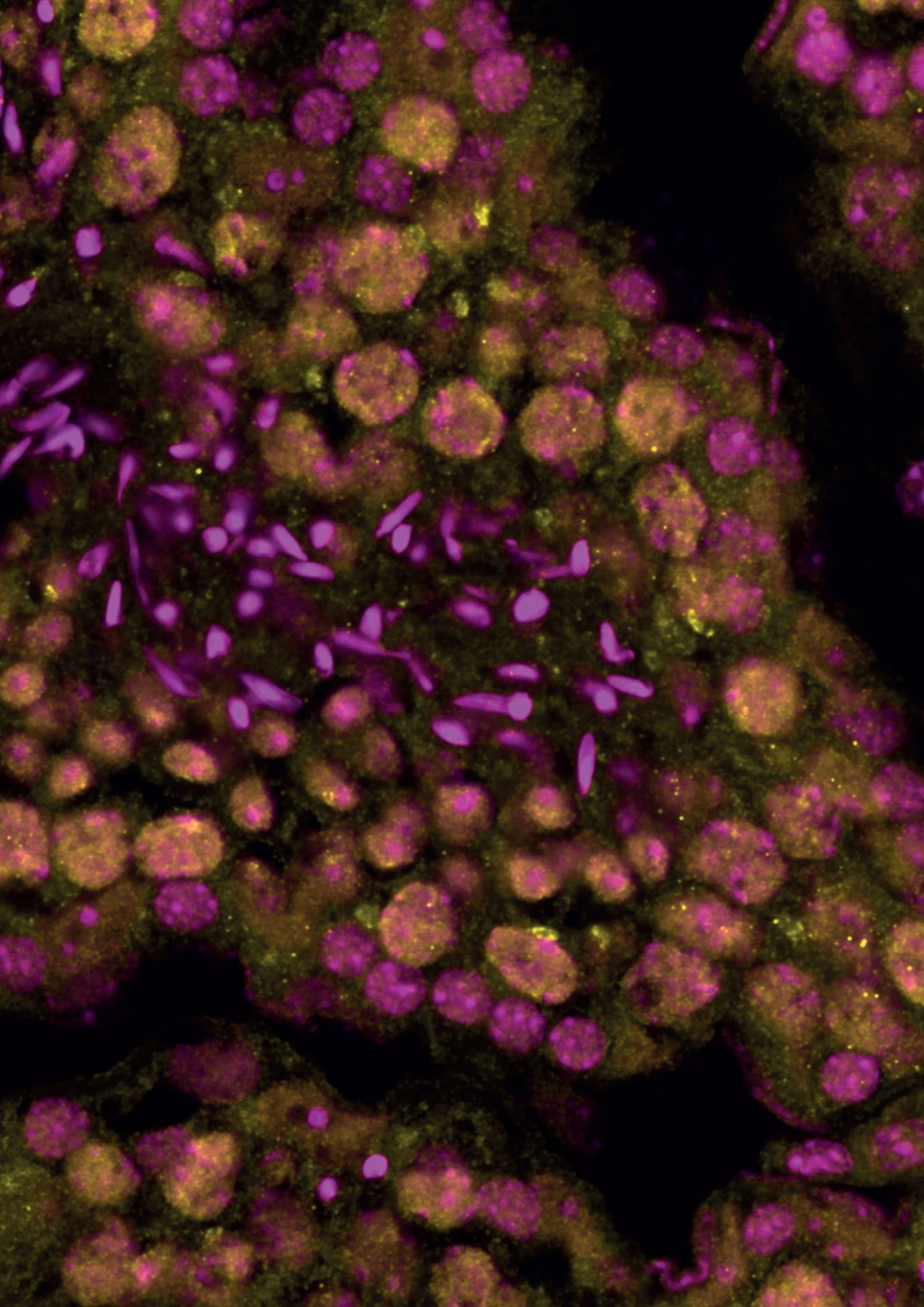


ANNUAL REPORT 2023

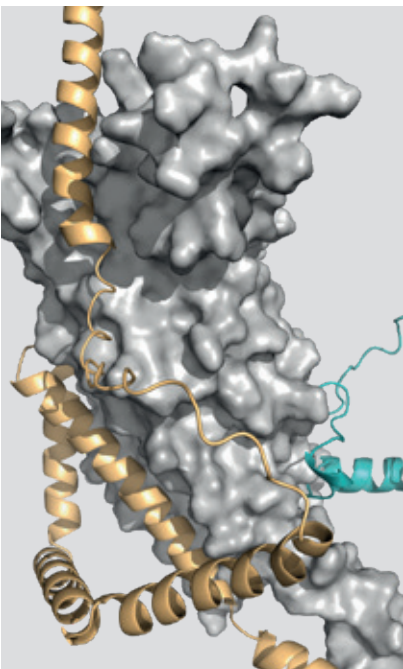


ANNUAL REPORT 2023

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Foreword

Welcome to IMB's 2023 Annual Report. It has been an eventful year with exciting, high-impact publications, as well as the establishment of major new initiatives.



New initiatives

Firstly, we were delighted to announce that the DFG renewed its funding of the Research Training Group (RTG) on “Gene Regulation in Evolution” (GenEvo), a collaboration between Johannes Gutenberg University Mainz (JGU) and IMB. This initiative is led by Susanne Foitzik at JGU and myself, and investigates how complex and multi-layered gene regulatory systems have both evolved and driven evolution. GenEvo will be granted an additional €7 million until June 2028.

Secondly, the DFG approved €8.3 million in funding for a new RTG on “R-loop Regulation in Robustness and Resilience” (4R) until 2028. 4R brings together research groups from IMB, JGU and the University Medical Center Mainz (UMC) and is led by Brian Luke (IMB/JGU) and myself. This initiative will delve into the profound impact of R-loops on the orchestration of complex cellular processes that promote organismal robustness and resilience.

Furthermore, Rhineland-Palatinate’s Ministry of Science and Health provided €1.2 million to fund the new Centre for Healthy Ageing (CHA) Programme for Clinician Scientists (CHANCE) until 2026. This joint programme between IMB, JGU and UMC is led by Christof Niehrs (IMB), Wolfram Ruf (UMC) and Klaus Lieb (UMC), and will fund clinician scientists to help them establish independent research programmes to study ageing and age-related diseases.



New papers & grants

