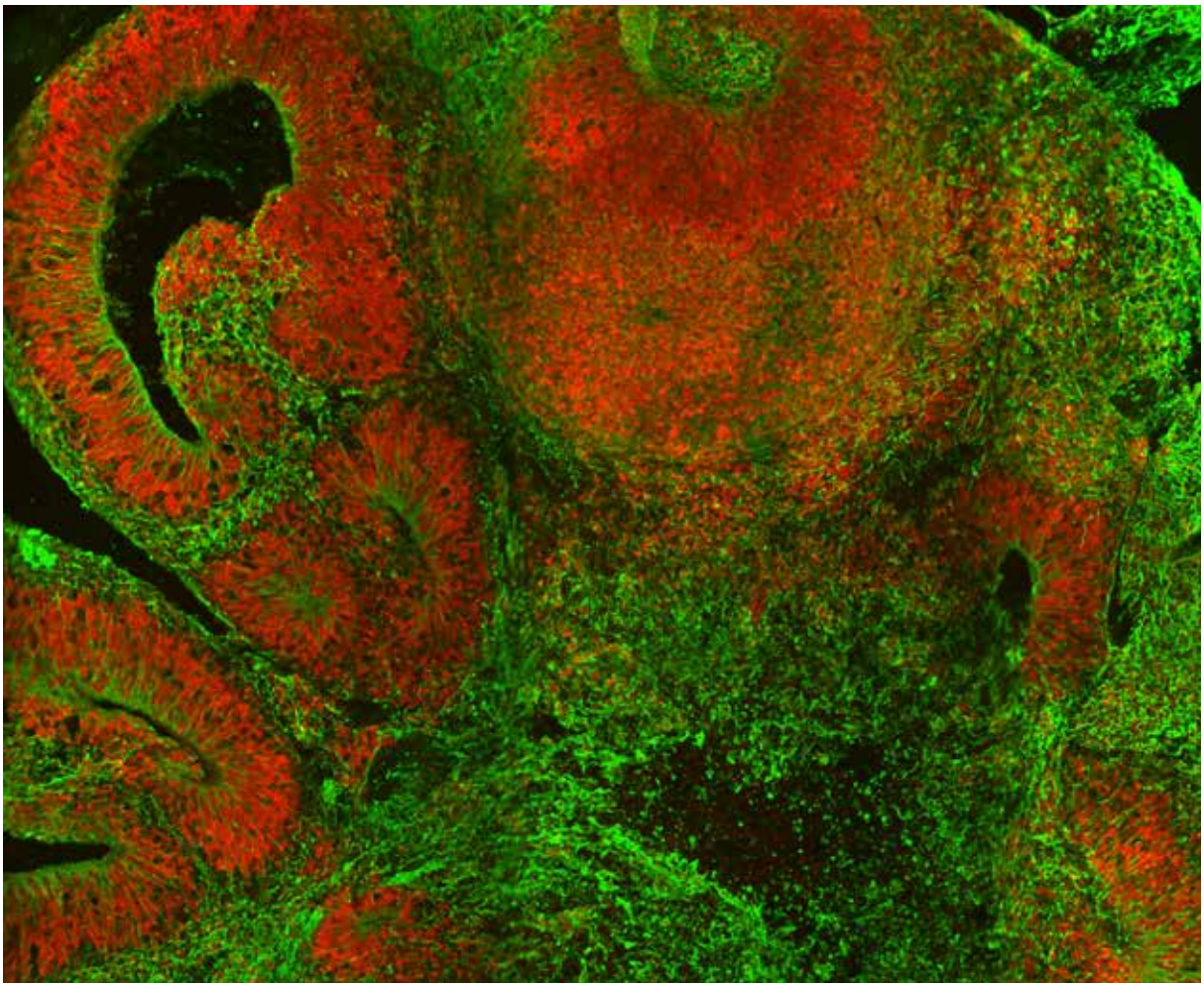
ÖAW AUSTRIAN ACADEMY OF SCIENCES

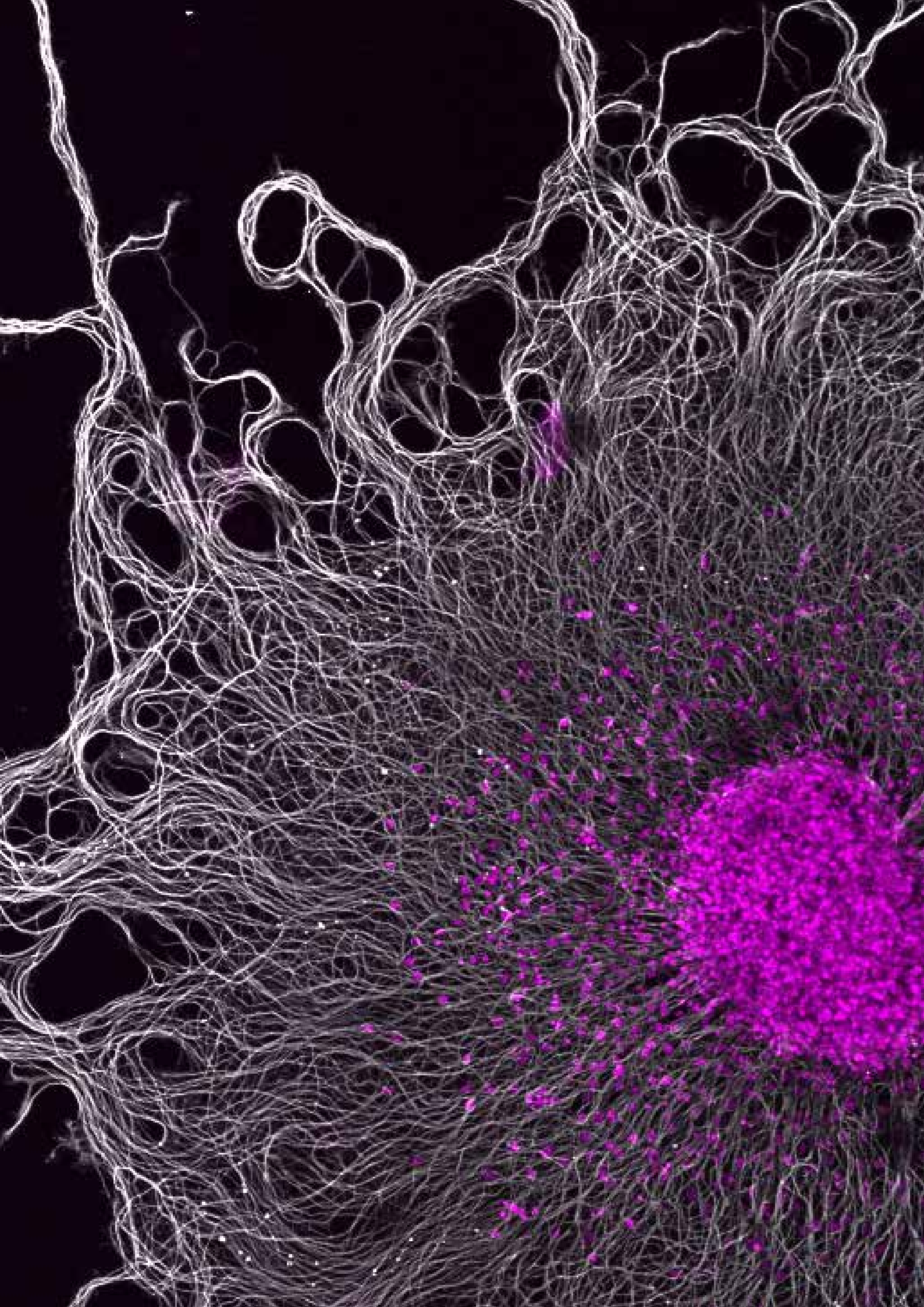


IMBA - INSTITUTE OF MOLECULAR BIOTECHNOLOGY

RESEARCH REPORT 2016 - 17

IMBA Institute of Molecular Biotechnology of the Austrian Academy of Sciences

CONTENT



INTRODUCTION

ABOUT IMBA

IMBA is the largest research institute of the Austrian Academy of Science and conducts basic research in the areas of Molecular Biology and Biomedicine. Main fields include Stem Cell Biology, Disease Modelling, Epigenetics and RNA Biology. IMBA is located at the Vienna BioCenter, a leading international life sciences cluster and home to research institutes, universities and biotech companies.

IMBA fosters creativity. All scientists - from established, world-class experts to promising, new talents - follow their visions with the utmost financial and technical support. These resources give IMBA scientists the freedom to develop new approaches, design innovative technologies, create novel model systems – and make groundbreaking discoveries.

IMBA especially helps young scientists on their path towards excellence in research. Key assets of IMBA include an outstanding infrastructure, a world-renowned team of interdisciplinary scientists, and a vibrant and synergistic environment in one of the world's top-ranked places to work and live.

MANAGEMENT

SCIENTIFIC DIRECTOR
Josef Penninger, MD was formerly a lead researcher at the Amgen Research Institute in Toronto. In 2002 he accepted the appointment as founding director of the newly established Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences in Vienna, Austria. Major achievements include pioneering insights into the molecular basis of osteoporosis and breast cancer, as well as the study of metastatic spread. His group has also developed the first haploid embryonic stem cells for functional genetics.

DEPUTY SCIENTIFIC DIRECTOR
Jürgen Knoblich obtained his PhD at the Max Planck Institute in Tübingen. He worked for three years at the Univ. of California in San Francisco before he became a group leader at the IMP in 1997. In 2004, he joined IMBA as a senior scientist and became deputy director in 2005. In 2013 his group developed the first brain-organoids derived from human stem cells worldwide.

ADMINISTRATIVE DIRECTOR
Michael Krebs joined the institute in January 2004 and has a degree in Business Administration as well as an Executive MBA in "Mergers & Acquisitions". He worked for more than 5 years for early stage Biotech companies as a co-founder, CFO, and external consultant. At IMBA, Michael bears responsibility for all financial, administrative and business-related matters.

SCIENTIFIC ADVISORY BOARD

ERIC KANDEL, Columbia University, New York, USA

ANTHONY HYMAN, Max Planck Institute of Molecular Cell Biology and Genetics

FIONA WATT, Centre for Stem Cells and Regenerative Medicine, King's College London, UK

ELAINE FUCHS, Rockefeller University / Howard Hughes Medical Institute, New York, USA

GREGORY HANNON, Cold Spring Harbor Laborartory / Howard Hughes Medical Institute, New York, USA; Cancer Research UK, University of Cambridge, UK

GUIDO KROEMER, Cordeliers Research Center University of Paris Descartes, Paris, France

GARY RUVKUN, Department of Genetics / Harvard Medical School, Boston, USA

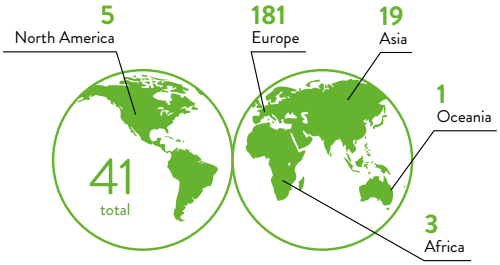
MARIA LEPTIN, Institute of Genetics, University Cologne, Germany

JOSEPH SCHLESSINGER, Yale School of Medicine New Haven, USA

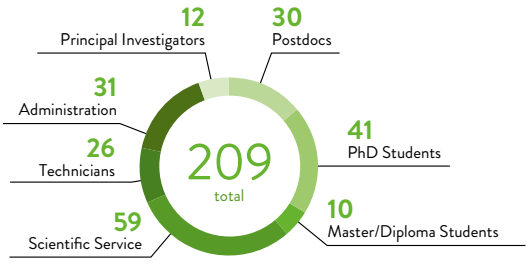
KEY FACTS

STAFF

Gender Distribution*



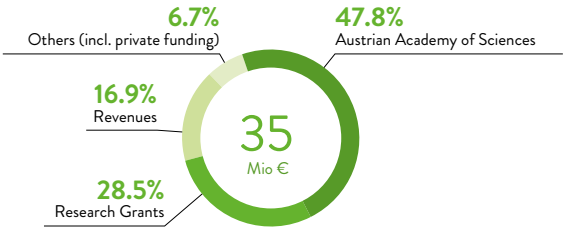
Nationalities*



Functions*

*as of 12/2017

BUDGET



IMBA Budget 2017

PUBLICATIONS

Publications since IMBA´s foundation in 2003

30% of all IMBA publications are in the Top 10% most cited articles in their respective fields
Source: InCites dataset updated Jan 13, 2018

ERC GRANTS*

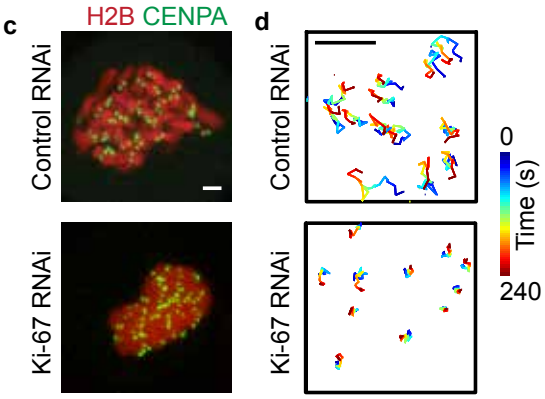
Starting	5
Advanced	4
Consolidator	2
Proof of Concept	1

