-dimensional tracing of actin filaments (green) through the tomogram. The membrane boundary is shown in blue. Bar, 250nm.

Figure 2: Interference of vesicular trafficking pathways by siRNA depletion of beta-COP (vesicular COPI coat) and Eps15 (vesicular clathrin coat) causes defects in focal adhesion organisation accompanied by rearrangement of the actin cytoskeleton. HeLa cells were stained with anti-paxillin antibody and phalloidin to visualise focal adhesions (in green) and actin (in red) respectively.

Figure 3: Wild type (A) and a homozygous "Wanderlust" mutant egg chamber (B) stained for singed, E-Cadherin and DNA. Both are stage 10 egg chambers. In egg chambers depleted of Wanderlust, the border cell cluster is trapped at the anterior pole (arrowhead, B) and fails to migrate to the oocyte boundary as in the wild type control (arrowhead, A).

Membrane trafficking and adhesion recycling

Adhesion structures that form at cell–matrix and cell–cell junctions are complex assemblies of transmembrane receptors, structural adaptors and signaling proteins. The means by which molecules are cycled into and out of adhesion complexes are currently unknown. Evidence has however accumulated for a role of membrane trafficking for the recycling of transmembrane integrins at cell–matrix adhesions. Our recent studies suggest that other components of adhesion complexes may be recycled via this route. Thus, we have shown that interference of trafficking pathways involving coated vesicles causes defects in focal adhesion organisation in HeLa cells (Fig. 2) and that one scaffolding protein in adhesion complexes associates with components of coated vesicles.

Border cell migration in *Drosophila*

In a genome-wide RNAi screen of border cell migration we identified the cell adhesion molecule "Wanderlust" as necessary for migration of the cluster through the egg chamber (Fig. 3). Hitherto, molecules of this family have been considered as restricted to the neuronal synapse. Current interest focuses on creating mutants for a more detailed analysis of the role of this molecule in migration of the border cell group and on determining its localisation by immunoelectron microscopy.

Figure 2

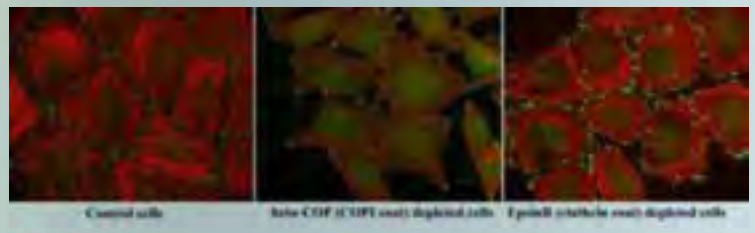
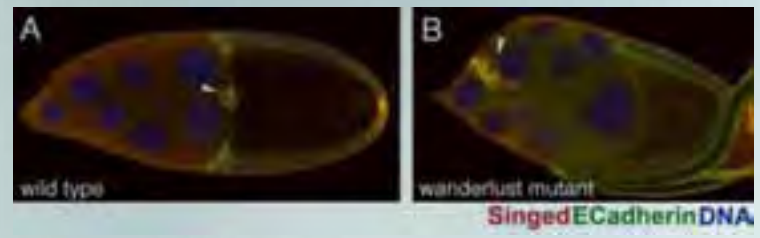


Figure 3



FLY HOUSE

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GERALD HAAS ---------- TECHNICAL ASSISTANT
LISA KIRSCHNER [3] ---------- TECHNICAL ASSISTANT
THERESA PRITZ [4] ---------- TECHNICAL ASSISTANT
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PEDRO SERRANO DROZDOWSKYJ ---------- PROGRAMMER

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[2] UNTIL MARCH
[3] UNTIL JULY
[4] UNTIL NOVEMBER
[5] SINCE MAY
[6] UNTIL FEBRUARY

The Fly House provides research support for those scientists at the institute working with the fruit fly Drosophila melanogaster as a genetic model system.

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 targeted integration, and subsequently perform all the necessary crosses to establish mapped and balanced transgenic stocks.

Gene targeting

Although the use of homologous recombination to generate site-specific mutations is a long established technique in several genetic model organisms, it has only recently become possible in *Drosophila*. During the past year, we have started to generate knock-out flies using an ends-out gene targeting method. With the need to confirm the knock-down phenotypes obtained by several large-scale RNAi screens with traditional loss-of-function alleles, the demand for this service is expected to increase.

Fly stock maintenance and plasmid collection

In addition to looking after lab stock collections, we also keep several commonly used fly stocks. We also have a small plasmid collection consisting mainly of vectors used for homologous recombination, and are working towards improving available vectors by adding new features.

Research support

The Fly House also provides support and expertise for research groups conducting large-scale projects such as RNAi screens, where we help with setting up crosses and scoring phenotypes.

With the growing number of researchers at the institute working with fruit flies, we are aiming to enhance the efficiency of our methods in order to increase capacities over the next year, and additionally plan to extend our support for database programming and the management of large data sets.

STEM CELL CENTER – GENE TARGETING UNIT

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Manipulation of gene expression is an important tool with which to unravel current questions of development and disease. In particular, the generation of transgenic and gene targeted mice has proven to be one of the most powerful approaches to studying gene function both in physiological and pathological contexts. The main objective of the "Stem Cell Centre – Gene Targeting Unit" is to provide state of the art technologies for the manipulation of the mouse genome and the generation of genetically modified mouse strains.

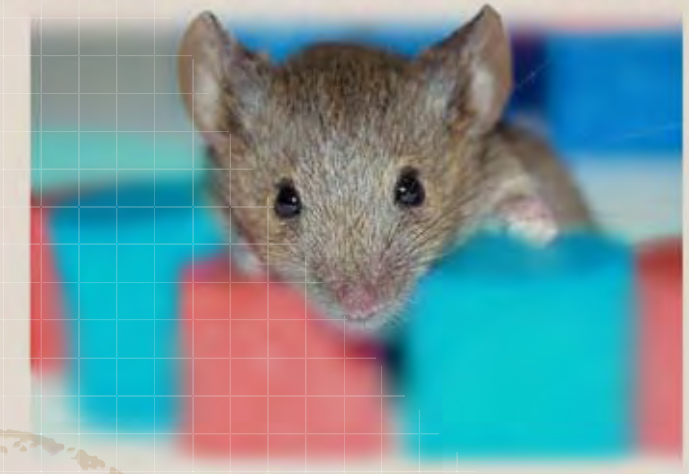
The "Stem Cell Centre - Gene Targeting" platform initiated by GEN-AU supports researchers in the field of embryonic stem (ES) cells and gene targeting. Following targeting construct synthesis and validation, the service provides ES cells and feeder cell dishes, and electroporation of ES cells with the targeting construct.

The Unit also collects and maintains multiple "tool strains" – transgenic mouse lines used for the genetic manipulation of the mouse genome. This collection includes Cre and Flp recombinase-expressing transgenic lines and Cre and Flp activity-reporter lines that are essential for the generation and characterisation of conditional, inducible, and/or tissue specific mutant mice. A collection of "ES and vector tools", neo resistant or neo/hygro/puro resistant feeders, various ES cells, targeting vectors, overexpression vectors, and RNAi vectors can be distributed on demand.

One major interest is the development and implementation of technologies to improve and accelerate the generation of genetically modified mice. We have developed a set of optimised techniques that allow the successful and efficient isolation of ES cells independent of their genetic background, such as C57BL/6 x 129SvJ F1 crosses, but also FVB/N and C57BL/6N. The methods envisaged comprise the analysis of the karyotype, detection of specific markers for pluripotency (Oct-4, SSEA-1, alkaline phosphatase) as well as the ability of ES cells to colonise the germline of a developing mouse embryo.

