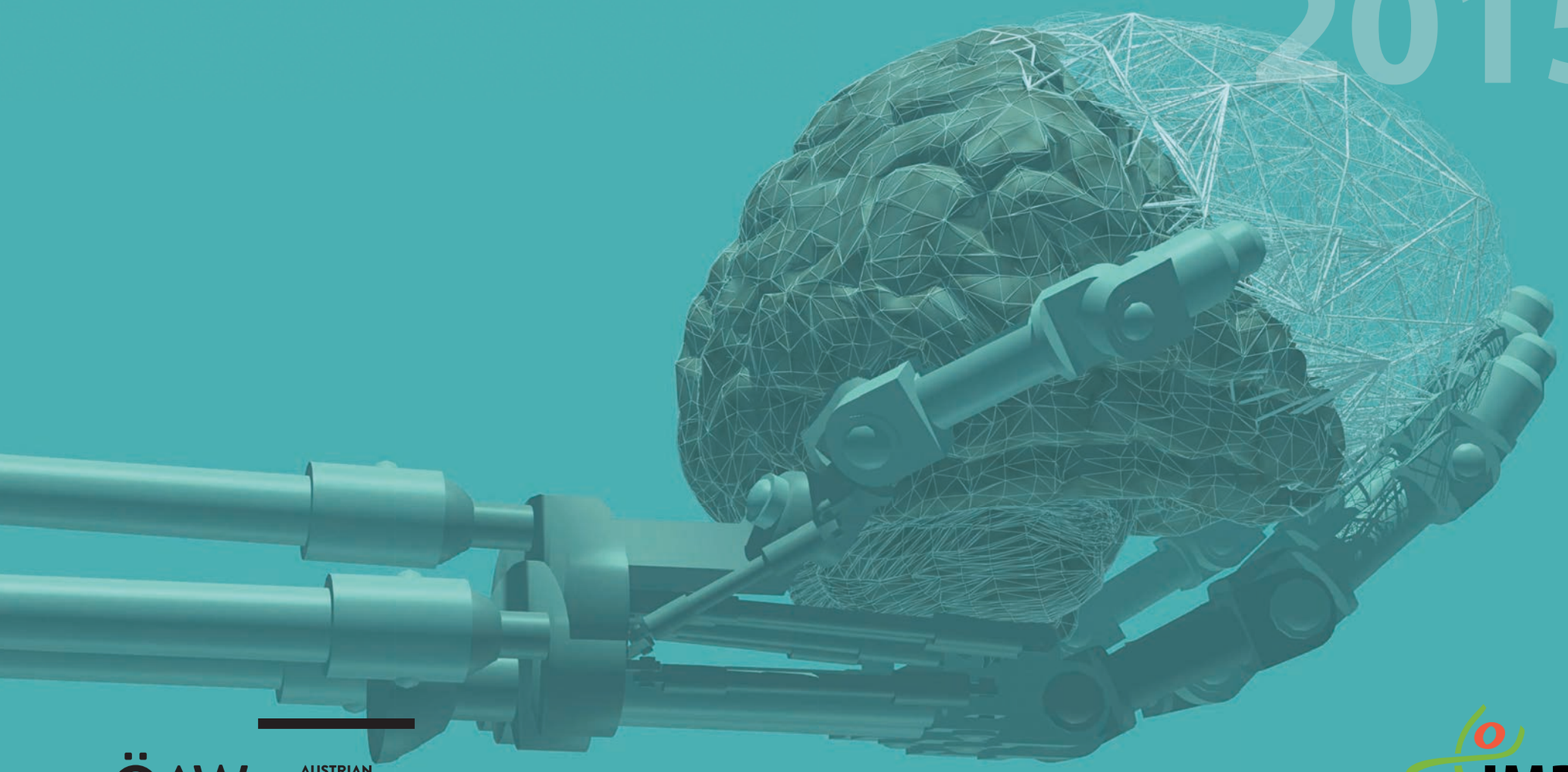
INSTITUTE OF MOLECULAR BIOTECHNOLOGY

OF THE AUSTRIAN ACADEMY OF SCIENCES

VIENNA BIOCENTER

2015



ÖAW AUSTRIAN ACADEMY OF SCIENCES

IMBA
Institute of Molecular Biotechnology
of the Austrian Academy of Sciences

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Introduction

It has always been our philosophy here at IMBA to achieve scientific excellence through investing in the best minds and giving them the necessary freedom to succeed in the growingly competitive world of science. It is today's basic research that enables us to develop the therapies of tomorrow and to better understand the molecular make up of the human body.

IMBA is proud to be part of the Vienna Biocenter (VBC), a vibrant place full of enthusiasm for science. One indicator for this are the many brilliant speakers at seminars and symposia we were able to attract during the last year. Amongst others, Nobel Prize winner Eric Betzig presented new developments in microscopy in April. His newly developed Bessel beam light-sheet microscope mechanisms allows real timr visualization of cellular processes at unprecedented resolution. This bio-imaging tool will be implemented at the VBC under the supervision of group leader Daniel Gerlich.

This year also saw the 10th anniversary of the Microsymposium on Small RNAs. Since it was established by IMBA group leader Javier Martinez, this conference has grown into a true hotspot for RNA biology all over Europe. Stefan Ameres and Julius Brennecke have recently joined the organizing committee together with two other colleagues from the Gregor Mendel Institute of Molecular Plant Biology (GMI) and the Research Institute of Molecular Pathology (IMP). Their distinct focuses on various aspects of small RNA Biology have allowed the incorporation of various aspects in the field and the fruitful exchange of ideas. The large number of renowned participants for this anniversary clearly reflects the excellent status of IMBA and the Vienna Biocenter (VBC) within the field of small RNA Biology.

The last year saw the establishment of a new research group in IMBA. We would like to welcome Sasha Mendjan, whose strong expertise in human pluripotent stem cell biology will be a very valuable addition to our research portfolio. Sashas previous positions in Heidelberg and Cambridge have endowed him with profound expertise in the areas of cell and developmental biology. He is planning to apply his knowledge and establish a competitive research program to study cardiac and adipocyte lineage decisions and tissue interactions. His ultimate goal is to join the growing IMBA organoid community and to grow heart and related tissues in vitro. Sasha Mendjan's research focus will help us to further strengthen our research efforts in the field of stem cell biology.

Congratulations go to Daniel Gerlich, who received a grant from the Vienna Science and Technology Fund's (WWTF) recent Life Science Call for Innovative biological applications of novel imaging technologies. Moreover, IMBA Deputy Scientific Director Jürgen Knoblich could secure an ERC Proof of Concept grant that will allow him and his team to explore the commercial opportunities of cerebral organoid research. The grant builds on a 3D culture method developed by the group that resembles the early stages of human embryonic brain development at a remarkable level of detail and opens up new possibilities for studying disease and testing compounds directly on human tissue. Last but not least we should highlight the outstanding success of IMBA senior scientist Julius Brennecke. His group has been tremendously successful in characterizing the piRNA pathway, a small RNA based biological pathway that acts in defending organisms against selfish genetic elements like transposons or retroviruses. Their tremendous work and visionary future plans secured them an ERC Consolidator Grant, one of the most prestigious research grants available in Europe.

Great scientists have always accompanied IMBA on our path to scientific prosperity. All the more we were very sad to hear that Prof. Dr. Carl Djerassi passed away at the beginning of this year. He was a true polymath, who had dedicated his life to science and the arts. As a member of our Fundraising Committee, many of us have had the privilege to listen to his lectures and meet him in person. His scientific discoveries have affected many lives and his dedication can be a great inspiration for us.

This year the joint VBC PhD Programme was able to attract 30 outstanding young scientists to do their PhD at the VBC. 14 of them joined IMBA research groups. Among other activities, the graduate students organized the 13th VBC PhD symposium that allowed them to discuss cutting edge science with top scientists and build a network of their own. This year's topic – communication – shed light on the different levels of interaction from the intra-cellular to the inter-individual level.

All the excellent research preformed at IMBA would not be possible without the support of public funding agencies such as the ERC, FWF and WWTF, to name just three. We are also grateful for the support of the Austrian Academy of Sciences and their vision for the life sciences in Austria. Last but not least we want to thank our private sponsors – big and small – for their continuous support. Without all these different stakeholders, an institute like ours with so many unique assets, would not be possible.

This annual report is a showcase of the flourishing science conducted at IMBA. Ultimately, 2015 marked yet another successful year for IMBA and we would like to thank all our colleagues at the institute as well as our partners at the VBC for the rewarding collaborations. We are looking forward to a prosperous future together.

Jürgen Knoblich, Michael Krebs, Josef Penninger

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Managing Director/Science

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Deputy Director/Science

RESEARCH HIGHLIGHTS

2015 has been scientifically a successful year for IMBA. The following pages show IMBA's "Research Highlights", a selection of highly visible research articles IMBA scientists have published during this year.

The histone chaperone CAF-1 safeguards somatic cell identity during transcription factor-induced reprogramming

Cheloufi, S.; Elling, U.; Hopfgartner, B.; Jung, Y.; Murn, J.: Ninova, M.; Hubmann, M.; Badeaux, A.; Ang, CE.: Tenen, D.; Wesche, DJ.; Abazova, N.; Hogue, M.; Tasdemir, N.; Pathert, P.; Jude, J.; Ferrari, F.; Blanco, A.; Fellner, M.; Wenzel, D.; Zinner, M.; Vidal, SE.; Stadtfeld, M.; Chang, HY.; Almouzni, G.; Lowe, SW.; Rinn, J.; Wernig, M.; Aravin, A.; Shi, Y.; Park, P.; Penninger, JM.; Zuber, J.; Hochedlinger, K. (2015) Nature 528:218-224

During development, lineage-specific transcriptional programs establish cellular diversity. While this process involves profound changes in the chromatic landscape, the mechanisms by which somatic cell identity is subsequently maintained remain incompletely understood. To further elucidate regulatory pathways that safeguard the somatic state, we performed two comprehensive RNAi screens targeting known and predicted chromatin factors during transcription factor-mediated reprogramming of mouse fibroblasts to induced pluripotent stem cells (iPSCs). Remarkably, subunits of the chromatin assembly factor-1 (CAF-1) complex emerged as the most prominent hits from both screens, followed by modulators of lysine sumoylation, DNA methylation and heterochromatin maintenance. Suppression of CAF-1 increased reprogramming efficiency by several orders of magnitude and facilitated iPSC formation in as little as four days. Mechanistically, CAF-1 suppression led to a more accessible chromatin structure specifically at enhancer elements early during reprogramming. These changes were accompanied by a decrease in H3K9me3-marked somatic heterochromatin domains, increased binding of the reprogramming factor Sox2 to pluripotency-specific regulatory elements and activation of associated genes. Notably, suppression of CAF-1 also enhanced iPSC formation from blood progenitors as well as the direct conversion of B cells into macrophages and fibroblasts into neurons. Together, our findings reveal the histone chaperone CAF-1 as a novel regulator of somatic cell identity during transcription factor-induced cell fate transitions and provide a potential strategy to modulate cellular plasticity in a regenerative setting.

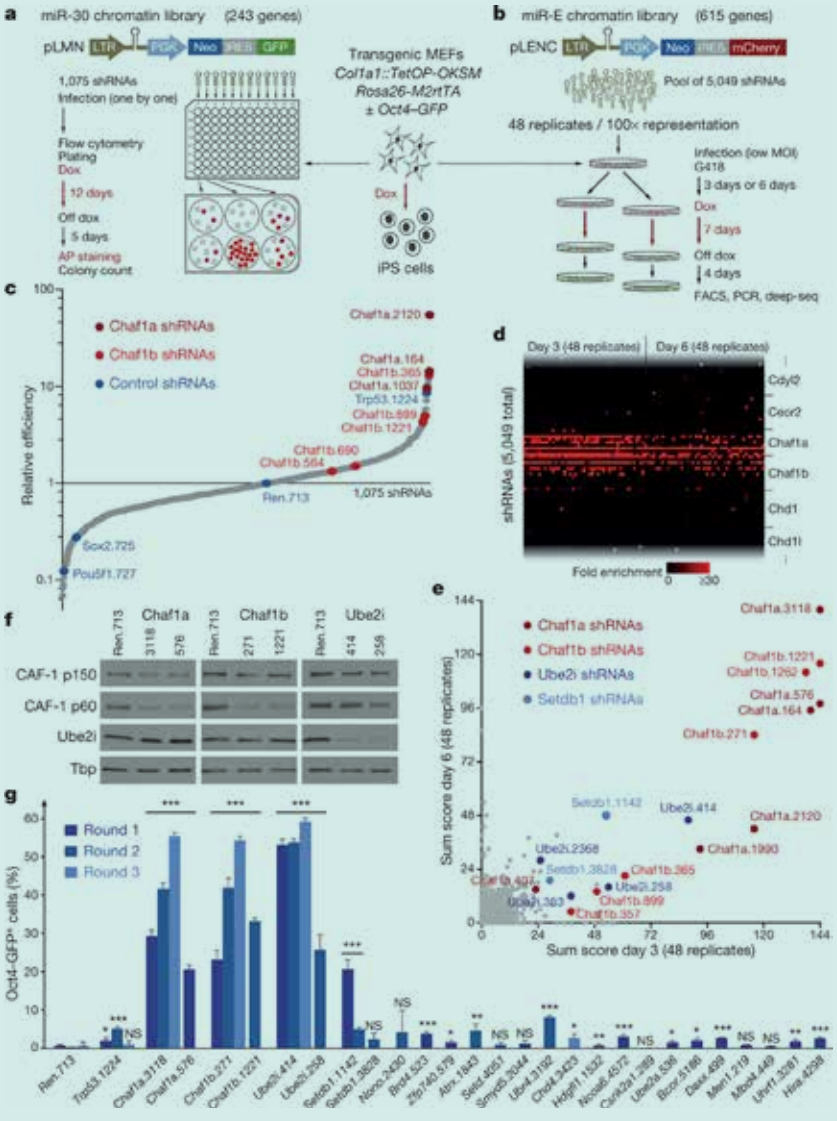


Figure Legend

a, ***b***, *Schematic of arrayed (**a**) and multiplexed (**b**) RNAi screens. Dox, doxycycline.* ***c***, *Results from arrayed screen, depicting average reprogramming efficiency ratios of two biological replicates normalized to Renilla (Ren.713) shRNA control.* ***d***, *Heatmap depicting enrichment of selected shRNAs (shown in rows, ordered by gene symbol) over all 96 replicates (columns).* ***e***, *Scatter plot representing sum score of enriched shRNAs across all replicates.* ***f***, *Western blot analysis confirming shRNA suppression of CAF-1 p150 (Chaf1a), CAF-1 p60 (Chaf1b) and Ube2i at day 3 of reprogramming.* ***g***, *Validation of hits from multiplex screen. Values are the mean from biological triplicates; error bars indicate standard deviation (*P < 0.05; **P < 0.01; ***P < 0.001).*

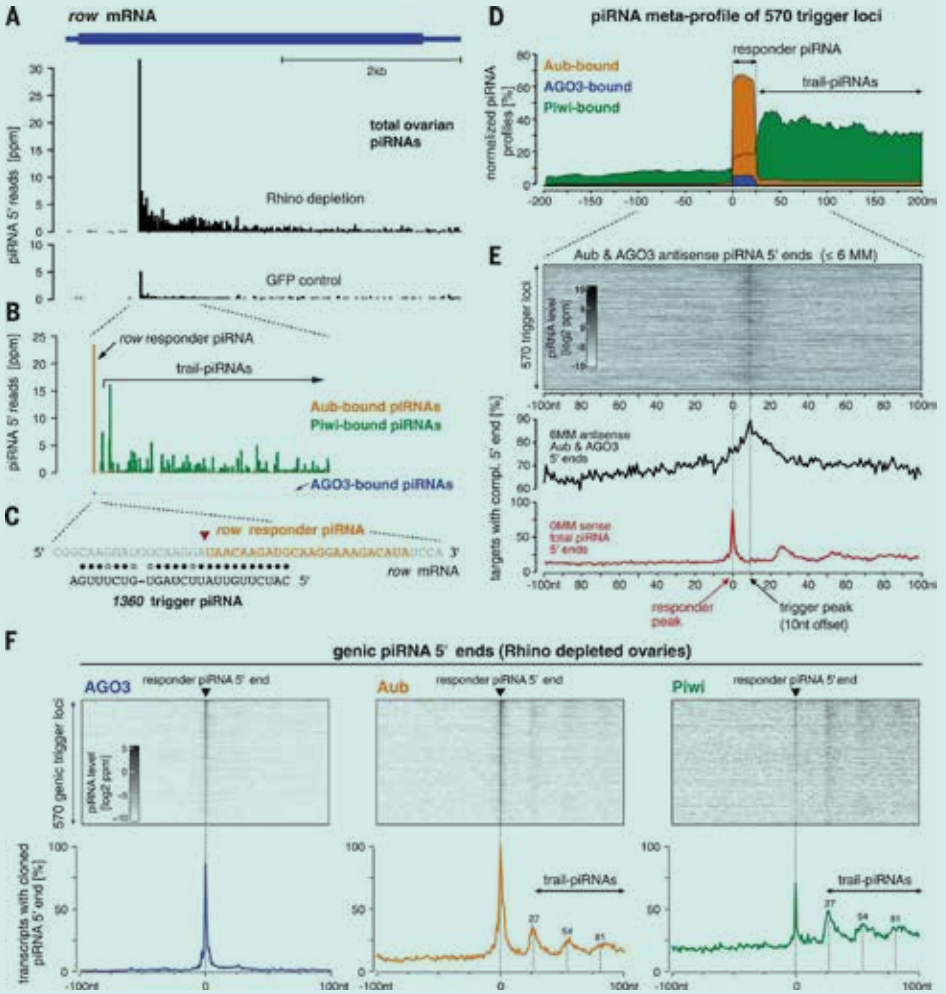
Noncoding RNA. piRNA-guided slicing specifies transcripts for Zucchini-dependent, phased piRNA biogenesis.

Mohn, F.; Handler, D.; Brennecke, J. (2015) Science. 348(6236):812-7

In animal gonads, PIWI-clade Argonaute proteins repress transposons sequence-specifically via bound Piwi-interacting RNAs (piRNAs). These are processed from single-stranded precursor RNAs by largely unknown mechanisms. Here we show that primary piRNA biogenesis is a 3′-directed and phased process that, in the Drosophila germ line, is initiated by secondary piRNA-guided transcript cleavage. Phasing results from consecutive endonucleolytic cleavages catalyzed by Zucchini, implying coupled formation of 3′ and 5′ ends of flanking piRNAs. Unexpectedly, Zucchini also participates in 3′ end formation of secondary piRNAs. Its function can, however, be bypassed by downstream piRNA-guided precursor cleavages coupled to exonucleolytic trimming. Our data uncover an evolutionarily conserved piRNA biogenesis mechanism in which Zucchini plays a central role in defining piRNA 5′ and 3′ ends.

Figure Legend

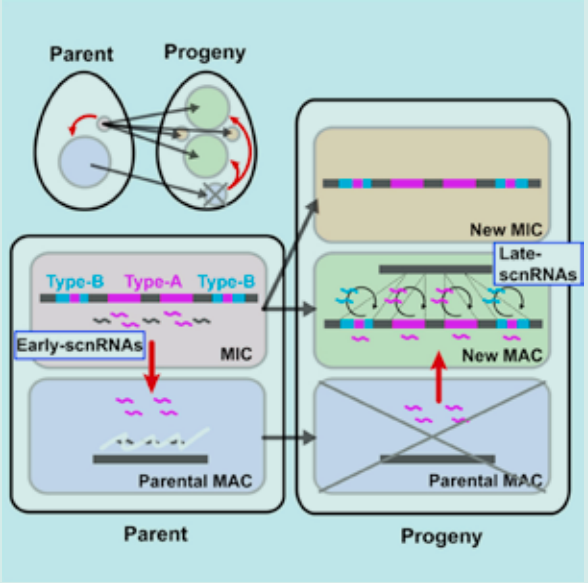
Fig. 1 Aub/AGO3-mediated slicing triggers phased piRNA biogenesis.
*(**A**) Normalized piRNA populations from Rhino-depleted ovaries or from control ovaries mapping to the row mRNA. ppm, parts per million. (**B**) As in (A), but piRNAs bound to Aub/AGO3/Piwi (22) are shown individually. (**C**) Alignment of the 1360 trigger-piRNA with the row mRNA. The inverted triangle denotes the slicer cleavage position. (**D**) Metaplots showing profiles of Aub/AGO3/Piwi-bound piRNAs (from Rhino-depleted ovaries) at genic trigger sites. Profiles represent the median of normalized values; responder peak: 100%. (E) Heat map indicating piRNA levels (Σ Aub/AGO3 5´ ends) mapping antisense (≤six mismatches) to 570 mRNAs with trigger events. Position 0 denotes the responder-piRNA 5´ end. The binary histograms show the percentage of transcripts with a cloned 5´ end of indicated piRNAs mapping in sense/antisense orientation at nucleotide resolution. (F) Heat maps indicating AGO3/Aub/Piwi-bound piRNA 5´ end levels from Rhino-depleted ovaries in a window centered on 570 genic responder-piRNAs. The corresponding binary histograms indicate the percentage of transcripts that exhibit a cloned piRNA 5´ end at a given position.*



Small-RNA-Mediated Genome-wide trans-Recognition Network in Tetrahymena DNA Elimination.

Noto, T.; Kataoka, K.; Suhren, JH.; Hayashi, A.; Woolcock, KJ.; Gorovsky, MA.; Mochizuki, K. (2015) Mol. Cell. 59(2):229-42

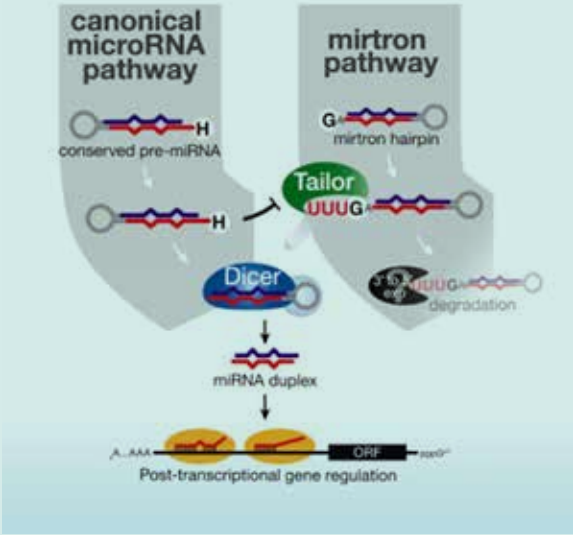
Small RNAs are used to silence transposable elements (TEs) in many eukaryotes, which use diverse evolutionary solutions to identify TEs. In ciliated protozoans, small-RNA-mediated comparison of the germline and somatic genomes underlies identification of TE-related sequences, which are then eliminated from the soma. Here, we describe an additional mechanism of small-RNA-mediated identification of TE-related sequences in the ciliate Tetrahymena. We show that a limited set of internal eliminated sequences (IESs) containing potentially active TEs produces a class of small RNAs that recognize not only the IESs from which they are derived, but also other IESs in trans. This trans recognition triggers the expression of yet another class of small RNAs that identify other IESs. Therefore, TE-related sequences in Tetrahymena are robustly targeted for elimination by a genome-wide trans-recognition network accompanied by a chain reaction of small RNA production.



Uridylation of RNA Hairpins by Tailor Confines the Emergence of MicroRNAs in Drosophila.

Reimão-Pinto, M., Ignatova, V., Burkard, T.R., Hung, J.-H., Manzenreither, R. A., Sowemimo, I., Herzog, V. A., Reichholf, B., Fariña-Lopez, S., and Ameres, S.L. (2015) Mol. Cell. 59:203-16

Uridylation of RNA species represents an emerging theme in post-transcriptional gene regulation. In the microRNA pathway, such modifications regulate small RNA biogenesis and stability in plants, worms, and mammals. Here, we report Tailor, an uridylyltransferase that is required for the majority of 3′ end modifications of microRNAs in Drosophila and predominantly targets precursor hairpins. Uridylation modulates the characteristic two-nucleotide 3′ overhang of microRNA hairpins, which regulates processing by Dicer-1 and destabilizes RNA hairpins. Tailor preferentially uridylates mirtron hairpins, thereby impeding the production of non-canonical microRNAs. Mirtron selectivity is explained by primary sequence specificity of Tailor, selecting substrates ending with a 3′ guanosine. In contrast to mirtrons, conserved Drosophila precursor microRNAs are significantly depleted in 3′ guanosine, thereby escaping regulatory uridylation. Our data support the hypothesis that evolutionary adaptation to Tailor-directed uridylation shapes the nucleotide composition of precursor microRNA 3′ ends. Hence, hairpin uridylation may serve as a barrier for the de novo creation of microRNAs in Drosophila.



