INSTITUTE OF MOLECULAR BIOTECHNOLOGY

OF THE AUSTRIAN ACADEMY OF SCIENCES

VIENNA BIOCENTER

2013

IMBA

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Austrian Academy
of Sciences

IMBA
Institute of Molecular Biotechnology
of the Austrian Academy of Sciences


ART &
SCIENCE

CONTENTS

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Introduction

This was a special year for IMBA, we celebrated our 10th anniversary! Many things have happened, with the grand vision to establish a world-class research institute that attracts the brightest minds, provides state-of-the art infrastructures, and allows our scientists to not only think outside the box, but to also make new discoveries happen. We have been able to enter the Champions League of research institutes. We have created a very unique international island for truly innovative research. Yet science is a very long and hard walk, a walk that was a lot of fun and can get even better.

Following a vision of the Academy of Sciences and Boehringer Ingelheim, the first researchers started at IMBA ten years ago. At that time still a virtual institute hosted by our close and trusted partner IMP and the University of Vienna/Medical University of Vienna. From these grounds, we then built and populated our new research center, with new infrastructures, great lab spaces, a very successful Open Lab (run together with Open Science) for kids that has already had more than 30,000 visitors and impressive artwork that even made it into the latest book by Dan Brown. Along the way, IMBA has now grown to nearly 200 people tirelessly working to advance top science.

Over the past 10 years, we have not only seen the birth and growth of IMBA, but the entire Campus Vienna Biocenter - including the IMP, the Gregor Mendel Institute (GMI), the newly inaugurated Max F. Perutz Laboratories (MFPL), the FH Campus Wien and multiple, successful Biotech companies - has developed in ways that nobody could have predicted. Our campus has clearly become one of the premier research arenas in the world, a great place to have IMBA embedded in. Together with the GMI and the IMP we continue to provide state-of-the art infrastructure, which is one of our secrets for continued success.The last years have seen the development of the Campus Support Facility (CSF), which provides new services for the entire campus and beyond. The CSF now also runs the Vienna Drosophila Library, initially developed at IMBA and IMP, and installed the strongest MRI in the world, a 15.2 Tesla MRI for mouse imaging.

At our 10 years celebration, we welcomed the Austrian Federal President Heinz Fischer, the Vice-Chancellor Michael Spindelegger, the Minister of Science Karlheinz Töchterle, the former Chancellor Wolfgang Schüssel, many Heads of Universities and funding agencies, representatives of Boehringer Ingelheim, the President and members of the Austrian Academy of Sciences, many other prominent persons of the public and scientific arena and friends and family of IMBA. We apologize for naming not all of you, who helped us over the years with financial support and advice. A special "Thank You" must go to our mother, the Academy of Sciences, who always supported us, even in difficult times.

The keynote speech was held by the world-famous Tenor José Carreras, who just flew to Vienna for our event to make a strong case on the importance of science and innovation for the wealth of a nation and the personal lives of all human beings. We also organized a scientific meeting "Thinking the Unthinkable – the Future of Biology" with a stellar list of speakers including, just to name one, Nobel-Prize winner Sir John Gurdon. And of course, we had some great parties! A big "Thank You" to everybody who made it all happen!

During the last year, IMBA researchers have continued to make discoveries that indeed break new grounds. These discoveries and the individual research groups are represented in our special "10 Years-Anniversary" issue of the annual report. The most stunning achievement, among other significant discoveries, was certainly the creation of the first ever human brain organoids, so called mini-brains, in the laboratory of Jürgen Knoblich, a stunning feast of combining bioreactors and human stem cell technologies. This paper also gained tremendous international interest in virtually all major media.

Four IMBA group leaders received ERC grants: Josef Penninger received his second ERC Advanced grant, Fumiyo Ikeda received an ERC Consolidator grant, and Kikue Tachibana-Konwalski and Stefan Ameres each received an ERC Starting grant. Stefan Ameres also received a START award from the FWF. Many other young group leaders at the IMP and the MFPL also received ERC grants, making our Campus one the prime sites of life science research in Austria and Europe.

We also welcome Oliver Bell, who joined IMBA as a young group leader from Stanford University, bringing with him a cutting edge technology to directly visualize and label epigenetic inheritance throughout the cell cycle. Oliver was also one of three recipients of a New Frontier Award, a new granting scheme by the Austrian Academy of Sciences to bring top talents to Academy Institutes. Moreover, after extensive external evaluation and following a recommendation of our Scientific Advisory Board, we offered Julius Brennecke a position as Senior Scientist, to nucleate research in RNA biology, which he – we are happy to report – accepted. IMBA has now four Senior Scientists: Josef Penninger, Jürgen Knoblich, Daniel Gerlich, and Julius Brennecke. Thus, we have been able to continue developing the IMBA further and bring and tie top talents to the institute.

Vic Small, currently also Senior Scientist at IMBA, will retire at the end of 2013. In a top scientific meeting and a party to celebrate his life and scientific achievement, he was graduated from finding actin comets for Baculoviruses and bacteria using microscopy. Vic has made multiple groundbreaking contributions to cytoskeletal research and, together with Thomas Marlovits, contributed enormously to develop our Cryo-EM facility, the only facility of its kind in Austria. We will miss Vic – as a scientist and trusted advisor!

Unfortunately we also have to say Goodbye to Thomas Marlovits, who had a joint IMBA/IMP appointment, and has now taken up the directorship at a newly established Institute for Structural Biology in Hamburg. Thomas and his group will remain in part at our institute for the next three years. It is certainly great to see that our young faculty members have garnered such an international standing that they move on to top international directorships! We also have to say "goodbye" to Barry Dickson and Kristyna Keleman, both of who moved to the Howard Hughes Janelia Farm. Barry and Krystina initially worked at IMBA, from where Barry then took directorship of our neighbouring institute, the IMP. Barry Dickson is a tremendous scientist who has markedly contributed to the success of the IMP and our entire campus. We wish Barry, Krystina, and Thomas all the best for the future. They will certainly continue to do groundbreaking research. And finally we want to welcome Jan-Michael Peters as the new IMP director. His appointment is a great choice made by Boehringer Ingelheim and we are looking forward to a very fruitful future.

To finish with the words of José Carreras: *"Science has unlocked the deepest secrets of life, and based on these secrets we have entirely new medicines at our disposal, medicines that have saved the lives of millions, medicines that have benefited all of us. We live in a world that can and must be improved, however modern knowledge and insights have already contributed to a world that was unthinkable in previous generations. IMBA, the institute we celebrate today, has become one of the temples of modern sciences, a world-class orchestra where the best and brightest have come together to unlock the mysteries of our world."*

The first 10 years were great. All of this could only happen because of the absolutely amazing people who have worked and currently work at IMBA! The next might be even better!

Jürgen Knoblich, Michael Krebs, Josef Penninger

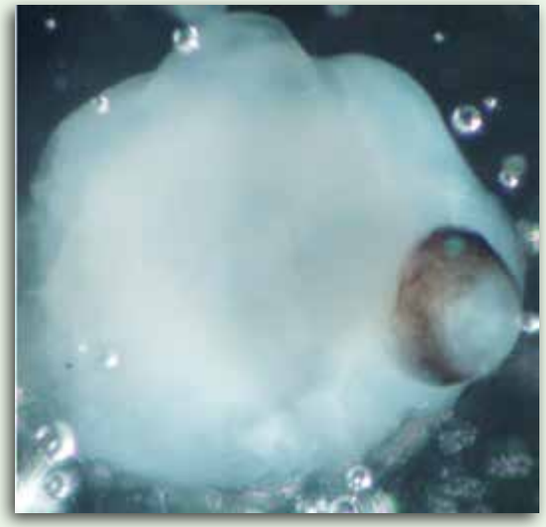
RESEARCH HIGHLIGHTS

2013 has been scientifically a successful year for IMBA. This double page shows IMBA's "Research Highlights", a selection of highly visible research articles IMBA scientists have published during this year.

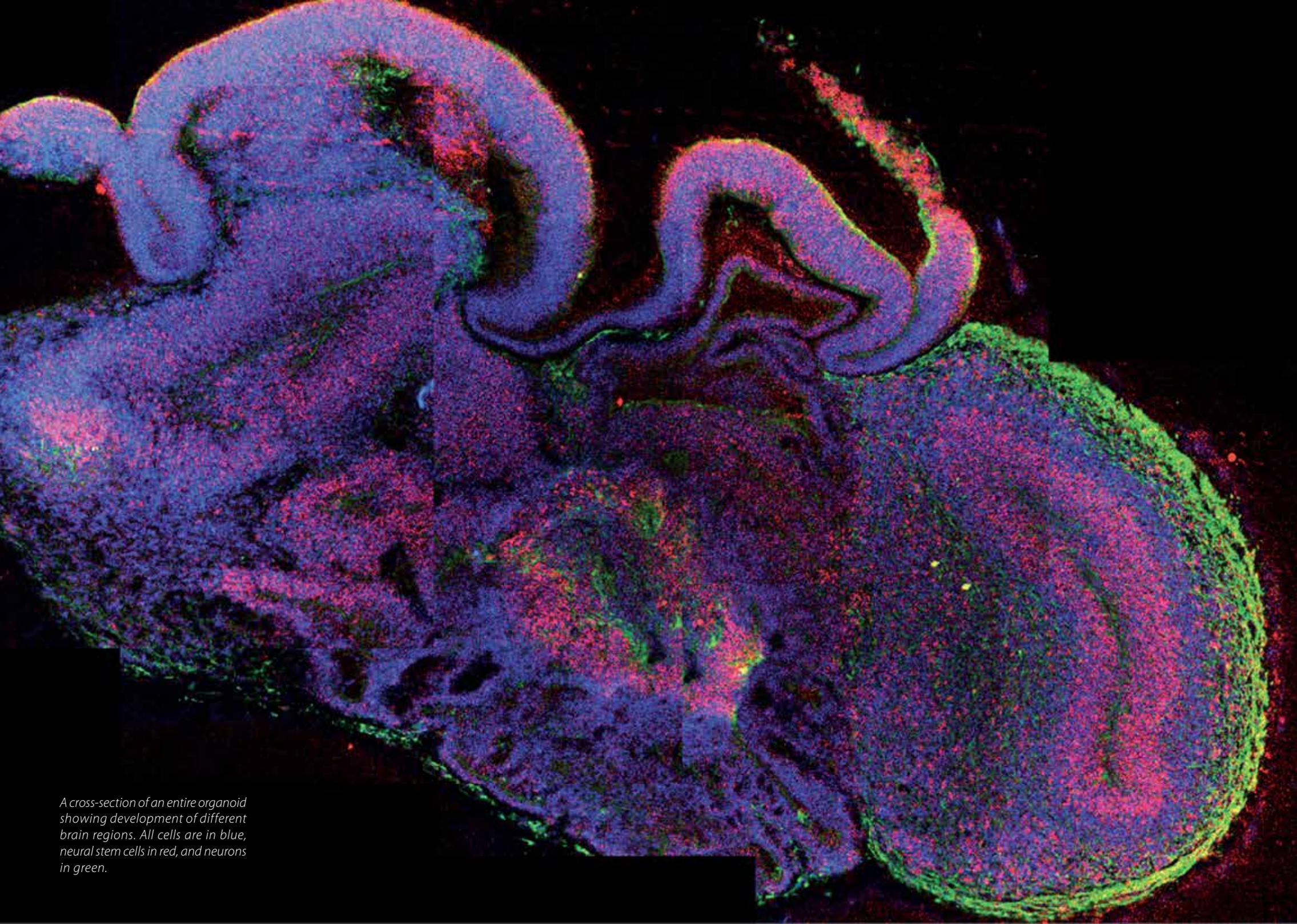
Cerebral organoids model human brain development and microcephaly

Lancaster MA, Renner M, Martin C-A, Wenzel D, Bicknell LS, Hurles ME, Homfray T, Penninger JM, Jackson AP, Knoblich JA. Nature 2013 Sep 19;501(7467):373-379

The complexity of the human brain has made it difficult to study many brain disorders in model organisms, highlighting the need for an in vitro model of human brain development. We have developed a human pluripotent stem cell-derived three-dimensional organoid culture system, termed cerebral organoids, that develop various discrete, although interdependent, brain regions. These include a cerebral cortex containing progenitor populations that organize and produce mature cortical neuron subtypes. Furthermore, cerebral organoids are shown to recapitulate features of human cortical development, namely characteristic progenitor zone organization with abundant outer radial glial stem cells. Finally, we used RNA interference and patient-specific induced pluripotent stem cells to model microcephaly, a disorder that has been difficult to recapitulate in mice. We demonstrate premature neuronal differentiation in patient organoids, a defect that could help to explain the disease phenotype. Together, these data show that three-dimensional organoids can recapitulate development and disease even in this most complex human tissue.



Brightfield image of a whole organoid showing brain tissue with an adjacent region containing retinal identity, part of the developing eye, which contains retinal pigmented epithelium (the brown circular pigmented region)

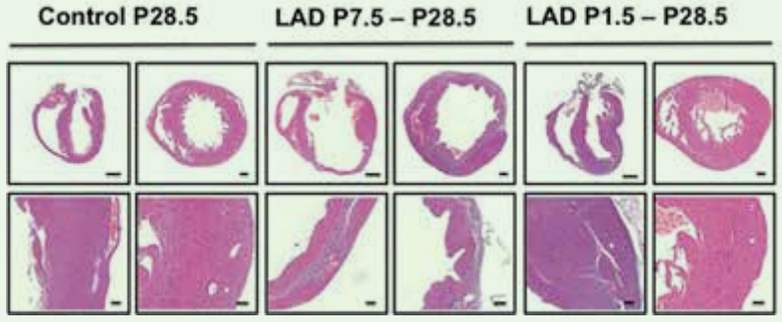


A cross-section of an entire organoid showing development of different brain regions. All cells are in blue, neural stem cells in red, and neurons in green.

Complete cardiac regeneration in a mouse model of myocardial infarction

Haubner, BJ., Adamowicz-Brice, M., Khadayate, S., Tiefenthaler, V., Metzler, B., Aitman, T., Penninger, JM. Aging (Albany NY) 2012 Dec;4(12):966-977

Cardiac remodeling and subsequent heart failure remain critical issues after myocardial infarction despite improved treatment and reperfusion strategies. Recently, complete cardiac regeneration has been demonstrated in fish and newborn mice following resection of the cardiac apex. However, it remained entirely unclear whether the mammalian heart can also completely regenerate following a complex cardiac ischemic injury. We established a protocol to induce a severe heart attack in one-day-old mice using left anterior descending artery (LAD) ligation. LAD ligation triggered substantial cardiac injury in the left ventricle defined by Caspase 3 activation and massive cell death. Ischemia-induced cardiomyocyte death was also visible on day 4 after LAD ligation. Remarkably, 7 days after the initial ischemic insult, we observed complete cardiac regeneration without any signs of tissue damage or scarring. This tissue regeneration translated into long-term normal heart functions as assessed by echocardiography. In contrast, LAD ligations in 7-day-old mice resulted in extensive scarring comparable to adult mice, indicating that the regenerative capacity for complete cardiac healing after heart attacks can be traced to the first week after birth. This novel model system provides the unique opportunity to uncover molecular and cellular pathways that can induce cardiac regeneration after ischemic injury, findings that one day could be translated to human heart attack patients.

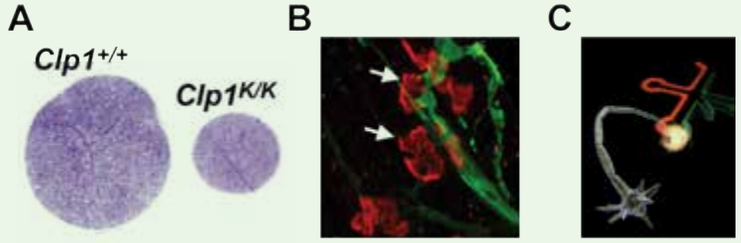


Neonatal myocardial infarction is regenerated after 21 days. This regenerative capacity is lost within the first week after birth.

CLP1 links tRNA metabolism to progressive motor-neuron loss

Hanada T, Weitzer S, Mair B, Bernreuther C, Wainger BJ, Ichida J, Hanada R, Orthofer M, Cronin SJ, Komnenovic V, Minis A, Sato F, Mimata H, Yoshimura A, Tamir I, Rainer J, Kofler R, Yaron A, Eggan KC, Woolf CJ, Glatzel M, Herbst R, Martinez J, Penninger JM. Nature 2013 Mar 28;495(7442):474-480

CLP1 was the first mammalian RNA kinase to be identified. However, determining its *in vivo* function has been elusive. We generated kinase-dead *Clp1* (*Clp1*$^{K/K}$) mice that show a progressive loss of spinal motor neurons associated with axonal degeneration in the peripheral nerves and denervation of neuromuscular junctions, resulting in impaired motor function, muscle weakness, paralysis and fatal respiratory failure. Transgenic rescue experiments show that CLP1 functions in motor neurons. Mechanistically, loss of CLP1 activity results in accumulation of a novel set of small RNA fragments, derived from aberrant processing of tyrosine pre-transfer RNA. These tRNA fragments sensitize cells to oxidative-stress-induced p53 activation and p53-dependent cell death. Genetic inactivation of p53 rescues *Clp1*$^{K/K}$ mice from the motor neuron loss, muscle denervation and respiratory failure. Our experiments uncover a mechanistic link between tRNA processing, formation of a new RNA species and progressive loss of lower motor neurons regulated by p53.

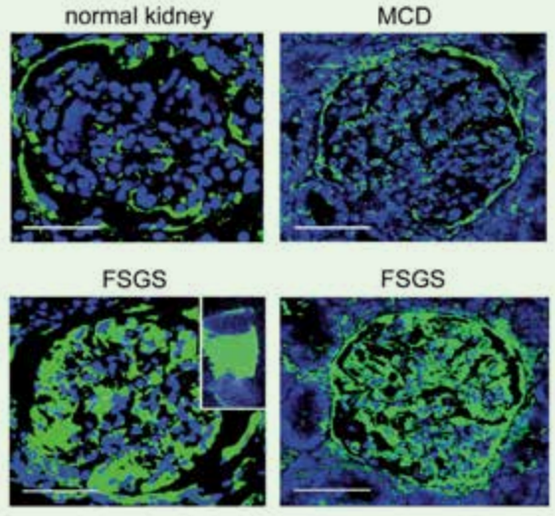


Clp1$^{K/K}$ *mice show axonopathy of peripheral nerves such as the sciatic nerve (cross-section, Figure A), and denervation and fragmentation (arrows) of neuromuscular junctions (Figure B, stained in red), resulting in a progressive loss of motor functions. Figure C: Artistic illustration showing tRNA fragments "hitting" a neuronal cell in Clp1*$^{K/K}$ *mice.*

Focal segmental glomerulosclerosis is induced by microRNA-193a and its downregulation of WT1

Gebeshuber CA, Kornauth C, Dong L, Sierig R, Seibler J, Reiss M, Tauber S, Bilban M, Wang S, Kain R, Böhmig GA, Moeller MJ, Gröne H-J, Englert C, Martinez J, Kerjaschki D. Nature Medicine 2013 Apr;19(4):481-487

Focal segmental glomerulosclerosis (FSGS) is a frequent and severe glomerular disease characterized by destabilization of podocyte foot processes. We report that transgenic expression of the microRNA miR-193a in mice rapidly induces FSGS with extensive podocyte foot process effacement. Mechanistically, miR-193a inhibits the expression of the Wilms' tumor protein WT1, a transcription factor and master regulator of podocyte differentiation and homeostasis. Decreased expression levels of WT1 lead to downregulation of its target genes PODXL (podocalyxin) and NPHS1 (nephrin), as well as several other genes crucial for the architecture of podocytes, initiating a catastrophic collapse of the entire podocyte-stabilizing system. We found upregulation of miR-193a in isolated glomeruli from individuals with FSGS compared to normal kidneys or individuals with other glomerular diseases. Thus, upregulation of miR-193a provides a new pathogenic mechanism for FSGS and is a potential therapeutic target.

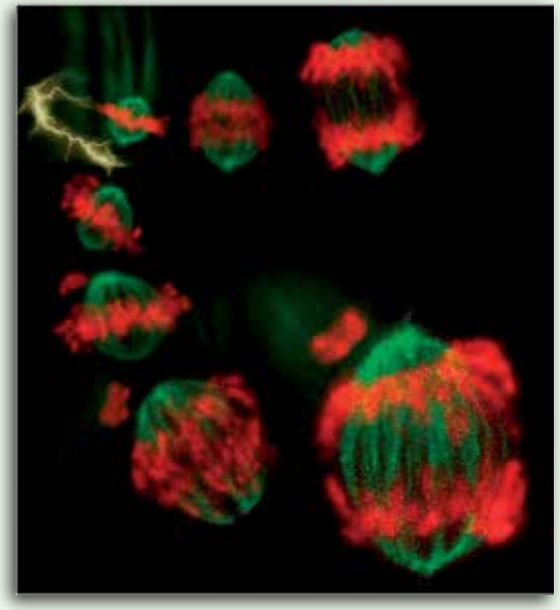


This picture shows kidney glomeruli, the area of the primary blood filtration. The green staining represents miRNA-193a, which is strongly expressed in FSGS patients, but not in the kidney glomeruli of a healthy individual or kidney glomeruli of patients with MCD (minimal change disease, a disease similar to FSGS, but less severe).

Kinetic framework of spindle assembly checkpoint signalling

Dick AE, Gerlich DW. Nature Cell Biology 2013 Nov; 15(11):1370-715:1370–1377.

The mitotic spindle assembly checkpoint (SAC) delays anaphase onset until all chromosomes have attached to both spindle poles. Here, we investigated SAC signalling kinetics in response to acute detachment of individual chromosomes using laser microsurgery. Most detached chromosomes delayed anaphase until they had realigned to the metaphase plate. A substantial fraction of cells, however, entered anaphase in the presence of unaligned chromosomes. We identify two mechanisms by which cells can bypass the SAC: first, single unattached chromosomes inhibit the anaphase-promoting complex/cyclosome (APC/C) less efficiently than a full complement of unattached chromosomes; second, because of the relatively slow kinetics of re-imposing APC/C inhibition during metaphase, cells were unresponsive to chromosome detachment up to several minutes before anaphase onset. Our study defines when cells irreversibly commit to enter anaphase and shows that the SAC signal strength correlates with the number of unattached chromosomes. Detailed knowledge about SAC signalling kinetics is important for understanding the emergence of aneuploidy and the response of cancer cells to chemotherapeutics targeting the mitotic spindle.



Chromosome detachment from the metaphase spindle by laser microsurgery in human HeLa cells. Spindle microtubules and chromatin are visualized by a green and red fluorescent proteins, respectively. The upper path illustrates correct chromosome segregation. The lower path shows chromosome segregation despite the presence of a laser-detached chromosome (illustrated by lightening).

STEFAN AMERES GROUP

Mechanism and biology of RNA silencing in flies and mammals

www.imba.oeaw.ac.at/research/stefan-ameres/

Small silencing RNAs regulate gene expression in nearly all eukaryotes and have enormous biotechnological and therapeutic potential. MicroRNAs belong to the largest family of trans-acting gene regulatory molecules in multicellular organisms. In flies and mammals, they control more than a half of the protein-coding transcriptome, and act as key regulators of organismal development, physiology, and disease. We are interested in understanding the molecular mechanisms that govern small RNA-mediated gene silencing in flies and mammals.

We aim to dissect the molecular processes that regulate the production of small RNAs, their assembly into ribonucleoprotein complexes, and their sequence-specific decay. Our goal is to define the principles that establish and maintain small RNA profiles in a given tissue or cell type in order to understand the molecular mechanisms that regulate miRNA homeostasis. To do so we utilize a combination of *Drosophila* genetics and biochemistry, as well as RNomics. The hypotheses emerging from our studies in flies are directly tested for their conservation in mammals.

Exonucleolytic microRNA maturation

MicroRNAs (miRNAs) are produced from longer hairpin-containing RNA transcripts by the RNase III enzymes Drosha and/or Dicer. The resulting 21-24 nt mature miRNAs are then loaded into an Argonaute protein - the core protein component of the RNA-induced silencing complex (RISC) - to silence mRNAs with complementary sequences. We recently found that more than a quarter of all miRNAs in *Drosophila* undergo 3´ end processing after their production by Dicer, a process that is mediated by the 3´ to 5´ exoribonuclease Nibbler (Figure 1). miRNA 3´ end processing occurs after loading of the small RNAs into RISC, and may be the final step in RISC assembly. Nibbler is required for normal fly development. Molecular signatures in small RNA deep sequencing libraries indicate that the process is conserved in mammals. We are currently testing our hypothesis that Nibbler converts miRNAs into isoforms that are compatible with the preferred length of small RNAs within functional RISC complexes.

Target RNA-directed small RNA decay

Small RNAs guide Argonaute proteins to complementary sequences within mRNAs. In animals, miRNAs typically show just partial complementarity to the targets they regulate. We recently showed that high complementarity between miRNAs and their targets causes small RNAs to decay. This occurs in a process that involves the addition of non-templated nucleotides to the 3´ end of small RNAs (tailing) and their 3´ to 5´ exonucleolytic degradation (trimming) (Figure 2). We aim to characterize the molecular details of this novel miRNA decay pathway, identify its enzymatic components, and determine the biological function of the pathway. Our hypothesis is that mRNAs not only serve as targets for miRNA-mediated gene regulation, but also influence the abundance, and therefore the function of miRNAs themselves.