We are also currently developing new tools for high-throughput mouse generation, such as QUICK-Knock-Ins, tissue-specific and inducible expression of transgenes, the "generation of homozygous ES cell clones" and establishment of feeder-free and serum-free ES cells.

ANFMG Austrian Network for Functional Mouse Genomics



RESEARCH SUPPORT

VIENNA DROSOPHILA RNAi CENTER (VDRC)

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THOMAS MICHELER---------- SOFTWARE DEVELOPER
VIRGINIA SALVA MILLAN----------ADMINISTRATION
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BARBARA STEPIEN [2] ---------- PHD STUDENT
REINHARD HÄMMERLE ---------- DIPLOMA STUDENT

[1] FROM AUGUST 2008
[2] FROM SEPTEMBER 2008

Genome-wide RNAi and memory formation

A Drosophila genome-wide transgenic RNAi library has been generated, allowing researchers to systematically study gene functions in specific tissues at specific developmental stages. The VDRC maintains, further develops and distributes this library to Drosophila researchers world-wide.
In our own research group, we use this and other methods to understand how the fly forms memories that shape its mating behaviour.

Genome-wide RNAi

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 (Figure 1).
The creation of a genome-wide transgenic RNAi library [1] has revolutionised *Drosophila* genetics. The VDRC, a joint IMP-IMBA initiative, maintains, further develops and distributes this library. In its first year and a half, the VDRC has already delivered over 100,000 lines to more than 1,000 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. We continue to further develop both the library and the service. Since summer 2008, we are also able to host external researchers who wish to conduct their RNAi screens in our on-site screening centre. The VDRC also provides such support for researchers in-house, having delivered over 50,000 lines to IMBA and IMP groups in 2008.

Learning and memory

The evolutionary mission of a male fly is to father as many offspring as possible. With an almost unlimited supply of sperm, his success depends almost entirely on his ability to discriminate receptive virgin females from unreceptive females. If he is too promiscuous, he may waste a lot of time and energy in futile courtship; if he is too choosy, he will miss out on excellent mating opportunities. The right balance appears not to be hard-wired into the fly's brain, but is rather something he learns by trial-and-error during his first few courtship experiences (Figure 2). This memory of these first sexual encounters can shape the male's mating strategy for several days – a long time in the life of a fly.

We are trying to understand the molecular and cellular mechanisms that underlie this robust and powerful form of long-term memory. We have recently demonstrated that the CPEB protein Orb2 – a regulator of mRNA

Figure 1: RNAi in *Drosophila*

Figure 2: Courtship conditioning. When tested with unreceptive mated females, males previously exposed to mated females (that) less than naïve (sham-trained) males (CI = courtship index; CI trained < CI naïve).

Figure 3: Mushroom body neurons in the fly's brain – Orb2 is required in these neurons for courtship conditioning.

Figure 1

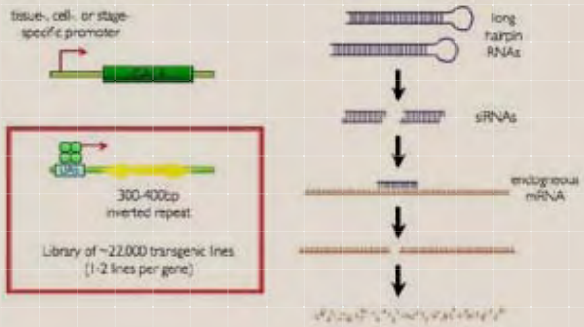
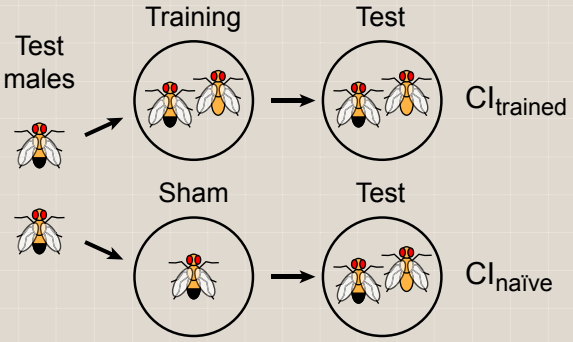


Figure 2

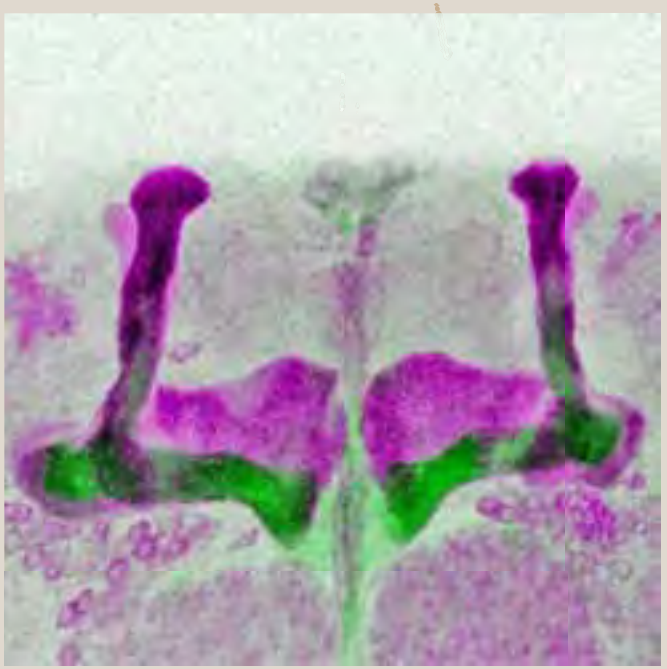


translation – plays a critical role in this process [2]. We found that Orb2 function is required in a specific set of mushroom body neurons during or shortly after training (Figure 3). Without Orb2, or more specifically without its intriguing glutamine-rich domain, a memory initially forms but decays within just a few hours.

To learn more about how Orb2 functions in *Drosophila* long-term memory, we are dissecting its structural and functional requirements using both genetic and biochemical approaches. We are also planning to identify Orb2-interacting proteins and target mRNAs, and to assess their roles in long-term memory. Meanwhile, we are also using the transgenic RNAi library in unbiased approaches to find other factors involved in long-term memory function and dysfunction.

We are also trying to find out exactly what the *Drosophila* male learns during courtship conditioning. What are the specific cues – probably pheromones – that the male learns to discriminate?

Figure 3



BIOOPTICS

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KARIN AUMAYR---------- HEAD OF FACILITY

PAWEL PASIERBEK ---------- MICROSCOPY
GABRIELE STENGL ----------FLOW CYTOMETRY

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

Current activities

Our newest addition is a Total Internal Reflection Fluorescence (TIRF) microscope, which substantially broadens the range of cutting-edge imaging tools available to the researchers' community at the IMP and IMBA. A second aspect of our recent activities is the use of deconvolution image analysis, especially for low light imaging.

TIRF microscopy enables selective visualisation of surface regions such as the basal plasma membrane or the growth of microtubules bound to the coverslip in a sea of fluorescence. The underlying optical principle is the generation of so-called evanescent waves if the incident light is totally reflected at a glass–water interface to selectively excite the sample in an approximately 100–200 nm thin layer above the cover slip surface. Thus, TIRFM provides crisp images of surfaces and can highlight cell membrane features without creating background light.