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 (miRNAs) 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 investigate 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, and RNomics. The hypotheses derived from our studies in flies are directly tested in regard of their applicability in mammals.

Regulation of microRNA biogenesis

The post-transcriptional addition of uridine nucleotides to the 3´ end of RNA species represents an emerging theme in post-transcriptional gene regulation. In the microRNA pathway, such modifications regulate small RNA biogenesis and stability in plants, worms, and mammals. Recently, we identified Tailor, an uridylyltransferase that is required for the majority of 3´ end modifications of miRNAs in *Drosophila* which predominantly targets precursor hairpins. Uridylation modulates the characteristic two-nucleotide 3´ overhang of miRNA hairpins, which regulates processing by Dicer-1 and destabilizes RNA hairpins. Tailor preferentially uridylates mirtron hairpins, a class of non-canonical miRNA precursors generated directly by splicing of introns from messenger RNAs. Mirtron selectivity is explained by the primary sequence specificity of Tailor, selecting substrates ending with a 3´ guanosine, a hallmark of introns. In contrast to mirtrons, conserved *Drosophila* precursor miRNAs are significantly depleted in 3´ guanosine, thus evading regulatory uridylation. Our data support the hypothesis that evolutionary adaptation to Tailor-directed uridylation shapes the nucleotide composition of precursor miRNA 3´ ends. Hence, hairpin uridylation may serve as a barrier for the de novo creation of miRNAs in *Drosophila*.

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 found 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). Notably, some herpes viruses highjack the cellular miRNA decay machinery to trigger the destruction of host miRNAs in order to counteract the antiviral function of the microRNA pathway. 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 instance, the inhibition of miR-122 – a liver-specific regulator of lipid metabolism – reduces 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 and 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 means of studying miRNA function in adult mammals and may serve as a treatment for dyslipidemia and other miRNA-related human diseases.

Publication highlights:

Reimão-Pinto, M., Ignatova, V., Burkard, T.R., Hung, J.-H., Manzenreither, R. A., Sowemimo, I., Herzog, V. A., Reichholf, B., Fariña-Lopez, S., and Ameres, S.L. (2015) Uridylation of RNA Hairpins by Tailor Confines the Emergence of MicroRNAs in Drosophila. Drosophila. Mol. Cell. 59:203-16

Ameres SL, Zamore PD (2013) Diversifying microRNA sequence and function. Nat Rev Mol Cell Bio 14(8): 475-488

Ameres SL, Horwich MD, Hung J-H, Xu J, Ghildiyal M, Wenig Z, Zamore PD (2010) Target RNA-directed trimming and tailing of small silencing RNAs. Science, 328(5985): 1534-39

Figure 1

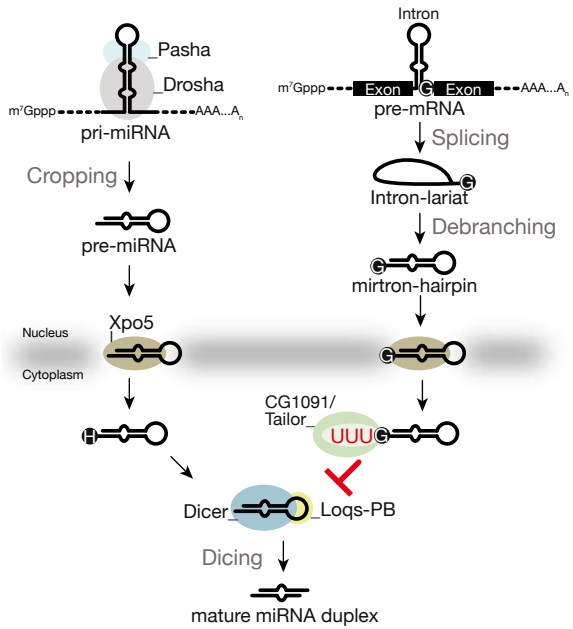


Figure 2

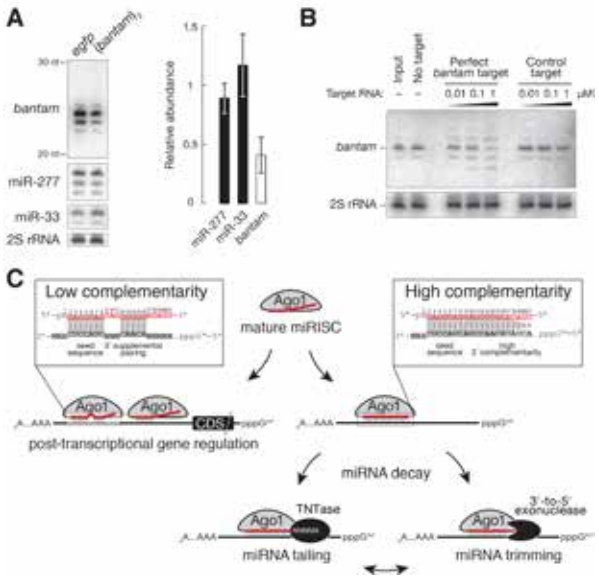


Figure 3

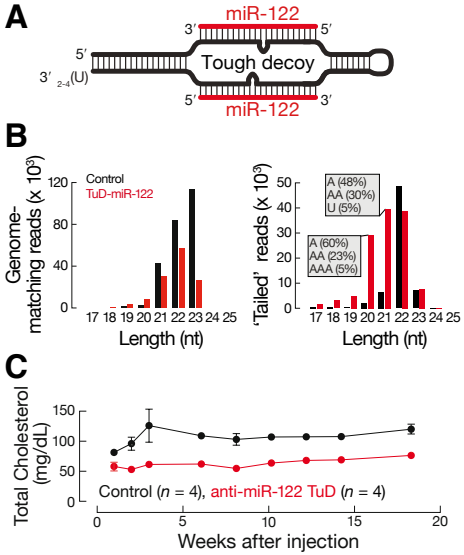


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Figure 1: Uridylation of RNA hairpins confines the emergence of microRNAs in Drosophila. The terminal uridylyltransferase Tailor uridylates hairpins derived from the mirtron pathway, producing mature miRNAs from introns of protein-coding gene transcripts (right). Tailor preferentially acts on hairpins ending in 3′ G, a hallmark of introns, and uridylation prevents efficient recognition and processing of hairpins by Dicer. In contrast, conserved microRNAs generated via the canonical pathway, through the action of Drosha (left), are evolutionarily selected to not end in 3′ G, thus circumventing regulatory uridylation by Tailor.

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 deviations are shown 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 causes exonucleolytic trimming and non-templated nucleotide addition (tailing) of the miRNA. miRNA tailing and trimming ultimately result 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 crucial 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 in order 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 undergoes 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, thus contributing to the dynamic organization of chromatin in regulatory regions of the mammalian genome.
Traditional genetic and biochemical analyses have yielded a largely static view 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 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

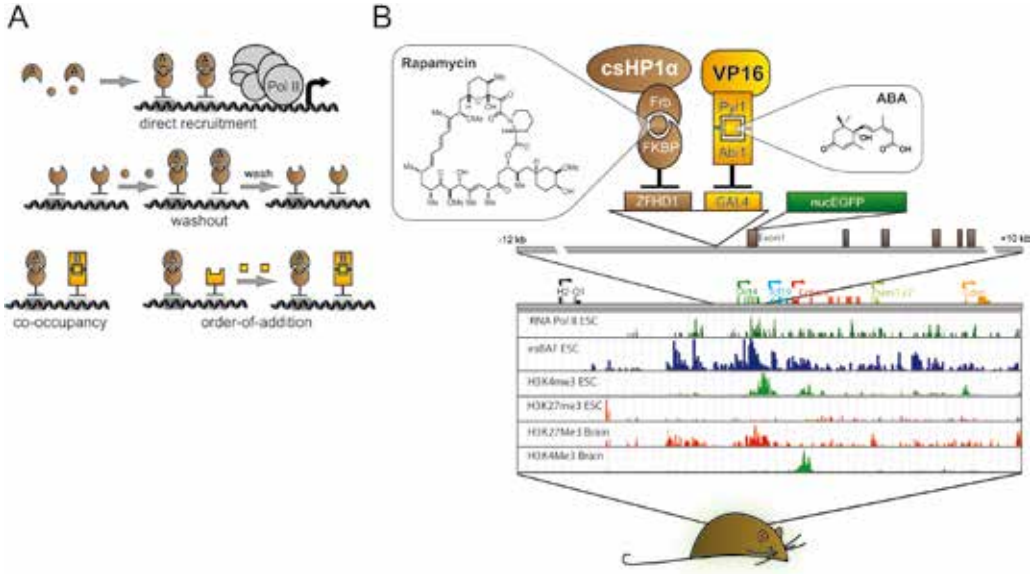
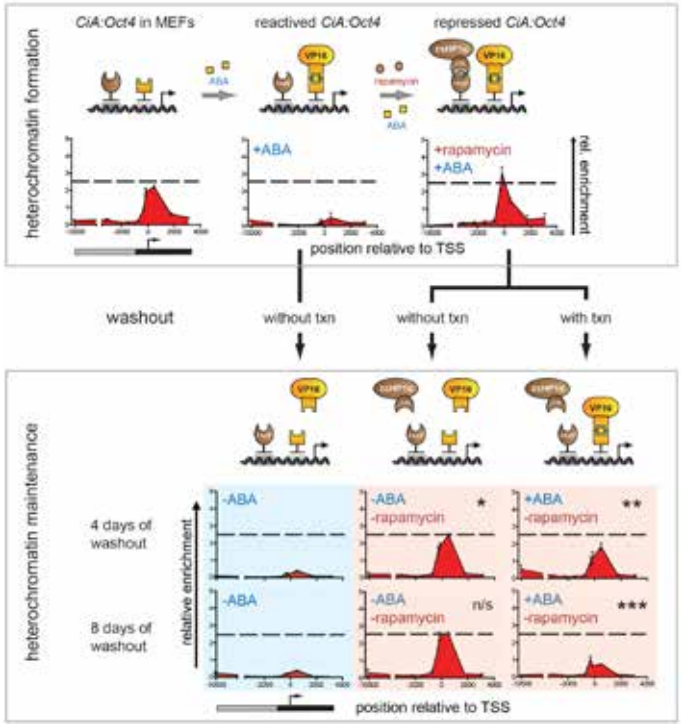


Figure 2



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POSTDOC: RAMESH YELAGANDULA
PHD STUDENTS: HAGAR MOUSSA, JORGE ARTURO ZEPEDA MARTINEZ, KARIN STECHER
MASTER STUDENT: DANIEL BSTEH

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

The PIWI/piRNA pathway: Genome defense guided by small RNAs

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

Transposons and other selfish genetic elements populate every eukaryotic genome, indicating an ancient genetic conflict. To amplify and spread within host DNA, transposons utilize the cellular gene expression machinery. Their selective silencing therefore poses a complex challenge for the host cell. In plants, fungi, and animals, small RNA silencing pathways—commonly referred to as RNA interference processes—meet this challenge. We focus on the PIWI/piRNA pathway, which is the central transposon silencing system in animal gonads. This pathway has remarkable conceptual similarities to adaptive immune systems and intersects the fascinating world of small RNAs with heterochromatin biology and epigenetic phenomena that play central roles in evolution.

RNA interference & transposon silencing

Transposons are universal components of eukaryotic genomes and contribute significantly to genome size (~50% in humans). These selfish genetic elements are central agents for genome evolution by diversifying the gene regulatory landscape or by serving as building blocks of heterochromatin. On the other hand, their mobility causes DNA double-strand breaks and insertional mutagenesis.
To safeguard genome integrity and to prevent the uncontrolled spread of transposons, host defense systems evolved early in evolution. After the discovery of RNA interference it became clear that small RNA-silencing systems are at the root of transposon control in fungi, plants, and animals. Central to all small RNA pathways are Argonaute proteins. These silencing machines are guided to their target transcripts via bound small RNAs. The success of small RNA pathways in the battle against transposons likely rests upon their conceptual set-up: *By fuelling small RNA biogenesis with transcripts of the targets themselves, these pathways provide flexibility to any nucleic acid sequence and adaptability to new challenges originating from sequence drift or the horizontal invasion of new elements.*

The conceptual logic of small RNA-guided genome defense pathways

Figure 1 shows the three core principles that characterize small RNA-based genome defense pathways: (1) Silencing information is stored in genomic loci. These are insertions of active transposons or large loci composed of libraries of transposon fragments. The memory loci are evolutionarily plastic and acquire or loose transposon sequences over time. Transcription of the genomic storage loci provides the small RNA precursors. (2) Dedicated RNA processing systems parse precursor transcripts into small RNAs, which are loaded into Argonaute proteins. (3) Argonaute proteins act at the center of small RNA pathways. Their bound small RNAs are sequence-specific guides that target the RNA-induced silencing complex (RISC) to complementary transcripts. RISC recruitment elicits target silencing at the transcriptional or post-transcriptional level. Remarkably, recent insights into CRISPR/Cas—bacterial small RNA-based defense systems against phage—indicate intriguing conceptual similarities between eukaryotic and prokaryotic host genome defense systems.

The PIWI/piRNA pathway

The key transposon silencing system in animal gonads is the piRNA pathway, which utilizes Argonaute proteins of the PIWI clade. In contrast to the much better understood micro-RNA and siRNA pathways, its mechanistic framework is largely unknown. We study this fascinating genome surveillance system in *Drosophila melanogaster,* combining our strong expertise in genetics with biochemistry, cell biology, next-generation sequencing, and computational biology. Our interest is focused on three main areas (Fig. 2):

1. piRNA biogenesis: Thousands of different ~23 to 30 nt long piRNAs are processed from single-stranded precursor RNAs in a poorly understood manner. Genetic screens have disclosed more than a dozen proteins to be required for piRNA biogenesis. Among these are RNA helicases and several uncharacterized proteins. Interestingly, several of them are transmembrane proteins of the outer mitochondrial membrane. We aim to discover the rules of piRNA biogenesis and to dissect the underlying molecular mechanisms in order to understand how the cell distinguishes piRNA precursor transcripts from other RNAs in the cell.

2. Piwi-mediated transcriptional silencing: Of the three *Drosophila* PIWI clade proteins, one (Piwi) localizes to the nucleus. Based on our recent work, piRNAs guide Piwi to nascent transposon transcripts to trigger the buildup of a potent silencing complex that represses target transcription and leads to local heterochromatin formation. Our aim is to understand how Piwi-RISC recruitment to a nascent RNA elicits these processes.

3. The biology of piRNA clusters: piRNA clusters are the system's heritable repositories for transposon sequence information as they provide the piRNA precursors transcripts. These up to several hundreds of kilobase long heterochromatic regions resemble transposon graveyards and encompass a selection of selfish sequences that a population has been exposed to. Our recent findings indicate that piRNA clusters recruit a battery of germline specific factors that bypass the canonical rules of gene expression. We are interested in the transcription of piRNA clusters as well as in the specification, export and processing of their transcripts.

Publication highlights:

Sienski G, Dönertas D, Brennecke J. (2012) Transcriptional Silencing of Transposons by Piwi and Maelstrom and Its Impact on Chromatin State and Gene Expression Cell. 22;151(5)

Olivieri D, Senti KA, Subramanian S, Sachidanandam R, Brennecke J. (2012). The Cochaperone Shutdown Defines a Group of Biogenesis Factors Essential for All piRNA Populations in Drosophila. Mol Cell. 28;47(6):954-69.

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

Figure 1

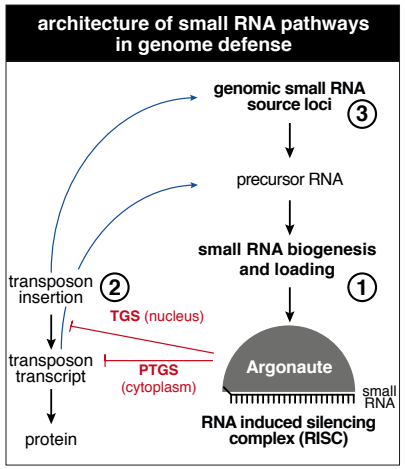
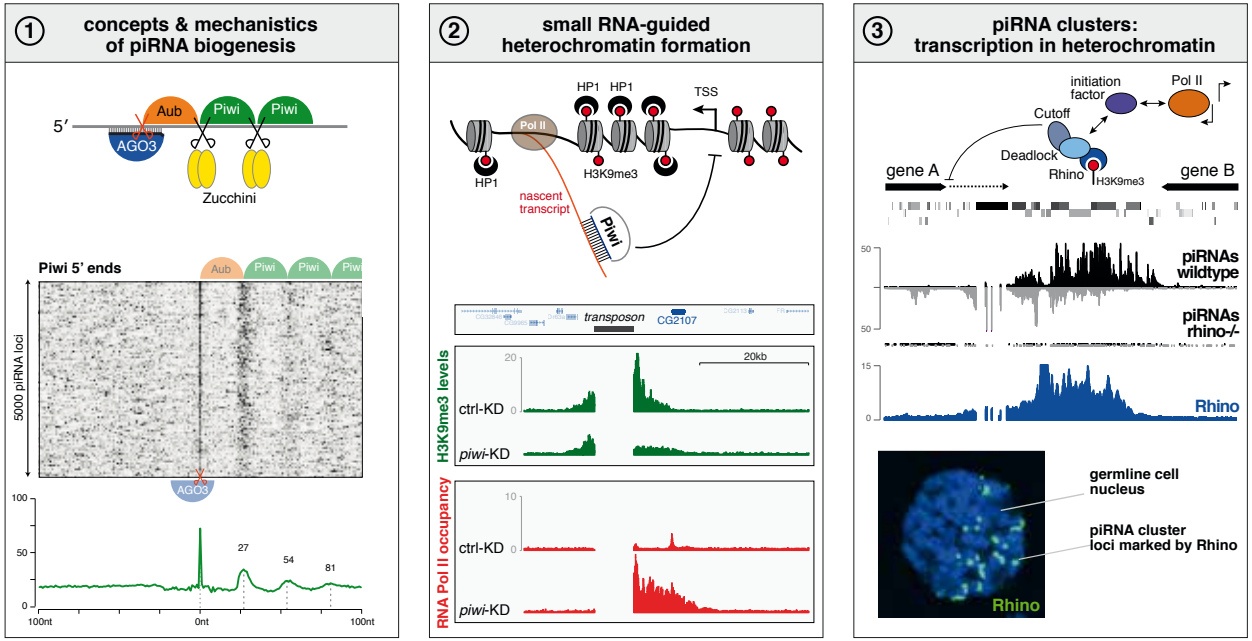


Figure 2



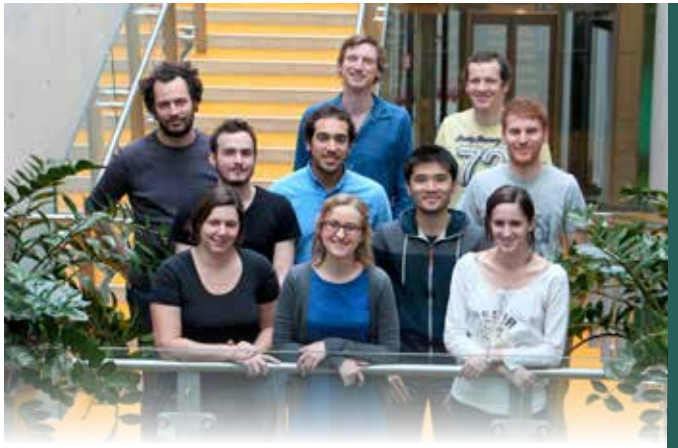


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Figure 1: This cartoon shows the conceptual setup of small RNA-guided genome defense pathways in eukaryotes. The three central steps are (1) small RNA biogenesis, (2) small RNA-guided silencing, and (3) the biology of the genomic memory loci. These three areas are the focus of the group's research projects.

Figure 2: The three main research areas. Left: Using genetics coupled with computational analyses of large sequencing datasets, we discover the principles of piRNA biogenesis and the underlying molecular mechanisms. **Middle:** Recruitment of nuclear Piwi-RISC to a nascent transposon transcript leads to a potent transcriptional silencing response (red) that is accompanied by the formation of H3K9me3 marked heterochromatin (green). **Right:** Large loci within heterochromatin—so-called piRNA clusters—recruit Rhino, which is a germline-specific HP1 protein. This leads to the assembly of a multifunctional complex that licenses the initiation and elongation of transcription, and coordinates the export of the emerging RNAs to the cytoplasmic piRNA biogenesis sites. The microscope image shows the discrete localization of Rhino in a germline nucleus (DNA in blue).

ULRICH ELLING GROUP

Functional Genomics in Embryonic Stem Cells

http://www.imba.oeaw.ac.at/research/ulrich-elling

Embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells) are likely to transform personalized medicine because they can be infinitely expanded and differentiated in several tissue types. Hence they permit in vitro modeling of disease and possibly even tissue replacement in patients. Our group tries to clarify the genetic cascades governing cell state and lineage decisions of early development by systematic genetic approaches employing genome-wide screens, facilitated by the generation of haploid ES cells.

Embryonic stem cells represent the fascinating *in vitro* capture of a transient developmental state of pluripotency found in blastocysts prior to implantation in the uterine wall (Figure A). Such immortal cells can be infinitely expanded in cell culture and differentiated in virtually all cell types of our body. While we understand much about the governing transcription factors defining the state, we know much less about the genetic factors controlling entrance to and exit from pluripotency.

Using genome-wide genetics, our team systematically investigates the genetic framework governing early embryonic development, including differentiation, dedifferentiation, reprogramming, lineage decisions, and epigenetic modifications. Some of the questions we address are the specific genes required for ES cell maintenance and those needed for differentiation. What genes are involved in lineage decisions and control of the epigenetic environment?

Even today, random mutagenesis is by far the most efficient way of generating a multitude of mutations to be used in pooled screening approaches. However, such mutations are masked in diploid cells due to the presence of a second allele (Figure C). In order to achieve systematic saturating screens in ES cells based on random mutagenesis, we generated haploid murine embryonic stem cells via parthenogenesis and developed genetic tools for forward and reverse genomic approaches. Such cells display all features of pluripotent ES cells and contain a precisely haploid chromosome set (Figure B). This setup combines the power of "yeast genetics" with the pluripotency of embryonic stem cells. We complement our haploid genetic platform with small RNA-based approaches such as RNAi and CRISPR for tool generation, validation, and targeted mutagenesis to subsets of genes. Our goal is to identify genetic triggers for more efficient lineage transition and thus create a better experimental regimen of ES cell dedifferentiation and differentiation.

ES cells may be derived directly from blastocysts or generated by dedifferentiation of differentiated cell types; these are known as induced pluripotent stem cells (iPS cells). Dedifferentiation is achieved by nuclear transfer to oocytes or via the expression of 4 transcription factors. While overexpression of these lineage-defining activators may be sufficient to reawaken pluripotency, the process is highly inefficient and rare. We aimed to understand the nature of epigenetic roadblocks inhibiting the generation of induced pluripotent stem cells arising from the expression of these 4 transcription factors, namely Oct4, Sox2, Klf4, and Myc. By employing a very rigorous screen using optimized shRNA technology, we were able to identify new epigenetic barriers to the change of lineage identity, namely the CAF-1 complex depositing core histones to nascent DNA, as well as the sumoylation pathway (Figure D). The project was performed in close collaboration with the laboratories of Johannes Zuber (IMP) and Konrad Hochedlinger (Harvard).