EMBO MEMBERSHIPS*

EMBO full members	4
EMBO YIPs (active)	2

*as of 12/2017

RESEARCH HIGHLIGHTS

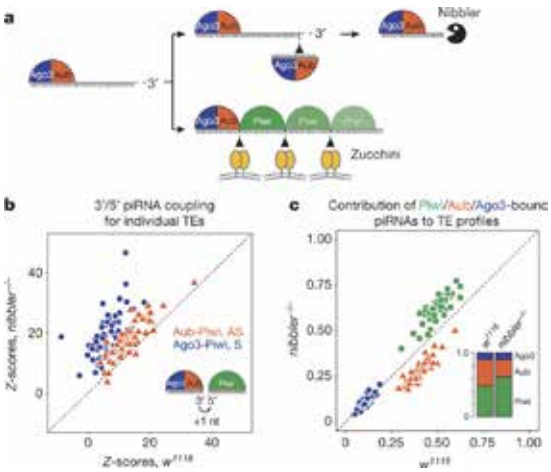


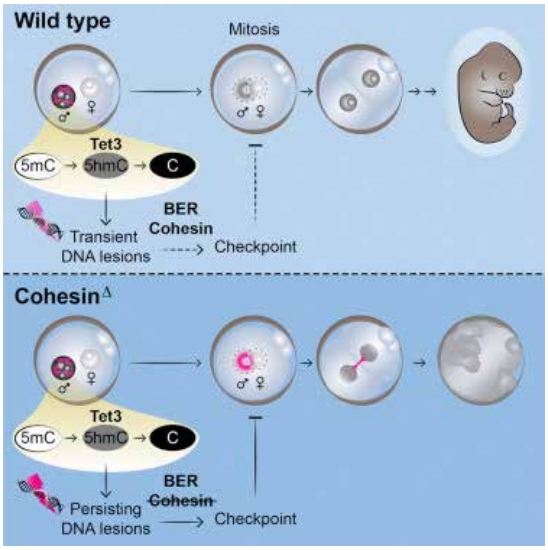
Cuylen S, Blaukopf C, Politi AZ, Müller-Reichert T, Neumann B, Poser I, Ellenberg J, Hyman AA, Gerlich DW: Ki-67 acts as a biological surfactant to disperse mitotic chromosomes. *Nature 2016, 535:308-312. http://dx.doi.org/10.1038/nature18610*

Eukaryotic genomes are partitioned into chromosomes that form compact and spatially well-separated mechanical bodies during mitosis. This enables chromosomes to move independently of each other for segregation of precisely one copy of the genome to each of the nascent daughter cells. Despite insights into the spatial organization of mitotic chromosomes and the discovery of proteins at the chromosome surface, the molecular and biophysical bases of mitotic chromosome structural individuality have remained unclear. Here we report that the proliferation marker protein Ki-67 (encoded by the *MKI67* gene), a component of the mitotic chromosome periphery, prevents chromosomes from collapsing into a single chromatin mass after nuclear envelope disassembly, thus enabling independent chromosome motility and efficient interactions with the mitotic spindle. The chromosome separation function of human Ki-67 is not confined within a specific protein domain, but correlates with size and net charge of truncation mutants that apparently lack secondary structure. This suggests that Ki-67 forms a steric and electrostatic charge barrier, similar to surface-active agents (surfactants) that disperse particles or phase-separated liquid droplets in solvents. Fluorescence correlation spectroscopy showed a high surface density of Ki-67 and dual-colour labelling of both protein termini revealed an extended molecular conformation, indicating brush-like arrangements that are characteristic of polymeric surfactants. Our study thus elucidates a biomechanical role of the mitotic chromosome periphery in mammalian cells and suggests that natural proteins can function as surfactants in intracellular compartmentalization.

Hayashi R, Schnabl J, Handler D, Mohn F, Ameres SL, Brennecke J: Genetic and mechanistic diversity of piRNA 3′-end formation. *Nature 2016, 539:588-592. http://dx.doi.org/10.1038/nature20162*

Small regulatory RNAs guide Argonaute (Ago) proteins in a sequence-specific manner to their targets and therefore have important roles in eukaryotic gene silencing. Of the three small RNA classes, microRNAs and short interfering RNAs are processed from double-stranded precursors into defined 21- to 23-mers by Dicer, an endoribonuclease with intrinsic ruler function. PIWI-interacting RNAs (piRNAs)—the 22–30-nt-long guides for PIWI-clade Ago proteins that silence transposons in animal gonads—are generated independently of Dicer from single-stranded precursors. piRNA 5′ ends are defined either by Zucchini, the *Drosophila* homologue of mitoPLD—a mitochondria-anchored endonuclease, or by piRNA-guided target cleavage. Formation of piRNA 3′ ends is poorly understood. Here we report that two genetically and mechanistically distinct pathways generate piRNA 3′ ends in *Drosophila*. The initiating nucleases are either Zucchini or the PIWI-clade proteins Aubergine (Aub) or Ago3. While Zucchini-mediated cleavages directly define mature piRNA 3′ ends, Aub/Ago3-mediated cleavages liberate pre-piRNAs that require extensive resection by the 3′-to-5′ exoribonuclease Nibbler (*Drosophila* homologue of Mut-7). The relative activity of these two pathways dictates the extent to which piRNAs are directed to cytoplasmic or nuclear PIWI-clade proteins and thereby sets the balance between post-transcriptional and transcriptional silencing. Notably, loss of both Zucchini and Nibbler reveals a minimal, Argonaute-driven small RNA biogenesis pathway in which piRNA 5′ and 3′ ends are directly produced by closely spaced Aub/Ago3-mediated cleavage events. Our data reveal a coherent model for piRNA biogenesis, and should aid the mechanistic dissection of the processes that govern piRNA 3′-end formation.



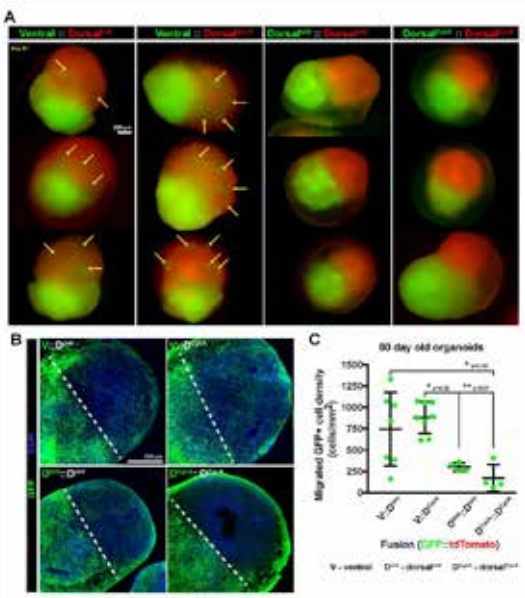


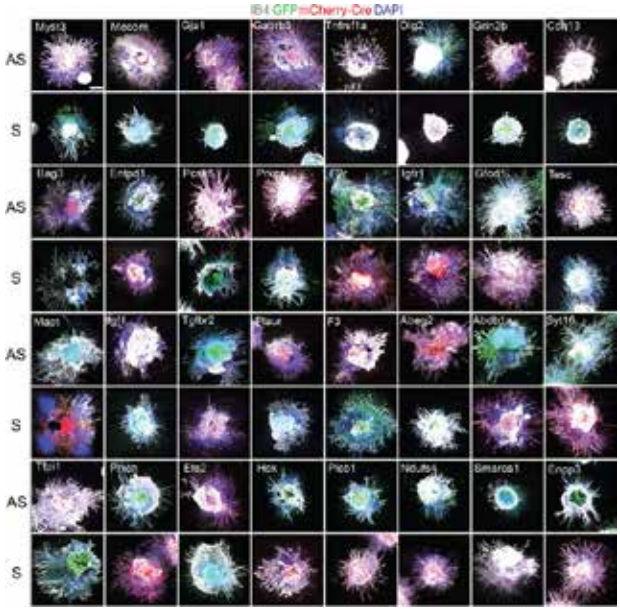
Ladstätter S, Tachibana-Konwalski K: A Surveillance Mechanism Ensures Repair of DNA Lesions during Zygotic Reprogramming. *Cell 2016, 167:1774-1787. e1713. http://dx.doi.org/10.1016/j.cell.2016.11.009*

Sexual reproduction culminates in a totipotent zygote with the potential to produce a whole organism. Sperm chromatin reorganization and epigenetic reprogramming that alter DNA and histone modifications generate a totipotent embryo. Active DNA demethylation of the paternal genome has been proposed to involve base excision and DNA repair-based mechanisms. The nature and consequence of DNA lesions generated during reprogramming are not known. Using mouse genetics and chemical biology, we discovered that Tet3-dependent zygotic reprogramming generates paternal DNA lesions that are monitored by a surveillance mechanism. In vivo structure-function rescue assays revealed that cohesin-dependent repair of paternal DNA lesions prevents activation of a Chk1-dependent checkpoint that delays mitotic entry. Culturing conditions affect checkpoint stringency, which has implications for human in vitro fertilization. We propose the zygotic checkpoint senses DNA lesions generated during paternal DNA demethylation and ensures reprogrammed loci are repaired before mitosis to prevent chromosome fragmentation, embryo loss, and infertility.

Bagley JA, Reumann D, Bian S, Lévi-Strauss J, Knoblich JA: Fused cerebral organoids model interactions between brain regions. *Nature Methods 2017, 13:107-751. http://dx.doi.org/10.1038/nmeth.4304*

Human brain development involves complex interactions between different areas, including long distance neuronal migration or formation of major axonal tracts. 3D cerebral organoids allow the growth of diverse brain regions *in vitro*, but the random arrangement of regional identities limits the reliable analysis of complex phenotypes. Here, we describe a co-culture method combining various brain regions of choice within one organoid tissue. By fusing organoids specified toward dorsal and ventral forebrain, we generate a dorsal-ventral axis. Using fluorescent reporters, we demonstrate robust directional GABAergic interneuron migration from ventral into dorsal forebrain. We describe methodology for time-lapse imaging of human interneuron migration that is inhibited by the CXCR4 antagonist AMD3100. Our results demonstrate that cerebral organoid fusion cultures can model complex interactions between different brain regions. Combined with reprogramming technology, fusions offer the possibility to analyze complex neurodevelopmental defects using cells from neurological disease patients, and to test potential therapeutic compounds.



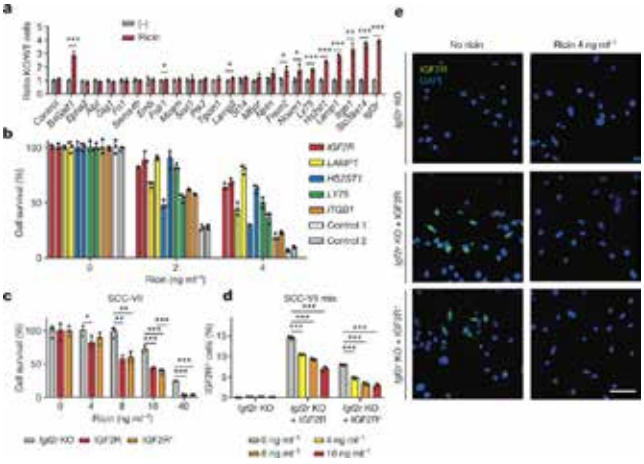


Elling U, Wimmer RA, Leibbrandt A, Burkard T, Michlits G, Leopoldi A, Micheler T, Abdeen D, Zhuk S, Aspalter IM, Handl C, Liebergesell J, Hubmann M, Husa A-M, Kinzer M, Schuller N, Wetzel E, van de Loo N, Martinez JAZ, Estoppey D, Riedl R, Yang F, Fu B, Dechat T, Ivics Z, Agu CA, Bell O, Blaas D, Gerhardt H, Hoepfner D, Stark A, Penninger JM: A reversible haploid mouse embryonic stem cell biobank resource for functional genomics. *Nature 2017, 550:114-118. http://dx.doi.org/10.1038/nature24027*

The ability to directly uncover the contributions of genes to a given phenotype is fundamental for biology research. However, ostensibly homogeneous cell populations exhibit large clonal variance that can confound analyses and undermine reproducibility. Here we used genome-saturated mutagenesis to create a biobank of over 100,000 individual haploid mouse embryonic stem (mES) cell lines targeting 16,970 genes with genetically barcoded, conditional and reversible mutations. This Haplobank is, to our knowledge, the largest resource of hemi/homozygous mutant mES cells to date and is available to all researchers. Reversible mutagenesis overcomes clonal variance by permitting functional annotation of the genome directly in sister cells. We use the Haplobank in reverse genetic screens to investigate the temporal resolution of essential genes in mES cells, and to identify novel genes that control sprouting angiogenesis and lineage specification of blood vessels. Furthermore, a genome-wide forward screen with Haplobank identified PLA2G16 as a host factor that is required for cytotoxicity by rhinoviruses, which cause the common cold. Therefore, clones from the Haplobank combined with the use of reversible technologies enable high-throughput, reproducible, functional annotation of the genome.

