

The background of the entire page is a detailed, multi-colored illustration. It features a large, complex structure on the left, possibly a cell or a molecular assembly, rendered in shades of brown, orange, and purple. To its right, there are several green, rounded structures that resemble cells or organelles. In the lower right, there are more green, rounded structures, some of which appear to be connected by thin, branching lines. The overall style is that of a scientific illustration or a biological diagram.

# INSTITUTE OF MOLECULAR BIOTECHNOLOGY

OF THE AUSTRIAN ACADEMY OF SCIENCES  
VIENNA BIOCENTER

2009



**OAW**  
Austrian Academy  
of Sciences







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When we started IMBA in 2003, the challenge was how to develop a new research institute that is indeed competitive at the international level? How does one convince the best young scientists to come to a new institute in Vienna? How could we establish and run an institute that can compete against the best research organizations in the world, many of which operate with much higher budgets? Or in terms of sports teams, how can we develop a team that can play in the Champions-league of research for a long time? Our answer was to try to set up a place where the best scientists can follow their visions with the utmost financial and academic freedom. Since there are many clever scientists, and in many cases research success is also driven by access

to new technologies, we created an academic and technological candy store where young researchers can succeed.

IMBA has had a very good year in science. IMBA scientists have already performed groundbreaking research. As an example, around 50% of all publications that directly come from Austrian institutions in the top scientific journals Nature, Science, and Cell have been published by IMBA/IMP researchers in the last 5 years; half of this scientific output comes from IMBA. Moreover, in the last 5 years the Wittgenstein prize, the top science prize in Austria, has been awarded twice to researchers working at IMBA. In 2009, the Wittgenstein prize went

to Jürgen Knoblich, a testament to the excellence of Jürgen and his brilliant team. IMBA scientists have also been successful winning Junior and Advanced European Research Council (ERC) grants. Everybody at the institute from the kitchen, the workshop, all scientific infrastructure and administration has had an important part in these successes.

Governments and by extension research institutes and universities therefore must find a way to develop and retain the best talents. One of these great minds who joined us this year is Julius Brennecke. Julius published some of the key experiments in microRNA biology. He discovered the role of PiWi RNA in transposon



inactivation in *Drosophila*, in essence an entirely novel and adaptive immune system based on RNA. Julius was awarded the EMBL Young Scientist award 2009. The implementation of an international summer student programme – together with our partner the IMP – is another great step into bringing the future top scientists to Vienna.

Scientific excellence and world-renowned research centers are not defined by the quantities of publication but by the promotion of the best scientists and some key breakthroughs that can change scientific thinking. For instance this year, using whole genome RNAi knock-down in *Drosophila*, IMBA scientists have generated the first genome maps for Notch signaling (Mummery-Widmer et al., *Nature*) and innate immunity to intestinal bacterial infections (Cronin et al., *Science*). Moreover, IMBA researchers identified a new central regulator of the fever response in the brain (Hanada et al., *Nature*) and showed that the TRIM32 protein activates microRNAs and prevents self-renewal in mouse neural progenitors (Schwamborn et al., *Cell*).

Science is driven by good ideas and clever people. However, these people need access to state-of-the-art technologies and services. The common IMBA/IMP service infrastructure remains one of IMBA's key success factors. We are therefore committed to further improve and continuously upgrade the central scientific infrastructure to provide researchers with the best environment possible to do their work and be successful.

In 2009, a new facility consisting of deep sequencing and microarray services has been established to offer new opportunities in functional genomics research. Moreover, we have opened most of the IMP/IMBA scientific infrastructure to the Gregor Mendel Institute of Molecular Plant Biology (GMI), another institute of the Austrian Academy of Sciences.

We want to thank all service teams for their excellent work and the integration of the GMI with no notable impact on the service quality. We also thank all people in the Administration for their high degree of motivation and very valuable contributions. One major focus has been the improvement of the IT services, which is essential for the day-to-day work of everybody in our institute. The IT team has done a tremendous job. We also thank our graphics, PR and fundraising departments for another successful year and initiatives such as our new cooperation with DEBRA Austria or the ongoing cooperation with the Raiffeisenlandesbank Oberösterreich.

Finally, we want to thank our Scientific Advisory Board, our Supervisory Board, the Austrian Academy of Sciences, our partner institute the IMP, Boehringer Ingelheim, the City of Vienna, the Federal Government and many others who have helped us to now become the largest Institute of the Austrian Academy of Sciences.

Besides all the advances in our science, we have also had a very sad year. We were all shocked by the news of the sudden deaths of two of our colleagues,

Andrea Salva Giro and Mitra Kashinath. Andrea was an excellent and very dedicated PhD student in the laboratory of Javier Martinez and was at the beginning of a brilliant career in science. Mitra had been with the IMP for over ten years and with IMBA since our conception and always did his job in the store with a high degree of dedication and a very positive attitude. We will always remember the two and keep them in our hearts. Our thoughts and wishes are with their families.

The least we can do is to respect everybody's contribution and work at all levels of our institute, and to create a place where everybody feels welcome, comfortable, and happy to work, a place where we indeed live the concept of personal dignity. We are all human beings and we all have a lot to give.



## JULIUS BRENNECKE GROUP

The piRNA pathway in the *Drosophila* germline – a small RNA-based genome immune system

[www.imba.oeaw.ac.at/research/julius-brennecke](http://www.imba.oeaw.ac.at/research/julius-brennecke)

*Protection against the activity of selfish genetic elements such as transposons is of paramount importance for all species in order to ensure genetic stability. In the animal germline, a highly specialized small RNA pathway known as the piRNA pathway has been evolved to suppress these so-called genome parasites. Our group is interested in understanding the molecular and genetic structure of this pathway as well as its biological functions.*

### Background

Small RNA pathways (referred to as RNA interference (RNAi) pathways) have revolutionized our understanding of diverse biological processes. Nearly all eukaryotes possess RNAi pathways and they have been implicated in viral defense, the definition of chromatin domains, regulation of endogenous gene expression, silencing of transposons, DNA elimination, and transcriptional silencing. This enormous diversity in function likely reflects the ingenious and versatile principle common to all RNAi pathways: *To use the basic rules of nucleic acid hybridization in order to guide a protein effector complex via an incorporated small RNA to target RNAs.* As an RNA intermediate is found at the base of all gene expression programs, the principle of RNAi pathways could be applied to all cellular processes. In

fact, evolution has provided an astounding array of distinct RNAi pathways. One of the most sophisticated RNAi processes is the piRNA pathway; it was recently shown to be at the heart of transposon silencing in the invertebrate and vertebrate germline.

### Silencing selfish genetic elements

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

The piRNA pathway is an excellent example of the much greater sophistication of nature’s solutions compared to those devised by the human intellect. In essence, the piRNA pathway acts as an RNA-based genome immune system. It possesses an inheritable genetic component and an



acute response system that enables it to specifically combat active transposons. Briefly, the transcription of discrete loci within heterochromatin (termed piRNA clusters) provides a template from which primary piRNAs are produced. These loci contain vast collections of immobile and broken copies of transposons, which are or have been active in a population. If a primary piRNA encounters a target (active transposon), cleavage of the transposon RNA by the piRNA-complex leads to the synthesis of a novel and complementary piRNA. This piRNA, in turn, guides the production of more antisense piRNAs derived from the piRNA cluster transcript. Thus, piRNA clusters act not only as a genetically inherited memory component but also as relay stations to boost the production of silencing competent piRNAs.

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

#### We are mainly interested in the following areas:

1. Systematic identification of novel piRNA pathway components using genome-wide RNAi screens and biochemical co-purification strategies: About a dozen genes are known to act in the piRNA pathway, but there is ample evidence to show that we lack knowledge of several key players.
2. Analysis of transposon gene expression patterns and the genomic consequences of uncontrolled transposition upon deletion of the germline or the somatic piRNA pathway: No systematic analysis on transposon activity and transposition frequency or patterns has been conducted thus far. We use high throughput sequencing strategies to gain insight into these issues.
3. Understanding the enigmatic piRNA clusters: piRNA clusters are typically located at telomeres or at the border between euchromatin and heterochromatin. Their transcripts are believed to traverse large (up to several hundreds of kb) heterochromatic regions. We are interested in the regulation and processing of piRNA clusters. Using sophisticated genetic techniques, we aim to understand how the cell is able to distinguish these transcripts from other RNAs in the cell.

## JULIUS BRENNECKE

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

#### Publication highlights:

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

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

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

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Figure 2

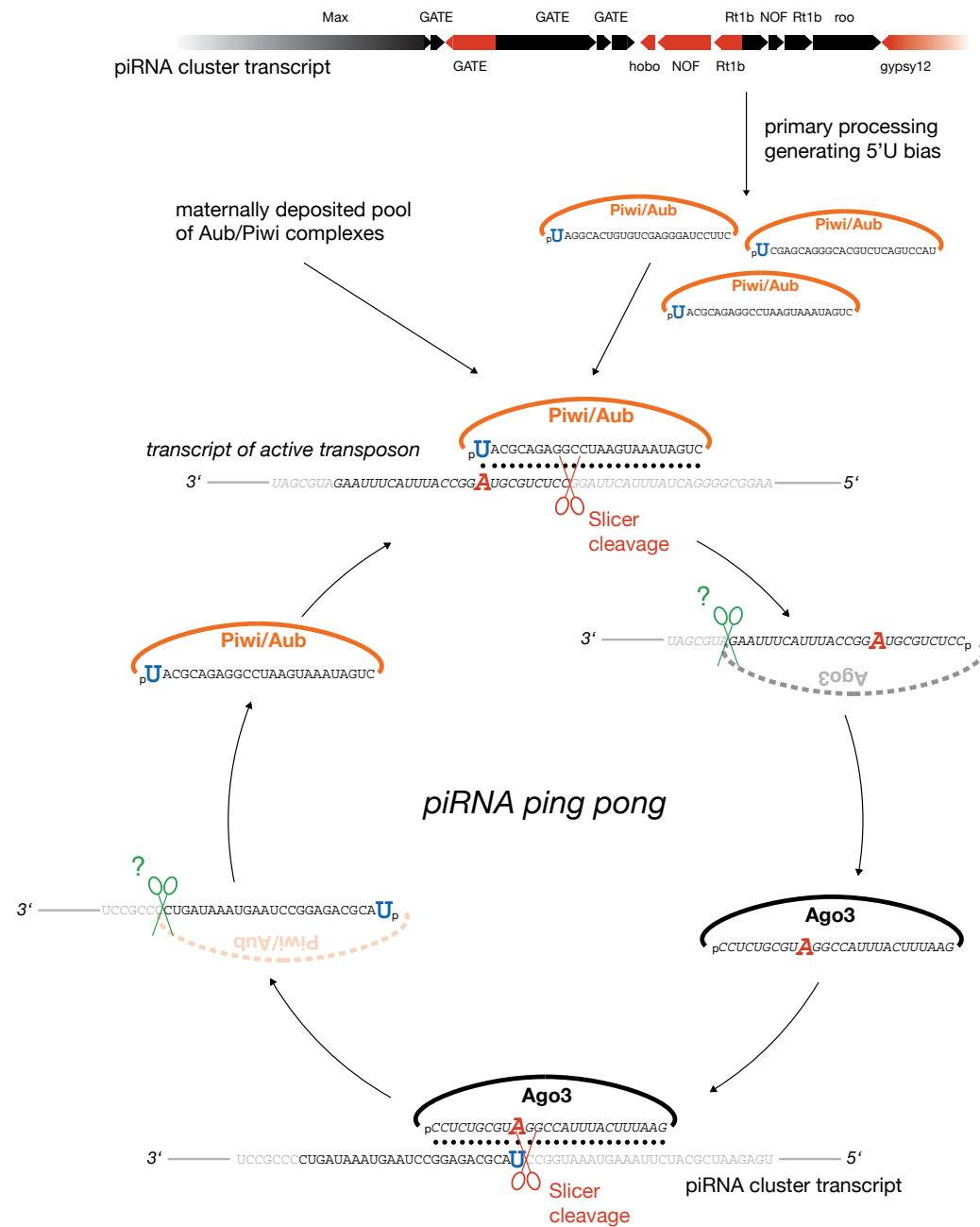
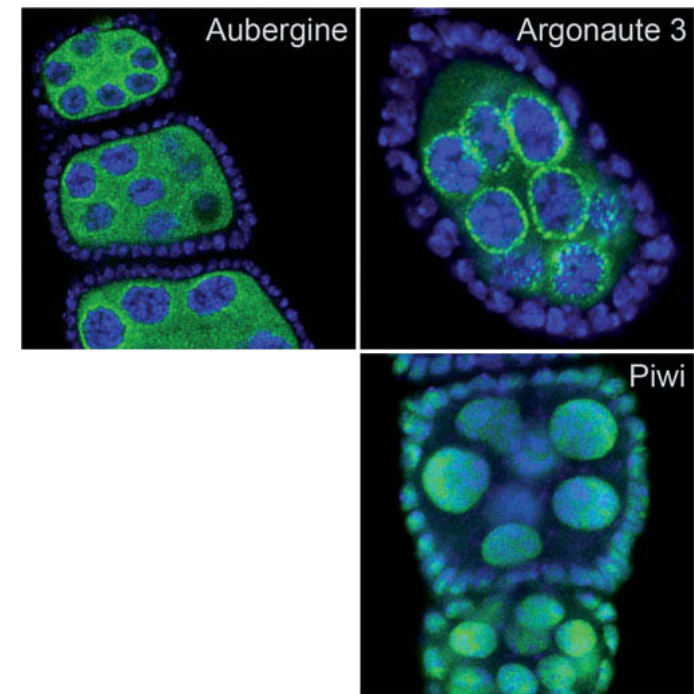


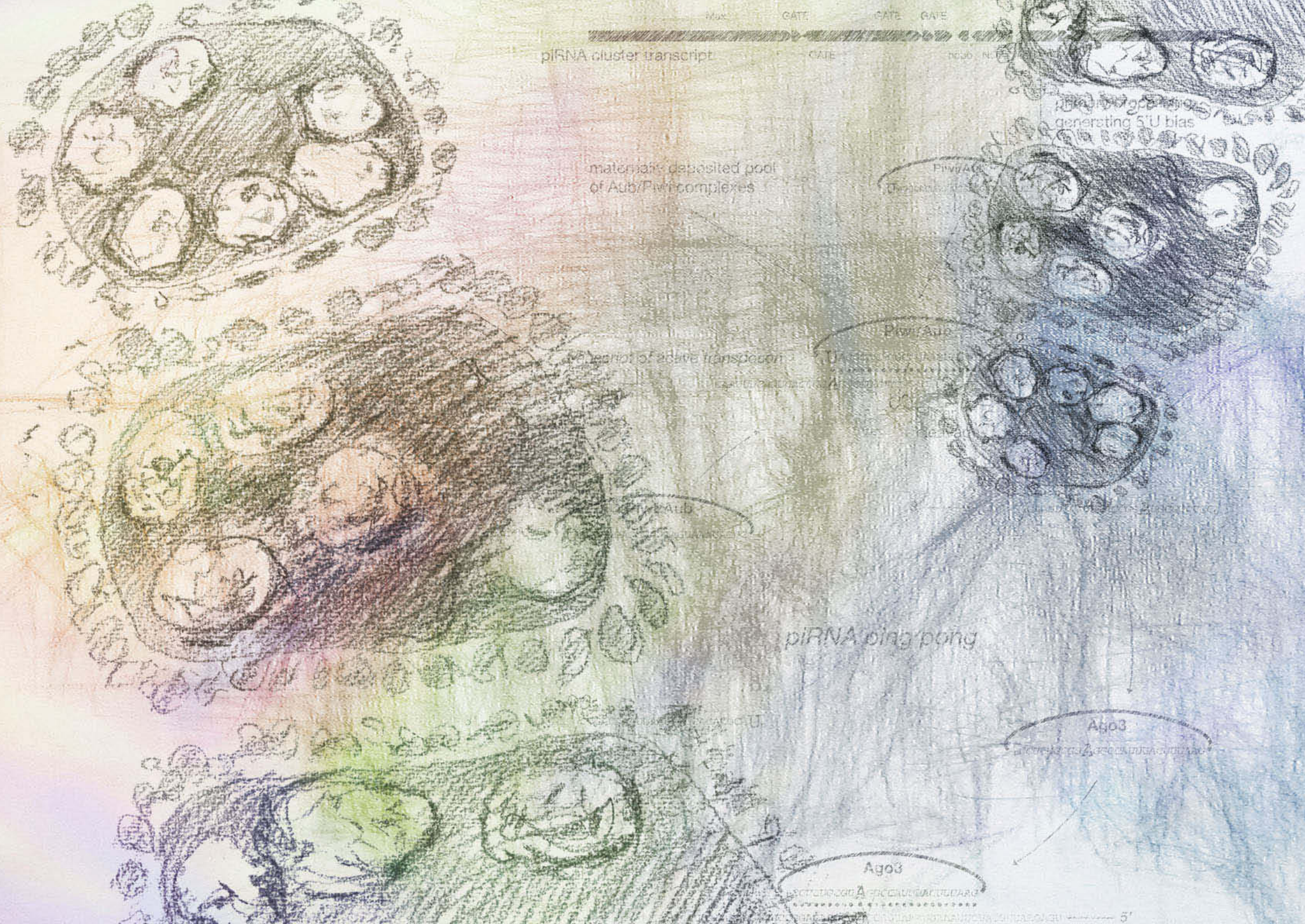
Figure 1



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

**Figure 2: Scheme of the piRNA pathway in the *Drosophila* germline.** Processing of piRNA cluster transcripts leads to the generation of primary piRNAs, which are loaded into Piwi or Aubergine. Upon recognition of the target, a sense strand piRNA is formed and incorporated into AGO3 which, in turn, prompts the biogenesis of additional silencing competent antisense piRNAs from piRNA cluster transcripts (ping pong cycle).









## JÜRGEN KNOBLICH GROUP

Asymmetric cell division and proliferation control in neural stem cells

[www.imba.oeaw.ac.at/research/juergeen-knoblich](http://www.imba.oeaw.ac.at/research/juergeen-knoblich)

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

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

### Stem cell tumors in *Drosophila*

During each neuroblast division, the cell fate determinants Numb, Prospero and Brat segregate into the smaller, basal daughter cell where they prevent self-renewal and induce differentiation (Figure 1B). We have identified

the molecular mechanism underlying this unusual asymmetric protein segregation. The process starts with the establishment of a polarity axis by the PDZ domain proteins Par-3 and Par-6 and the protein kinase aPKC. During interphase, these proteins localize to the apical side of *Drosophila* neuroblasts. In mitosis, they require the adaptor proteins Inscuteable and Pins as well as the microtubule binding protein Mud to generate a localized microtubule attachment site and thereby orient the mitotic spindle. aPKC can phosphorylate the membrane-binding domain of Numb to remove it from the apical pole occupied by Par-3/6 and aPKC. As a result, Numb concentrates on the basal side and will segregate into the basal daughter cell. Segregation of Prospero and Brat follows a similar principle, indicating that this is a general mechanism of asymmetric cell division.

In the absence of Brat, Numb or Prospero, both daughter cells retain the ability to self-renewal. As a consequence, stem cell numbers grow exponentially, leading to tissue overgrowth and the formation of a gigantic lethal brain tumor (Figure 1C). Mutations in other regulators of asymmetric cell division cause tumors as well, suggesting a fundamentally important connection. Understanding how the formation of stem-cell-derived tumors is related to defects in asymmetric cell division is one of the key questions we are currently investigating.



## Asymmetric cell division in mouse stem cells

Can we transfer our results from *Drosophila* to mammalian, and ultimately human stem cells as well? To analyze mammalian stem cells, we use *in utero* electroporation into the mouse brain to overexpress or knockdown homologs of the genes we identify in flies (Figure 2). One of the mammalian *brat* homologs is named TRIM32. We find that overexpression of TRIM32 depletes stem cells and promotes neurogenesis while RNAi knockdown of the gene has the opposite effect. Interestingly, TRIM32 concentrates on the basal side of dividing mouse neural progenitors. Although we are currently unaware of the significance of TRIM32 localization, this asymmetric segregation suggests a striking level of conservation between *Drosophila* neuroblasts and mouse neural stem cells. TRIM32 acts as a bi-functional molecule: The N-terminus is a ubiquitin ligase for c-Myc while the C-terminus can bind to the micro RNA regulator Argonaute-1 and regulate micro RNAs during mouse neurogenesis. We are currently analyzing the role of other mouse homologs in order to understand how vertebrate stem cells control proliferation and differentiation, and how these processes are deregulated in tumor development.