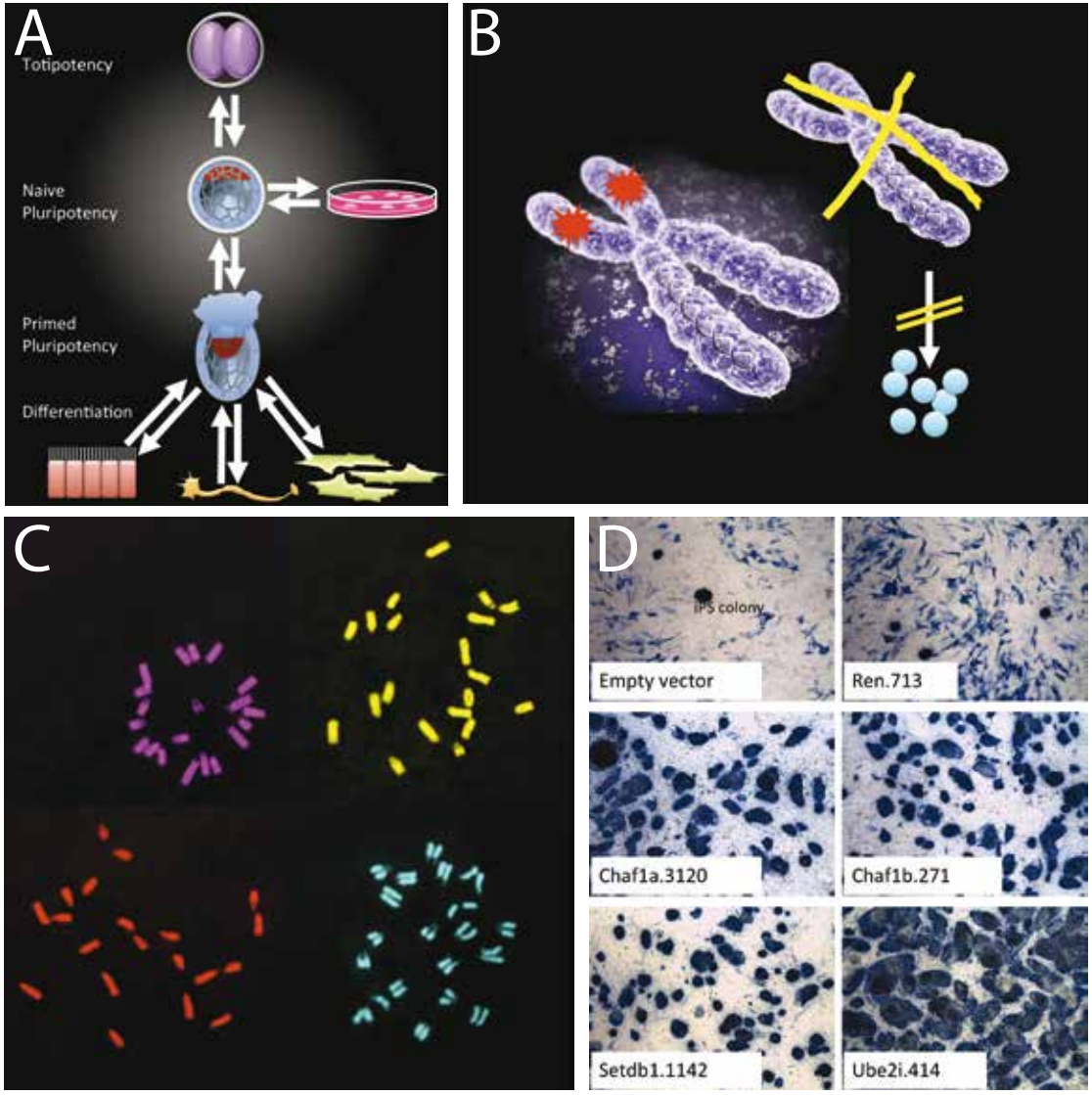
For technical reasons, most genome-wide screens are based on a positive selection of hits. Dropout screens are a standing challenge for functional genomics because of the high demands in terms of signal-to-noise ratios and the quantity of data required for analysis. However, they provide a more direct genetic understanding of pathways. Haploid genomics combined with optimized mutagenesis tools such as CRISPR are likely to produce genome-wide depletion screens. We intend to raise and answer questions beyond what is currently possible by traditional means, such as what mutations are lethal in synergy with an oncogenic lesion? What mutations hypersensitize to compounds with unknown specificity, i.e. destabilize the drug target pathway? What genes are required for specific cell states and cellular responses? We use improved massive parallel sequencing protocols as well as genetic and bioinformatics tools to address these questions.

Our lab focuses on developing new tools with wide applicability. This fosters academic interaction and collaboration within and beyond the campus. In close collaboration with several industrial partners, we also use genomics for drug target prediction. Our team interacts closely with Haplobank, an archive of mutated and sequenced conditional ES cell lines we have jointly set up and operated over the last few years. Of the 100,000 available cell lines, testing those that harbor specific conditional mutations allows for rapid validation of hits identified in genetic screens as well as candidate approaches.

Publication highlights:

Cheloufi, S., Elling, U.*, Hopfgartner, B., Jung, Y., Murn, J., Ninova, M., Hubmann, M., Badeaux, A., Ang, C.E., Tenen, D., et al. (2015). The histone chaperone CAF-1 safeguards somatic cell identity during transcription factor-induced reprogramming. Nature article, in press*
*(*equal contribution)*

Figure



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TECHNICAL ASSISTENT: MARIA HUBMANN

Figure A: Embryonic stem cells represent the *in vitro* capture of a transient cell identity in development, namely the inner cell mass state of a preimplantation embryo. Our lab aims to understand the genetic circuitries governing early lineage transitions.

Figure B: Random mutagenesis in diploid cells leads to heterozygous mutations. Such mutations usually do not manifest phenotypically due to the presence of a second allele sufficient for protein synthesis. The missing second allele (yellow) in haploid cells unmasks the phenotype.

Figure C: Pseudo-colored chromosome spreads of haploid embryonic stem cells.

Figure D: Alkaline phosphatase staining (dark blue cell colonies) of iPS colonies derived under normal conditions in the absence of shRNA or the presence of neutral shRNA (Ren.713) or knockdown of CAF-1 complex (Chaf1a, Chaf1b), Setdb1, or SUMOylation (Ube2i). Knockdown results in greatly enhanced iPS formation.

DANIEL GERLICH GROUP

Assembly and function of the cell division machinery

www.imba.oeaw.ac.at/research/daniel-gerlich

Dividing cells extensively reorganize their internal organelles to build a machinery for chromosome segregation and cytokinesis. Our goal is to understand how molecular components self-organize into large assemblies like mitotic chromosomes, the mitotic spindle, and the actomyosin ring. With this, we aim to elucidate general principles of cellular morphogenesis and biomechanics.

Mitotic chromosome assembly

When cells enter mitosis, they reorganize their chromosomes into compact and spatially separate mechanical bodies that move independently on the mitotic spindle (Figure 1). Despite the fundamental importance for faithful genome segregation, we know very little about the three-dimensional organization of mitotic chromosomes and their biophysical properties. Our laboratory has developed methods to visualize genomic loci in live cells and investigate the biomechanical properties of mitotic chromosomes. We discovered that chromosomes change their surface properties as cells progress through mitosis. During mitotic entry, chromosomes assemble a non-adhesive surface to move independently, whereas during mitotic exit, chromosomes cluster to form a single mass of chromatin that is enwrapped by nuclear envelope membranes. We are currently performing systematic loss-of-function screening and mass spectrometric analysis of purified mitotic chromosomes to elucidate the molecular components and mechanisms contributing to the biomechanics of mitotic chromosomes.

Mechanics of cytokinesis

Once sister chromatids have segregated towards opposing spindle poles, cytokinesis engages two filament systems that partition nascent daughter cells. First, a contractile ring composed of actin and myosin filaments mediates ingression of the cleavage furrow between the two spindle poles. This results in the formation of an intercellular bridge, which subsequently splits during abscission by secondary constriction of the intercellular bridge, involving filaments of the endosomal sorting complex required for transport (ESCRT-III). Although the actomyosin ring was discovered several decades ago, the spatial organization of its filaments and the force-generating mechanism remain poorly understood. We have established super-resolution fluorescence microscopy and fluorescence polarization imaging approaches to resolve the actin network reorganization of the actin network during cytokinesis (Figure 2), and we developed assays to probe cortical tension based on the response to laser microsurgery. Our data suggest that the actomyosin ring self-organizes by aligning filaments along the direction of equatorial tension.
ESCRT-III is believed to mediate a secondary membrane tube constriction during abscission by remodeling helical filament assemblies, which we revealed by electron tomography (Figure 3). Yet, how ESCRT-III polymers generate force and adapt to narrowing membrane tubes is poorly understood. Using photobleaching assays and fluorescently-tagged subunits, we found that ESCRT-III polymers continuously exchange their subunits with cytoplasmic pools. Current research is focused on elucidating the molecular components regulating ESCRT-III subunit turnover and its contribution to membrane deformation during constriction of the intercellular bridge.

Computer vision and machine learning for cell biology

Automated live-cell microscopy of dynamic processes such as cell division generates data of tremendous complexity. Our laboratory has developed computer vision and machine learning methods for automated cell phenotyping. We have established the open-source software platform CellCognition (*http://www.cellcognition.org*) for cellular phenotype discovery by supervised and unsupervised machine learning methods. The computer vision and machine learning methods have been integrated into microscope-controlling software to establish a fully automated experimental workflow for complex interactive perturbation experiments while cells divide on the microscope.

Publication highlights:

A. E. Dick and D. W. Gerlich. Kinetic framework of spindle assembly checkpoint signalling. Nature Cell Biology (2013).

Q. Zhong, A. G. Busetto, J. P. Fededa, J. M. Buhmann, and D. W. Gerlich. Unsupervised modeling of cell morphology dynamics for time-lapse microscopy. Nature Methods (2012) 9(7): 711-713

J. Guizetti, L. Schermelleh, J. Mäntler, S. Maar, I. Poser, H. Leonhardt, T. Müller-Reichert, and D. W. Gerlich. Helices of ESCRT-III-dependent filaments in a cortical constriction mechanism of abscission. Science (2011) 331(6024): 1616-20

P. Steigemann, M. Schmitz, C. Wurzenberger, J. Guizetti, M. Held, S. Maar, and D. W. Gerlich. Aurora B-mediated abscission checkpoint protects against tetraploidization. Cell (2009) 136(3): 473-84

Figure 1

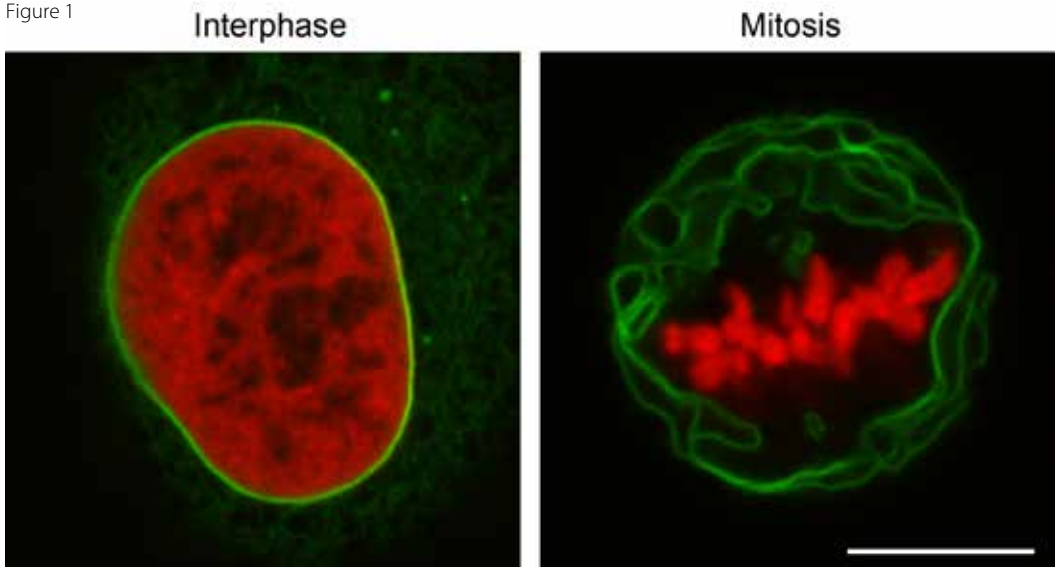

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Figure 2

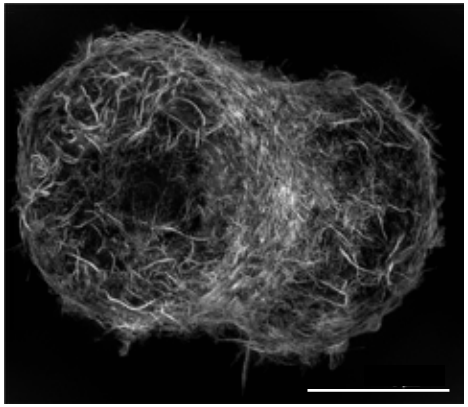

Figure 3

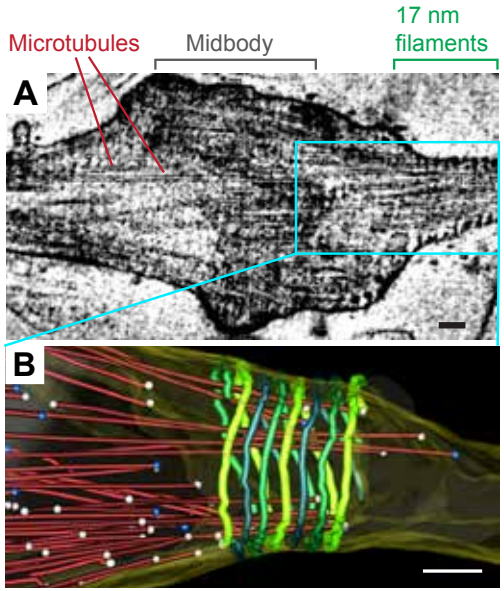

Figure 1. Chromosome morphology during interphase and mitosis. Confocal microscopy images of live HeLa cells expressing a marker for chromatin (histone 2B fused to mCherry, red) and the nuclear envelope (Lap2β fused to EGFP, green). The set of chromosomes fills the nuclear volume as a single mass of chromatin during the interphase. During mitosis, the nuclear envelope disassembles and Lap2β-EGFP localizes to the endoplasmic reticulum. Mitotic chromosomes appear as spatially separate, rod-shaped bodies. Scale bar, 10 μm.

Figure 2. Super-resolution fluorescence microscopy of the actomyosin ring. A human RPE1 cell that is ingressing the cytokinetic cleavage furrow was stained with fluorescent phalloidin and imaged on a 3D-structured illumination microscope. Scale bar, 10 μm.

Figure 3. ESCRT-III filaments at the abscission site. (A) Electron tomogram of a high pressure-frozen HeLa cell with a late-stage intercellular bridge containing 17 nm diameter filaments. (A) Overview of a central tomogram section, showing mid-body and lateral constriction zone. (B) 3D-reconstruction of the tomogram shown in (A) reveals spiral geometry of 17 nm filaments. Red, microtubules; different shades of green, 17 nm filaments; yellow, plasma membrane; white balls, open microtubule ends; blue balls, closed microtubule ends. Scale bars, 100 nm. Adapted from Guizetti et al., Science (2011).

FUMIYO IKEDA GROUP

Dynamic arrangement of linear ubiquitination

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Ubiquitin is an important regulatory protein used for post-translational modification and plays a crucial role in several biological functions, including inflammation, cell death, autophagy, cancer, and cell cycle. By an enzymatic reaction, ubiquitin modifies substrates with different linkage types of ubiquitin chains. We are particularly interested in understanding the roles of novel type of ubiquitin chains known as linear ubiquitin chains in the regulation of various stress-induced cellular responses.

Linear ubiquitination is induced by the LUBAC E3 ligase complex

Linear ubiquitin chain is a unique linkage type of ubiquitin polymer, linked through an intrinsic residue Met 1 instead of commonly used 7 Lys residues (Figure 1A). Ubiquitination is induced by a three-step enzymatic reaction of E1 activating enzyme, E2 conjugating enzyme and E3 ligase. For the linear ubiquitination, E3 ligase complex called Linear Ubiquitin Assembly Complex (LUBAC) plays a crucial role (Figure 1B). LUBAC consists of a catalytic RBR E3 ligase HOIP, and two regulatory subunits Sharpin and HOIL-1L (Figure 1B). We have previously demonstrated that the LUBAC plays a critical role in the regulation of Tumor Necrosis Factor (TNF) -induced NF-kB signalling (Ikeda et al., 2011). However, it is not known whether the enzymatic activity of HOIP is regulated in a similar manner as that of other known E3 ligases such as Parkin.

To elucidate the molecular mechanisms that regulate the HOIP activity we first established an in vitro ubiquitination assay. This assay monitors ubiquitin chain formation by using purified proteins, HOIP, Sharpin and HOIL-1L. Similar to the HHARI E3 ligase, which was shown to be the first example of the 'HECT-RING hybrid' type of E3 ligase, we identified a conserved Cys885 residue in the HOIP catalytic domain (Figure 1C). Our current research has shown that this is crucial for the enzymatic activity (Figure 1D). This suggests that the Cys885 residue is used for the ubiquitin loading site at the intermediate status of the ubiquitin transfer to substrates like HHARI, in line with the data reported by Stieglitz et al., 2013. Moreover, the HOIP Cys885 mutant no longer activated the NF-kB in cells determined by the gene reporter assay (Figure 1E).

Collectively these observations suggest that HOIP functions as a HECT-RING type of E3 ligase, and that the process of linear ubiquitination is critical for the NF-kB activation. We are further analyzing how the catalytic activity of HOIP is regulated upon TNF stimulation by focusing on the formation of the specific signalling complex and protein modifications.

LUBAC plays a crucial role in the regulation of apoptosis

We have shown that systemic inflammation, including skin inflammation is observed in Sharpin deficient (Cpdm) mice (Ikeda et al., 2011). Based on histological analysis using an apoptosis marker cleaved-caspase 3, we found that apoptosis is significantly upregulated in the Cpdm skin tissue (Figure 2A). In order to establish whether this is a cell intrinsic effect of keratinocytes, we generated a Sharpin-knockdown keratinocyte line (HaCaT) by stably expressing shRNA against Sharpin. Identical to the in vivo situation, shShapin HaCaT cells were sensitized to TNF-induced apoptosis determined by caspase-8 activity assay (Figure 2B). Upregulation of apoptosis signal (caspase-8 activity) in Sharpin-knockdown HaCaT was rescued by additional depletion of FADD (Figure 2B), which is a critical factor for apoptosis induction. These observations suggest that Sharpin regulates apoptosis signalling through FADD-containing complex called TNF-receptor complex II. Interestingly, we found that the knockdown of other LUBAC components, HOIP in HaCaT, also sensitized cells to apoptosis (Figure 2C).

This result strongly suggests that the LUBAC as a complex plays a role in the regulation of apoptosis. Currently, we are trying to identify the targets of LUBAC-induced linear ubiquitination in the apoptosis signalling pathway, and to understand how linear ubiquitination regulates apoptosis at the molecular level.

Publication highlights:

Asaoka, T., Ikeda, F. (2015). New Insights into the Role of Ubiquitin Networks in the Regulation of Antiapoptosis Pathways. Int Rev Cell Mol Biol. 318:121-58

Ikeda, F. (2015). Linear ubiquitination signals in adaptive immune responses. Immunol Rev. 266(1):222-36

Figure 1

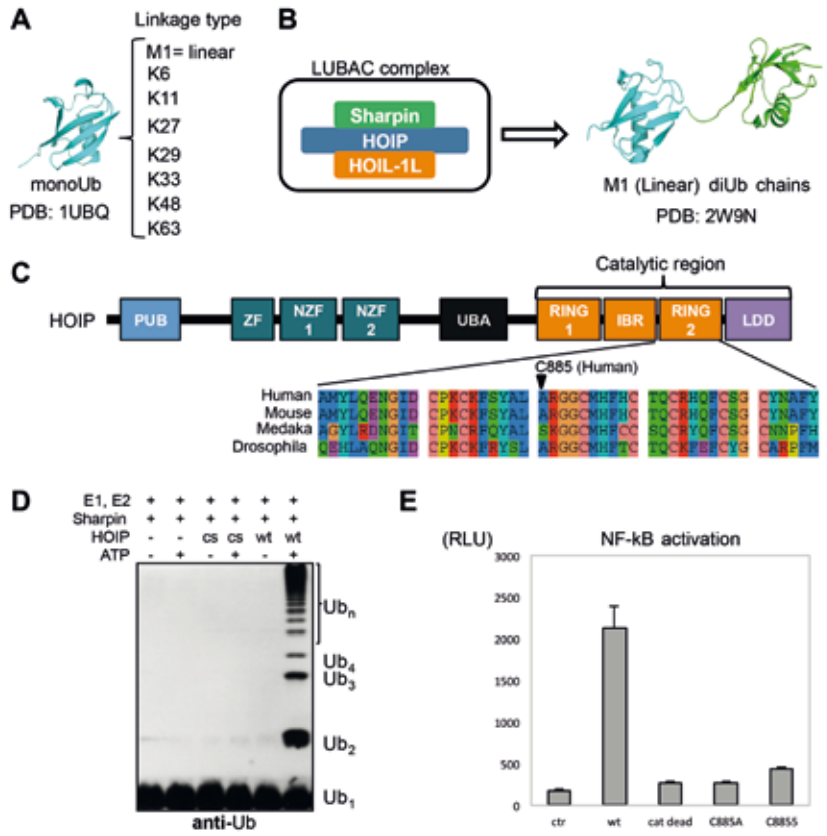

Figure 2

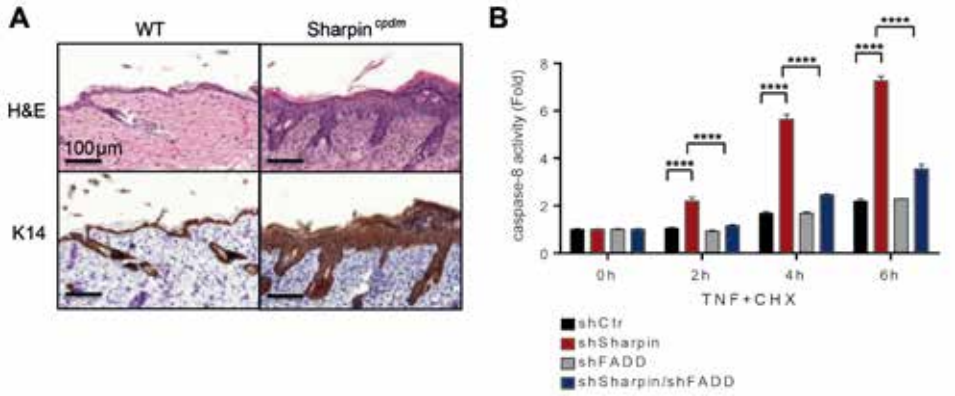

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Figure 1: Linear ubiquitination is induced by the LUBAC E3 ligase complex
A) Mono-ubiquitin molecule and intrinsic amino acid residues used for the formation of the ubiquitin polymer. **B**) LUBAC components Sharpin, HOIL-1L and HOIP for the formation of the linear ubiquitin chain. **C**) A catalytic center located in the 2nd RING domain (RING2) of HOIP. The alignment of the HOIP-RING2 in different species shows high conservation. The arrow indicates C885 in human HOIP, which is conserved in the different species. **D**) In vitro ubiquitination assay using recombinant LUBAC. In comparison to HOIP wild type (wt) (lane 6), the HOIP-C885 mutant (lane 4) fails to generate ATP-dependent linear Ub chains. **E**) HOIP-C885 plays a crucial role in NF-kB signalling. The NF-kB reporter assay was performed using C885 mutants (CA and CS). Both mutants abolished the ability to mediate NF-kB activation as the catalytic dead (cat dead) mutant.

Figure 2: LUBAC plays a critical role in the regulation of apoptosis
A) Histological analysis of skin tissue of wild type (wt) and Sharpin-deficient (Cpdm) mice. Apoptosis is strongly induced in Cpdm keratinocytes (Cleaved-Casp3). H&E and K14 staining of the skin shows greater thickness of the epidermis in Cpdm. **B**) TNF-dependent Caspase-8 activity assay using control, Sharpin knockdown (shSharpin), FADD knockdown (shFADD) human keratinocytes. Compared to controls (shCtr), shSharpin cells stimulated by TNF showed higher caspase-8 activation. Additional knockdown of FADD in shSharpin cells (shSharpin/shFADD) significantly inhibited the activity.