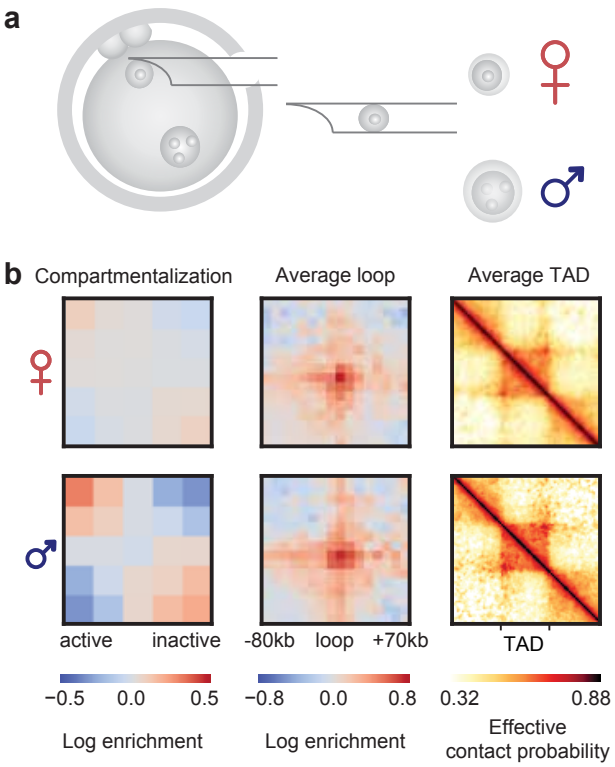
Stadlmann J, Taubenschmid J, Wenzel D, Gattinger A, Dürnberger G, Dusberger F, Elling U, Mach L, Mechtler K, Penninger JM: Comparative glycoproteomics of stem cells identifies new players in ricin toxicity. *Nature 2017, 549:538-542. http://dx.doi.org/10.1038/nature24015*

Glycosylation, the covalent attachment of carbohydrate structures onto proteins, is the most abundant post-translational modification. Over 50% of human proteins are glycosylated, which alters their activities in diverse fundamental biological processes. Despite the importance of glycosylation in biology, the identification and functional validation of complex glycoproteins has remained largely unexplored. Here we develop a novel quantitative approach to identify intact glycopeptides from comparative proteomic data sets, allowing us not only to infer complex glycan structures but also to directly map them to sites within the associated proteins at the proteome scale. We apply this method to human and mouse embryonic stem cells to illuminate the stem cell glycoproteome. This analysis nearly doubles the number of experimentally confirmed glycoproteins, identifies previously unknown glycosylation sites and multiple glycosylated stemness factors, and uncovers evolutionarily conserved as well as species-specific glycoproteins in embryonic stem cells. The specificity of our method is confirmed using sister stem cells carrying repairable mutations in enzymes required for fucosylation, Fut9 and Slc35c1. Ablation of fucosylation confers resistance to the bioweapon ricin, and we discover proteins that carry a fucosylation-dependent sugar code for ricin toxicity. Mutations disrupting a subset of these proteins render cells ricin resistant, revealing new players that orchestrate ricin toxicity. Our comparative glycoproteomics platform, SugarQb, enables genome-wide insights into protein glycosylation and glycan modifications in complex biological systems.



Flyamer IM, Gassler J, Imakaev M, Brandão HB, Ulianov SV, Abdennur N, Razin SV, Mirny LA, Tachibana-Konwalski K1: Single-nucleus Hi-C reveals unique chromatin reorganization at oocyte-to-zygote transition. *Nature. 2017 Apr 6;544(7648):110-114. doi: 10.1038/nature21711*

Chromatin is reprogrammed after fertilization to produce a totipotent zygote with the potential to generate a new organism. The maternal genome inherited from the oocyte and the paternal genome provided by sperm coexist as separate haploid nuclei in the zygote. How these two epigenetically distinct genomes are spatially organized is poorly understood. Existing chromosome conformation capture-based methods are not applicable to oocytes and zygotes owing to a paucity of material. To study three-dimensional chromatin organization in rare cell types, we developed a single-nucleus Hi-C (high-resolution chromosome conformation capture) protocol that provides greater than tenfold more contacts per cell than the previous method. Here we show that chromatin architecture is uniquely reorganized during the oocyte-to-zygote transition in mice and is distinct in paternal and maternal nuclei within single-cell zygotes. Features of genomic organization including compartments, topologically associating domains (TADs) and loops are present in individual oocytes when averaged over the genome, but the presence of each feature at a locus varies between cells. At the sub-megabase level, we observed stochastic clusters of contacts that can occur across TAD boundaries but average into TADs. Notably, we found that TADs and loops, but not compartments, are present in zygotic maternal chromatin, suggesting that these are generated by different mechanisms. Our results demonstrate that the global chromatin organization of zygote nuclei is fundamentally different from that of other interphase cells. An understanding of this zygotic chromatin ‚ground state' could potentially provide insights into reprogramming cells to a state of totipotency.



STEFAN AMERES

SMALL RNA SILENCING AND THE EPITRANSCRIPTOME

Stefan Ameres, Group Leader

The Ameres lab studies fundamental mechanisms of post-transcriptional gene regulation. Small silencing RNAs, such as microRNAs, control over half of the protein-coding transcriptome in flies and mammals, regulating development, physiology, and disease. We are interested in the processes that regulate small RNA production, as well as the assembly and disassembly of functional small RNA/protein complexes in response to external triggers. Our goal is to unravel mechanistic principles of small RNA-mediated gene regulation.

In addition, numerous chemical modifications of RNA have evolved to sculpt its physical and functional interactions. Hundreds of distinct RNA modifications contribute to the "epitranscriptome", but their mode of action remains elusive. We are studying the function of RNA modifications at the intersection of small RNA silencing pathways and general RNA metabolism. To dissect the regulation of microRNA biogenesis and function, we study the post-transcriptional addition of nucleotides to the 3′ end of RNA by the terminal nucleotidyltransferases. Further, we investigate the role of small RNA ribose methylation to gain insights into the RNAi-mediated antiviral immune response in insects. The emerging concepts will inevitably illuminate the broader roles of post-transcriptional modifications in RNA metabolism.

Finally, we apply our mechanistic insights to engineer novel epitranscriptomic technologies that facilitate global analyses of post-transcriptional gene regulatory networks. For instance, we developed thiol(SH)-linked alkylation for the metabolic sequencing of RNA (SLAM seq), which detects 4-thiouridine incorporation in RNA at single-nucleotide resolution. Coupled to well-established metabolic RNA labeling protocols and standard, low-input, high-throughput RNA sequencing methods, SLAM seq enables global kinetic analysis of RNA synthesis and turnover (Herzog et al., 2017 Nature Methods).

KEYWORDS

Post-transcriptional gene regulation | RNA biochemistry RNP enzymology | RNA modifications | small non-coding RNAs

SELECTED PUBLICATIONS

Herzog, VA., Reichholf, B., Neumann, T., Rescheneder, P., Bhat, P., Burkard, TR., Wlotzka, W., von Haeseler, A., Zuber, J., Ameres, SL. Thiol-linked alkylation of RNA to assess expression dynamics. Nature Methods*, 2017 Dec, 14(12):1198-1204*

Hayashi, R., Schnabl, J., Handler, D., Ameres, S.L., Brennecke, J.** Genetic and mechanistic diversity of piRNA 3′ end formation. *Nature, 2016 Nov 24, 539: 588-92*

Reimão-Pinto, M.M., Manzenreither, R.A., Burkard, T.R., Sledz, P., Jinek, M., Mechtler, K., and Ameres, S.L. Molecular basis for cytoplasmic RNA surveillance by uridylation-triggered decay in Drosophila. *EMBO Journal, 2016 Nov 15, 35(22):2417-34*

SELECTED GRANTS & AWARDS

Life Science Call 2017 – Chemical Biology
Vienna Science, Research and Technology Fund (WWTF)

Selected for the Young Investigator Program (EMBO YIP)

European Molecular Biology Organization (EMBO)

TEAM MEMBERS

PostDoc
Herzog, Veronika

PhD students
Bhat, Pooja
Manzenreither, Raphael
Reichholf, Brian
Reimao Pinto, Madalena
Rodrigues Viana, Angela Maria,
Staltner, Moritz

Research Assistant
Sowemimo, Ivica
Fasching, Nina

Summer School Student
Navalayeu, Tsimafei

OLIVER BELL
MECHANISMS OF EPIGENETIC MEMORY

Oliver Bell, Group Leader

The Bell lab studies the mechanisms that underlie epigenetic memory of cell fate decisions. In metazoans, genomic DNA is organized into chromatin, providing an opportunity to regulate differential gene accessibility and expression. Diverse chemical modifications of nucleosomes and DNA shape chromatin structure and are thought to help maintain gene expression states through genome replication, independently of the initial stimulus. However, the dynamic regulation of chromatin modifications and their contribution to the epigenetic inheritance of cell identity remains enigmatic.

We use synthetic biology approaches in mouse stem cells to manipulate chromatin modifications and study their dynamics and inheritance. We want to illuminate the epigenetic mechanisms that establish and maintain stable gene expression states. Ultimately, we aim to unravel the crosstalk between epigenetic regulation and cell plasticity. In addition to genetic and biochemical analyses of chromatin regulatory activities, we apply innovative biosynthetic technologies that enable reversible targeting of complexes to chromatin. By integrating small molecule-dependent control with precise biochemical analyses of chromatin changes, we determine how complexes form repressive chromatin, and how gene silencing is initiated and propagated. This reductionist approach to recapitulate complex chromatin landscapes offers a unique entry point to use genetic and pharmacological tools to dissect the mechanism of epigenetic regulation. In addition, kinetic measurements at high temporal resolution enable mathematical modelling of complex histone modification dynamics and patterns.

Key epigenetic regulators have been implicated in tumorigenesis, thus elucidating the molecular underpinnings of normal and aberrant chromatin regulation is critical on the path to developing effective clinical therapies.

KEYWORDS

epigenetics | chromatin | development | polycomb histone modifications

SELECTED PUBLICATIONS

Hathaway, NA., Bell, O., Hodges, C., Miller, EL., Neel, DS., Crabtree, GR. (2012). Dynamics and memory of heterochromatin in living cells. *Cell. 149(7):1447-60*

Bell, O., Tiwari, VK., Thomä, NH., Schübeler, D. (2011). Determinants and dynamics of genome accessibility. *Nat Rev Genet. 12(8):554-64*

Bell, O., Schwaiger, M., Oakeley, EJ., Lienert, F., Beisel, C., Stadler, MB., Schübeler, D. (2010). Accessibility of the Drosophila genome discriminates PcG repression, H4K16 acetylation and replication timing. *Nat Struct Mol Biol. 17(7):894-900*

TEAM MEMBERS

PostDoc
Yelagandula, Ramesh

PhD students
Bsteh, Daniel
Moussa, Hagar
Stecher, Karin
Jorge Arturo, Zepeda Mertines
Master Students
Handler, Kristina
Szalay, Michael Florian

Research Assistant
Pribitzer, Carina

Summer School Student
Michetti, Luca

JULIUS BRENNECKE

SMALL RNAS, HETEROCHROMATIN, AND THE GENOME-TRANSPOSON CONFLICT

Julius Brennecke, Senior Scientist

The Brennecke lab studies the biology and mechanism of the piRNA pathway, a defense system that silences transposons and protects the animal genome against ectopic recombination. This RNA interference pathway acts like a small RNA-mediated genome immune system: it selectively silences transposons, establishes heterochromatin at repeats, and quickly adapts to new genome invaders. piRNA-mediated repression safeguards genome integrity and fertility, and thus is crucial for species survival.

We aim to provide molecular explanations for the biological processes that underlie or are controlled by the piRNA pathway. Combining genetics, genomics and bioinformatics, we recently uncovered how piRNAs are processed from their long precursors in Drosophila (Mohn et al., Science 2015; Hayashi, Nature 2016). We identified two pathways, which fuel piRNAs either into cytoplasmic or nuclear PIWI-clade proteins, and thereby set the balance between post-transcriptional and transcriptional silencing. Transposons are silenced by piRNAs, but at the same time also provide the piRNA precursors. We wondered how piRNA source loci are efficiently transcribed within heterochromatin. We found that Moonshiner, a paralogue of a basal transcription initiation factor IIA (TFIIA) subunit, is recruited to piRNA clusters via the HP1 variant Rhino. Moonshiner triggers transcription initiation within piRNA clusters by recruiting the TATA-box binding protein (TBP)-related factor TRF2, a TFIID core variant. Thus, transcription of piRNAs relies on direct recruitment of the core transcriptional machinery to heterochromatin via histone marks rather than sequence motifs (Andersen et al., Nature 2017).

We are also fascinated by the intersection of the piRNA pathway with germline biology. For example, piRNAs are maternally inherited across generations and they act as true epigenetic vectors for silencing information.