Our researchers were highly productive, publishing 111 papers this year. We are especially proud of our three *Nature* papers: “Visualizing the disordered nuclear transport machinery *in situ*” by Edward Lemke’s group, “The sex-specific factor SOA controls dosage compensation in *Anopheles* mosquitoes” by Claudia Keller Valsecchi’s group, and “piRNA processing by a trimeric Schlafen-domain nuclease” by my group. In regards to grants, our scientists raised more than €6 million in additional research funding. Notable mentions include an ERC Consolidator Grant for Dorothee Dormann, an ERC Starting Grant for Stamatis Papatthasiou and a Heisenberg position awarded to Julian König.

Notable events

IMB continued to expand its research focus on cellular and organismic ageing with high-profile events.

In October, IMB hosted a Gutenberg Workshop on Longitudinal Cohorts in Healthy Ageing and Disease Prevention. This workshop welcomed 65 scientists, including 17 speakers from Germany, Europe and the US, and highlighted cutting-edge methods to study the mechanisms of health and disease in ageing human populations.

In June, we also hosted a public lecture on “Rejuvenation is possible: the latest findings in cell biology” with Nina Ruge, a well-known host of German TV programmes and magazine author. Nina discussed the newest findings in ageing research and their significance with leading experts at IMB and JGU together with Clemens Hoch (Minister for Science and Health of the State of Rhineland-Palatinate).

The International Summer School also took place in-person again for the first time since the COVID-19 pandemic,

bringing 12 undergraduate participants from 8 countries to IMB. Furthermore, IMB held a Postdoc Symposium and Alumni Career Event, which brought back some of our amazing alumni to share their achievements with us.

Staff changes

IMB’s vibrant research community also continues to grow and thrive. We welcomed three new group leaders in 2023: Stamatis Papatthasiou, who studies how errors in mitosis contribute to DNA damage and cancer development, Siyao Wang, who investigates whether DNA damage causes transgenerational effects on longevity, and Sina Wittmann, who is an expert on how cells use intrinsically disordered proteins and phase separation to activate gene expression.