JÜRGEN KNOBLICH GROUP

Brain development and Neural Stem Cells

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The human brain is the most complex and fascinating of all organs. We are interested in understanding how a relatively small number of stem and progenitor cells is able to generate the complex structure of the brain during development. Our group uses Drosophila, mouse and human genetics to understand how neural stem cells generate the right neurons at the right time, and how defects in neurogenesis lead to the formation of brain tumors or heritable brain disorders.

Neural Stem Cells in *Drosophila*

In the fruit fly *Drosophila*, about 400 neural stem cells known as neuroblasts create all neurons and glia cells in the adult brain (Fig. 1A). For this purpose they undergo repeated asymmetric cell divisions, giving rise to a large daughter cell that remains a dividing stem cell and a smaller daughter that differentiates after a limited number of transit amplifying divisions. During each neuroblast division, the cell fate determinants Numb, Prospero and Brat segregate into the smaller daughter cell where they prevent self-renewal and induce differentiation (Fig. 1A, B). When they are missing, both daughter cells become stem cells, leading to exponential proliferation and the formation of a lethal and transplantable brain tumor.

Eventually, neuroblasts exit the cell cycle and differentiate; there is no proliferation in the adult brain. We found that this is due to a cell-intrinsic mechanism that uncouples cell cycle progression from cell growth in a precisely defined period during development, resulting in cell shrinkage and differentiation. In a transgenic RNAi screen for factors responsible for neuroblast shrinkage, we identified several components of the mitochondrial respiratory chain. Our genetic and biochemical experiments support a model in which a change in energy metabolism induced by Ecdysone is responsible for reduced cell growth. We propose that the induction of oxidative phosphorylation deprives cells of the building blocks for lipid and amino acid biosynthesis, which accumulate as end products of glycolysis. Our data show that changes in energy metabolism may be a cause rather than a consequence of changes in the fate of the cell. Furthermore, they reveal a surprising connection between energy metabolism and stem cell self-renewal, which has not been observed earlier in vivo.

Brain development in humans and neurological disorders

The human brain is unique in terms of its size and complexity. While many of its characteristics have been successfully studied in model organisms, recent experiments have disclosed unique features that cannot easily be modeled in animals. We developed a 3D organoid culture system that permitted us to generate human brain tissue, starting from pluripotent stem cells (Lancaster et al., Nature 2013). Our culture model recapitulates the three-dimensional architecture of the developing human cortex in remarkable detail (Fig. 3). Cerebral organoids contain the human dorsal and ventral cortex, the choroid plexus, retina, and occasionally the hippocampus. They recapitulate human-specific cortical features such as the presence of an outer subventricular zone or an inner fiber layer. Furthermore, the stem cell properties and progenitor zone organization of human cerebral organoids is marked by characteristics very specific to humans. Most importantly, our organoid protocol can be combined with cellular reprogramming to model the genetically determined characteristics of brain development in any human individual.

We determined the power of this approach by modeling microcephaly, a genetic disorder resulting in a severe reduction of cortical volume and, consequently, intellectual ability. Our experiments revealed a premature switch from symmetric and expansive to asymmetric neurogenic progenitor cell divisions in microcephalic organoids. We showed that mutations in the centrosomal gene CDK5Rap2 lead to defects in mitotic spindle orientation, which were responsible for the differentiation defect in the specific patient we analyzed. We are currently extending this approach to other more common neurological disorders. In these settings organoid systems offer – for the first time – the possibility to recapitulate human disease without the need for animal experiments. Our work has set a precedence, showing that the development and physiology of even the most complex human organ can be recapitulated in 3D culture. It opens revolutionary possibilities for the analysis of neurological disorders and will hopefully translate into novel therapeutic strategies for these devastating diseases.

Publication highlights:

Eroglu, E., Burkard, TR., Jiang, Y., Saini, N., Homem, CC., Reichert, H., Knoblich, JA. (2014). SWI/SNF complex prevents lineage reversion and induces temporal patterning in neural stem cells. Cell. 156(6):1259-73

Homem, CC., Steinmann, V., Burkard, TR., Jais, A., Esterbauer, H., Knoblich, JA. (2014). Ecdysone and mediator change energy metabolism to terminate proliferation in Drosophila neural stem cells. Cell. 158(4):874-88

Lancaster, MA., Renner, M., Martin, CA., Wenzel, D., Bicknell, LS., Hurles, ME., Homfray, T., Penninger, JM., Jackson, AP., Knoblich, JA. (2013). Cerebral organoids model human brain development and microcephaly. Nature. 501(7467):373-9

Xie, Y., Jüschke, C., Esk, C., Hirotsune, S., Knoblich, JA. (2013). The phosphatase PP4c controls spindle orientation to maintain proliferative symmetric divisions in the developing neocortex. Neuron. 79(2):254-65

Figure 1

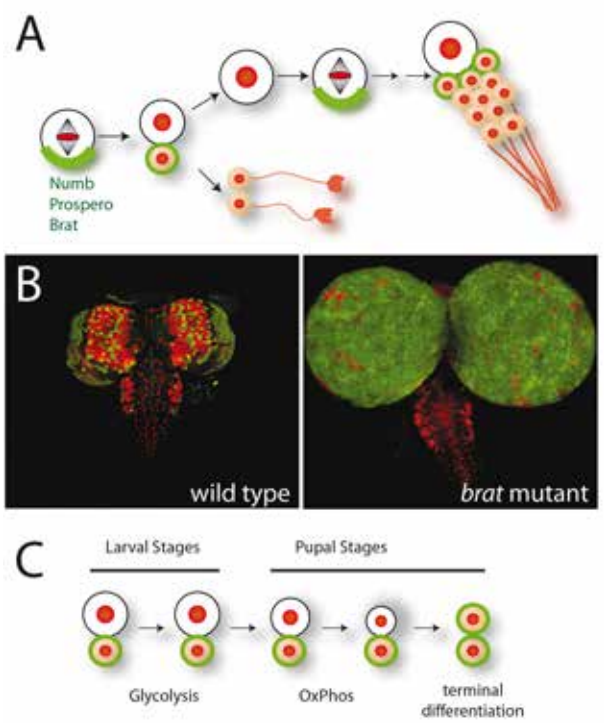

Figure 2

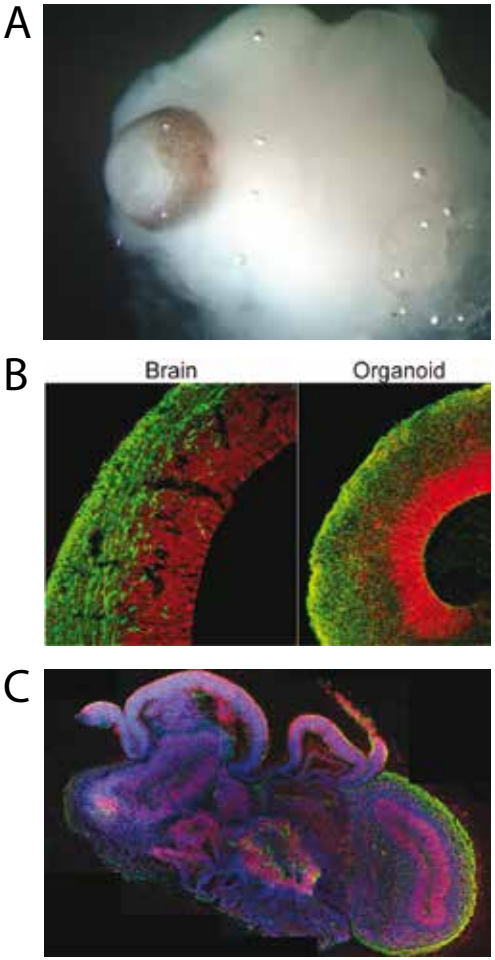

Figure 1: How cells divide asymmetrically. A. Drosophila neuroblasts (white) divide asymmetrically to generate self renewing stem cells (white) and differentiating neurons (red). During each neuroblast division, Brat, Prospero and Numb (green) segregate into the differentiating daughter cell. **B.** Larval brain from a wild type (left) and *brat* mutant animal. Neuroblasts are green, differentiating neurons are red. *brat* brains show a dramatic overproliferation of neuroblasts. **C.** Neuroblasts regrow after each division during the larval proliferative stages. After pupariation, they switch to oxidative phosphorylation. As a result, they reduce growth, become smaller and ultimately undergo a terminal symmetric division.

Figure 2: Cerebral organoids: A 3D culture model for human brain development. A. Cerebral organoids can be derived from human ES or iPS cells. Pigmented area in this brightfield 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. Red are proliferating progenitor cells (labelled by anti Sox2) differentiating neurons are green (marked by anti TuJ1), and DNA is blue. See Lancaster et al, Nature 2013 for details.

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THOMAS MARLOVITS GROUP

Molecular Machines in Action

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A fundamental property of many biological processes is that they are performed by highly organized, multicomponent macromolecular assemblies, often referred to as molecular machines. My lab studies the structural basis for assembly, regulation, and function of transmembrane molecular machines. We use a multidisciplinary approach, by combining molecular biology, genetic, cellular, biochemical, and a wide-range of structural (EM, X-ray, NMR, X-linking/mass spectrometry) tools. We are developing novel imaging and modeling technologies to visualize dynamic molecular processes in unprecedented detail in situ and in action.

Microbial pathogenesis

Gram-negative pathogens such *Yersinia, Shigella, Pseudomonas*, enteropathogenic/enterohemorrhagic *E. coli* (*EPEC/EHEC*) and *Salmonella* are the causative agent for many diseases known to animals or humans. They range from mild to deadly outcomes and often originate as food-borne diseases. Bacterial toxins (so called effectors) are a major aspect of their pathogenicity. They are delivered via the type III secretion system (a large membrane-embedded machinery, also known as injectisome) 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 make the host accessible to bacterial infection.

Type III secretion system: Unfolded protein transport across membranes

Our recent structural analysis (Schraidt & Marlovits, Science 2010) of the injectisome, the most prominent, cylindrical structure of 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.

To investigate type III secretion of human pathogens, we focused (1) to determine the secretion path of injectisomes, (2) to understand the mechanism of transport, and (3) to visualize protein transport in situ. We discovered that substrates are inserted into the secretion path in a polar fashion - N-terminal regions first – and that they are transported in an unfolded state. To establish whether such behavior does in fact occur in situ, we analyzed protein transport across membranes in a near-native state by cryo electron tomography (Radics et al 2014). For the first time, we were able to visualize pathogenic type III secretion systems from *Salmonella* in action.

Technological development - determination of atomic structure from lower resolution cryo-EM maps

Direct electron detectors are a key aspect of the recent revolution in structural biology because they have enabled the determination of electron density maps at near atomic resolution from non-crystalline sample material, using cryo electron microscopy. However, building accurate models into these 3-5Å maps remains a challenge. We thus recently reported a new modeling approach that integrates Monte Carlo optimization with local density guided moves, Rosetta all-atom refinement, and real space B-factor fitting, yielding accurate models from experimental maps for three different systems with resolutions as low as 4.5Å (DiMaio et al Nature Methods 2015). Recently we expanded this work and developed easily used modeling tools to build accurate models at the highest possible resolution from single particle electron microscopy maps.

Publication highlights:

Galan JE, Lara-Tejero M, Marlovits TC, Wagner S (2014). Bacterial type III secretion systems: specialized nanomachines for protein delivery into target cells. Ann Rev Microbiology 8;68:415-38

Radics J, Königsmaier L, Marlovits TC (2014). Structure of a pathogenic type 3 secretion system in action. Nature Structural & Molecular Biology 21(1):82-7

Schraidt O., Marlovits TC (2011). Three-dimensional model of Salmonella's Needle Complex at Subnanometer Resolution. Science 331:1192-95

Figure

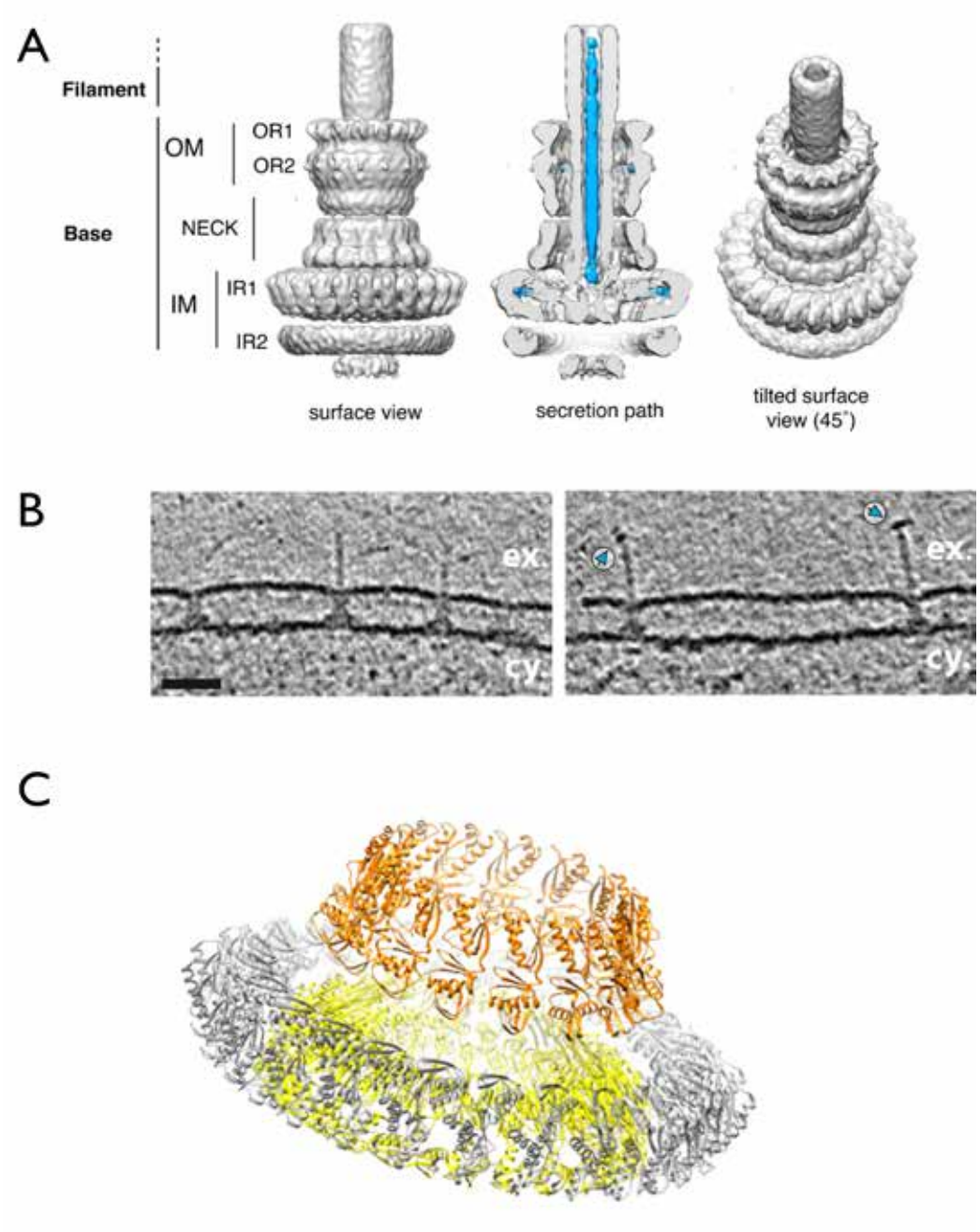

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Figure: **(A)** Structure of the membrane embedded (grey) and substrate trapped (blue) injectisome resolved by cryo electron microscopy and single particle analysis
(B) *in-situ* visualization of substrate-free and substrate-trapped injectiosomes by cryo electron tomography
(C) Atomic model of the major part of the type III secretion system

JAVIER MARTINEZ GROUP

Biochemistry, physiology and disease of the tRNA splicing pathway in mammalian cells

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In mice and humans some tRNAs are exclusively encoded as intron-containing genes, thus highlighting the importance of tRNA splicing as an essential process. Introns are excised in the nucleus by the tRNA splicing endonuclease (TSEN) complex. The resulting exon halves are subsequently ligated to generate mature tRNAs. We have combined chromatography, mass spectrometry, RNAi and phylogenetic analysis to identify key components of the human tRNA splicing pathway, and discovered the RNA kinase CLP1 as part of the TSEN complex (S. Weitzer and J. Martinez, 2007). We also discovered the tRNA ligase complex which has been elusive for 30 years, established RTCB/HSPC117 as the catalytic subunit (J. Popow et al., 2011 and 2012), and archease as an essential co-factor of the tRNA ligase complex (J. Popow et al., 2014).
Recently we showed that the tRNA ligase and archease play critical roles in the unfolded protein response and that CLP1, when mutated, causes neurological diseases both in humans and mice. In this annual report we describe the unexpected sensitivity of the tRNA ligase complex to oxidative stress and our attempts to identify a novel RNA processing activity associated with the mammalian RNA 3' phosphate cyclase RTCD1.

The tRNA ligase complex is inhibited by oxidative stress

In collaboration with Josef Penninger's group, we recently generated and analyzed a mouse encoding a catalytically dead version of the RNA-kinase CLP1, the product of the single point mutation K127A (Hanada et al., 2013). This mutation affects the interaction between CLP1 and the subunits of the tRNA splicing endonuclease. Consequently, the removal of tRNA introns is severely impaired *in vitro*. Hence it was surprising to note the accumulation of tRNA fragments, largely derived from tyrosine tRNAs and composed of the 5' leader sequence and the 5' exon. Interestingly, the overexpression of such tRNA fragments results in enhanced p53 activation in response to oxidative stress, a possible cause of p53-dependent cell death of motor neurons in *Clp1* kinase-dead mutant mice. In principle, 5' tRNA fragments should not accumulate in the presence of defective tRNA splicing endonuclease, unless the tRNA ligase is unable to join them to 3' exon sequences. Importantly, the same type of fragments accumulate massively when cells are exposed to agents known to cause oxidative stress, such as hydrogen peroxide (H_2O_2) or menadione. Therefore we hypothesized that the tRNA ligase might be inhibited by oxidative stress, leading to the accumulation of tRNA fragments (Figure 1).

We tested tRNA ligation *in vitro* by exposing cells to H_2O_2. As shown in Figure 2A, the ligase activity was severely inhibited. We obtained a similar result by depleting RTCB by RNAi and monitoring the accumulation of tRNA fragments (Fig. 2B). These experiments indicate that 5'-leader-exon tRNA fragments accumulate due to the lack of ligation activity. We are currently investigating the chemical basis of such inhibition by means of mass spectrometry. In terms of biology, it is interesting to note that Nature has equipped the tRNA ligase complex with the ability to sense or be the target of oxidative stress.

A putative cyclic phosphodiesterase activity is associated with the RNA cyclase RTCD1

Last year we reported initial studies on RTCD1, a mammalian enzyme that resides primarily in the cytoplasm and acts on 3' phosphate-ended RNAs to generate 2', 3'-cyclic phosphates. While its *in vivo* function remains elusive – a knockout mouse is being analyzed in our laboratory – we have detected a novel enzymatic activity associated with RTCD1 that converts terminal 2', 3'-cyclic phosphates into nucleotides displaying a 3' OH group; the chemistry at the 2' position remains to be elucidated. To identify such activity, we purified a FLAG-tagged RTCD1 complex on a cation exchange column and managed to separate two enzymatic activities: FLAG-RTCD1 eluted at ~250mM NaCl (Figure 3, upper panel) and the novel activity - a putative cyclic phosphodiesterase - eluted at ~500mM NaCl (Figure 3, lower panel). Candidates obtained from an ongoing mass spectrometry analysis will be depleted by means of RNA interference and cellular extracts will be inspected for the absence of such enzymatic activity. Identifying the RTCD1-associated putative cyclic phosphodiesterase should reveal a new component of the mammalian RNA repair system. One possible function of the dual activity complex is to target 3' phosphate-ended RNAs to exonucleolytic degradation by successive conversion into 2', 3'-cyclic phosphates, and further into nucleotides containing a 3' OH group.

Publication highlights:

Toshikatsu Hanada, Stefan Weitzer, Josef M Penninger and Javier Martinez. CLP1 as a novel player in linking tRNA splicing to neurodegenerative disorders. Wiley Interdiscip Rev RNA. 2015 Jan-Feb;6(1):47-63. doi: 10.1002/wrna.1255. Epub 2014 Aug 20.

Figure 1

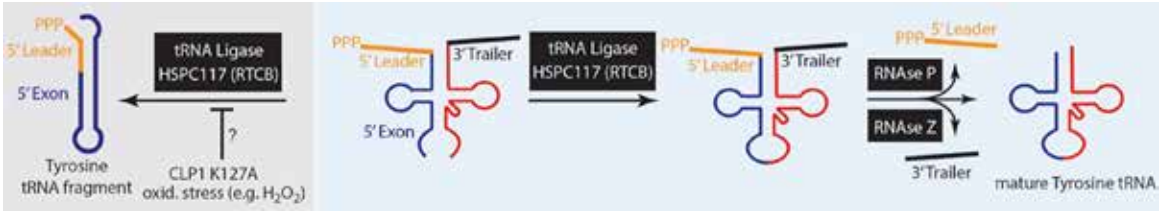

Figure 2

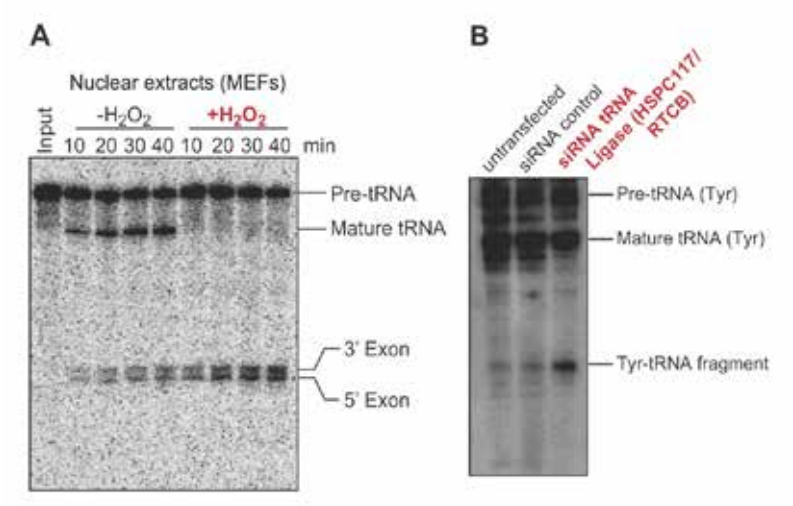

Figure 3

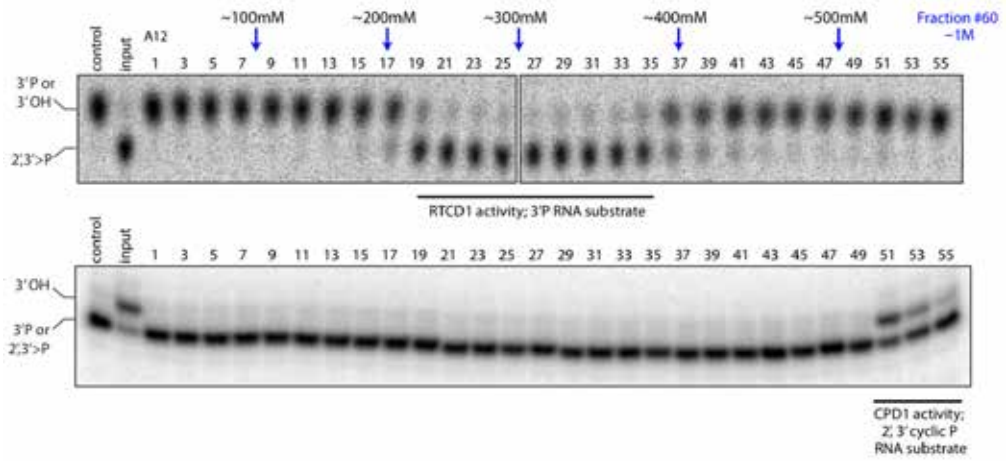

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Figure 1: Model of the biogenesis pathway of 5′ leader-exon tRNA fragments upon oxidative stress. Normal processing of a pre-tRNA is shown on the right (light blue box). Upon oxidative stress, or due to a mutation affecting the active site of CLP1 (grey box), tRNA fragments encompassing the 5′ leader and 5′ exon accumulate. We hypothesize that this is due to the inhibition of tRNA ligase activity.