## Genome-wide analysis of biological processes

To analyze asymmetric cell division on a genome-wide level, we use the transgenic RNAi library maintained at the VDRC. We have used the RNAi collection to

analyze the development of external sensory organs, a key model system for asymmetric cell division, and the Notch signaling pathway. Our screen assigned a potential loss-of-function phenotype to more than 20% of the protein-coding *Drosophila* genes and enabled us to discover 23 new global regulators of the Notch signaling pathway. We used bioinformatics to assemble a functionally validated interaction network for the Notch pathway. Computer analysis of this network allowed us to identify nuclear pore and nuclear import complexes as well as the COP9 signalosome as rate-limiting components of the Notch pathway.

We now apply similar genome-wide approaches to various stem cell populations in *Drosophila*. We analyzed proliferation, cell growth and tumor formation in *Drosophila* neuroblasts, and generated a functional interaction network for the pathways controlling self-renewal in the fly brain. By combining phenotypic data with gene expression analysis, we try to decode the circuits that regulate self-renewal in *Drosophila* neural stem cells. Our aim is to describe how those circuits are reprogrammed when one of the two daughter cells is driven towards terminal differentiation, and to understand how defects in this reprogramming event lead to the formation of a lethal stem-cell-derived brain tumor.

## JÜRGEN KNOBLICH

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

### Publication highlights:

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

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

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

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Figure 1

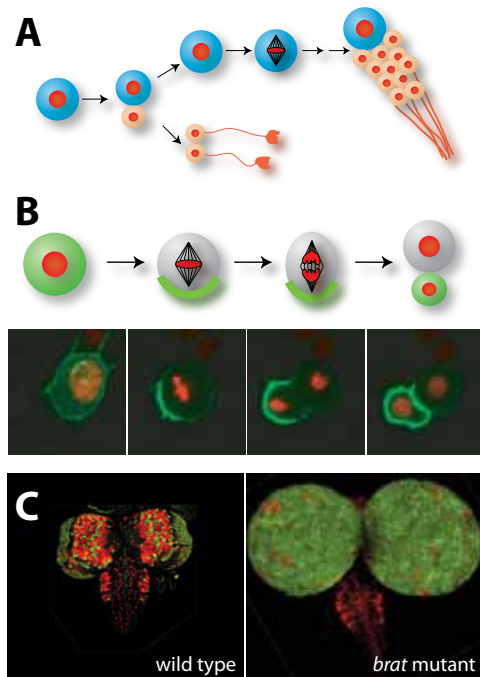


Figure 2

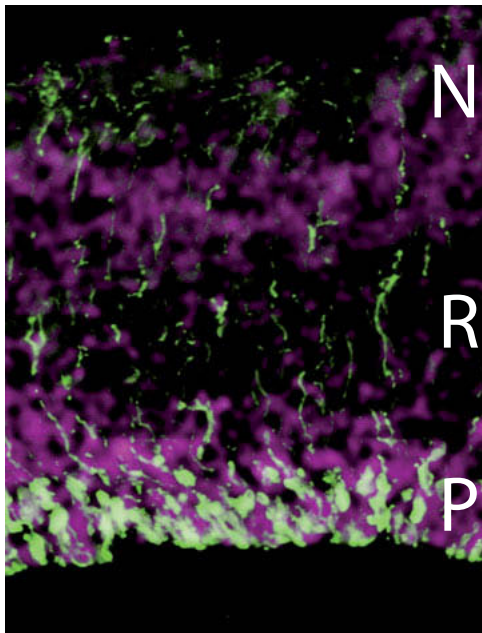
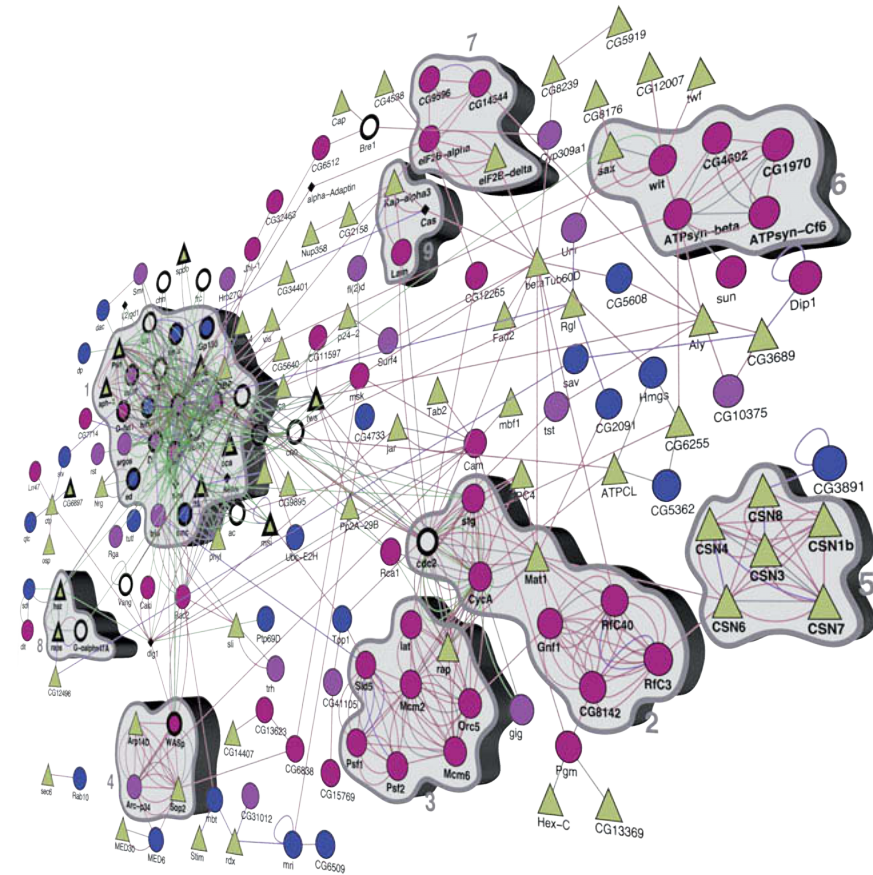


Figure 3

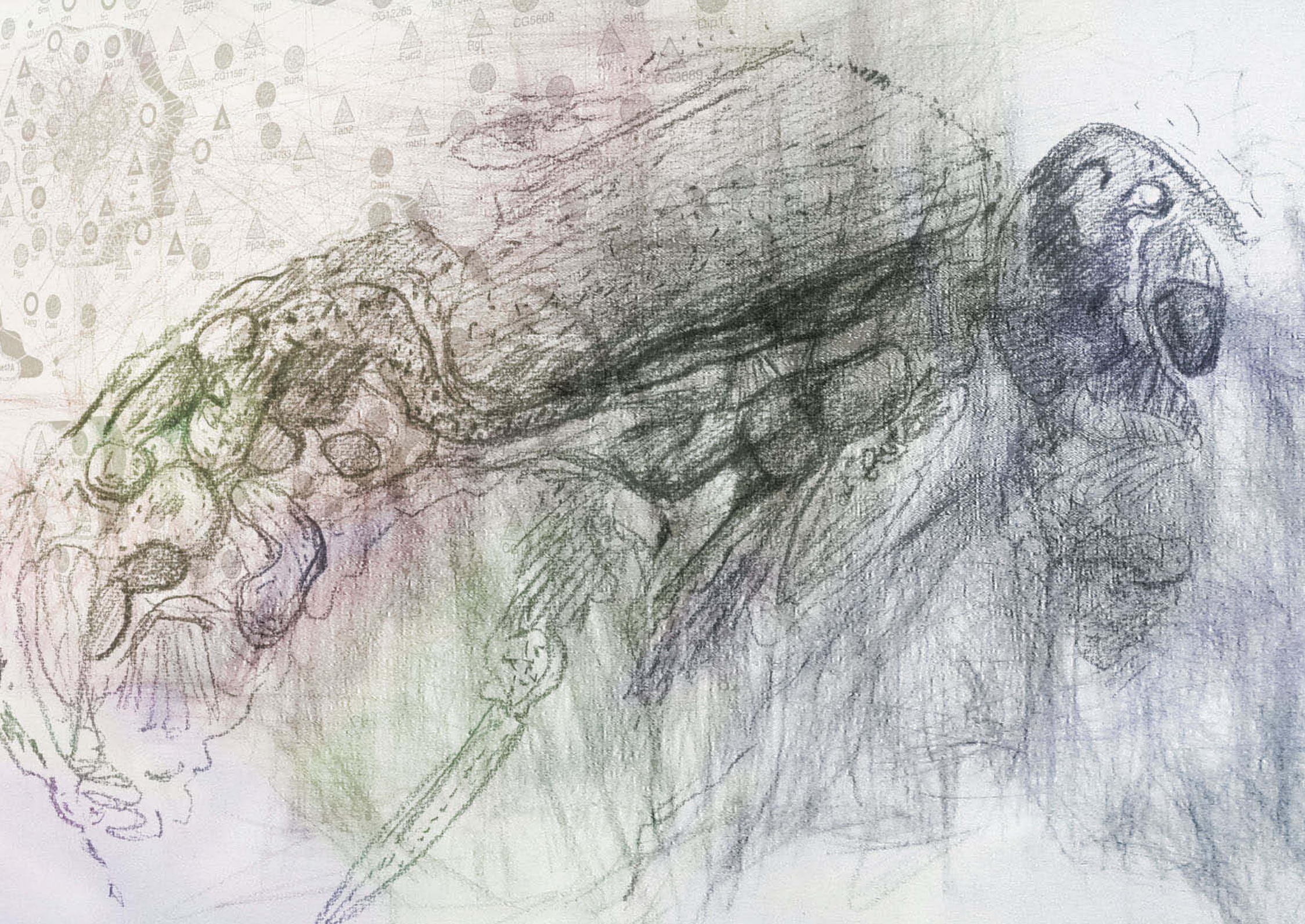


**Figure 1: How cells divide asymmetrically.** A. *Drosophila* neuroblasts divide asymmetrically in a stem cell-like fashion. B. During each neuroblast division, Brat, Prospero and Numb (green) are inherited by only one of the two daughter cells. A schematic view of the process is shown at the top; stills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

**Figure 2: 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 developed from these (N) are visible.

**Figure 3: Genome-wide analysis of biological processes in a whole organism.** Functionally validated interaction network of the Notch signaling pathway assembled from genome-wide analysis of *Drosophila* external sensory organ development. The network shows genes that cause phenotypes in external sensory organs and have previously been shown to interact biochemically or genetically. The encircled groups are protein complexes identified by a clustering algorithm.









## THOMAS MARLOVITS GROUP

### Molecular Machines

[www.imba.oeaw.ac.at/research/thomas-marlovits](http://www.imba.oeaw.ac.at/research/thomas-marlovits)

*Molecular machines are essential to maintain life at the cellular level. We aim to understand the fundamental molecular design, assembly processes, and mechanistic details of such higher-order structures. At our laboratory we are specifically interested in protein translocation machineries that are essential for microbial infection.*

#### Microbial Pathogenesis – the Type III Secretion System

One of the most exciting discoveries in the field of bacterial pathogenesis is the fact that many bacterial pathogens utilize supramolecular nanomachines to deliver bacterial proteins into eukaryotic cells. These proteins, which are collectively referred to as effectors, have the capacity to modulate a variety of cellular functions including cytoskeleton dynamics, vesicle traffic, cell cycle progression, and transcription. Probably one of the best understood machineries is the type III secretion system (TTSS), which is made up of more than 20 different proteins. Using *Salmonella typhimurium*, we are investigating the molecular mechanisms and structural framework required to translocate effector proteins specifically and safely into eukaryotic cells.

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 1). The needle complex is believed to serve as a conduit for 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 constitute the membrane-associated base structure, PrgJ the inner rod, and PrgI the needle filament extending into the extracellular environment (Figure 2).

In order to investigate the molecular mechanism of type III secretion, we first set out to determine structural components of the TTSS (Figure 3). We were challenged by the mega-dalton size of the complex, its natural composition (membrane and soluble proteins), and its limited availability. Nevertheless, we were able to purify sufficient quantities 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 a new structural component, the inner rod, which is located at the center 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 into the base. During assembly, the inner rod and the needle filament are added as new structural components to the base (Figure 2, 3). As a consequence, it must undergo large conformational rearrangements which demonstrates the flexible but also stable qualities of the base. Functionally, this dynamic behavior is a crucial event in the assembly phase during which the secretion machine is reprogrammed to become competent for the secretion of virulence factors. Structurally, it underlines the importance of specific interaction epitopes critical for the assembly into a functional unit.

Recent crystallographic analyses of individual separated domains which are predicted to be periplasmically located, revealed a common structural motif organized in repeating modules. Attempts have been made to "dock" these protein domains into the needle complex structure, which resulted in different and mutually incompatible locations. We used a combination of methods, including bacterial genetics, biochemistry, mass spectrometry and cryo-electron microscopy/ single-particle analysis, to experimentally determine which specific protein domains correspond to different substructures of the needle complex. In addition, we identified specific interaction sites among components of the needle complex, which are critical for stable assembly and consequently functional complex. In combination, this analysis provides the first experimentally validated

topographic map of different components of the needle complex of the *S. Typhimurium* TTSS.

Although the design of the TTSS appears to be conceptually simple, several questions remain unanswered: What nucleates the assembly of the TTSS? How dynamic is the entire assembly process? And how are substrates recognized and translocated? We have started to address some of these questions. Understanding the molecular mechanism of TTSS-mediated protein transport should provide a basis for the development of novel therapeutic strategies to either inhibit its activity or modify the system for the purpose of achieving targeted drug delivery.

## THOMAS MARLOVITS

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

### Publication highlights:

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

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

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Figure 1

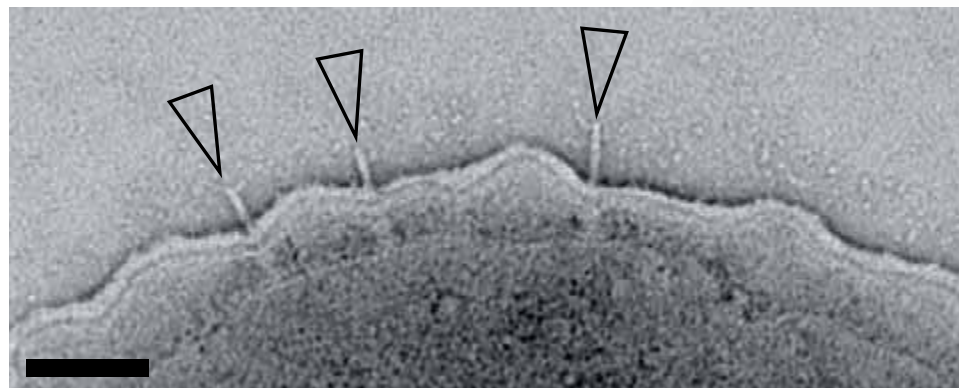


Figure 3

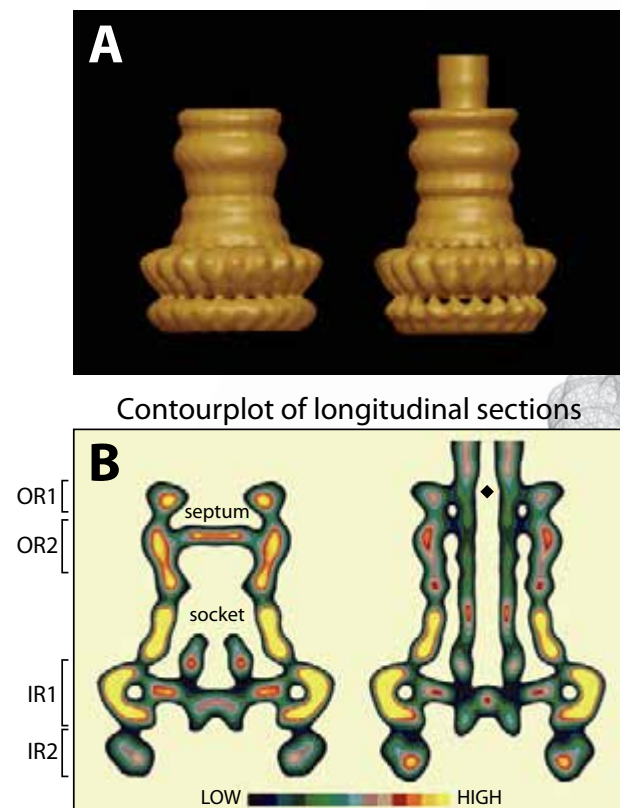
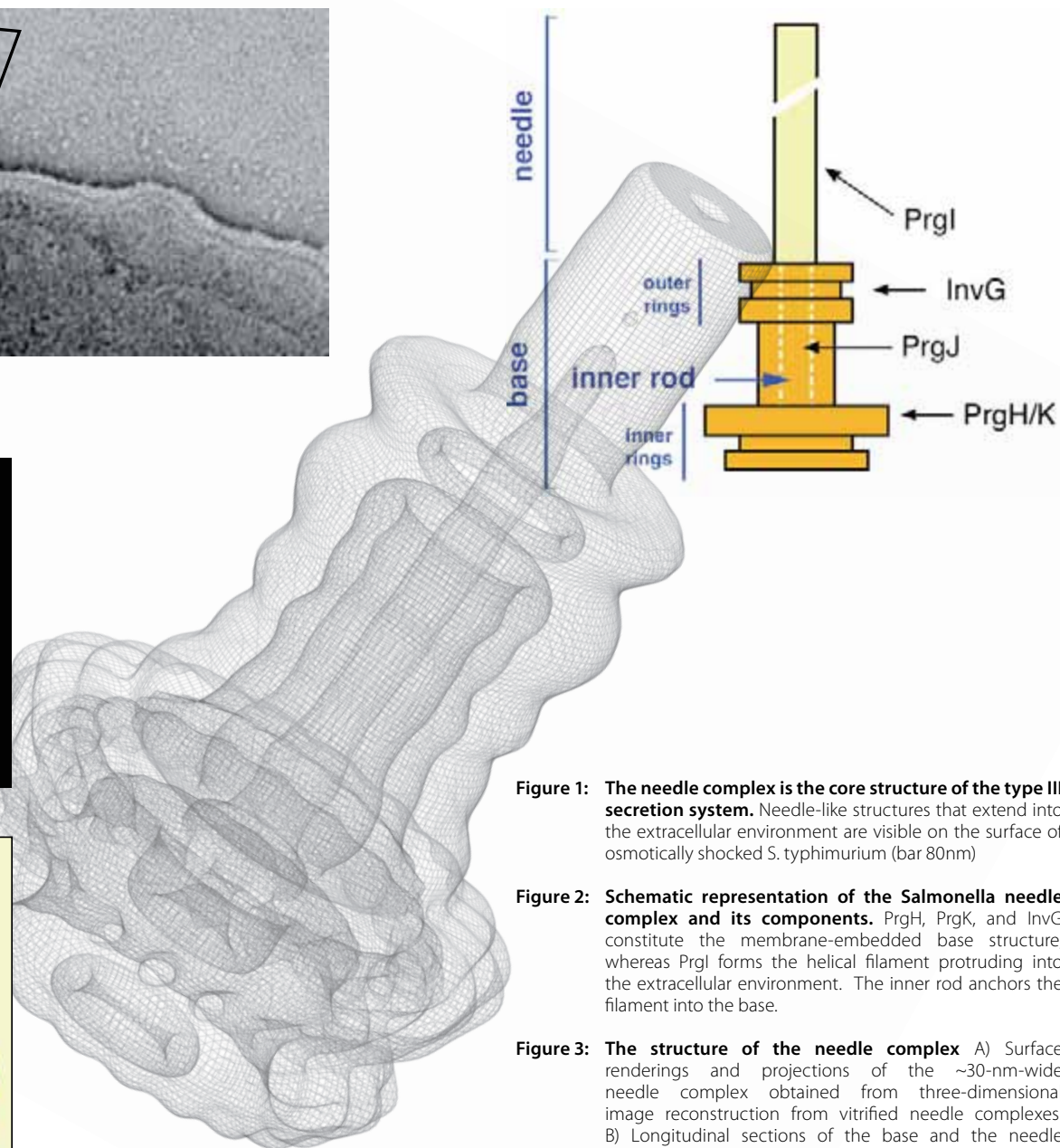