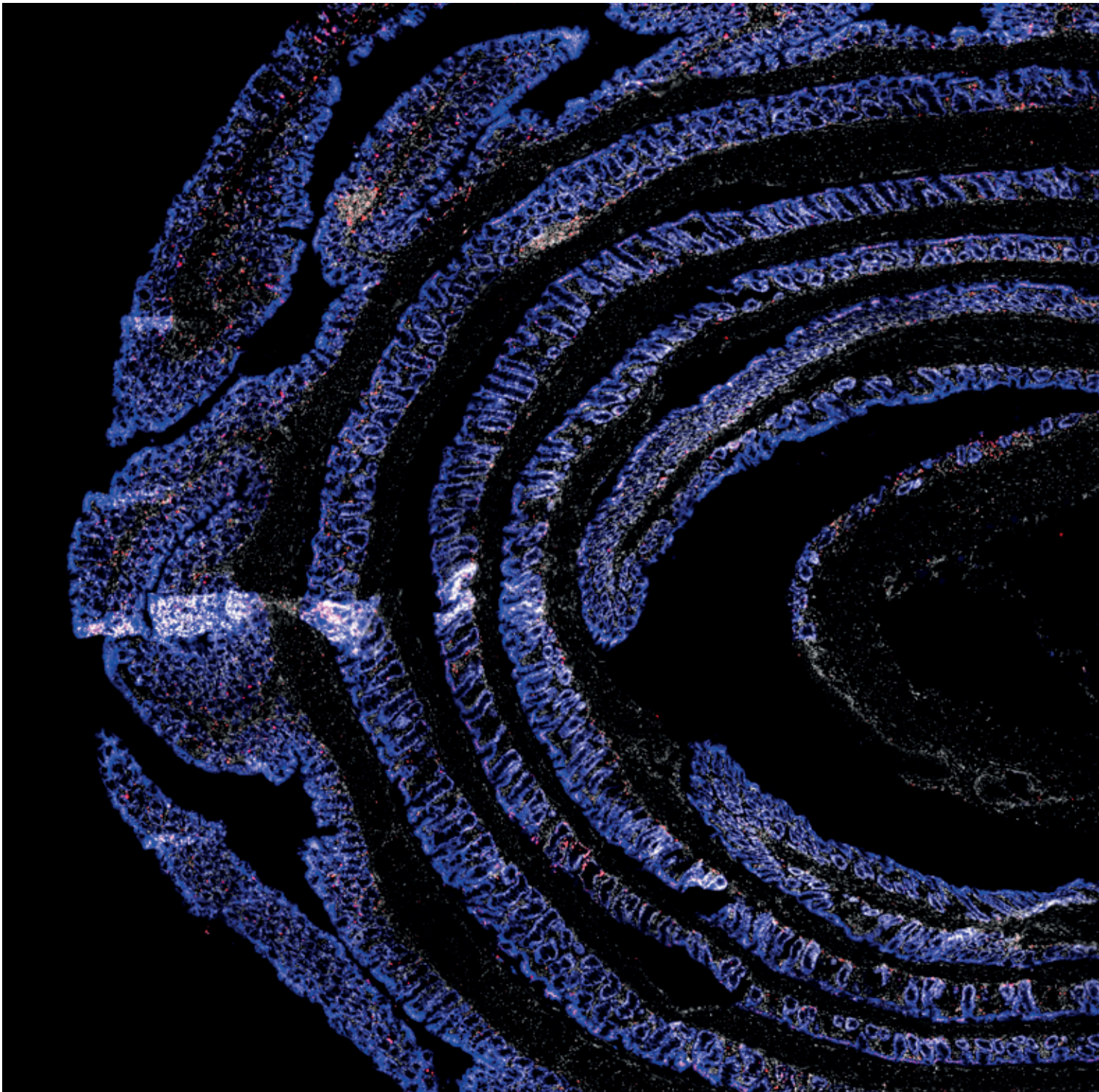
Our International PhD Programme (IPP) now includes 211 students from 44 countries and celebrated 22 defences this year.



As we look back on a productive and successful year, I would like to finish as always by thanking the Boehringer Ingelheim Foundation and the State of Rhineland-Palatinate for their continued support and generous funding, and the members of our Scientific Advisory Board, whose advice and feedback have helped IMB develop into the powerhouse it is today. I would also like to thank all my colleagues for their contributions to IMB’s successes this year.