Figure 2: tRNA ligation is abolished upon oxidative stress, resulting in the accumulation of tRNA fragments. A: Ligation of tRNA exon halves is abolished by oxidative stress. A tRNA splicing assay (using an internally labeled intron-containing yeast pre-$tRNA^{Phe}$) was performed using nuclear extracts from mouse embryonic fibroblasts (MEFs) that were either left unstressed or exposed to 100 µM H_2O_2 for 1 hour. **B**: Accumulation of 5′ leader-exon tRNA fragments by RNAi-mediated depletion of HSPC117/RTCB, the catalytic subunit of the tRNA ligase complex. Northern blot analysis (using a complementary sequence to the tyrosine 5′ exon) was performed to assess the levels of tyrosine tRNA 5′ leader-exon fragments in HeLa cells treated with control siRNAs or siRNAs against HSPC117/RTCB).

Figure 3: Chromatographic separation of RNA 3′ phosphate cyclase (RTCD1) and a putative novel cyclic phosphodiesterase activity. A FLAG-RTCD1-purified complex was applied into a cation exchange column and proteins eluted with a gradient of NaCl. Thin-layer chromatography was used to monitor the conversion of the RNA 3′-terminal phosphate into a 2′, 3′-cyclic phosphate (upper panel, fractions 19-37). A denaturing polyacrylamide gel revealed the conversion of a 2′, 3′-cyclic phosphate into a nucleotide displaying with a 3′ OH group (lower panel, fractions 50-55).

SASHA MENDJAN GROUP

Stem Cells and Human Mesodermal Organogenesis

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Key human organs and tissues including the heart, blood, fat, muscle, and vessels are derived from the embryonic germ layer called mesoderm. The fascinating journey from early mesodermal precursors to functioning organs is not well understood, and in particular not for human development and disease. Our group is using stem cells to decipher the molecular control of human mesodermal organogenesis and pathogenesis. Based on molecular and developmental insights, our aim is to generate and study functional mesodermal tissues and organ-like structures in a dish.

Pluripotent stem cells have revolutionised human developmental biology and opened new avenues to regenerative medicine. Their extraordinary qualities include self-renewal in culture, amenability to genetic modifications and the potential to differentiate into specialised cell types, including mesodermal tissues (Figure 1). This makes them a powerful tool for the purpose of a) study the molecular control of human mesodermal development and disease, b) discover and testing drugs, and c) using them in transplantation therapy. We are employing pluripotent stem cells to investigate the following questions:

How do molecular interactions control cardiac and somitic mesoderm specification?

Human congenital disorders and other pathologies arise early in embryonic development due to mutations and deregulation of key genes. Many of these genes operate in regulatory networks that control mesoderm induction, patterning and specification of mesodermal subtypes (e.g. cardiac, lateral plate and somitic) into distinct progenitors and tissues (Figure 2). We can mimic mesodermal gene regulatory networks *in vitro* by using defined signals and specific timing to differentiate pluripotent stem cells into therapeutically relevant cells including cardiomyocytes, vascular cells, chondrocytes and adipocytes.
Our aim is to explore the interactions between signalling, epigenetic, RNA and transcription factor networks that drive cardiac and somitic mesoderm specification. We use powerful genetic (mutagenesis, tagging and fluorescent reporters), imaging (3D and live), proteomic (interaction and phospho mass spectrometry) and computational methods (regulatory networks analysis) to elucidate how specification works and how it goes wrong in disease. Finding answers to these fundamental questions will greatly enhance our understanding of human development and disclose new avenues of clinical application.

How do tissue interactions drive cardiac and somitic organogenesis?

In the vertebrate embryo, signalling and interactions between different progenitor tissues drive organogenesis. For instance, the heart is developing from interacting lateral plate mesoderm tissues that give rise to cardiac muscle, vasculature and pacemaker cells. Similarly, growing fat depots depend on interactions between (pre)-adipocytes and vascular cells. The crosstalk between different cell types is vital for the derivation, self-organisation and growth of organ-like structures *in vitro* and during organ regeneration *in vivo*. Our aim is to understand how tissues communicate and thereby control human organ morphogenesis, growth and functional maturation. Our approach is to combine distinct lateral plate and somitic progenitors that express fluorescent reporters, thus permitting the imaging, physical separation and molecular analysis of interacting tissues (Figure 3). We also explore how perturbed signalling interactions between tissues result in defective organogenesis when mutant tissues are combined. Our key goal is to mimic human cardiac and somitic congenital defects in a dish and understand the biochemistry connecting mutant genotypes to clinically relevant phenotypes. Functional and molecularly defined human mesodermal organ-like structures will be invaluable for effective disease modelling and drug discovery.

Publication highlights:

Alessandro Bertero, Pedro Madrigal, Antonella Galli, Nina C. Hubner, Deborah Burks, Roger Pedersen, Daniel Gaffney, Mendjan S, Siim Pauklin*, and Ludovic Vallier*. (2015). Genes & Development.*
*(*equal contribution)*

Figure 1

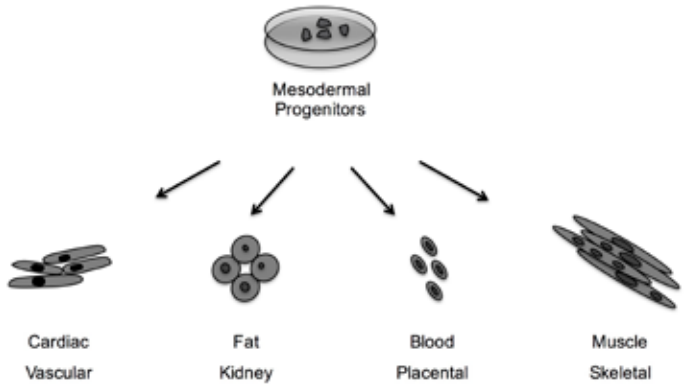

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Figure 2

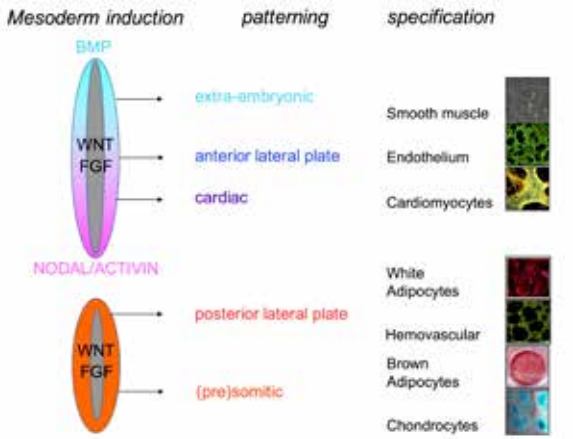

Figure 3

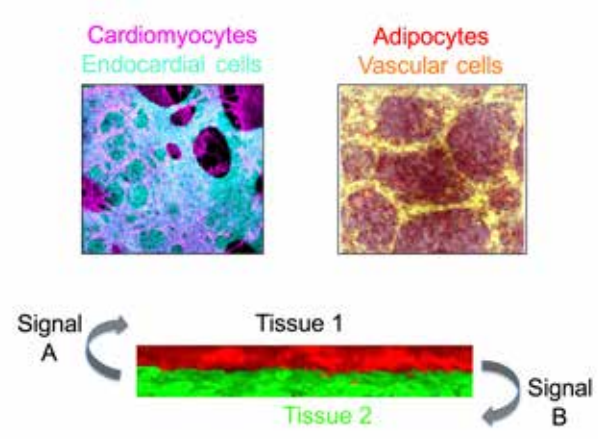

Figure 1: The mesoderm germ layer gives rise to key tissues and organs.

Figure 2: The induction of mesoderm by different signalling gradients results in patterning into distinct mesodermal subtypes. These restricted precursors further specify into more specialised cell types.

Figure 3: Combining fluorescently labeled mesodermal progenitors. The signaling crosstalk between tissues results in fluorescent reporter gene activation.

KAZUFUMI MOCHIZUKI GROUP

Small RNA-directed heterochromat in formation in DNA elimination of *Tetrahymena*

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Heterochromatin is a closed and mostly transcriptionally repressed state of chromatin, which is critical for gene silencing, cell differentiation and genome maintenance. The maintenance heterochromatin in cell proliferations is well understood, but its initial formation is still poorly understood. Heterochromatin is established de novo during the programmed DNA elimination in the ciliated protozoan Tetrahymena and this process can be synchronously induced in laboratory in a large scale. Therefore, DNA elimination in Tetrahymena serves as a unique model for initiation, spreading and aggregation processes of heterochromatin that can be studied genetically and biochemically.

Small RNA-mediated genome-wide trans-recognition network in *Tetrahymena* DNA elimination

Small RNAs are used to silence transposable elements (TEs) by heterochromatin formation in many eukaryotes. In ciliated protozoans, small RNA-mediated comparison of the germline and somatic genomes underlies identification of TE-related sequences, which are then eliminated from the soma. We reported that an additional mechanism of small RNA-mediated identification of TE-related sequences in the ciliate *Tetrahymena*. We showed that a limited set of internal eliminated sequences (IESs) containing potentially active TEs produces a class of small RNAs that recognize not only the IESs from which they are derived but also other IESs in trans. This trans-recognition triggers the expression of yet another novel class of small RNAs that identify other IESs. Therefore, TE-related sequences in *Tetrahymena* are robustly targeted for heterochromatin formation and subsequent elimination by a genome-wide trans-recognition network accompanied by a chain reaction of small RNA production.

Regulation of the heterochromatin aggregation process by phosphorylation of HP1-like protein

In addition to the local compaction of a single heterochromatin locus, in some cell types, multiple heterochromatic loci are assembled into aggregated higher-order structures called heterochromatin bodies. The formation and biological roles of heterochromatin bodies are poorly understood. In *Tetrahymena*, de novo heterochromatin body formation is accompanied by programmed DNA elimination. We reported that the novel heterochromatin body component Jub1p promotes heterochromatin body formation and dephosphorylation of the heterochromatin protein 1 (HP1)-like protein Pdd1p. Through the identification and mutagenesis of the phosphorylated residues of Pdd1p, we demonstrated that Pdd1p dephosphorylation promotes the electrostatic interaction between Pdd1p and RNA in vitro and heterochromatin body formation in vivo. We therefore suggested that heterochromatin bodies are assembled by the Pdd1p-RNA interaction. Jub1p and Pdd1p dephosphorylation are required for heterochromatin body formation and DNA elimination but not for local heterochromatin assembly, indicating that heterochromatin body of itself plays an essential role in DNA elimination.

Publication highlights:

Woehrer, S. L, Aronica, L., Suhren, J. H., Busch, C. J., Noto, T and Mochizuki, K. (2015) A Tetrahymena Hsp90 co-chaperone promotes siRNA loading by ATP-dependent and ATP-independent mechanisms. EMBO Journal 34, 559-577.

Noto, T., Kataoka, K., Suhren, J. H., Hayashi, A., Woolcock, K. J., Gorovsky, M. A. and Mochizuki, K. (2015) Small RNA-mediated genome-wide trans-recognition network in Tetrahymena DNA elimination. Mol Cell 59, 229-242.

Kataoka, K., and Mochizuki, K. (2015) Phosphorylation of an HP1-like protein regulates RNA-bridged heterochromatin body assembly for DNA elimination. Dev Cell 35, 775-788.

Figure 1

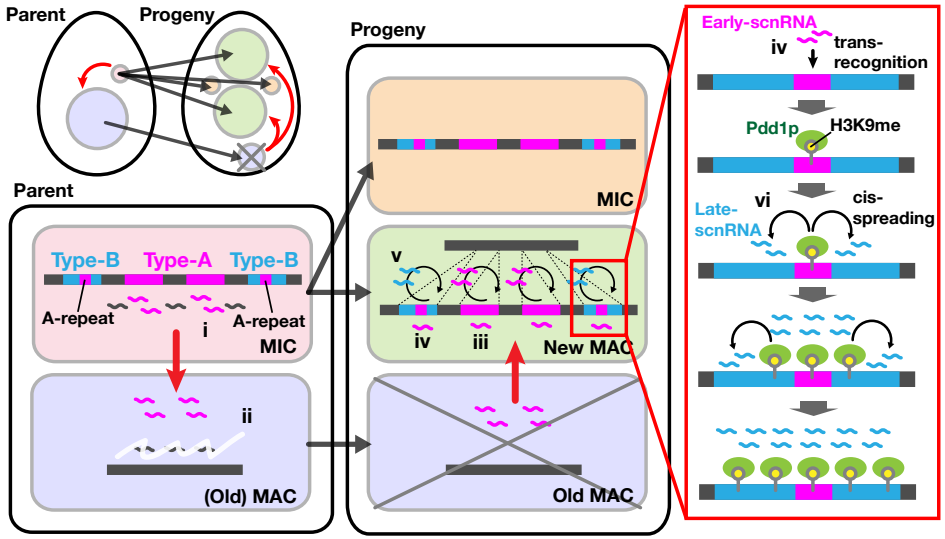
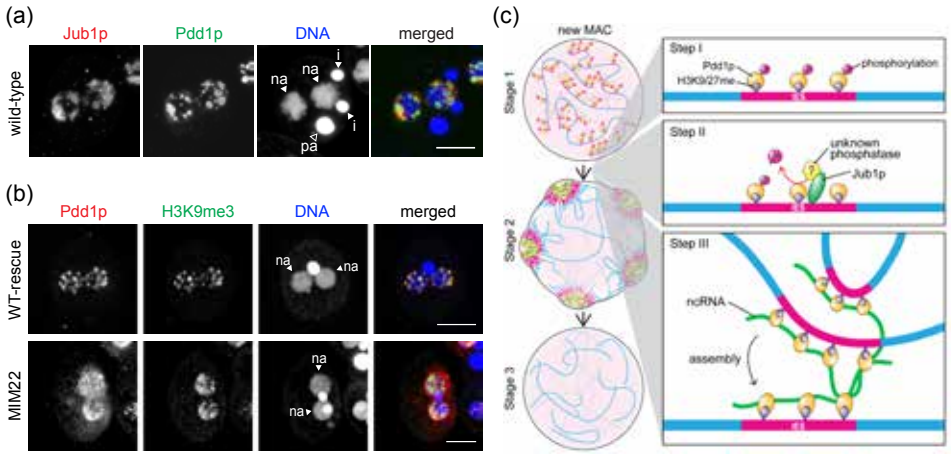


Figure 2



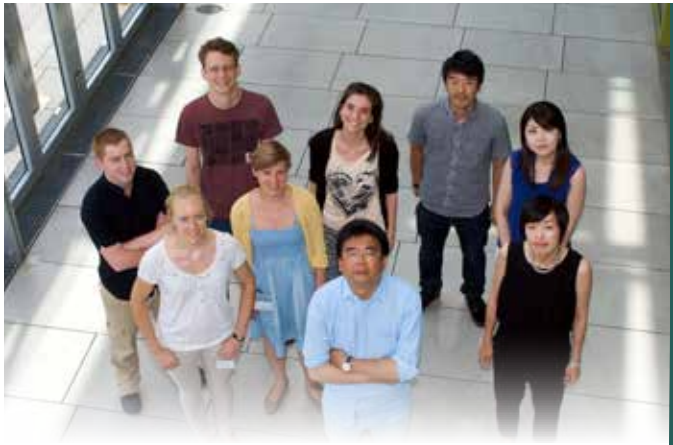


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Figure 1: A model for a trans-recognition network in IES recognition.
Early-scnRNAs are expressed from type-A IESs (magenta boxes) and their flanking sequences in the MIC (i), and the latter are degraded in the parental MAC (ii). In the new MAC, Early-scnRNAs recognize the IESs from which they are derived (iii) as well as other Type-A and Type-B (sky-blue boxes) IESs in trans (iv) through A-repeats to trigger Late-scnRNA production (v). In an IES, regions producing Late-scnRNAs spread in cis (vi) in heterochromatin component (Pdd1p, H3K9me)-dependent manner.

Figure 2: Jub1p is a heterochromatin component required for heterochromatin body formation
(**a**) Jub1p (red) co-localizes with a known heterochromatin component Pdd1p (green). DNA was counterstained with DAPI (blue). Arrowheads indicate the MIC (i), new MAC (na) and parental MAC (pa). Scale bar = 10 µm. (**b**) A mutant mimicking constitutively phosphorylated Pdd1p (MIM22) does not support heterochromatin body formation. Red: Pdd1p, Green: H3K9me3, Blue: DNA. The new MACs are marked with an arrowhead (na). (**c**) A model for heterochromatin body assembly. Step I: phosphorylated Pdd1p is deposited onto IESs through its interaction with H3K9/27me. At this stage (Stage 1), heterochromatin is distributed homogeneously. Step II: Jub1p triggers dephosphorylation of Pdd1p, which reduces the net negative charge of Pdd1p and restores its RNA binding activity. Step III: The Pdd1p-RNA interaction likely "glues" multiple IESs into a heterochromatin body (Stage 2). Finally, the IESs are excised within the heterochromatin body (Stage 3).

JOSEF PENNINGER GROUP

Genetic dissection of disease mechanisms

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

Our basic approach is to genetically manipulate and change genes in mice and to determine the effects of these mutations in development of the whole organism and in diseases. From these mutations we are trying to establish basic principles of development and basic mechanisms of disease pathogenesis.

First evidence of complete cardiac regeneration in humans.

Each year, 17 million people around the world die of cardiovascular diseases, 2 million of them in the EU alone (WHO). Even though medical care for cardiac patients has improved tremendously and the immediate fatality rate has dropped, most patients still face permanent damage leading to chronic heart failure. During a heart attack, cardiac muscle cells die and are replaced by scar tissue. But scar tissue cannot pump, which leads to limitations in cardiac function and a weakening of the heart muscle. So far, heart muscle cells lost in adults cannot be efficiently regenerated despite innovative approaches such as stem cell therapy. Pioneering experiments demonstrated that fish can completely regenerate the heart following resection of the heart apex, spurning a plethora of studies using fish as a model organism.

Our group and Olson's group have recently reported complete morphologic and functional cardiac repair in newborn mice following severe myocardial infarction. Two key issues remain to translate findings in model organisms to future therapies in humans: what is the mechanism and can cardiac regeneration indeed occur in newborn humans? We now report the case of a newborn child suffering from a severe myocardial infarction due to coronary artery occlusion. The child developed massive cardiac damage as defined by serum markers for cardiomyocyte cell death, electrocardiograms, echocardiography, and cardiac angiography (Figure 1). Remarkably, within weeks after the initial ischemic insult, we observed functional cardiac recovery, which translated into long-term normal heart function. These data indicate that, similar to neonatal rodents, newborn humans have the intrinsic capacity to repair myocardial damage and completely recover cardiac function (Haubner et al. Circ. Research 2015).

Identification of a critical transcriptional regulator of pain perception.

Chronic and acute pain affects millions of people worldwide producing an enormous financial and quality of life burden. The detection of noxious or damaging stimuli (nociception) is an ancient process that alerts living organisms to environmental dangers. Harmful stimuli activate receptors on specific sensory neurons called nociceptors, which mediate information transfer via the spinal cord to higher order processing centers resulting in protective behaviors and awareness of pain. Pain perception is essential for an animal to thrive, and human patients that cannot sense pain, such as patients with hereditary sensory and autonomic neuropathy (HSAN), die prematurely due to multiple injuries.

PR homology domain-containing member 12 (PRDM12) belongs to a family of conserved transcription factors implicated in cell fate decisions. We show that PRDM12 is a key regulator of sensory neuronal specification in *Xenopus*. Modeling of human *PRDM12* mutations that cause hereditary sensory and autonomic neuropathy (HSAN) revealed remarkable conservation of the mutated residues in evolution. Expression of wild-type human *PRDM12* in *Xenopus* induced the expression of sensory neuronal markers, which was reduced using various human *PRDM12* mutants. In *Drosophila*, we identified Hamlet as the functional PRDM12 homologue that controls nociceptive behavior in sensory neurons. Furthermore, expression analysis of human patient fibroblasts with *PRDM12* mutations uncovered possible downstream target genes. Knockdown of several of these target genes including thyrotropin-releasing hormone degrading enzyme (TRHDE) in *Drosophila* sensory neurons resulted in altered cellular morphology and impaired nociception. These data show that PRDM12 and its functional fly homologue Hamlet are evolutionary conserved master regulators of sensory neuronal specification and play a critical role in pain perception. Our data also uncover novel pathways in multiple species that regulate evolutionary conserved nociception (*Nagy et al. Cell Cycle 2015*).

Publication highlights:

Haubner, BJ., Schneider, J., Schweigmann, UU., Schuetz, T., Dichtl, W., Velik-Salchner, C., Stein, JI., Penninger, JM. (2015). Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction. Circ Res. Epub 2015 Dec 9.

Nagy, V., Cole, T., Van Campenhout, C., Khoung, TM., Leung, C., Vermeiren, S., Novatchkova, M., Wenzel, D., Cikes, D., Polyansky, AA., Kozieradzki, I., Meixner, A., Bellefroid, EJ., Neely, GG., Penninger, JM. (2015). The evolutionarily conserved transcription factor PRDM12 controls sensory neuron development and pain perception. Cell Cycle 14(12): 1799-808

Figure 1

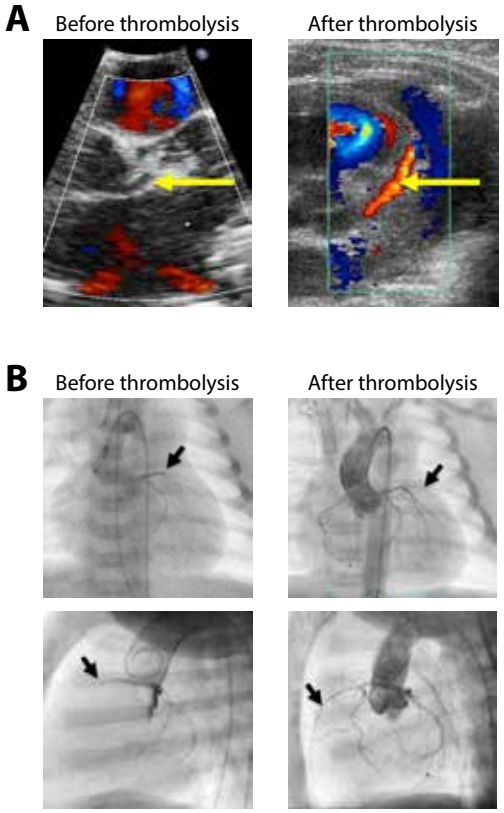

Figure 2

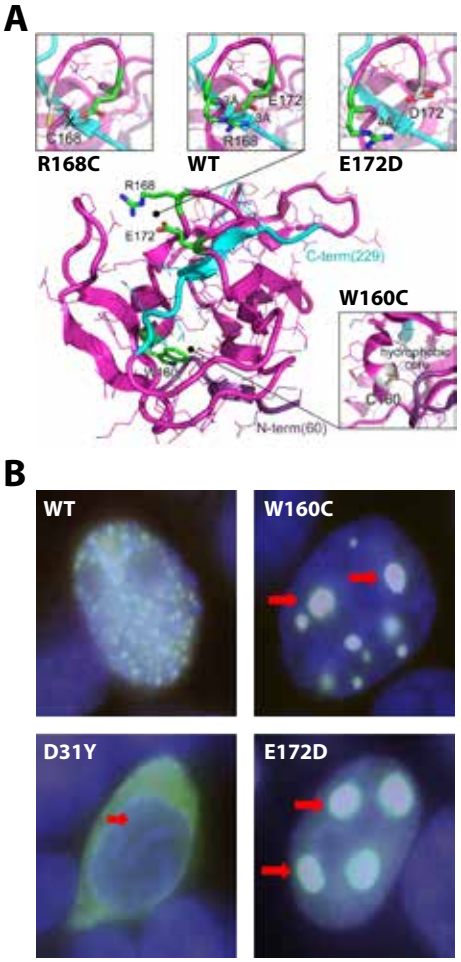

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Figure 1: Thrombotic occlusion of the proximal left anterior descending artery (LAD). A, Doppler echocardiography of the patient's LAD before and after thrombolysis. Data are from the day of birth (before thrombolysis) and three days later (after thrombolysis). **B**, Invasive coronary angiography confirmed a proximal thrombotic LAD occlusion leading to antero-septal myocardial infarction. Left panels show angiographic pictures of the target lesion (arrows) from two different imaging planes (upper panel = antero-posterior view, lower panel = lateral view). After initiation of thrombolysis, angiography proved re-opening of the coronary vessel (right panels). Data are from the day of birth (before thrombolysis) and three days later (after thrombolysis).