Figure 2

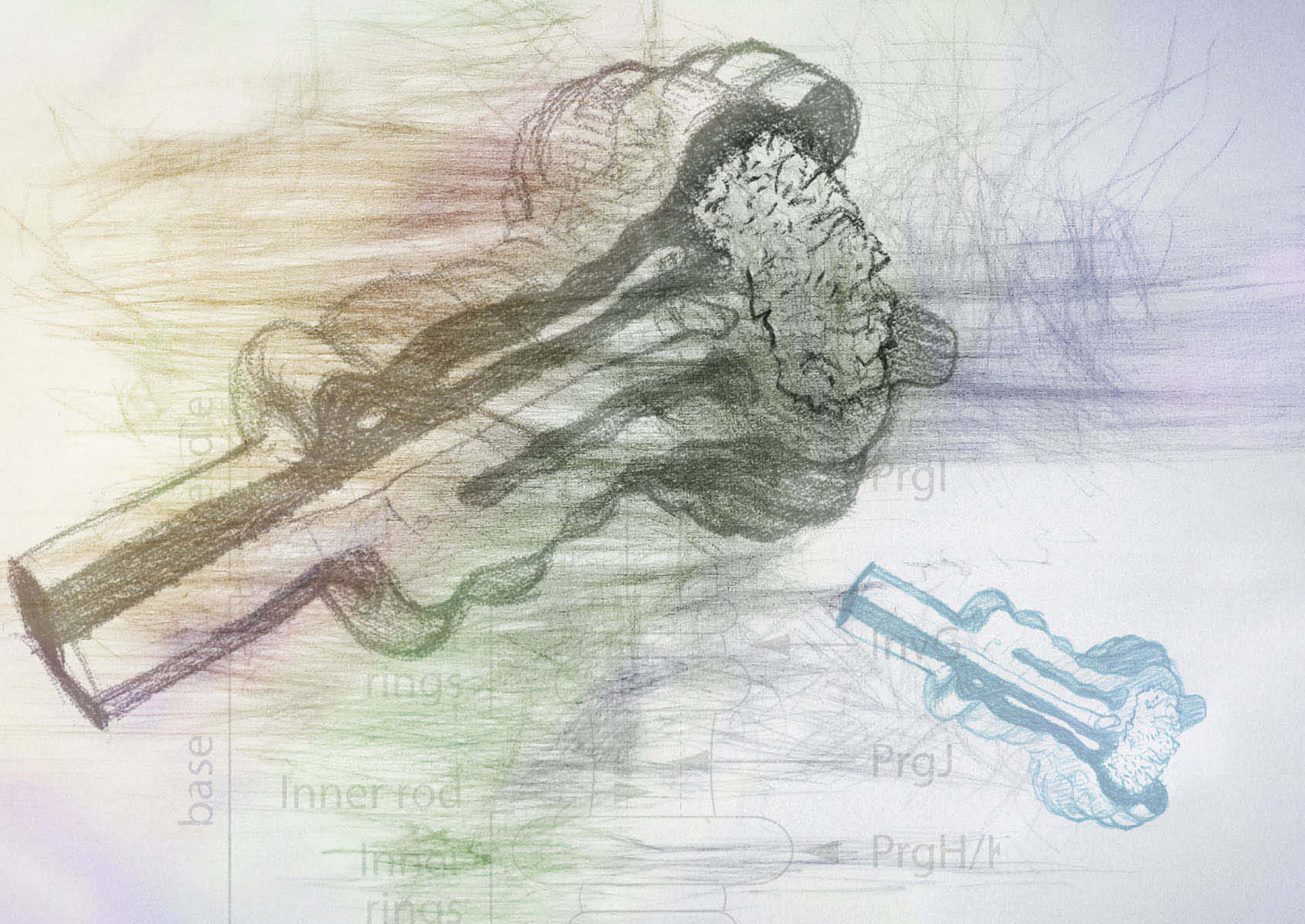


**Figure 1: The needle complex is the core structure of the type III secretion system.** Needle-like structures that extend into the extracellular environment are visible on the surface of osmotically shocked *S. typhimurium* (bar 80nm)

**Figure 2: Schematic representation of the Salmonella needle complex and its components.** PrgH, PrgK, and InvG constitute 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 3: The structure of the needle complex** A) Surface renderings and projections of the ~30-nm-wide needle complex obtained from three-dimensional image reconstruction from vitrified needle complexes. B) Longitudinal sections of the base and the needle complex reveal the overall distribution of protein density within the complexes.





die

PrgI

rings

ring

base

Inner rod

PrgJ

Inner

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## JAVIER MARTINEZ GROUP

RNA metabolism: processing and silencing of RNA molecules in mammalian cells

[www.imba.oeaw.ac.at/research/javier-martinez](http://www.imba.oeaw.ac.at/research/javier-martinez)

*Our aim is to provide a new perspective on aspects of RNA metabolism through the discovery and characterization of novel enzymatic activities. We are currently identifying endogenous RNA substrates and studying the in vivo function of Clp1, the first RNA-kinase identified in human cells. One of the major pursuits at the laboratory is to discover more about the hitherto elusive human RNA ligases. This concerns the enzymatic activity that ligates exon halves during tRNA splicing and the factor that re-ligates Xbp1-mRNA during the unfolded protein response. We also aim to discover protein factors that read the intrinsic asymmetry of siRNA molecules during the assembly of RISC, the RNA-induced silencing complex.*

The discovery of novel enzymatic activities usually requires chromatographic separation of cellular extracts combined with a robust biochemical assay to monitor activity. Highly purified fractions are subjected to mass spectrometry and candidate factors analyzed via bioinformatics. RNAi experiments should link the gene to the investigated activity. What is the cellular function of the newly identified enzyme? In vitro and in vivo approaches are needed to answer this question. In this annual report we outline a genome-wide RNAi screen in *Drosophila* Schneider cells as a powerful alternative means of discovering elusive RNA metabolic enzymes.

### Non-canonical splicing of Xbp1 mRNA in the unfolded protein response.

Secretory and membrane proteins progress through the endoplasmic reticulum (ER), where they are folded, modified, and subjected to quality control. Perturbation of the homeostasis of ER, such as the accumulation of mis- or unfolded proteins, activates an adaptive response - the so-called unfolded protein response (UPR) - in order to relieve ER stress.

In mammals, one of the three pathways activated as a consequence of ER stress involves the ER transmembrane protein Ire1. Under homeostatic conditions, Ire1 binds to the heat shock protein BiP via its luminal domain (Figure 1, left panel). However, upon ER stress, BiP dissociates from Ire1 and binds to hydrophobic stretches displayed by mis- or unfolded proteins (Figure 1, right panel). As a consequence, the Ire1 protein dimerizes, autophosphorylates and activates its cytosolic RNase domain. The activated Ire1-dimer removes a 23-nt intron within the Xbp1 mRNA, thereby introducing a frame shift after re-ligation. Thus, the Xbp1 protein gains stability and moves to the nucleus behaving as a potent transcription factor, which activates genes required for effective UPR.



Splicing of Xbp1 mRNA by Ire1 generates a 2'-3' cyclic phosphate at the 3' end of the 5' fragment, and an OH group at the 5' end of the 3' fragment. Interestingly, during pre-tRNA splicing, the Sen endonuclease cleaves intronic sequences as well generates 2'-3' cyclic phosphate and a 5' OH group. Moreover, it has been reported that re-ligation of the yeast counterpart of mammalian Xbp1 mRNA requires the ligase activity of the tRNA splicing pathway. The question to be addressed is whether mammalian Xbp1 mRNA and tRNA halves share a common ligation mechanism.

We conducted a genome-wide RNAi screen in *Drosophila* Schneider cells to identify factors involved in "non-canonical" splicing of the Xbp1 mRNA (Figure 2). Under normal conditions the luciferase reporter gene is out of frame. Under stress, the Xbp1 fragment becomes spliced and the correct frame is achieved, resulting in luciferase activity. Finally, RNAi-mediated knockdown of factors involved in the splicing event, such as the Ire1 endonuclease, lead to RNA degradation and the consequent absence of luciferase activity. Candidates from the screen are currently being validated and characterized. In this process, we expect to identify the elusive Xbp1-mRNA ligase.

RNA-metabolic enzymes seem to be multifunctional, and influence various RNA pathways. Identifying their substrates is essential to define their potential roles in areas such as RNA repair and turnover. In the long term, we aim to integrate this knowledge and provide a revised and extended view of RNA metabolism.

## JAVIER MARTINEZ

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Javier Martinez studied biology and obtained his PhD in Buenos Aires, Argentina. He joined the RNAi field in 2001, contributing with studies on the anatomy and composition of RISC, the RNA-induced silencing complex. As a Group Leader at IMBA he explored the assembly of RISC and how secondary structures in target RNAs influence the cleavage activity of RISC. The finding of the RNA-kinase hClp1, the first of its class in human cells, opened a new direction in the laboratory, towards aspects of global RNA metabolism, including tRNA splicing and mRNA 3' end formation.

Besides the routine lab work, every year Javier organizes the "Microsymposium on small RNAs", a free-attendance meeting fully sponsored by companies and scientific societies. In addition, Javier teaches about the RNAi revolution in the "Advance Cell Biology Series" at the University of Vienna, and also participates in the annual Series of Lectures on Epigenetics.

### Publication highlights:

Stefan Ameres, Javier Martinez† and Renee Schroedert (2007). "Molecular basis for target RNA recognition and cleavage by human RISC". *Cell*, 130, 101-112. †corresponding authors.

Stefan Weitzer and Javier Martinez (2007). "hClp1 is a novel human RNA-kinase that phosphorylates siRNAs and 3' exons during pre-tRNA splicing". *Nature*, 447, 222-226.

Philipp Leuschner, Stefan Ameres, Stephanie Kueng and Javier Martinez (2006). "Cleavage of the siRNA-passenger strand during RISC assembly in human cells". *EMBO Reports*, 7, 314-320.

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Figure 1

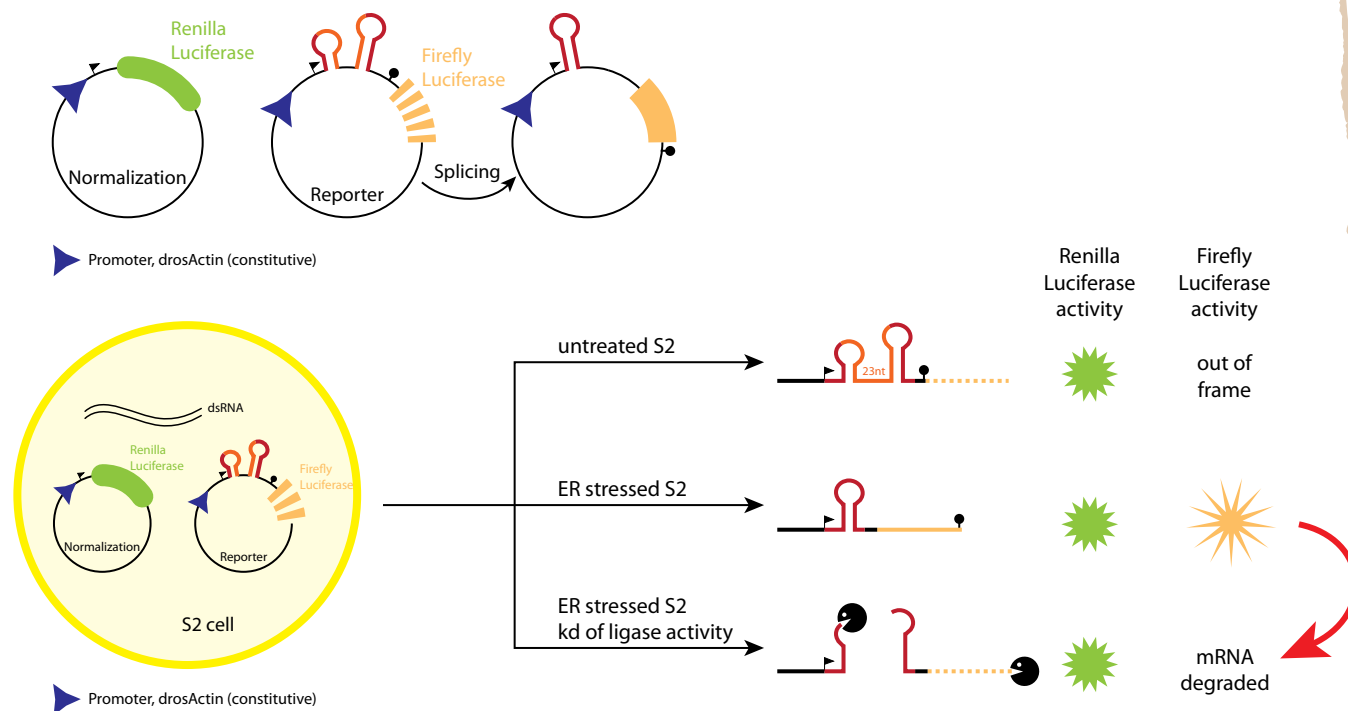


Figure 2

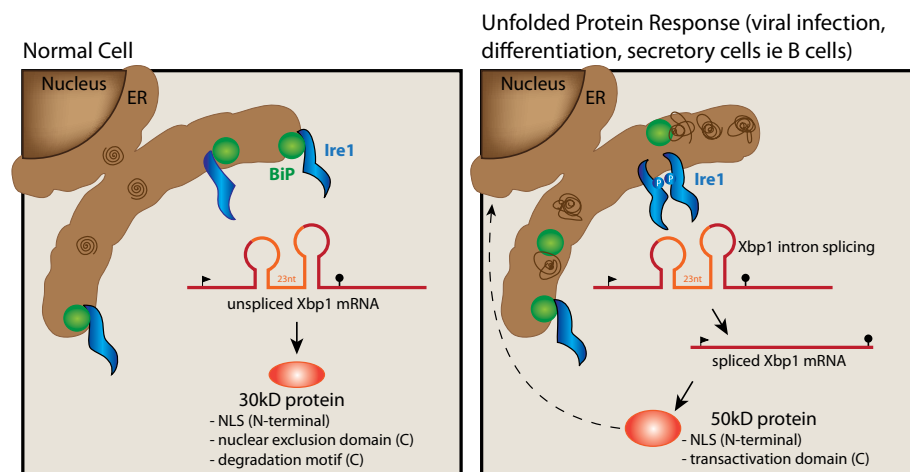
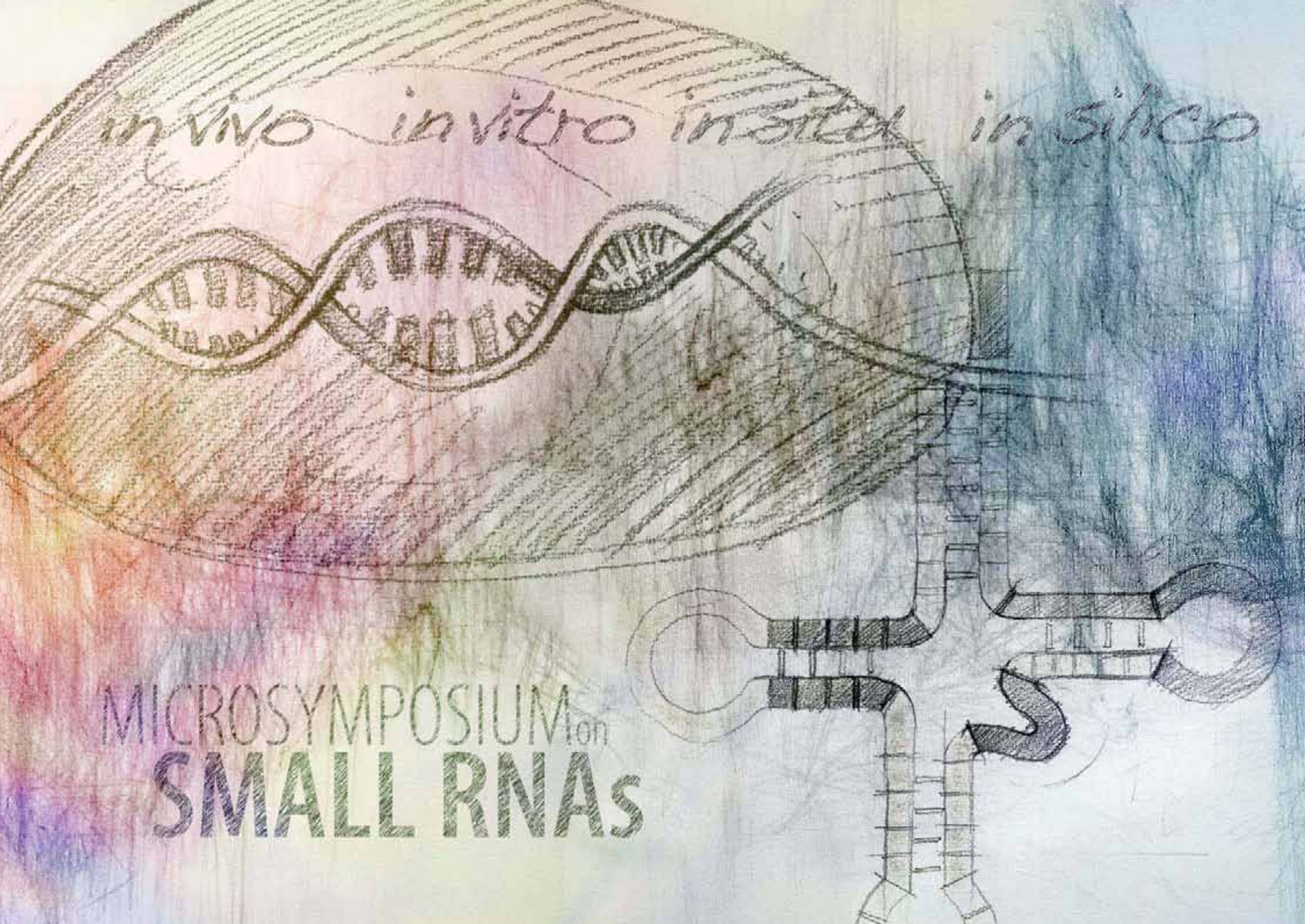


Figure 1: Unfolded protein response and Xbp1 mRNA splicing.

Figure 2: Screen for factors involved in Xbp1 mRNA splicing in *Drosophila* Schneider cells. A) Vector maps of normalization and reporter constructs. The reporter constructs contain a short stretch of the Xbp1 mRNA cloned upstream of the luciferase gene, disrupting the open reading frame. Red: exon. Orange: intron. B) Outline of the screen. Normalization and reporter constructs are co-transfected into Schneider cells together with a dsRNA. The ratio between Renilla and firefly luciferase activity serves as read out.



*in vivo* *in vitro* *in silico* *in silico*



MICROSYMPOSIUM on  
**SMALL RNAs**





## KAZUFUMI MOCHIZUKI GROUP

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. Cells in our body are equipped with a mechanism to silence these potentially harmful elements: locking transposable element into a closed type of chromatin known as heterochromatin. Chemically, both transposable elements and other parts of the genome are merely stretches of DNA. How are cells able to distinguish junk from precious DNA? Evidence suggests that tiny RNAs, ~20-30 nucleotides in length, act as security guards to identify transposable elements. We use the tiny-hairy protozoan *Tetrahymena* as a model to study how these short RNAs lock transposable elements into heterochromatin.*

### 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 gives rise to a new Mac and a Mic, and the parental Mac is destroyed. During the development of the new Mac, ~6000 Internal Eliminated Sequences (IESs) are removed (DNA elimination) and the remaining Mac-destined sequences re-ligated. The majority of IESs are moderately repeated in the Mic, and many of them

are related to transposable elements. Heterochromatin is involved in the IES elimination process. In *Tetrahymena*, heterochromatin components, including histone H3 methylated on lysine 9 (H3K9me) or on lysine 27 (H3K27me), and the chromodomain protein Pdd1p are specifically associated with eliminated IES sequences and are essential for DNA elimination. We previously demonstrated that small (~28nt) scan (scn) RNAs are also required for the elimination of DNA. 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 is formed downstream of the RNAi-related mechanism in the DNA elimination pathway.