Deconvolution is the process of reversing the optical distortion imposed by an optical microscope by software algorithms and has been demonstrated to dramatically improve the final image quality. In the last couple of years, this software-based image processing technique has been preferentially used by users of the Deltavision Microscope System. We are now able to extend it to all suitable images taken on both widefield as well as on the various confocal systems because of additional improvements of the algorithm itself, the possibility to batch-process many images with a minimal amount of user interaction using the Huygens deconvolution software as well as increased computer power and therefore increased speed. Beside the general enhancement of the analysed images this technique also allows the amount of light for imaging to be reduced without impairing data quality. Minimising light exposure is especially important in live cell imaging to avoid both bleaching and damage to the cell caused by phototoxicity.

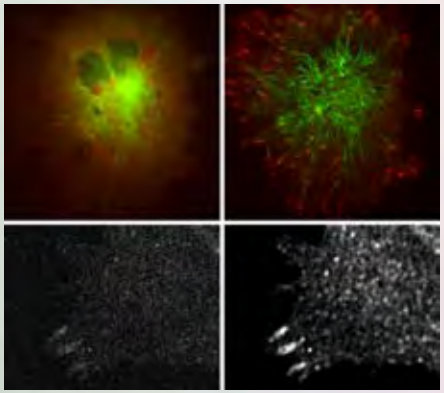

Figure: The upper panel shows the comparison of a widefield (left) and a TIRF image (right) of a CAR cell stained with EB1 in red and alpha-Tubulin in green (Maria Nemethova). The lower panel shows an example for deconvolution of a low light image (left: image before and right: image after deconvolution) of a HeLaCell with Paxillin-GFP (Martin Breuss).

ELECTRON MICROSCOPY

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The Electron Microscopy Facility provides a wide variety of preparation techniques for tissues, cells, and purified molecules for transmission electron microscopy, as well as facilities for microscopy, data management and image processing.

Specimen Preparation

Know-how, training and instrumentation for a wide variety of preparation techniques for visualisation of ultrastructure in tissues or cells and of purified biomolecules by transmission electron microscopy (TEM) are being provided by the Electron Microscopy Facility. Techniques routinely used by both IMP and IMBA researchers are chemical and physical fixation, resin embedding in epoxy- and acrylic resins, freeze substitution, ultrathin sectioning of resin embedded or frozen samples, production of support films, negative staining of molecules and organelles, rotary shadowing of sprayed molecules, and others. Depending on future developments and the focus of the demand from the institutes, additional preparative approaches will be introduced.

Microscopy

One cornerstone of the facility is the FEI Morgagni. This robust and easy to use 100 kV TEM equipped with a 11 megapixel CCD camera is tailored for routine needs in the multiuser environment of the facility.

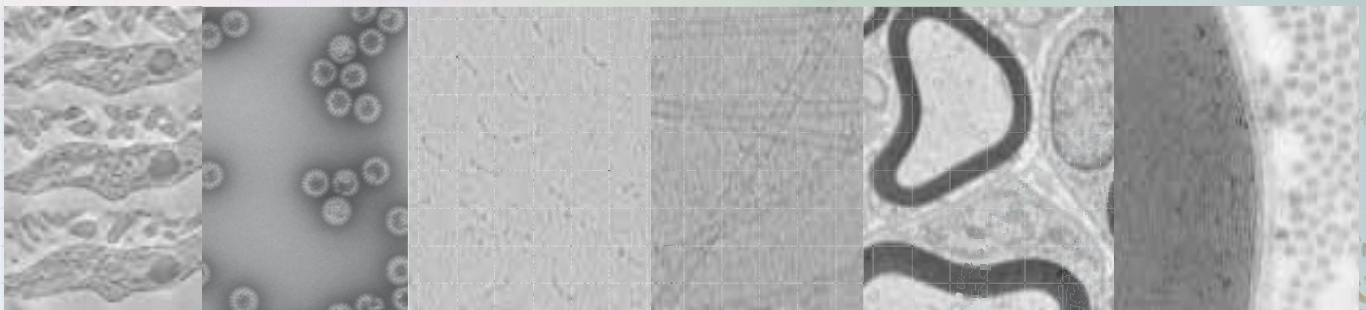
While the Morgagni is an excellent tool for conventional TEM, advanced applications are the domain of the FEI TF30 Polara. This 300 kV TEM, unique in Austria and equipped with the most advanced imaging systems, was funded by a Vienna Spot of Excellence grant and became fully operational at the beginning of 2008. It is primarily being used for cryo-TEM of molecules and cells, and electron tomography.

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 in 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 for automated image acquisition (predominantly for single particle EM; collaboration with the Marlovits Group) and for status monitoring of the microscope was developed on the Polara. For image processing of EM data, especially from electron tomography, workstations and training are being provided.

GÜNTER RESCH ---------- HEAD OF FACILITY

MARLENE BRANDSTETTER ---------- TECHNICAL ASSISTANT
MATTHIAS BRUNNER ---------- PROGRAMMER



A: z-Sections from a three-dimensional reconstruction of the endothelial lining in a blood vessel by electron tomography.
B: Negatively stained rotavirus-like particles (micrograph courtesy of Cornelia Gänger, Ringrose Group)
C: Glycerol sprayed and rotary shadowed α-actinin molecules
D. Dam1-decorated microtubules visualised by cryo-electron microscopy (sample: Fabienne Lampert, Westermann Group, IMP)
E+F: Cross-section of myelinated neurons (sample: Toshikatsu Hanada, Penninger Group)

BIOINFORMATICS

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MARIA NOVATCHKOVA ----------COMPUTATIONAL BIOLOGIST
ALEXANDER SCHLEIFFER----------COMPUTATIONAL BIOLOGIST

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 IMP-IMBA Bioinformatics unit has its main expertise in the field of sequence analysis. Typical tasks include the functional and structural characterisation of proteins and genomic regions using methods such as pattern matching, complexity analysis and homology searches. As bioinformatics conclusions are a synthesis of results from multiple algorithms, we maintain and develop a set of specialised software tools to support this type of meta-analysis.

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, a user-friendly web application and 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 now managed by the Sun Grid Engine (SGE) software, which provides policy-based workload management for a large number of jobs and nodes.

Training

We provide hands-on training courses on the ANNOTATOR, where participants learn the basis and limitations of sequence analysis and data integration.

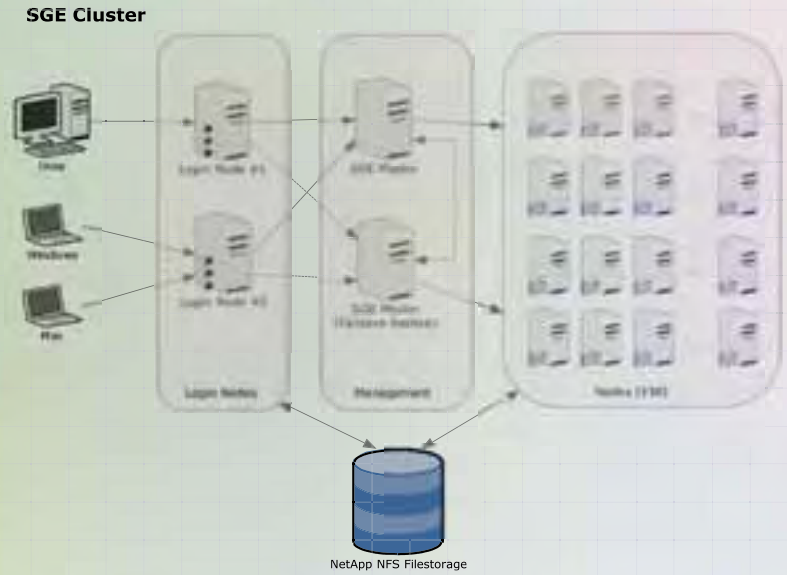

Figure: The IMP/IMBA high-performance computing (HPC) cluster. Users can submit jobs on dedicated login nodes to the Sun Grid Engine (SGE) master, which is responsible for running these jobs on the cluster nodes.