KEYWORDS

transposons | piRNAs | heterochromatin | epigenetics small RNAs

SELECTED PUBLICATIONS

Andersen, PR., Tirian, L., Vunjak, M., Brennecke, J.: A heterochromatin-dependent transcription machinery drives piRNA expression. *Nature (2017)*

Hayashi, R., Schnabl, J., Handler, D., Mohn, F., Ameres, SL., Brennecke, J.: Genetic and mechanistic diversity of piRNA 3'-end formation. *Nature (2016)*

Mohn, F., Handler, D., Brennecke, J.: Noncoding RNA. piRNA-guided slicing specifies transcripts for Zucchini-dependent, phased piRNA biogenesis. *Science (2015)*

SELECTED GRANTS & AWARDS

ERC Consolidator Grant

TEAM MEMBERS

PostDocs
Andersen, Peter
Hayashi, Rippei
Mari Ordonez, Arturo

PhD students
Batki, Julia
Baumgartner, Lisa
Elmaghraby, Mostafa
Schnabl, Jakob
Veselin, Andreev

Master Students
Bellec, Maelle**
Helmrath, Sabine*
Pühringer, Florian
Vunjak, Milica*

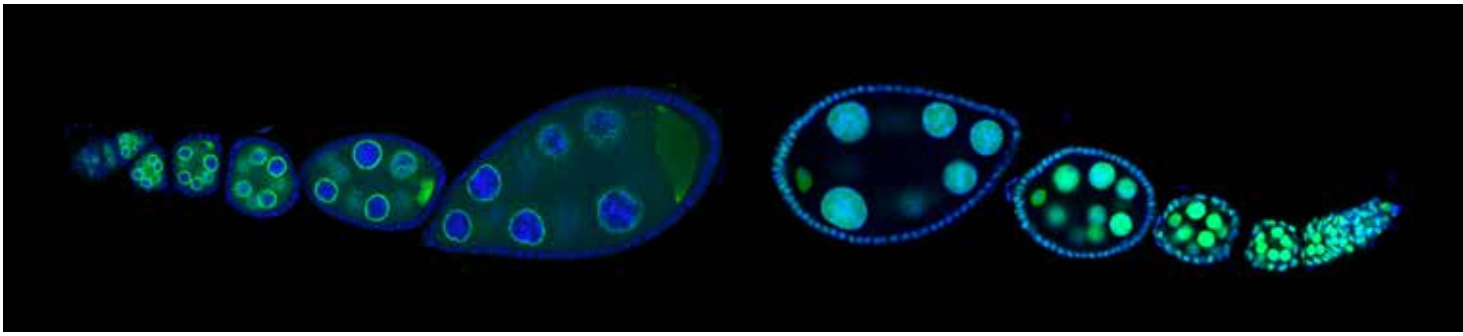
Research Associate
Handler, Dominik
Tirian, Laszlo

Research Assistant
Meixner, Katharina

Trainee
Felder, Anna-Karina**
Lampersberger, Lisa**

Summer School Students
Kauneckaite, Kotryna
Pandey, Aparna

**left in 2016*
***left in 2017*



ULRICH ELLING
FUNCTIONAL GENOMICS IN EMBRYONIC STEM CELLS

Ulrich Elling, Group Leader

The Elling lab studies cell identity, and how cells transition from one type to another. In this context, we study foremost embryonic stem cells, pluripotent cells that can differentiate into any cell type in the body. The core transcriptional circuitry defining embryonic stem cells is well-established, but the mechanisms controlling entrance to and exit from pluripotency are poorly understood.

Cell identity conversions had been accomplished long before by expression of lineage defining transcription factors and the field has seen a vast expansion in recent years. Most cell types are in principle convertible into other cell types, however, the molecular mechanisms promoting or preventing such conversions are largely unknown. Our work aims to fill this knowledge gap and provides critical insight into the field of cell lineage stability and conversions, that might hold great potential for regenerative medicine.

To systematically probe cellular mechanisms for their role in cell identity conversions, we use genetic screening. To this end, we develop novel screening approaches to uncover genes required for reprogramming, as well as those required for differentiation, cell type identity, and epigenetic control of cellular state. Amongst them, we recently reported a biobank of 100 000 conditionally mutated mouse ES cell lines (Haplobank, Elling et al., Nature 2017). In addition, we generated custom CRISPR libraries to perform genome editing-based genetic screens that track single cell clones (CRISPR-UMI, Michlits et al., Nature Methods 2017). Instead of examining cell populations with variable genetic status, we can now look at hundreds of independent single cell-derived clones separately, improving sensitivity and robustness of negative selection screens.

Further, in a positive selection screen to identify barriers to reprogramming, CRISPR-UMI allowed us to quantify the number and size of independent iPS cell colonies. Lastly, we recently established point mutagenesis screens as a paradigm to separate function within proteins (Horn et al., 2018). Taken together, these novel screening methodologies enable us to pinpoint new molecular players in an unbiased way.

KEYWORDS

haploid | screen | CRISPR/Cas | embryonic stem cell cell fate

SELECTED PUBLICATIONS

Michlits G, Hubmann M, Wu SH, Vainorius G, Budusan E, Zhuk S, Burkard TR, Novatchkova M, Aichinger M, Lu Y, Reece-Hoyes J, Nitsch R, Schramek D, Hoepfner D, Elling U. CRISPR-UMI: single-cell lineage tracing of pooled CRISPR-Cas9 screens. *Nat Methods. (2017)*

Elling, U., Wimmer, RA., Leibbrandt, A., Burkard, T., Michlits, G., Leopoldi, A., Micheler, T., Abdeen, D., Zhuk, S., Aspalter, IM., Handl, C., Liebergesell, J., Hubmann, M., Husa, AM., Kinzer, M., Schuller, N., Wetzel, E., van de Loo, N., Martinez, JAZ., Estoppey, D., Riedl, R., Yang, F., Fu, B., Dechat, T., Ivics, Z., Agu, CA., Bell, O., Blaas, D., Gerhardt, H., Hoepfner, D., Stark, A., Penninger, JM.: A reversible haploid mouse embryonic stem cell biobank resource for functional genomics. *Nature (2017)*

Stadlmann, J., Taubenschmid, J., Wenzel, D., Gattinger, A., Dürnberger, G., Dusberger, F., Elling, U., Mach, L., Mechtler, K., Penninger, JM.: Comparative glycoproteomics of stem cells identifies new players in ricin toxicity. *Nature (2017)*

Cheloufi S, Elling U, Hopfgartner B, Jung YL, Murn J, Ninova M, Hubmann M, Badeaux AI, Euong Ang C, Tenen D, Wesche DJ, Abazova N, Hogue M, Tasdemir N, Brumbaugh J, Rathert P, Jude J, Ferrari F, Blanco A, Fellner M, Wenzel D, Zinner M, Vidal SE, Bell O, Stadtfeld M, Chang HY, Almouzni G, Lowe SW, Rinn J, Wernig M, Aravin A, Shi Y, Park PJ, Penninger JM, Zuber J, Hochedlinger K. The histone chaperone CAF-1 safeguards somatic cell identity. *Nature (2015)*

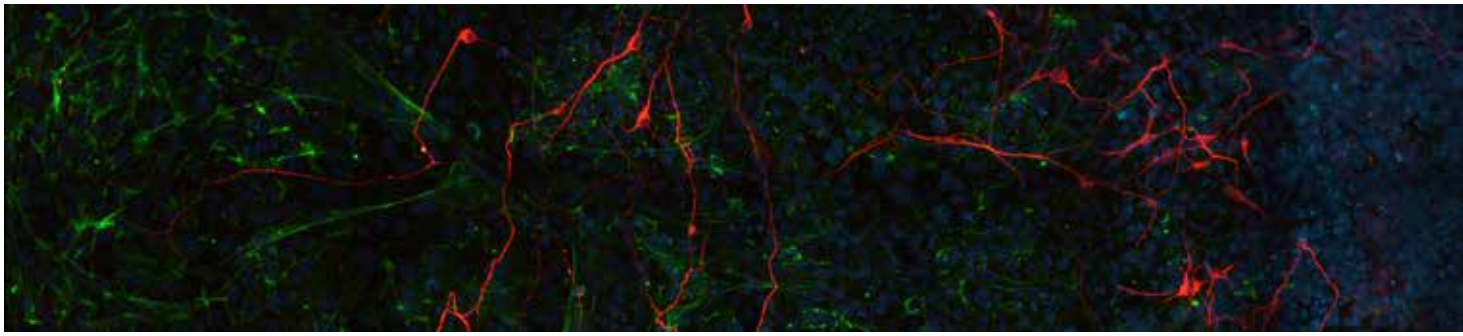
Elling, U., Taubenschmid, J., Wirnsberger, G., O'Malley, R., Demers, SP., Vanhaelen, Q., Shukalyuk, AI., Schmauss, G., Schramek, D., Schnuetgen, F., von Melchner, H., Ecker, JR., Stanford, WL., Zuber, J., Stark, A., Penninger, JM. (2011). Forward and reverse genetics through derivation of haploid mouse embryonic stem cells. *Cell Stem Cell. 9(6):563-74*

TEAM MEMBERS

PhD students
Michlits, Georg
Vainorius, Gintautas
Zhuk, Sergei

Master Student
Gijsbertsen, Max
Hauth, Antonia Raphaela

Research Assistant
Hubmann, Maria



DANIEL GERLICH

ASSEMBLY AND FUNCTION OF THE CELL DIVISION MACHINERY

Daniel Gerlich, Senior Scientist

The Gerlich laboratory studies how human cells reorganize their internal components during the cell cycle to establish distinct functions. We are particularly interested in the compartmentalization of the mitotic cytoplasm, the structure and biophysical properties of chromosomes, and chromosome interactions with cytoskeleton and membranes.

Cell organelles undergo dramatic and highly regulated changes during mitosis, including nuclear envelope breakdown, chromosome condensation, organelle segregation, and nuclear reassembly. Insight into the mechanisms underlying these changes has remained elusive due to the difficulty of linking molecular activities to microscopic phenomena involving distinct complexes. Our interdisciplinary team utilizes microscopy, biophysical assays, computational technologies, and biochemical reconstitution to uncover how the cell division machinery assembles during mitotic entry, and how interphase cells rebuild during mitotic exit. We aim to understand how various large complexes collectively build and reshape microscopic cell structures through self-organization.

Mitotic chromosomes are non-membrane-bounded organelles, separated from the cytoplasm by regulated surface properties. Using high-content screening, we discovered that a surfactant-like protein disperses mitotic chromosomes in the cytoplasm. We have also identified a protein that forms a network surrounding anaphase chromosomes, thus shaping a single nucleus during mitotic exit. We will further dissect the phase boundary between cytoplasm and chromatin. We will also elucidate how chromosomes, the cytoskeleton, and membranes coordinate to form functional interphase cells during mitotic exit.

Improper chromosome segregation or perturbed cell assembly after cell division underlie many diseases. Insight into the mechanisms of proper mitosis is anticipated to reveal potential strategies for disease intervention. Moreover, our research will reveal general principles of organelle morphogenesis, with broad implications for other biological processes such as differentiation.

KEYWORDS

mitosis | chromosomes | cell organelles | high-content screening | computer vision | biophysics

SELECTED PUBLICATIONS

Mierzwa, BE., Chiaruttini, N., Redondo-Morata, L., von Filseck, JM., König, J., Larios, J., Poser, I., Müller-Reichert, T., Scheuring, S., Roux, A., Gerlich, DW. (2017). Dynamic subunit turnover in ESCRT-III assemblies is regulated by Vps4 to mediate membrane remodelling during cytokinesis. *Nat Cell Biol. 19(7):787-798*

Samwer, M., Schneider, MWG., Hoefler, R., Schmalhorst, PS., Jude, JG., Zuber, J., Gerlich, DW. (2017). DNA Cross-Bridging Shapes a Single Nucleus from a Set of Mitotic Chromosomes. *Cell. 170(5):956-972.e23*

Cuylen, S., Blaukopf, C., Politi, AZ., Müller-Reichert, T., Neumann, B., Poser, I., Ellenberg, J., Hyman, AA., Gerlich, DW. (2016). Ki-67 acts as a biological surfactant to disperse mitotic chromosomes. *Nature. 535(7611):308-12*

Guizetti, J., Schermelleh, L., Mäntler, J., Maar, S., Poser, I., Leonhardt, H., Müller-Reichert, T., Gerlich, DW. (2011). Cortical constriction during abscission involves helices of ESCRT-III-dependent filaments. *Science. 331(6024):1616-20*

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

SELECTED GRANTS & AWARDS

ERC Starting Grant (consolidator) (2012-2017)

FWF SFB Grant „Chromosome dynamics“ (2015-2018)

FWF Doctoral Program “Chromosome dynamics” (2015-2018)

WWTF Grant “Imaging” (2015-2019)

WWTF Grant “Chemical Biology” (2018-2022)

TEAM MEMBERS

PostDocs
Cuylen, Sara**
Fededa, Juan Pablo**
Samwer, Matthias**

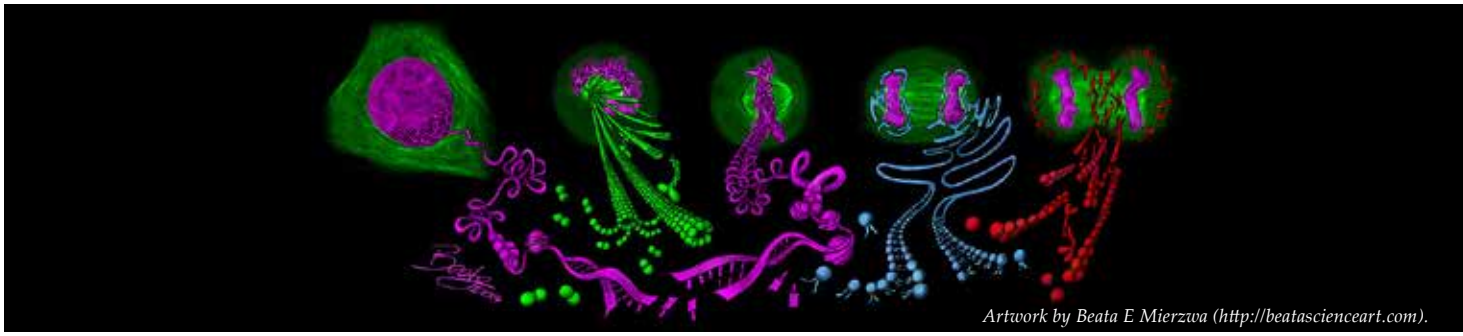
PhD students
David, Ana
Mierzwa, Beata**
Mitter, Michael
Petrovic, Mina
Schneider, Maximilian
Stanyte, Rugile

Senior Research Assistant
Blaukopf, Claudia

Bioinformatician
Höfler, Rudolf

Computer Scientist
Sommer, Christoph**

*****left in 2017*



Artwork by Beata E Mierzwa (http://beatascienceart.com).