How does the Argonaute-small RNA complex localize to the nucleus?

Recent data suggest that RNAi-related processes act in the cytoplasm as well as the nucleus in many eukaryotes. However, the process by which the RNAi machinery is transported into the nucleus is still poorly understood. The *Tetrahymena* Argonaute protein Twi1p localizes to the nucleus and is crucial for DNA elimination. We recently showed that the nuclear localization of Twi1p depends on a novel Twi1p-binding protein, Giw1p, and the



endoribonuclease (Slicer)-activity of Twi1p. We also demonstrated that Slicer activity plays a pivotal role in the removal of one of the two strands of Twi1p-associated scnRNAs, leading to a functionally mature Twi1p-scnRNA complex. Slicer activity is also shown to be involved in the interaction between Giw1p and Twi1p. These data suggest that Giw1p is a sensor for the state of Twi1p-associated scnRNAs and is required for selective transport of the mature Twi1p-siRNA complex into the nucleus (Figure 2). As it is still uncertain whether the maturation of Argonaute-small RNA complexes is required for nuclear import of Argonaute proteins in other eukaryotes, it would be meaningful to investigate the location of Slicer-dead Argonautes in other systems as well.

### Molecular scissors for DNA elimination

For a long time now, a transposase-like endonuclease activity was considered to be involved in DNA elimination while the enzyme responsible for this activity remained unknown. We and other investigators have recently identified a PiggyBac transposase-like enzyme (Tpb2p) which is essential for DNA elimination. *TPB2* appears to have undergone a domestication process in order to become a host gene and be maintained in the macronucleus. As Tpb2p co-localizes to Pdd1p-containing DNA elimination structures *in vivo* (Figure 3), and recombinantly expressed Tpb2p can produce double-strand breaks *in vitro*, we believe Tpb2p is an enzyme catalyzing the elimination of DNA. Based on this discovery, we are going to analyze how heterochromatin serves as a binding platform to recruit

the DNA elimination machinery, how the specificity of the boundary of DNA elimination is determined, and how DNA elimination is linked to subsequent DNA repair process. Although several domesticated transposon-derived proteins are known to be involved in host genome regulations in other eukaryotes, their individual evolutionary history is not clear. Investigation of Tpb2p may throw light on how a transposon can be domesticated to regulate a eukaryotic genome.

## KAZUFUMI MOCHIZUKI

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

### Publication highlights:

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

Mochizuki, K., and Gorovsky, M. A. (2005) A Dicer-like protein in *Tetrahymena* has distinct functions in genome rearrangement, chromosome segregation, and meiotic prophase. *Genes Dev.* 19, 77-89.

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

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Figure 1

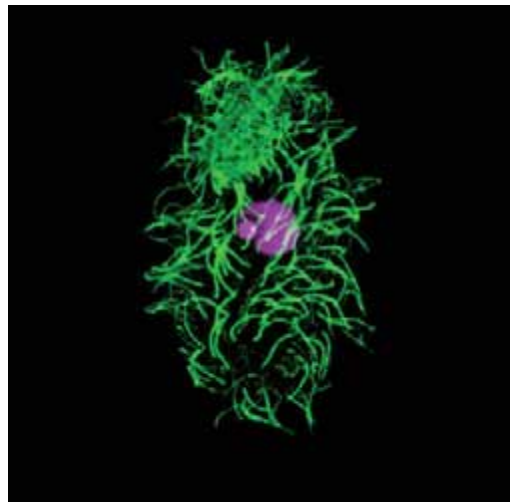


Figure 2

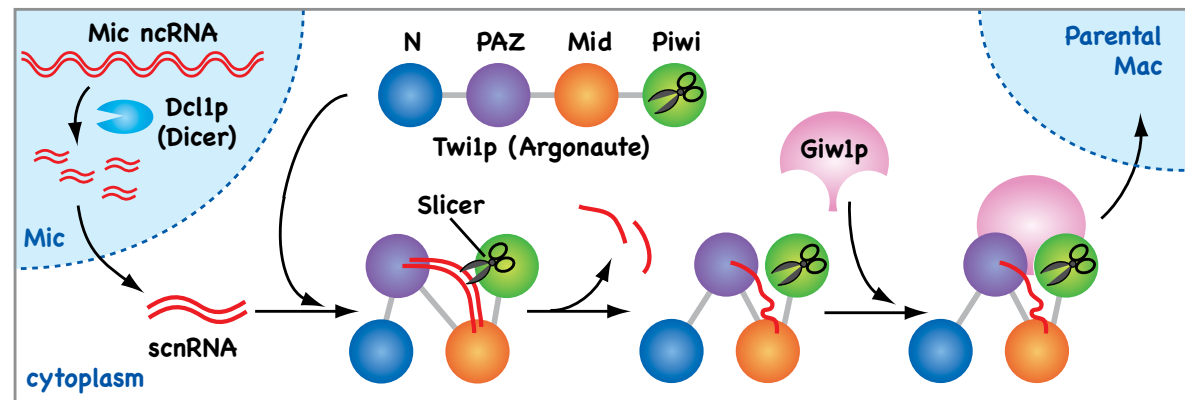
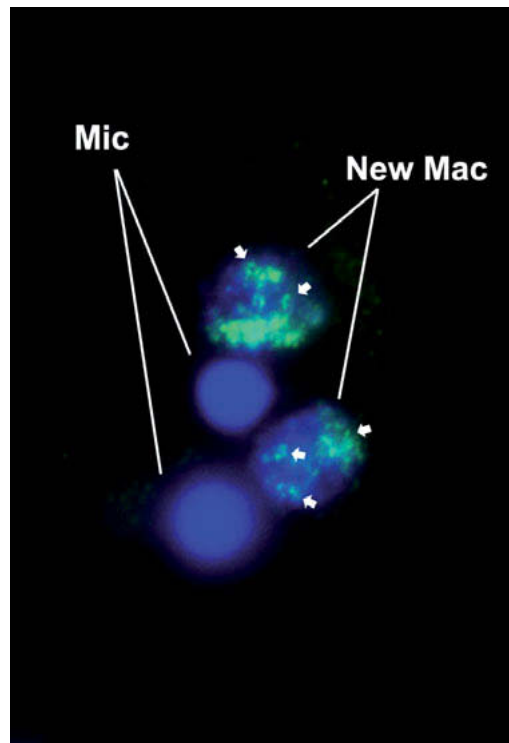


Figure 3

**Figure 1: *Tetrahymena thermophila***

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

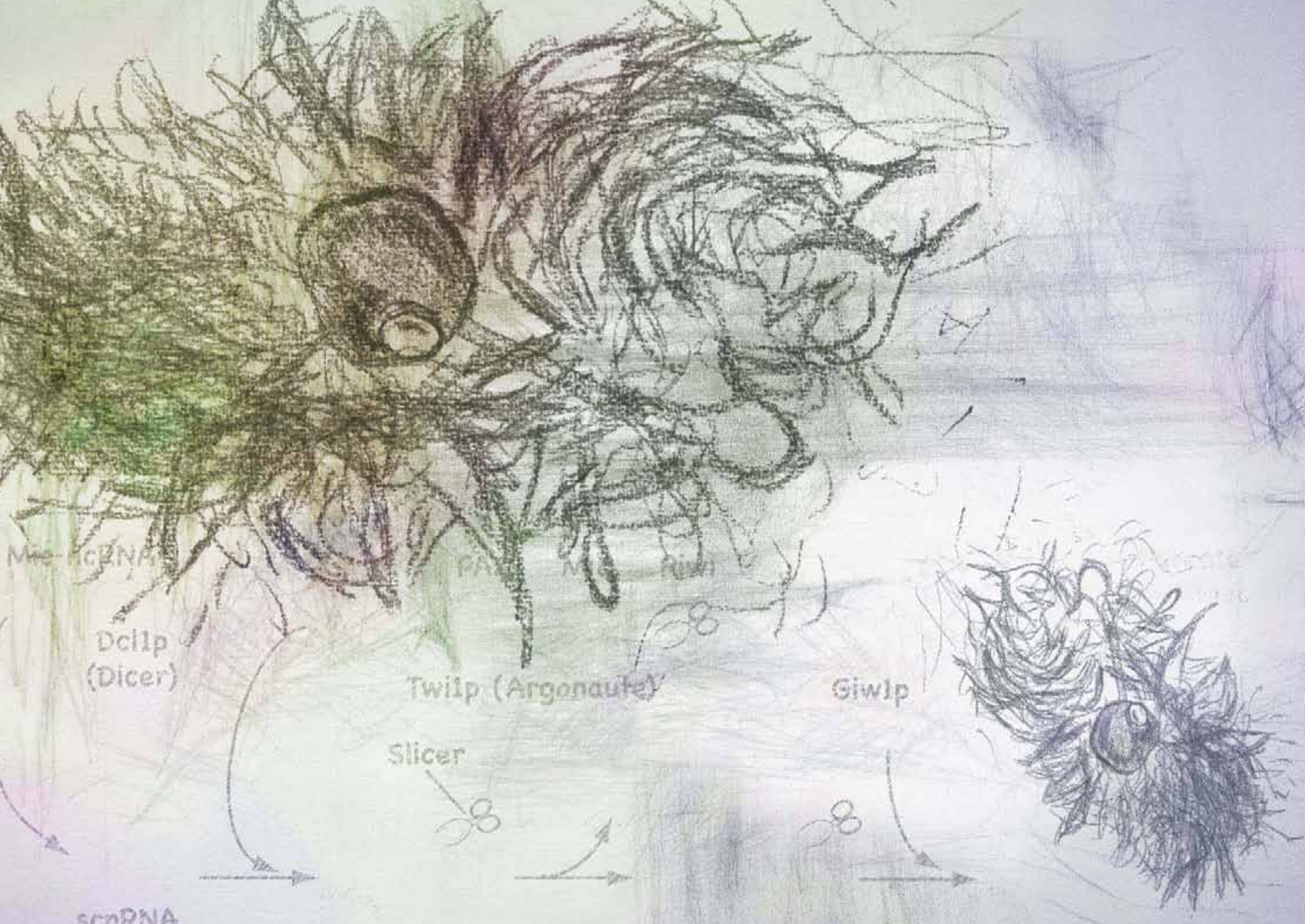
**Figure 2: A model for the molecular mechanism regulating macronuclear import of Twi1p**

First, scnRNAs are processed from micronuclear noncoding RNA by the Dicer homolog Dcl1p in the micronucleus and exported to the cytoplasm where they complex with Twi1p. The Slicer activity of Twi1p cuts one of the two strands (passenger strand) of the scnRNA, helping to remove this strand. Passenger strand removal is believed to alter the conformation of Twi1p. Giw1p specifically recognizes Twi1p complexed with single-stranded scnRNA, probably by sensing the suggested conformational change. Finally, the Twi1p-scRNA-Giw1p complex is transported into the macronucleus, presumably by the action of a nuclear-specific import machinery (importin).

**Figure 3: A piggy-Bac transposase like protein, Tpb2p, localizes to DNA elimination structures**

Localization of Tpb2p was analyzed by immunofluorescent staining using an anti-Tpb2p antibody (green). DNA was counterstained by DAPI (blue). Tpb2p localizes in DNA elimination structures at the nuclear periphery (arrowheads).









## JOSEF PENNINGER GROUP

Genetic dissection of disease mechanisms

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*With the advent of human genetics, a plethora of genes have been correlated with human disease. Genetic animal models proved to be extremely valuable in elucidating the essential functions of genes in normal physiology and the pathogenesis of disease. We create models of human disease using gene-targeted mice to investigate the genetic basis of disease mechanisms.*

### A genome-wide *in vivo* RNAi screen on innate immunity to intestinal pathogenic infections

Due to its lack of adaptive immunity, *Drosophila* serves as a powerful model. It permits investigation of the innate immune response at the level of the entire organism. *Drosophila* innate immunity consists of a humoral and a cellular immune system. The *Drosophila* humoral immune system localizes to the fat body and barrier epithelia where, in response to microbial infection, invariant antimicrobial peptides (AMPs) are synthesized. The cell-mediated system involves circulating hemocytes that can phagocytose and kill invading microorganisms. Most of our knowledge on *Drosophila* immunity is based on the analysis of host reactions after injection of non-pathogenic bacteria (e.g., *E. coli*) by pricking the body wall with a sharp needle coated with bacteria. Using this system, researchers initially identified the Toll pathway.

One of the limitations of using this infection model is that it bypasses the initial steps of naturally occurring infection, namely the local mucosal immune response and cellular defense. The human digestive tract is complex: it harbors more than 400 distinct microbial species and is protected by innate as well as adaptive immune responses. *Drosophila* immunity is much simpler than, yet strikingly similar to, many mammalian innate immune defenses. In collaboration with Dominique Ferrandon in Strasbourg, we performed the first *in vivo* *Drosophila* RNAi screening to identify innate immune regulators which confer susceptibility or resistance to natural oral infection with the highly infectious bacteria *Serratia marcescens* (Fig. 1). We used a ubiquitous inducible driver in conjunction with tissue-specific lines in gut epithelium and macrophage-like cells to identify and map several hundred genes involved in intestinal anti-bacterial immunity, many of which are conserved in mammals. Intestinal *Serratia marcescens* infections were found to trigger the activation of JAK-STAT, which is required for effective host defense. Interestingly, the Jak/STAT pathway plays an integral role in the gut of the fly controlling intestinal stem cell homeostasis during infection. It would be meaningful to define the global requirements for innate inflammatory responses in *Drosophila*.



*Drosophila* could then be used as a powerful tool to study intestinal pathogenesis in mammals and identify new potential anti-inflammatory drug targets (Cronin, Nehme et al., Science 2009).

### RANKL regulates fever responses in the central nervous system

Our group was the first to obtain genetic evidence of RANKL (OPGL, ODF, TRANCE, TNFSF11) as a key regulator of bone remodeling and the formation of a lactating mammary gland via its receptor RANK. We showed that RANKL controls the formation of lymph nodes and the development of thymic medullary epithelial cells. RANKL and RANK mRNA were also found in the brain. The functional relevance of RANKL/RANK in the brain was entirely unknown.

We have now been able to show that RANKL and RANK are expressed in specific regions of the brain, and that injection of RANKL in the central nervous system triggers severe and long-lasting fever responses in mice and rats. To investigate this in genetic terms, we generated a RANK<sup>flox</sup> allele. Using tissue-specific Nestin-Cre and GFAP-Cre *rank*<sup>flox</sup> deleter mice, the function of RANK in the fever response was genetically mapped to astrocytes.

Importantly, Nestin-Cre and GFAP-Cre *rank*<sup>flox</sup> deleter mice are resistant to LPS-induced septic fever as well as fever in response to the key inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$ . Mechanistically, RANKL activates brain regions involved in thermoregulation and induces fever via the COX2-PGE2/EP3R pathway. Moreover, female Nestin-Cre and GFAP-Cre *rank*<sup>flox</sup> mice have elevated basal body temperatures, suggesting that RANKL/RANK control thermoregulation during normal female physiology. We also showed that two children with RANK mutations exhibit impaired fever during pneumonia. These data revealed an entirely novel and unexpected function of the key osteoclast differentiation factors RANKL/RANK in female thermoregulation and the central fever response in inflammation (Hanada et al., Nature, 2009).

## JOSEF PENNINGER

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Josef Penninger received an MD's degree from the University in Innsbruck in 1990 and then moved to the Ontario Cancer Institute and University of Toronto where he still holds adjunct Full Professorships in Immunology and Medical Biophysics. In 2003, Josef came back to Europe to become the founding director of IMBA. Josef has published more than 300 scientific papers, is a recipient of the first round of Advanced ERC grants, and he currently holds a Full Professorship of Genetics at the University of Vienna.

### Publication highlights:

Hanada, R., Leibbrandt, A., Hanada, T., Kitaoka, S., Furuyashiki, T., Fujihara, H., Trichereau, J., Paolino, M., Qadri, F., Plehm, R., Klaere, S., Komnenovic, V., Mimata, H., Yoshimatsu, H., Takahashi, N., Haeseler, A., Bader, M., Kilic, A. S., Ueta, Y., Pifl, C., Narumiya, A., and J. M. Penninger. (2009). Central control of fever and female body temperature by RANKL/RANK. *Nature*, 462, 505-509.

Cronin, S. J. F., Nehme, N. T., Limmer, S., Liegeois, S., Pospisilik, J. A., Schramek, D., Leibbrandt, A., de Matos Simoes, R., Gruber, S., Puc, U., Ebersberger, I., Zoranovic, T., Neely, G. G., von Haeseler, A., Ferrandon, D., and Josef M. Penninger. (2009). Genome-Wide RNAi Screen Identifies Genes Involved in Intestinal Pathogenic Bacterial Infection. *Science*, 325:340-343.

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Figure 1

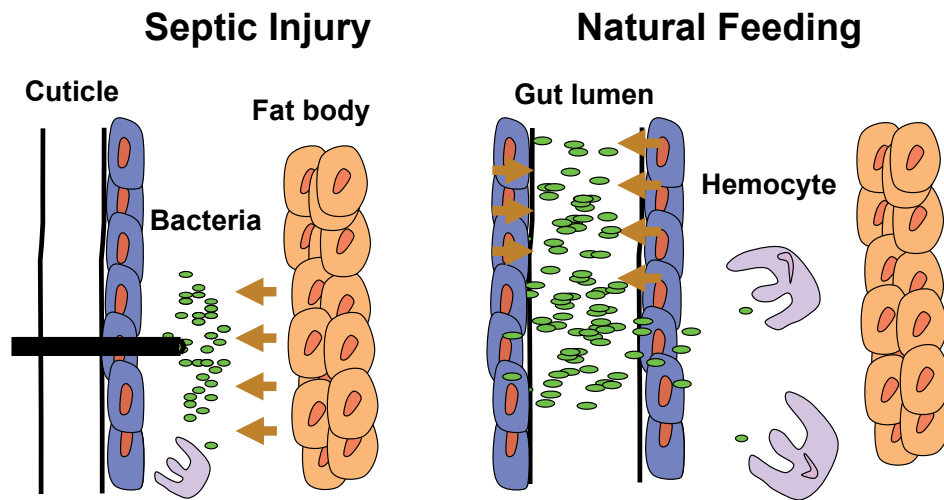
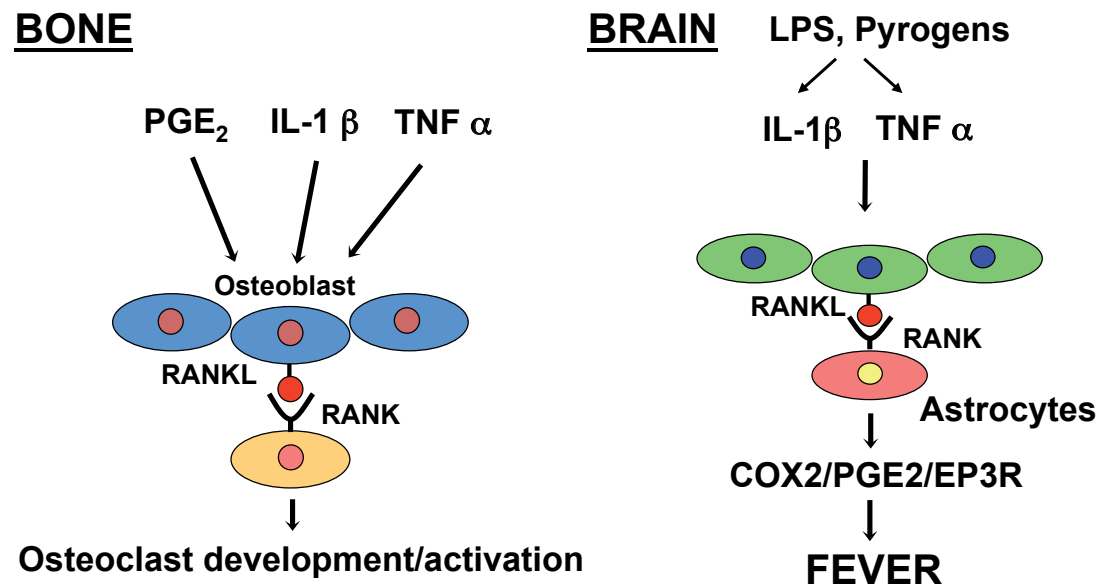