René Ketting
Executive Director

Research Groups



Joan Barau	8	Christof Niehrs	32
Peter Baumann	10	Jan Padeken	34
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Joan Barau

“*We decipher how transposons impact evolution, development and disease.*”



POSITIONS HELD

Since 2019 Group Leader, Institute of Molecular Biology (IMB), Mainz

2013 – 2019 Postdoc, Institut Curie, Paris

EDUCATION

2012 PhD in Genetics and Molecular Biology, University of Campinas

2005 BSc in Biology, University of Campinas

GROUP MEMBERS

Staff Scientist Liana Marengo

PhD Students Ishita Amar, Styliani Eirini Kanta, Jessica Leissmann, Srinivasa Abishek Prakash, Anna Szczepinska

Lab Manager Violeta Morin

Student Assistants Hannah Gonzalez Dammers, Julia Isabet Zamora Interiano

OVERVIEW

Transposable elements, or TEs, are abundant genomic repeats linked to genome instability and regulatory perturbations that can lead to phenotypic consequences. In addition, TE-encoded proteins can be co-opted into functional components of our genomes, and their genomic sequences into elements that instruct genomic regulation. Our lab's work focuses on understanding transposon biology as a proxy to uncover new mechanisms that affect gene regulation, genome stability and inheritance. In the past year, our lab has been working on three fronts aimed at discovering (i) how transposons are targeted for epigenetic silencing in mouse germ cells, (ii) how transposon sequences and their epigenetic status impact their regulatory potential in mouse germ cells, and (iii) novel regulators of the transposon 'life cycle' in pluripotent and differentiated stages of mammalian development.

RESEARCH HIGHLIGHTS

How transposons are targeted for epigenetic silencing in mouse germ cells

Germ cells have the demanding task of distinguishing 'normal' functioning genes from active TEs, which should be inactivated. This is achieved by processing TE mRNAs into small PIWI-interacting RNAs (piRNAs). Production of piRNAs allows germ cells to specifically degrade TE mRNA and guide nuclear silencing factors to active TE loci, which leads to stable, life-long epigenetic silencing by DNA methylation. We now know that the final, stable step of TE transcriptional silencing in germ cells depends on the epigenetic modifier DNMT3C. In the past year, we have experimentally connected DNMT3C with the core components of the piRNA pathway. We are now focusing on understanding the mechanisms of piRNA-guided DNA methylation and how

chromatin modifications and nuclear organisation impact this process.

How transposon-induced DNA damage can trigger development

Transposons live dual lives in mammalian genomes: an individual transposon can act as a developmentally important enhancer of gene expression, but it can also promote its own transposition, with potentially dire consequences for genome stability. We hypothesise that DNA methylation at TE promoters can tip the scale towards either of these opposing roles by impacting the binding of regulatory factors and interactions with readers and writers of chromatin modifications. In the past year, we learned a lot about DNA-binding factors that may drive the activity of a TE as a selfish promoter or an enhancer of gene expression. We are now investigating how these factors are important for genome regulation during development and how TEs exploit them for their selfish activity.

Evolution of transposon-derived protein-coding genes and their functions

Genomes have many protein-coding genes whose origin can be traced to transposable elements. Throughout evolution, these have contributed to innovations that quickly became essential in modern humans. An example is the RAG transposases, which are key to the V(D)J recombination process

that generates antibody diversity in the genome of immune cell progenitors. Thanks to the “domestication” of these transposases, vertebrates have an adaptive immune system that allows them to fight recurrent infections. In our lab, we recently discovered one domesticated transposase of unknown function. Despite 500 million years of evolution, its ability to cut DNA has been kept and its current physiological function is unknown. We are studying this gene and its functions, and are very excited about the biological and biotechnological implications that may follow.

FUTURE DIRECTIONS

The achievements outlined above will allow us to dive deeper into mechanistic studies focused on understanding how epigenetic settings are laid out at TE promoters in mouse germ cells and how this impacts the behaviour of germ cells during gametogenesis. The lab has developed and optimised tools for applying epigenomics to very specific cell types across gametogenesis. We will develop mouse models to couple these genome-wide studies with functional genomic studies. We are also excited to continue exploring the relationship between TEs and DNA damage and repair using cell lines in which TE activity can be controlled and hope to present exciting novel data about this relationship in stem cells in the upcoming year.