GENOMICS

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MARTIN RADOLF ---------- ENGINEER
MARKUS SONNTAGBAUER ---------- TRAINEE

The newly founded Genomics Department currently comprises the microarray services, the cDNA clone repository and liquid handling robotics, formerly part of the Biooptics Department. Next Generation (Solexa) Sequencing will be offered as a new service to IMP and IMBA researchers in 2009.

Current activities

A major effort in 2008 was the re-arraying of RIKEN (FANTOM I to III) clones to provide a single chip representing more than 22,500 murine genes. To date, almost 100,000 RIKEN clones have been processed and spotted on a set of four chips (200 chips per batch). Hybridisation information from more than 500 hybridised samples was used to identify clones that reproducibly yielded good hybridisation signals in at least three independent experiments. This information was used to re-array a non-redundant set of 22,500 clones that were subsequently processed for printing.

The reduction in the number of slides used for hybridisation will not only reduce the cost per experiment but also the time for analysis by a factor of three, allowing the processing of more samples. Currently we are trying to establish hybridisation of labeled RNA instead of cDNA; this will also substantially shorten the handling time and decrease the cost per experiment.

Processing of microarray data has been completely automated by combining several packages from the BioConductor project. We can now provide users with fully annotated lists of differentially regulated genes.

In the past six months, together with scientists from the Busslinger and Jenuwein labs we have set up the infrastructure for Next Generation Sequencing. Sample preparation and in-process quality control have been established and are currently being optimised.

We expect a throughput of up to two runs per week yielding up to 2.7 Gigabases per run depending on sample quality. By the end of this year, deep sequencing applications like ChIP-seq and sequencing of small RNAs will be offered as a service to scientists of both institutes.

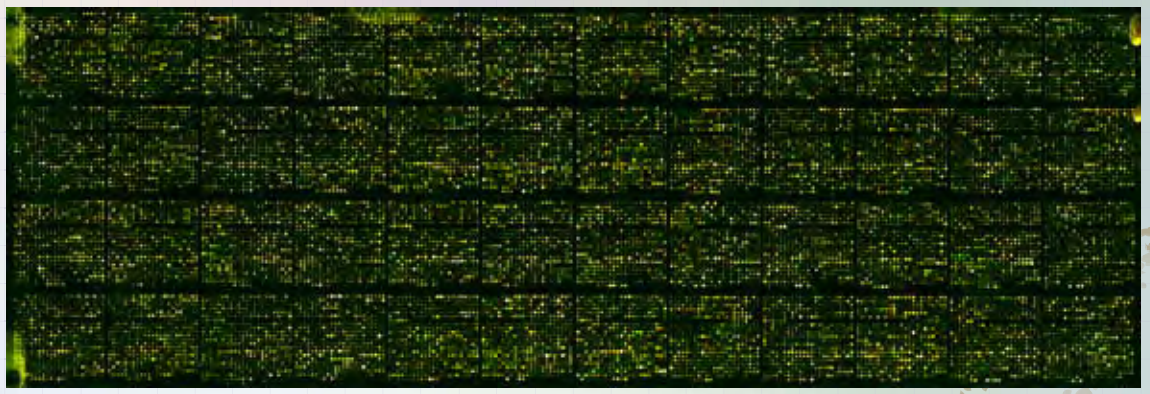

Figure: The new 23 K microarray comprising a non redundant set of cDNAs.

PROTEIN CHEMISTRY FACILITY

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MICHAEL SCHUTZBIER---------- TECHNICAL ASSISTANT
INES STEINMACHER---------- LAB MANAGER

[1] *SINCE NOVEMBER 2008,*
JOINT APPOINTMENT WITH STEFAN WESTERMANN

The IMP-IMBA Protein Chemistry Facility performs a large variety of mass spectrometry experiments, including identification of proteins, characterisation of post-translational modifications and their quantification. Finally, our facility specialises in peptide synthesis and antibody purification.

Establishing and improving iTRAQ-based protein quantification

During the last decade there has been a growing interest in the description of biological systems in a quantitative and systematic manner. In parallel, methods have been developed for quantifying and identifying proteins in an unbiased way. One of these methods, termed isobaric tags for relative and absolute quantitation (iTRAQ), has become increasingly popular (Fig.1). We have applied iTRAQ to the analysis of protein complexes, which we analysed under different conditions in order to elucidate their dynamic behaviour.

The methodology can be used in conjunction with many mass spectrometers and different fragmentation techniques. We evaluated the different approaches and developed a novel analytical strategy.

Quantitative analysis of knock-out mice

Many proteins regulated in disease may serve as candidates for clinically useful biomarkers and may also provide insight into the molecular mechanisms of disease processes. We successfully applied iTRAQ methodology to a mouse liver hepatitis model utilising c-jun knock-out mice.

Continuous improvements in the qualitative and quantitative analysis of phosphorylation sites

Protein phosphorylation is one of the most important post-translational modifications. We have developed several approaches for the selective enrichment of phosphorylated peptides based on the different metal-based enrichment methods such as immobilised metal affinity chromatography (IMAC) or affinity chromatography with titanium oxide. During the last few years we have also started to combine large-scale phosphorylation site analysis with relative quantification. We have applied these techniques to the large-scale analysis of kinase networks under different biological conditions.

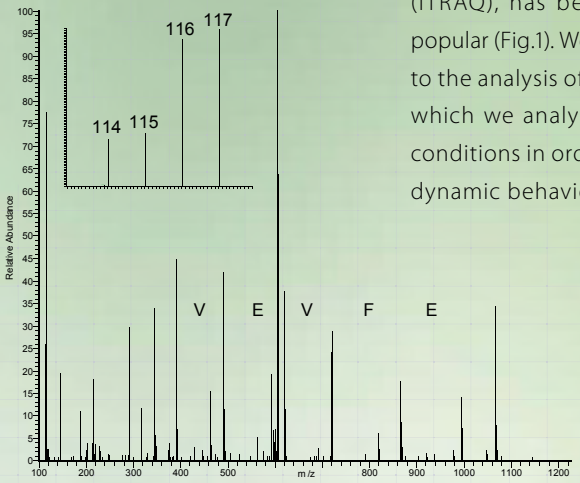

Figure: The spectrum of the iTRAQ-labeled peptide AEFVEVTK is shown. A sufficient number of fragment ions allows its identification with high confidence. Part of the sequence is indicated. The insert shows the four iTRAQ reporter ions allowing the relative quantification of the samples. The ratio of the reporter ions reflects the original protein ratios.

SERVICE DEPARTMENT

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The Service Department offers a variety of high quality and rapid services to IMP and IMBA scientists. The majority of our effort involves DNA sequencing, fly food production and 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 staff have moved back to the IMP building. There is now more space to create better and more convenient working conditions for preparing fly food and for storing all the goods we need. We also prepare many selected reagents such as DNA molecular weight markers, enzymes, a variety of transformation-competent E. coli strains and we maintain a stock of cloning vectors, sequencing primers and other reagents.

Production of antibodies

The production and isolation of many different monoclonal antibodies in hybridomas in collaboration with IMP group members, and organising antibody production in rabbits with an outside company, takes some of our working time capacity.