Therapeutic miRNA inhibition

The sequence-specific decay of miRNAs harbors considerable therapeutic potential. For example, the inhibition of miR-122 – a liver-specific regulator of lipid metabolism – results in a decrease in serum cholesterol levels and interferes with replication of the hepatitis C virus (HCV). We recently developed a novel approach for efficient long-term inhibition of miRNA function *in vivo* in mice. The expression of tough decoy RNAs (TuDs, Fig. 3) – structured RNA polymerase III transcripts with accessible, highly complementary miRNA target sites – efficiently triggers miRNA decay by inducing the tailing and trimming pathway in cultured human cells and *in vivo* in mice, after recombinant adeno-associated virus (rAAV) vector delivery. rAAV-mediated miRNA inhibition provides a simple way to study miRNA function in adult mammals and may serve as a therapy for dyslipidemia and other miRNA-related human diseases.

Publication highlights:

Ameres, S.L. and Zamore, P.D., Diversifying microRNA sequence and function. Nat Rev Mol Cell Biol., 2013, 14(8):475-88, doi: 10.1038/nrm3611

Figure 1

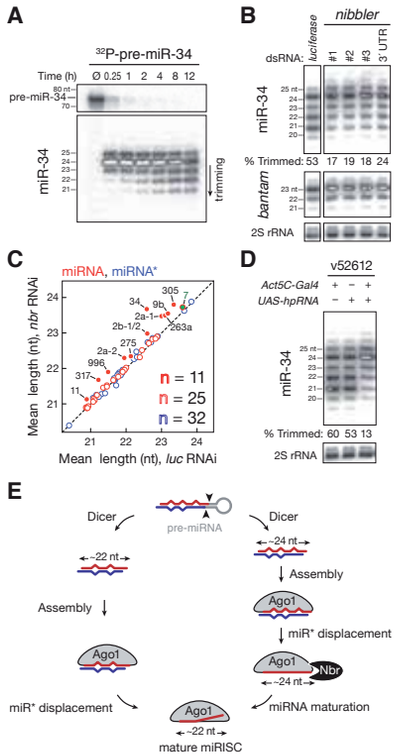


Figure 2

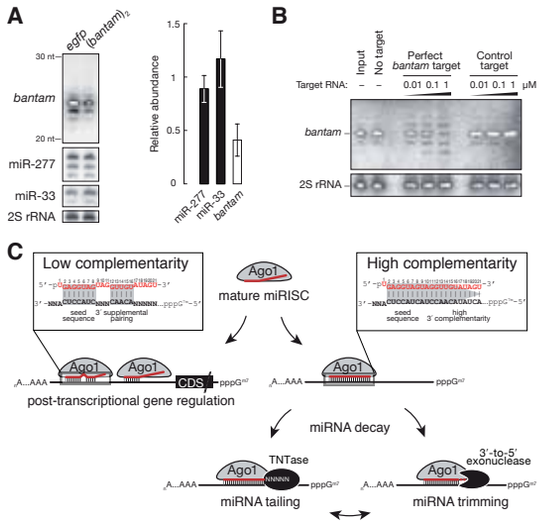
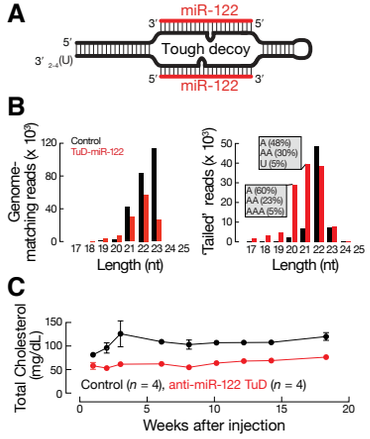


Figure 3



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RESEARCH TECHNICIAN: SARA FARIÑA-LÓPEZ

Figure 1: Exonucleolytic maturation of microRNAs. (A) Incubation of 5′ ^{32}P-radiolabeled pre-miR-34 in *Drosophila* embryo lysate results in exonucleolytic maturation of the mature miR-34 after its production by Dicer-1. (B) The 3′-to-5′ exoribonuclease Nibbler trims miRNAs. Depletion of the Nibbler in *Drosophila* S2 cells by RNA interference results in the accumulation of longer 24-nucleotide miR-34 isoforms. miR-34, *bantam* and 2S rRNA were detected by Northern hybridization. (C) More than 25% of all miRNAs in S2 cells are subjected to Nibbler-meditated trimming. The mean length of miRNAs (red) and miRNA*s (blue) in small RNA libraries generated from S2 cells after treatment with double-stranded (ds) RNA to deplete Nibbler (y-axis) or control dsRNA (luciferase, luc, x-axis). miRNAs that increase in length after depletion of Nibbler are highlighted. (D) Gal4-directed expression of a hairpin RNA (hp-RNA) targeting Nibbler *in vivo* in flies results in the inhibition of miR-34 trimming. (E) Model for Nibbler-mediated miRNA maturation. A fraction of non-canonical *Drosophila* miRNAs are generated as long ~24-nt miRNAs and require exonucleolytic trimming by Nibbler (Nbr) to form an active silencing complex.

Figure 2: Target RNA-directed microRNA decay. (A) Northern analysis of total RNA from a clonal S2 cell line expressing *egfp* mRNA, bearing in its 3′ UTR two target sites for bantam [(bantam)$_2$] and a clonal control cell line expressing sole *egfp* mRNA. Mean ± standard deviation for three biologically independent replicates of the experiment is shown (right). (B) Endogenous *bantam* miRNA was tailed and trimmed when *Drosophila* embryo extract was incubated overnight with a fully complementary target RNA, but not a control target. *bantam* and 2S rRNA were detected by Northern blotting. (C) Model for target RNA-directed tailing and trimming of miRNAs in flies. Binding of miRNAs to perfectly complementary target mRNA results in the exonucleolytic trimming and non-templated nucleotide addition (tailing) of the miRNA. miRNA tailing and trimming ultimately results in small RNA decay. The protein components of the tailing and trimming pathway are currently unknown. In contrast, miRNA binding to targets with low complementarity results in post-transcriptional gene silencing.

Figure 3: Therapeutic miRNA inhibition. (A) Tough decoy RNAs are structured RNA polymerase III transcripts containing accessible sites highly complementary to miRNAs. (B) Size distribution of genome matching and 'tailed' miR-122 reads in the liver of mice injected with AAV control (black) or AAV expressing a tough decoy RNA targeting miR-122 (red). (C) Total serum cholesterol levels of mice injected with AAV control (black) or AAV expressing a tough decoy RNA targeting miR-122 (red).

OLIVER BELL GROUP

Plasticity and Memory of Chromatin Structure

www.imba.oeaw.ac.at/research/oliver-bell/

Epigenetic mechanisms are of critical importance for the faithful transmission of gene expression states through cell division, and for the maintenance of cellular identities from one generation to the next. These mechanisms also need to support the plasticity of gene expression to facilitate the acquisition of new cell fates in animal development. Chromatin modifications have emerged as important regulators of transcription, and are believed to contribute to the inheritance of gene expression states.

Research activities

We investigate the dynamics and epigenetic inheritance of nucleosome modifications in the context of physiological chromatin structure in living cells. Chromatin is undergoing constant remodeling to facilitate changes in gene expression and DNA accessibility in response to cell-intrinsic and cell-extrinsic stimuli. Specifically, the antagonizing activities of histone modifying complexes add and remove post-translational histone modifications, contributing to the dynamic organization of chromatin at regulatory regions in the mammalian genome.

Traditional genetic and biochemical analyses have yielded a largely static picture of chromatin regulation. These approaches have failed to provide a comprehensive understanding of the actual function of chromatin modifications in gene regulation. Thus, separating cause from consequence will require approaches that delineate the sequence of events involved in gene induction or repression.

Chromatin *in vivo* assay (CiA)

We employ a novel technique using chemical inducers of proximity to dissect the sequence of events and measure histone modification kinetics at high resolution during cell-fate transitions, cellular reprogramming, and signal-dependent gene regulation. This technology integrates the complex nature of chromatin with precise biochemical analysis of the sequence of events during chromatin remodeling. We have generated a murine strain that permits rapid addition and removal of chromatin regulatory activities to a genetically modified Oct4 allele in any cell type using small-molecule-mediated recruitment (Figure 1). Chemically induced proximity (CIP) provides high temporal control, permitting the examination of the kinetics and epigenetic memory of histone modifications in single cell resolution.

Dynamics and memory of heterochromatin

In embryonic stem (ES) cells, Oct4 expression is essential for pluripotency and self-renewal. Upon differentiation, Oct4 is silenced. This involves the HP1 heterochromatin pathway (with H3K9 trimethylation) and the Polycomb pathway (with H3K27 trimethylation). Previously, we have investigated the kinetics of heterochromatin formation by recruiting HP1α to the modified Oct4 promoter in ES cells and fibroblasts. Tethering of HP1α induced gene repression and the formation of heterochromatic domains of up to 10kb. Measuring H3K9me3 changes after HP1α recruitment permitted the description of *in vivo* rates of heterochromatin spread in ES cells and fibroblasts. In addition, after HP1α removal we tested epigenetic properties and found that H3K9me3 can be faithfully transmitted through cell divisions (Figure 2). Yet, we also showed that the memory and spreading of H3K9me3 may be antagonized by transcriptional activators, indicating the high plasticity of chromatin regulation. Based on the balance between the antagonizing activities of H3K9me3 addition and removal, we proposed a mathematical model, which accurately expresses our empirical observation at the Oct4 locus and also predicts the dynamics of heterochromatin formation and turnover at the majority of facultative H3K9me3 domains in the mammalian genome.

The CiA system is a powerful approach to study the kinetic regulation of any chromatin modifying activity in any murine cell type, and obtaining quantitative models for testing.

Figure 1

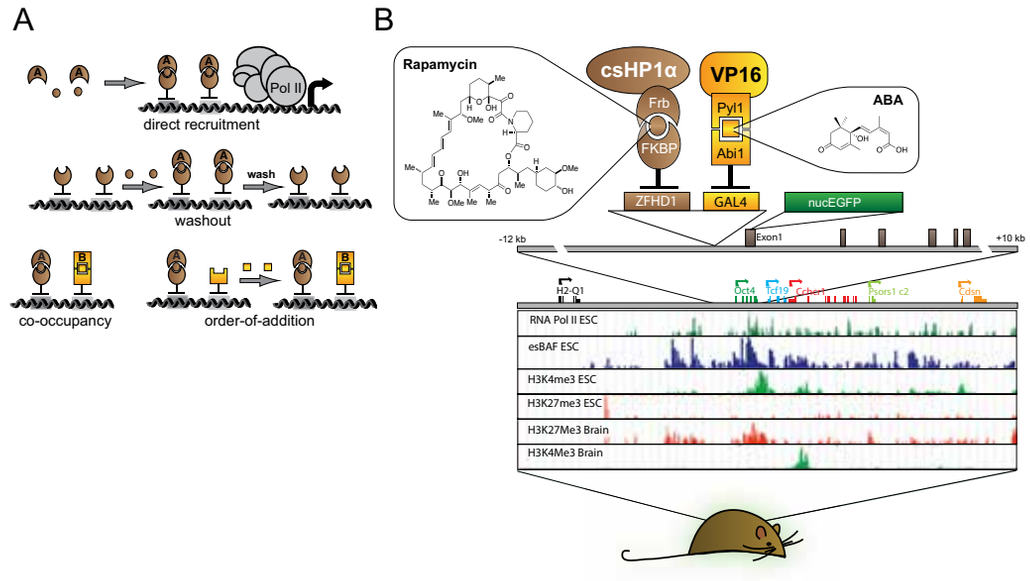
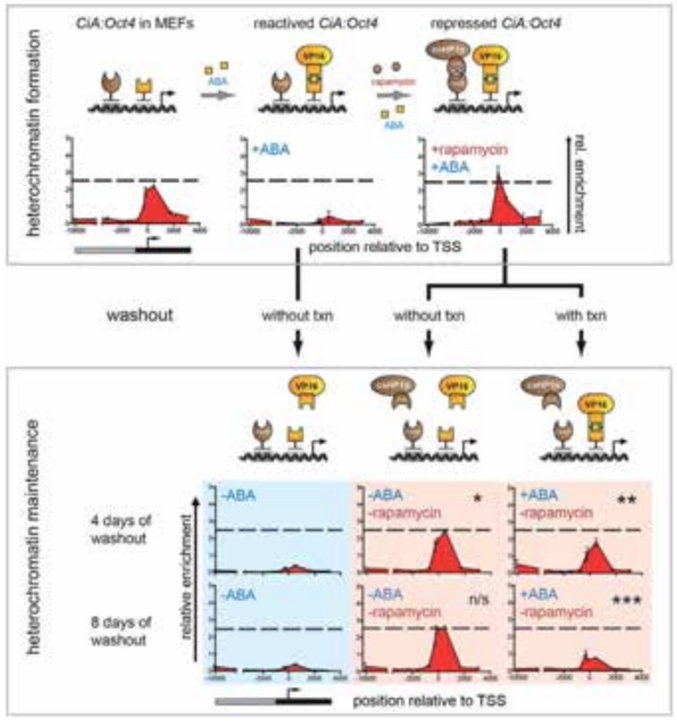


Figure 2



GROUP LEADER:
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PHD STUDENTS: ALEKSANDRA ARCZEWSKA, JORGE ARTURO ZEPEDA MARTINEZ
RESEARCH ASSISTANT: KATARINA BARTALSKA

Figure 1: Schematic diagram of the chromatin *in vivo* assay (CiA) system. The addition of small molecules mediates reversible recruitment of desired chromatin activities to modulate the local chromatin structure and gene expression of any murine cell type.

Figure 2: Initiation and maintenance of heterochromatin. Induced recruitment of HP1a leads to the formation of an H3K9me3 island, which is inherited through cell divisions. Targeting of the transcriptional activator VP16 antagonizes the epigenetic maintenance of heterochromatin.

JULIUS BRENNECKE GROUP

Genetics and genomics of transposon control by small RNAs

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

Throughout the eukaryotic lineage, small RNA silencing pathways safeguard the genome against selfish genetic elements such as transposons. In animals, a specialized pathway centered on PIWI proteins and their interacting piRNAs silences transposons within the gonads. Genetic and bioinformatics studies have uncovered the fascinating conceptual framework of the piRNA pathway, which is conserved from invertebrates to mammals. Our group systematically studies the piRNA pathway in respect to its molecular architecture as well as its biological functions in Drosophila.

The importance of silencing selfish genetic elements

Eukaryotic genomes contain numerous types of selfish genetic elements. Among these, the most widespread members belong to the class of mobile elements known as transposons. As an example, close to 50% of the human genome consists of transposons and their sequence remnants. The remarkable success of these "genome parasites" is based on their ability to multiply within the genome by transposition to new sites. This leads to widespread defects ranging from insertional mutagenesis to ectopic chromosomal recombination, ultimately reducing the long-term fitness of the host. The acute threat posed by transposable elements has triggered the evolution of powerful defense- systems in eukaryotes. Although early genetic studies pointed to the existence of such host defense systems, their molecular nature remained unknown for a long time. After the discovery of RNA interference (RNAi) in 1998, however, it became increasingly evident that small RNA pathways are at the root of the eukaryotic answer to the transposon challenge.

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

The piRNA pathway is an evolutionarily conserved small RNA silencing pathway acting in animal gonads. It is the central genome surveillance system that suppresses the activity of transposons. Over the last 5-10 years a conceptual framework for this pathway emerged: The genome stores transposon sequences in defined heterochromatic loci known as piRNA clusters. These provide the RNA substrates for the biogenesis of 23-29 nt long piRNAs. Within germline cells, an intricate amplification cycle steers piRNA production predominantly to those cluster regions that are complementary to transposons being active at a given time. Finally, piRNAs guide a protein complex centered on PIWI proteins to complementary transposon RNAs in the cell, leading to their silencing (Figure 1A, B).

In stark contrast to other RNAi pathways, the mechanistic framework of the piRNA pathway is largely unknown. We are just beginning to understand processes such as piRNA biogenesis or PIWI-mediated silencing. Moreover, the spectrum of biological processes influenced by the piRNA pathway is poorly understood. piRNAs are not only derived from transposon sequences, but also from various other genomic repeats that are enriched at telomeres or within heterochromatin. The presence of repetitive sequences throughout the genome is probably being used to control vital aspects of chromosome biology. It would not be very surprising if the piRNA pathway were also a key player in this rather mutual relationship between genome and transposons.

To study this fascinating genome surveillance system, we use *Drosophila melanogaster* as a model system. For most projects we combine genetics, biochemistry, cell biology and bioinformatics. The main areas of our work are the following:

1. Identifying and characterizing novel piRNA pathway members: We have established robust RNAi conditions for both, the somatic ovarian cells where a simplified piRNA pathway is active, as well as for germline cells in which many piRNA pathway factors act in a specific manner (Figure 1, 2). Using these *in vivo* RNAi systems, we performed genome-wide screens and identified several novel piRNA pathway genes in *Drosophila*. Their genetic and molecular characterization promises to yield a better understanding of all levels of this pathway from piRNA cluster biology to piRNA biogenesis and piRNA-mediated silencing.

2. Dissecting Piwi-mediated transcriptional silencing: Of the three *Drosophila* PIWI family proteins, Piwi is the only nuclear protein. Recent work has shown that Piwi is guided to nascent transposon RNAs and orchestrates highly effective transcriptional silencing, accompanied by the formation of heterochromatin. We are actively investigating the genetic and molecular basis of this process.

3. Understanding the biology of piRNA clusters: piRNA clusters are at the heart of the pathway because they serve as sequence repositories for transposons. They 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 transcription, specification, export and processing of piRNA clusters or their transcripts. Ultimately, we wish to understand how the cell distinguishes cluster transcripts from other RNAs in the cell and how chromatin signatures of clusters participate in their biology.

Publication highlights

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Figure 1

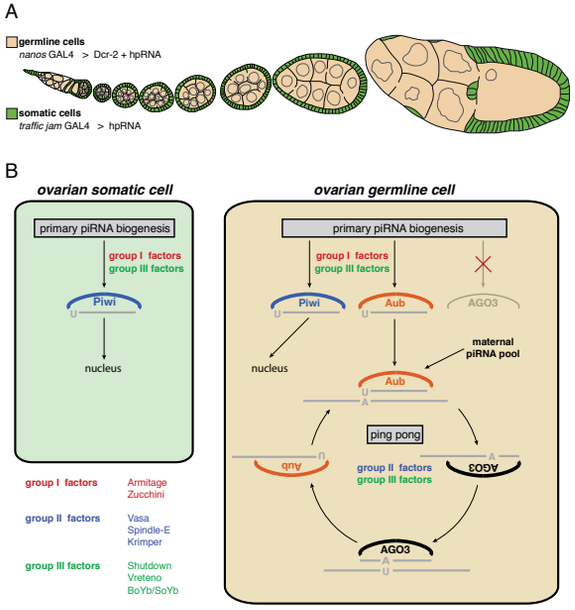

Figure 2

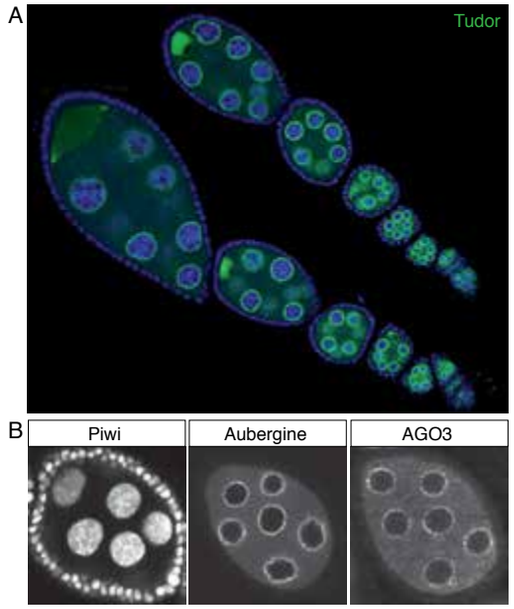

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Figure 1: Scheme illustrating the piRNA pathway acting in the *Drosophila* ovary. (**A**) This cartoon depicts an ovariole, one of the functional units of an ovary. The two major cell types (somatic support cells and germline cells) are shown in green and beige. (**B**) Schematic summary of the piRNA pathway architecture in somatic (left) and germline cells (right). The wiring of the three PIWI family proteins Piwi, Aubergine and AGO3 into piRNA biogenesis processes is shown. Genetically identified piRNA biogenesis factors that act at the various indicated steps are also indicated.

Figure 2: Subcellular localization of PIWI family proteins. (**A**) Two ovarioles stained for DNA (blue) and the piRNA pathway protein Tudor (green). Tudor is enriched in a peri-nuclear structure known as nuage, where piRNA biogenesis is believed to occur. (**B**) Sub-cellular localizations of the three PIWI family proteins. Note that only Piwi is a nuclear protein while Aubergine and AGO3 are enriched in nuage.

DANIEL GERLICH GROUP

Assembly and function of the cell division machinery

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Cells entering mitosis extensively reorganize the cytoskeleton and many other cellular organelles, in order to support chromosome segregation and partitioning of the cytoplasm to emerging daughter cells. Our interdisciplinary team of biologists and computer scientists uses state-of-the-art imaging approaches to elucidate the structure and function of the cell division machinery, and to understand the coordination of various cell division processes.

Spindle assembly checkpoint signaling

The spindle assembly checkpoint contributes to faithful chromosome segregation by delaying the onset of anaphase until all chromosomes have attached to opposing spindle poles. Little is known about the kinetics by which the spindle assembly checkpoint responds to individual unattached chromosomes. We developed a laser microsurgery procedure to measure signaling kinetics in live cells after spindle detachment of individual chromosomes (Figure 1). These studies disclosed two routes by which unattached chromosomes may escape detection by the spindle assembly checkpoint. First, we found that single unattached chromosomes prevented mitotic exit less efficiently than did a full complement of unattached chromosomes. Second, cells were unresponsive to chromosome detachment for several minutes before the onset of anaphase. This shows that the spindle assembly checkpoint does not signal as an instantaneous on/off switch, but rather through a graded response. In the future, we intend to explore how these limitations in the response kinetics of the spindle assembly checkpoint may contribute to the emergence of aneuploidy or the development of cancer cell resistance against therapeutics that target the mitotic spindle.

Morphogenesis of mitotic chromosomes

A key requirement for chromosome segregation is the compaction of chromatin into rod-shaped rigid bodies of mitotic chromosomes. However, very little is known about the three-dimensional organization of DNA in mitotic chromosomes and the factors that shape mitotic chromosomes. Using a combined imaging and biochemical approach, we aim to understand how distinct chromosome subdomains form and how this contributes to the biophysical properties of mitotic chromosomes.

Cytokinetic abscission

Animal cell cytokinesis proceeds by ingression of a cleavage furrow, followed by membrane separation during abscission. It has been known for a long time that cleavage furrow ingression is driven by contraction of a cortex-associated actomyosin ring. The mechanism of abscission, however, has been poorly understood. At our laboratory we found that abscission proceeds by a secondary constriction of the cell cortex within the intercellular bridge at sites that are devoid of f-actin (Figure 2). By correlative light and electron microscopy, we discovered a new type of filament with a diameter of 17 nm. 17-nm filaments colocalize with the Endosomal Sorting Complex Required for Transport (ESCRT-III), and do not assemble after depletion of ESCRT-III subunits. This supports a model in which ESCRT-III forms a contractile helical filament system that constricts the intercellular bridge for plasma membrane fission. Using super-resolution fluorescence microscopy and quantitative time-lapse imaging, we aim to obtain further insight into the composition, structure, and dynamics of 17-nm diameter filaments. We are also characterizing the final membrane fission event using a variety of biophysical approaches.

High-throughput imaging and computer vision

Recent advances in microscope automation permit systematic high-throughput analysis of dynamic processes such as cell division. Our laboratory develops computer vision and machine learning methods for automated cell phenotyping in time-resolved imaging. We have established the integrated software platform CellCognition (http://www.cellcognition.org), which contains a suite of object detection, tracking, and supervised and unsupervised classification methods. This permits fully objective phenotype quantification in high-throughput live-cell microscopy. Our purpose is to integrate machine learning and computer vision methods into the microscope-controlling software, in order to establish a fully automated workflow for complex interactive perturbation experiments.

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Figure 1

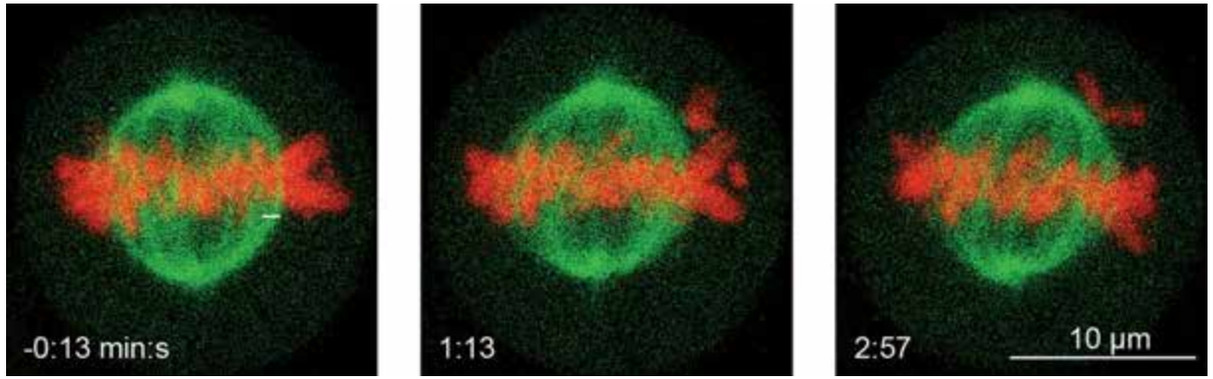

Figure 2

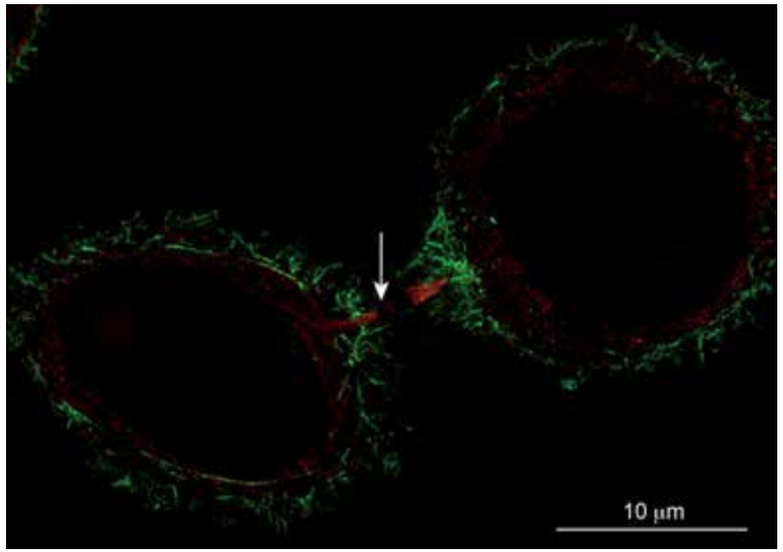

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Figure 1: Laser microsurgery to trigger mitotic spindle assembly checkpoint signaling. A live metaphase HeLa cell with a red chromatin marker (Histon2B-mCherry) and a green spindle marker (mEGFP α-tubulin) was cut with a high-energy 2-photon laser (white line, 0.00 min) to detach a single chromosome from the metaphase plate. This assay was used to measure the response kinetics of the spindle assembly checkpoint. See Dick and Gerlich, Nature Cell Biology (2013).