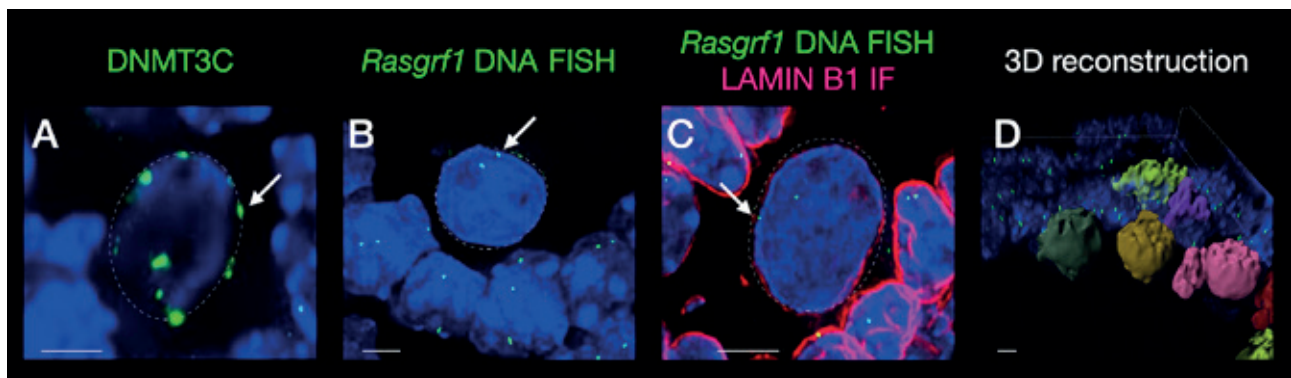


Figure 1. DNMT3C localisation within the nucleus provides clues about the mechanisms of piRNA-guided DNA methylation. A) DNMT3C protein concentrates as foci that form close to the nuclear lamina during the last stages of *de novo* methylation. B) DNA FISH of a DNMT3C target locus, *Rasgrf1*, as a proxy to track DNMT3C targets. C) Immuno-FISH showing the nuclear localisation of *Rasgrf1* and staining of LAMIN B1. D) 3D reconstruction of the nuclear volume after LAMIN B1-*Rasgrf1* immuno-FISH as a tool to quantify the proximity of DNMT3C targets to the nuclear lamina.

SELECTED PUBLICATIONS

Dura M, Teissandier A, Armand M, Barau J, Lapoujade C, Fouchet P, Bonneville L, Schulz M, Weber M, Baudrin LG, Lameiras S and Bourc'his D (2022) DNMT3A-dependent DNA methylation is required for spermatogonial stem cells to commit to spermatogenesis. *Nat Genet*, 54:469-480

Mosler T, Conte F, Longo GMC, Mikicic I, Kreim N, Möckel MM, Petrosino G, Flach J, Barau J, Luke B, Roukos V and Beli P (2021) R-loop proximity proteomics identifies a role of DDX41 in transcription-associated genomic instability. *Nat Commun*, 12:7314

Prakash SA and Barau J (2021) Chromatin profiling in mouse embryonic germ cells by CUT&RUN. Pages 253-264 in: *Epigenetic reprogramming during mouse embryogenesis*. *Methods in Molecular Biology*, vol 2214 (eds. Ancelin K & Borensztein M), Springer US, New York

Peter Baumann

“*We study ageing using molecular and computational tools.*”



POSITIONS HELD

- Since 2023** Founding Director, Institute for Quantitative and Computational Biosciences (IQCB)
- Since 2021** Director, Centre for Healthy Ageing (CHA), Mainz
- Since 2018** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
- Since 2017** Alexander von Humboldt Professor, Johannes Gutenberg University Mainz (JGU)
- 2013 - 2019** Professor, Kansas University Medical Center
- 2013 - 2018** Investigator, Howard Hughes Medical Institute, Kansas City
- 2013 - 2018** Priscilla Wood-Neaves Endowed Chair in the Biomedical Sciences, Stowers Institute for Medical Research, Kansas City
- 2013 - 2018** Investigator, Stowers Institute for Medical Research, Kansas City
- 2009 - 2013** Early Career Scientist, Howard Hughes Medical Institute, Kansas City
- 2009 - 2013** Associate Professor, Kansas University Medical Center
- 2009 - 2012** Associate Investigator, Stowers Institute for Medical Research, Kansas City
- 2004 - 2009** Assistant Professor, Kansas University Medical Center
- 2002 - 2008** Assistant Investigator, Stowers Institute for Medical Research, Kansas City
- 1998 - 2002** Research Associate, University of Colorado, Boulder