Figure 2: Human PRDM12 mutations cause structural instability. A, The structural modelling of the human *PRDM12* mutations is based on the crystal structure of the human PRDM12 methyltransferase domain (PDB:3EP0). Mutated residues and the substitutions are colored in green and grey, respectively, and shown in stick representation. Protein is shown using cartoon and bonds representations. N- and C-terminal parts are colored in violet and cyan, respectively. **B**, Immunofluorescence analysis of HEK cells transiently transfected with DDK-tagged human wild type PRDM12 (WT) or the human R160C, D31Y, and E172D PRDM12 mutants. Arrows indicate protein aggregates of the mutant R160C and E172D protein as well as loss of nuclear staining for the mutant D31Y. The DDK-tag was visualized with anti-flag antibodies (green); nuclei are counterstained with DAPI (blue). Overlays appear in white. Representative images are shown. Magnifications 100X.

KIKUE TACHIBANA-KONWALSKI GROUP

Molecular control of the oocyte-to-zygote transition

www.imba.oeaw.ac.at/research/kikue-tachibana-konwalski

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 zygote, the cell cycle machinery switches from meiosis to mitosis and 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.

The oocyte-to-zygote transition is one of the most dramatic cell conversions in biology. It refers to the female germ cell or oocyte, which undergoes two rounds of meiotic chromosome segregation and, following fertilization, is converted into a mitotically dividing embryo (Figure 1). 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 mediated by the cohesin complex. Cohesin is especially important in meiosis, the specialized cell division giving rise to haploid gametes, egg and sperm. The paradigm of mammalian reproductive biology is that all oocytes are generated before birth (Figure 2). Cohesion is established during meiotic DNA replication in fetal oocytes, recombination occurs before birth, and oocytes remain arrested until ovulation triggers the first meiotic division (Figure 1). Remarkably, the arrested state lasts for months in the mouse and possibly decades in the human. Is cohesin maintained with or without turnover during the long arrest? Using TEV protease technology that we pioneered in the mouse, molecular genetics and 4D confocal live-cell imaging, we have discovered that sister chromatid cohesion established in fetal oocytes is maintained after birth in arrested oocytes without turnover for months. This implies that women's fertility depends on the longevity of cohesin proteins that established cohesion *in utero*. Future work using mass spectrometry and CRISPR genome editing to generate novel mouse mutants will address the mechanisms responsible for cohesion maintenance and how they might go awry with age.

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. This requires an interdisciplinary approach combining novel genome-wide methods to study chromatin organization with cell cycle kinetics documented by live-cell imaging.

We are testing candidate factors required for this process using conditional knockout mice. 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. (2015). Cell division: Hold on and let go. Nature 517, 441-442.

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. 23: 2534-2539.

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: 467-71.*

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: 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. 20:1880-4.*
*(*equal contribution)*

Figure 1

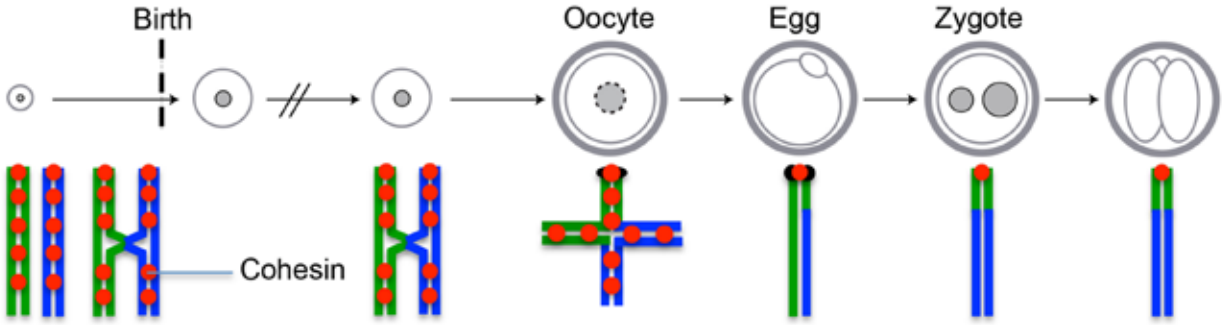


Figure 2

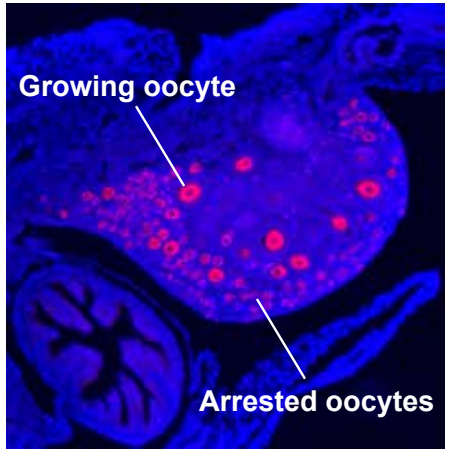
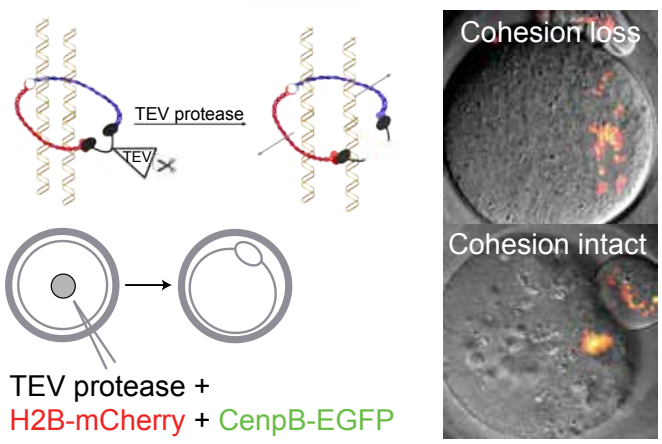


Figure 3



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DIPLOMA STUDENTS: ILYA FLYAMER, ANDREA HIRSCH
RESEARCH ASSISTANT: KERSTIN KLIEN

Figure 1: The mammalian oocyte-to-zygote transition. Meiotic DNA replication and recombination occur in fetal oocytes. After birth, oocytes remain arrested until recruited to grow into mature oocytes, which undergo the first meiotic division at ovulation. Fertilization of egg by sperm produces the zygote. Cohesion establishment occurs in fetal oocytes, cohesion is maintained during the arrest and cohesin is removed from chromosomes at the meiotic divisions.

Figure 2: Females are born with oocytes. A neonatal ovary filled with arrested oocytes and some growing oocytes. The germ cell marker DDX4 marks oocytes (red) and DNA is visualized with Hoechst (blue).

Figure 3: Testing cohesin turnover in mouse oocytes. Cohesin consists of an Smc1/Smc3 heterodimer (red/blue) bridged by a kleisin subunit (black). The kleisin is genetically engineered to contain TEV protease recognition sites. TEV protease-mediated cleavage of cohesin destroys cohesion. Genetically engineered oocytes were injected with mRNA encoding TEV protease, H2B-mCherry to mark chromosomes (red) and CenpB-EGFP to mark kinetochores (green). Cohesion is lost (top) or remains intact (bottom).

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TECHNICAL ASSISTANTS: MICHELLE FOONG, PAUL MÖSENEDER, ESTHER RAUSCHER, ROMAN FERDINAND STEMBERGER
DIPLOMA STUDENT: JONATHAN BAYERL

STEM CELL CENTER – GENE TARGETING UNIT

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The main objective of the Stem Cell Center is to broaden and strengthen stem cell research. Ideal human disease models can be engineered by genetic modification using pluripotent stem cells owing their ability to differentiate into any cell type in the body. Induced pluripotent stem cells (iPSC) technology enables the development of a wide range of cell-based disease models from genetically disposed patients. Our goals are to translate our findings to clinical applications and advancing the field of regenerative medicine.

Mouse pluripotent stem cells core facility

The several missions of the embryonic stem (ES) cell core facility include the production of quality-controlled ES cell lines with genetic mutations, the creation and handling of quality-controlled ES cell lines, and teaching mouse genetics, ES cell culture, and manipulation. 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.

Human pluripotent stem cells core facility

Our iPSC core facility supports research in the stem cell field by facilitating the derivation of mouse and human iPSC cell lines. In recent years, we have refined the iPSC core to better meet investigator needs. We offer three non-integrating technologies (Sendai virus, modified mRNA, and episomal vector) for reprogramming of a variety of somatic cell types. We provide teaching such as hands-on technical training in current reprogramming methodologies, characterization methods for reprogrammed cells, how to maintain iPSC on feeder-free culture, evaluation of iPSC cell quality and passaging, banking and cryopreservation. We also envision the development of patient-specific iPSC followed by treatment with autologous repaired cells. Over the last year, we have further developed and optimized protocols for high efficient isolation and growth of stem cells from urine. Non-invasively harvested, patient-specific urine cells will be reprogrammed into induced pluripotent stem cells using integration-free methods. We currently offer TALEN or CRISPR genome editing technologies to generate knock-out or knock-in lines for repair or introduction of mutations.

IPSC-based therapy for recessive dystrophic epidermolysis bullosa

Epidermolysis bullosa (EB), a rare skin disease, that arises from multiple different mutations, many of which are in collagen genes, is characterized by chronic fragility and skin blistering. To date, only symptomatic treatment of severe blistering exists, 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 for the underlying molecular defects in EB. We have already successfully established mouse repaired iPSC, differentiated these cells into dermal fibroblasts, transplanted such cells into diseased *Col7a1* mutant mice, and showed that no blisters occurred upon mechanical stress. Thus, genetically corrected iPSC appear to be a viable and well tolerated therapeutic strategy for the treatment of EB. Although keratinocytes can be generated from pluripotent stem cells, they are restricted in their differentiation potential. To restore all functional skin components, including hair follicles, sweat glands, or nerves cells, the generation of most primitive epidermal progenitor out of pluripotent stem cells is of high importance for proper skin sheet transplantation for rare genetic disease such as EB. Future work will also focus to develop differentiation protocols of gene corrected iPSC towards hematopoietic stem cells for systemic applications.

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FLY HOUSE

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The Fly House provides research support for those scientists at IMBA using the fruit fly Drosophila melanogaster as a genetic model system. Our services include the generation of transgenic fly lines, gene targeting to generate knock-out or knock-in mutants, and large-scale in vivo RNAi screens.

Embryo injections

A fundamental service 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. Over the course of a year, more than 300 different constructs get injected at the facility.

Gene targeting

Genome engineering in *Drosophila* via traditional homologous recombination is a time-consuming and labour-intensive process. Recent advances in the development and application of programmable nucleases significantly enhanced gene targeting rates. After setting up a versatile and efficient genome engineering platform using the CRISPR/Cas9 technology, we applied this strategy to target around 70 genomic loci in the past year, generating frame-shift mutations (indels), defined point mutations, precise deletions as well as adding short epitope tags to endogenous genes. Rather than screening $5x10^5$ flies required with the conventional method, we are now able to isolate targeted mutations from 100 flies in a process that takes two months.

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 candidate genes.

HEAD OF FACILITY:
ANDREAS LEIBBRANDT

RESEARCH ASSISTANTS:
MANUELA KINZER, NICOLLE SCHULLER, ELLEN WETZEL

HAPLOBANK

Genome-wide recessive genetics in murine embryonic stem cells

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In the post-genomic era, science is accumulating large datasets from high-throughput screening. Validation of hits from such screens still requires genetic testing. To this end, Haplobank generated a genome-wide library of murine embryonic stem cell lines with defined genetic mutations, which can be used to functionally validate predictions or to study in-depth phenotypic effects of gene loss, thereby helping to phenotypically annotate the mouse genome.

Somatic mammalian cells, including embryonic stem cells, usually carry two copies of all chromosomes masking recessive phenotypes in heterozygosity. 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. As haploid mESCs can be readily mutagenized by random insertional mutagenesis ("gene trapping") at their haploid state resulting in complete homozygous mutants, very large pools of defined mutations can easily be generated for reverse and high-throughput forward genetic screens. We use various conditional transposon-, lentiviral-, and retroviral-based mutagenic gene trap vectors to account for insertional biases and to hit as many genes as possible. Each introduced single mutation carries a unique internal DNA barcode, which can be used e.g. for haploinsufficiency profiling. Most importantly, all gene traps contain an invertible splice acceptor cassette, which allows for the identification of non-disruptive antisense integrations in all genes. Therefore, our cell lines can be used to study otherwise essential genes as such genes can be acutely disrupted upon inversion of the splice acceptor from its non-disruptive/viable to its disruptive/lethal state in large cell numbers or in specific differentiated cell lines.

Haplobank has achieved its goal of generating, sequencing, and mapping more than 100'000 homozygously mutated ES cell lines for functional genomics by streamlined and automatized cell culture, DNA preparation, and deep sequencing protocols using a Hamilton robotic platform. We identified either single or multiple gene trap insertions in 16'970 unique genes. Taking only clones carrying a single gene trap, we hit 11'703 unique genes. Currently, we distribute clones on campus and to a few collaborators around the world, and have since its inception in 2012 distributed over 800 clones from our collection for such diverse projects as sprouting angiogenesis, metabolic switches, or resistance to viral infections. Protocols for cell culture, FACS, splice acceptor inversion, etc. can be found on our homepage at:

http://www.haplobank.at (only from internal IP addresses).

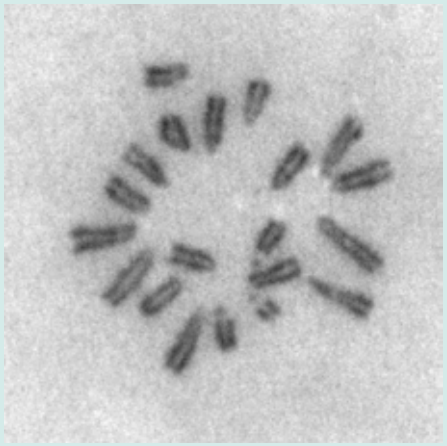
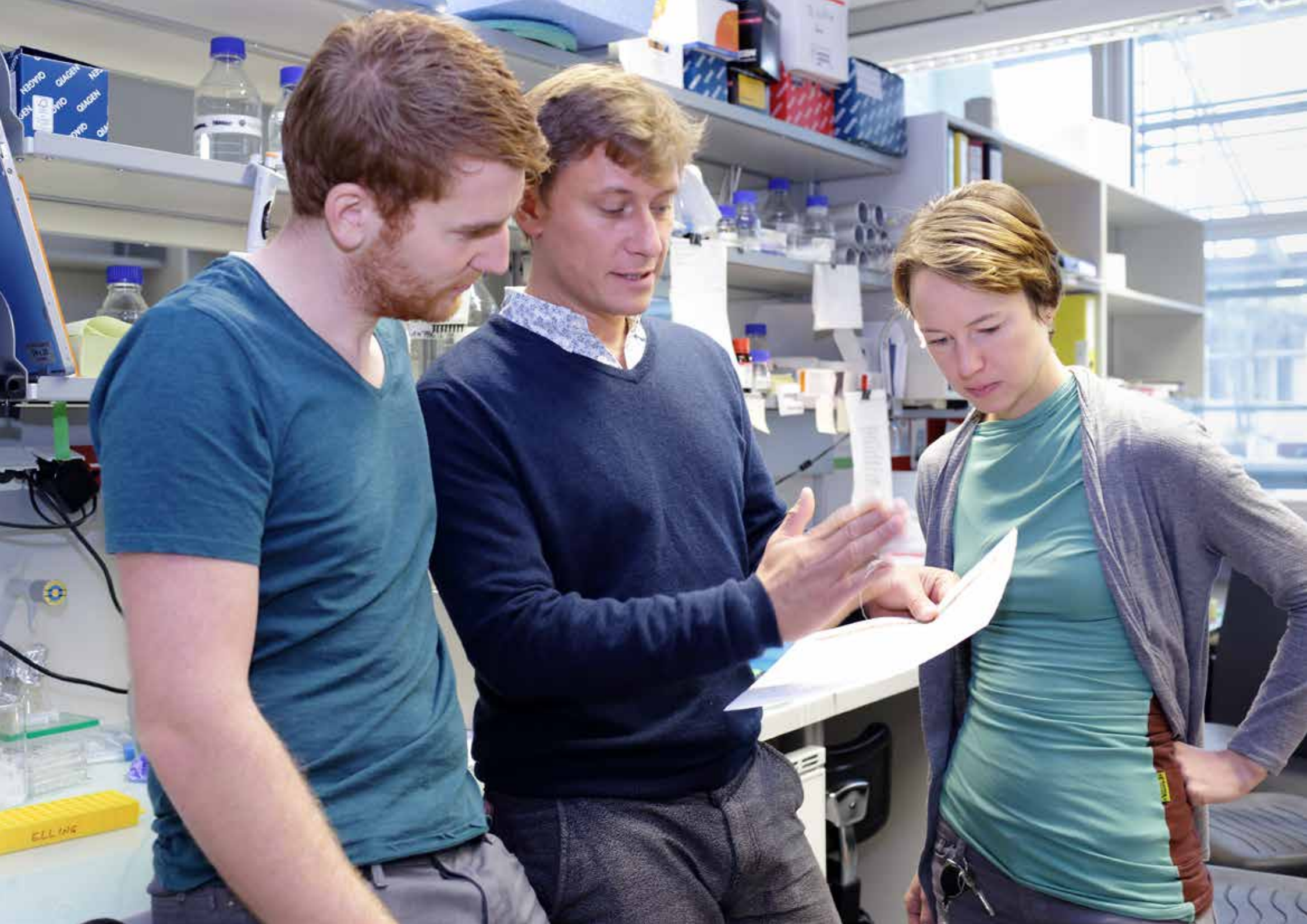


Figure: Chromosome spread of haploid ES cell line


QIAGEN
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MICROSCOPY/FLOW CYTOMETRY: GABRIELE PETRI
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FLOW CYTOMETRY/IMAGE ANALYSIS: THOMAS LENDL, GERALD SCHMAUSS

BIOOPTICS FACILITY

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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, 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 analysis. Three 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, confocal laser scanning and airyscan, two-photon, light sheet, total internal reflection, and structured illumination microscopy techniques, automated slide scanning as well as access to laser microdissection and fluorescent lifetime imaging microscopy. 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 and open-source image processing and visualization software. A server solution with a Web-based interface permits efficient, multi-user, parallel, batch deconvolution of microscopy images. Users are trained in the use of specific software, depending on their demands and are trained in an annual course on image processing and analysis, focusing on the Fiji software with lectures and hands-on sessions by the BioOptics staff. 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/

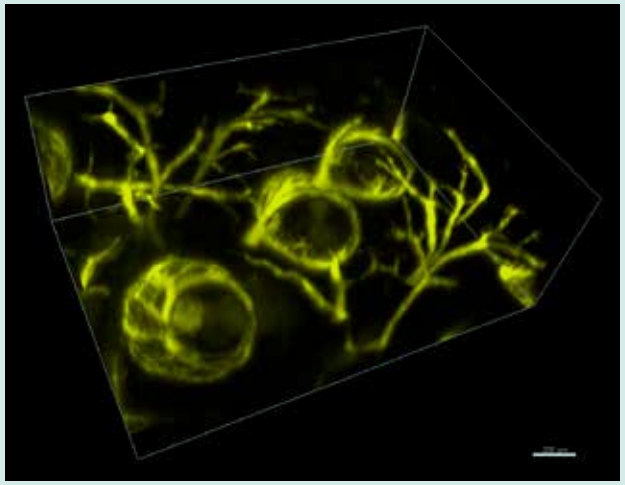

Figure: Image shows developing nerve fibers innervating the vibrissa (whiskers) of a mouse embryo at E14.5 marked by eGFP (Tg(Tubb2b-eGFP)). Tissue was prepared using Scale tissue clearing prior to imaging with light sheet microscopy.

COMPUTATIONAL BIOLOGISTS: THOMAS BURKARD, MARIA NOVATCHKOVA, ALEXANDER SCHLEIFFER

BIOINFORMATICS

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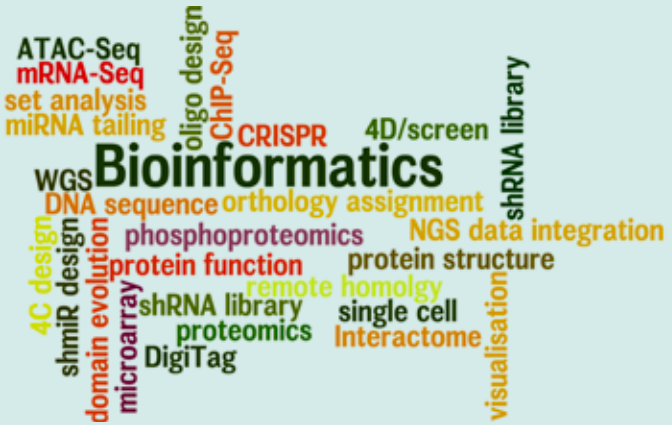
The Bioinformatics unit assists research groups in molecular-biology-related fields by providing scientific data mining, sequence analysis services, software infrastructure, and training in bioinformatics.

Data analysis

We investigate large functional genomics and high-throughput biological datasets. Assistance is provided in experimental design and subsequent analysis of next-generation sequencing, microarray, and mass-spectrometry-based proteomics experiments. The current main focus is on the analysis of small RNA-Seq, mRNA-Seq and haploid ES cell screen data. Gene lists derived from publicly available studies or generated from in-house high-throughput experiments (NGS, microarray, proteomics) are analyzed for the overrepresentation of pathways, GO-terms, functional domains, or placed in interaction networks to visualize their relationships. Genome-wide expression patterns are contextualized with known processes and pathways using Gene Set Enrichment Analysis (GSEA). Local instances of integrated model organism databases 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. Project-specific hands-on trainings on applications for computational biology is provided on individual basis.

Sequence analysis

Key insights into the molecular mechanisms of a protein's function are obtained by integrated sequence/structure analysis. This includes exploration of the protein family space, multiple sequence alignments, discovery of deterministic motifs, combined with fold recognition, homology modeling, 3D structure representation and analysis. The study of evolutionary relationships (phylogenetic reconstruction, orthology assignments, remote homology detection) provides complementary information for understanding functional conservation and diversity. Common nucleotide sequence analysis tasks comprise sequence alignment, promotor and gene identification, motif discovery and enrichment analysis, prediction of transcription factor binding sites, conservation detection, phylogenetic footprinting, de-novo repeat identification and de-novo assembly. We provide genome-wide CRISPR gDNA design that can be enhanced by gene properties and functional annotations.



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PROTEIN CHEMISTRY

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The protein chemistry facility provides characterization of proteins by mass spectrometry, peptide synthesis and purification of antibodies to all researchers at the IMP, IMBA and GMI.

Analysis of proteins by mass spectrometry

The facility operates a variety of HPLC-MS platforms, which are provided by the CSF, for protein identification and quantification. The submitted protein samples are proteolytically digested and analyzed via LC-MS on the appropriate platform. In case of complex mixtures, multi-dimensional fractionation methods of tryptic peptides are employed, reducing the sample complexity prior to the LC-MS analysis.
Additionally, the facility performs the analysis of posttranslational modifications, such as phosphorylation, acetylation, methylation, or ubiquitination. For the relative and absolute quantitation of proteins, both label-free and isotopic labeling methods are applied. To interpret the acquired data, different bioinformatic analyses are performed.
In cooperation with the MFPL mass spectrometry facility, the facility is currently establishing an LC-MS setup for the characterization of intact proteins, which will be provided as a service in the near future.

Peptide Synthesis and antibody purification

Peptide synthesis for sequences up to 35 amino acids is offered on a routine bases, yielding between 10 mg to 50 mg. Synthesized peptides are HPLC-purified and validated by mass spectrometry. In another approach, peptides are synthesized in a 96 well plate format at a microgram scale. For both approaches, different modifications can be introduced at specific positions of the sequence. Additionally, carrier-peptide conjugates for immunization of animals and affinity purification of antibodies are provided.