Figure 2: Super-resolution fluorescence microscopy of the cytoskeleton during abscission. A HeLa cell at the abscission stage was stained with fluorescent phalloidin (green) to visualize the actin cytoskeleton and anti-alpha-tubulin antibody (red) to visualize microtubules, using a 3D-structured illumination microscope. The arrow marks the site of abscission. See Fededa and Gerlich, Nature Cell Biology (2012) and Guizetti et al., Science (2011)

FUMIYO IKEDA GROUP

Generation of the linear ubiquitin chain by the E3 ligase complex, LUBAC

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Ubiquitin is a small modifier protein which is highly conserved in a wide range of organisms from yeast to humans. The modification of ubiquitin is one of the most sophisticated and versatile post-translational modifications. It regulates several biological functions, including inflammation, apoptosis, autophagy, cancer, cell cycle, DNA repair, Parkinson's disease, and endocytosis. We are specifically interested in the role of a type of ubiquitination known as linear ubiquitination in the regulation of immune response.

The linear ubiquitin chain is a unique linkage type of chain linked via a Met residue instead of commonly used Lys residues. As this atypical type of ubiquitin chain was discovered very recently, little is known about its regulation. The only known linear-ubiquitination-specific E3 ligase is LUBAC (Linear Ubiquitin Assembly Complex), which consists of HOIP, SHARPIN and HOIL-1L (Figure 1A). We have shown that an E3 ligase complex, LUBAC, plays a critical role in the regulation of TNFα-induced NF-κB signaling.

The molecular basis of the LUBAC E3 ligase complex

We aim to understand a) how LUBAC generates linear ubiquitin chains, and b) its target substrates. In the lab, we established an *in vitro* ubiquitination assay to monitor the formation of the ubiquitin chain by using purified proteins, HOIP, SHARPIN and HOIL-1L. We identified a critical residue Cys885 in the HOIP catalytic domain, which is involved in the regulation of the linear ubiquitin chain. Cys885 is conserved in various species, and is located at the 2nd RING domain (Figure 1A). In HHARI E3 ligase, Cys is a ubiquitin-loading residue for the intermediate status of ubiquitin transfer to the substrates, which was the first example of the 'HECT-RING hybrid' type of E3 ligase. In line with this data, the purified HOIP-C885S mutant no longer generated linear ubiquitin chains in vitro (Figure 1B) and no longer activated NF-κB (Figure 1C), suggesting HOIP as the HECT-RING type of E3 ligase. Nevertheless, how HOIP yields specificity for generating linear ubiquitin chains is entirely unclear. By further analyzing the catalytic activity of HOIP, we aim to elucidate the enzymatic regulation of LUBAC in the generation of linear ubiquitin chains. Moreover, we are currently setting up a system to screen new targets of LUBAC E3 ligase by combining the *in vitro* ubiquitin assay with a protein chip array.

The role of the LUBAC E3 ligase complex *in vivo*

SHARPIN, one of the non-catalytic subunits of LUBAC, plays a critical role in the regulation of inflammatory responses *in vivo*. In SHARPIN-deficient (Cpdm) mice, the immune system is defective and inflammation in multiple organs is significantly upregulated (Figure 2A). Histological analysis of skin tissue of Cpdm mice clearly shows that a SHARPIN deficiency leads to chronic proliferative dermatitis (H&E and K14 staining) and apoptosis (cleaved caspase 3 staining) (Figure 2A). We identified FADD as a new substrate of LUBAC that regulates the TNF-induced apoptosis pathway. FADD is ubiquitinated by LUBAC E3 ligase *in vitro* (Figure 2B), and this ubiquitination event is required for the anti-apoptosis signaling cascade. Using genetically modified mouse models, we aim to determine whether apoptosis in keratinocytes plays a role in the regulation of skin inflammation in Cpdm mice.

To further understand the linear ubiquitination signal in biological functions *in vivo*, we are establishing a mutant mouse line of HOIP. Depletion of HOIP in mice leads to embryonic lethality before the age of E11 because of developmental defects. A similar phenomenon has been observed in many NF-κB-deficient mice, including NEMO, IKK2, and p65. We aim to determine how HOIP functions during development. Based on the results of screening, we will focus on the roles of HOIP in various diseases, using genetically modified mouse lines. We intend to discover new biological functions of the linear ubiquitination signal.

In summary, we aim to elucidate novel functions of the linear ubiquitin signal by combining the biochemical screening method to identify new targets of LUBAC and genetically modified animal models.

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Figure 1

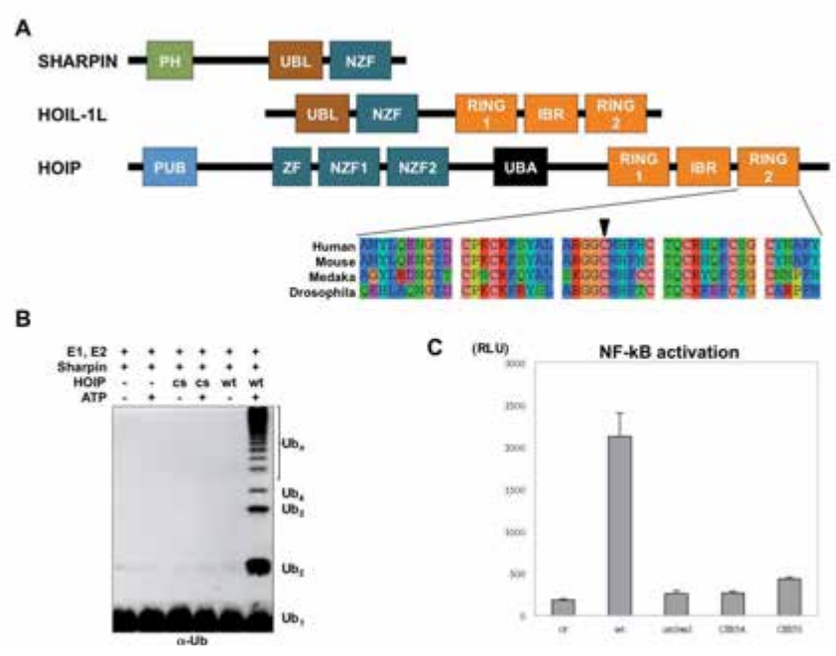

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Figure 2

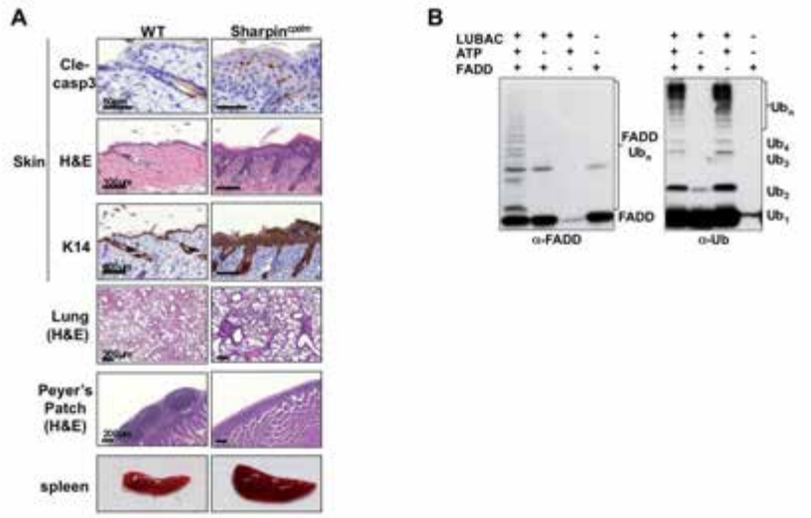

Figure 1: Linear ubiquitination is induced by the LUBAC E3 ligase complex. A) LUBAC components, SHARPIN, HOIL-1L and HOIP. A catalytic center is located in the 2nd RING domain (RING2) of HOIP. Alignment of HOIP-RING2 in different species shows high conservation. The arrow indicates the C885 in human, which is perfectly conserved in various types of species. **B**) HOIP-C885 mutant fails to generate linear Ub chains. **C**) HOIP-C885 is critical for NF-κB signaling. The NF-κB reporter assay was performed using C885 mutants, which abolished the ability to mediate NF-κB activation as a catalytic dead mutant.

Figure 2: The linear ubiquitination signal plays a role in the regulation of apoptosis. A) Histological analysis of multiple tissues of wild type (wt) and SHARPIN-deficient (Cpdm) mice. Apoptosis in Cpdm keratinocytes is induced to a great extent (Cleaved-Casp3). H&E and K14 staining of the skin shows an increase in the thickness of the epidermis in Cpdm. H&E staining of the lung shows an increase in inflammation. A defect in Peyer's patch and splenomegaly are also observed. **B**) The *in vitro* ubiquitination assay using purified LUBAC and FADD shows the ubiquitination of FADD (left panel). Free linear ubiquitin chains are generated, regardless of the addition of FADD to the reaction (right panel).

JÜRGEN KNOBLICH GROUP

Neural stem cells and brain development

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The human brain undoubtedly is the most complex of all organs. We are interested in how its enormous complexity arises from a relatively small number of stem and progenitor cells. Our group uses Drosophila and mouse genetics to understand how neural stem cells generate the right neurons at the right time, and how defects in neurogenesis may lead to brain tumors or heritable brain disorders.

Neural stem cells in *Drosophila*

In the developing *Drosophila* brain, all neurons and glia cells arise from neural stem cells known as neuroblasts, in repeated rounds of asymmetric cell division (Fig. 1A). One of the resulting daughter cells continues to divide in a stem-cell-like manner while the other cell generates two differentiating neurons. 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 (Fig. 1A, B). This happens because the protein kinase aPKC localizes to the opposite apical side and removes the determinants by phosphorylating their membrane localization domains. Simultaneously, aPKC associates with microtubule-binding proteins to ensure that the mitotic spindle is set in apical-basal orientation. As a result, the determinants are specifically inherited by the basal daughter cell. In the absence of Brat, Numb or Prospero, both daughter cells retain their ability of self-renewal. As a consequence, stem cells expand exponentially and pervade the entire brain. Eventually they form gigantic brain tumors that may be propagated by serial transplantation into host flies, where they become aneuploid and undergo metastasis (Fig. 1C). Our major goals include understanding how the transcriptional changes induced in one daughter cell irreversibly target this cell to differentiation, and how defects in this reprogramming event lead to tumorigenesis.

In a large-scale transgenic RNAi screen, we identified more than 600 genes that regulate self-renewal in Drosophila neuroblasts. Among these are 18 tumor suppressors that cause neuroblast overproliferation. Besides the asymmetric cell division machinery, this set includes six nuclear proteins that we believe form the transcriptional machinery acting downstream of the segregating determinants. Three of these are part of the SWI/SNF chromatin-remodeling complex. One is a known binding partner of histone deacetylase while two others are implicated in the control of transcriptional elongation. We recently developed a technology that allows us to purify neuroblasts and their differentiating daughter cells in large quantities, and determine their transcriptomes by deep sequencing technology. Together with the enormously powerful genetic tools available in *Drosophila*, this permits the determination of transcriptional changes upon removal of any of the nuclear regulators in a time-resolved manner. We identified a network of transcription factors that act in neuroblasts and establish a stable self-renewing state. Some of the key questions we are addressing include how this state is reprogrammed towards differentiation and how the epigenetic changes become irreversible to establish directionality in stem cell lineages.

Asymmetric cell division in mouse stem cells

In the mouse brain, progenitor cells known as radial glia generate neurons of the cortex through lineages that are strikingly similar to *Drosophila* neuroblasts (Fig. 2A). Neural progenitors are located in the neuroepithelium. Initially they expand through symmetric divisions but later divide asymmetrically, giving rise to differentiating daughter cells as well (Fig. 2B). While the early symmetric divisions are parallel to the surface of the neuroepithelium, later divisions may be oblique or – in rare cases – even vertical. We are using our knowledge from *Drosophila* to understand how cortical progenitor divisions become asymmetric and how lineages are established in the developing cortex.

In a *Drosophila* RNAi screen at our laboratory we identified the protein phosphatase PP4 as a key regulator of asymmetric cell division and mitotic spindle orientation. We used a conditional knockout strategy to characterize the single mouse PP4 homolog. PP4 was found to regulate the Lis1/Ndel1 complex and is essential for correct orientation of the mitotic spindle in mouse cortical progenitor divisions. This raised the question as to whether spindle orientation is important for neurogenesis. Surprisingly, we found that spindle orientation is not relevant during the peak stages of neurogenesis, but regulates the transition from symmetric to asymmetric division modes. As this transition determines the number of progenitors, our data suggest a potential connection between spindle orientation and brain size in mammals (see Xie, et al. Neuron 2013 for details).

Modeling human cortical development

To determine whether mechanisms regulating asymmetric cell division and stem cell lineages are conserved in humans as well, we developed a 3D culture model for human forebrain development (Lancaster et al., Nature 2013). Established human ES cell lines or iPS cells are used to create cerebral organoids that recapitulate, in remarkable detail, the development of the human brain in culture (Fig. 3). Cerebral organoids contain the human dorsal and ventral cortex, the choroid plexus, the retina, and sometimes the hippocampus. They recapitulate human-specific cortical features such as the presence of an outer subventricular zone or an inner fiber layer. We demonstrated the usefulness of our organoid system by modeling microcephaly, a human disorder resulting in a severely reduced size of the cortex. Our data reveal spindle orientation defects leading to premature neural differentiation at the expense of the progenitor population that could be responsible for the disease. The establishment of a 3D culture system that recapitulates the key aspects of human forebrain development will allow us to efficiently transfer our knowledge from *Drosophila* to humans, and determine the cellular basis for developmental disease in the human brain.

Figure 1

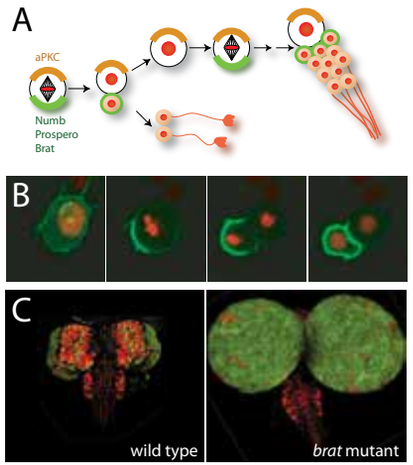

Figure 2

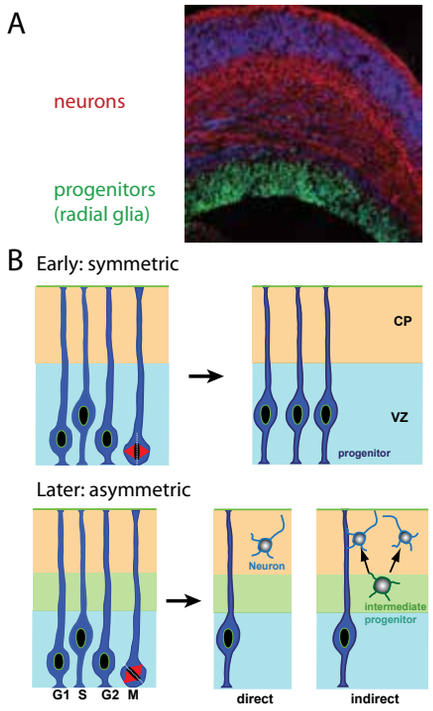

Figure 3

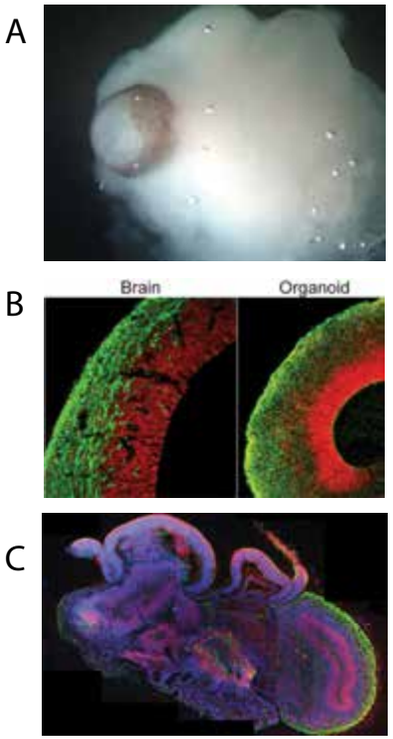

Figure 1: How cells divide asymmetrically. A. Drosophila neuroblasts (white) divide asymmetrically to generate self-renewing stem cells (white) and differentiating neurons (red). During each neuroblast division, aPKC (orange) guides the asymmetric segregation of Brat, Prospero and Numb (green) into the differentiating daughter cell. **B**. Stills from a time-lapse movie of Histone-RFP (red, to visualize chromatin) and Pon-GFP (green, to visualize the Numb protein) separating into one of the two daughter cells during asymmetric division. **C**. Larval brain from a wild type (left) and *brat* mutant animal. Neuroblasts are green; differentiating neurons are red. *Brat* brains are marked by dramatic overproliferation of neuroblasts.

Figure 2: Analysis of progenitor cell proliferation in the mouse brain. A. Cross-section through the developing mouse neocortex (DNA in blue) on day 15 of embryonic development. Anti-TuJ1 labels early differentiating neurons (red) while radial glia progenitors are marked by anti-Pax-6 (green). **B**. Cortical progenitors (blue) in the ventricular zone (VZ, light blue) divide symmetrically during early stages of cortical development and switch to an asymmetric mode of division during neurogenesis. While symmetric divisions are strictly parallel to the epithelial surface (mitotic spindles are in red), asymmetric divisions occur at oblique or even vertical angles. Asymmetric divisions give rise to differentiating neurons that migrate into the cortical plate (CP, orange), or intermediate progenitors (green) that divide again to generate two neurons. These two modes, known as direct and indirect neurogenesis, are regulated by *inscuteable* (see text).

Figure 3: Cerebral organoids model human brain development. A. Cerebral organoids can be derived from human ES or iPS cells. The pigmented area in this bright field image is a developing human eye. **B**. Comparison of a developing mouse cortex and the corresponding stage in a human cerebral organoids. Red: progenitor cells, Green: differentiating neurons. **C**. Cross-section through a cerebral organoid. The red entities are proliferating progenitor cells (labeled by anti Sox2; green ones are differentiating neurons (marked by anti TuJ1), and blue is DNA. See Lancaster et al, Nature 2013 for details.

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Publication highlights:

Lancaster, M.A., Renner, M., Martin, C.-A., Wenzel, D., Bicknell, L.S., Hurles, M.E., Homfray, T., Penninger J.M., Jackson, A.P. and Knoblich, J. A. (2013). Cerebral organoids model human brain development and microcephaly. Nature, 501, 373-9.

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Molecular Machines

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

Microbial pathogenesis

Gram-negative pathogens such *Yersinia, Shigella, Pseudomonas, enteropathogenic/enterohemorrhagic E. coli* (*EPEC/EHEC*) and *Salmonella* as well as *Erwinia, Ralstonia* and *Xanthomona* are causative agents for many diseases in animals, humans, and plants. They range from mild to deadly outcomes, and include food-borne diseases such as diarrhea or bubonic plaque, or induced cell necrosis in plants. A central aspect of pathogenicity are bacterial toxins ('effectors'), which are delivered via the type-III secretion system, a large membrane-embedded machinery, from the bacterium to its host cell. As a consequence, translocated effector proteins have the remarkable capacity to modulate various host-cell pathways, including endocytic trafficking, gene expression, programmed cell death, or cytoskeleton dynamics that induce membrane ruffling and subsequently render the host accessible to bacterial infection.

Unfolded protein transport across membranes?

The hallmark function of all type-III secretion is the safe and directional transport of effector proteins across membranes. Our recent structural analysis (Schraidt and Marlovits, Science 2011) of the injectisome, the most prominent and cylindrical structure of the type-III secretion system, revealed a potential secretion path through the central part of the membrane-embedded complex. However, the inner diameter of this path is too small to accommodate a fully folded effector protein, suggesting that either the injectisome must undergo large conformational changes during transport, or effector proteins need to be unfolded. Thus, during the last year we focused on the following: a) determining the secretion path of injectisomes, b) understanding the mechanism of transport, and c) visualizing protein transport in situ. To address these questions, we first analyzed the requirements for substrate association with, transport through, and exit from the injectisome. To our surprise we found that the size and length of novel substrates does not have a major impact on their secretability. We learned that the fusion of thermodynamically stable protein domains to otherwise secreted substrates does not influence successful engagement to the injectisome, but prevents complete transport across membranes. Such designed and trapped substrates are highly associated with injectiosmes. We discovered that such substrates are inserted into the secretion path in a polar fashion - N-terminal regions first - suggesting that other substrates with a similar domain organization follow the same principle. Our structural analysis of trapped substrates clearly revealed for the first time that they are in an unfolded state during transport, suggesting that the type-III-specific ATPase acts as an unfoldase. In contrast, injectisomes stay largely invariant during protein transport. To understand, whether such behavior is in fact observed in situ, we performed cryo-electron tomography. This method permits the investigation of molecular structures within cells in a spatiotemporal manner and in a near-native state. For the first time we were able to visualize pathogenic type-III secretion systems from Salmonella in action and - more generally - protein transport across several membranes.

By understanding the molecular mechanism of TTSS-mediated protein transport, we hope to provide a basis for the development of novel therapeutic strategies that will either inhibit its activity or modify the system for targeted drug delivery.

Publication highlights:

Brunner MJ, Fronzes R, Marlovits TC. Envelope spanning secretion systems in Gram-negative bacteria. In: Bacterial Membranes: Structural and Molecular Biology Fronzes R. (eds) (in press)

Kosarewicz, A, Konigsmaier, L & Marlovits, TC. The blueprint of the type-3 injectisome. Philos Trans R Soc Lond B Biol Sci 367, 1140-1154 (2012).

Radics J, Königsmaier L, Marlovits TC (2013). Structure of a pathogenic type III secretion system in action. Nature Struct. Mol. Biol. AOP Dec. 8, doi:10.1038/nsmb.2722

Figure 1

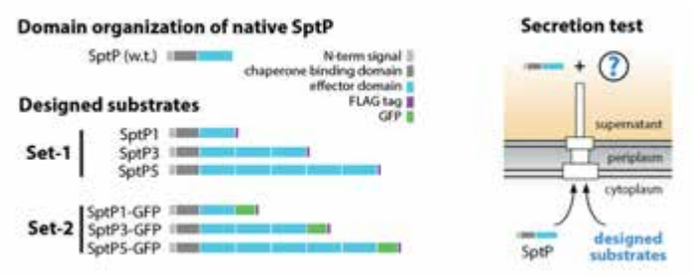
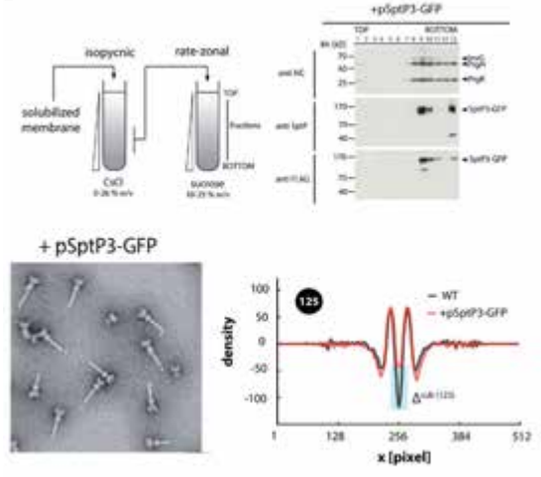


Figure 2



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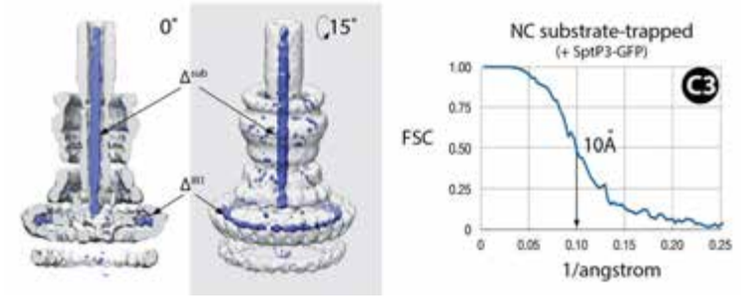

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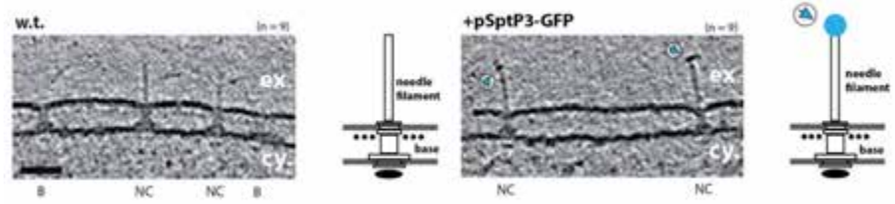

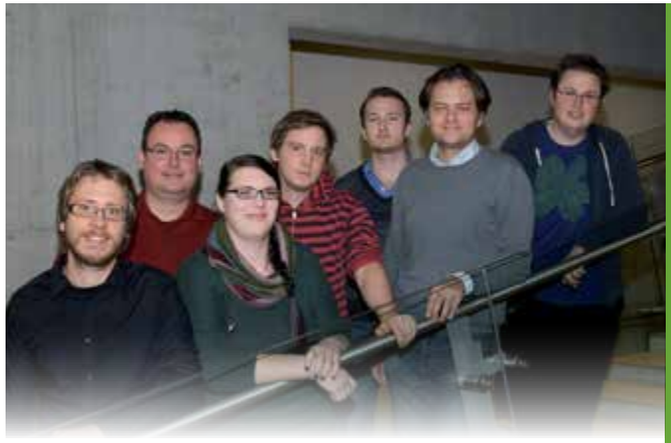

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Figure 1: Design of novel type-III secretion substrates and experimental set-up

Figure 2: Purification and analysis of substrate-trapped injectisomes

Figure 3: Structural analysis of substrate-trapped injectisomes

Figure 4: Unfolded protein transport across membranes revealed by cryo-electron tomography

JAVIER MARTINEZ GROUP

Novel RNA metabolic Enzymes: Mechanisms, Biology, and Disease.