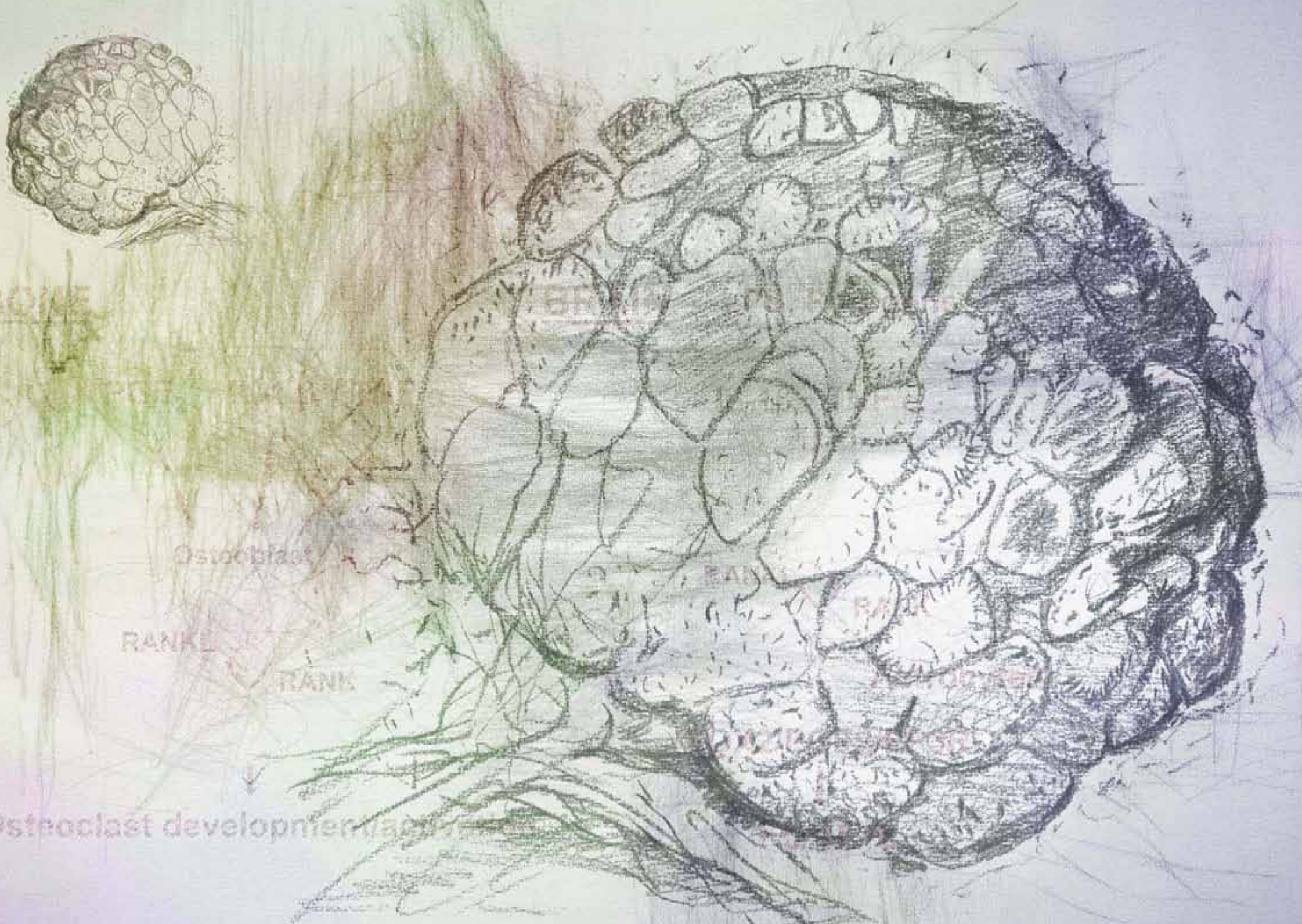
Figure 2



**Figure 1:** A whole genome screen for innate immunity in *Drosophila*. The septic injury model of infection elicits a systemic immune response in the fly through the fat body. In contrast, natural infection by *Serratia marcescens* (strain Db11) results in complementary local and cellular immune responses by the gut and hemocytes, respectively.

**Figure 2:** Proposed molecular hierarchy of the RANKL/RANK pathway in controlling osteoclast activation in bone and the fever response in the brain.









## RINGROSE GROUP

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.*

### Research activities:

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 specialized DNA elements called PRE/TREs (Polycomb/Trithorax Response elements, Figure 1A).

### How does PRE/TRE 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 across several cell divisions, 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). 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 1B to D). We combine quantitative measurements with fluorescence bleaching experiments (Figure 1E to G). In this way, we hope to understand in quantitative terms, how a system in constant flux can ensure both stability and flexibility.

### What makes a PRE/TRE?

Fly PRE/TREs are complex combinatorial DNA elements with 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, GMI Vienna). We have examined the evolution of these elements across several *Drosophila* species, showing



that PRE/TRE evolution is extraordinarily dynamic. (Figure 2). By showing that the evolution of PRE/TREs goes far beyond the gradual 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 in the embryo for the development of the peripheral nervous system, and in the larva, to determine wing identity. Remarkably, we find that early expression of the *vg* PRE/TRE RNA correlates with transient activation of the *vg* gene, but is also required for later silencing. We are now working to elucidate the molecular mechanism of this developmental switch. We are also using a mouse neural differentiation system to investigate whether similar regulated non-coding PRE/TRE RNAs exist in mammals.

## LEONIE RINGROSE

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

### Publication highlights:

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

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

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

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Figure 1

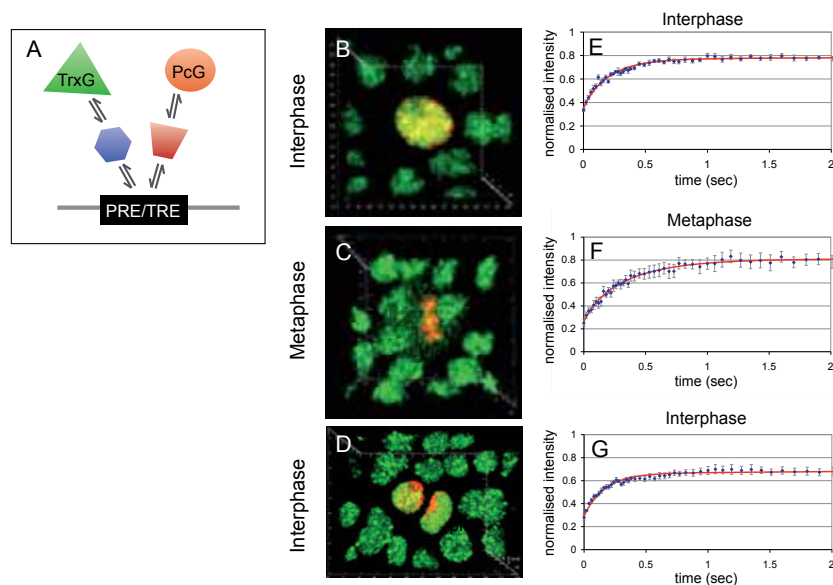
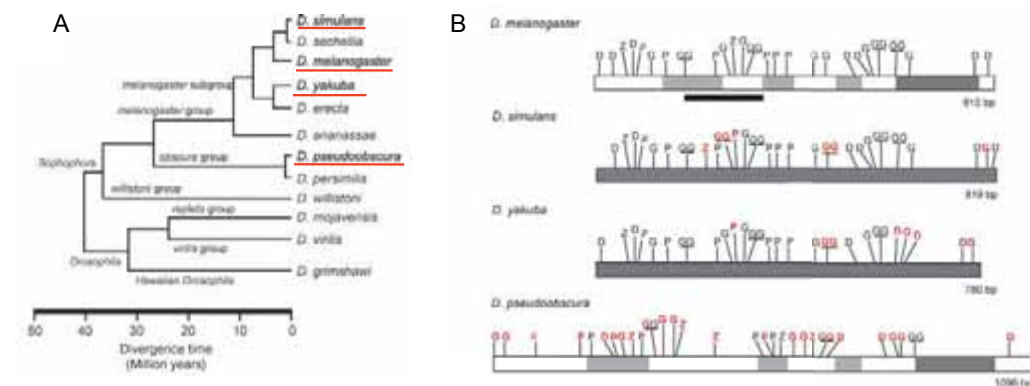


Figure 2

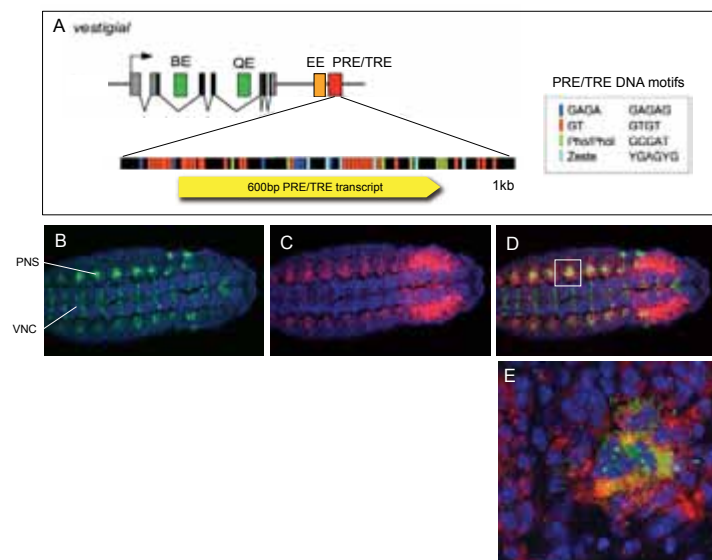


**Figure 1:** (A) PcG and TrxG proteins are recruited to their targets by DNA binding proteins (blue and red symbols), that recognise DNA elements called PRE/TREs. This binding is highly dynamic. (B-D) Live imaging of Polycomb-GFP in mitosis and differentiation of *Drosophila* pupal sensory organ precursor cells (SOP). PC:EGFP is green (all cells). Chromatin is red (SOP only). The two daughter cells in (D) have different identities from the parent cell (B). (E-G) Fluorescence recovery after photobleaching (FRAP) analysis of chromatin bound PC:EGFP reveals different recovery kinetics on interphase (E,G) and metaphase (F) chromosomes. Imaging and FRAP, Joao Fonseca.

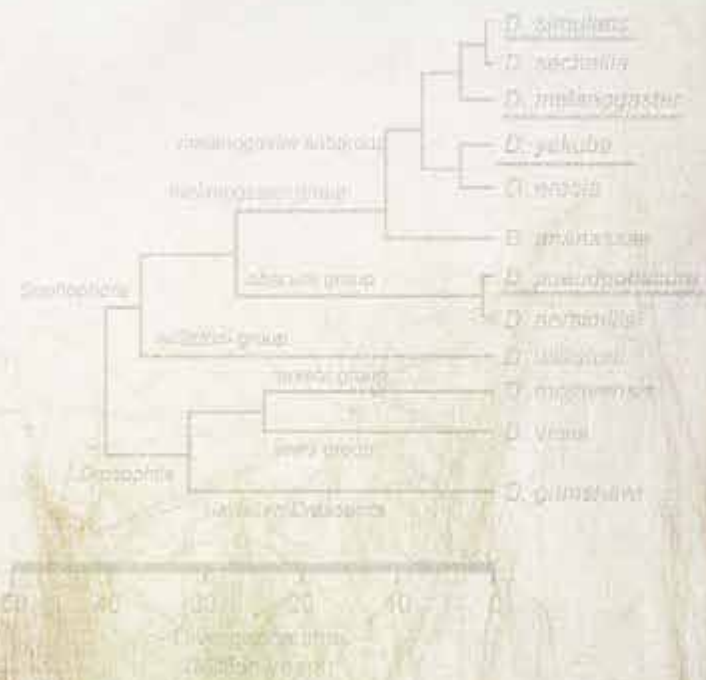
**Figure 2:** PRE/TRE motif occurrence is independent of sequence conservation. (A) PRE/TRE evolution was evaluated for four *Drosophila* species, underlined in red. (B) bxd PRE/TRE, which regulates the *Ubx* gene. The core *D. melanogaster* bxd PRE and the orthologous regions from the other three species are shown. Black bar below *D. melanogaster* diagram indicates minimal functional PRE/TRE fragment. Conservation between *D. melanogaster* and *D. pseudoobscura* is marked on the diagrams for these two species: Dark grey: regions of over 70% identity. Light grey: 50%–70% identity. *D. simulans* and *D. yakuba* conservation to *D. melanogaster* is indicated (the *D. melanogaster*, *D. simulans*, and *D. yakuba* sequences are over 90% identical). Motif positions are indicated above the figure. Motifs shown in red on *D. simulans*, *D. yakuba*, and *D. pseudoobscura* are not present in the *D. melanogaster* PRE. *D. Dsp1*; G, GAGA; P, p, PHO/PHOL; Z, Zeste. Underlined motifs indicate overlapping runs of motif separated by two bases. G5 indicates five consecutive GAs. Adapted from Hauenschild et al., 2008.

**Figure 3:** (A) The *Drosophila vestigial* locus contains a PRE/TRE that is transcribed into non-coding RNA. Green: enhancers involved in wing expression: BE, boundary enhancer; QE, quadrant enhancer. Yellow, EE: embryonic enhancer. Red: PRE/TRE element. DNA motifs important for PRE/TRE function are shown. Yellow arrow: the non-coding transcript arises from within the PRE/TRE element. (B-E) Double fluorescent in situ hybridisations show colocalisation of the *vestigial* mRNA (green) and the non-coding PRE/TRE transcript (red) in specific cells of the peripheral nervous system (PNS on B). The ventral nerve cord (VNC on B) in which the *vestigial* mRNA, but not the non-coding RNA is present, is also marked. (E) zoom of box in (D), showing colocalisation of mRNA and non coding RNA. The non-coding transcript is seen both in the nucleus and the cytoplasm. Non-coding RNA transcript mapping, Heidi Lempradl/Christina Altmutter; in situ hybridisations: Frank Ruge.

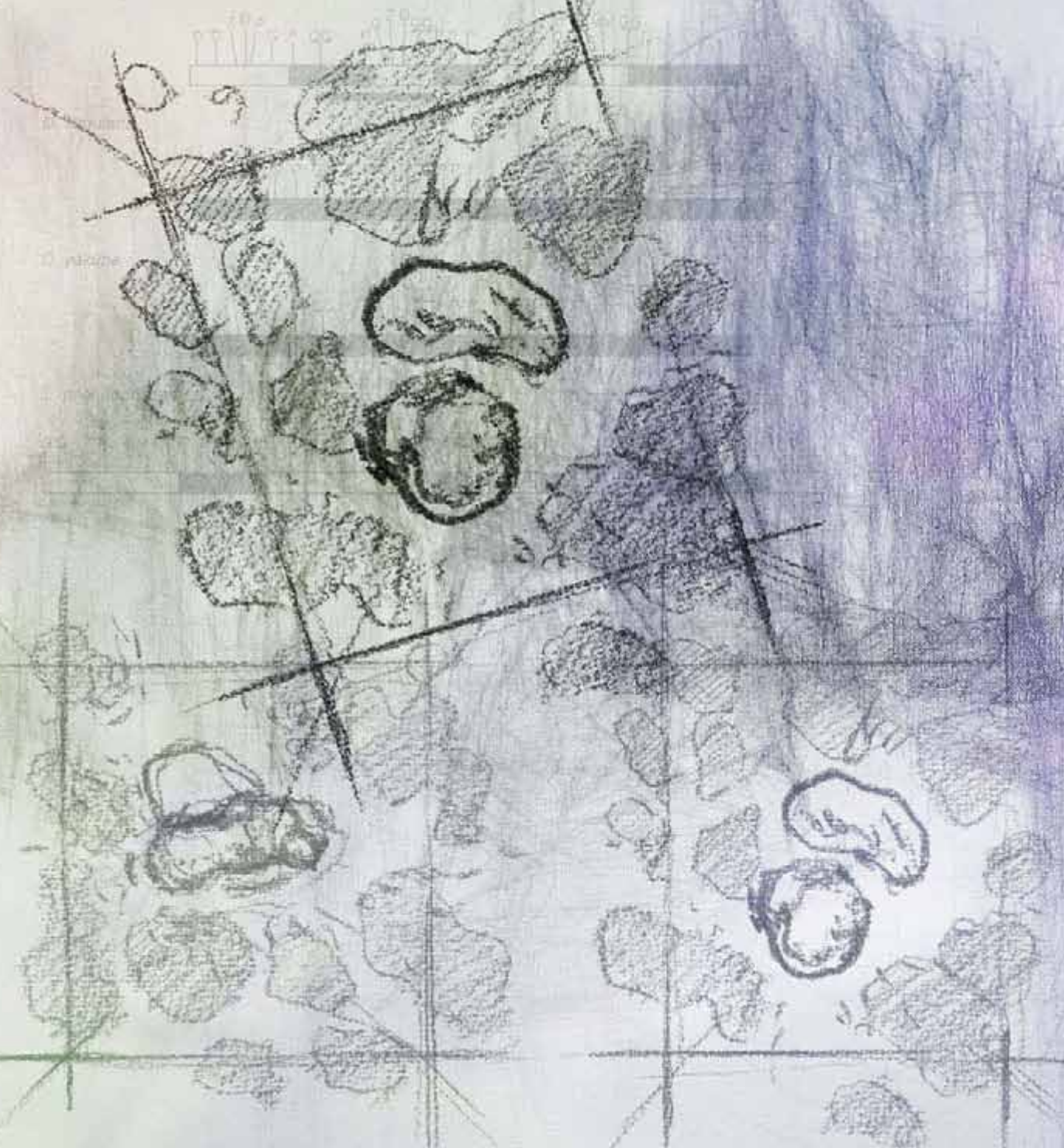
Figure 3







B *D. melanogaster*





## VIC SMALL GROUP

Unveiling the mechanisms of cell migration

[www.imba.oeaw.ac.at/research/vic-small](http://www.imba.oeaw.ac.at/research/vic-small)

*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 disperse by migration to propagate in multiple sites elsewhere. Discovering how cells move is therefore important for understanding normal and pathological processes, with perspectives of bringing unwanted events under control. So what do we already know about cell movement and migration?*

In order to move, eukaryotic cells have developed subtle variations in strategy, all based on remodelling the actin cytoskeleton. Net translocation is achieved by protrusion at the cell front, followed by retraction at the rear. Protrusion is effected by lamellipodia, thin sheets of cytoplasm composed of networks of actin filaments and filopodia, finger-like rods of bundled actin filaments. 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, 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.

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 actin networks in migrating cells

Since actin filaments are densely packed in lamellipodia it has not been possible by conventional electron microscopy to properly resolve the architecture of the filament networks that push at the cell front. This situation has dramatically changed with the advent of electron microscope tomography (ET) that allows three-dimensional visualization of cytoplasmic structure in thin, peripheral zones of whole cells, or in sections up to around 300nm thick. For structural information obtained by ET to be useful, it must be related to a biological phenomenon, in our case to cell movement. We have therefore invested efforts in developing techniques that allow live imaging of cells by fluorescence microscopy up to the point of fixation to be combined with 3D imaging by ET. Issues of how to prepare cells for ET to avoid artifacts however remain.



Living cells can also be frozen and subjected to cryo-electron tomography (cryo-ET), avoiding any fixation steps (Fig. 1A). With this method, correlated live cell imaging is not yet possible and there are limitations in resolution. But using cryo-ET we have been able to validate the ET images obtained from fixed cells (Fig. 1B) opening the way to meaningful correlations between structure and function. We are applying these approaches to probe the roles of actin nucleators and cross-linkers in the generation of actin filament assemblies.

### Border cell migration in *Drosophila*

In a genome wide RNAi screen of border cell migration we identified a cell adhesion molecule "Wanderlust" (Wadl), homologous to neuroligin, as necessary for migration of the border cell cluster through the egg chamber. Targeted depletion of Wadl in the follicle epithelium of the egg chamber causes a loss of epithelial integrity (Fig. 2) supporting the idea that Wadl is a co-regulator of cell-cell junction turnover, required for border cells to move. We are currently looking for molecular partners that function with Wadl in regulating cluster migration.