Method Development

The facility constantly evaluates technological advancements in MS-based protein analysis and establishes new protocols. The focus of methods development is sensitivity of protein identification, accuracy of quantification and protein cross-linking mass spectrometry. In addition, the group established a strong branch of methods development for data interpretation and other bioinformatic processes. Naturally, methods development is linked to the needs of the biological research performed at IMP, IMBA and GMI.

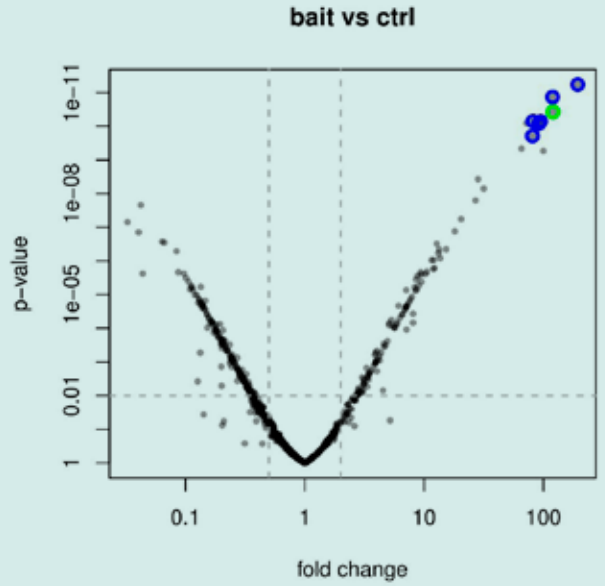
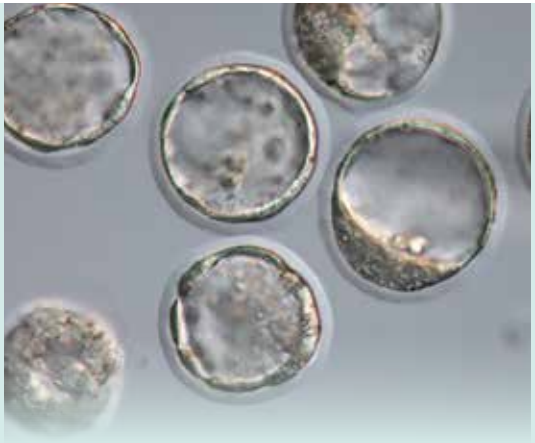


Figure: Typical volcano plot comparing affinity purified bait against control samples. The difference in abundance is displayed on the x-axis and the statistical significance on the y-axis. The bait (green) and members of a known interacting complex (blue) are highlighted.

1



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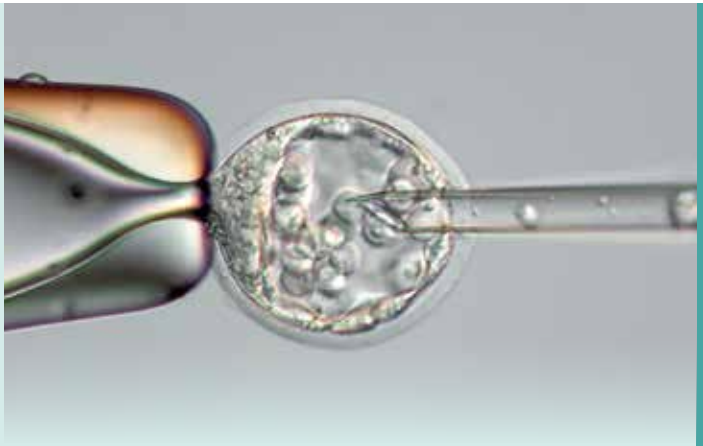


COMPARATIVE MEDICINE

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

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

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 Facility was set up at the IMP in 1998 to cope with the increasing demand for mouse studies and generation of transgenic mice. The facility is shared by IMP and IMBA, and has 2 members since October 2005.

The main duties of this service unit are the injection of ES cells into blastocysts or 8-cell embryos, and of DNA into the pronucleus of fertilized mouse eggs.

This service also provides for the transfer of 'clean' embryos into our Animal House, the freezing of embryos for the preservation of specified mouse strains and the teaching of basic embryological techniques to the IMP and IMBA staff.

Many different ES cell clones, and DNA/BAC constructs are being injected per year. And since recently an ever-increasing demand for injections utilizing the CRISPR/Cas9 system has arisen.

The activities of this department are overseen by an Animal User Committee, which meets on a regular basis to set priorities and to coordinate the duties. At present, 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

SEQUENCING SPECIALISTS: ZUZANA DZUPINKOVA, CAROLINE SCHUSTER, MARKUS HOHL
PROTEIN EXPRESSION SPECIALIST: KRISTINA MARINOVA UZUNOVA
MOLECULAR BIOLOGY SPECIALIST AND ANTIBODY SPECIALIST: ROBERT HEINEN
TECHNICAL ASSISTANTS: SABINA MARIA KULA, ZSUZSANNA MUHARI-PORTIK
TRAINEES: ELISA HAHN, ANNA HAYDN

TEAM MEDIA LAB:
CHRISTA DETZ-JADERNY, GABRIELE BOTTO, ULRIKE WINDHOLZ, JENS SCHAICH, JISS JOHN

TEAM DISH WASHING:
AYSEL AYKUT, SULTAN CAN, NORBERT DEMETER, NURAY KILIC, SVETLANA PEKEZ-NIKOLIC, BETTINA RADICH

MOLECULAR BIOLOGY SERVICE

harald.scheuch@imba.oeaw.ac.at

The facility offers a wide variety of standard services to all scientists at IMP/IMBA and GMI. These include Sanger Sequencing, a "Speed Congenics Service", the preparation of competent cells of various E. coli strains, production of monoclonal antibodies, a routine mycoplasma testing service for tissue culture cells and plasmid prep in 96 well formats to mention the most important ones. In addition, we provide instrumentation and expertise for lab automation and high-throughput methods.

In the last years, the protein production service grew substantially. We now produce more than 35 growth factors and enzymes to support the research groups with high quality proteins as a routine service.

The management of the Media Lab and Dish Washing unit was handed over to Molecular Biology Service. Especially in the Media Lab several improvements have been introduced, e.g. the installation of a clean room for the production of tissue culture media, the implementation of SOPs and the first steps for a rigorous quality management.

Example of a Hazard Label

Cleanroom Media Lab
In accordance with with Austrian and European legislation, new labels with hazard information are currently introduced. In addition to these hazard information, a QR-code links to the manufacturing SOPs.

HEAD OF FACILITY: KARLO PAVLOVIC

MAX PERUTZ LIBRARY

library@imp.ac.at

The Max Perutz Library is a specialized reference library located at the Vienna Biocenter (VBC). Its mission is to develop and maintain collections and services that support research at the IMP, IMBA and GMI.

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 several hundred 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. Management as well as researchers are supported with bibliometric services.

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, a printer, a book scanner and a spiral binding machine 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. The more, teaching is also provided during the VBC PhD Curriculum twice a year.

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 (VBC) are welcome to visit the library premises.

VIENNA BIOCENTER CORE FACILITIES GMBH (VBCF)

The Vienna Biocenter Core Facilities GmbH (VBCF) was established in 2011 at the Vienna Biocenter (VBC) to provide top scientific infrastructure, operated and constantly further developed by highly qualified experts. The VBCF supports IMP, IMBA and other research institutions and companies situated at the Vienna Biocenter at the forefront of science. Besides scientific infrastructure, VBCF also offers social infrastructure such as the Child Care Center. For more information visit: www.vbcf.ac.at.

Preclinical Phenotyping (pcPHENO)

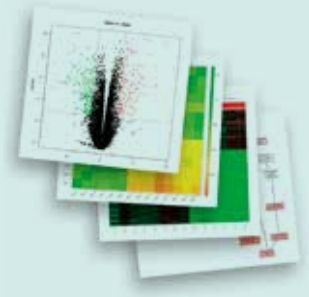
The Preclinical Phenotyping Facility (pcPHENO) provides state of the art equipment and services to test mouse behavior, motor functions, physiology, and metabolism. Phenotypic screening is becoming an increasingly important step in the characterization of genetically modified mice, aiming to link molecular mechanisms to whole-body effects. After training under expert supervision, researchers can perform their experiments alone or make use of our services, ranging from the planning and performing of the experiments to final data analysis and interpretation.

Next Generation Sequencing (NGS)

The goal of the Next Generation Sequencing Core Facility is to provide cutting edge next generation sequencing technology to its users. Next Generation Sequencing has become a key analysis method for biological research. The capacity to expand analysis from more or less defined genomic regions to genome wide studies has boosted the pace of research discovery and enabled researchers to obtain a global view on biological processes. Advice and guidance of sequencing projects are offered by our team that relies on years of experience with sequencing systems and sequencing data analysis. All common sequencing applications are supported and the development of novel methods and protocols encouraged. Currently, requests are processed on Illumina HiSeq2500 and MiSeq instruments. Through our Core4Life partners we have access to all current sequencing platforms.

Bioinformatics & Scientific Computing (BioComp)

The Bioinformatics & Scientific Computing Facility offers data analysis services and scientific software development for academic research groups and industrial research laboratories. Our wide range of services provides help to understand and exploit the large-scale data sets generated in modern biological and biomedical research. As a "knowledge hub" our facility also offers training, consultation and help-desk for all Vienna Biocenter (VBC) researchers in the fields of biostatistics, programming and bioinformatics.



Protein Technologies Facility (ProTech)

The mission of the Protein Technologies Facility (ProTech) is to help researchers at the Vienna Biocenter overcome two major experimental bottlenecks: protein production and purification. In addition we offer services upstream and downstream of these areas, including molecular cloning and biophysical protein characterization, and can provide expertise and advice on most protein-related technologies. We also provide consulting and reagent generation for CRISPR/Cas9 genome engineering through CRISPR Lab. Our customers use the proteins and other reagents we generate for antibody generation, biochemical and cell biological assays, structural analysis, study of biomolecular interactions, and genome engineering experiments. Furthermore, we are open to larger/longer-term collaboration projects on technology development in the fields of protein production or genome engineering.

Electron Microscopy Facility (EM)

The EM Facility offers a large range of instruments, techniques and expertise to visualize the ultrastructure of biological samples - from molecules to cells & tissues. We have scanning (SEM) and transmission electron microscopes (TEM) and apply numerous techniques (from negative staining to cutting edge cryo-EM) to deliver quick sample screening and high resolution 2D or 3D imaging. Users chose whether they wish to get trained on how to use our equipment themselves or if they prefer us to do everything for them.

Vienna Drosophila Resource Center (VDRC)

The Vienna Drosophila Resource Center, established in 2007, is a professionally organized bio-resource center of international significance. Our primary aim is to facilitate systematic analysis of gene function in Drosophila using in vivo transgenic technology via distribution of our public stock collections. We maintain and distribute over 38,000 unique transgenic Drosophila stocks, including an almost genome-wide collection of RNAi lines, enhancer-GAL4 driver lines and Tagged FlyFos TransgeneOme lines. To date the VDRC has delivered more than 1,050,000 lines to over 2300 registered customers worldwide. We additionally offer a private stock keeping service and are further developing and expanding our resources according to emerging technologies and research community needs.

Plant Sciences (PlantS)

The Plant Sciences Facility (PlantS) operates 22 high quality state-of-the-art and highly specialized plant growth chambers and provides professional support to research groups at the VBC.
Several chambers are capable of providing exceptional environmental conditions i.e. low temperature (frost), high temperature, different light intensities, different light spectra and different gas conditions allowing precise environmental simulation across different climate zones and the simulation of various environmental stress conditions. Additionally, one of our chambers is equipped with a robotic plant phenotyping system linked to LemnaTec image analysis software.

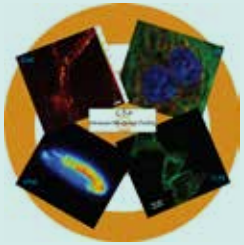
Preclinical Imaging Facility (pcIMAG)

Preclinical Imaging (pcIMAG) facility offers state of the art ultra-high-field magnetic resonance imaging on a 15.2 T Bruker magnet. We are continuously increasing our range of services to stay current with emerging applications relevant for biological systems. We are currently offering anatomical characterization of organ systems, axonal track tracing, quantitative perfusion measurement, angiography and proton magnetic resonance spectroscopy (1H MRS). Special focus is laid on top quality image analysis, data processing and 3D visualization. Our future outlook includes setting up combination of functional MRI (fMRI) and optogenetics.

Advanced Microscopy (advMICRO)

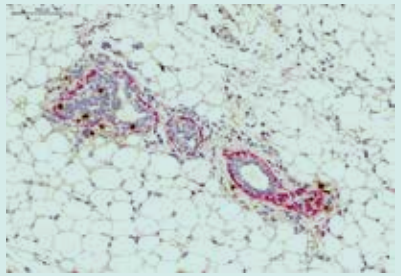
The Advanced Microscopy Facility offers users access to a selection of cutting-edge optical microscopy and spectroscopy techniques, along with assistance in their implementation and data analysis. They also offer the development or customization of microscopes for applications where commercial solutions are not available.

Whether one is interested in measuring the dynamics of single molecules in live cells, the morphology and mechanical properties of entire embryos, or something in between – the Advanced Microscopy Facility has an expanding inventory of techniques at your disposal.



Histo Pathology (HP)

The HistoPathology facility aims to combine expertise in histological techniques with scientific input from certified veterinary pathologist to provide customers with means for complete analysis of tissues. We offer top quality of standard services such as tissue processing, sectioning and most of the common histological stains for both paraffin and cryoblocks. In addition, customers can benefit from automatic immunostaining protocols, a continuously growing list of optimized antibodies and advanced pathological evaluations. Finally, our service includes consultation before and during the course of the experiment, interpretation of the results and pathology reporting.



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** Equal contribution*

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Publications Research Support & Core Facilities

BIOINFORMATICS

Nagy V, Cole T, Van Campenhout C, Khoung TM, Leung C, Vermeiren S, Novatchkova M, Wenzel D, Cikes D, Polyansky AA, Kozieradzki I, Meixner A, Bellefroid EJ, Neely GG, Penninger JM. The evolutionarily conserved transcription factor PRDM12 controls sensory neuron development and pain perception. Cell Cycle. 2015;14(12):1799-808.

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PROTEIN CHEMISTRY

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STEM CELL CENTER

Nagy V, Cole T, Van Campenhout C, Khoung TM, Leung C, Vermeiren S, Novatchkova M, Wenzel D, Cikes D, Polyansky AA, Kozieradzki I, Meixner A, Bellefroid EJ, Neely GG, Penninger JM. The evolutionarily conserved transcription factor PRDM12 controls sensory neuron development and pain perception.
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TRANSGENIC SERVICE FACILITY

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Awards & Honors 2015

Stefan Ameres

- *Elected member of the „Young Academy" of the Austrian Academy of Sciences (OeAW)*

Julia Batki (Brennecke Group)

- *BIF Fellowship*

Oliver Bell

- *EMBO Long-Term Fellowship*

Daniel Gerlich

- *Winner of the Life Science Call by the Vienna Science and Technology Fund (WWTF) for „Innovative biological and biomedical applications of novel imaging technologies"*

Dominik Handler (Brennecke Group)

- *VBC PhD Award*

Jürgen Knoblich

- *Proof of Concept Grant from the European Research Council (ERC)*
- *Hans Krebs Medal (FEBS)*
- *Ernst Klenk Lecture (University of Cologne)*

Javier Martinez

- *Elected member of the European Molecular Biology Organization (EMBO)*

Josef Penninger

- *Elected member of the European Academy of Sciences and Arts*

Greg Sienski (Brennecke Group)

- *Kirsten Rabitsch Award*
- *VBC PhD Award*

JANUARY

08.01.15 Bas Van Steensel
Netherlands Cancer Institute
Architecture and dynamics of genome - nuclear lamina interactions

09.01.15 Ines Anna Drinnenberg [1]
Fred Hutchinson Cancer Research
Evolutionary transitions provide insights into RNAi and centromere biology

15.01.15 Cyril Zipfel
The Sainsbury Laboratory
Regulation of receptor-kinase mediated innate immunity

20.01.15 Songhai Shi
Sloan Kettering Institute
Centrosome regulation and function in the developing mouse cortex

22.01.15 Ian Baldwin
MPI for Chemical Ecology
Timing is everything in ecology

28.01.15 Maaike Welling
Hubrecht Institute
Dazlin' germ cells and pluripotent stem cells

29.01.15 Jose Henrique Veiga Fernandes
IMM
Environmental sensing by immune cells

FEBRUARY

03.02.15 Carolina Rezaval [1]
University of Oxford
Neural circuit controlling mating behaviours in the female fruit fly

05.02.15 Björn Schumacher
University of Cologne
DNA damage responses in development, aging, and disease: Insights from C. elegans

09.02.15 Anna Obenauf
Memorial Sloan Kettering Cancer Center
Unintended consequences of targeted therapy: Therapy-induced secretomes fuel drug resistance and tumor progression

09.02.15 Giulio Tomassy
Harvard University
A White' Matter of Identity: Distinct Profiles of Myelin Distribution in the Neocortex

10.02.15 Elly Tanaka [1]
Center for Regenerative Therapies, Dresden
Evolving limb regeneration, a story of conservation and innovation

12.02.15 Eduardo Moreno
University of Bern
Cell Fitness Fingerprints and cell selection in ageing, neurobiology and cancer

17.02.15 Taro Toyoizumi [1]
RIKEN Brain Science Institute
Untangling Complex Neuronal Dynamics by Cross-Embedding

26.02.15 Matthias Lütolf
EPFL Lausanne
Engineering tissues via artificial extracellular matrix-guided stem cell self-organisation

MARCH

10.03.15 Petra Wendler [1]
Gene Center Munich
Cryo EM structure of the contractile VipA/B nanomachine in type VI effector secretion

17.03.15 Shawn Lockery [1]
University of Oregon
To model the Connectome, or not: a case study in C. elegans

18.03.15 Sidi Chen
MIT
In vivo cancer modeling and genetic screening using genome engineering

19.03.15 Francis Barr
Department of Biochemistry, University of Oxford
Temporal and spatial regulation of mitosis and cytokinesis by protein phosphatase 2A

23.03.15 Takanori Takebe
Yokohama City University
Realization of iPSC-organ bud transplantation therapy

24.03.15 Ivan Bedzhov
University of Cambridge
From blastocyst to egg cylinder: setting up the foundations of the body

30.03.15 Sasha Mendjan
University of Cambridge
Exit from Pluripotency and Human Mesodermal Organogenesis

31.03.15 Arthur Mortha
Mount Sinai Medical Center
Regulation of intestinal immune homeostasis

31.03.15 Gonzalo Polavieja [1]
Champalimaud Institute
Decision-making in animal groups

APRIL

09.04.15 David Komander
MRC Laboratory of Molecular Biology
Specificity in the ubiquitin system

14.04.15 Olivier Ganier
Institute of Human Genetics, Montpellier
Mitosis, DNA replication and cell identity: new insights into functional interdependences

16.04.15 Norbert Perrimon
Harvard Medical School, HHMI
Organ communication in Drosophila

23.04.15 Eric Betzig
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Imaging Life at High Spatiotemporal Resolution

24.04.15 Toshiyuki Yoneda
Indiana University School of Medicine
Bone microenvironment and breast cancer colonization

30.04.15 Eric Greene
Columbia University
Single molecule imaging of DNA recombination

MAY

05.05.15 Rebecca Beveridge
University of Manchester
A mass spectrometry- based framework to investigate (un) structural characteristics of p27

21.05.15 Meritxell Huch
Gurdon Institute, University of Cambridge
Gastrointestinal, Liver and pancreas Stem/Progenitor cells and 3D-organoid cultures

27.05.15 Martin Krzywinski
Canada's Michael Smith Genome Sciences Centre
Sense and Sensibility—Visual Design Principles for Scientific Data

JUNE

03.06.15 Mark Estelle
University of California San Diego
Auxin: A Versatile Regulator of Plant Growth and Development

05.06.15 Ben Fulcher [1]
Monash University
A highly comparative time-series analysis engine

10.06.15 Ross Levine [1]
Memorial Sloan Kettering Cancer Center
Role of TET, DNMT3A, and Cohesin mutations in AML Pathogenesis

11.06.15 Monica Bettencourt Dias
Instituto Gulbenkian de Ciencia
Different cells count differently: centrosome number regulation in development and disease

23.06.15 Katrin Rittinger
National Institute for Medical Research (UK)
Structural and mechanistic characterisation of multi-domain E3 ligases that regulate immune signalling

23.06.15 Joel Sussman [1]
Weizmann Institute
3D Structure of Acetylcholinesterase: How are anti-Alzheimer Drugs, Nerve Agents and Autism Related?

25.06.15 Michel Steinmetz
Paul Scherrer Institute
Molecular mechanisms of microtubule tip tracking and centriole formation

JULY

02.07.15 Peter Fraser
The Babraham Institute
3D architecture of the genome and control of genome functions

09.07.15 Keiji Tanaka
Tokyo Metropolitan Institute of Medical Science
Basic Mechanisms and Physiopathology of The Proteasome

16.07.15 Harmit Malik
Fred Hutchinson Cancer Research Center Seattle
Genetic conflicts: beyond the usual suspects

17.07.15 Jonathan Flint [1]
Wellcome Trust Centre for Human Genetics, University of Oxford
The genetic basis of major depression

23.07.15 György Buzsáki
NYU Neuroscience Institute
Emergence of cognition from action

28.07.15 Konstanze Winklhofer
Ruhr University Bochum
Ubiquitin Signaling and Mitochondrial Integrity: Implications for Neurodegenerative Diseases

SEPTEMBER

01.09.15 Manuel Alonso Y Adell
Biocenter, Medical University of Innsbruck
Towards understanding the molecular mechanism of ESCRT mediated MVB vesicle formation

03.09.15 Dominique Bergmann
Stanford University
Birth, life and death of a plant epidermal stem cell lineage

04.09.15 I-hsin Su [1]
Nanyang Technological University
Ezh2 controls cell adhesion and migration via talin methylation

17.09.15 Karl Friston
Wellcome Trust Centre for Neuroimaging at UCL
Free energy and self organisation

18.09.15 Le Ma [1]
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Molecular Regulation of Axonal and Dendritic Branches During Development

21.09.15 Dirk Schüler [1]
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Making magnets by microbes: Molecular genetics, cell biology and function of bacterial magnetosome biosynthesis

24.09.15 Michael Shadlen
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The neural basis of speed, accuracy and confidence in a decision

25.09.15 Jai Yu [1]
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29.09.15 Ari Melnick [1]
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Epigenetic switches and targeted therapies for B-cell Lymphomas

OCTOBER

12.10.15 Masayuki Miura
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Active roles of cell death during development, regeneration and tissue homeostasis

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How High-Tech Polymers Leveraging Viral Biophysics Can Enhance the Transfection of Nucleic Acids

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Direct in-vivo shRNA screening for accelerated target discovery in gastrointestinal tumors

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The interplay between protein phosphorylation and protein ubiquitylation in regulating the innate immune system

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How to divide a very large cell? New functions for actin in oocyte meiosis

NOVEMBER

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Epigenetic mechanism during development: Polycomb and chromatin dynamics

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Phase separation and transport selectivity of nuclear pores

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INSERMRegulation of neuronal migration during postnatal neurogenesis

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Genome Stability and the control of homologous recombination

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The role of chromatin in repression and activation of the zygotic genome

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VCP/p97 complexes sort out ubiquitin in cell cycle signalling, proteostasis and autophagy

DECEMBER

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Prefrontal neuronal circuits and mechanisms controlling fear behaviour

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Johns Hopkins University School of Medicine
Finding new roles for histone methylation

[1] hosted by IMP Group Leaders

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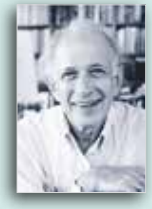

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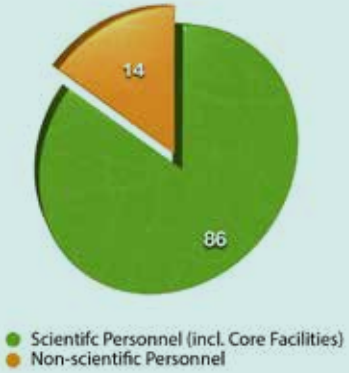

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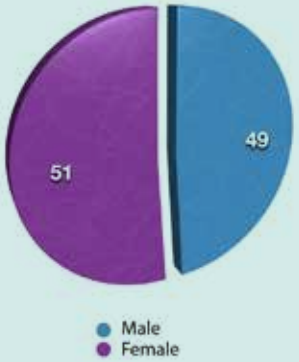
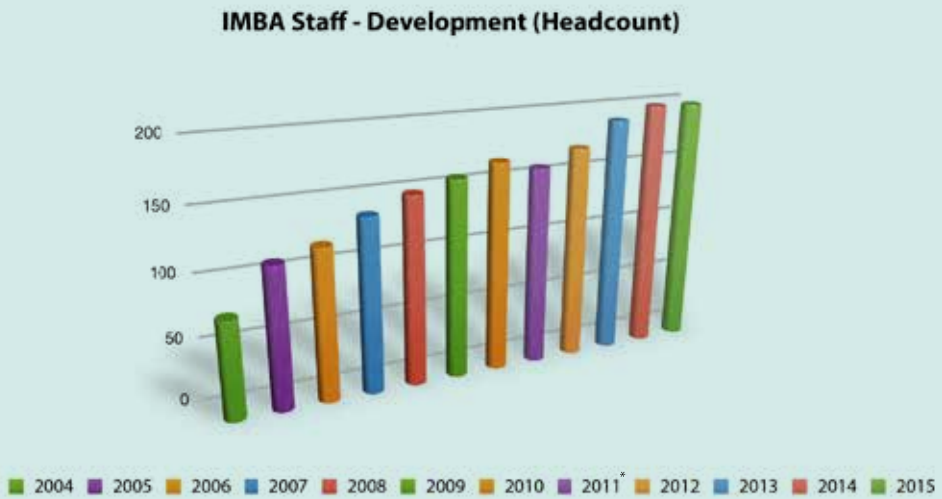


IMBA Staff - Development (Headcount)



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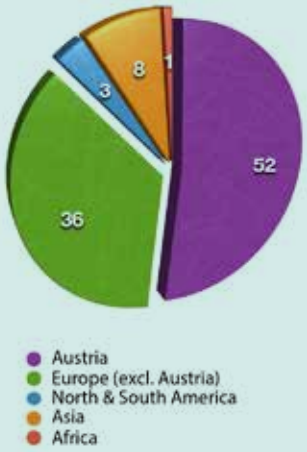
Scientific Staff - Functions (in %)

Scientific Staff - Nationalities (in %)



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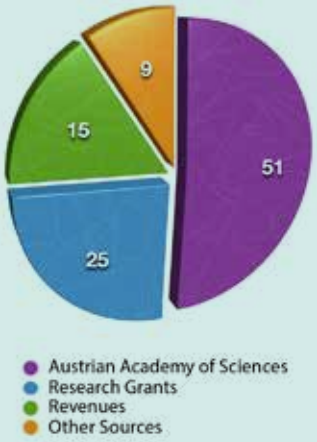
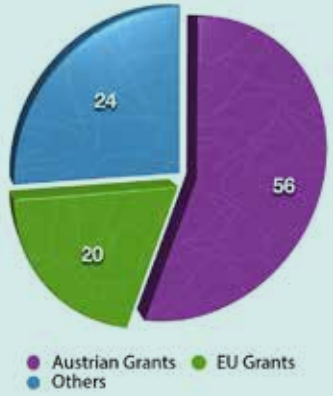


Public Research Grants 2015 (in %)



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.