EDUCATION

- 1998** PhD in Biochemistry, University College London
- 1994** MPhil, University of Cambridge

GROUP MEMBERS

Postdocs Zoe Gill, Lili Pan, Valentine Patterson

PhD Students Wafa Abuhashem, Nadine Bobon, Nathaniel Deimler, David Ho, Yu-Chia Ku, Abinaya Manivannan, Alex Orioli, Jayaprakash Srinivasan

Project Manager Yasmin Luke

Technician Elisa Thomas

Animal Caretaker Martin Fahr

Personal Assistant Thomas Faust

OVERVIEW

The maintenance and protection of telomeres, the nucleoprotein structures at the ends of linear chromosomes, has far-reaching implications for age-related diseases including cancer, cardiovascular disease and immune senescence. Furthermore, genetic defects in the machinery that maintains and replenishes telomeric DNA cause diseases now referred to as telomere biology disorders (TBD). At the cellular level, TBDs are characterised by premature loss of replicative potential, accumulation of senescent cells in tissues and stem cell exhaustion. Phenotypically, TBDs cause many symptoms of premature ageing. Studying the mutations that underlie TBDs thus provides valuable insights into the changes in the molecular and cellular processes that lead to the functional decline that is a hallmark of ageing. Our group studies two key aspects of telomere maintenance: (i) the biogenesis and regulation of the enzyme telomerase, and (ii) the mechanistic basis of chromosome end protection. We are guided by the conviction that understanding telomerase biogenesis will help us identify compounds that modulate telomere length. Telomerase inhibitors will have therapeutic uses to limit tumour cell proliferation, and compounds that stimulate telomerase can boost the proliferation of desired cell populations, such as bone marrow stem cells. The latter could not only help patients with telomerase insufficiency, but may also counteract manifestations of normal ageing, such as increased susceptibility to infections and diminished response to vaccinations. To reach these goals, we employ computational, molecular and cell biological approaches, and have built a network of collaborators to examine telomere dynamics in the contexts of immune senescence, frailty and ageing of the enteric nervous system.

RESEARCH HIGHLIGHTS

Telomerase biogenesis and regulation

Progressive telomere shortening is intrinsically linked to cell division via the “end replication problem” and critically short telomeres trigger cellular senescence, thus preventing further proliferation and telomere shortening. Mechanisms that replenish telomeric sequences are a double-edged sword: on one hand, they extend the replicative lifespan of a cell population and are vital for tissue renewal, but on the other hand, replenishing telomeres permits the continued proliferation of cells (including malignant cells) and lack of telomerase activity is a powerful mechanism of tumour suppression. Consequently, telomere addition is tightly controlled in many multicellular organisms including humans. Important layers of control affect the biogenesis of telomerase from transcription and RNA processing to complex assembly and recruitment to telomeres. Our group has studied these processes in fission yeast and human cells and has established a paradigm for telomerase biogenesis. Continuing this work, we recently identified three additional factors and deciphered their roles in the telomerase assembly process.

In collaboration with the Human Genetics Department at the University Medical Center, we are studying mutations responsible for telomere biology disorders, including dyskeratosis congenita and idiopathic pulmonary fibrosis. Combining clinical with cell biological, biochemical and bioinformatic analysis, we recently characterised a new class of telomerase mutations that affects telomere maintenance in two ways: (i) diminished activity and processivity causes accelerated telomere shortening, and (ii) incorporation of non-canonical repeat sequences affects shelterin binding and may increase genome instability driven by impaired chromosome end protection.

Although telomere length is frequently used as a biomarker in the context of ageing and stress and to predict various disease outcomes, reliably and accurately measuring telomere length has been mired by technical challenges. Classical approaches require large amounts of genomic DNA or fresh tissue, and alternative approaches suffered from issues of reproducibility and reagent availability. This has hampered the acquisition of longitudinal and large-scale datasets in the context of cohort studies. Third-generation sequencing technologies promise to reshape the field by providing a low-cost, accurate and reliable method of determining telomere length (Figure 1). Over the past year, our group has invested considerable resources in developing telomere enrichment and sequencing protocols, as well as base calling and analysis pipelines. We are now applying this in the context of the Healthy Body and Brain Ageing (HBBA) and Biomarkers of Frailty projects.