## VIC SMALL

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

#### Publication highlights:

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

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

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

VIC SMALL ----- SENIOR SCIENTIST

EDIT URBAN ----- POSTDOC

NATALIA ANDREYEVA ----- POSTDOC

HANNAH NEUMEIER ----- POSTDOC

ZHENG RUI XI ----- POSTDOC

MARIA NEMETHOVA ----- STAFF SCIENTIST

SONJA AUINGER (JACOB) ----- LAB MANAGER

MARLENE VINZENZ ----- TECHNICIAN

MARTIN BREUSS ----- DIPLOMA STUDENT

ANTONIA ALEXANDROVA ----- SHORT TERM EMBO FELLOW

Figure 1

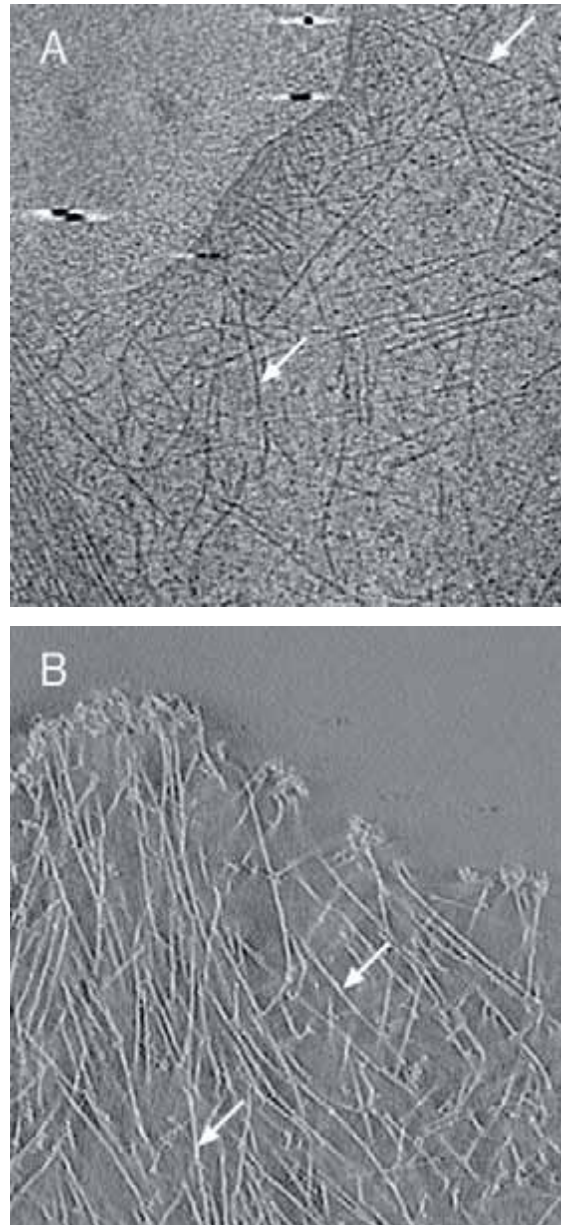
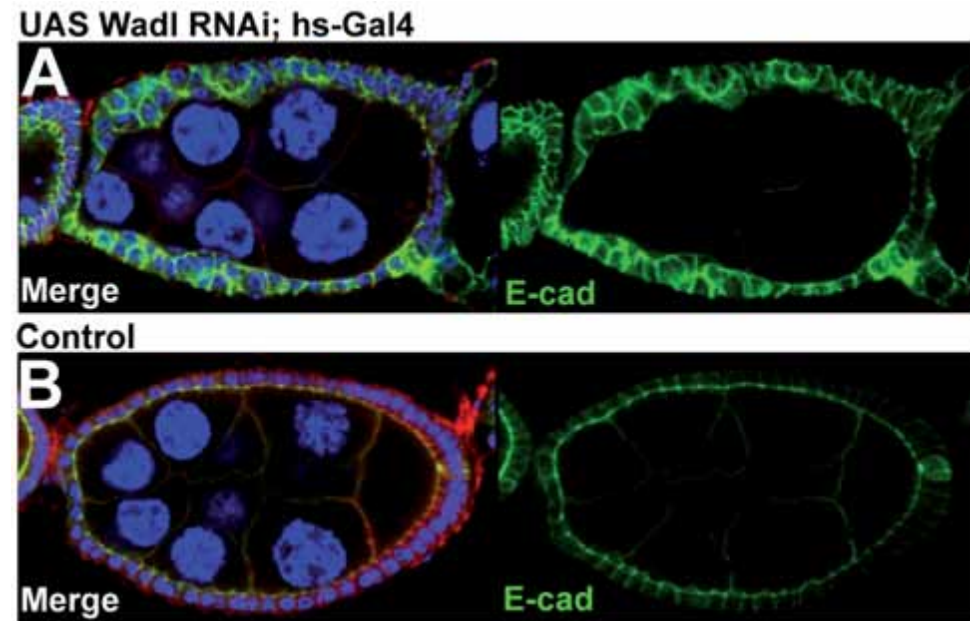


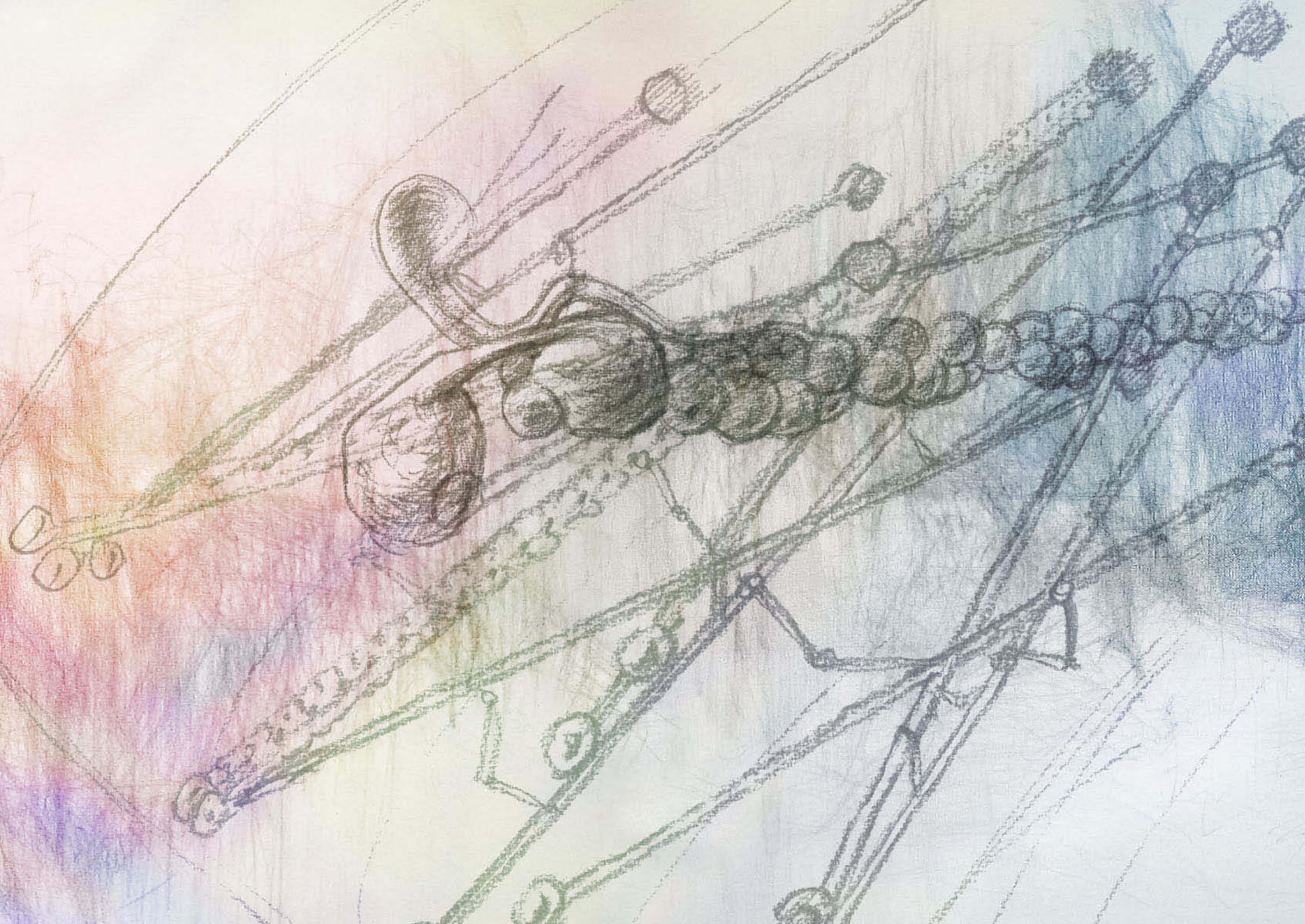
Figure 2



**Figure 1: The 3D organization of actin networks in lamellipodia is preserved after fixation, facilitating correlated live cell imaging and electron tomography.** A. Section of a tomogram obtained from the lamellipodium of a fibroblast that was rapidly frozen without fixation and imaged in ice. B. Tomogram of a similar region to A in a fibroblast that was first imaged live by fluorescence microscopy, fixed and then embedded in a heavy metal salt (negative staining). Arrows indicate actin filaments. The general arrangement and number of filaments in the frozen and fixed preparations are essentially equivalent.

**Figure 2: Down regulation of Wadl in the follicle epithelium of *Drosophila* egg chambers disrupts epithelial polarity.** A. Egg chamber in which expression of UAS-Wadl RNAi was induced by three periods of heat shock (hs) via an hs-Gal4 promoter. B. Control egg chamber subjected to same heat shock routine. E-cad, E-cadherin. Other labels in merged images on left: blue, DAPI; red, Discs large.







# FLY HOUSE

Peter Duchek

peter.duchek@imba.oeaw.ac.at

PETER DUCHEK / HEAD OF FACILITY

SABINE AMANN <sup>1</sup>	TECHNICAL ASSISTANT
SABINE BRYNDA	TECHNICAL ASSISTANT
SARA FARINA LOPEZ	TECHNICAL ASSISTANT
GERALD HAAS <sup>2</sup>	TECHNICAL ASSISTANT
URSZULA PUC <sup>2</sup>	TECHNICAL ASSISTANT
CLAUDIA VALENTA <sup>2</sup>	TECHNICAL ASSISTANT

<sup>1</sup> UNTIL APRIL  
<sup>2</sup> PART TIME

## RESEARCH SUPPORT

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

### Embryo injections

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

### Gene targeting

Although the use of homologous recombination to generate defined mutations is a well-established technique in several genetic model organisms, gene targeting in *Drosophila* has been developed very recently. As it is necessary to confirm the RNAi knock-down phenotypes of candidate genes with classical loss-of-function alleles, we have set up a *Drosophila* gene targeting service at the institute. Over the last twelve months, we successfully generated knock-out flies for several genes using an ends-out gene targeting strategy.

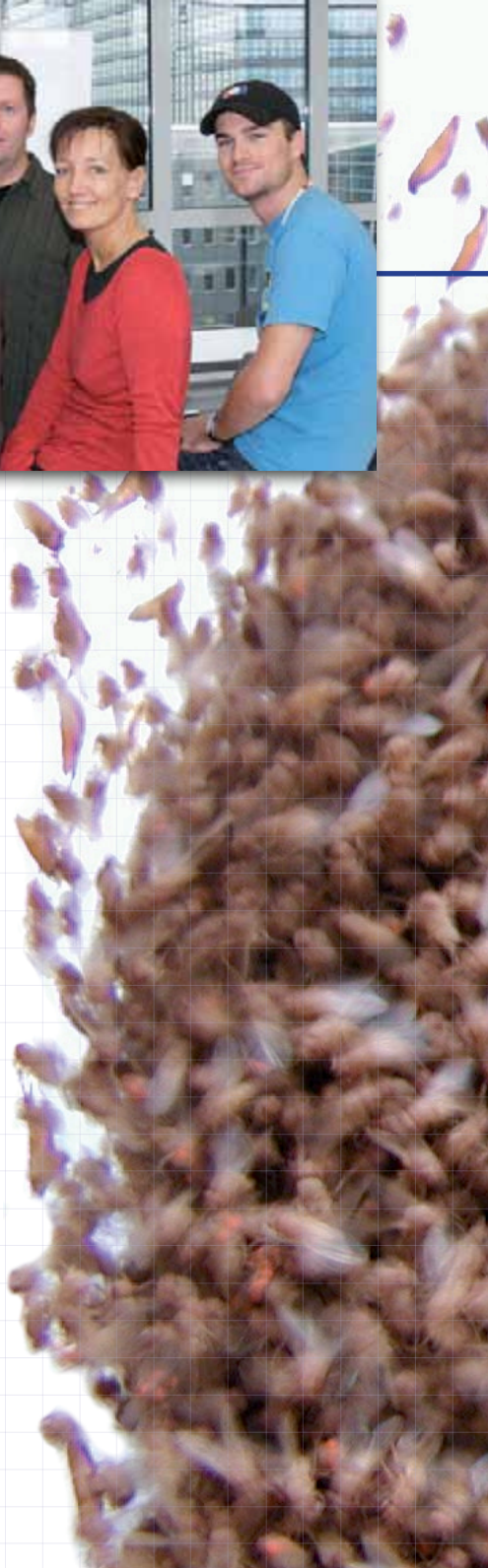
### Research support

The first genome-wide collection of inducible RNAi lines, now available through the Vienna *Drosophila* RNAi Center (VDRC), has revolutionized

loss-of-function genetic screens in *Drosophila*. It is now possible to systematically investigate the function of each gene in a tissue of interest. We support scientists conducting large-scale in vivo RNAi screens by setting up crosses and scoring phenotypes as well as with subsequent follow-up experiments to validate their hits.

### Fly stock maintenance and plasmid collection

In addition to looking after lab stock collections, we keep various commonly used fly stocks such as balancers and virginizer lines. We also have a growing plasmid collection consisting mainly of vectors used for targeted integration or homologous recombination, and work towards improving available tools by introducing new features.







## STEM CELL CENTER - GENE TARGETING UNIT

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*The Stem Cell Center – Gene Targeting Unit has been set up for handling and manipulating mouse embryonic stem (ES) cells. By combining homologous recombination, site-specific recombination and transgenesis, genetic changes described in human disease can be copied into the mouse genome, thus engineering ideal disease models.*

### ES cell gene targeting

The several missions of the ES cell core facility include the production of quality-controlled ES cell lines with mutations introduced by homologous recombination using a targeting vector provided by the researcher, the creation and handling of quality-controlled ES cell lines using state-of-the-art reagents, and enhancing knowledge of mouse genetics, ES cell culture

and manipulation. Procedures for the manipulation of ES cells and the generation of mice are labour-intensive and technically demanding. Facilitating experiments of this type is one of the purposes of the Unit. Targeted ES cells can be used to generate germline ES cell-mouse chimeras that can be bred to generate mouse lines or for *in vitro* assays. We also develop *in vivo* inducible gene targeting systems focusing on breast cancer using female ES cell lines, and try to generate new transgenic recombinase mouse models.

### Gene targeting tool box

We maintain a “gene targeting tool box” in addition to providing expertise, cell lines, efficient exchange of information, and stem cell assays. The collection includes Cre and Flp

recombinase-expressing transgenic lines and Cre and Flp activity-reporter lines, which are essential for the generation and characterization of conditional, inducible, and/or tissue-specific mutant mice. The Unit also maintains a collection of “ES and vectors tools”, reagents, feeders (neomycin resistant or neo/hygro/puro resistant), cell lines, and plasmid vectors.

### Derivation of novel ES cell lines

The availability of highly germline-competent ES cells derived from inbred strains, which are preferentially used in biomedical research, would greatly facilitate the generation of targeted mutations in appropriate genetic backgrounds. We now have the expertise and skills to isolate and culture inbred

ES cells, such as FVB/N and C57BL6/N ES cell lines. This provides essential tools for analysis of the mutations, especially when the phenotype is embryonic lethal at the early stages of development. Currently our interest is focused on generating induced pluripotent stem cells.

ANFM<sup>G</sup> Austrian Network for Functional Mouse Genomics



RESEARCH SUPPORT



# VIENNA DROSOPHILA RNAi CENTER (VDRC)

Krystyna Kelemann

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KRISTYNA KELEMAN / STAFF SCIENTIST/HEAD OF THE VDRC

## RNAi LIBRARY MAINTENANCE AND DEVELOPMENT

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THOMAS MICHELER	SOFTWARE DEVELOPER
VIRGINIA SALVA MILLAN <sup>1</sup>	ADMINISTRATION
MARTIN KINBERG	TECHNICAL ASSISTANT
ANDREAS GANSCH	TECHNICAL ASSISTANT
JUDITH UTNER <sup>1</sup>	TECHNICAL ASSISTANT
ALISHER TASHPULATOV	TECHNICAL ASSISTANT
KAISER RENÉ	TECHNICAL ASSISTANT
IRINA KOLAROV	TECHNICAL ASSISTANT
MICHAELA ECKMANN	TECHNICAL ASSISTANT
KRISTINA BELOGRADOVA	TECHNICAL ASSISTANT
SELEN IREZ	TECHNICAL ASSISTANT
SONJA LANG <sup>1</sup>	TECHNICAL ASSISTANT
FLORENCE MAXWELL	TECHNICAL ASSISTANT
LUIZA DESZCZ <sup>1</sup>	TECHNICAL ASSISTANT
MICHAELA FELLNER	TECHNICAL ASSISTANT
LASZLO HUNOR	TECHNICAL ASSISTANT
ANGELA GRAF <sup>1</sup>	TECHNICAL ASSISTANT
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SANDOR URMOSI – INCZE	TECHNICAL ASSISTANT
ELENA POPOWICH	TECHNICAL ASSISTANT
STEFANIE WANDL	TECHNICAL ASSISTANT
ZSUZSANNA PORTIK DOBOS	TECHNICAL ASSISTANT

## KELEMAN RESEARCH GROUP MEMBERS

SEBASTIAN KRÜTTNER	PHD STUDENT
BARBARA STEPIEN	PHD STUDENT
KATHARINA JANDRASITS	TECHNICAL ASSISTANT

## Genome-wide RNAi and memory formation

*We have generated two independent genome-wide transgenic RNAi libraries for Drosophila, allowing researchers to systematically study gene functions in specific tissues at specific developmental stages. The VDRC maintains and further develops these libraries, and distributes RNAi lines to Drosophila researchers world-wide. In our own research group, we use transgenic RNAi 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 (Figure1). The initial creation of a genome-wide transgenic RNAi library

[1] has revolutionized *Drosophila* genetics. The VDRC, maintains, further develops and distributes this library.

Recently, we have embarked on the construction of a new RNAi library (the KK library) that exploits site-specific transgene integration and to overcome some of the problems associated with random insertion of the P element transgenes of the original collection (GD library). In the new KK library, all RNAi transgenes are targeted to the VIE-260b site, selected on the basis of its low basal expression and high levels of GAL4-induced expression. An additional attractive feature of our new collection is that it targets a different gene fragments than our first library. We have completed 10,000 RNAi lines, which were made available to researchers world-wide in March this year.

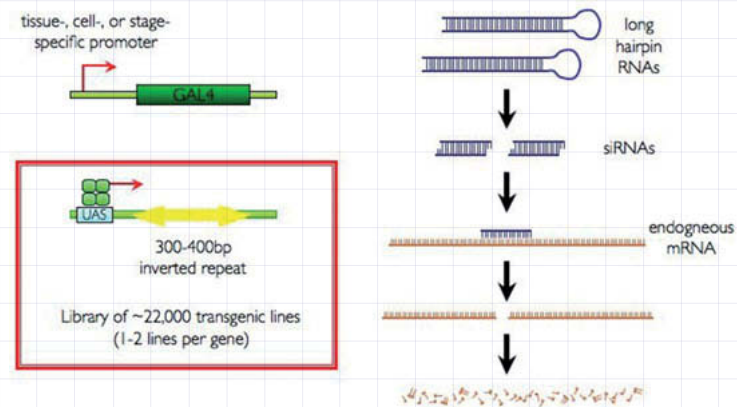
Since the VDRC opened two and a half years ago, we have already delivered over 200,000 lines to more than 1,500 registered users world-wide. This has been made possible in part through core funding provided by the city of Vienna and the federal government, with the rest of the costs covered by user fees. The VDRC also provides such support for researchers in house, having delivered over 80,000 lines to IMBA and IMP groups.