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Soon after being synthesized, RNA molecules undergo a series of modifications and processing steps that are essential for their cellular functions. Defects in these events can have deleterious consequences for cells and have been linked to disease. In this scenario, our laboratory is characterizing novel RNA metabolic enzymes both at the molecular level and in vivo, using mouse models as well as samples from patients carrying mutations in the genes encoding these factors. We focus on biochemical pathways entailing ligation and phosphorylation of RNA molecules, which have remained largely unexplored due to the absence of putative enzymatic factors. Conducting activity-guided protein purification with siRNAs as substrates followed by mass spectrometry and RNAi-mediated silencing of candidate genes, our group has already identified two major players: We discovered CLP1 as an RNA-kinase activity associated with the tRNA splicing endonuclease (S. Weitzer and J. Martinez, 2007) and the long-sought human tRNA ligase, a pentameric complex with the subunit RTCB as a catalyst to join exon halves (J. Popow et al., 2011 and 2012). Moreover, by combining bioinformatics and biochemical analysis, we have recently identified Archease as an essential co-factor of the tRNA ligase complex (J. Popow et al., under revision). Crucially, RTCB seems to bind additional targets besides tRNAs, suggesting that the tRNA ligase might play a role in other biological processes. With the aim of characterizing such functions, we have generated full and conditional knockout mice for CLP1, RTCB and Archease. In the ongoing characterization of phenotypes, we are particularly interested in the topics of development, stress response and eventual diseases. Our ultimate goal is to perform "RNA biochemistry in vivo" to understand the molecular mechanisms driving those events.

1- Linking tRNA metabolism and neurodegeneration: The surprising *in vivo* function of CLP1.

The identification of the RNA-kinase CLP1 as a component of the human tRNA splicing endonuclease (TSEN) triggered our interest in tRNA splicing, an intriguing process in terms of molecular mechanisms, phyletic distribution and links to neurological diseases. In collaboration with the laboratory of Josef Penninger, we have investigated the *in vivo* function of CLP1 and found that, depending on the genetic background, knock-in mice ubiquitously expressing a catalytically inactive version of CLP1 (a single amino acid change – K127A – in the ATP binding site) develop a progressive loss of spinal motor neurons associated with axonal degeneration in peripheral nerves and denervation of neuromuscular junctions leading to motor function impairment, muscle weakness and paralysis (T. Hanada et al., 2013). Strikingly, transgenic expression of CLP1 in motor neurons fully rescued the phenotype. The inactivating mutation in CLP1 severely impaired pre-tRNA processing most probably due to the disturbed stoichiometry of the TSEN complex. In addition, we detected the accumulation of a novel type of tRNA fragment that mainly derives from Tyrosine-tRNAs – and is already present, although at much lower levels, in wild type cells (**Figure 1**). This tRNA fragment also accumulates when wild type cells are treated with peroxide and other inducers of oxidative stress like glucose oxidase. This observation suggests that the mutation in CLP1 creates oxidative stress-like conditions in the cell. In turn, tRNA fragments sensitize cells to oxidative stress-induced p53 activation and p53-dependent cell death. Two critical questions emerge from this study. First, how do Tyrosine-tRNA fragments trigger p53 hyperphosphorylation? Pull downs with biotinylated tRNA fragments followed by Mass Spectrometry analysis should help identifying potential tRNA-binding proteins as candidates to directly or indirectly phosphorylate p53. Second, why do tRNA fragments accumulate in cells that display poor endonuclease activity?

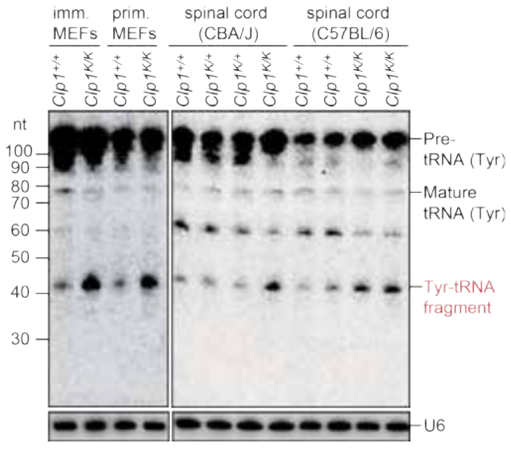
We have recently teamed up with Prof. Jim Lupski (Baylor College of Medicine, Texas) who has identified five families with a missense mutation in CLP1. Homozygous children display microcephaly and develop a neurological disease affecting the central and peripheral nervous system. The mutation diminishes the kinase activity of CLP1 and abolishes the formation of TSEN impairing tRNA splicing in extracts from patient fibroblasts. Children display normal levels of both mature and precursor tRNA molecules in fibroblasts but surprisingly accumulate Isoleucine and Tyrosine-tRNA introns (**Figure 2**). Re-examination of the CLP1 K127A mutant mouse revealed microcephaly. This finding turns the CLP1 mouse into an animal model for a new type of human neurological disease (E. Karaca et al., under revision).

2- Mouse models to study the *in vivo* function of tRNA ligase and its co-factor, Archease.

We are generating full, conditional and ligase-dead (knock-in) RTCB knockout mice as well as an Archease knockout mouse (**Figure 3**). The RTCB full knockout turned out to be embryonically lethal, and we are therefore focusing on the role of RTCB in specific tissues. Analysis of the Archease knockout mouse will allow the assessment of the RTCB-Archease partnership that we recently discovered at the biochemical level (J. Popow et al, under revision). We envision a regulatory role of Archease for the ligation activity of RTCB and thus a modulation of the initial RTCB knockout mouse phenotype. Impairing the tRNA splicing machinery in the mouse is lethal most probably because two tRNA family genes, Leucine-CAA and Tyrosine-GTA are exclusively encoded as intron-containing tRNAs. We will therefore apply two strategies to reveal the functions of the tRNA ligase and Archease "bypassing" tRNA splicing. Since tRNA splicing is a nuclear event and RTCB localizes in both the nucleus and the cytoplasm, we will add a nuclear localization signal to force RTCB into the nucleus. Thus, the potential role of RTCB in cytoplasmic RNA splicing could be studied. We are also designing transgenic mice expressing intron-less versions of Leucine-ATA and Tyrosine-GTA to be crossed to RTCB knockout mice.

In summary, the finding of the mammalian tRNA ligase complex together with its regulator Archease, the elucidation of CLP1's function in motor neurons and the ongoing research of RTCB and Archease knockout mice bring exciting perspectives for the study of tRNA splicing and other RNA pathways at the molecular level and in health and disease.

Figure 1



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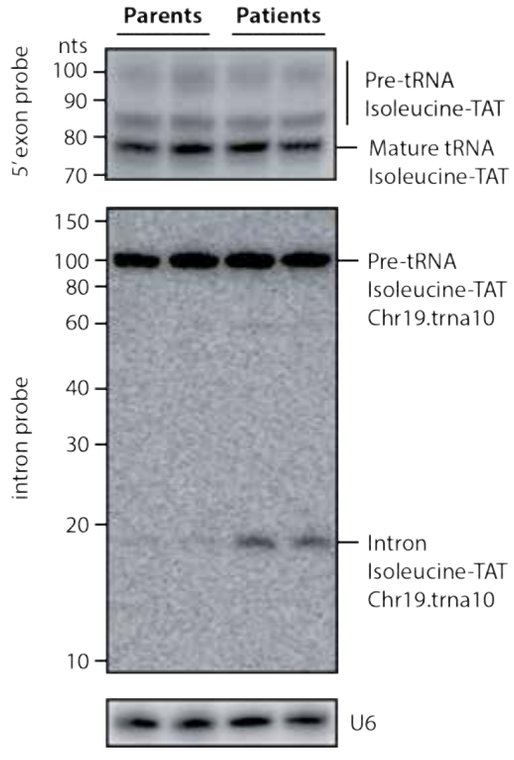

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Publication highlights:

Barbara Mair, Johannes Popow, Karl Mechtler, Stefan Weitzer and Javier Martinez. Intron excision from precursor tRNA molecules in mammalian cells requires ATP hydrolysis and phosphorylation of tRNA splicing endonuclease components. Biochem Soc Trans. 2013 Aug 1;41(4):831-7.

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Hanada, T., Weitzer, S.*, Mair, B., Bernreuther, C., Wainger, B.J., Ichida, J., Hanada, R., Orthofer, M., Cronin, S.J., Komnenovic, V., Minis, A., Sato, F., Mimata, H., Yoshimura, A., Tamir, I., Rainer, J., Kofler, R., Yaron, A., Eggan, K.C., Woolf, C.J., Glatzel, M., Herbst, R., Martinez, J.[§], and Penninger, J.M.[§] The RNA kinase CLP1 links tRNA metabolism to progressive motor-neuron loss. *co-first authors; [§]co-corresponding authors. Nature. Advance online publication March 10th 2013.*

Figure 3

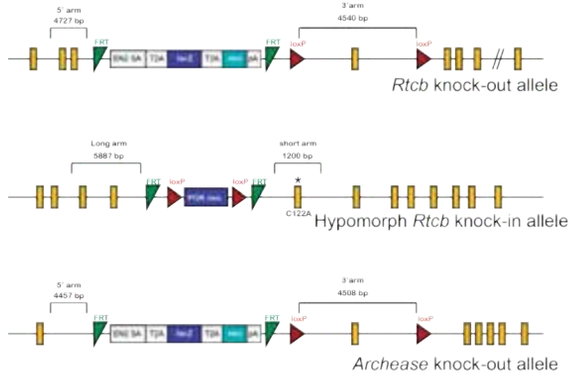

Figure 1: 41–46-nucleotide (nt) Tyr-tRNA fragments (in red) accumulate in primary (Prim.) and immortalized (Imm.) Clp1$^{K/K}$ mouse embryonic fibroblasts (MEFs) and spinal cords of 4-month-old CBA/J Clp1$^{K/K}$ and newborn C57BL/6 Clp1$^{K/K}$ mice. Northern blot analysis of total RNA were performed with a DNA/LNA probe complementary to the 5′ exon of Tyr-tRNA. U6 RNA served as a loading control.

Figure 2: Northern blot analyses of RNA from parental and patient fibroblasts. A probe complementary to the 5′ exon of Isoleucine-TAT tRNAs was used to detect mature and pre-tRNA species (upper panel). Probes specifically directed against intron sequences were used to detect the pre-tRNAs encoded in Chr.19.tRNA10 (middle panel; human February 2009 (hg19) genome assembly). U6 RNA served as loading control (lower panel).

Figure 3: Gene targeting to create conditional and hypomorphic alleles of RTCB and Archease.

KAZUFUMI MOCHIZUKI GROUP

Small RNA-directed transgenerational epigenetic inheritance in *Tetrahymena*

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The phenotypes of a parent can be epigenetically transmitted to offspring through the germline in many different eukaryotes. Epigenetic information can be inherited as chromatin modifications that are incompletely reprogrammed in gametes. Alternatively, some diffusible factors can transmit epigenetic information from parents to progeny through the germline. Transgenerational epigenetic inheritance potentially allows organisms to transmit acquired characteristics to the next generation, and could thus increase the fitness of progeny in rapidly changing environments. However, the detailed molecular mechanism of transgenerational epigenetic inheritance is largely unclear. Several lines of evidence suggest that the patterns of programmed DNA elimination in ciliated protozoa are epigenetically and transgenerationally inherited. Therefore, DNA elimination in ciliated protozoa serves as a model to understand how transgenerational epigenetic inheritance can be achieved at a molecular level.

DNA elimination in *Tetrahymena* involves in small RNA-mediated heterochromatin formation

The ciliated protozoan *Tetrahymena* possesses a somatic macronucleus (Mac) and a germline micronucleus (Mic) in each cell. Mac is polyploid and transcriptionally active, whereas Mic is diploid and transcriptionally inert during vegetative growth. In the sexual process of conjugation, Mic gives rise to a new Mac and a new Mic, and the parental Mac is destroyed (Figure 1). During the development of the new Mac, ~9000 internal eliminated sequences (IESs) are removed (DNA elimination) and the remaining Mac-destined sequences are re-ligated. Most IESs are moderately repeated in the Mic and many of them are related to transposable elements. Small RNA-directed heterochromatin formation is involved in the IES elimination process. In *Tetrahymena*, heterochromatin components, including histone H3 methylated on lysine 9 (H3K9me) and on lysine 27 (H3K27me), and the chromodomain protein Pdd1p, are specifically associated with eliminated IES sequences (Figure 1). Heterochromatin recruits the endonuclease Tpb2p, which catalyzes DNA elimination. Small (~28-29 nt) RNAs known as scnRNAs are produced by the Dicer protein Dcl1p, and associate with the Argonaute protein Twi1p. Dcl1p and Twi1p are required for the accumulation of H3K9me/H3K27me/Pdd1p as well as for DNA elimination. Thus, the formation of heterochromatin occurs downstream of the RNAi-related mechanism in the DNA elimination pathway (Figure 2). As transposable elements are silenced by a heterochromatin and/or RNAi-related mechanism in many different eukaryotes, further study of the programmed DNA elimination process in *Tetrahymena* should reveal how transposons are silenced by RNAi-directed formation of heterochromatin in eukaryotes.

DNA elimination is epigenetically regulated by transnuclear genome comparison

The fact that IESs do not share any common sequence motifs raises the following question: how is *Tetrahymena* able to identify IESs to induce DNA elimination? *Tetrahymena* solves this problem by transnuclear comparison of whole genomes. In a single cell, *Tetrahymena* has a germline Mic, which contains complete genome including IESs, and a somatic Mac in which IESs are removed during the last sexual reproduction. Thus, the cell is able to identify IESs as sequences existing in Mic but not in Mac. *Tetrahymena* utilizes scnRNAs for this trans-nuclear whole genome comparison (Figure 3 top). This system is able to perfectly sweep away not only the existing transposons, but also any newly invaded transposons from the transcriptionally active Mac. We are trying to understand the exact molecular mechanism regulating this transnuclear whole genome comparison by small RNAs. We recently reported that only scnRNAs complementary to IESs escape degradation during conjugation, and this selective turnover of scnRNAs mediates transnuclear whole genome comparison (Figure 3, bottom). We also showed that the selective turnover of scnRNAs alone does not fully explain the observed sequence specificity of scnRNAs to IESs, because scnRNAs are produced to a greater extent from IESs than from the rest of the genome (Figure 3, lower section).

We proposed that scnRNAs target not only IESs in the new Mac for DNA elimination, but also IESs in the germline Mic to mark sites for future biased production of scnRNAs (Figure 3 top, g). Thus, DNA elimination in the new Mac may be epigenetically and transgenerationally controlled not only by the genome contents of the parental Mac through selective degradation of scnRNAs, but also by those of the grandparental Mac through transcriptional regulation of Mic. We believe that understanding the mechanism of DNA elimination in *Tetrahymena* will shed light on how ancestral genomes can epigenetically regulate the behavior of genomes of successive generations in general eukaryotes.

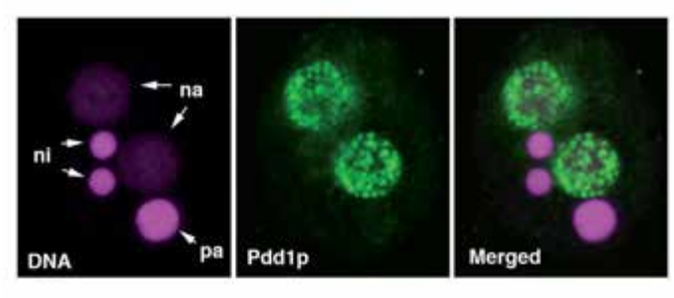
Publication highlights

Schoeberl, U. E., Kurth, H. M., Noto, T. and Mochizuki, K. (2012) Biased transcription and selective degradation of small RNAs shape the pattern of DNA elimination in Tetrahymena. Genes Dev 26, 1729-1742.

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

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

Figure 1



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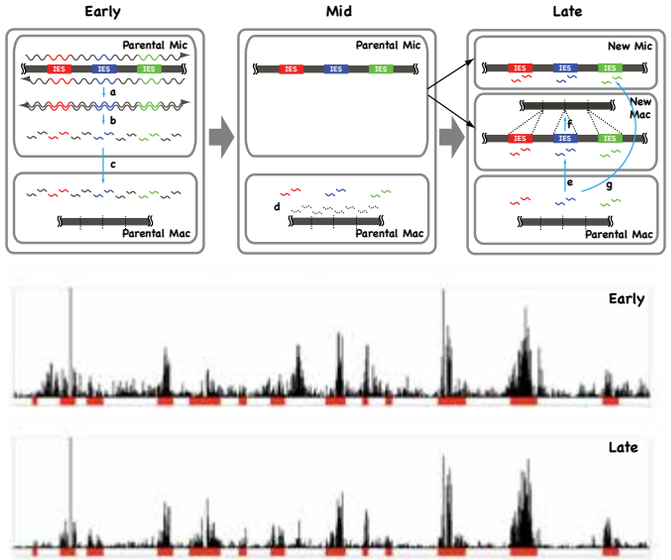
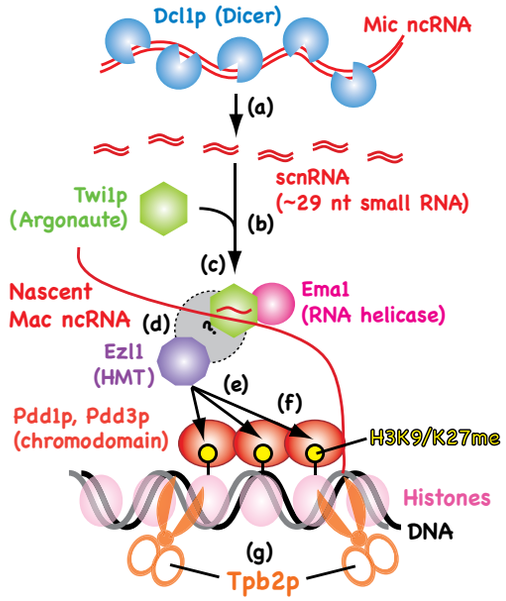


Figure 2



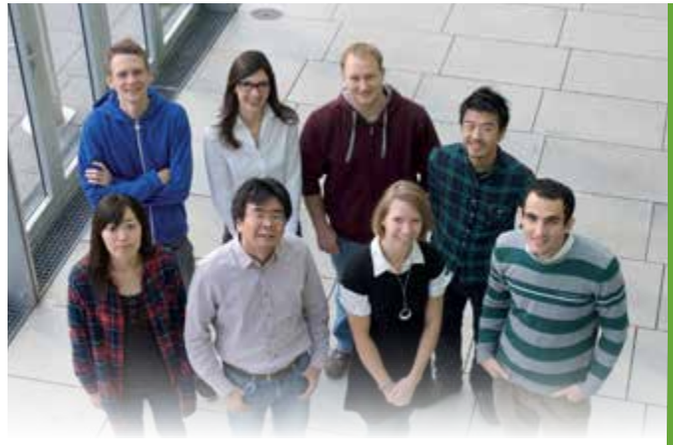


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Figure 1: Macronuclear differentiation during sexual reproduction in *Tetrahymena*. In the sexual process of conjugation, the Mic gives rise to the new Mac (na) and the new Mic (ni), and the parental Mac (pa) is destroyed. Small RNA-mediated processes induce the formation of heterochromatin, including the accumulation of the chromodomain protein Pdd1p (green), and eventually induce DNA elimination of transposon-related sequences from the new Mac. DNA was labeled with DAPI (magenta).

Figure 2: Small RNA-directed heterochromatin formation induces DNA elimination. Non-coding (nc) RNAs derived from the Mic genome, including transposons, are processed to scnRNAs by Dcl1p (a). scnRNA forms a complex with the Argonaute protein Twi1p (b). Ema1p facilitates interaction between the complex and nascent Mac ncRNA (c). This interaction recruits Ezl1p (d), which catalyzes methylations of histone H3 at lys9 and lys27 (e). Pdd1p and Pdd3p bind to the methylated histone H3 and establish heterochromatin structure (f). Tpb2p mediates the final DNA excision process (g).

Figure 3: Biased transcription and selective degradation of small RNAs shape the pattern of DNA elimination. (Top) A model for small RNA-directed DNA elimination. In the early developmental stages, the Mic genome is transcribed bi-directionally and the transcripts form double-stranded RNAs (a), which are processed into scnRNAs (b). scnRNAs are transferred to the parental Mac (c). In mid stages, scnRNAs complementary to the parental Mac genome are degraded (d). In late stages, the remaining scnRNAs are transferred to the developing new Mac (e) and target IESs to be eliminated (f). It has also been proposed that scnRNAs may move to the new Mic, leaving a signature on IESs for biased production of scnRNAs in the next sexual reproduction (g). (Below) Comparison of scnRNAs from different conjugation stages. Sequences of scnRNAs from various stages of development were obtained by deep sequencing and were mapped to a Mic locus. IESs are marked in red.

JOSEF PENNINGER GROUP

Genetic dissection of disease mechanisms

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Gene targeting and mutagenesis using stem cell technologies are powerful tools to elucidate essential functions of genes in normal physiology and in the pathogenesis of disease. Using gene-targeted mice, my group tries to genetically dissect disease mechanisms and establish new models of tissue regeneration.

The RNA kinase CLP1 links tRNA metabolism to progressive motor neuron loss

CLP1 was the first mammalian RNA kinase discovered by Javier Martinez at IMBA (Weitzer & Martinez, Nature 2007). However, its *in vivo* function was elusive. We joined forces with Javier's lab to generate kinase-dead *Clp1* (*Clp1*$^{K/K}$) mice. Amazingly, these mice exhibit a progressive loss of spinal motor neurons, along with axonal degeneration in peripheral nerves and denervation of neuromuscular junctions (**Figure 1**), ultimately resulting in impaired motor function, muscle weakness, paralysis, and fatal respiratory failure.

Mechanistically, the loss of *CLP1* activity leads to the accumulation of an entirely novel set of small RNA fragments, derived from aberrant processing of tyrosine pre-tRNA. These tRNA fragments sensitize cells to oxidative stress-induced p53 activation and p53-dependent cell death. Genetic inactivation of p53 rescued *Clp1*$^{K/K}$ mice from motor neuron loss, muscle denervation, and respiratory failure. Finally, transgenic rescue experiments re-expressing wild type CLP1 using the Hb9 promoter confirmed that CLP1 must function in motor neurons (**Figure 2**). Thus, our experiments have uncovered a mechanistic link between tRNA processing, the formation of a new RNA species, and progressive loss of lower motor neurons regulated by p53. (***Hanada, Weitzer et al. Full Article in Nature 2013***).

Complete cardiac regeneration in a mouse model of myocardial infarction

Cardiac remodeling and subsequent heart failure remain critical issues after myocardial infarction, despite improved treatment and reperfusion strategies. Recently, complete cardiac regeneration was achieved in fish and newborn mice after resection of the cardiac apex. However, it remained unclear whether the mammalian heart is also able to regenerate after a complex cardiac ischemic injury. We therefore established a protocol to induce a severe heart attack in one-day-old mice using ligation of the left anterior descending artery (LAD). LAD ligation caused substantial cardiac injury in the left ventricle, as manifested by caspase 3 activation and massive cell death. Ischemia-induced cardiomyocyte death was also seen on day 4 after LAD ligation. Remarkably, within 7 days after the initial ischemic stroke, we observed complete cardiac regeneration with no signs of tissue damage or scarring (**Figure 3**). This tissue regeneration translated into long-term normal cardiac function, as evidenced by echocardiography. In contrast, LAD ligations in 7-day-old mice resulted in extensive scarring similar to that in adult mice (**Figure 3**), indicating that the regenerative capacity for complete cardiac healing after a heart attack can be traced to the first week after birth.