FUMIYO IKEDA

LINEAR UBIQUITINATION IN INFLAMMATION, CELL DEATH AND AUTOPHAGY

Fumiyo Ikeda, Group Leader

The Ikeda lab is interested in protein modification by ubiquitin, which diversifies protein functions and thus influences many biological processes. Ubiquitin chains can form eight different linkage types with the intrinsic seven lysine (Lys) residues or the single initiating methionine (Met 1).

Among the eight linkage types, we are particularly interested in a non-classical type of chain, the linear ubiquitin chain. These chains look like "pearls-on-a-string", with the C-terminus of a distal ubiquitin linked to the Met 1 residue of a proximal ubiquitin. Compared to the classical Lys-linked ubiquitin chains, linear ubiquitin chains have unique biochemical and structural properties, though their biological importance is unclear.

We investigate a specific ubiquitin E3 ligase complex, the Linear Ubiquitin Chain Assembly Complex (LUBAC), which is the only ligase known to generate linear ubiquitin chains and is critical for a proper immune response in people. LUBAC consists of 3 proteins (HOIP, HOIL-1L and Sharpin), all of which are important for the adaptive immune signaling cascade, namely TNF-induced NF-kB activation, cell death and autophagy. Mutations in HOIP and HOIL-1 are associated with autoimmune disease as well as myopathy in humans. In mice, knockout of HOIP and HOIL-1L leads to embryonic lethality, whereas Sharpin-deficient mice suffer from systemic inflammation. We recently demonstrated that the homologous Linear Ubiquitin E3 Ligase (LUBEL) in flies regulates heat tolerance (Asaoka et al., EMBO Rep 2017).

Since essential enzymes regulating linear ubiquitination were found to be important for proper immunity and to control tumorigenesis in humans, it is critical to understand how linear ubiquitination is regulated and how it impacts diverse cellular responses. Our research is expected to shed light on therapeutic strategies that correct or manipulate protein ubiquitination.

KEYWORDS

Ubiquitin signal | E3 ligase | immune responses cell death | autophagy

SELECTED PUBLICATIONS

Asaoka, T., Almagro, J., Ehrhardt, C., Tsai, I., Schleiffer, A., Deszcz, L., Junttila, S., Ringrose, L., Mechtler, K., Kavirayani, A., Gyenesei, A., Hofmann, K., Duchek, P., Rittinger, K., Ikeda, F. (2016). Linear ubiquitination by LUBEL has a role in Drosophila heat stress response. *EMBO Rep. 17(11):1624-1640*

Kumari, S., Redouane, Y., Lopez-Mosqueda, J., Shiraishi, R., Romanowska, M., Lutzmayer, S., Kuiper, J., Martinez, C., Dikic, I., Pasparakis, M., Ikeda, F. (2014). Sharpin prevents skin inflammation by inhibiting TNFR1-induced keratinocyte apoptosis. *Elife. 3*

Ikeda, F., Deribe, YL., Skånland, SS., Stieglitz, B., Grabbe, C., Franz-Wachtel, M., van Wijk, SJ., Goswami, P., Nagy, V., Terzic, J., Tokunaga, F., Androulidaki, A., Nakagawa, T., Pasparakis, M., Iwai, K., Sundberg, JP., Schaefer, L., Rittinger, K., Macek, B., Dikic, I. (2011). SHARPIN forms a linear ubiquitin ligase complex regulating NF-?B activity and apoptosis. *Nature. 471(7340):637-41*

Rahighi, S., Ikeda, F., Kawasaki, M., Akutsu, M., Suzuki, N., Kato, R., Kensche, T., Uejima, T., Bloor, S., Komander, D., Randow, F., Wakatsuki, S., Dikic, I. (2009). Specific recognition of linear ubiquitin chains by NEMO is important for NF-kappaB activation. *Cell. 136(6):1098-109*

SELECTED GRANTS & AWARDS

ERC Consolidator Grant,
European Research Council (2014 - 2020)

TEAM MEMBERS

PostDoc
Asaoka, Tomoko**

PhD students
Ebner, Petra
Fennell, Lilian
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Redouane, Younes*
Rodrigues Carvajal, Alan

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Bachtrog, Iris
Dupard, Steven**
Hofer, Franziska

Research Assistant
Deszcz, Luiza
Pötsch, Isabella**
Schodl, Katrin

Summer School Students
Morlock, Michaela
Dukhoff, Irini

**left in 2016*
***left in 2017*

JÜRGEN KNOBLICH
BRAIN DEVELOPMENT AND DISEASE

Jürgen Knoblich, Deputy Scientific Director

The Knoblich lab studies brain development and tumorigenesis. To understand fundamental mechanisms of these processes, we analyze the simple nervous system of the fruit fly Drosophila. We recently discovered that the RNA binding protein Brain tumor (Brat) acts as a tumor suppressor by controlling cell fate in neural stem cell lineages via differential repression of the transcription factors Deadpan and Zelda (Reichardt et al., EMBO Rep 2017). Further, we found that the splicing co-factor Barricade works with the U2 snRNP complex to control stem cell lineage progression during brain development and facilitates correct splicing of a subset of introns (Abramczuk et al., Development 2017).

Additionally, we model early steps of human brain development in 'cerebral organoids'. We generate organoids from human embryonic stem cells or patient-derived induced pluripotent cells using a combination of 3D cell culture and/or bioengineering. Our 3D culture model recapitulates the formation of a layered human cortex with distinct ventricular zone and cortical plate. We can see the migration of neurons along radial glia fibers and can observe their neuronal activities by calcium imaging and electrophysiology. By fusing two separately patterned organoids, we study interactions between distinct brain areas, such as the long-distance migration of interneurons or generation of the major axon tracts. This allows us to identify defects in cells from patients suffering from epilepsy or autism. We can repair genetic aberrations in patient cells to determine their contribution to the defect, and can mutate genes to test their role in brain development. We aim to utilize large scale screening approaches in human organoids to comprehensively identify genes involved in neurodevelopment and neurological disease. (Renner et al., EMBO J 2017; Bagley et al., Nat Methods 2017; Lancaster et al., Nat Biotechnol. 2017)

KEYWORDS

stem cell | brain | organoids | cancer

SELECTED PUBLICATIONS

Lancaster, MA., Corsini, NS., Wolfinger, S., Gustafson, EH., Phillips, AW., Burkard, TR., Otani, T., Livesey, FJ., Knoblich, JA. (2017). Guided self-organization and cortical plate formation in human brain organoids. *Nat Biotechnol. 35(7):659-666*

Bagley, JA., Reumann, D., Bian, S., Lévi-Strauss, J., Knoblich, JA. (2017). Fused cerebral organoids model interactions between brain regions. *Nat Methods. 14(7):743-751*

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*

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*

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*

TEAM MEMBERS

Post Docs
Bagley, Joshua Adam
Bian, Shan
Bonnay, Francois
Corsini, Nina Stefanie
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Kruitwagen, Tom
Nowak, Jakub**
Wüseke, Oliver**

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Wissel, Sebastian

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Levi-Strass, Julie**
Schroeder, Benoit

Trainee
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Senior Research Assistant
Peer, Angela Maria

Research Associates
Kleiner, Elke
Martinez, Guzman Segundo, Jose

**left in 2016*
***left in 2017*

BON-KYOUNG KOO

HOMEOSTATIC REGULATION OF ADULT STEM CELLS

*Group at IMBA since 9/2017

Bon-Kyong Koo, Group Leader

The Koo lab studies the cellular and molecular mechanisms that govern homeostatic turnover, repair, and pre-neoplastic transformation of tissue. How adult tissue stem cells balance the ratio of stem cells and specialized, differentiated cells during homeostasis is currently unclear. Further, how adult tissue stem cells respond to tissue damage and restore homeostasis is poorly understood. We are investigating the regulatory mechanisms that control homeostatic turnover, and how their perturbations contribute to disease progression.

To study the mechanisms regulating adult stem cells, we perform functional genetic studies using in vitro and in vivo models in combination with biochemical analyses and mathematical modelling. In particular, we use transgenic mice in combination with lineage tracing approaches to monitor the behaviour of intestinal and gastric adult stem cells during homeostasis and injury repair. In addition, we use mouse and patient-derived 3D organoids as a screening platform to identify new players regulating adult stem cells. We recently discovered that human mucosa-derived intestinal epithelial organoids display strikingly similar epigenetic signatures to matching primary epithelium. Our work suggests that intestinal stem cell-intrinsic DNA methylation patterns establish and maintain regional gut specification and are involved in early epithelial development and disease (Kraiczy et al., Gut 2017).

We are learning that regeneration is tightly controlled by complex molecular signals. Specifically, negative feedback regulation via post-translational control of proteins plays a crucial role in maintaining adult tissue integrity as well as adult stem cell activity. Insight into the mechanisms that regulate adult gastro-intestinal stem cells will aid in the prediction and prevention of disorders, and lead to novel therapeutic strategies to treat cancers and ulcers.

KEYWORDS

adult stem cells | organoids | genetics | E3 ubiquitin ligases | cancer

SELECTED PUBLICATIONS

Kraiczy J, Nayak K, Howell K, Forbester J, Ross A, Vallier L, Andersson-Rolf A, Leenen E, Rosenstiel P, Stegle O, Dougan G, Heuschkel R, Koo BK†, Zilbauer M†. Stable DNA methylation signatures define the regional identity of human intestinal epithelial organoid cultures. *Gut 2017 Nov 15. doi: 10.1136/gutjnl-2017-314817.*

Andersson-Rolf A, Zilbauer M, Koo BK†, Clevers H†. Stem Cells in Repair of Gastrointestinal Epithelia. *Physiology 2017 Jul;32(4):278-289*

Turco MY, Gardner L, Hughes J, Cindrova-Davies T, Gomez MJ, Farrell L, Marsh SGE, Brosens JJ, Critchley HO, Simons BD, Hemberger M, Koo BK, Moffett A and Burton GJ. Hormone-responsive organoid cultures of human endometrium. *Nat Cell Biol 2017 May;19(5): 568-577*

Andersson-Rolf A, Mustata RC, Merenda A, Perera S, Grego T, Kim J, Andrews K, Fink J, Skarnes WC†, Koo BK†. One-step generation of conditional and reversible gene knockouts. *Nat Methods 2017 Jan 30.*

Broutier L, Andersson-Rolf A, Hindley CJ, Boj SF, Clevers H, Koo BK†, Huch M†. Culture and establishment of self-renewing human and mouse adult liver and pancreas 3D organoids and their genetic manipulation. *Nat Protoc. 2016 Sep;11(9):1724-43.*

SELECTED GRANTS & AWARDS

12th Mystery of Life Awards by the Korean Catholic Church (2017)

CRUK - Multidisciplinary Project Award – Tracing the cellular basis of cancer development (£499,898) (2016)

ERC starting grant – Troy Stem Cells, European Research Council (€1,570,399) (2015)

Sir Henry Dale Fellowship, the Wellcome Trust & the Royal Society (£1,075,543) (2013)

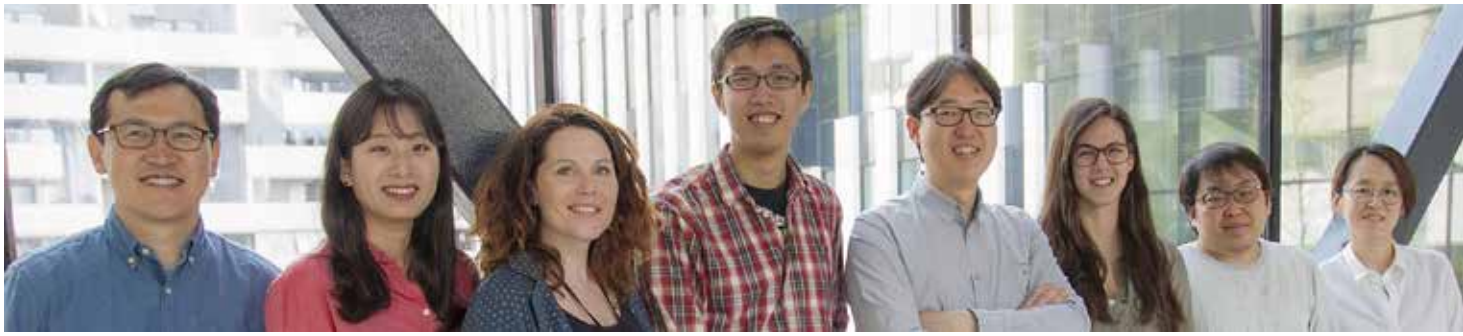
TEAM MEMBERS

PostDocs
Andersson Rolf, Amanda Maria**
Kim, Jihoon
Lee, Ji-Hyun
Na, Hyelin

PhD Student
Wu, Szu-Hsien

Senior Research Assistant
Pilat-Carotta, Sandra

*****left in 2017*



SASHA MENDJAN
MOLECULAR CONTROL OF HUMAN ORGANOGENESIS

Sasha Mendjan, Group Leader

The Mendjan explores the mechanisms underlying organogenesis, particularly the formation of the human heart. The embryonic heart, the first functional organ to form in humans, develops by patterning of endocardial, myocardial and epicardial progenitors from the mesoderm germ layer. These organ precursors crosstalk and co-specify resulting in a rapid succession of self-organising events.