## 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 largely on his ability to discriminate receptive virgins 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.



Figure 1



The right balance appears not to be hard-wired into the fly's brain, but is something he learns by trial-and-error during his first few courtship experiences (Figure 2). His 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 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 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? And, as the ultimate goal, we would like to define the specific molecular and cellular changes in the brain that underlie this form of learning.

**Figure 1:** RNAi in *Drosophila*.**Figure 2:** Courtship conditioning. When tested with unreceptive mated females, males previously exposed to mated females court less than naïve (sham-trained) males ( $CI = \text{courtship index}$ ;  $CI_{\text{trained}} < CI_{\text{naïve}}$ )**Figure 3:** Mushroom body neurons in the fly's brain – Orb2 is required in these neurons for courtship conditioning.

Figure 2

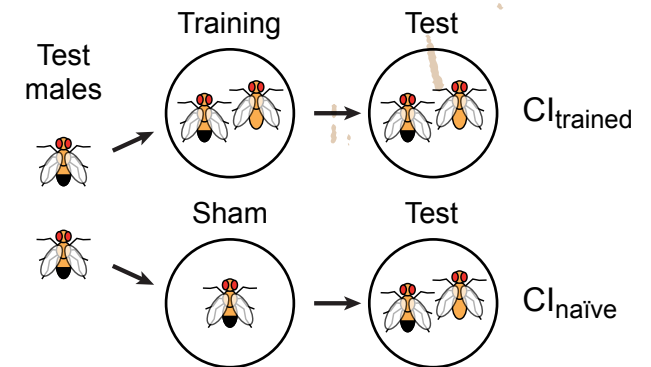
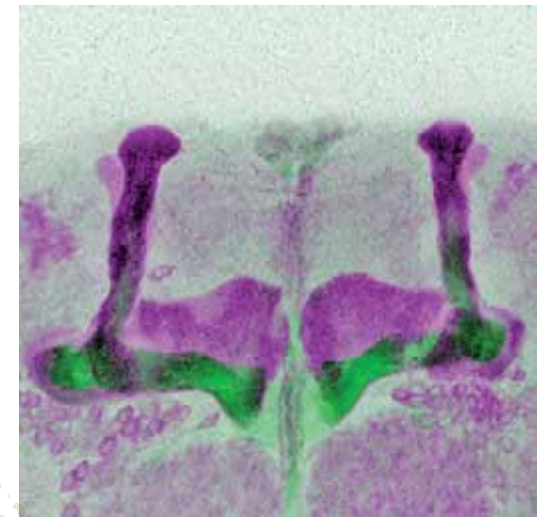


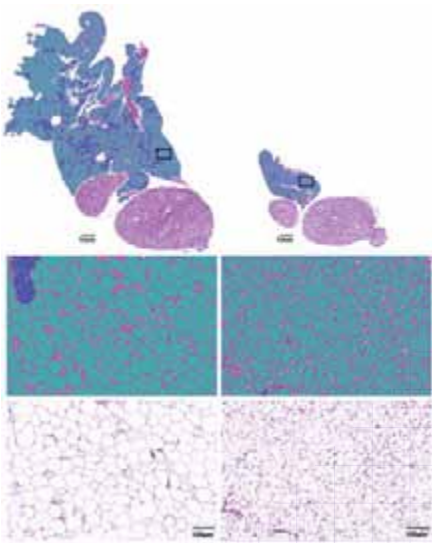
Figure 3



# BIOOPTICS FACILITY

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KARIN AUMAYR ----- HEAD OF BIOOPTICS  
PAWEŁ PASIERBEK ----- MICROSCOPY  
GABRIELE STENGL ----- FLOW CYTOMETRY/MICROSCOPY  
GERALD SCHMAUSS ----- FLOW CYTOMETRY/IMAGE ANALYSIS



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

## Flow Cytometry

We provide instrumentation, education and expertise for all flow cytometry requiring experiments, and offer high-speed cell sorting as well as advanced and general flow cytometry analysis. Users are given guidance and support with the planning of experiments and implementation of new fluorophore combinations. They are trained in the use of hardware and software for all of the three available state-of-the-art flow cytometers, as well as in data processing and analysis.

Two cell sorters are operated by the staff of the facility to sort up to four cell populations simultaneously in bulk, or conduct single cell sorting.

## Microscopy

The BioOptics Facility currently manages more than twenty microscopy systems, covering widefield microscopy, confocal laser scanning microscopy (CLSM), two-photon (2P) microscopy, total internal reflection (TIRF) microscopy techniques, and an automated slide scanner for samples with or without fluorescence. Most of the systems are motorized, thus providing automation for higher throughput, and are suitable for both fixed samples and live cell experiments. The facility provides assisted use and training on all instrumentation and consultation



concerning all microscopy-related subjects, including project planning, staining, microscope selection, etc.

## Image Processing and Analysis

Five state-of-the-art computer workstations are available at the BioOptics Facility, operating most of the common commercial image processing and visualization software. For the deconvolution of microscopy images, a server solution with a web-based interface has been set up in order to provide efficient, multi-user, parallel, batch deconvolution that can easily be started from the individual scientist's computer. Users are trained in the use of specific software, depending on their demands. Several image analysis algorithms are available, such as object

tracking and tracing, determination of measurement parameters like intensity, distance, area, volume and co-localization. For advanced image analysis and automated object recognition, customized classification and measuring algorithms are developed within the facility.

**Figure:** Morphometric analysis of adipose tissue, performed on complete HE stained sections scanned with the MIRAX scanner. Panel left: WT section. Panel right: KO section. Adipocytes in blue. Automatic image analysis with the application of the internally developed Definiens algorithm permits analysis of cell size and number throughout entire sections (more than 35,000 individual cells from control animals and more than 10,000 cells for knockout animals).





*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. Access to scanning electron microscopy can be provided via an external collaboration.*

## Specimen Preparation

Know-how, training and instrumentation for a wide variety of preparation techniques for visualization of ultrastructure in tissues or cells, and biomolecules by transmission electron microscopy (TEM), are being offered by the Electron Microscopy Facility. Techniques routinely used at the facility

include the production of support films, negative staining, rotary shadowing of sprayed molecules, chemical and physical fixation, resin embedding in epoxy- and acrylic resins, and ultrathin sectioning of resin-embedded or frozen samples. In 2009, high-pressure freezing was established to produce optimally preserved specimens in conjunction with freeze substitution.

## Microscopy

The FEI Morgagni is a robust and easy-to-use 100 kV TEM equipped with a 11 megapixel CCD camera. It is tailored for routine applications in the multiuser environment of the facility. Advanced applications run on the FEI

TF30 Polara. This 300 kV TEM, unique in Austria and equipped with the most advanced imaging systems, was funded by a Vienna Spot of Excellence grant and became fully operational at the beginning of 2008. It is primarily used for cryo-TEM of molecules and cells, electron tomography, and electron energy loss spectroscopy.

## Software Development and Image Processing

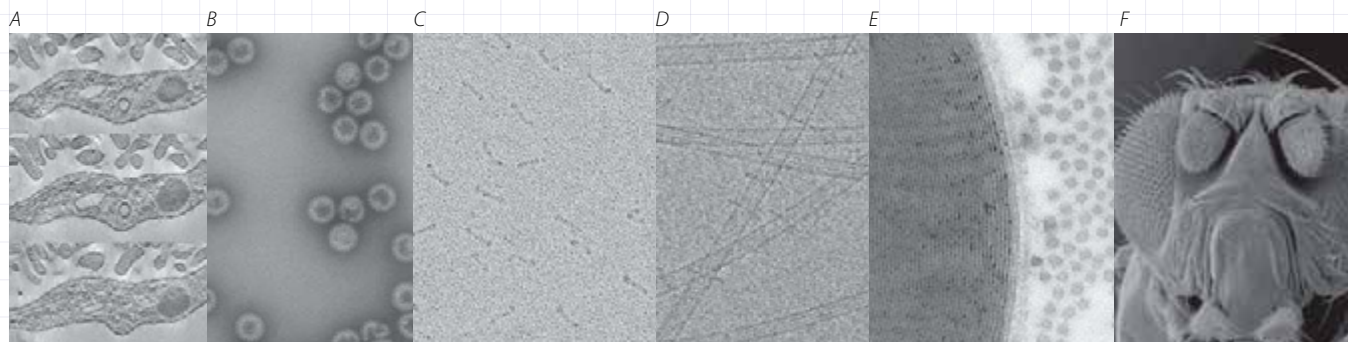
To support users with data management, a web-based project-oriented database system named MIMAS was developed by, and is being run at the facility. Electron micrographs from both microscopes including meta data can

be stored on and accessed from this database on a user-restricted basis. Furthermore, software solutions for automated image acquisition and status monitoring of the microscope were developed on the Polara. Workstations and training are provided for image processing of EM data, especially those obtained from electron tomography.

GUENTER RESCH ----- HEAD OF ELECTRON MICROSCOPY FACILITY

MARLENE BRANDSTETTER ----- TECHNICAL ASSISTANT

NICOLE FELLNER ----- TECHNICAL ASSISTANT



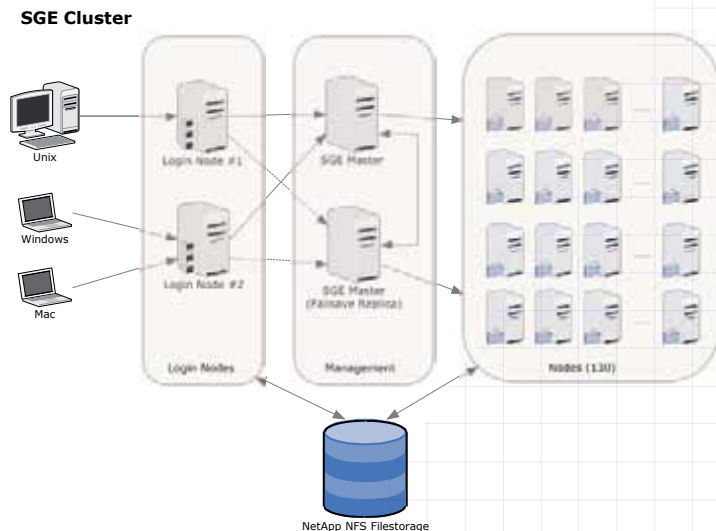
- A: z-Sections from a three-dimensional reconstruction of the endothelial lining in a blood vessel by electron tomography.
- B: Negatively stained rotavirus-like particles (micrograph courtesy of Cornelia Gänger, Ringrose Group)
- C: Glycerol sprayed and rotary shadowed  $\alpha$ -actinin molecules
- D: Dam1-decorated microtubules visualised by cryo-electron microscopy (sample: Fabienne Lampert, Westermann Group, IMP)
- E: Myelin sheath of a neuron in cross-section (sample: Toshikatsu Hanada, Penninger Group).
- F: Wild type *Drosophila* visualised by scanning electron microscopy.

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

Web access is being provided for widely used scientific applications related to protein motif analysis, similarity searching (BLAST, PSI-BLAST, FASTA), whole-genome viewing (GBrowse), transcription factor analysis (Transfac), and various sequence manipulation and exploration tasks (EMBOSS).



## Large-scale data analysis

Additional demands arise from the investigation of large functional genomics or high-throughput biological datasets. We engage in custom software and database development, and design computational and mathematical solutions that can cope with the higher load and memory requirements. To perform complex sequence analysis tasks, we also maintain the IMP ANNOTATOR, which is a user-friendly web application and a high-throughput protein annotation system.

For heterogeneous computational tasks, the main computing cluster has been updated to a state-of-the-art processing system using batch and parallel computing environments. The cluster is managed by the Sun Grid Engine (SGE) software, which provides policy-based workload management

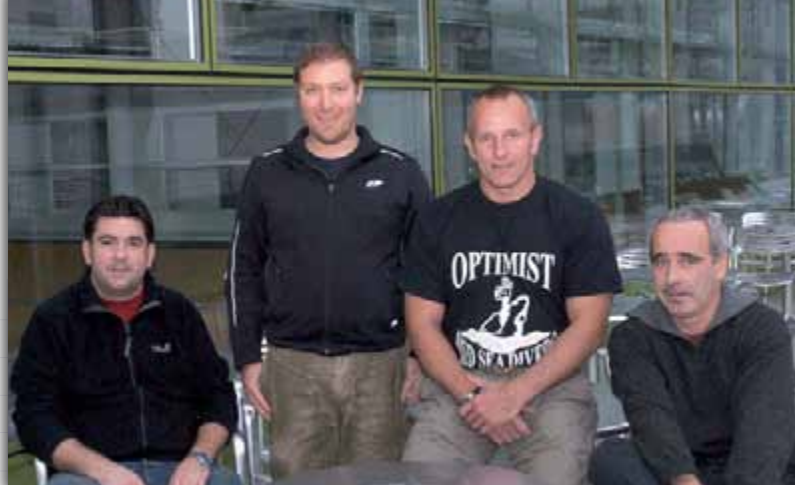
for a large number of jobs and nodes. Software installed and maintained on the bioinformatics cluster includes tools for statistical computing (e.g. R, Bioconductor), motif discovery and analysis (e.g. AlignAce, MDscan, MEME, Weeder), structural biology (e.g. VMD, pyMOL, NAMD), a wide range of sequence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

## Training

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

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





*The Genomics Department comprises the microarray services, the cDNA clone repository, liquid handling robotics and next-generation sequencing. Major projects and accomplishments in 2009:*

### Microarray:

After re-arraying the RIKEN (FANTOM I to III) library in 2008, we hybridized more than 200 microarrays. Over 22,500 genes per array were analyzed and processed with an internal programmed fully automated analysis software tool. We offer Spotfire from the summer of 2009 onward. Spotfire is a powerful tool to visualize and analyze microarray data. We now use the IBD extension for Spotfire, which is a tool for visualization and analysis of microarray data. An additional technology we have established in cooperation with MFPL is the hybridization of Agilent arrays. We set up the entire equipment for hybridization at the Genomics Department; scanning is performed

at MFPL (special thanks to Walter Glaser). Although more expensive, Agilent arrays are of better quality and equipped with more features than our cDNA arrays. With Agilent we can also offer microarrays to analyze DNA Methylation, microRNAs, and custom-made microarrays for various model organisms.

### Robotics:

A further noteworthy aspect of our work at the Genomics Department is the use of robotics in the lab. We are currently working with a Tecan TeMO provided with 96 channels, and a Biotek Precision XS for 8-channel and single pipetting. In the near future we will also have the XIRIL 100 which will assist us in one of our main projects, namely automated genomic DNA isolation for genotyping and automated plasmid mini-preparation.

### Next-generation Sequencing:

The capacity of next-generation sequencing has been increased by the addition of two genome analyzers to the facility at the beginning of 2009. Each is equipped with a paired-end module which permits the sequencing of both ends of DNA fragments. The superior software and hardware of the instruments led to a significant (>30%) increase in sequence yield. Due to improved sequencing reagents, we are now able to standardly sequence 72 base-pair read lengths.

Next-generation sequencing offers a wide range of applications and new ones are being consistently added. So far we have successfully adopted protocols for ChIP-Seq, mRNA-Seq, ncRNA-Seq and whole genome/SNP sequencing.

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**Figure:** Illumina Genome Analyzer II

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<sup>1</sup> JOINT APPOINTMENT WITH STEFAN WESTERMANN, IMP

## Absolute Quantification of Proteins and Determination of Protein Complex Stoichiometry

We developed a novel method that permits accurate and cost-effective absolute quantification and determination of the stoichiometry of protein complexes. Using our method, which we call Equimolarity through Equalizer Peptide (EtEP), we verified the 1:1 stoichiometry of the MP1-p14 scaffolding complex with great accuracy and precision. Importantly, EtEP is compatible with state-of-the-art analytical techniques and protein complex isolation methods such as affinity purifications. (Lit. Holzmann et al.)

## iTRAQ-based Relative Quantitation of Proteins

While the demand for mass spectrometry data in biological research has been steadily increasing in recent years, quantitative analysis of proteomic

samples is also used extensively. We developed an iTRAQ (isobaric tags for relative and absolute quantification)-based method for the LTQ-Orbitrap, the instrumentation of choice in most proteomics laboratories, which dramatically increases the number of identified and quantified peptides. Simultaneously, the analytical precision of quantitation was improved significantly.

We reported the evidence obtained from our principal experiments, and applied the method to protein expression profiling experiments in an in vivo cardiovascular disease mouse model. (Lit. Koecher et al.)

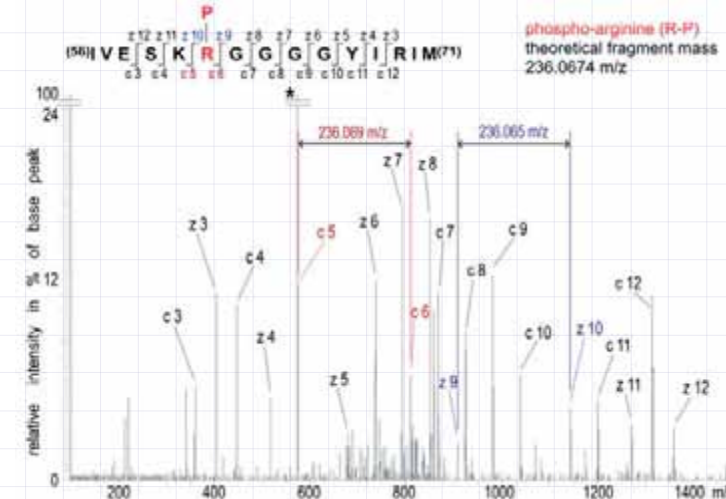
## Detection of Arginine-Phosphorylation

In cooperation with Tim Clausen's group (IMP), we identified a rarely described protein modification using mass spectrometry, namely the N-phosphorylation of arginine. The modified protein, the



bacterial transcription factor CtsR, is impaired in its DNA-binding abilities after phosphorylation. This might be an indication of the importance of arginine phosphorylation for processes that involve protein-DNA binding. We developed a novel enrichment procedure for this chemically labile modification, followed by a

specialized mass spectrometry analysis to potentially identify other arginine-phosphorylated proteins. (Lit. Fuhrmann et al.)



**Figure:** ECD-MS/MS spectrum of the arginine-phosphorylated peptide IVESK(pR)GGGGYIRIM. The mass spectrum exhibits fragment ions for a phosphorylated arginine ( $\Delta M = 236.067$  Da) in both investigated ion series (c- and z- ions).





*The Service Department offers a variety of high-quality rapid services to IMP, IMBA and GMI scientists. Our work mainly consists of DNA sequencing, fly food production, and the preparation of various media and solutions.*

Our Media Kitchen and Fly Food staff prepare substantial quantities of reagent quality solutions and media for cell culture, flies (more than 1,700,000 tubes and bottles per year), and other organisms. The Fly Food facilities are fully accommodated at the new premises within the IMP building. These rooms provide daylight and much more space to create better and more convenient working conditions for preparing fly food and storing all the goods we need. We also prepare selected reagents such as DNA

molecular weight markers, enzymes, a variety of transformation-competent E.coli strains, and maintain a stock of cloning vectors, sequencing primers and other reagents.

### Production of antibodies

The production and isolation of several monoclonal antibodies in hybridomas in collaboration with IMP group members, and organizing antibody production in rabbits with an external company, occupy a part of our work capacity in terms of time.

### Sequencing and DNA isolation

The ABI 3730 DNA Genetic Analyzer with 48 capillaries is the only work horse. The 16 capillaries ABI 3100 Genetic Analyzer is solely used as a

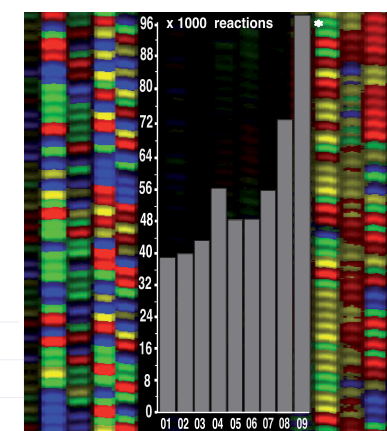
back-up sequencer for emergencies. We sequenced approximately 73,000 samples during the first 9 months of this year. The demand has again increased substantially due to screening projects, the new fly library and new groups at IMBA and IMP plus the GMI, who joined our services this summer. We mainly use the 3730 DNA Analyzer because of its sensitivity and of lower running costs in terms of consumables. The standard read-length is 850-900 bases for good DNA samples. DNA sample quality and concentration, even when prepared with sophisticated Qiagen Kits such as Midi-, Maxi- or Minipreps is a problem. The same is true for inappropriate primer sets or insufficiently documented plasmid constructs from external sources. Sequencing is done faster and more

easily than analyzing the samples by restriction digests or running them on an agarose gel. The clean-up protocol with Sephadex G50 superfine columns on 96-well microtiter plate format with optimized sephadex consistency and centrifugation conditions is now 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 no "dye blobs" arise when DNA samples of good quality are used.