RNAseq analyses of hearts on day 1, day 3, and day 10, and comparison of LAD-ligated and sham-operated mice revealed a transcriptional program of major changes in genes mediating mitosis and cell division postnatally, and a very limited set of genes, including genes regulating cell cycle and extracellular matrix synthesis, being differentially regulated in the regenerating hearts. We thus presented, for the first time, a mammalian model of complete cardiac regeneration after severe ischemic cardiac injury. This novel model provides a unique opportunity to uncover molecular and cellular pathways that can regulate cardiac regeneration after ischemic injury. The findings could be translated someday to human heart attack patients. (***Haubner et al. Aging 2012***; of note: the same finding was reported by Eric Olson's group, and both papers were published in the same month).

Figure 1

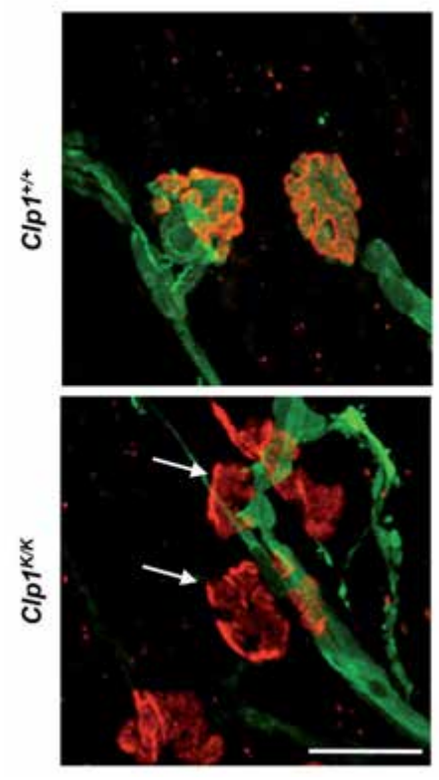

Figure 2

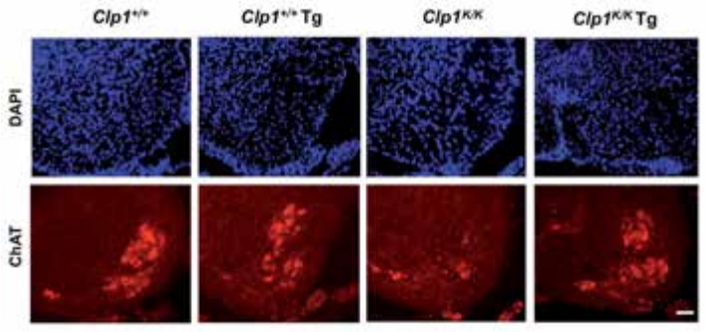

Figure 3

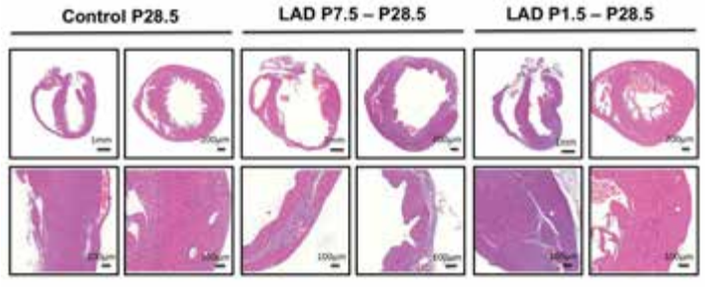

Figure 1: Denervation and fragmentation of neuromuscular junctions (NMJs) in the diaphragm. Whole-mount immunostaining depicting NMJs in the diaphragms of 5-month-old control $Clp1^{+/+}$ and kinase-dead $Clp1^{K/K}$ littermates. Post-synaptic AChR clusters are stained with α-bungarotoxin (red), and Schwann cells are labeled with anti-S100 antibodies (green). Arrows in show NMJ fragmentations. Scale bar: 100 µm.

Figure 2: Transgenic expression of wild-type CLP1 restores normal numbers of $ChAT^+$ motor neurons in the spinal cord of newborn mice. Immunostaining for ChAT1 (red) motor neurons in the lumbar (L5) spinal cord of newborn $Clp1^{+/+}$, $Clp1^{+/+}$ transgenic, $Clp1^{K/K}$ and $Clp1^{K/K}$ transgenic mice on a C57BL/6 background. DAPI staining.

Figure 3: Complete cardiac regeneration in newborn mice with massive myocardial infarction. Whole hearts and magnifications at the infarction areas are shown on postnatal day 28.5 (P28.5) after ligation of the anterior descending artery (LAD) of newborn mice at P1.5, and LAD ligation in mice at P7.5 after birth. Note that complete regeneration of the infarction zone was achieved when the mice received LAD ligation on P1.5, whereas no regeneration was seen when mice were LAD-ligated on day P7.5.

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LEONIE RINGROSE GROUP

Epigenetic regulation by proteins of the Polycomb and Trithorax group

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The aim of research in epigenetics is to understand how a single cell, with a single genomic DNA sequence, can give rise to and maintain the extraordinary diversity of cell identities and functions that comprise the adult organism. Modifications in chromatin and the binding of other chromatin proteins and non-coding RNAs provide a regulatory layer that modulates genome function, so that one genome gives rise to several 'epigenomes'. The highly conserved Polycomb (PcG) and Trithorax (TrxG) groups of proteins are essential components of the epigenome in every cell type studied so far.

The PcG and TrxG proteins constitute an epigenetic "cellular memory" system that is essential for maintaining the correct identity of both stem cells and differentiated cells, and for orchestrating transitions between them. Aberrant expression of these proteins leads to developmental defects and cancer. PcG and TrxG proteins work antagonistically on several hundred developmentally important target genes to maintain repressed (PcG) or active (TrxG) transcription states. Since the PcG/TrxG proteins are able to maintain stable states of gene expression over several rounds of cell division, it was long believed that they must form stable static structures on their chromatin target sites. However, this system is extraordinarily dynamic: both PcG and TrxG proteins exchange rapidly on chromatin within seconds. This in turn offers opportunities for regulation, permitting switching or modulation of output in response to cell cycle, developmental, environmental or metabolic signaling. We focus on three key questions.

1) How does the system maintain memory? PcG and TrxG proteins bind mitotic chromatin. Using quantitative live imaging, FRAP and FCS, we have established an "*in vivo* biochemistry" approach to perform absolute quantification and kinetic analysis of PcG and TrxG protein dynamics in living *Drosophila* in single defined cells that undergo mitosis and differentiation. This shows that both PcG and TrxG proteins bind mitotic chromatin, and enables us to address two important questions: What is the molecular mechanism by which these proteins attach to mitotic chromatin? Is mitotic chromatin attachment important for cell identity and viability in the living animal? These questions are closely interconnected. If we understand mechanisms, we can extrapolate specific interactions to address their function. Using quantitative live imaging in combination with genetic analysis in living *Drosophila*, we dissected and quantified molecular mechanisms by which the TrxG protein ASH1 binds to chromatin *in vivo*, identifying distinct protein domains that mediate chromatin binding in the interphase and during mitosis. Using genetic rescue experiments, we show that mitotic chromatin attachment of ASH1 is essential for survival to adulthood as well as for the maintenance of correct cell identity in living animals (Steffen et al., submitted).

2) How does the system switch between active and silent states? Non-coding RNA strand switching defines the PRE/TRE status. PcG and TrxG proteins work through specialized DNA elements known as Polycomb/Trithorax Response Elements (PRE/TREs). We made the exciting discovery that, in both vertebrates and flies, specific developmentally regulated non-coding RNAs transcribed from these elements are involved in both silencing and activation by PcG/TrxG proteins. Remarkably, a *Drosophila* PRE/TRE switches its function by alternating between forward and reverse strands of its non-coding RNA. Our work identified a novel and potentially widespread class of PRE/TREs that switch their function by switching between forward and reverse strand non-coding RNA transcription (Herzog, Lempradl et al., in revision). Current work is focused on the mechanism by which these ncRNAs influence the properties of chromatin binding proteins.

3) What makes a PRE/TRE? Principles of DNA sequence in flies and mammals. We use quantitative assays to identify novel motifs required for PRE/TRE function in flies (Okulski et al., in preparation). However, the analogous elements in mammals proved to be highly elusive. The race to understand the sequence principles of mammalian PRE/TREs is currently one of the most active and controversial areas in the field of PcG/TrxG. Based on previous work in flies, we established a computational tool that can accurately identify candidate PRE/TRE elements on the basis of the DNA sequence alone (collaboration with Marc Rehmsmeier, University of Bergen, Norway). We are currently testing these predictions in quantitative experimental assays. Future work will be focused on identifying mammalian PRE/TREs on a genome-wide basis and understanding the relationship between DNA sequence and function in quantitative assays (Trupke et al., in preparation).

In addition, we recently showed that PREs and CpG islands are distinct regulatory entities, in contrast to current models. CpG islands and CpG-rich sequences were found to be necessary. In some cases they are sufficient to recruit vertebrate PcG proteins. We now show that the CpG island potentiates while the PRE consolidates recruitment and confers regulation (Figure 3; Heinen et al., submitted). The interplay between enhancers, CpG islands and PREs will be a key issue in future investigations.

Publication highlights:

Steffen P.A., Fonseca J.P., Gänger, C., Dworschak. E., Kockmann, T., Beisel, C., and Ringrose, L. Quantitative in vivo analysis of chromatin binding of Polycomb and Trithorax group proteins reveals retention of ASH1 on mitotic chromatin. Nucleic Acids Research 2013, 41, 5235-50.

Figure 1

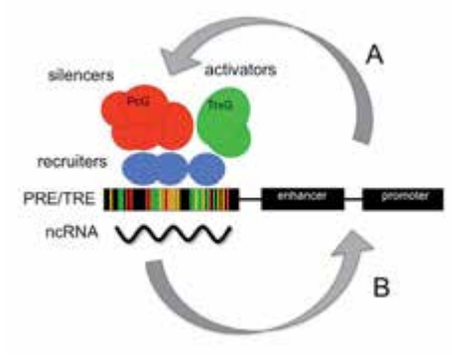

Figure 1: Polycomb/Trithorax response elements (PRE/TREs). PRE/TREs are cis-regulatory elements that can recruit both the silencing Polycomb group (PcG) proteins (red) and activating Trithorax group (TrxG) proteins (green) via a platform of sequence-specific DNA binding proteins (blue). Fly PRE/TRE elements contain multiple recognition motifs for these DNA-binding proteins (colored bars). Many fly PRE/TREs are transcribed into non-coding RNA. (A) Depending on the activity of the nearby enhancer and promoter, PRE/TRE elements can switch between stably active and silent states. (B) Many fly PRE/TREs can then propagate a memory of this active or silent state through several rounds of mitosis, in the absence of the transcription factors that initially determined the state of expression of the gene. Thus, they act as epigenetic memory elements.

Figure 2

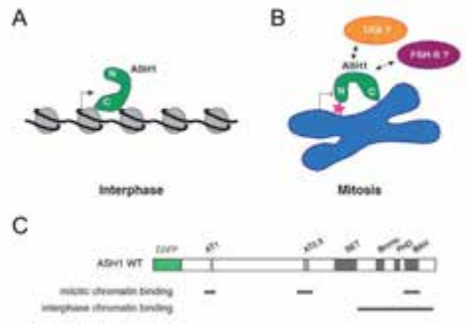

Figure 2: ASH1 binds interphase and mitotic chromatin via distinct domains. (A) ASH1 (green) interacts with chromatin mainly via its C-terminal domains. (B) During mitosis ASH1 switches its binding mode and binds chromatin via its N-terminal AT-hooks and the C-terminal BAH domain. The AT-hooks might be involved in the recognition of DNA features which act as bookmarks for active transcription (star), such as distorted or single-stranded DNA. Retention of ASH1 on active target genes during mitosis might cause accelerated re-activation of those targets after mitosis by the recruitment of factors such as TRX or FSH-S. (C) Domain structure of ASH1. Lines indicate protein domains required for chromatin binding during mitosis or interphase. (Steffen et al., submitted).

Figure 3

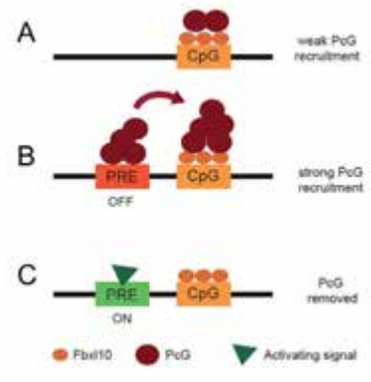

Figure 3: Vertebrate PRE/TREs are distinct from CpG islands. We wished to determine whether CpG islands are sufficient to confer PcG responsiveness on reporters in mouse ESCs. We integrated all constructs at the same genomic locus and were thus able to perform quantitative comparisons. This identified three novel mouse PRE/TREs. None of these three PRE/TREs contained a CpG island, whereas the five elements that failed to respond to PcG regulation in this assay all contained a CpG island. These results led to the following model: (A) A CpG island alone mediates weak recruitment of PcG proteins, but does not per se confer PcG-mediated regulation. (B) If a CpG island is flanked by a silent PRE, this results in stronger PcG recruitment and confers PcG responsiveness to the site. (C) If the PRE flanking the CpG island becomes activated, PcG proteins will be cleared from the PRE as well as the CpG island. (Heinen et al., submitted).

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VIC SMALL GROUP

Moving with actin

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

There is no life without motion at any level of metazoan organization from - individual cells to animal forms. During development, cells migrate from the germ layers and establish a blueprint of the body. In the adult organism, migrating cells play a key role in immune defense and tissue repair. Tumor dissemination and atherosclerosis also involve cell migration. In addition, several bacterial and viral pathogens recruit the motile machinery of cells to propagate their infection. Our studies focus on unraveling the structural basis of these processes and using this information to develop mathematical models of motility.

We know that cell motility is initiated by the extension of thin sheets of cytoplasm, so-called lamellipodia. However, the mechanism responsible for generating a 100- to 200-nm-thick sheet is not known. Cryo-electron tomography of B16 and NIH 3T3 cells, observed in vitreous ice, was used to provide single filament coordinates as well as determine membrane morphology at the leading edge. A stochastic mathematical model in which polymerization, branching, and capping depend on the local membrane curvature, determined by BAR proteins, was shown to mimic the flat shape of the membrane during cellular protrusion without any prescribed geometric restrictions. A feedback loop of local activation of filament polymerization and the dependence of branching on membrane curvature, together with a deformation of the membrane by growing filaments, adequately explained the 3D organization of actin filaments and the flat morphology of lamellipodia.

One class of pathogens, including the Gram-positive bacterium Listeria and the Vaccinia virus, hijack the motile apparatus of cells they infect in order to spread infection. They achieve this by nucleating comet tails of actin to propel them from one cell to the next. The smallest member of this class of pathogens is an insect baculovirus. Baculovirus measures just 40 nm in diameter (contrasted with the Vaccinia virus, which has a diameter of 300 nm) and generates actin comets small enough to permit resolution of all actin filaments constituting the comet tail by electron tomography. We developed a mathematical model that simulates the structural parameters of the comet tails determined by electron tomography, as well as the tracking characteristics of baculovirus in cytoplasm. In current conflicting models of pathogen propulsion, there is disagreement concerning the extent to which filaments may be bound to the pathogen surface as they polymerize and push. Our simulations support a model of propulsion in which filaments are continuously tethered to the pathogen surface. Analysis of cryo-electron tomograms of actin comets propelling Vaccinia virus reveals the same basic structural features of comet tail organization as determined for baculovirus, but with correspondingly more filaments involved in pushing. The mathematical modelling was performed in collaboration with Christian Schmeiser and Christoph Winkler at RICAM, Austrian Academy of Sciences and the Faculty of Mathematics, University of Vienna.

In separate studies electron tomography was used to obtain new insights into the role of the Arp2/3 complex and co-regulators in the formation and turnover of lamellipodia (Flynn et al., 2012; Koestler et al, 2012), as well as the relative roles of lamellipodia and filopodia in protrusion (Steffen et al.,2012). In further collaboration, we contributed to the characterization of Arpin, a protein inhibitor of the Arp2/3 complex implicated in cell steering (Dang et al.,2012), and the structural organization of lamellipodia in dendritic cells (with Michael Sixt at IST, Austria).

A Video Tour of Cell Motility

For an Introduction to the cytoskeleton and cell motility see our Video Tour website: http://cellix.imba.oeaw.ac.at/

Figure 1

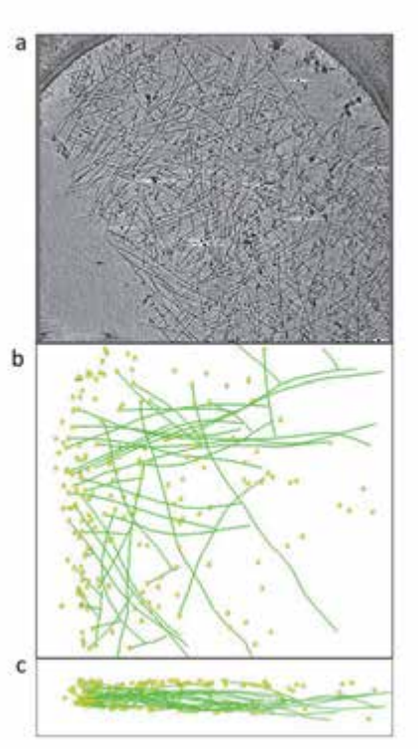


Figure 2

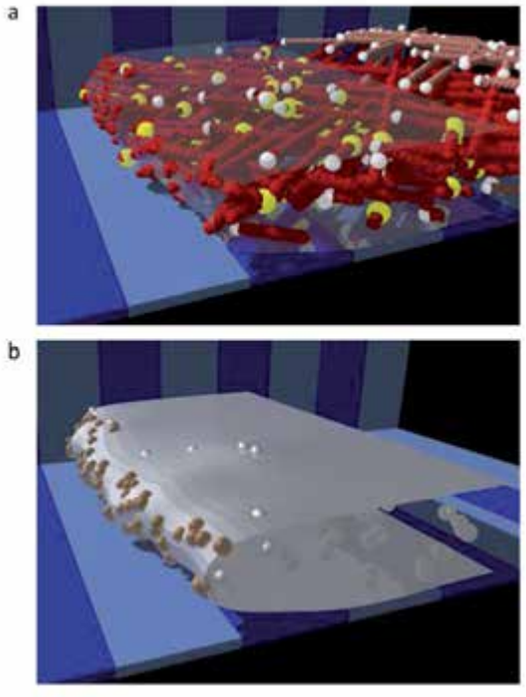
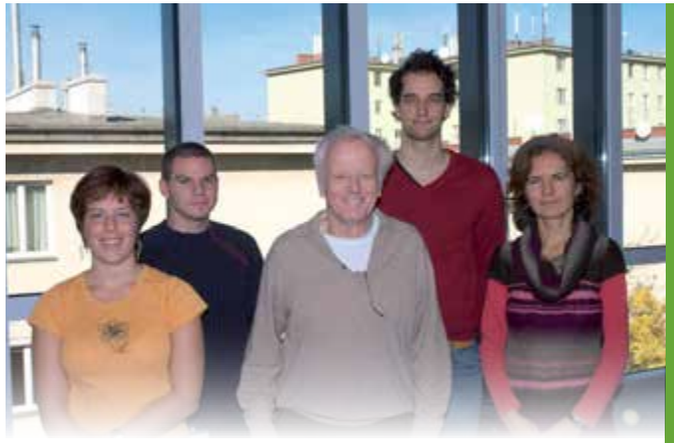


Figure 1: **a**, Cryo-electron micrograph of a lamellipodium in a fibroblast cytoskeleton showing the actin filament network. **b**, **c**, top and side views of the model derived from the tomogram in a, with the ends of the actin filaments marked with yellow spots and a subset of actin filaments tracked in green.

Figure 2: Mathematical model of the actin network of the lamellipodium (**a**) and the enveloping plasma membrane (**b**). Actin filaments are in red. Yellow spots indicate branch points in the network; gold spots in b indicate ends of filaments that are still growing. White spots in a and surface bumps in b indicate the end of filaments that are capped and blocked from further growth.
Images in a and b, by courtesy of Christoph Winkler, RICAM.



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KIKUE TACHIBANA-KONWALSKI GROUP

Molecular control of the oocyte-to-zygote transition

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The challenge in fertilization is to transform two highly differentiated cells, egg and sperm, into a single totipotent cell - the zygote - with vastly different properties compared to its parental cells. To generate a viable zygote, the meiotic cell cycle machinery switches to the mitotic form and sperm chromatin is reorganized and reprogrammed. How these fascinating processes are regulated at the molecular level and how their deterioration impacts fertility are key questions we aim to address in our research.

One of the most dramatic transitions in biology is the oocyte-to-zygote transition. This process refers to the maturation of the female germ cell or oocyte, which undergoes two rounds of meiotic chromosome segregation and, following fertilization, is converted into a mitotically dividing embryo. We are addressing fundamental questions relating to the processes that ensure the inheritance of genomes from one generation to the next by combining germ cell and chromosome biology with cell cycle and epigenetic studies. Achieving a molecular understanding of key players such as cohesin is a requisite step for investigating how deterioration of these factors contributes to maternal age-dependent aneuploidy and infertility. The current trend towards advanced maternal age has increased the frequency of trisomic fetuses by 71% in the past ten years. Therefore, a better understanding of mammalian meiosis is relevant to human health.

How is sister chromatid cohesion maintained for months and decades in oocytes?

The inheritance of chromosomes from mother to daughter cell and from one generation to the next depends on sister chromatid cohesion, which is mediated by the cohesin complex. Cohesin is especially important in meiosis, which is a specialized cell division giving rise to haploid gametes, egg, and sperm. The paradigm of reproductive biology is that sister chromatid cohesion is established during meiotic DNA replication in oocytes of the embryo, recombination occurs before birth, but oocytes remain arrested until ovulation triggers the first meiotic division several months (mouse) or decades (human) later. Must cohesin therefore hold sister chromatids together for months and possibly decades? Alternatively, is cohesion regenerated during the long arrest period? We have shown that, remarkably, there is no detectable cohesin turnover for several weeks in oocytes. Whether cohesion is regenerated over months remains a crucial question. We are addressing this using TEV protease technology that we have pioneered in the mouse (Figures 1 and 2), molecular genetics, microinjection, and 4D confocal live-cell imaging. To elucidate the mechanisms maintaining cohesion in oocytes, we are complementing cell biological assays with biochemical approaches and mass spectrometry.

How does the spindle assembly checkpoint function at the oocyte-to-zygote transition?

It has been known for decades that the first round of chromosome segregation in oocytes is error prone, leading to chromosomal abnormalities such as trisomy 21 or Down's syndrome, but the molecular basis has remained elusive. In mitotic cells, the spindle assembly checkpoint (SAC) monitors kinetochore-microtubule attachments and delays the onset of anaphase until the last chromosome has bi-oriented on the spindle. The SAC also regulates the timing of chromosome segregation in oocytes, but how it functions at the level of kinetochores is less clear. By specifically targeting TEV protease to kinetochores in oocytes expressing TEV-cleavable cohesin, we demonstrated that cohesin is necessary for sister kinetochore mono-orientation and robust SAC activity, which has important implications for aging oocytes with cohesin deterioration. We also discovered that zygotes with TEV-cleaved cohesin arrest in mitosis (Figure 3). Future work will focus on the molecular basis of differences in the checkpoint activity of oocytes and zygotes.

How is chromatin reprogramming coordinated with cell cycle progression in zygotes?

Fertilization triggers the second meiotic division and entry into the first embryonic cell cycle. During the zygote stage, maternal and paternal genomes remain as separate entities with distinct chromatin signatures. Maternal factors control sperm chromatin reorganization as protamines are replaced by histones and chromatin remodeling erases cell-type specific epigenetic marks. We are specifically interested in how chromatin organization, epigenetic reprogramming, and cell cycle progression are coordinated, which is currently poorly understood. We adopt a conditional knockout approach, combined with cell cycle kinetic studies, to investigate candidate factors required for these processes. Genetic knockout zygotes have the potential to be rescued by microinjection of mRNAs encoding target proteins. We are therefore developing this powerful system for *in vivo* structure-function studies in order to dissect the mechanisms of chromatin organization and cell cycle regulation in zygotes.

Publication highlights:

Tachibana-Konwalski, K., Godwin, J., Borsos, M., Rattani, A., Adams, D.J., Nasmyth, K. (2013). Spindle assembly checkpoint of oocytes depends on a kinetochore structure determined by cohesin in meiosis I. Curr Biol, in press.

Seitan, VC., Hao, B.*, Tachibana-Konwalski, K.*, Lavagnolli, T., Mira-Bontenbal, H., Brown, KE., Teng, G., Carroll, T., Terry, A., Horan, K., Marks, H., Adams, DJ., Schatz, DG., Aragon, L., Fisher, AG., Krangel, MS., Nasmyth, K., Merkenschlager, M. (2011). A role for cohesin in T-cell-receptor rearrangement and thymocyte differentiation. Nature. 476(7361):467-71. (*equal contribution)*

Tachibana-Konwalski, K., Godwin, J., van der Weyden, L., Champion, L., Kudo, NR., Adams, DJ., Nasmyth, K. (2010). Rec8-containing cohesin maintains bivalents without turnover during the growing phase of mouse oocytes. Genes Dev. 24(22):2505-16.