Sequencing and DNA isolation

The 48 capillary ABI 3730 DNA Genetic Analyser is the only work horse. The 16 capillary ABI 3100 Genetic Analyser is solely used as a back-up sequencer for emergencies.

We sequenced approximately 55,000 samples in the first 9 months of this year. This substantially increased demand is due to screening projects and the new fly library, but also to new groups at IMBA as well as at the IMP.

We are primarily using the 3730 DNA Analyser because of its sensitivity and lower consumables running costs. The average read-length is 700–900 bases for standard DNA samples with 50 cm ABI 3730 capillaries.

DNA sample quality and concentration are a problem even when prepared by sophisticated Qiagen Kits like Midi-, Maxi- or Minipreps, as are wrong primer sets or insufficiently documented plasmid constructs from outside sources. Compared to analysis by restriction digest, sequencing is faster and easier. The clean-up protocol with Sephadex G50 superfine columns on a 96-well microtiter plate format with optimised Sephadex consistency and centrifugation conditions has been transferred to a BioTek benchtop minirobot. The results tell us that there is no difference between the plates prepared by the robot and those prepared manually and they do not show "dye blobs" with good quality DNA samples.

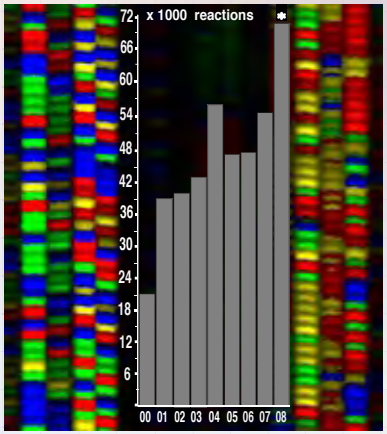

Figure: A sequencing run on an ABI 377 PRISM and number of reactions analysed on ABI 377 (- 2001), on ABI 3100 (since 2001) and on ABI 3730 (since June 2004) with dye deoxy terminators (v3.1 since 2001) in the years 2000 to 2008 (scale 0 to 72,000). *calculated from January 2008 to September 2008 data

GOTTHOLD SCHAFFNER ---------- HEAD OF FACILITY

IVAN BOTTO ---------- TECHNICAL ASSISTANT
MARKUS HOHL ---------- TECHNICAL ASSISTANT
SHAHRYAR TAGHYBEEGLU ---------- TECHNICAL ASSISTANT
GABRIELE BOTTO ---------- MEDIA KITCHEN
CHRISTA DETZ-JADERNY ---------- MEDIA KITCHEN
ULRIKE WINDHOLZ ---------- MEDIA KITCHEN
SABINE JUNGWIRTH ---------- FLY FOOD PREPARATION
FRANZISKA STRANSKY ---------- FLY FOOD PREPARATION
OLIVER BOTTO ----------HELP FLY FOOD PREPARATION
THOMAS HAYDN----------HELP FLY FOOD PREPARATION
ANNA WINDHOLZ----------HELP FLY FOOD PREPARATION

HISTOLOGY

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VUKOSLAV KOMNENOVIC ---------- HEAD OF FACILITY

MIHAELA GRIVEJ ---------- TECHNICAL ASSISTANT

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

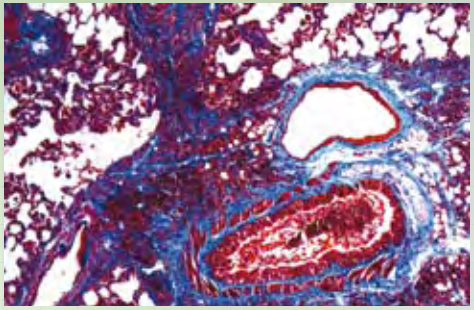
In our group we have developed a high throughput method to cut paraffin and frozen tissues. Using this method, we could increase the quality and also the quantity of services.

Immunohistochemistry

The Histology Service Department also provides automated preparation and processing facilities for standard-ized 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), I-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

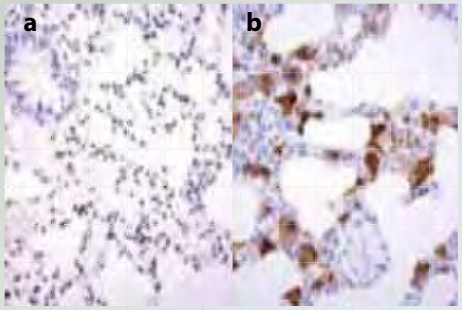


Figure 1: Trichrom blue staining. The picture shows 4 different signals, light blue for Lung fibrosis, red for Mast cells and Neutrophils, pink for Myeloiud cells and dark blue for the Nuclei.

Figure 2: (a and b) Immunohistochemistry reveals that osteopontin (brown signal), absent from the wild type (a), was predominantly expressed by alveolar macrophages (b) in fra-2tg lungs (17 weeks of age)

SCIENTIFIC SERVICES

1

ANIMAL HOUSE

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Animal House

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 attandants - 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.

Animal House Services:

Veterinary services, such as monitoring of the facility's health-status (sentinel-program etc.), experimental procedures in animals such as collection of blood, implantation of tumor cells and administration of substances. 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.

MOUSE SERVICE

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

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 into our Animal House, the freezing of embryos for the preservation of specified mouse strains and the teaching of basic embryological techniques to the IMP and IMBA staff.

Many different ES cell clones and DNA/BAC constructs are being injected per year. The activities of this department are overseen by an Animal User Committee, which meets bimonthly to set priorities and to coordinate the duties. At present, it is chaired by Meinrad Busslinger.