The most common human birth defects originate from the faulty co-specification and aberrant self-organisation of mesodermal precursors during cardiogenesis. The resulting congenital heart disorders affect many pregnancies, children and a growing number of adults with life-long complications. Importantly, cardiac developmental genes and processes play also an important role in the aetiology of cardiovascular disease - the major cause of death in humans. Insights into the underlying mechanisms will advance our understanding of heart disease and lead to development of new treatment strategies.

While human pluripotent stem cells can be differentiated into multiple cardiac cell types, the key self-organising processes of heart tube formation, looping, trabeculation, ballooning, septation, valve development and functional maturation remain elusive. Further challenges comprise modelling heart-specific vascularisation, innervation and interactions with adipose tissue, which have a major impact on cardiac development, function and disease.

Our objective is to discover how signalling and gene expression drive patterning, self-organisation and functional maturation of cardiac structures, and how mutations cause disorders of cardiogenesis. To this end, we combine 2D and 3D stem cell differentiation and functional perturbations with quantitative imaging, as well as with global epigenome, transcriptome and proteome analysis.

KEYWORDS

Cardiac organogenesis | human pluripotent stem cells mesoderm | patterning | self-organisation | maturation

SELECTED PUBLICATIONS

Bertero, A., Madrigal, P., Galli, A., Hubner, NC., Moreno, I., Burks, D., Brown, S., Pedersen, RA., Gaffney, D., Mendjan, S., Pauklin, S., Vallier, L. (2015). Activin/nodal signaling and NANOG orchestrate human embryonic stem cell fate decisions by controlling the H3K4me3 chromatin mark. *Genes Dev. 29(7):702-17*

Mendjan, S., Mascetti, VL., Ortmann, D., Ortiz, M., Karjosukarso, DW., Ng, Y., Moreau, T., Pedersen, RA. (2014). NANOG and CDX2 pattern distinct subtypes of human mesoderm during exit from pluripotency. *Cell Stem Cell. 15(3):310-25*

Pedersen, RA., Mascetti, V., Mendjan, S. (2012). Synthetic organs for regenerative medicine. *Cell Stem Cell. 10(6):646-7*

Vallier, L., Mendjan, S., Brown, S., Chng, Z., Teo, A., Smithers, LE., Trotter, MW., Cho, CH., Martinez, A., Rugg-Gunn, P., Brons, G., Pedersen, RA. (2009). Activin/Nodal signalling maintains pluripotency by controlling Nanog expression. *Development. 136(8):1339-49*

Mendjan, S., Taipale, M., Kind, J., Holz, H., Gebhardt, P., Schelder, M., Vermeulen, M., Buscaino, A., Duncan, K., Mueller, J., Wilm, M., Stunnenberg, HG., Saumweber, H., Akhtar, A. (2006). Nuclear pore components are involved in the transcriptional regulation of dosage compensation in Drosophila. *Mol Cell. 21(6):811-23*

TEAM MEMBERS

PhD students
Hofbauer, Pablo-Andres
Papai, Nora

Master students
Da Silva Lapao, Ana Sofia**
Hahn, Elisa Maria**
Leitner ,Marie**
Tavernini, Katherina
Pilz, Axel
Salic, Sejla**

Research Assistant
Mirea, Madalina**
Warczok, Katarzyna

Summer School Students
Keller, Anna-Lena
Sola Castrillo, Paloma

***left in 2017*

KAZUFUMI MOCHIZUKI

SMALL RNA-DIRECTED HETEROCHROMATIN FORMATION IN DNA ELIMINATION OF TETRAHYMENA

** Group left IMBA in 2016*

Kazufumi Mochizuki, Group Leader

The Mochizuki lab studies the formation of heterochromatin - a closed state of chromatin that is critical for gene silencing, cell differentiation and genome maintenance. Although heterochromatin maintenance is well-understood, how heterochromatin forms *de novo* is not clear. The ciliated protozoan *Tetrahymena* establishes heterochromatin *de novo* during programmed DNA elimination as the germline genome differentiates, thus providing a model for the initiation, spread and maintenance of heterochromatin.

Multiple heterochromatic loci are often clustered into a higher order nuclear architecture called a heterochromatin body. We previously found that dephosphorylation of the HP1-like protein Pdd1p is required to form heterochromatin bodies during programmed DNA elimination (Kataoka, Dev Cell 2015). Our recent work shows that the heterochromatin body component Jub4p is required for Pdd1p phosphorylation, heterochromatin body formation, and DNA elimination. Therefore, heterochromatin body formation requires phosphorylation-dephosphorylation of the core component of heterochromatin (Kataoka, PNAS 2016).

Positive feedback loops between RNAi and heterochromatin are pivotal for the maintenance of heterochromatin in various eukaryotes. We previously showed that such positive feedback loop is important for assembling heterochromatin on the eliminated sequences during programmed DNA elimination (Noto, Mol Cell 2015). Our recent work shows that the HP1-like protein Coi6p is crucial for confining heterochromatin to the eliminated sequences and for preventing ectopic DNA elimination. We suggest that Coi6p counteracts the RNAi- heterochromatin positive feedback loop at heterochromatin-euchromatin borders (Suhren, 2017 Cell Rep).

ONGOING PROJECTS

small RNA | heterochromatin | epigenetics | Tetrahymena

SELECTED PUBLICATIONS (MAX. 5)

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.*

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.*

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.*

Vogt, A., and Mochizuki, K. (2013) A domesticated piggyBac transposase interacts with heterochromatin and catalyzes DNA elimination in Tetrahymena. *PLoS Genet 8, e1002732. PMID: 24348275*

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

SELECTED GRANTS & AWARDS

The French National Research Agency (ANR), Labex Advanced Grant (2017-2021)

The French National Research Agency (ANR), ACHN Grant (2016-2020)

The Sumitomo Foundation Grant (2015-2017)

FWF Stand Alone Grant (2014-2016)

FWF Doctoral Program "RNA Biology" (2007-2016)

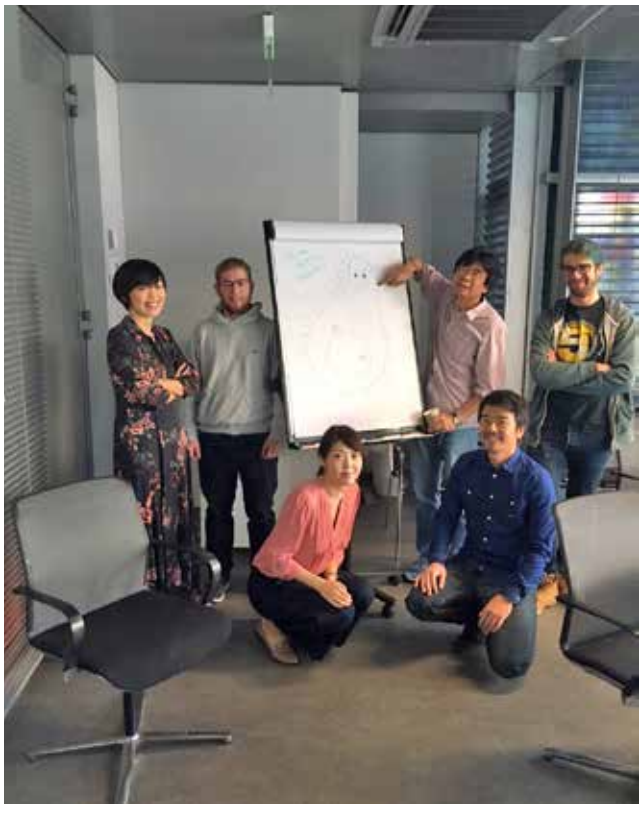
TEAM MEMBERS

PostDocs
Kataoka, Kensuke
Suhren, Jan Henrik

PhD Student
Rahms, Quentin

Master Student
Geraud, Eliot

Research Assistant
Hayashi, Azusa
Noto, Tomoko



JOSEF PENNINGER
MODELLING HUMAN DISEASE

Josef Penninger, Scientific Director

The Penninger lab aims to discover the genetic mechanisms driving development and disease. To expedite these discoveries, we recently created "Haplobank" - a biobank of over 100,000 individual haploid mouse embryonic stem (mES) cell lines targeting 16,970 genes with genetically barcoded, conditional and reversible mutations. We used Haplobank in a reverse genetic screen to uncover the temporal resolution of essential genes in mES cells, and to identify novel genes that control blood vessel development. Using Haplobank in a forward genetic screen, we discovered a novel host factor that is required for cytotoxicity by the common cold virus. (Elling et al., Nature 2017)

Our research into cancer has revealed unexpected roles for the osteoclast differentiation factor RANK. We found that elevated RANK levels in tumors associates with poor outcome in both heritable breast cancer (BRCA1) and in lung cancer. In both cases, RANK triggers an expansion of stem/progenitor cells. We showed that female sex hormones promote lung cancer progression via the RANK pathway in mice, potentially explaining the higher incidence of lung cancer in women. RANK inhibition reduced tumorigenesis in mouse models of these cancers, providing an avenue for new therapies. (Sigl et al., Cell Res 2016; Rao et al., Genes and Development 2017)

We are also investigating the biological roles of the protein modification glycosylation. We developed a novel comparative glycoproteomics platform, SugarQb, to identify intact glycopeptides from comparative proteomic datasets. We discovered two fucosylation enzymes that are required for sensitivity to the bioweapon ricin, and used SugarQb to identify proteins that carry a fucosylation-dependent sugar code for ricin toxicity. Depletion of these proteins renders cells ricin resistant. Mechanistically, reduced fucosylation triggers increased sialylation of Lewis X structures, thereby masking ricin binding sites and rendering cells resistant. (Staldmann et al., Nature 2017; Taubenschmid et al., Cell Res 2017)

KEYWORDS

embryonic stem cells | organoids | development | cancer disease | mouse models

SELECTED PUBLICATIONS

Stadlmann, J., Taubenschmid, J., Wenzel, D., Gattinger, A., Dürnberger, G., Dusberger, F., Elling, U., Mach, L., Mechtler, K., Penninger, JM. (2017). Comparative glycoproteomics of stem cells identifies new players in ricin toxicity. *Nature. 549(7673):538-542*

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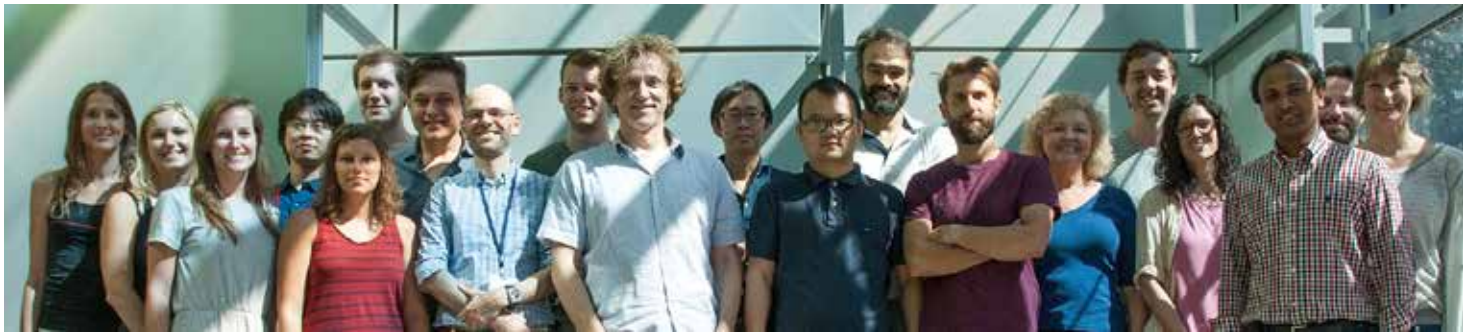
**left in 2016*
***left in 2017*



KIKUË TACHIBANA

CHROMATIN REPROGRAMMING IN TOTIPOTENT STEM CELLS

Kikue Tachibana, Group Leader

The Tachibana lab studies how chromatin is reprogrammed after fertilization to produce a totipotent one-cell embryo or zygote. We are interested in the mechanisms of zygotic reprogramming, how these modulate 3D chromatin organization and promote embryonic genome activation.