Gonzalez, MA., Tachibana, KE.*, Adams*, DJ., van der Weyden, L., Hemberger, M., Coleman, N., Bradley, A., Laskey, RA. (2006). Geminin is essential to prevent endoreduplication and to form pluripotent cells during mammalian development. Genes Dev. 20(14):1880-4. (*equal contribution)*

Figure 1

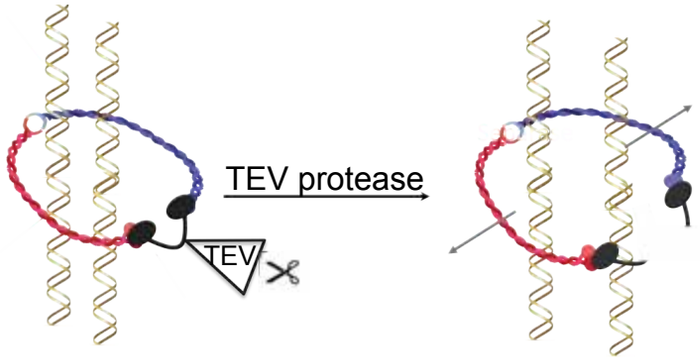
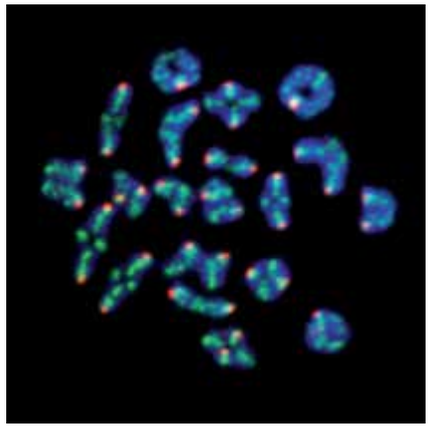


Figure 2



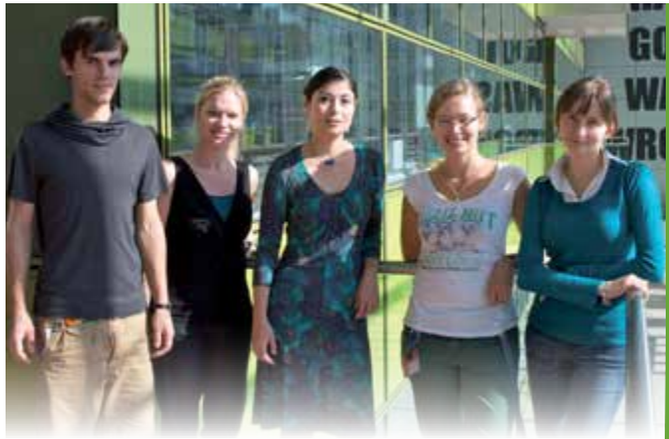


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Figure 3

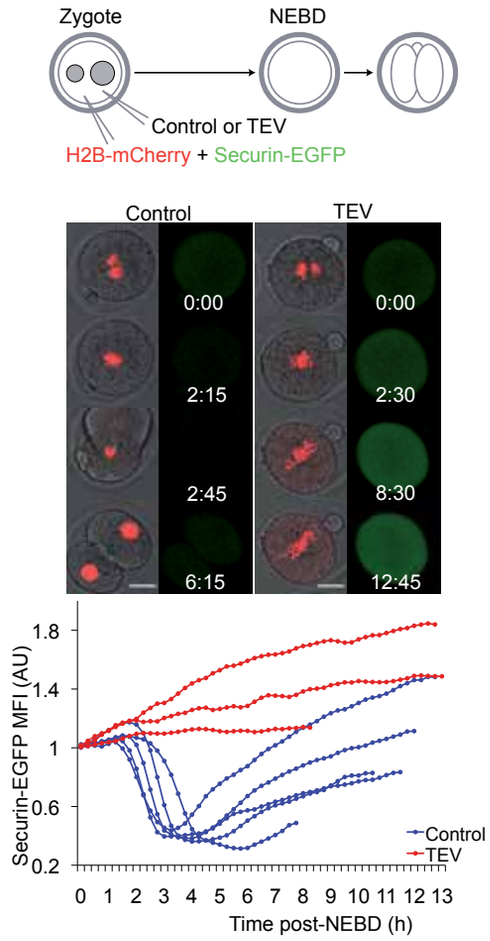
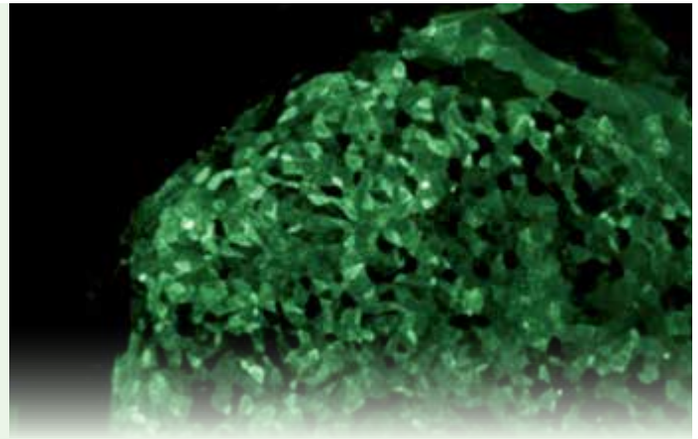


Figure 1: Development of TEV protease technology to cleave mammalian cohesin complexes *in vivo*. Schematic diagram of the cohesin ring consisting of an Smc1/Smc3 heterodimer (red/blue) bridged by a kleisin subunit (black), which is Rec8 in meiosis and Scc1 in mitosis. Rec8 or Scc1 have been genetically engineered to contain TEV protease recognition sites. TEV protease-mediated cleavage of cohesin induces ring opening and destroys sister chromatid cohesion.

Figure 2: Rec8-cohesin complexes maintain sister chromatid cohesion in oocytes. Chromosome spread prepared from a mouse oocyte and stained with c-Myc antibody to visualize Rec8-Myc (green) expressed from a constitutive BAC transgene, CREST to mark centromeres (red) and Hoechst to visualize DNA (blue).

Figure 3: Scc1-cohesin complexes maintain sister chromatid cohesion in zygotes. Zygotes expressing TEV-cleavable Scc1 were injected with mRNA encoding H2B-mCherry to mark chromosomes (red), and Securin-EGFP to monitor cell cycle progression (green) and control buffer or TEV protease. Still images of zygotes are shown, starting with nuclear envelope breakdown (NEBD) that marks entry into mitosis (h:mm).



Human iPSC cells generated from adult dermal fibroblasts express the pluripotent stem cellmarker Tra-1-81.

STEM CELL CENTER - GENE TARGETING UNIT

The main objective of the Stem Cell Center is to broaden and strengthen stem cell research. Ideal human disease models can be engineered by combining homologous recombination, site-specific recombination, and transgenesis using mouse ES (embryonic stem) cells. Our iPSCs (induced pluripotent stem) cells core facility was created to accelerate research in the stem cell field by facilitating the derivation of iPSCs cell lines. iPSCs technology allows to generate high-quality iPSCs from human primary cells with the ability to differentiate into a cell type of interest, e.g. skin cells. Moreover, disease causing defects can be readily 'repaired" in iPSCs derived from patients. Thus, iPSCs provide a potential avenue to study regulation of pluripotency and differentiation, drug screening and cell-based therapies.

ES core facility

The several missions of the ES cell core facility include the production of quality-controlled ES cell lines with mutations introduced by homologous recombination, the creation and handling of quality-controlled ES cell lines, and enhancing knowledge of mouse genetics, ES cell culture, and manipulation. Targeted ES cells can be used to generate germline ES cell-mouse chimeras. In addition, highly germline-competent ES cells derived from inbred strains, which are preferentially used in biomedical research, would greatly facilitate the generation of targeted mutations in appropriate genetic backgrounds, such as FVB/N and C57BL6/N ES cell lines. We also develop *in vivo* inducible gene targeting systems new transgenic recombinase mouse models.

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

iPS core facility

Our iPS core facility was created to accelerate research in the stem cell field by facilitating the derivation of iPSC cell lines. In order to extrapolate this technology to the clinical setting, we have established the generation of human iPSCs using 4F or microRNAi lentiviral, sendaiviral or synthetic mRNAs for virus-free iPSCs from dermal fibroblasts or keratinocytes. Next, we need to develop protocols to generate clinical-grade, integration-free, and xeno-free iPSCs and transfer and adapt our differentiation protocols to GMP standards. Finally, our vision is to create a bank of GMP-iPSCs from patients from cells isolated from non-invasive approaches such as urine stem cells or keratinocytes from plucked hair. This simple isolation technology offers benefit over skin biopsies in terms of ease of collection. To overcome the limitations of conventional gene targeting in human pluripotent cells, TALEN or CRISPR/Cas9 technology has been developed that can be used to repair disease-associated mutations in patients.

iPSCs-based therapy for Epidermolysis bullosa

Epidermolysis Bullosa (EB) is one of the most sever rare inherited skin disorders affecting children and adults. To date, only symptomatic treatment of severe blistering exist ultimately resulting in local and systemic complications such as fusion of the digits, malnutrition, infections, growth retardation and skin cancers. No drug is known to compensate the underlying molecular defects in EB. In order to establish iPSCs-based therapies for the treatment of EB, we have already addressed several key issues. We have successfully developed human iPSCs from EB patients and two different mutant mouse strains that develop EB-like syndromes. Secondly, we established protocols to differentiate mouse and human iPCSs into Collagen 7-secreting prototypic keratinocytes and prototypic fibroblasts. Currently, we assess the therapeutic efficacy and optimal grafting conditions, stability and safety. Our results might also serve as a model for the treatment of other severe genetic skin diseases as well as non-dermatological disorders. Although "multiple hills need to be climbed", iPSCs provide a potential avenue for a cure of this "yet incurable" disease. Combination of conventional approaches with iPSCs technology should translate this knowledge to the benefit of rare disease patients.

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The Fly House provides research support for the scientists at IMBA working with the fruitfly Drosophila melanogaster as a genetic model system. Our service includes the generation of transgenic fly lines, gene targeting 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, including large BAC clones, into a range of commonly used host strains as well as attP landing site stocks for phiC31-mediated targeted integration, and subsequently perform all crosses to establish mapped and balanced transgenic stocks.

Genome engineering

Gene targeting via homologous recombination has only recently been established in *Drosophila*, but is time-consuming and labour intensive. The recent advent of sequence-specific nucleases allows to speed up this process significantly. During this year, we have successfully established the CRISPR/Cas9 system to generate mutants as well as to tag endogenous genes at high frequency, and expect a growing demand for this targeting service in the coming year.

Research support

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

HEAD OF FACILITY:
ANDREAS LEIBBRANDT
COORDINATOR HAPLOID STEM CELL LIBRARY
ULRICH ELLING

RESEARCH ASSISTANTS:
ANNA-MARIA HUSA, JULIA LIEBERGESELL, ELLEN WETZEL

HAPLOBANK

Genome-wide recessive genetics in ES cells

haplobank@imba.oeaw.ac.at

In the post genomic era, science is accumulating large amounts of (high-throughput) datasets. Validation of such data often requires genetic testing. Haplobank sets out to generate a genome-wide library of mutant embryonic stem cell lines with defined mutations in order to functionally validate predictions, study phenotypic effects of gene loss in more detail, and thus helps to phenotypically annotate the genome.

Some organisms such as yeast are haploid, i.e. they carry a single set of chromosomes, and thus provide a basis for genetic analyses where recessive mutations of genes will show a clear phenotype due to the absence of a second gene copy. However, all somatic mammalian cells carry two copies of chromosomes (diploidy) that complicate mutational screens. We have previously described the generation of mammalian haploid embryonic stem cells from parthenogenetic mouse embryos. Haploid mESCs show stable growth over multiple passages, can be efficiently subcloned, and differentiate *in vitro* and *in vivo*. Importantly, haploid mESCs can be readily mutagenized at the haploid state to generate complete, homozygous mutants for virtually any gene allowing for reverse and high-throughput forward genetic screens.

We have recently developed and optimized various conditional transposon-, lentiviral-, and retroviral-based mutagenic gene trap vectors. In addition, each introduced single mutation carries an unique internal DNA barcode.

Using this optimized mutagenesis, Haplobank generates an archive of homozygously mutated ES cell lines for functional genomics. Our aim is to generate 100'000 independent mutant ES cell clones with mapped mutations. In order to allow for such a high-throughput, we streamline and automatize cell culture, DNA preparation, and deep sequencing protocols using a Hamilton robotic platform. Currently, Haplobank comprises about 30'000 clones with mapped mutations hitting 6210 genes and will be made available to the entire scientific community. We already distribute available cell lines on campus. In addition, we supply protocols for cell culture, confirmation of mutations, reversion of conditional mutations, etc. on our homepage. Clones, protocols and further information can be found from internal IP addresses at: http://haploidweb/home

Achievements 2013:
Funding and collaboration contract with Nestle Institute of Health Science (NIHS)
Collaboration contract with Novartis Institute of BioMedical Research (NIBR)

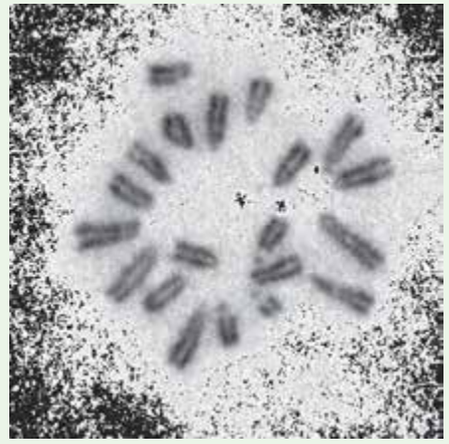
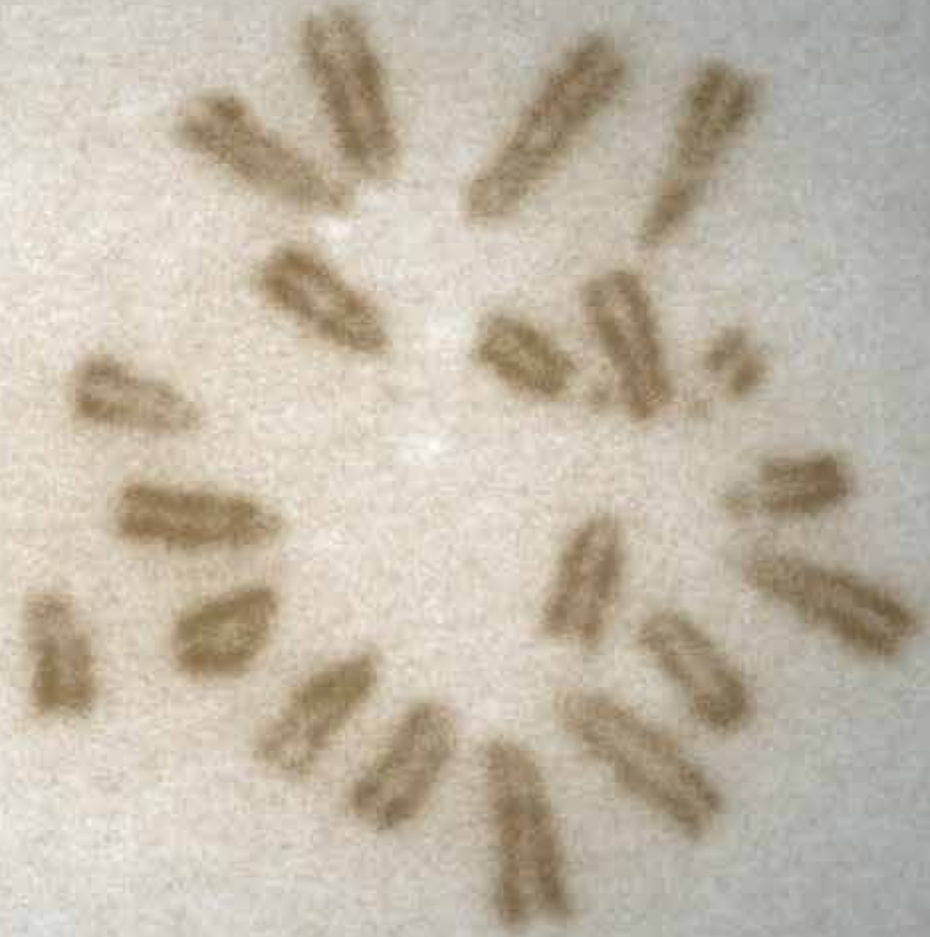


Figure: Chromosome spread of haploid ES cell line



HEAD OF BIOOPTICS: KARIN AUMAYR

FLOW CYTOMETRY/IMAGE ANALYSIS: THOMAS LENDL, GERALD SCHMAUSS
MICROSCOPY: TOBIAS MÜLLER, PAWEL PASIERBEK
MICROSCOPY/FLOW CYTOMETRY: GABRIELE STENGL

BIOOPTICS FACILITY

aumayr@imp.ac.at

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

Flow Cytometry

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

Microscopy

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

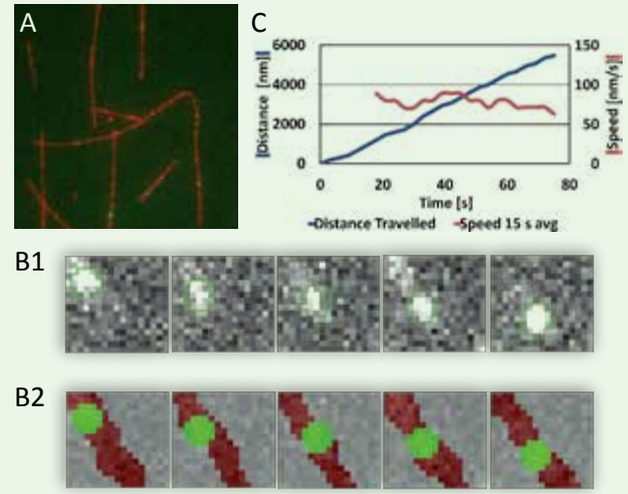
Image Processing and Analysis

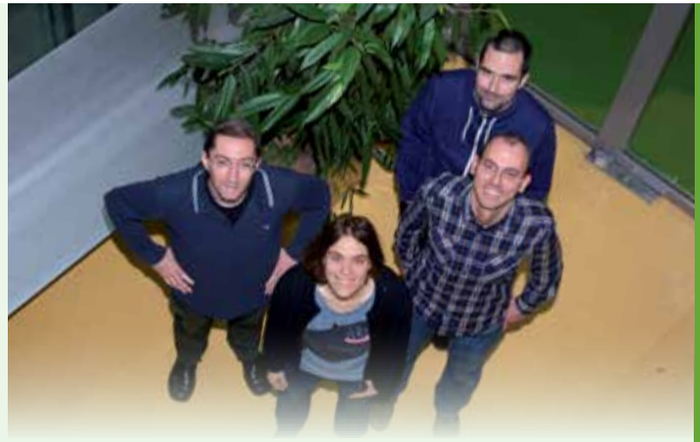
Five state-of-the-art computer workstations are available at the BioOptics Facility, operating most of the common commercial image processing and visualization software. A server solution with a Web-based interface has been set up to enable deconvolution of microscopy images. The server permits efficient,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

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

Figure: Motor proteins moving along microtubules were imaged using a TIRF microscope (A), automatically identified, classified and tracked through direct overlap (B1; B2). Information on distance travelled and speed of the tracked objects was acquired (C).

Legend for Fig. B1 and B2: *Motor protein* *Microtubules*





COMPUTATIONAL BIOLOGIST: THOMAS BURKARD, MARIA NOVATCHKOVA, ALEXANDER SCHLEIFFER
SOFTWARE ENGINEERS: BENJAMIN ALMEIDA [1], WOLFGANG LUGMAYR [2], HANNES SCHABAUER [3]

[1] FROM OCTOBER
[2] UNTIL SEPTEMBER
[3] FROM DECEMBER

BIOINFORMATICS

bioinfo.grp@imp.ac.at

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

One of the principal areas of expertise at IMP-IMBA Bioinformatics is 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 provided for widely used scientific applications related to protein motif analysis (in-house development), similarity searching (BLAST, PSI-BLAST, FASTA), whole-genome viewing (GBrowse, UCSC browser), 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. Assistance is provided in experimental design and subsequent analysis of next generation sequencing, microarray, and mass-spectrometry-based proteomics experiments. We also engage in custom software and database development, and design computational and mathematical solutions that can cope with higher loads and memory requirements. To perform complex sequence analysis tasks we maintain the IMP ANNOTATOR, which is a user-friendly Web application and a high-throughput protein annotation system. Local instances of integrated model organism databases (Wormbase) and genome annotation portals permit visualization and analysis of in-house data with dedicated resources and additional privacy. User-driven data exploration is supported by the Ingenuity Pathway Analysis System.

For heterogeneous computational tasks, we maintain a high-performance computing cluster in which dedicated software is adapted to run in a batch and parallel computing environment. This 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, HKL2000), image processing (e.g. Xmipp), 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, at which attendees learn the basic principles and limitations of sequence analysis and data integration. To enable researchers to use our server environment in an optimal way, we also provide training in BASH and Unix command line tools specific to the IMP/IMBA infrastructure.

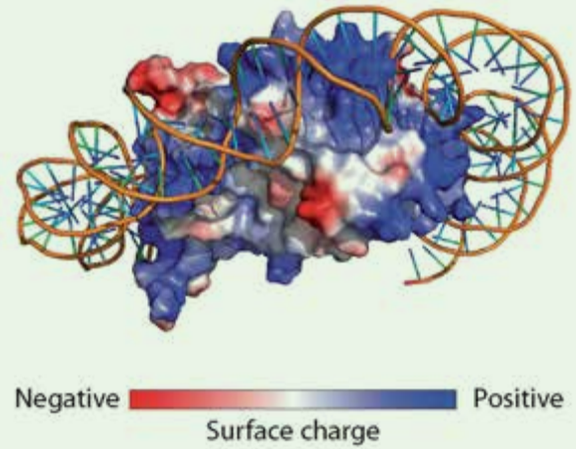


Figure: Hypothetical model of the non-canonical histone fold proteins CENP-T/W/S/X enclosed by a 73bp DNA fragment. The model is based on crystal structures of the CENP-T/W/S/X heterotetramer (PDB: 3VH5) superimposed on one half of the nucleosome core particle (only the DNA fragment is shown, PDB: 1KX5). The CENP-T/W/S/X heterotetramer is plotted as electrostatic surface potentials, illustrating the high density of positively charged surface residues (blue) that form the putative DNA interface.

HEAD OF FACILITY: KARL MECHTLER

POSTDOCS: ZUZANA DEMIANOVA, CHRISTOPH JÜSCHKE [1], THOMAS KÖCHER, NIKOLAI MISCHERIKOW, EVELYN RAMPLER, JOHANNES STADLMANN, WERNER STRAUBE
BIOINFORMATICIAN: GERHARD DÜRNBERGER, SERGEY MALTSEV, THOMAS STRANZL, THOMAS TAUS
PHD STUDENT: DEBORA BROCH TRENTINI
TECHNICAL ASSISTANTS: JOHANNES FUCHS, OTTO HUDECZ, RICHARD IMRE, GABRIELA KRSSAKOVA, MATHIAS MADALINSKI, MICHAEL MAZANEK [2], SUSANNE OPRAVIL, ELISABETH ROITINGER [2], MICHAEL SCHUTZBIER, INES STEINMACHER
TRAINEES: ETIENNE BELTZUNG, DOMINIK MAYER, FLORIAN STANEK

[1] UNTIL 31.12.2013, [2] PART TIME

PROTEIN CHEMISTRY

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At the Mechtler laboratory we analyze biological samples with mass spectrometric (MS) methods. We also develop novel MS-based methods to answer fundamental biological questions.

Glycoproteomics

Glycosylation is an abundant - yet functionally not well characterized - post-translational modification of proteins. Due to the structural complexity and the unfavorable fragmentation behavior of glycopeptides, the carbohydrates are removed from the peptide prior to MS analysis. As a consequence, the majority of MS-based glycoproteomic strategies do not yield information on glycan structures. Using our newly developed glycoproteomic workflow comprising a number of novel in-house software tools, we are able to provide comprehensive information about the primary structure of glycopeptides. In collaboration with the Penninger group we use the methodology for the characterization of glycoproteins from murine disease models.

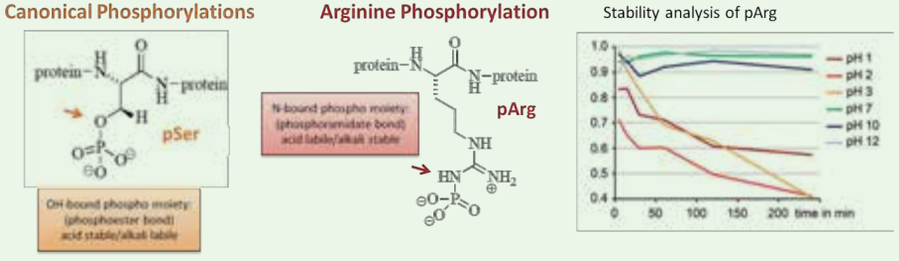
Stoichiometry of the kinetochore protein complex

Targeted proteomics approaches are widely used to quantify sets of predefined proteins in biological samples. In addition to selected reaction monitoring (SRM), a recently introduced method can be used to quantify a potentially larger number of proteins. SWATH-MS tries to combine the advantages of SRM and untargeted MS, potentially monitoring fragment ions of all precursor ions simultaneously. We recently established the novel method in our laboratory. In collaboration with the Westermann group, we use the approach to study dynamic changes in the stoichiometry of the kinetochore complex during the cell cycle.

Systematic detection of N-phosphorylation in bacteria and higher organisms

Across all life forms, the reversible phosphorylation of proteins is a universal regulator of biological systems. Protein phosphorylation analysis has therefore become one of the main targets for the development of MS methods. Today we have a wealth of information about serine, threonine and tyrosine phosphorylation sites. In contrast, very little is known about N-phosphorylation, modifying the side chain of histidine, arginine and lysine. The phosphoramidate bond is unstable at low pH – a condition commonly used in standard proteomic methods. The main focus of our work is to improve the MS-based toolbox for the study of arginine phosphorylation sites.