## SERVICE DEPARTMENT

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ANNA WINDHOLZ	HELP FLY FOOD PREPARATION



**Figure:** A sequencing run on an ABI 377 PRISM and numbers of reactions analyzed on ABI 3100 (from 2001 onward) and ABI 3730 (from June 2004 onward) with dye deoxy terminators (v3.0 from 2001 onward) from 2001 to 2009 (scale 0 to 96,000).  
\*calculated from data collected between January 2009 and September 2009

# HISTOLOGY

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

## Histology Services

The histology services include the embedding of tissues, assistance with the sectioning of paraffin and cryo-preserved tissues, and preparation of slides for standard H&E stains, as well as specialized stainings such as PAS, Alcian blue, Cab, Gomeri,

MayGruenwald-Giemsa and van Kossa stains for human, mouse, *Xenopus* and *Drosophila* studies. With these services, we are able to offer support to get quick results.

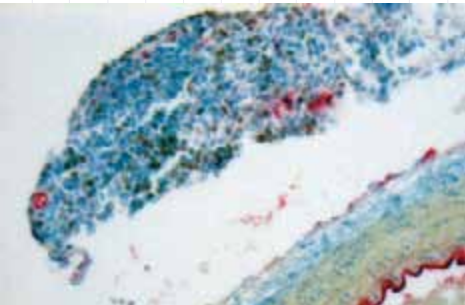
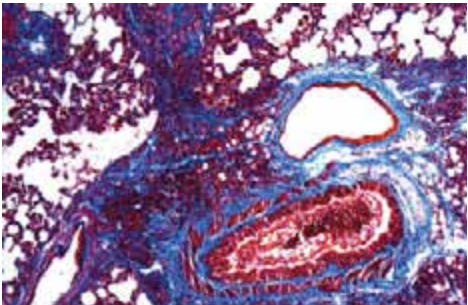
## Sectioning of Paraffin and Frozen Tissues

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

## Immunohistochemistry

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



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

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



## ANIMAL HOUSE

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## MOUSE SERVICE

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

**Figure 2:** Mouse blastocysts.

**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 attendants - provides husbandry of animals and services for the various research groups.*

**Husbandry:**

The largest area of the animal house is the mouse section, which comprises breeding colonies, stock and experimental animals including many

transgenic and knock-out mouse lines. To provide a constant supply of mice for the various projects, commonly used standard strains are routinely bred in-house.

**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.

*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.

## Publications

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13.01.09 W. Judson Hervey, IV  
Oak Ridge National Laboratory, USA  
Evaluation of Affinity-Tagged Protein Expression Strategies using Local and Global Isotope Ratio Measurements

## FEBRUARY

06.02.09 Patrik Rorsman  
Oxford Centre for Diabetes, Endocrinology and Metabolism  
Chronic exposure of beta-cells to lipids inhibit insulin secretion

09.02.09 Torsten Bossing  
School of Biological Sciences, University of Southampton  
Transcriptional changes in single cells reveal a new mechanism for damage repair in the developing CNS

12.02.09 Daniel Finley  
Harvard Medical School  
Regulation of Proteasome Activity

19.02.09 Ivan Dikic  
Goethe University Medical School  
Ubiquitin signaling networks - from structures to functions

20.02.09 Poul Sorensen  
University of British Columbia  
Adventures in cancer signaling from molecular biomarker discovery

26.02.09 Elaine Fuchs  
Howard Hughes Medical Institute, New York  
Stem Cells: The Privileged Few

## MARCH

05.03.09 Thomas Langer  
Universität zu Köln  
AAA proteases, mitochondrial membrane dynamics, and neurodegeneration

06.03.09 Alpha Yap  
Institute for Molecular Bioscience, University of Queensland  
Cadherin-actin cooperativity: adhesion, signaling and the cytoskeleton

13.03.09 Dinshaw J. Patel  
Memorial Sloan-Kettering Cancer Center  
Small RNAs: Mediators of Gene Regulation and Silencing

## APRIL

02.04.09 Matthias Peter  
Institute of Biochemistry, ETH  
Regulation and function of cullin-based E3-ligases

08.04.09 Manuel Mayer  
King's College, University of London  
New insights from an -omic approach to cardiovascular disease

16.04.09 Roland Lill  
Philipps-University, Marburg  
Biogenesis of cellular iron-sulfur proteins: The essential and minimal function of mitochondria.

21.04.09 Pascal Vallotton  
CSIRO Mathematical & Information Sciences  
Differential Aberration Correction (DAC) Microscopy: a New Molecular Ruler

## MAY

05.05.09 Wolfgang Weninger  
Centenary Institute for Cancer Medicine and Cell Biology, Australia  
Visualising immune responses in tumours and infections in real time

07.05.09 Nenad Ban  
ETH Zurich  
Springs, tethers, hinges, latches and switchblades: mechanistic insights into the functioning of large macromolecular assemblies

18.05.09 Yechiel Elkabetz  
Sloan-Kettering Institute  
Human ES Cell Derived Neural Rosettes: The Paradigm of a Universal Neural Stem Cell

28.05.09 Hans Wolf-Watz  
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Virulence factors as drug targets; What can be expected?

## JUNE

04.06.09 Maria Carmo-Fonseca  
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In vivo tools to visualize co-transcriptional RNA processing

18.06.09 Jan Karlseder  
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Telomere dynamics in mammals and nematodes: C. elegans as a cancer model?

25.06.09 Roger Y. Tsien  
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Breeding and building molecules to spy on cells and tumors

29.06.09 Mario Amendola  
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New Lentiviral Vectors for Co-ordinate Transgene Expression and miRNA/siRNA Delivery



## JULY

- 02.07.09 Stephen Baylin  
*The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins*  
Epigenetic Gene Silencing - Embryonic Stem Cells, Induced Pluripotent Stem Cells and Cancer
- 03.07.09 Andrew Alpert  
*PolyLC Inc. Columbia*  
Selective Isolation of Phosphopeptides and Sialylated Glycopeptides by ERLIC
- 16.07.09 Frauke Melchior  
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- 23.07.09 Alex Schier  
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Morphogens and microRNAs in vertebrate embryogenesis

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- 27.08.09 Müzeyyen Sevim  
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Identification of hypoxia-associated proteins in human glioblastoma cell lines with 2D-DIGE and mass spectrometry

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- 03.09.09 Bryan R. Cullen  
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Viruses, microRNAs and RNA interference

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The Unfolded Protein Response in Health and Disease
- 26.11.09 Austin Smith  
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Capturing Pluripotency

## DECEMBER

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*Weizmann Institute*  
Reading the genome: from DNA sequence to expression

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- *Third prize in FameLab finals, Cheltenham, GB (June)*

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- *Research Award of the Sanofi-Aventis Foundation 2009 (December)*

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- *Theodor-Körner-Award, Vienna, Austria (April)*

## Jennifer Mummery-Widmer

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## Josef Penninger

- *2009 ESCI Award for Excellence in Biomedical Investigation by the European Society for Clinical Investigation (April)*
- *Elected to the Academia Europea (Academy of Europe), UK (April)*
- *ASMR Medal 2009 by the Australian Society for Medical Research (June)*



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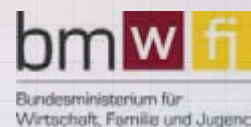
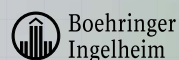
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Oberösterreich Aktiengesellschaft

## IMBA and Its Surroundings

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

### The Campus Vienna Biocenter

IMBA is situated at the "Campus Vienna Biocenter" (VBC), a rapidly growing biotechnology hub located halfway between Vienna's international airport and the city center. Apart from IMBA and its partner institute IMP, the VBC is also home to the Max F. Perutz Laboratories (MFPL; University and Medical University of Vienna), the Gregor Mendel Institute of Molecular Plant Biology (GMI; Austrian Academy of Sciences), a University of Applied Sciences, several biotech companies, a 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 160 scientists and administrative staff.

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

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

If you come to work at IMBA, you'll obviously come in the first place for the science. We do, however, appreciate your private needs and try to make relocation as smooth as possible. For newcomers, there are several in-house apartments to bridge the time until they have found a place of their own. Our administrative staff is helpful in finding housing, and our personnel department

will take care of your legal requirements including visas, registration, health insurance and family matters. For parents with young children, the campus has its own Kindergarten, offering child care from the age of three months and opening hours according to the needs of scientists. For school-age children, Vienna offers a large range of different types of schooling, from public to private, German- or foreign language-speaking, traditional or with more experimental concepts.

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

More information about career opportunities at IMBA is available at: [www.imba.oeaw.ac.at/career](http://www.imba.oeaw.ac.at/career)





### MICROSYMPOSIUM ON SMALL RNAS

The Microsymposium on Small RNA's was held for the fourth time from May 18 to 20, 2009. Established scientists, young group leaders and advanced post-doctoral fellows came to IMBA on this occasion. Once again the highlight was the workshop for PhD students. It served as a forum for very young scientists. The four best lecturers received awards by way of books, pens, and a voucher to attend the next EMBO Meeting in Amsterdam. In addition to basic science, innovative companies working in the field of RNA Silencing and small RNAs presented their work. The organizers welcomed more than 250 attendees from several European countries, the United States, and even India. Vibrant Q&A sessions created a dynamic atmosphere, leaving all attendees pleased and looking forward to the 5th Microsymposium in 2010. <http://www.imba.oeaw.ac.at/microsymposium>

May 09

June 09

July 09

### VBC SUMMER CONCERT

The VBC is fortunate to have music as a part of its cultural program. The solo program of this year's summer concert featured music by Mozart, Debussy and Bach, two Turkish love songs, and readings of poetry.

In the second part of the concert the MolBioOrchestra took center stage. The twenty-piece orchestra featuring students and staff from all over the campus presented an extensive program which included piano concertos by Mozart and Beethoven, "Water Music" by Handel, a waltz composed by the resident pianist Klemens Kunz and, as a final highlight, an arrangement of "Bohemian Rhapsody" by Queen.



### POSTDOC RETREAT

This year's Postdoc Retreat took place from August 18 to 20 in the Salzkammergut region in Upper Austria. An old monastery was chosen as the location: it now hosts the newly founded "International Academy of Traunkirchen". This institution aims to support top-level Austrian research and fosters young scientists who wish to widen their horizons. The scientific highlights included a talk by Anton Zeilinger, the physicist who demonstrated that particles may exist simultaneously in two places at once, thus proving that teleportation was more science than fiction. This was followed by a lesson in science ethics, as virologist Tim Skern from the MFPL presented a detailed political perspective on the HIV/AIDS situation in Africa. Finally, Michael Kiebler from the Medical University of Vienna delivered a talk on neuronal cell biology. The official part of the retreat was followed by a walk along the beautiful Traunsee lake and a visit to the historic salt mines of Hallstatt.



September 09

### VBC PHD RETREAT

This year's PhD Retreat took place from June 4 to 5 in the green hills of Semmering in Lower Austria. The two days were fruitfully spent with talks on science, discussions of careers, strengthening relationships with colleagues, and generally having fun. The absolute highlight of the event was Tony Hyman's brilliant teamwork. Tony Hyman was an invited speaker. The Nobel Prize laureate Tim Hunt joined the retreat spontaneously after delivering a scientific lecture at the VBC the previous day. Together, they shared their experiences with the students and gave them valuable advice. "Choose your mentor wisely", "Work on something you are really interested in" and "Interact with good people" were some of their salient messages. Tim Hunt's talk titled "How to win a Noble Prize" was especially fascinating; he spoke about the scientific and social stepladder that led him to the Nobel Prize.

The next morning was reserved for discussions on how a PhD program could be made more attractive, based on the results of a recent survey conducted among PhD students on the campus. Despite the active program the attendees had time to relax and enjoy the beautiful scenery of Semmering.





## EUROPEAN RESEARCHERS' NIGHT 2009

"Research is art" was the motto of the VBC-ERN which took place on September 25 at the Campus Vienna Biocenter. ERN stands for the "European Researchers' Night" - a multinational public science event sponsored by the European Commission. It consisted of a one-night event offering "edutainment" activities which provided an opportunity for the attendees to improve their knowledge about researchers and research. On the day of the event, approximately 2500 visitors came to witness science in action. More than 100 VBC colleagues gave demonstrations of their current research and lent a helping hand to visitors who were eager to try out an experiment for themselves. From IMP and IMBA, the Dickson and Knoblich Groups and the Histology Unit were represented. Apart from research demonstrations the visitors could enjoy an enactment of DiNA on the Road, take part in the quiz "Spot the Scientist", and play the VBC game. The Walk of Fame ceremony highlighted the merits of the VBC's founding fathers, including the first IMP Director Max Birnstiel who had travelled a long distance from Switzerland to grace the occasion. One of the highlights was the Paint your PhD contest. Fifteen scientists were placed on an impressive scaffolding construction, equipped with paints and brushes, and given one hour to translate the topics of their dissertation into a piece of art. The IMP and IMBA were well represented by Lucia Aronica, Arabella Meixner, Mark Palfreyman (first prize, postdocs), Anne Philipsborn and Ivana Primorac (first prize, students). The paintings were auctioned and the money earned - 3000 Euros in total - was donated to St. Anna Children's Cancer Research Institute (CCRI).



## VBC-PHD SYMPOSIUM "ANDROID AND EVE"

The topic of this year's PhD Symposium from November 12th to 13th was dedicated to the advancing fusion of the human and the computer world. We can no longer envisage our daily lives without the computer. The aim of the symposium was to bring together leading scientists in the fields of neuronal interfaces, artificial organs, nanobiotechnology and biological microdevices. About 190 interested students, 70 off-campus guests from all over Europe, and a large number of journalists took part in this event. The scientific highlights were Carlo Montemagno who gave fascinating insights into his work about bio-machines, Miguel Nicolelis and Andrew Schwartz who explained how the human brain could be connected to computers which move roboter devices, Jackie Ying on smart synthetic materials, and Niels Bierbaumer about his work on stroke and locked-in patients. The most controversial talk was Kevin Warwick's: he presented his vision of the Cyborg world in which all humans will, sooner or later, become Cyborgs by incorporation of microchip implants, as predicted in the film "Matrix".

## October 09

### RECESS

From September 30 to October 2 IMBA scientists met with members of the Scientific Advisory Board (SAB) to present their work and discuss their research. The SAB, consisting of internationally recognized scientists, were once more impressed by the scientific performance and high standards of the research presented. IMBA would like to thank all its SAB members and the representatives of the Austrian Academy of Sciences for their tremendous support. IMBA SAB members: page 51 in this booklet.



### IMBA TRIP TO BRATISLAVA

The IMBA autumn event 2009 on October 5 took the IMBA employees on a boat trip to Bratislava. It was a beautiful autumn day and everyone enjoyed the relaxed and quiet atmosphere on the upper deck. Lunch was taken on board, before arriving at Bratislava, where the program continued with a guided tour through the city. It was an interesting walk and there was a lot to learn about the relationship between Austria, Bratislava and Hungary. The tour also left some time to discover Bratislava. A few colleagues visited the expertly restored buildings while others could not resist the temptation to try the pastry at the oldest coffee house in Bratislava. Another group preferred to go for a traditional meal and yet others climbed up the hill to visit the castle. In the afternoon the boat left for Vienna. The executives of IMBA utilized the return trip for a presentation and an update on plans and targets for the coming year.



## November 09

### IMBA SCIENTIST JÜRGEN KNOBLICH RECEIVES THE WITTGENSTEIN AWARD 2009

The Wittgenstein prize is awarded on behalf of the Federal Ministry for Science and Research and is the most prestigious recognition of excellence in research in Austria. Jürgen Knoblich received the prize for his outstanding contributions in the field of stem cell biology.

The prize consists of 1.4 million Euros and gives Jürgen Knoblich the opportunity to extend his research into new fields. As the first step, the conclusions drawn from investigations on flies will be extrapolated to higher organisms such as mice. In the long term, Jürgen Knoblich plans to ground his work on a system-biology-based approach.



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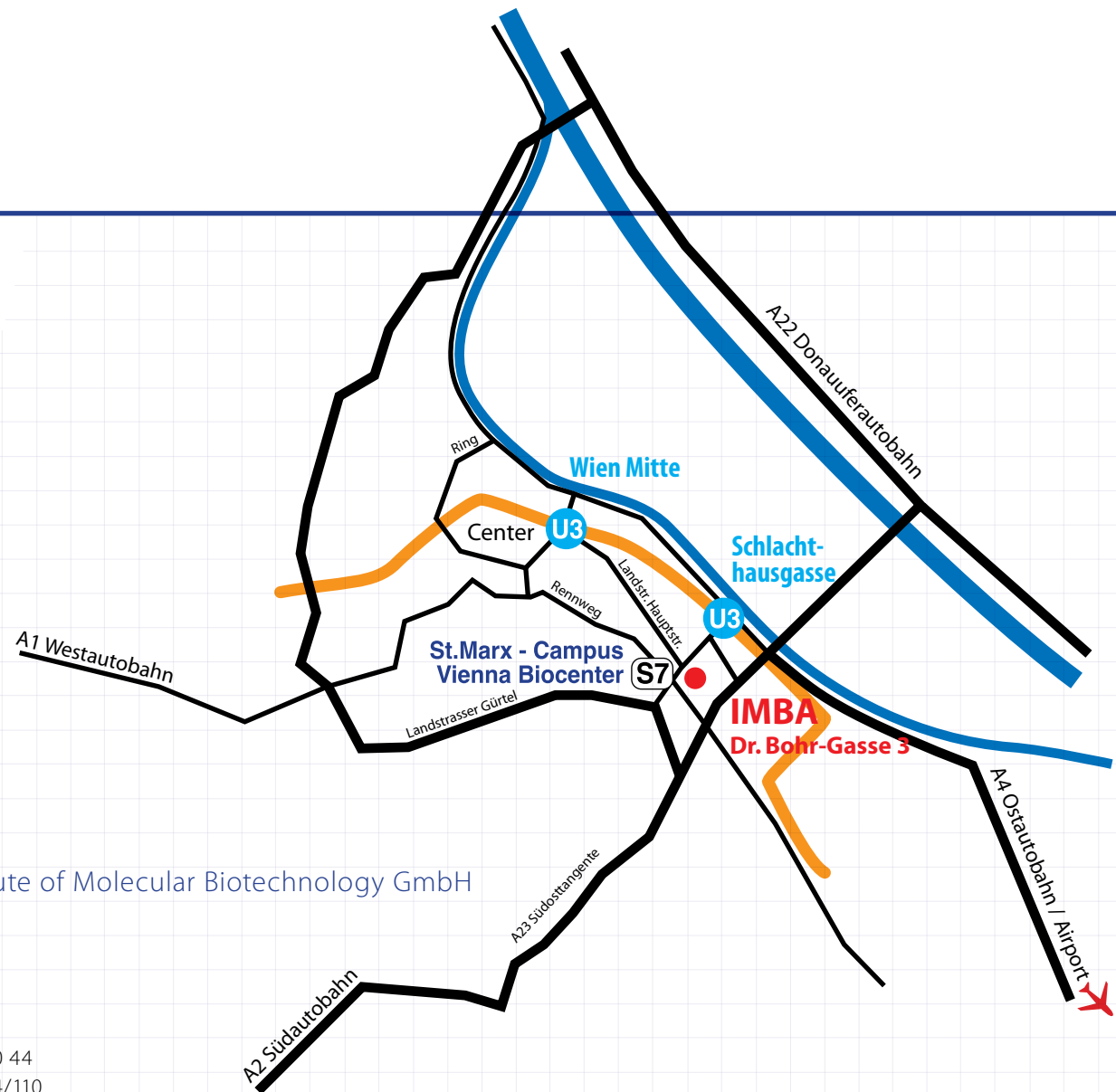
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