Totipotency, the developmental potential to give rise to all cell types, is achieved when egg and sperm form a zygote. How chromatin is reprogrammed to totipotency remains a central question in biology. We investigate reprogramming mechanisms and chromatin reorganisation in mammalian zygotes using mechanistic cell biology, genetics and genomics. An understanding of how cells reprogram chromatin to totipotency, a state upstream of pluripotency, has the potential to improve induced reprogramming technology and revolutionize regenerative medicine.

To illuminate how chromatin is spatially reorganized in totipotent cells, we pioneered single-nucleus Hi-C (snHi-C) (Flyamer et al., 2017). By extracting maternal and paternal nuclei from zygotes and separately subjecting these to snHi-C, we discovered that their genomes have a distinct organization from each other and other genomes. snHi-C of knockout zygotes showed that the zygotic genome folds into cohesin-dependent loops (Gassler et al., 2017).

We investigated the mechanism of active DNA demethylation using mechanistic cell biology. Erasure of sperm epigenetic memory includes loss of methylated cytosine. We provided the first genetic evidence that this DNA demethylation event proceeds by a DNA repair-based mechanism and discovered that a surveillance mechanism monitors zygotic programming (Ladstätter et al., 2016).

Lastly, we are interested in the causes of increased chromosome missegregation in ageing oocytes, the maternal age effect. We demonstrated that cohesin holds chromosomes together without renewal for months (Burkhardt et al., 2016). We aim to understand what causes cohesin loss with age and how this can be delayed to preserve female fertility.

KEYWORDS

totipotency | stem cells | chromatin organization epigenetic reprogramming | zygotes | oocytes

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SELECTED GRANTS & AWARDS

Walther Flemming Award of the German Society for Cell Biology (2017)

EMBO Young Investigator (2016)

Member of the Young Academy of the Austrian Academy of Sciences (2014)

TEAM MEMBERS

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NOELIA URBÁN

SYSTEMIC REGULATION OF ADULT NEUROGENESIS

*Group at IMBA since 10/2017

Noelia Urbán, Group Leader

The Urbán lab is interested in adult neurogenesis. Reduced activity of adult hippocampal stem cells (AHSCs) is linked to impaired memory as well as affective and mood disorders, including depression.

We use in vitro models of neural stem cell quiescence to explore the molecular mechanisms underlying changes in AHSC behavior. Quiescence is essential for long-term maintenance of adult stem cells. We recently discovered that the E3-ubiquitin ligase Huwe1 destabilizes a proactivation transcription factor in proliferating AHSCs, and is required for their return to quiescence. Failing to return to quiescence depletes the proliferative AHSC pool. Thus, maintenance of hippocampal neurogenesis depends on the return of AHSCs to a transient quiescent state through the rapid degradation of a key proactivation factor (Urban et al., 2017 Science).

Neurogenesis is regulated by physiological, pathological and pharmacological stimuli, such as exercise, diet, stress or antidepressants. We want to determine how changes in systemic metabolism affect AHSCs. We use mouse models of ageing, diabetes and caloric restriction in combination with transgenic mice to monitor the response of AHSCs to metabolic changes.

Finally, by using patient-derived lines we will elucidate how mutations and genetic variation affect AHSC function. This approach also enables high-throughput screening to identify drugs that modulate AHSC functions. We are also investigating how stem cells interact with the niche. This will allow us to further improve our in vitro model by adding niche-like signals and structures, including 3D-scaffolding and local delivery of signaling.

Understanding the crosstalk between metabolism and the regulation of AHSCs will help us to predict and prevent neurological disorders, and perhaps even to devise strategies that reverse AHSC failure.

KEYWORDS

brain | stem cells | niche | metabolism | memory emotions

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SELECTED GRANTS & AWARDS

Young Investigator Award 2017, Stem Cell Center, Lund, Sweden.

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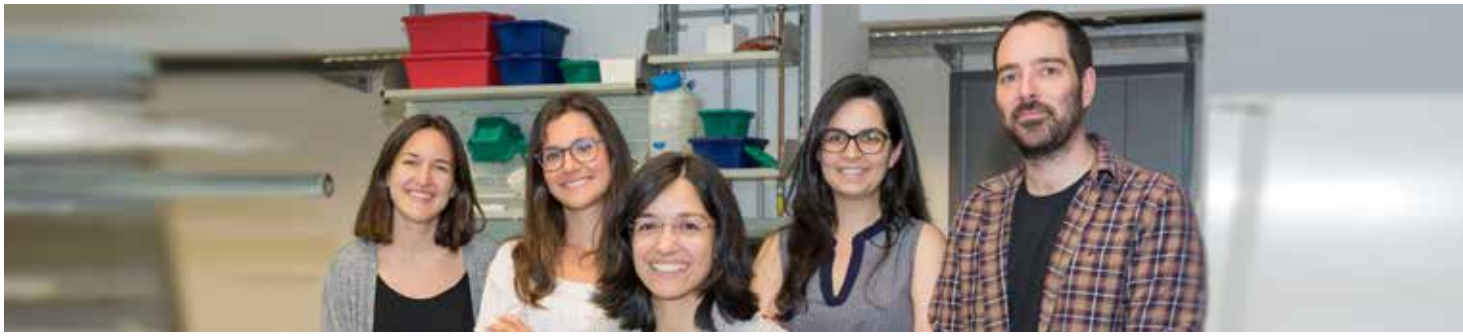

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MOCHIZUKI GROUP

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SEMINAR SPEAKERS 2016/17

03.02.16 Petr Svoboda
Institute of Molecular Genetics, Prague
A sobering look at the mammalian RNAi pathway

04.02.16 Andres Aguilera
Andalusian Center for Molecular Biology and Regenerative Medicine
Crosstalk between RNA processing and chromatin remodelling as a modulator of genome integrity

11.02.16 Ivan Dikic
Goethe University Frankfurt, Institute of Biochemistry
Ubiquitin and Autophagy Networks in Health and Disease

12.02.16 Armel NICOLAS
University of Dundee
A Cell Biologist's Unexpected Journey into the Realms of Proteomics and Data Analysis

18.02.16 Misha Ahrens
Janelia Farm
Neural mechanisms of spontaneous and learned behavior in zebrafish

25.02.16 Adrian Hill
University of Oxford
Vaccine design for malaria and Ebola

03.03.16 David Ish-Horowicz
University College London and Oxford University
Post-transcriptional regulation during Drosophila neurogenesis

08.03.16 Lars Nitschke
University of Erlangen
Siglecs: inhibitory receptors on immune cells

17.03.16 Doris Bachtrog
University of California, Berkeley
Chromatin sinks and sex-specific aging in Drosophila: a role for the Y chromosome

18.03.16 Paul Sondel
University of Wisconsin School of Medicine and Public Health
Intratumoral hu14.18-IL2 combination immunotherapy, to activate innate and adaptive immunity as an in situ vaccine

24.03.16 Yaniv Erlich
Columbia University
Genetic media

31.03.16 Wade Harper
Harvard Medical School
mitochondrial quality control

07.04.16 Nils A. Kulak
Max Planck Institute of Biochemistry
Streamlined high-throughput technologies for clinical proteomics

07.04.16 Blake Meyers
Danforth Center, St. Louis
Phased siRNAs in plant reproductive organs

13.04.16 Dominik Paquet
The Rockefeller University
iPS and CRISPR/Cas: a human way to tackle dementia

14.04.16 John Diffley
The Francis Crick Institute, Clare Hall Laboratory
Reconstitution of chromosome replication

18.04.16 David Teis
Innsbruck Medical University
Dynamics of the ESCRT Machinery and its Role in Cellular Homeostasis

19.04.16 Harald Stenmark
University of Oslo
From endosomes to the nucleus: ESCRT proteins in membrane scission

19.04.16 Philipp Jost
TU München
Evasion of cell death as a milestone in tumorigenesis: the contribution of necrptosis

28.04.16 Alex Bortvin
Carnegie Institution for Science
Sex-specific strategies and outcomes of transposon silencing in mouse germ cells

12.05.16 Jesper Svejstrup
Francis Crick Institute
The transcription-related DNA damage response

23.05.16 Ludovic Vallier
Stem Cell Institute, University of Cambridge
Human pluripotent stem cells to study disease and early development

30.05.16 Petra Gutenbrunner
Wellcome Trust Sanger Institute, Cambridge
Computational Proteomics Pipeline for Phosphorylation Site-Localisation Identification

02.06.16 Simon Alberti
MPI-CBG Dresden
Organizing living matter: the emerging role of phase transitions in cell biology and disease

07.06.16 Marius Wernig
Stanford University School of Medicine
Direct epigenetic reprogramming into the neural lineage

10.06.16 Gerald Shadel
Yale University School of Medicine
Mitochondrial Stress Signaling in Disease, Aging and Immunity

14.06.16 Christine Marizzi
DNA Learning Center, Cold Spring Harbor
Citizen Science Infrastructure-Urban Barcoding and BioArt at the Cold Spring Harbor Lab DNA Learning Center

16.06.16 Ali Brivanlou
Rockefeller University
Self-understanding of Self-organization

30.06.16 Lukas Dow
Sandra and Edward Meyer Cancer Center
Understanding tumor initiation and progression using in vivo gene silencing and genome editing

13.07.16 Gerlinde Wernig
Stanford University School of Medicine
A unifying mechanism for different fibrotic diseases

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University of Massachusetts
Interplay between RNA and chromatin remodelling factors in embryonic stem cells

28.07.16 Lionel Christiaen
New York University
Regulation of fate specification and cell behavior in the cardiopharyngeal lineage of a simple chordate

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Cardoso Lab, Technical University Darmstadt
Regulation of Tet proteins by methyl-CpG binding domain proteins

29.08.16 Tuomas Tammela
Koch Institute for Integrative Cancer Research at MIT
Cancer stem cell niches in Kras-driven carcinomas

15.09.16 Glen Barber
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STING Signaling and the Control of Infectious Disease, Inflammation, and Cancer

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Waseda University
Epigenetic regulation of genomic DNA via chromatin structure

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Karolinska Institutet
Biochemistry in the living cell

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University of Pennsylvania
Biology of bedtime: Understanding circadian rhythms and sleep

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Research Policy Advisor, Sanger Institute
From Pemberley to Eugenics: the debate on editing the genome+

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Harvard University
4D chromosome dynamics: commonalities from E.coli to mammalian cells

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EPFL Lausanne
Transposable elements, polydactyl proteins and the genesis of human-specific transcription networks

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FMI Basel
Hijacking the ubiquitin ligase system for a good cause

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Stanford University School of Medicine
ATP-dependent chromatin remodeling in cancer: new insights into altered Polycomb regulation

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Princeton University
Bacterial Quorum Sensing and its Control

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Max Planck Institute for Biophysical Chemistry
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15.12.16 Xiaole Shirley Liu
Dana Farber Cancer Institute
Computational biology in CRISPR screens and cancer immunology

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WPI Immunology Frontier Research Center, Osaka University
Exposure of phosphatidylserine in apoptotic cells

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MFPL Vienna
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Brillouin Light Scattering Microspectroscopy for Biological and Biomedical Research

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MDC Berlin
Knocking out circRNAs and reconstructing tissues from single-cell sequencing

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Regulatory Protein-RNA Interactions

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Rapid evolution of the cancer karyotype

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Genome organization in single cells

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Visualization of large and dynamic macromolecular complexes at high-resolution by cryo-EM

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Genome transcription: from molecules to systems

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Structural dynamics of translation elongation factor EF-Tu on and off the ribosome

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University of St. Andrews
Structural biology guided enzymology: making highly modified peptides macrocycles

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UCSF
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National Institute of Cardiovascular Research (CNIC)
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Centro de Biología Molecular Severo Ochoa
Factors linking cell proliferation potential, genome replication and chromatin dynamics

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University of California, San Diego
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Cells escape from a mitotic arrest via a stochastic process

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Role of IAP ubiquitin ligases in cell death and cell cycle regulation, and its application to protein knockdown technology

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University of California, San Diego
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Department of Chemistry, University of Calgary
Application of metallomics tools to probe and modulate metal exposure-disease relationships

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UCSF
Protein folding as an allosteric strategy: the yin and yang of chaperone-mediated client activation

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Department of Molecular Evolution and Development, University of Vienna
Insights into the evolution of muscles from the diploblastic sea anemone Nematostella vectensis

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TU Delft
Single-molecule approaches to unravel the mechanism of the condensin complex

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Helmholtz-Zentrum Berlin
Crystallographic fragment-screening: our activities at the Helmholtz-Zentrum Berlin

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Just Flexible Linkers? The Structural and Functional Properties of Intrinsically Disordered Protein Regions

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At the intersection of vertebrate DNA replication and repair