Recently the Clausen group discovered the first known protein arginine kinase, McsB, acting in the stress response of Gram-positive bacteria. Using this kinase for the generation of arginine-phosphorylated samples, we studied the stability of phosphoarginine (Figure 1) and adapted MS protocols accordingly. In collaboration with the Clausen laboratory, we apply the optimized methods to study the role of arginine phosphorylation in the stress response system of Bacillus subtilis. Furthermore, we work on developing specific enrichment procedures for phosphoarginine-containing peptides, which will permit the analysis of more complex biological systems.



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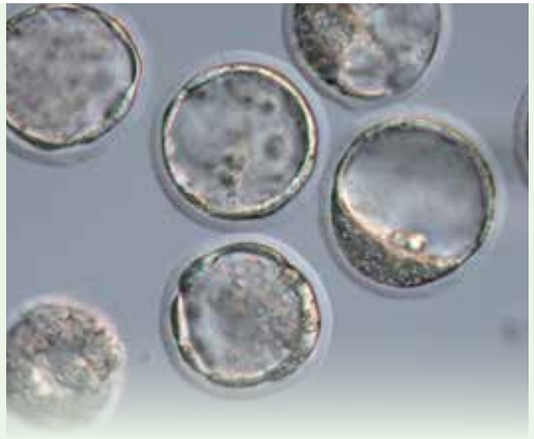

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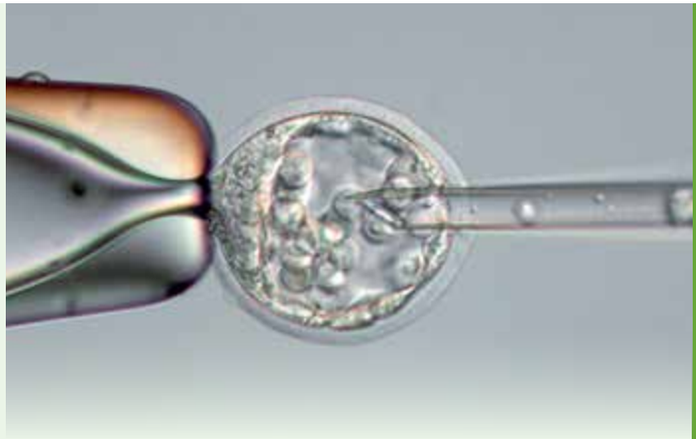


COMPARATIVE MEDICINE

animal@imp.ac.at

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

Husbandry:
The largest area of the animal house is the mouse section, which comprises breeding colonies, stock and experimental animals including many transgenic and knock-out mouse lines. To provide a constant supply of mice for the various projects, commonly used standard strains are routinely bred in-house.

Comparative Medicine Services:
Veterinary services, such as monitoring of the facility's health-status (sentinel-program etc.), experimental procedures in animals such as collection of blood, implantation of tumor cells and administration of substances. All procedures are performed to a high standard under appropriate anaesthetic regimes and in conjunction with the necessary project licenses.
Animal procurement, such as ordering of mice from external breeding companies, organizing and handling of incoming and outgoing mouse-shipments per year.
Administration of regulatory affairs in accordance with the Austrian laboratory animal law, which includes record-keeping and updating of laboratory animal statistics, specific documentation of laboratory animal experiments.

TRANSGENIC SERVICE

transgenic@imp.ac.at

The Transgenic Service Department was set up in the beginning of 1998 to cope with the increasing demand for mouse studies and generation of transgenic mice. The Transgenic Service Department is shared by the IMP and IMBA.

The main tasks of this service unit are the injection of ES cells into blastocysts [also tetraploid] and 8-cell morulae, and DNA into the pronucleus of fertilized mouse eggs. The service also provides for the transfer of 'clean' embryos into our Animal House, freezing of embryos for the preservation of specified mouse strains, and teaching basic embryological techniques to the staff of IMP and IMBA.

Many different ES cell clones and DNA/BAC constructs are being injected every year. The activities of the department are supervised by an Animal User Committee, which meets on a regular basis to set priorities and coordinate tasks. Currently it is chaired by Meinrad Busslinger.

Figure 1: Mouse blastocysts.

Figure 2: Injection of embryonic stem cells into mouse blastocyst.

HEAD OF FACILITY: HARALD SCHEUCH

SANGER SEQUENCING: ZUZANA DZUPINKOVA
PROTEIN EXPRESSION SPECIALIST: KRISTINA MARINOVA UZUNOVA
MOLECULAR BIOLOGY SPECIALIST: ROBERT HEINEN
TECHNICAL ASSISTANTS: IVAN BOTTO, MARKUS HOHL, SABINA MARIA KULA, CAROLINE SCHUSTER
TRAINEE: ELISA HAHN
FREELANCER: ANNA HAYDN

MOLECULAR BIOLOGY SERVICE

harald.scheuch@imba.oeaw.ac.at

The facility offers a variety of standard services and high-throughput methods for scientific experimentation for IMP, IMBA and GMI scientists. We also provide expertise in training and implementing molecular biology techniques.

Production of monoclonal antibodies, preparation of competent cells of various E-coli strains, Sanger DNA sequencing, a routine mycoplasma testing service for tissue culture cells, and robotics for high throughput liquid handling, still are the most prominent tasks performed at our department.

In 2013, we have established two new services, a "Speed Congenics" service and the expression of proteins.

"Speed Congenics" Service

Molecular Biology Service has started to offer a sequence length polymorphisms (SSLP)-based analysis of the genetic background of mice. The screening is achieved by using a set of approximately 90 markers evenly dispersed in a distance of 20 cM (≈ 20 - 40 Mbases) over the 19 autosomal chromosomes.

The information generated by this method is used for selecting only mice with the highest percentage of the genome of the receiver strain for further breeding.

The elimination of the donor genome can be achieved efficiently. Thus, a congenic strain can be developed within 4-5 backcross generations instead of 10 generations by using a traditional breeding strategy that is based on statistical assumptions. The time savings can also be translated to significant cost-savings for a research program, including mouse breeding and maintenance costs and accelerated phenotype analysis and data gathering.

Protein Expression

The use of recombinant proteins in daily scientific research has increased greatly in the last years. We have established *E.coli* expression systems for production of proteins like enzymes used for molecular biology experiments or growth factors for mammalian tissue culture to be used by our scientists. Since many of the proteins expressed in E.coli are found in inclusion bodies and thus require an additional re-folding step which lowers the protein yield and activity we are testing alternative expression sytems. In order to establish a more efficient method for producing growth factors that can also be used for other proteins we have started to explore *Pichia pastoris* as a eukaryotic expression system.

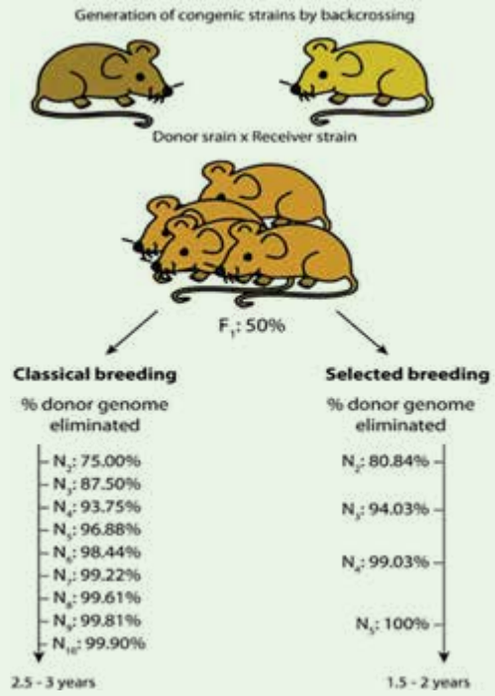


Figure: A comparison between classical breeding for backcrossing and selected breeding (Speed Congenics).

KARLO PAVLOVIC / LIBRARIAN

MAX PERUTZ LIBRARY

library@imp.ac.at

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

The main task of the library is to provide comprehensive scientific literature pertaining to the areas of research pursued at the institutes. The Max Perutz Library holds approximately 3000 titles in print. These are partly available in the library's premises itself, being labeled and shelved according to a specific classification system. A part of the titles are shelved in the group laboratories and offices. Increasingly, online books are being licensed in order to provide access for many readers simultaneously and from every workstation. Those 300 individually selected online books along with the print books can be searched for systematically in the online catalog, where each title is described in respect of its availability and accessibility. The most heavily used kind of literature resource are the licensed online journals.

Several bibliographic and full-text databases can be searched for relevant literature on a given topic. This also applies to literature on methods and protocols, including Springer Protocols, Current Protocols or the Journal of Visualized Experiments. A document delivery option is offered for the literature not held by the library, which is delivered within some hours for online content and one week for printed matter.

Study environment

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

Teaching

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

Users

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

CAMPUS SCIENCE SUPPORT FACILITIES

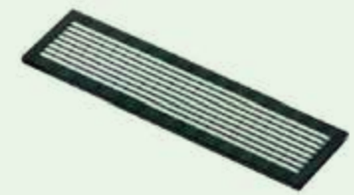
The Campus Science Support Facilities GmbH (CSF) was established in 2011 at the Campus Vienna Biocenter to provide top scientific infrastructure operated and constantly further developed by highly qualified experts. The CSF supports IMP, IMBA and other institutions and companies situated on the Campus at the forefront of science. Besides scientific infrastructure, the CSF also offers social infrastructure such as the Campus Child Care Facility. The CSF is located directly on the Vienna Biocenter Campus and is a non-profit organisation funded by a 10-year grant of the Austrian Ministry of Science and Research and the City of Vienna. For more information visit the CSF website: www.csf.ac.at

Preclinical Phenotyping (PPF)

Phenotypic screening is becoming increasingly important in the complex analysis of genetically manipulated mice. Thus, the primary objective of the Preclinical Phenotyping Facility (PPF) at CSF is to provide centralized support to investigators at the Campus Vienna Biocenter (and off-campus academic/Industrial companies), developing and studying genetically modified animal models relevant to human diseases.
We have designed a broad range of standardized tests for a high-throughput phenotypic screen in whole mouse including Metabolism, Neuro-Physiological and a range of Behavioral tests. In addition to the comprehensive panel of phenotyping tests, our facility provides a range of other services such as consultation, tailoring protocols to the need of the investigators, guidance, training, assistance to a complete performance and analysis of the experiments.

Next Generation Sequencing (NGS)

The NGS Facility provides cutting edge next generation DNA sequencing technology. We offer advice and guidance of sequencing projects as well as a set of selected bioinformatics tools. All common sequencing applications are supported, the development of novel methods and protocols encouraged.



Bioinformatics & Scientific Computing (BioComp)

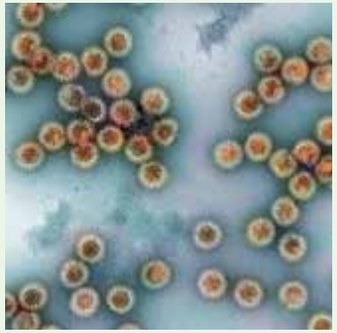
The Bioinformatics & Scientific Computing (BioComp) facility provides unique expertise and services in the areas of bioinformatics and scientific computing to academic and industrial researchers.
Our services include:

- Developing and applying advanced data analysis tools for the analysis of high-throughput data
- Providing innovative software solutions for biological experiments including image and video processing and hardware-related programming
- Delivering specific data management and processing tools to translate biological results into new insights
- Offering trainings and consultations in the area of bioinformatics, statistics and programming

Structural Biology (SBF)/ Protein Technologies Facility

The mission of the Structural Biology Facility (SBF) is to further research in protein biochemistry and structural biology by overcoming two major bottlenecks in these fields – protein production and purification. We provide services encompassing: molecular cloning; protein production in prokaryotic and eukaryotic expression systems; protein purification, including purification of antigens for antibody generation; biophysical characterization of proteins. We are currently working towards expanding our molecular cloning services to include preparation of constructs for genome editing/engineering projects as well as expression of fluorescently tagged proteins in a variety of systems.

In 2014 the name of the SBF will be changed to the Protein Technologies Facility (ProTech) in order to more accurately reflect our service portfolio.



Electron Microscopy Facility (EM)

The Electron Microscopy Facility offers a variety of preparation techniques for biological samples of diverse origin as a service: the techniques range from conventional preparation methods to cryo-preparation techniques for phenotyping the ultrastructure of tissues and cells. Furthermore, the EM Facility provides the processing of purified molecules for conventional and cryo-electron microscopy as well as sample preparation for scanning electron microscopy. Additionally, the facility offers trained users access to a comprehensive set of equipment for sample preparation and visualization of biological specimens at nanometer resolution, including the newly acquired FEI 200 kV transmission EM for tomography of resin embedded specimens and high resolution EM.

Vienna Drosophila RNAi Center (VDRC)

The Vienna Drosophila RNAi Center is a bioresource center maintaining and further developing one of the largest collections of transgenic RNAi lines, together with Gal4 driver lines, for conditional in vivo gene function studies. Currently, over 40,000 Drosophila lines are available to researchers world-wide. To date VDRC has shipped >800,000 lines to >2,000 registered users. We will further develop and expand our resources according to emerging new technologies and community needs.

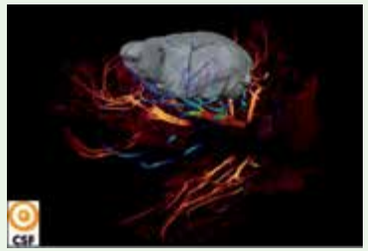
VDRC
VIENNA DROSOPHILA RNAi CENTER

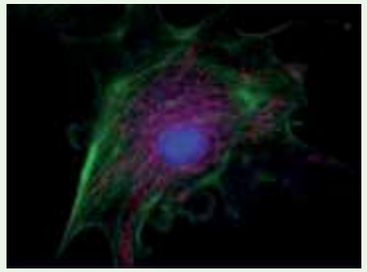
Plant Growth & Phenotyping (PG&P)

The PGP Facility operates 22 high quality, state-of-the-art and highly specialized plant growth chambers. Several chambers are capable of providing non-standard environmental conditions like for instance low temperature (frost), high temperature, different light intensities, light spectra and gas conditions (e.g. CO_2) allowing precise environmental simulation across different climate zones. In addition, the PGP offers an automated high throughput plant screening service. Parallel to basic plant research, the PGP facility will focus on the production of plant-derived biopharmaceuticals (molecular pharming) in the future. Within spare capacities all services will also be available for external customers.

Preclinical Imaging Facility

The Preclinical Imaging Facility offers ultrahigh field magnetic resonance imaging at 15.2 T for advanced anatomical and functional characterization of transgenic (mouse) models, both for whole animal screening and for focusing on specfic organs. Special expertise and support is provided in qualitative and quantitative image analysis.





Advanced Microscopy (AM)

The Advanced Microscopy facility provides access to cutting edge light microscopy techniques as well as the development of tailored light microscopy solutions. We also provide training and consulting on all our available microscopes, as well as sample preparation techniques and, in general, optical imaging techniques. Currently available techniques include 3D Structured Illumination Microscopy (SIM), time-domain Fluorescence Lifetime Imaging Microscopy (FLIM), Fluorescence Correlation Spectroscopy (FCS), and Fluorescence Anisotropy Microscopy. Through the continuous construction of "user friendly" microscopes that have already been determined to be cutting-edge, robust, and relevant to active research areas at the VBC, we give users access to the "technologies of tomorrow" – today (i.e. often before commercial solutions exist). Instrument development is typically in close collaboration with several research groups and financially partly also supported by them via the "Instrument Credit Point (ICP) Policy" (full details on CSF website). In this way the developed instruments and user interfaces are such that they are best suited to the desired applications.

Advanced Microscopy Facility

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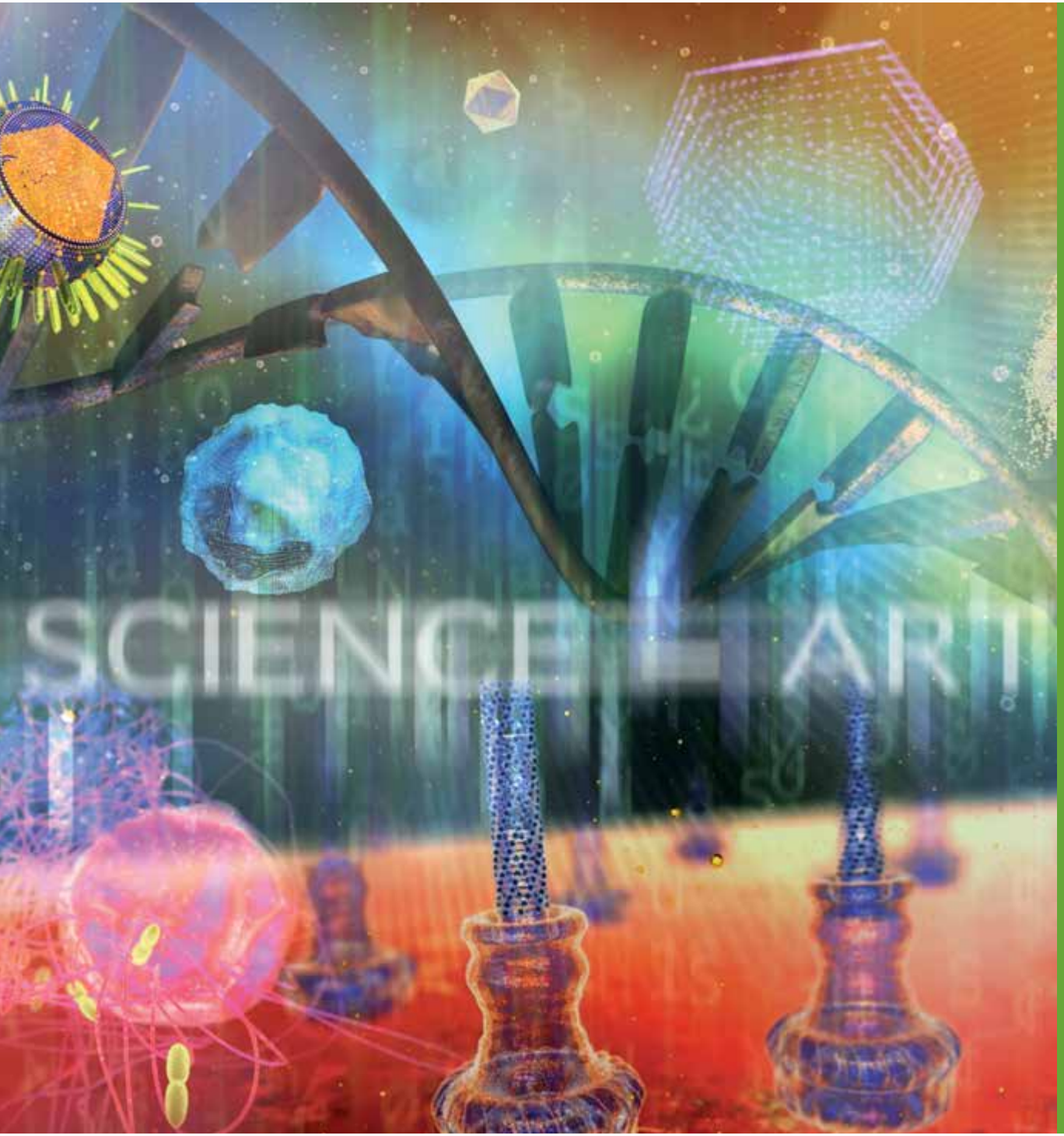

Awards & Honors 2013

Stefan Ameres

- *Starting independent Researcher Grant by the European Research Council ERC*
- *FWF START Award*

Oliver Bell

- *New Frontiers Group – OeAW Impulse Program Award*

Amalie Dick (Gerlich Group)

- *Kirsten Peter Rabitsch Award*

Fumiyo Ikeda

- *Consolidator Grant by the European Research Council ERC*

Jürgen Knoblich

- *Elected as Full member of the Austrian Academy of Sciences OeAW*
- *Elected as member of the Academia Europea*

Daniel Olivieri (Brennecke Group)

- *VBC PhD Award*

Josef Penninger

- *Advanced Investigator Grant by the European Research Council ERC*

Thomas Perlot (Penninger Group)

- *Research Prize 2013 from the Austrian Association of Molecular Life Sciences and Biotechnology (ÖGMBT)*

Grzegorz Sienski and Derya Donertas (Brennecke Group)

- *Best paper award of the Austrian Academy of Sciences*

Kikue Tachibana-Konwalski

- *Starting independent Researcher Grant by the European Research Council ERC*

JANUARY

15.01.13 Scott Emr
Cornell University
Protein quality control at the plasma membrane – Essential role for an arrestin - ubiquitin-ligase adaptor network

23.01.13 Thomas Walzthöni
Institute of Molecular Systems Biology, ETH Zurich
Structural characterization of macromolecular protein assemblies by protein cross-linking and mass spectrometry

24.01.13 Oliver Rando
University of Massachusetts Medical School
Epigenetic inheritance from yeast to mouse

31.01.13 Yves Barral
ETH Zurich
Nuclear dynamics and ageing: what can yeast tell us about it?

FEBRUARY

12.02.13 Zoltan Ivics
Paul Ehrlich Institute, Langen
Transposons: Evolution, Mechanism, Regulation and Genetic Applications

14.02.13 Anne Bertolotti
MRC Laboratory of Molecular Biology
Misfolded proteins: Prion-like propagation and potential cure

18.02.13 Florian Breitwieser
CeMM
isobar: Quantitative Analysis of Protein and PTM iTRAQ/TMT Data

28.02.13 Dirk Schuebeler
FMI Basel
Genetics and epigenetics: How DNA sequence guides the epigenome

MARCH

07.03.13 Mei Zhen
Samuel Lunenfeld Research Institute
The Genetic and Circuit Regulation of C. elegans Rhythmic Locomotion

14.03.13 Steven Reppert
University of Massachusetts Medical School
Monarch butterfly migration: from behavior to genes

20.03.13 Rippei Hayashi
London Research Institute Cancer Research UK
A genetic screen for maternal RNA mislocalisation identifies novel genes required for transposon silencing in Drosophila ovaries

28.03.13 Elmar Schiebel
ZMBH Heidelberg
The role of epidermal growth factor in regulating the timing of spindle assembly

APRIL

04.04.13 Gijs Versteeg
Department of Microbiology, Mount Sinai School of Medicine
The TRIM E3-Ligase Family Regulates Signaling Triggered by Innate Immune Pattern-Recognition Receptors

04.04.13 James Berger
University of California, Berkeley
Molecular mechanisms for initiating replication: running rings (and spirals) around DNA

09.04.13 Julius Brennecke / Luisa Cochella
VBC Lecture Series/IMBA/GMI
Forward genetic screens: from mutant isolation to gene identification

11.04.13 James Ferrell
Stanford University School of Medicine
Bistability and trigger waves in mitosis

16.04.13 Wolfgang Busch
VBC Lecture Series/IMBA/GMI
The identification of developmental regulators using large-scale phenotyping and genome wide association mapping

18.04.13 Daniel Zilberman
University of California, Berkeley
Evolution and function of DNA methylation in the context of chromatin

23.04.13 Alex Stark
VBC Lecture Series/IMBA/GMI
Gene regulatory regions - towards a regulatory code

25.04.13 Axel Borst
Max Planck Institute of Neurobiology
Neural Circuits for Fly Visual Course Control

30.04.13 Shukry J. Habib
Stanford University
A Localized Wnt Signal Orients Asymmetric Stem Cell Division

30.04.13 Ulrich Elling
VBC Lecture Series/IMBA/GMI
Forward and reverse genetics using haploid embryonic stem cells

MAY

02.05.13 Rene Ketting
Hubrecht Institute
Transgenerational effects of small RNAs

07.05.13 Juergen Knoblich
VBC Lecture Series/IMBA/GMI
RNAi screens in whole animals

14.05.13 Daniel Gerlich
VBC Lecture Series/IMBA/GMI
Machine learning in image-based screening

16.05.13 Joachim Wittbrodt
University of Heidelberg
Fate restriction and multipotency in retinal stem cells

21.05.13 Johannes Zuber
VBC Lecture Series/IMBA/GMI
Advanced RNAi systems for finding and probing therapeutic targets in human disease

23.05.13 Kristian Helin
BRIC/University of Copenhagen
Role of epigenetic regulators in stem cells and cancer

31.05.13 Matthias Groszer
INSERM & Université Paris Curie
Addicted to speak ? Foxp2 in reward circuits

JUNE

06.06.13 Walter Kolch
Systems Biology Ireland & Conway Institute
Dynamic protein-protein interactions coordinate signalling between the Raf and MST2/Hippo pathways

18.06.13 Phillip Zamore
University of Massachusetts Medical School
RNA silencing: Biology and Mechanism

19.06.13 Tiago Branco
MRC Laboratory of Molecular Biology
Dendritic computations in single neurons

21.06.13 Sebastian Carotta
The Walter & Eliza Hall Institute of Medical Research
Transcriptional regulation of hematopoietic stem cell formation and differentiation

JULY

11.07.13 Michael Orger
Centro Champalimaud
Whole brain imaging of neural circuit activity in behaving zebrafish

24.07.13 Evelyn Rampler
University of Natural Resources and Life Sciences
Quantitative mass spectrometric assays for yeast characterization

25.07.13 Nick Watkins
Institute for Cell and Molecular Biosciences, Newcastle University
Direct regulation of p53 by the ribosome biogenesis machinery

25.07.13 Magdalena Zernicka-Goetz
Gurdon Institute and Department of Physiology, Development and Neuroscience
Pluripotency and Differentiation in embryos and stem cells

25.07.13 David Glover
University of Cambridge
Plk4, not only the master regulator of centriole formation, but also…

SEPTEMBER

05.09.13 Mark Hochstrasser
Yale University
The ubiquitin-proteasome system: Tales from the beginning to the end

11.09.13 Mikko Taipale
Whitehead Institute, Cambridge
Quantitative profiling of protein/protein and drug/target interactions in mammalian cells

12.09.13 Frank Buchholz
MPI of Molecular Cell Biology and Genetics, Dresden
From high-throughput screens to biomedical knowledge

19.09.13 Gabriel Hayes
Editor, Cell
The Editorial Process and Being a Scientific Editor

19.09.13 Jan Löwe
MRC Laboratory of Molecular Biology
The Bacterial Cytoskeleton

24.09.13 Irina Kaverina
Vanderbilt University Medical Center
Golgi-derived microtubules and their functions

25.09.13 Clare Waterman
NIH Bethesda
Myosin II mediated endothelial cell branching morphogenesis in 3D by minimizing membrane curvature

26.09.13 Marian Walhout
University of Massachusetts Medical School
Integrative systems networks in the nematode C. elegans

OCTOBER

08.10.13 Alfredo Castello Palomares
EMBL
Insights into Biology and Disease from the first in vivo atlas of RNA-binding proteins

10.10.13 Frank Pugh
Pennsylvania State University
Integration of Chromatin Organization and Transcription Initiation on a Genomic Scale

17.10.13 Cedric Blanpain
WELBIO, Interdisciplinary Research Institute (IRIBHM)
Stem cells during development, homeostasis and cancer

22.10.13 Cheng-Yu Lee
University of Michigan
Discovering novel strategies to target cancer stem cells using Drosophila as an incubator

24.10.13 Yuh-Nung Jan
University of California, San Francisco (UCSF) / HHMI
Control of neuronal morphogenesis: from form to function and regeneration

24.10.13 Robert Schreiber
Washington University School of Medicine
Cancer Immunoediting: Basic Mechanisms and Therapeutic Implications

24.10.13 Charlie Roberts
Dana-Farber Cancer Institute, Harvard Medical School
SWI/SNF Chromatin Remodeling Complexes are Frequently Mutated in Cancer: Mechanisms and Potential Therapeutic Targeting

31.10.13 Kay Hofmann
University of Cologne
A common evolutionary basis for cell death signaling in animals, plants and fungi

NOVEMBER

14.11.13 Caetano Reis e Sousa
Cancer Research UK London
A DaNGeRous talk about dendritic cells

19.11.13 Esther Verheyen
Simon Fraser University
Genome wide analysis of phospho-regulation of Wnt/Wingless signalling

28.11.13 Lars Jansen
Gulbenkian Institute of Science
Self-propagating chromatin: the curious case of the mammalian centromere

DECEMBER

05.12.13 Pascal Genschik
IBMP CNRS Strasbourg
When protein degradation meets RNA silencing: Regulation of siRNA pathways by autophagy

05.12.13 Enrique Martinez-Perez
MRC Clinical Sciences Centre
Cohesin dynamics during meiotic prophase in C. elegans

12.12.13 Rafal Ciosk
FMI Basel
Regulation of pluripotency in animal development

16.12.13 Serge Luquet
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Dietary triglycerides act on mesolimbic structures to regulate the rewarding and motivational aspects of feeding

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

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Scientific excellence needs individual commitment. We would like to say THANK YOU to all of our supporters, donors and partners. Thank you for your contribution.