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.

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.

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/

Child Care Center (CCC)

Besides scientific infrastructure, the CSF is offering social infrastructure to the Vienna Biocenter, such as the Child Care Center. It is run by Wiener Kinderfreunde and hosts not only little researchers from the Vienna Biocenter but also young media kids from the Media Quarter Marx.
First and foremost the head of our Child Care Center, Dagmar Mirek, and her highly motivated team provide a loving and caring atmosphere for the children. Besides that they offer extended opening hours and the possibility to attend a crèche from 3 month on. Also important for the international surrounding of the Vienna Biocenter are the English lessons with native speaker Betsy Higgins-Pösinger.
The Child Care Center is a creative place for children where they undertake excursions into the countryside, visit kids theatre, grow vegetables, go ice skating and do everything else a children's heart desires.
For more information please visit our website or contract Dagmar Mirek under:
+43 (0)1 798 56 10 or kdg.campus@speed.at

Career and Training

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

The IMBA is part of the Vienna Biocenter (VBC), and you will be part of a large scientific community. Most of our training offers are run jointly with the other research institutes at the VBC: 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 stages:

Undergraduate students - Vienna Biocenter Summer School

Every year the Vienna Biocenter Summer School provides a unique opportunity for approx. 25 international undergraduate students to experience cutting-edge scientific research for a period of two months. Our summer fellows are provided with a stipend, accommodation, and a travel allowance. Throughout its first five years, we have received over 3000 applications from 97 nations, and have hosted 115 fellows.

"I would absolutely recommend the VBC Summer School. It's a not to be missed opportunity to broaden one's mind and enrich one's academic education. You will work hard but besides the research there are also many social events planned by the program as well as by the summer students." Testimonial from a member of the 2014 class

Every year we open a competitive call (from December 1 – January 31). *For more information visit our website: www.vbcsummerschool.at*

Graduate students – Vienna Biocenter PhD programme

As a VBC PhD student you can do virtually any experiment you can think of. Our goal is to train independent, critical, and creative researchers. The VBC PhD programme is based on a 4-year research project. The research project is primed by an introductory course at the beginning of your studies and further complemented by courses, lectures, and seminars that run continuously on campus. The PhD Students organize numerous networking activities, and the programme puts great emphasis on the career development of our students.

Most importantly, our faculty includes renowned scientists from all over the world, with outstanding publication records. They are all extremely committed to the training of young researchers. All PhD students benefit from the support extended by our scientific facilities, and are employed on a full-time contract.

The VBC PhD programme is open for applications twice a year (September-November and March-April). We invite the best candidates for an interview and to visit the research institutions at the VBC for a few days. Check out our website for detailed information: www.vbcphdprogramme.at

Postdocs

The Vienna Biocenter is the ideal scientific environment for Postdocs to further develop as scientists. Here, postdocs find a supportive and mentoring faculty, have access to state-of-the-art infrastructure, and are part of a lively scientific community.

The postdocs are part of a larger network – the Vienna Area Postdoc Association – that organizes an annual retreat, career development Initiatives, and a training program, specifically designed to give you a competitive edge on the job market. Currently the programme includes courses in scientific writing, project management, and leadership. Experienced and outstanding coaches facilitate all of the courses.

Applications for postdoc positions at the IMBA can be submitted directly to the relevant group leader. Funding is available from internal sources; however, postdoc applicants are strongly encouraged to apply for external fellowships to support their research.

VBC Career Days 2015

At the Vienna Biocenter we see the career development of our junior researchers as a priority. The faculty aims to provide effective mentoring to the PhD Students and Postdocs in order for them to progress and be successful. Most of our mentoring efforts are unavoidably towards success in a research career – that is what we know best. Yet, every year we organize events to promote the interaction of our young researchers with people from different career paths.
In 2015 we organized a two-day workshop, led by a prominent recruiting company in the Life Sciences, on how to apply to a non-academic position. Plus, we had a Career Day with speakers (many of them VBC alumni) following different non-academic (but research- or science-related) career paths. During this day the PhD Students and Postdocs had the opportunity to listen and talk to individuals – who also did a PhD and/or Postdoc – and are now in industry (namely Novartis or Nestlé) or working on science communication, policy, or management.

Organizing committee: Monika Abramczuk (PhD Student, IMBA); Ingrid Hums (PhD Student, IMP); Sabine Jurado (Postdoc, IMP); Magdalena Renner (PhD Student, IMBA); Jan Suhren (PhD Student, IMBA); Divya Vashisht (Postdoc, GMI) with Carmen Ilic (Human Resources, GMI) and Inês Crisóstomo (Scientific Training Coordinator, IMP/IMBA/GMI)

Highlights from 2015

Eight Students Graduated!
Ingrid Hums, Zimmer/IMP
Thomas Hoffmann, Zuber/IMP
Bettina Wurzer, Martens/MFPL
Eleonora Turco, Koehler/MFPL
Jan Suhren, Mochizuki/IMBA
Marcin Suskiewicz, Clausen/IMP
Johanna Trupke, Ringrose/IMBA
Paulina Troc, Westermann/IMP

AWARDS TO PHD STUDENTS:

VBC PhD Awards
For the most outstanding PhD Thesis in 2014/15
Bettina Wurzer, Martens/MFPL
Dominik Handler, Brennecke/IMBA
Krzysztof Chylinski, Charpentier & Schroeder/MFPL
Grzegorz Sienski, Brennecke/IMBA

Mattias Lauwers Award
For the best student speaker in the "Monday Seminars" series in 2014/15
Harris Kaplan, Zimmer/IMP

AWARDS FOR SUMMER SCHOOL STUDENTS:

Class of 2015 Best Talk Awardees
Maximilian Schneider, Gerlich/IMBA
Ezgi Taskopru, Shaefer/MFPL
Bruno Costa, Busslinger/IMP
Angela Rodrigues Viana, Ameres/IMBA

One of Europe's leading Life Science locations

- 4 Academic research centers
- 18 Biotech companies
- 3 Universities

- 1.400 Employees
- 250 PhD students
- 100 Scientific groups
- 40 Nationalities

- 90.000 m² lab and office space
- 45.000 Vienna Open Lab visitors

- 31 ERC Grants
- 11 Wittgenstein Awards
- 350 Publications / Year

VIENNA BIOCENTER

Around 25 research institutes and companies, 2.100 scientific employees and students, over 90.000 m² lab and office space for Life Sciences – the Vienna Biocenter at Neu Marx is one of Europe's leading Life Science hubs.

The success story of the Vienna Biocenter (VBC) began in the 1980s with the foundation of the Research Institute of Molecular Pathology (IMP), the basic research center of Boehringer Ingelheim. Following the relocation of five university departments – that are now under the umbrella of the Max F. Perutz Laboratories (MFPL) – to the Neu Marx area in Vienna's Third District, the VBC has grown continuously. Profiting from the assets offered at the location, the University of Applied Sciences and two flagship institutes of the Austrian Academy of Science round off the academic institutions at the VBC. Since their founding by the Academy, the Institute of Molecular Biotechnology (IMBA) and the Gregor Mendel Institute for Molecular Plant Biology (GMI) have developed rapidly into two of the most renowned Austrian research institutes in their respective fields.

Motivated and talented young students are offered two international PhD programs: the VBC PhD Program and the MFPL PhD Program. During the selections that take place twice a year, applicants from all over the world compete for the attractive positions. Furthermore, the VBC summer school provides a unique opportunity for undergraduate students to work together with leading scientists at the VBC.

Training and research associate with the commercial strategies of several companies located at the VBC. 18 companies currently reinforce the collaborative potential of academic and applied research at the Vienna Biocenter.

Moreover, the VBC hosts institutes and companies dedicated to science communication. The publicly funded organization Open Science aims at fostering the dialogue between the world of science and the public, and it also runs the Vienna Open Lab (a joint initiative with IMBA), which has already provided 45,000 visitors with an interactive glimpse into the Life Sciences. Biolution has established a reputation as a professional agency for science PR and EU-project application in the field of Life Siences.

The research institutes at the VBC are home to 1,400 experts and 700 students enrolled at the University of Vienna, the Medical University of Vienna and the University of Applied Sciences. The passionate and creative scientists in over 100 scientific groups and from 40 nations have acquired 32 ERC grants, 11 Wittgenstein Awards and publish around 350 scientific papers per year. They are supported by the Campus Science Support Facilities (CSF), providing first class scientific infrastructure. The successful cooperations, the broad expertise of the researchers and the established infrastructure offer unique working conditions that enable the VBC members to be at the forefront of Life Science research.


vienna
BIOCENTER

IMBA SPOTLIGHTS 2015

Scientific Spotlights...

New IMBA group leader: Sasha Mendjan

Sasha Mendjan completed his PhD at EMBL focusing on chromatin regulation via non-coding RNAs in Drosophila. After that he spent eight years at the Cambridge Stem Cell Institute before accepting his position as group leader at IMBA.

The main focus of his research group will be on cardiac adipocyte lineages. His aim is to understand how tissues communicate as they specify and thereby control human organ morphogenesis, growth and functional maturation. The long-term perspective of his research is to try and create a heart in the lab. With this he fits very well in the IMBA portfolio and has already established several connecting factors with the Knoblich, Penninger, Bell and Elling Labs.

VBC PhD Symposium

Communication was the keyword for the VBC PhD Students in 2015. The annual student symposium, which took place at the beginning of November, was also dedicated to this topic. The Symposium, entitled "Communication – let's talk about it", explored the different levels of information exchange in Life Sciences: intracellular, intercellular, intra-organismal, and inter-individual. An impressive speaker line-up - 16 speakers from all over the world – presented to a packed Lecture Hall! The audience included 100 external participants, including some special guests - our Travel Grants Awardees! Since 2014, Master Students studying in Europe can apply for a travel grant to participate in the Symposium. The VBC PhD Symposium is entirely organized by our amazing PhD Students, who each year volunteer, come up with a topic, and invite the speakers. They once again did a fabulous job – thank you for organizing!

Organizing committee:
Merve Abdusselamoglu (IMBA); Peter Boenelt (IMP); Louisa Hill (IMP); Falko Hofmann (GMI); Dhaarsini Koneswarakantha (IMBA); Asena Gülsah Pekgoz (IMP); Benoit Pignard (IMP); Friederike Schlumm (IMP/MFPL)

IMBA Recess

At the annual Recess, which took place from October 6-8, IMBA scientists met with members of the Scientific Advisory Board (SAB) to present their current research. The SAB consists of internationally recognized scientists, providing a good basis for the fruitful discussions. Across-the-board they were impressed by the high standards and scientific performance of the research presented. IMBA would like to thanks all SAB members for their tremendous support.

For IMBA SAB members please refer to page 50

10th Microsymposium on Small RNAs

This year saw the 10th anniversary of the Microsymposium an Small RNA Biology. It was held at IMBA from May 4th-6th and hosted 20 speakers from renowned research institutes including the University of Cambridge, the MIT in Boston, the Max Planck Institute for Developmental Biology in Tübingen and the California Institute of Technology. The Microsymposium was established by Javier Martinez in 2006 and has since grown into one of Europe's leading conferences on this topic. It manages to bring together the brightest minds working on different aspects of small RNA Biology.

Outings & Retreats...

Faculty Retreat

On the 3rd and 4th of June, IMP and IMBA Group Leaders met in Baden, near Vienna, for the annual Faculty Retreat. The two days were devoted to science, team building and the general exchange of ideas.

PhD Retreat

This year's PhD retreat started in the amazing Aggstein Castle, a ruin on the right bank of the Danube in the Wachau. At the castle we held "medieval games", ending with a tournament of knights and their "horses" from different teams of PhD Students. The students then continued to the Göstlinger Alps, where they had two workshops under the topic of Communication and numerous scientific discussions during poster sessions and chalk talks. The highlight of this year's retreat was Martin Krzywinski (Genome Sciences Centre BC Cancer Agency, Vancouver, Canada). Martin is an expert in Data Visualization, and a regular contributor to Nature Methods sections on data visualization and analysis. Martin gave a terrific workshop to the participants, and was an inspiring guest throughout the retreat. The retreat is always a great opportunity for students to bond and discuss science!

Postdoc Retreat

The postdoc retreat in September brought together members of all institutions at the VBC. The theme was "Science, technology and society". Through talks from esteemed speakers and a tour of the Zwentendorf Nuclear Power Plant as an example of how society can influence the use of science and technology the topic was explored. The retreat took place in Krems, which gave the group the opportunity to also experience culture at a Heurigen with some good food and wine.

Winter Trip

Over 200 colleagues from IMP, IMBA, GMI and CSF took part in this year's ski-trip from March 26-28. Spring feeling in the valley and deep winter on top of the mountains greeted everyone upon arrival. Schladming, being in the center of the Northern Alps, is an ideal location for sports and recreation. As in previous years, there were plenty of different activities to choose from, like skiing, hiking or just relaxing in the hotel spa. Those three days together always help strengthen the bond between all members of the participating institutes. Many thanks again to the organizing team, who put in a lot of effort to make this event possible every year.

Fundraising Activities...

Meet the expert

The Fundraising Event "Meet the expert" 2015 took place on June 12th and themed heart illnesses. Prof. Dr. Bernhard Metzler, a cardiologist of Innsbruck University, introduced the guests to state of the art treatment after a heart attack, then Dr. Bernhard Haubner, former post doc at the Penninger Lab, informed about new development in heart regeneration. Among the guests were cooperation partners, members of the IMBA Fundraising Committee, private donors and the event sponsor, Mag. Wilfried Opetnik.

Come.See.Meet

The IMBA Fundraising Department invited to a „Come.See.Meet"-Event on December 2nd 2015. Prof. Dr. Josef Penninger welcomed the guests, the FR-Department introduced the new members of the IMBA Fundraising Committee and informed about current Fundraising initiatives. The centerpiece of the evening was a presentation by IMBA group leader Dr. Kikue Tachibana-Konwalski on her research on egg cells and female fertility 30+, followed by a new hands-on activity at Vienna Open Lab on allergies or intolerances.

Soccer can cure

Since 2013, the soccer team FK Austria Wien supported the charity project „Soccer can cure", which is a joint initiative of IMBA and the patient organization DEBRA Austria. A fundamental goal of this cooperation was to raise financial suppport for the Epidermolysis Bullosa (EB) resesarch at IMBA. A variety of measures have been taken to address the broadest possible public. A spot with the players Manuel Ortlechner and Alexander Gorgon as well as Josef Penninger was broadcast on various TV channels, the logos were printed on the trainings jerseys and large posters during the last two seasons.
The successful cooperation between the FK Austria Wien, the DEBRA Austria and IMBA contributed significantly to raising money for research on the development of new therapies for „butterfly children". Another positive aspect was the broad publicity for IMBA over the course of two years. It was even presented in the Donors Guide oft he Fundraising Association as a Best Practice Example.

Heart & Sports

The fundraising campaign „Herz & Sport" („Heart & Sports") is a joint initiative of the FK Austria Wien soccer team, the Österreichischen Herzfonds (Austrian Heart Foundation) and IMBA. The main objective of this campaign is to raise financial support for the cardiac research at IMBA. More specifically donations will go to research into regenerative cardiomyocytes, which could greatly improve the quality of life for people who are suffering from heart disease and heart failure. The cooperation partners have high hopes for this research collaboration.
The athletes of the soccer team received the chance to visit IMBA. As part of „90 minutes for the research at IMBA", they could experience first hand how research is conducted. An instant heart check was carried out by the Herzfonds and the team visited the Vienna Open Lab

Social Activities & Summer School...

Drama Club

The 2015 Spring Play „A VBC Vaudeville" was the first production under new management after Brooke Morriswood (MFPL), the creator oft he club, left the insitute. It was performed by members of all 5 institutes at the VBC, including the CSF, and was comprised of a serious of short scenes in the format of a Caberet night. 3 scenes from Eugene Ionesco's surrealist play „The Bald Soprano" were interspersed between a VBC-adapted version of Kafka's Metamorphosis, a comedy short about the struggles of getting a foreign work permit in Vienna and an interactive fortune-telling mystic act. A Christmas Play is also set to take place on the 16th and 18th of December, where in the spirit of British Pantomime, the classic children's story Charlie and the Chocolate Factory has been adapted fort he audience of the Vienna Biocenter as a recap of the happenings on campus throughout the year.

Summer School

Once again the VBC Summer School was hugely popular. Out of the nearly 2000 applications from all over the world, 20 students were invited to join one of the labs at IMP, IMBA, GMI and MFPL for nine weeks. 8 students joined groups at IMBA. Each summer fellow can work on an independent research project under the close supervision of a graduate student. The results of each of their projects were presented at the final Summer School Symposium held in August. For more information on the Summer School please refer to page 56 [Career and Training] in this booklet.

IMP/IMBA Christmas Charity

On 17th November several service facilities from IMBA and IMP teamed up to organize the fourth "Charity Punsch Event". In front of the beautifully decorated stand in the VBC courtyard little snacks and steaming hot drinks with varying concentrations of ethanol, keeping the crowd warm, were served. A harmonious performance of a small brass band created a homely wintertime atmosphere. Next to all the merriment, giving to other, less fortunate people, is an important part of the Christmas spirit. That is why the money collected during this event was donated to the "Stiftung Kindertraum" (Children's Make-A-Wish Foundation).

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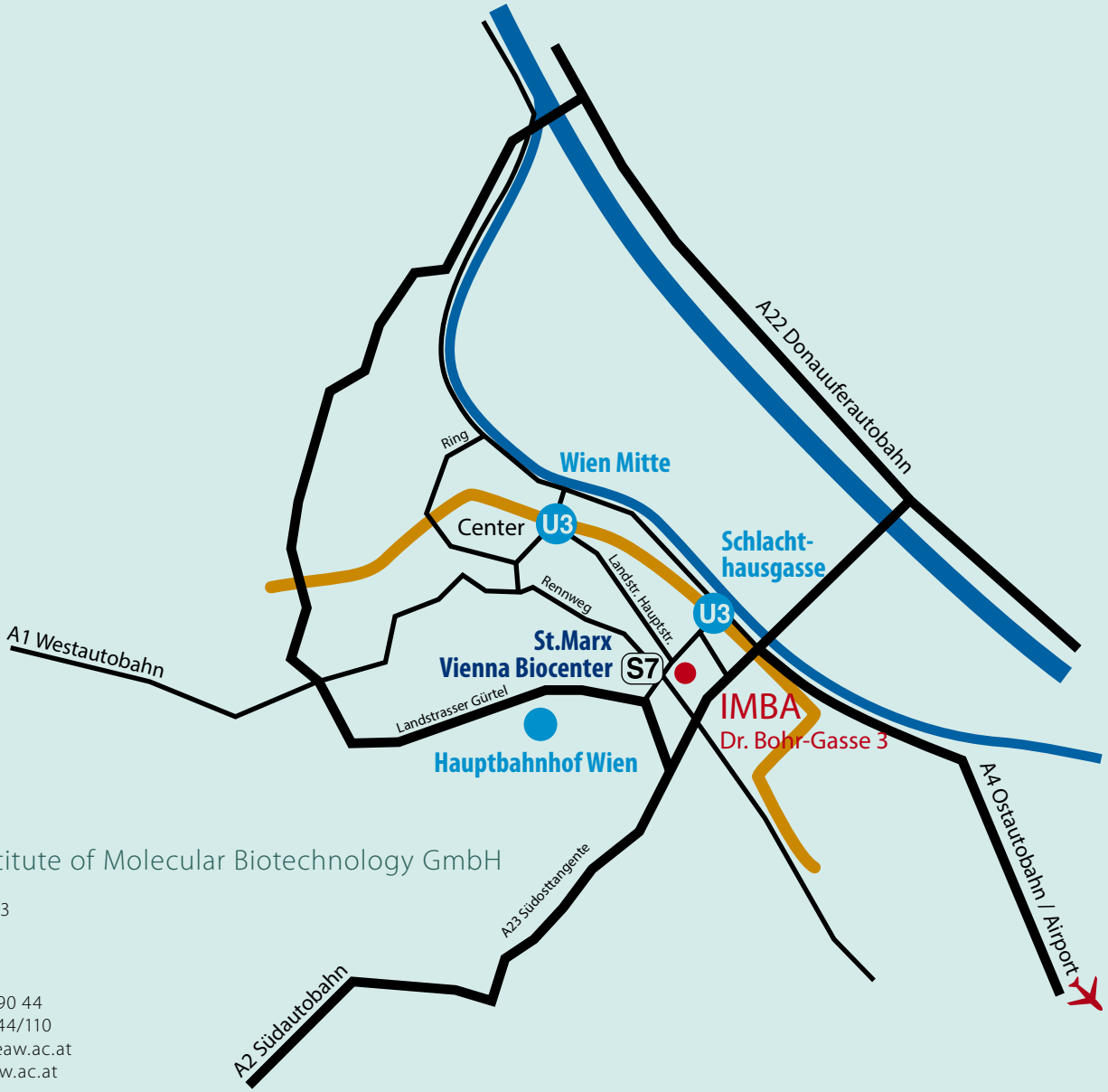

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