2

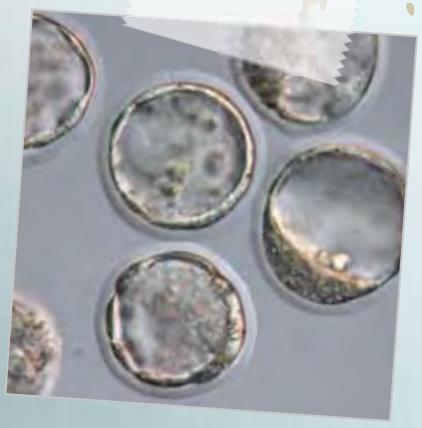
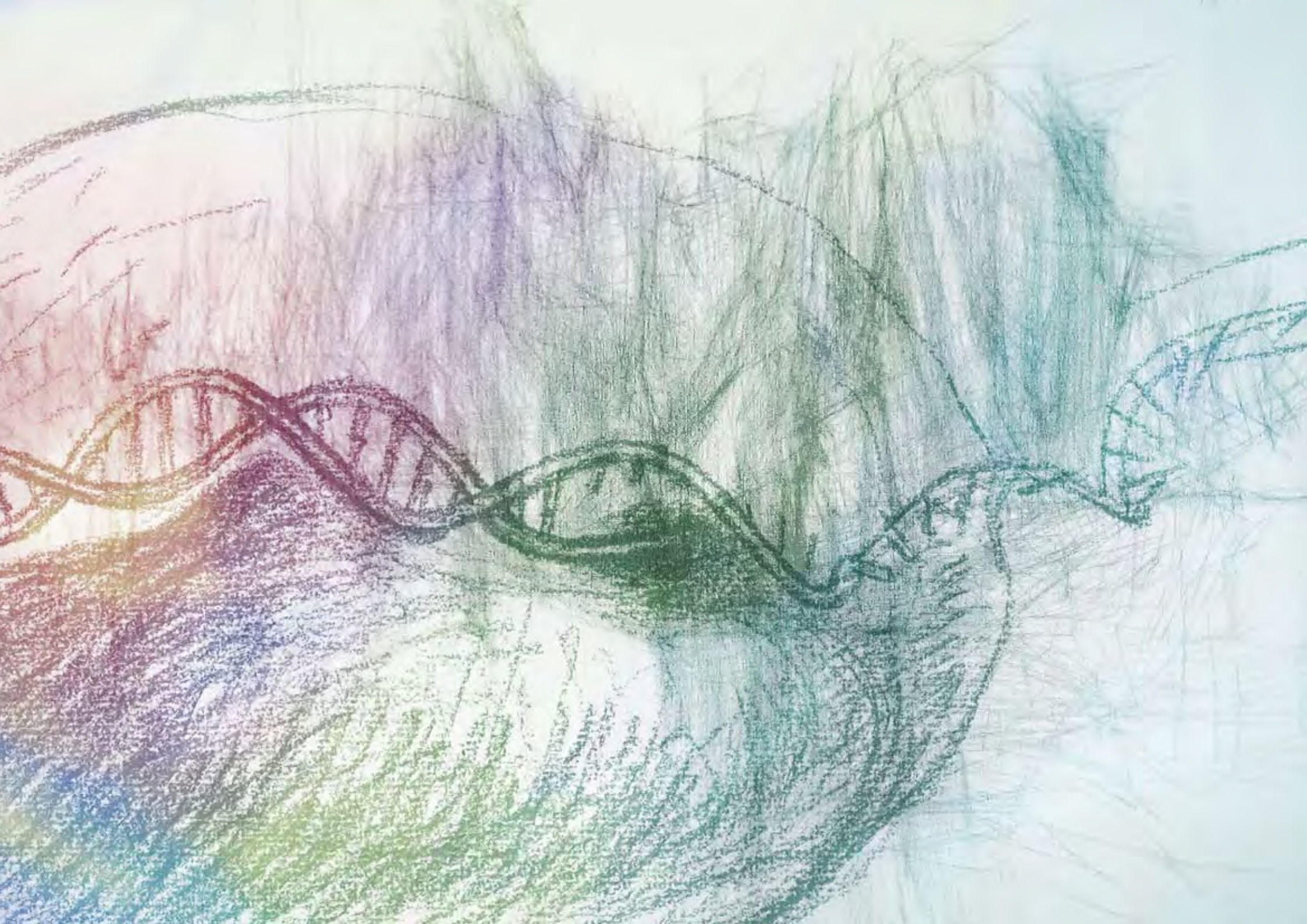


Figure 1: Injection of embryonic stem cells into mouse blastocyst.

Figure 2: Mouse blastocysts.



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**equally contributing authors.*
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STEM CELL CENTRE - GENE TARGETING UNIT

Meixner, A., Zenz, R., Schonthaler, HB., Kenner, L., Scheuch, H., Penninger, JM., Wagner, EF. (2008). Epidermal JunB represses G-CSF transcription and affects haematopoiesis and bone formation. Nat Cell Biol. 10(8):1003-11

ELECTRON MICROSCOPY

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Bozec, A., Bakiri, L., Hoebertz, A., Eferl, R., Schilling, AF., Komnenovic, V., Scheuch, H., Priemel, M., Stewart, CL., Amling, M., Wagner, EF. (2008). Osteoclast size is controlled by Fra-2 through LIF/LIF-receptor signalling and hypoxia. Nature. 454(7201):221-5

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GENOMICS

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IMBA Awards 2008

Frederik Wirtz-Peitz

- *VBC PhD Award (November)*

Reiko Hanada

- *Best Poster Award 2008 2nd International Conference on Osteoimmunology, Rhodos, Greece (June)*

Karl Mechtler

- *Outstanding ABRF Poster Award 2008, ABRF Conference, Salt Lake City, USA (Februar)*

Kazufumi Mochizuki

- *ERC Starting grant by the European Research Council (January)*
- *Elected to the Austrian Academy of Sciences as "Mitglied der Jungen Kurie" (April)*

Josef Penninger

- *Carus-Preis by the City of Schweinfurt, Germany (April)*
- *Karl Landsteiner prize founded by the Austrian Society of Allergology and Immunology (September)*
- *Advanced Investigator Grant by the European Research Council (October)*
- *Elected member of the European Molecular Biology Organization EMBO (October)*
- *Included to the list of the 1000 most important Austrian immigrant/emigrants in politics, arts, sports, philosophy, business, or music, from 1900-2008.*

Arabella Meixner

- *„Best supervising tutor" award GEN-AU SummerSchool 2008 (November)*
- *Kardinal-Innitzer acknowledgement award (December)*

Andrew Pospisilik

- *„Best supervising tutor" award GEN-AU SummerSchool 2008 (November)*

Daniel Schramek

- *„Best supervising tutor" award GEN-AU SummerSchool 2008 (November)*

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JANNUARY

10. Jannuary — Anne Ridley
Ludwig Institute for Cancer Research, London
Rho GTPases: signalling in cell adhesion and migration

11. Jannuary — Helge Grosshans
Friedrich Miescher Institute, Basel
let-7: Developmental Regulator and Model MicroRNA

15. Jannuary — Hans-Ulrich Dodt
Technical University of Vienna
The glass brain: Visualization of neuronal networks in the whole mouse brain by ultra microscopy

24. Jannuary — George Klein
Karolinska Institutet, MTC
Why do we not all die of cancer at an early age?

25. Jannuary — Marius Wernig
Whitehead Institute for Biomedical Research
Somatic Reprogramming and Neural Specification

FEBRUARY

01. February — Sylvia Synowsky
Department of Biomolecular Mass Spectrometry, Utrecht University
Macromolecular mass spectrometry of RNA regulating protein machineries

07. February — Pascale Cossart
Pasteur Institute, Paris
The fascinating strategies used by Listeria monocytogenes during infection: new concepts in infection biology and cell biology

07. February — Tobias Junt
Novartis Institues for BioMedical Research GmbH & Co KG
Subcapsular sinus macrophages in lymph nodes clear lymph-borne viruses and present them to antiviral B cells

19. February — Michael Petrascheck
Fred Hutchinson Cancer Research Center
An Antidepressant that increases lifespan in adult C.elegans

19. February — Julian Downward
Cancer research UK London research institute
Investigation of Ras oncogene signaling networks in tumorigenesis

20. February — Axel Visel
Lawrence Berkeley National Laboratory
Deciphering the Regulatory Genome

21. February — Petra Hajkova
Wellcome Trust / Cancer Research UK Gurdon Institute
Epigenetic reprogramming in the mouse germ line - beyond DNA demethylation

21. February — Jürgen Soll
Ludwig-Maximilians-University Munich
Protein and Metabolite Transport in Chloroplasts

27. February — Julius Brennecke
Cold Spring Harbor Laboratories
Small RNA pathways in Drosophila: ancient and versatile

MARCH

06. March — Scott Keeney
Memorial Sloan-Kettering Cancer Center
Mechanism and Regulation of Meiotic Recombination

18. March — Inke Naethke
University of Dundee
The adenomatous polyposis coli protein as a cytoskeletal architect: implications for early tumourigenesis

27. March — Michel Tremblay
McGill Cancer Centre
Tyrosine phosphatases in signaling and diseases

APRIL

10. April — Wendy Bickmore
MRC Human Genetics Unit, Edinburgh
Alteration of gene expression at the nuclear periphery of human cells

17. April — John Hammer
Lab of Cell Biology, NHLBI, Bethesda, USA
Design Principles for Myosin V-Dependent Organelle Transport