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RZB

ERSTE Bank – In jeder Beziehung zählen die Menschen.

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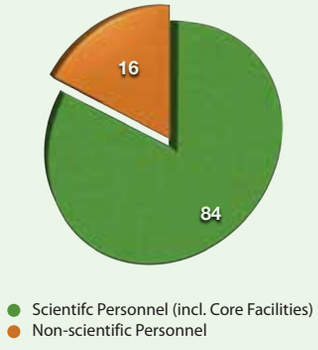
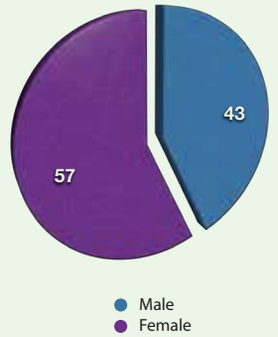
Spitz

IMBA Key Facts *(Data as of November 2013)*

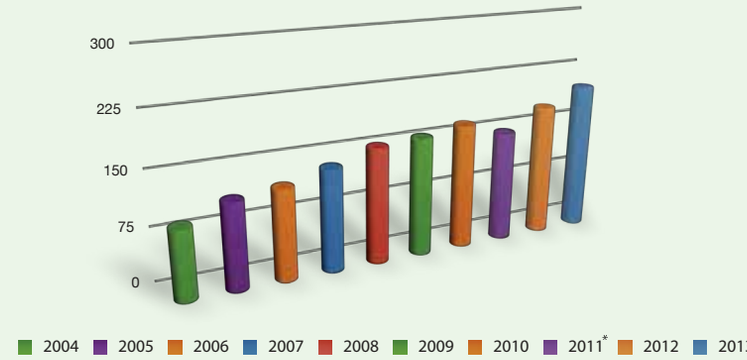
IMBA Staff (in %)



IMBA Staff - Gender Distribution (in %)

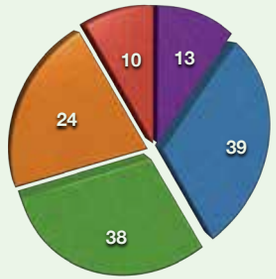


IMBA Staff - Development (Headcount)

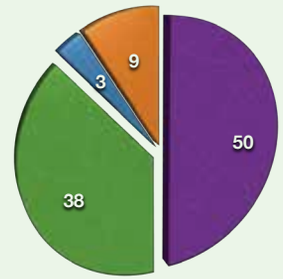


** Transfer of IMBA service units into Campus Science Support Facility GmbH*

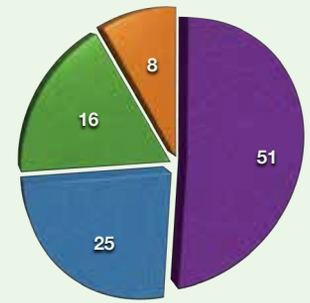
Scientific Staff - Functions (in %)



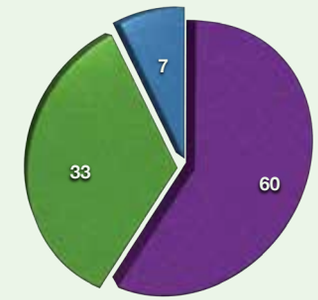
Scientific Staff - Nationalities (in %)



IMBA Budget 2013 (in %)



Public Research Grants 2013 (in %)



Your Career at IMBA!

IMBA focuses on providing an excellent environment for state of the art science as well as education, which makes it a perfect place to develop your career. We offer an excellent research environment for undergraduates, PhD students, postdocs, and principal investigators alike. All researchers have access to a superb infrastructure and generous funding, thus allowing for intellectual freedom.

IMBA is part of the Vienna Biocenter Campus. You will be part of a large scientific community. Most of our training offers are run jointly with the other research institutes on the campus: the Research Institute of Molecular Pathology (IMP), the Gregor Mendel Institute of Molecular Plant Biology (GMI), and Max F. Perutz Laboratories (MFPL).

We have specific educational programs for different career levels:

Undergraduate students - Vienna Biocenter Summer School

Every year the Vienna Biocenter Summer School provides a unique opportunity for 25 international undergraduate students to experience cutting-edge scientific research for a period of two months. Our summer fellows are provided with a stipend plus accommodation and a travel allowance. Throughout its four editions we received over 1800 applications from 97 nations, and have hosted 95 fellows.

"Great opportunity to learn new things, see how working in a leading European research institute looks like, meet new people from all over the world - altogether an amazing experience."
Testimonial from student from the 2013 class

Every year we open a competitive call (usually in December). For more information visit our website www.vbcsummerschool.at

Graduate students - Vienna Biocenter PhD program

As a PhD student at IMBA you can virtually do any experiment you can think of. Our goal is to train independent, critical and creative researchers. The VBC PhD program is focused on a 4-year research project with instructive courses, lectures, and also networking activities.

Most importantly, our faculty includes renowned scientists from all over the world, with outstanding publication records, all extremely committed to the training of young researchers.

All PhD students benefit from the support extended to our scientific facilities, and are employed with a full contract.

We open for applications twice a year (September-November and February-April). As part of the recruitment procedure we invite our top candidates for a week to the campus. Check out our website at www.vbcphdprogramme.at

Postdocs

The postdoc training program is designed to give you a competitive edge in the job market by providing a high level of training in soft skills. Currently the program includes courses in grant writing, paper writing and leadership. All of the courses are operated by experienced and outstanding coaches.

Applications for postdoc positions at IMBA can be submitted by direct email to the relevant group leader, along with an up-to-date CV. Funding is available from internal sources. However, postdoc applicants are strongly encouraged to apply for external fellowships to support their research.

No matter which stage of your career you are in, at IMBA you will always benefit from an

Outstanding scientific infrastructure

Scientific success at IMBA results, to a significant extent, from a wide array of scientific service facilities. The variety and quality of these units is unmatched by most of the top international research institutes. Support is provided for a wide range of subjects, including conventional and high-throughput sequencing, state-of-the-art mass spectrometry analysis, various microscopy and electron microscopy systems, and a bioinformatics unit. With very few exceptions, the scientist may access all of these facilities free of charge.

Attractive and family-friendly environment

IMBA cares a lot about the quality of life of its staff. We offer competitive salaries with health and social benefits. The campus has its own kindergarten (with opening hours suited to the scientists' needs). You may also avail yourself of a number of social activities - such as weekly social hours, a ski trip, and various retreats - which help you to get acquainted with your colleagues.

We try to make relocation as smooth as possible. Several in-house apartments are available to bridge the time until a staff member has found a place of his/her own. Our administrative staff is helpful in finding housing, and our personnel department takes care of your legal requirements including visas, registration, health insurance, and family matters. For school-aged children Vienna offers different types of schooling ranging from public to private, German or foreign language based.

More information about career opportunities at IMBA is available at: www.imba.oeaw.ac.at/career
http://life.imba.oeaw.ac.at/

IMBA and its Surroundings

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

The Campus Vienna Biocenter

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

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

Vienna–a City of many Facets

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

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

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

IMBA SPOTLIGHTS 2013

Kaleidoscope

This year's VBC Drama Club spring show "Kaleidoscope" was a joint production of the Amateur Drama Club (ADC) and members of the "MixTape Improv Group", which welcomes members from outside the campus as well. As the name suggests, it presented a spectrum of the many facets of improvisational theatre: surprising, funny, dramatic, interactive – the audience loved it all.

BI-IMP-IMBA meeting "Ubiquitin signalling and pharmacology"

BI-IMP-IMBA meeting 'Ubiquitin signalling and pharmacology' was held at the Hotel Turmhof in Gumpoldskirchen from January 16 till January 18, 2013. Fumiyo Ikeda (IMBA) co-organized the meeting together with Jan-Michael Peters (IMP), Guido Boehmelt (BI) and Nobert Kraut (BI). 10 external experts were invited in the field. The scientific discussion on site was very active and we heard the latest research progress of Ubiquitin research field. Fumiyo Ikeda contributed for chairing and making the sessions go smooth during the meeting.

8th "Microsymposium on Small RNAs"

At the end of May, the "Microsymposium on Small RNAs" was once again held at IMBA. The conference was initiated eight years ago by Javier Martinez and brings together leading researchers in the field of RNA interference. During the last years, the meeting has developed into one of the best known and most appreciated symposia of its kind in Europe.
This year's microsymposium was jointly organised by Javier Martinez, Stefan Ameres and Julius Brennecke. It offered an interactive platform to exchange ideas and discuss the latest scientific discoveries in the field of gene regulation by small, non-coding RNAs. As in previous years, special emphasis was placed on promoting young scientists and the PhD workshop was again a special highlight.

VBC Summer Concert

This year's VBC summer concert was held on June 12. The MolBio Orchestra was formed in 2006 by a group of molecular biology and biology students. It has featured concerts since 2010, which in the meantime have become a pleasant tradition on the campus. This year they collected donations for the charity "Kinderträume" at the concert.

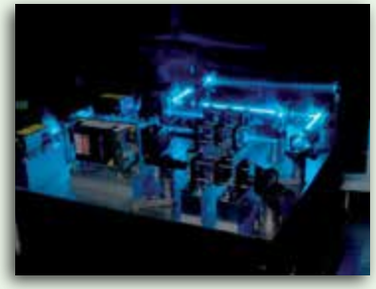
VBC PhD Retreat

This year the VBC PhD students organized a joint retreat with the Friedrich Miescher Institute for Biomedical Research (Switzerland). A total of 82 students attended (52 from the VBC and 30 from the FMI) this three-day event of intensive scientific discussion and networking. The students presented their projects either in an oral or poster format, and engaged in lively discussions. There were also career and scientific talks by four invited speakers: Bernd Pulverer (editor, EMBO Journal); Tiago Branco (group leader, LMB, Cambridge, UK); Jürg Müller (group leader, MPI, Martinsried, Germany), and Gerda Redl (patent attorney, Vienna). The weather was very pleasant, allowing for outdoor poster sessions and pleasant social evenings.

Ten Years of IMBA

From June 26 to 28, IMBA celebrated "Ten Years of Research". Distinguished guests from politics, academia and art, joined by family, friends and donors were invited to the festivities. During the course of the ceremony, the speakers congratulated IMBA, acknowledged its scientific achievements and pointed out the importance of intellectual and financial freedom in research.

Science Minister Karlheinz Töchterle referred to Josef Penninger as a "homo scientificus" and to IMBA as a "lighthouse for research".



5th QuEBS Workshop

The 5th International Workshop on Quantum Effects in Biological Systems was held at the IMBA lecture hall this summer. From June 29 to July 3, the leading experts of this young discipline met here to foster exchange and cooperation. As in the previous four workshops, the meeting covered the most recent advances in quantum phenomena in biological systems and chemical structures central to life. About 120 participants from all continents attended the meeting and listened to the talks of 22 invited speakers. Two poster-sessions complemented the lectures.

Oliver Bell: New IMBA Group Leader

Oliver Bell joined IMBA at the beginning of August. He obtained his PhD at the Friedrich Miescher Institute in Basel before moving to San Francisco for his postdoctoral training. At Stanford University he worked with the developmental biologist Gerald Crabtree in studying the regulation and function of chromatin modifications involved in gene repression. At IMBA Oliver will continue to investigate the dynamic regulation of the chromatin state and the contribution of chromatin modifications to the epigenetic inheritance of the gene expression state. Along with various genetic and biochemical methods, the Bell lab will capitalize on a novel approach known as the chromatin *in vivo* assay, which employs small molecules as "molecular pipettes" to turn the cell into a biochemical test tube.

VBC Amateur Dramatic Club Romeo&Juliet

On August 28 and 29, the Vienna Biocenter Amateur Dramatic Club performed its (partly) open-air summer spectacular - Shakespeare's "Romeo & Juliet". In this very special production, the action was transferred from Verona to Vienna, with the Montagues and the Capulets re-imagined as two warring tribes of Austrian soccer fans, while local government vainly tries to keep the peace.

Vienna Biocenter Summer School

The 4th Edition of the Vienna Biocenter Summer School from June 28 – August 30 was again a huge success. Twenty two students of 16 different nationalities joined at the campus for a two-month internship, which proved to be an unforgettable experience for one and all. Each summer fellow worked on an independent research project under the close supervision of a graduate student. Twice a week the students would gather around to listen to a 45-minute talk, and had the opportunity to ask questions and interact with our junior and senior faculty.
Throughout July and August the students worked hard, experienced life as researchers, but also had fun. The Summer School was concluded with a symposium at which the fellows presented their projects to the VBC scientific community.

7th Late Summer Practical Proteomics Seminar

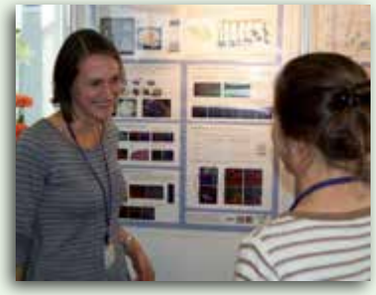
In September more than 160 scientists came to IMP in order to attend a meeting centered on technology. The seventh Late Summer Practical Proteomics Seminar at IMP was related to quantitative techniques in mass spectrometry and the analysis of post-translational modifications. The practical workshops were intended to give an introduction to bioanalytical methodologies. They covered a wide spectrum of topics ranging from phosphopeptide analysis with mass spectrometry to troubleshooting in nano-liquid chromatography. The short courses were complemented by talks from international speakers, who presented their recent work and current developments in mass spectrometry-based proteomics.

Postdoc Retreat

The postdoc retreat in September brought together 50 postdocs from all four institutions on the Campus VBC. In addition, the Research Center for Molecular Medicine – CeMM – and the Institute of Science and Technology (IST) Austria were represented. The retreat took place in Brno, Czech Republic, and was organized by the Vienna Area Postdoc Organization.

IMBA Recess

From October 2-4, 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, was once again impressed by the scientific performance and high standards of the research presented at the meeting. In 2013 3 new members joined IMBA's Scientific Advisory Board. IMBA would like to thank all SAB members and the representatives of the Austrian Academy of Sciences for their tremendous support. IMBA SAB members: page 52 in this booklet.



Birthday symposium

On October 24 Juergen Knoblich, the scientific deputy director of IMBA, celebrated his 50th birthday. A two-day birthday symposium started with a keynote lecture held by Juergen's former postdoctoral supervisor Yuh-Nung Jan, who came all the way from San Francisco. A reception with champagne and delicious food, followed by music, dance and drinks made the happy birthday complete. The following day was entirely devoted to science. Supervisors, collaborators and alumni came from all over the world to deliver talks on various topics, each enriched by a personal story.

VBC PhD Symposium TIME - How nature sets the clock

The subject of the 11th annual VBC PhD Symposium from November 7 - 8 was *time*. This event is entirely organized by the PhD students – in a very professional way! This year they had more than 400 registrations from the campus as well as other institutions, national and international.

The symposium gathered young scientists and leading experts from various fields to discover the many different timekeepers of biological systems, and fuel new and unconventional ideas for the future. As Nature has clocks for a variety of time scales, a wide range of topics were explored, such as biochemical oscillations, cell cycle timing, circadian rhythms, time perception, and time-driven population dynamics. The symposium also included an award ceremony for the best PhD thesis of the preceding academic year. The VBC PhD awardees this year were Evgeny Kvon (Stark group, IMP); Cosmas Arnold (Stark group, IMP); Doris Hellerschmied (Clausen, IMP); Fritz Sedlacek (von Haeseler, MFPL); and Daniel Olivieri (Brennecke, IMBA).

Farewell symposium Vic Small

Vic Small, currently Senior Scientist at IMBA will retire at the end of 2013. In a top scientific meeting named "Life at the leading Edge - Mechanisms of Actin Based Motility" and a great party on November 22, his friends and colleagues celebrated his life and scientific achievement. Vic has made multiple groundbreaking contributions to cytoskeletal research. His scientific work was directed towards understanding the structural basis of cytoskeleton turnover and the underlying molecular mechanisms. Will miss Vic greatly – as a scientist and trusted advisor.

TEN YEARS OF RESEARCH AT IMBA

At the beginning of summer, it was IMBA's time to celebrate. Ten years of research have put the institute on the scientific world-map and made Josef Penninger's dream a realistic goal: to become "the FC Barcelona of Science".

The institute was actually conceived as early as 1999, when the Austrian Academy of Sciences and the global Boehringer Ingelheim group signed a collaboration contract in Vienna. In 2001, Josef Penninger was appointed director and in 2003, the first research projects got under way.In 2006, when the new institute building was officially opened, several research projects were already well established. In the past ten years, the number of people working for IMBA rose to just under 200. Thirteen research groups are creating new insights and increasing our knowledge in fundamental biology, focused on contributing to the targeted medicine of the future.

We would like to say THANK YOU to all Partners and Sponsors of the IMBA 10 Years Symposium

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IMBA – celebrating ten years of research

From June 26 to 28, IMBA celebrated "Ten Years of Research". Distinguished guests from politics, academia and art, joined by family, friends and donors were invited to the festivities. During the course of the ceremony, the speakers congratulated IMBA, acknowledged its scientific achievements and pointed out the importance of intellectual and financial freedom in research.

Science Minister Karlheinz Töchterle referred to Josef Penninger as a "homo scientificus" and to IMBA as a "lighthouse for research". Foreign Minister Michael Spindelegger pointed out that IMBA had developed into a brand that was renowned internationally.

Michel Pairet, Senior Vice President for Corporate Research & Development non-clinical at Boehringer Ingelheim, told the audience how important basic research was for the pharmaceutical industry. Helmut Denk, the president of the Austrian Academy of Sciences, thanked Boehringer Ingelheim for their courage and foresight in supporting the collaboration between IMP and IMBA.

The surprise guest of the evening was the Catalan tenor José Carreras. Apart from his career as a singer, Carreras is also known for his humanitarian work as the president of the "José Carreras International Leukaemia Foundation", which he established following his own recovery from the disease. His wish for IMBA was that research in Austria would one day receive the same amount of attention as music and art.

Federal president Heinz Fischer delivered the closing remarks and pointed out the high international reputation that IMBA has gained in the ten years of its existence.

IMBA Symposium - Thinking the Unthinkable

Days two and three of the IMBA anniversary celebrations were devoted to science. A symposium entitled "Thinking the Unthinkable – The Future of Biology" assembled an impressive selection of speakers, among them Nobel laureate Sir John B. Gurdon. The presentations covered a broad range of topics: RNA- and chromatin-biology, advanced imaging techniques, stem cells and tissue modeling, and mechanisms of disease. The symposium was held in the historic "Aula der Wissenschaften", a 17th century building in the first district, originally used by the University of Vienna.

The symposium was accompanied by mouth-watering food and a "Jazz Lounge" on the first evening, which presented a tempting occasion for the participants to chill out and engage in networking.

IMPRESSIONS AND VIDEO
Some impressions from the IMBA Symposium
http://www.imba.oeaw.ac.at/symposium/impressions-and-video/

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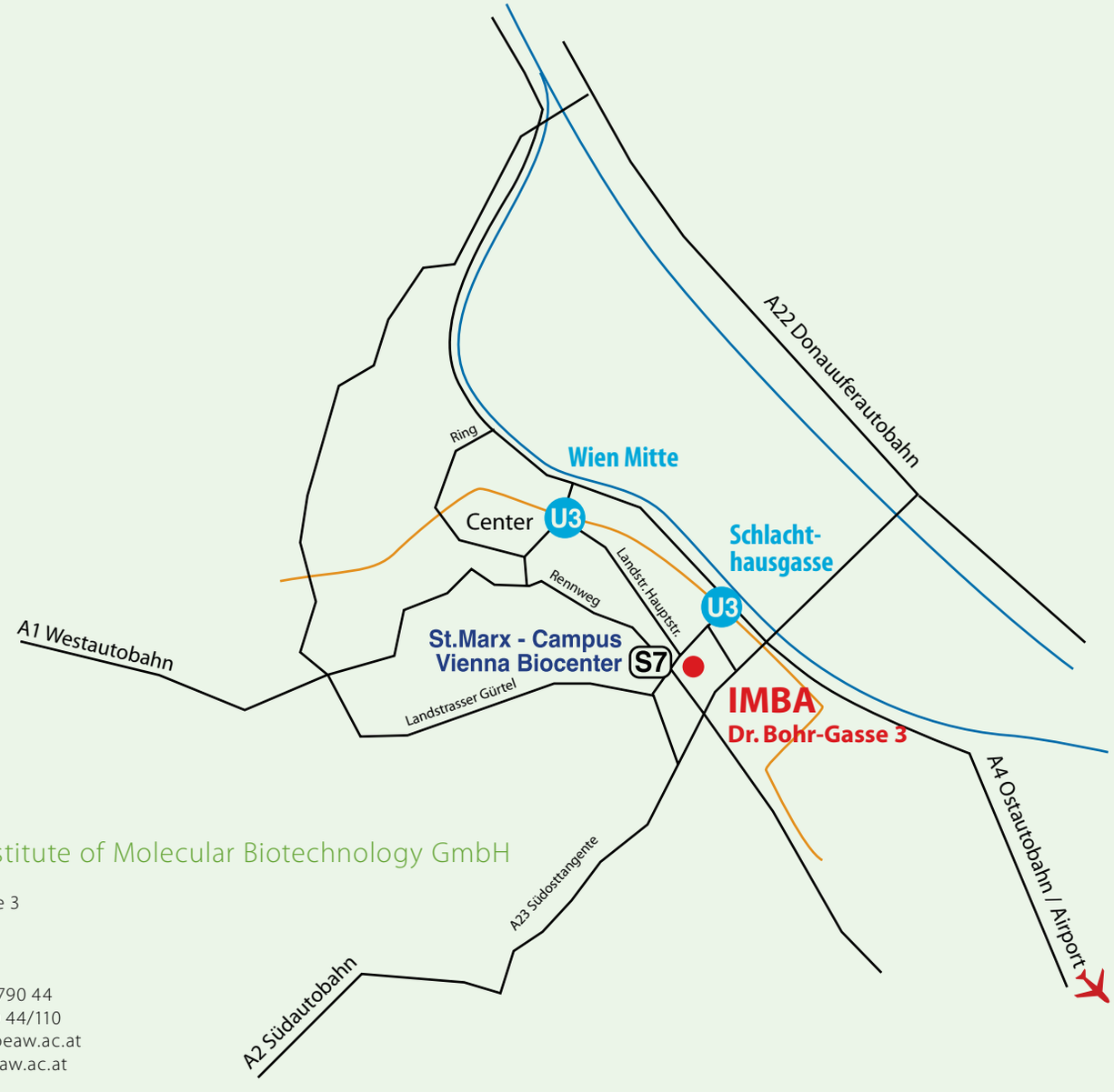

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