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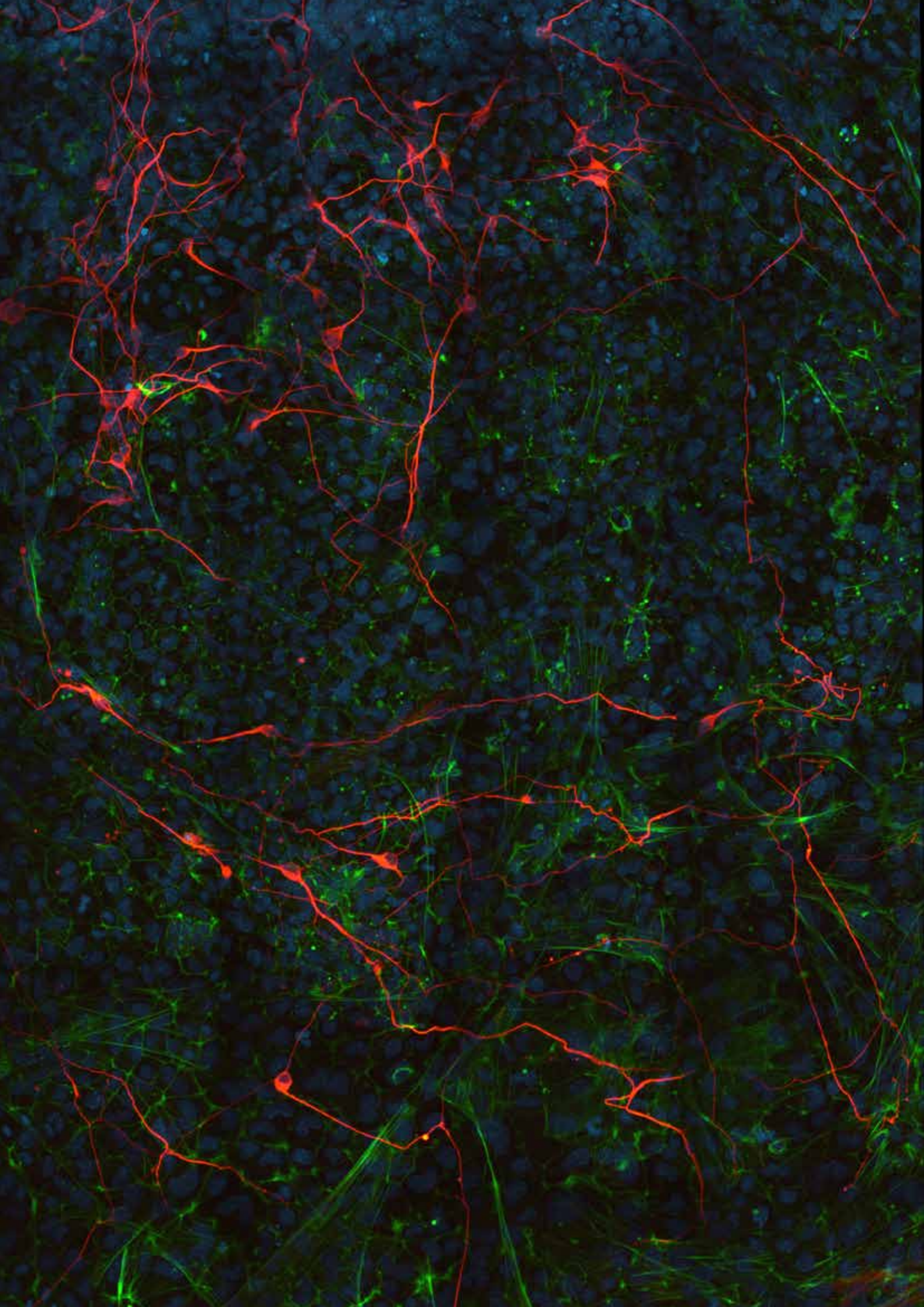

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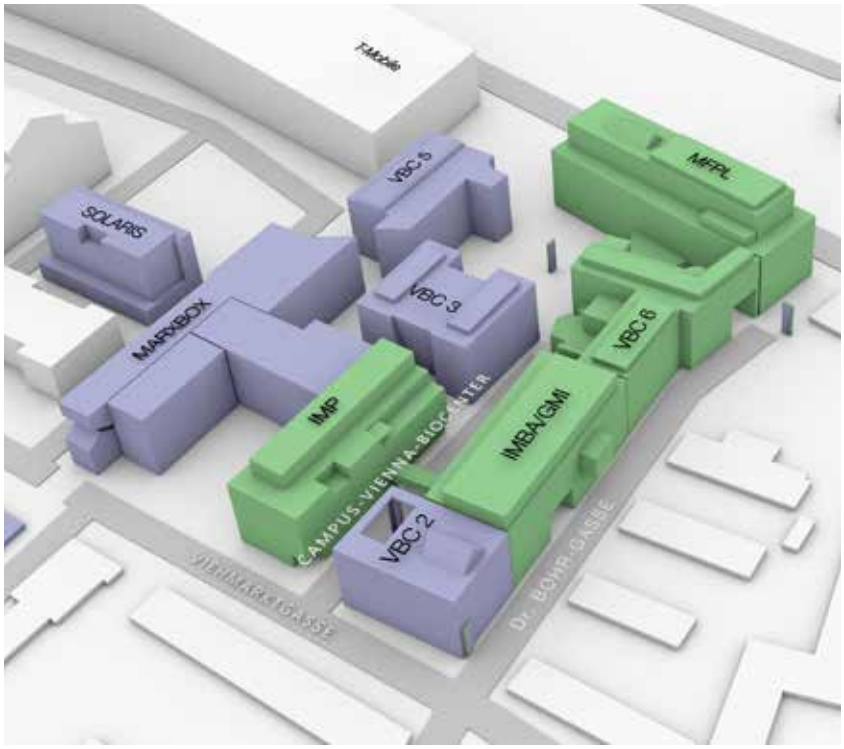

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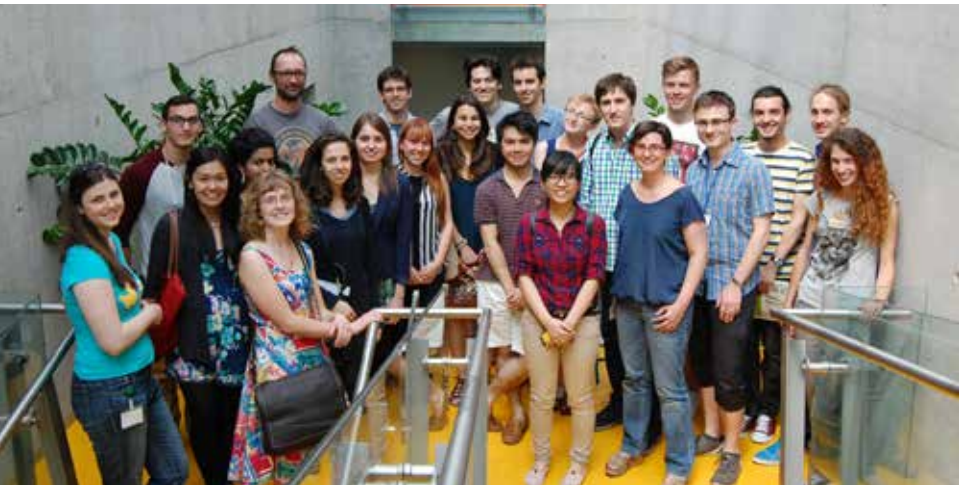

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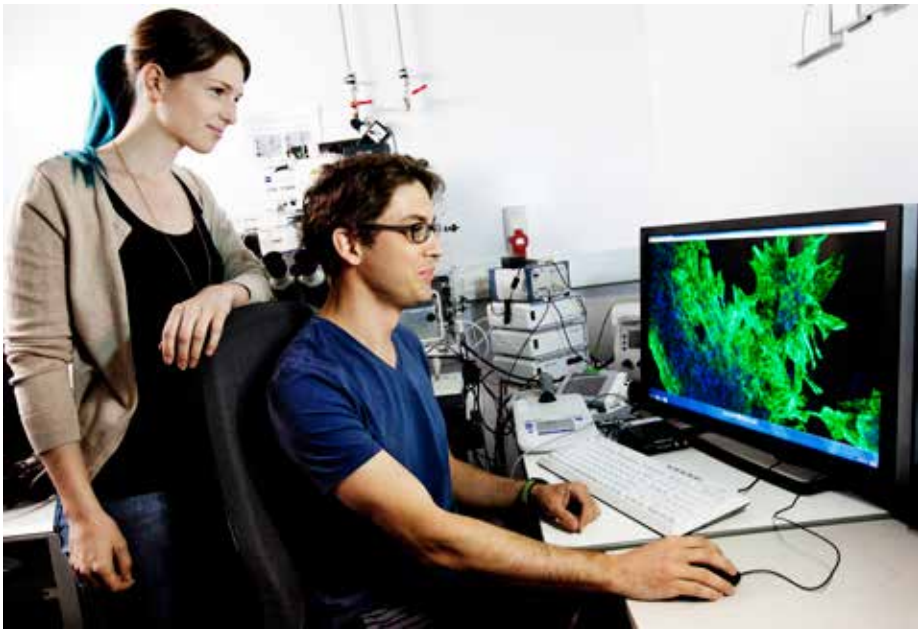

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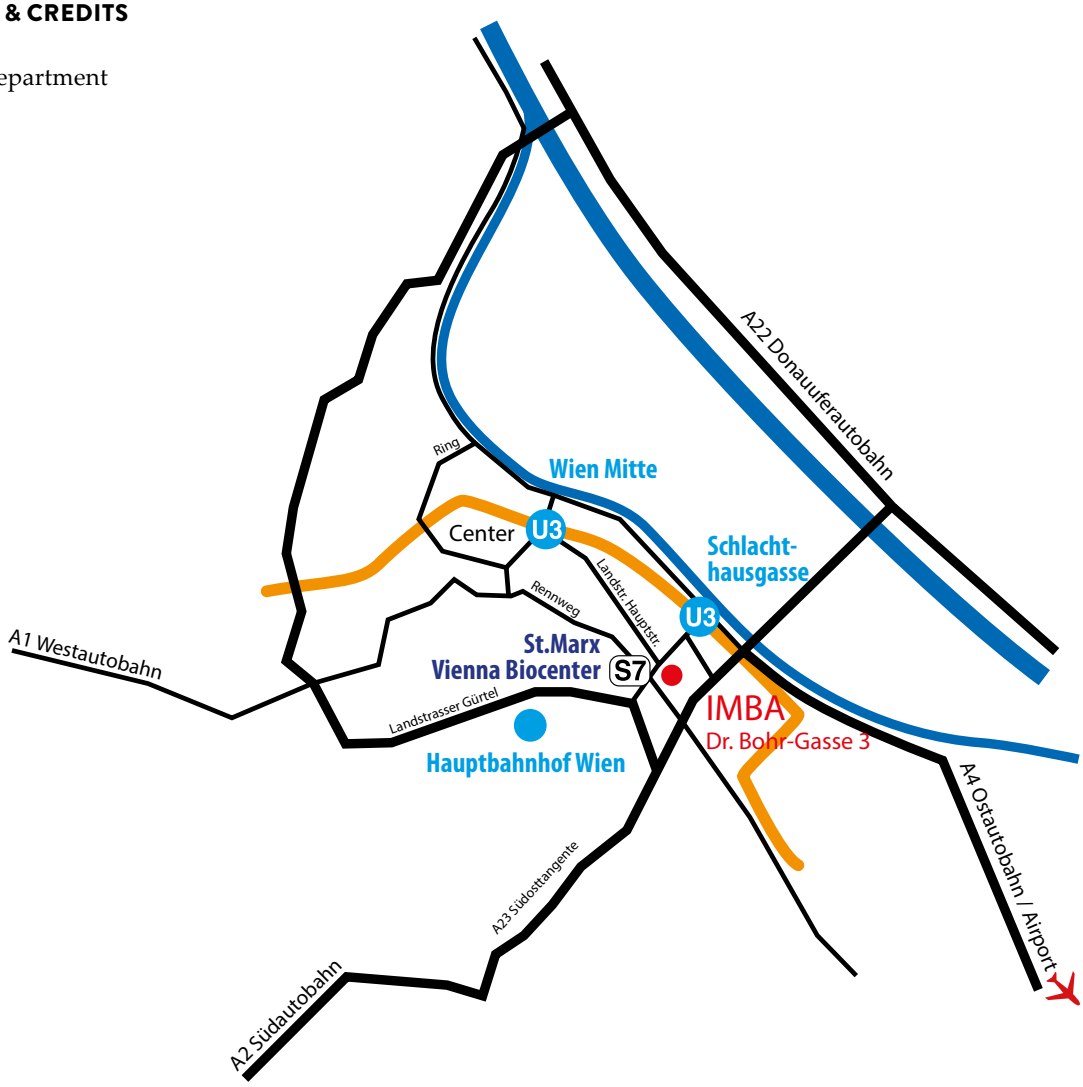

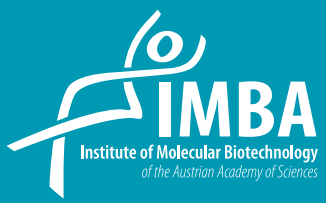
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