24. April — Craig Mello
Howard Hughes Medical Institute, University of Massachusetts
Return to the RNAi World: Rethinking Gene Expression, Evolution and Medicine

25. April — Jody Puglisi
Stanford University School of Medicine
Dynamics of translation

MAY

08. May — Rudolf Grosschedl
Max-Planck-Institute of Immunobiology
Regulation of B lymphopoiesis and hematopoiesis by EBF transcription factors

14. May — Marcello Maresca
Max Planck Institute of Molecular Cell Biology and Genetics, TU Dresden
Fundamental and applied recombineering

14. May — Masanori Mishima
Wellcome Trust/Cancer Research UK Gurdon Institute
The critical role of protein aggregation in cytokinesis

20. May — Ron Vale
University of California
Insights into mitotic spindle assembly through whole genome RNAi screening

SEMINAR SPEAKERS

29. May — Edwin Cuppen
Hubrecht Institute
Genome-wide tilling: from gene-based to organism-based screens

29. May — Thomas Cremer
LMU Biozentrum
Chromosome territories and nuclear organization: structural, functional and evolutionary aspects

JUNE

05. June — Sebastian Carotta
WEHI, Melbourne
Important Roles of PU.1 and IRF-8 in Plasma Cell Development and Leukemia

12. June — Masanori Hatakeyama
Institute for Genetic Medicine, Hokkaido University
Oncogenic mechanism of Helicobacter pylori

18. June — Karl-Ludwig Laugwitz
Technical University Munich
Islet-1 cardiovascular progenitors: From skin to heart cells

19. June — Steve Reiner
Abramson Family Cancer Research Institute, University of Pennsylvania
Asymmetric cell division during mammalian immunity

26. June — Miguel C. Seabra
Imperial College London, Faculty of Medicine
Rab GTPases, membrane traffic and disease

JULY

02. July — Tony Lam
University of Toronto
Nutrient sensing in the gut and the brain

03. July — Antonio Cassone
Instituto Superiore di Sanita, Rome
Beta glucan based fungal vaccines and anti-virulence antibodies

09. July — Barbora Maralikova
Royal Holloway University of London
Characterisation of Entamoeba histolytica proteome and search for mitosomes

10. July — Johann Holzmann
Medical University of Vienna, Center of Anatomy and Cell Biology
RNase P without RNA: Identification and Functional Reconstitution of the Human Mitochondrial tRNA Processing Enzyme

17. July — Mark Hochstrasser
Department of Molecular Biophysics & Biochemistry, Yale University
Regulation of the ubiquitin-proteasome system

17. July — Marcus Conrad
Helmholtz Zentrum München
The role of glutathione peroxidase 4 in cell fate decisions

24. July — Magdalena Götz
GSF-Institut für Stammzellforschung
Glial cells generate neurons: new views on reactive gliosis and neural repair

SEPTEMBER

04. September — Rachel Wilson
Harvard Medical School
Lessons from a tiny brain: using electrophysiology and genetics to understand sensory processing in Drosophila

18. September — Kristian Helin
Biotech Research & Innovation Centre, Copenhagen
Epigenetics, stem cells and cancer

25. September — Elisa Izaurralde
Max-Planck-Institute for Developmental Biology, Tuebingen
Mechanisms of miRNA-mediated gene silencing

26. September — Frank Bradke
Max Planck Institute, Martinsried
Intracellular mechanisms of axonal growth and regeneration

OCTOBER

09. October — Louis Staudt
National Cancer Institute, Bethesda
RNA interference genetic screening meets cancer gene resequencing

23. October — Paul Sharp
The University of Edinburgh
The origins and evolution of AIDS viruses

30. October — Pierre Vanderhaeghen
University of Brussels
Generating Neuronal Diversity from Pluripotent Stem Cells

NOVEMBER

04. November — Harvey McMahon
LMB, Cambridge
Sculpting Cell Membranes: Understanding pathways of endocytosis and exocytosis

06. November — Vicki Chandler
University of Arizona
Interchromosomal Mediated Epigenetic Silencing Across Generations

27. November — Caroline Dean
John Innes Centre, Norwich
Epigenetic regulation in the cold-induced switch to flowering

DECEMBER

11. December — Elena Conti
Max Planck Institute of Biochemistry
Molecular mechanisms of nonsense-mediated mRNA decay

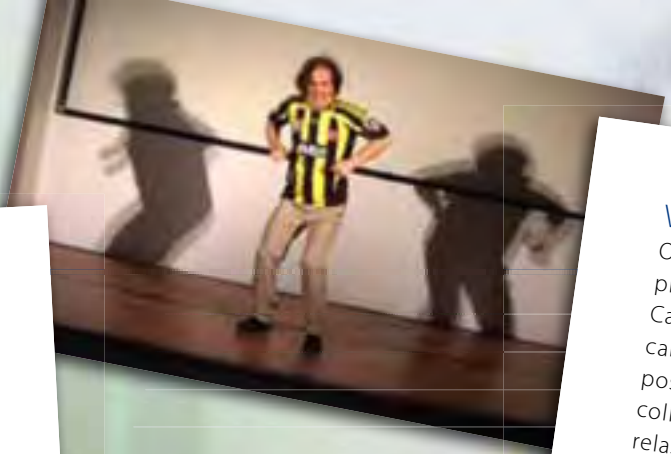
Science Dance Party

On 18th January 2008 the world's first 'Dance your PhD' contest took place at the IMP, organized by IMP-IMBA and John Bohannon, correspondent from Science magazine. In three categories (students, postdocs and group leaders) researchers where challenged to express their PhD theses using the medium of dance. Twelve dance entries were handed in and each performance was judged by a four-member panel, which included a professional dancer.

One dance entry came from IMBA: Joseph Penninger, with his thesis "Analysis of thymic nurse cells in the chicken" eminently rendered as the 'Birdie Dance'. He was awarded third place among three contesters.

In addition to the dance contest, five musical tracks using sounds recorded in the lab like a DNA sequencer, or courtship song of a fruit fly, were premiered at the event accompanied by vivid graphics. Also shown was Cell Dance: a compilation of movies depicting beauty on the microscopic scale like cultured human cells undergoing synchronous mitosis and rotating 3D protein structures.

The performances can be found on You Tube.



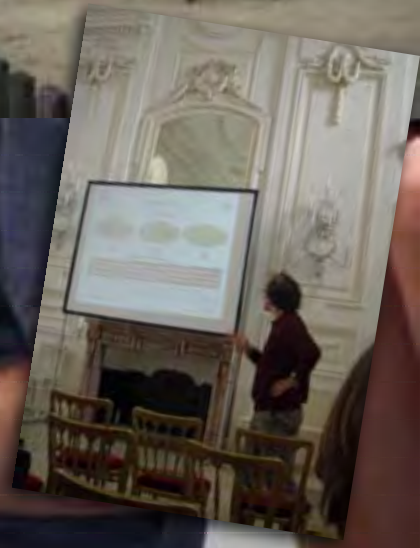
VBC PhD Retreat

On June 5 and 6, a record number of 55 students from the VBC PhD program headed to the Hotel Wende at Neusiedl am See for the 3rd Campus Vienna Biocenter PhD retreat. It was two days full of science, career perspectives, discussions, food, and lots of fun. Like last year, poster sessions gave the students a chance to get to know what their colleagues are working on and explain their own PhD projects in a relaxed and informal atmosphere.

The external speakers invited this year were Gottfried Himmler, CEO of F-Star, a biotech company based in Vienna and Alper Romano who did his PhD thesis at the IMP in the group of Michael Glotzer and is now patents examiner at the European Patent Office (EPO).

Microsymposium on Small RNAs

The by now 3rd edition of the Microsymposium took place from 19th to 21st of May at the IMBA. The meeting hosted a superb group of international young speakers and a very exciting PhD workshop, with 12 top-quality and "worldwide" talks, where laboratories as distant as Singapore, the US, South Korea and Argentina were represented. The Microsymposium was fully financed again this year by companies, the RNA Society, and journals like "RNA Biology" and "Nature Structural and Molecular Biology." The workshop for the PhD students was partly sponsored by "Forschungsprojekt/Wien," an initiative of the Austrian Academy of Sciences. The Microsymposium on Small RNAs is now established as an interactive, friendly and high profile meeting, bringing together voices from around the scientific world to discuss exciting aspects of RNA biology.



Post Doc Retreat

The third Postdoc Retreat took place in Bratislava on the 18th and 19th of September. The program started with a scientific lecture presented by Prof. Dontscho Kerjaschki of the Medical University of Vienna, followed by a talk by Claudia Fila sharing her experiences of being a postdoc at Roche with the audience. Finally, Brigitte Gschmeidler from the non-profit-organisation "Dialog Gentechnik" spoke about her efforts in trying to educate the public about DNA, gene technology and related topics. The official part was followed by a get together in the evening and a walk around the old town the next morning, the final highlight on the way back to Vienna being a visit to the Roman Ruins at Carnuntum.

IMBA Retreat

This year more than 100 colleagues joined the IMBA retreat on October 6th. The first stop was the imperial palace "Schloss Hof" east of Vienna where the group enjoyed excellent guided tours in English and German. Afterwards there was time to explore the spacious baroque park with its wonderful, extremely colorful flowers. Lunch was followed by a presentation from the IMBA management.

The afternoon was spent at Carnuntum/Petronell where the group was led through the Roman archeological excavations, the final highlight being the "Roman Games" where participants could try out hunting a wooden boar with a spear and putting a toga on the correct way.

Recess

From October 1-3 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. The IMBA would like to thank all its SAB members and the representatives of the Austrian Academy of Sciences for their tremendous support and welcome the new SAB member Gary Ruvkun from the Harvard Medical School, Boston, USA.

IMBA SAB members: page 46 in this booklet.

PhD Symposium

The PhD Symposium can be considered a fixed appointment of the scientific year at the Vienna Biocenter. This year, it was dedicated to the cutting edge topic of Synthetic Biology. On the 13th and 14th of November an audience of about 150 participants gathered in the IMP lecture hall for the symposium "Life under (re)contruction" to attend the talks of 16 well renowned scientists coming from various countries. The speakers presented the multi-faceted aspects of this scientific area to give an overview of the possibilities and challenges offered by the emerging field of Synthetic Biology. Among the speakers were well known experts such as Sven Panke, who talked about the possibility of engineering bological pathways, Ehud Shapiro, who described the new frontiers of DNA editing, and Steven Benner, who gave the closing lecture on the progress of molecular evolution and its applications to personalized medicine. The event was not only very successful, but also represented the first comprehensive symposium dedicated to Synthetic Biology in Austria.

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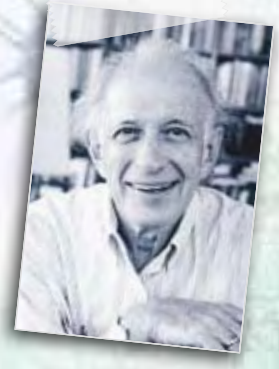

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In order to maintain the highest standard of research, IMBA has installed a process of review and feedback: the Scientific Advisory Board (SAB), consisting of internationally recognized scientists. The Board meets yearly at IMBA, and, together with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

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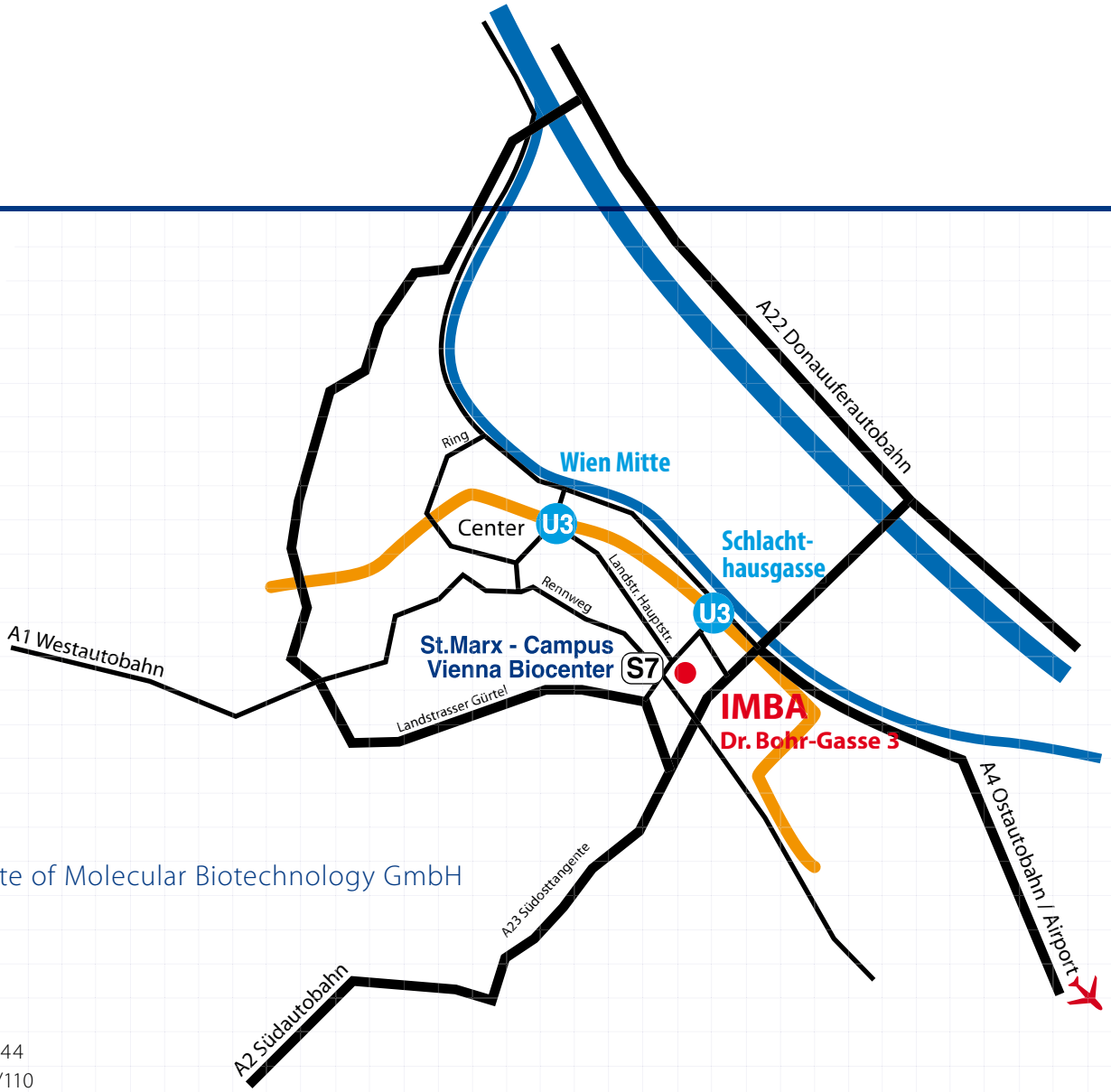

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