FUTURE DIRECTIONS

To gain a comprehensive understanding of human telomerase biogenesis, regulation and turnover, present studies are aimed at identifying additional factors and using biochemical and genetic means to elucidate their functions. Unravelling how telomerase is made and regulated has led us to several exciting questions: Can we modulate telomerase activity by manipulating RNA processing? Is increasing telomerase levels a genuine path toward treating premature ageing diseases? Does increased telomerase activity contribute to resilience and delay the onset of degenerative processes associated with normal ageing? Complementing these avenues of inquiry are projects to understand how chromosome end protection is accomplished across a naturally occurring

telomere length distribution and how different repair pathways engage denuded chromosome ends and contribute to genome instability.

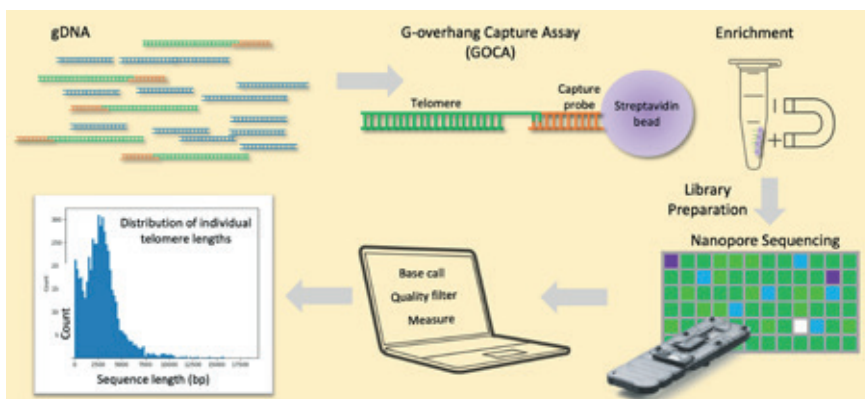


Figure 1. Schematic of telomere enrichment, nanopore sequencing and computational analysis to derive chromosome arm-specific telomere length information at single nucleotide resolution. Telomeres are enriched by G-overhang capture (GOCA), followed by barcoding, sequencing adapter ligation and sequencing on Oxford Nanopore Technology flow cells. Bioinformatic analysis yields individual telomere length measurements.

SELECTED PUBLICATIONS

Cole CJ, Baumann DP, Taylor HL, Bobon N, Ho DV, Neaves WB and Baumann P (2023) Reticulate phylogeny: a new tetraploid parthenogenetic whiptail lizard derived from hybridization among four bisexual ancestral species of *Aspidoscelis* (Reptilia: Squamata: Teiidae). *Bull Museum Comp Zool*, 163:247-279

Páez-Moscoso DJ, Ho DV, Pan L, Hildebrand K, Jensen KL, Levy MJ, Florens L and Baumann P (2022) A putative cap binding protein and the methyl phosphate capping enzyme Bin3/MePCE function in telomerase biogenesis. *Nat Commun*, 13:1067

Pan L, Tormey D, Bobon N and Baumann P (2022) Rap1 prevents fusions between long telomeres in fission yeast. *EMBO J*, 41:e110458

Petra Beli

“*We use quantitative proteomics to study stress-dependent proteome remodelling during ageing.*”



POSITIONS HELD

- Since 2020** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Full Professor of Quantitative Proteomics, Johannes Gutenberg University Mainz (JGU)
- 2013 – 2020** Emmy Noether Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2010 – 2013** Postdoctoral Fellow, Novo Nordisk Foundation Center for Protein Research, University of Copenhagen

EDUCATION

- 2011** PhD in Biology, Goethe University Frankfurt
- 2007** MSc in Molecular Biology, University of Zagreb

GROUP MEMBERS

- Postdocs** Thorsten Mosler, Aldwin Suryo Rahmanto
- PhD Students** Georges Blattner, Christian Blum, Francesca Conte, Caio Almeida Batista De Oliveira, Rebecca Hobrecht, Ekaterina Isaakova, Ivan Mikicic, Claudia Scalera, Eric Schmitt, Nadia da Silva Fernandes Lucas
- Master Students** Lukas Graf, Magdalena Schachtl-Rieß
- Lab Manager** Katharina Mayr
- Personal Assistant** Ute Sideris

OVERVIEW

Human cells are exposed to stress induced by pollutants from the environment, as well as compounds generated during normal metabolism, such as reactive aldehydes. Ageing is accompanied by a deterioration of proteome homeostasis, which is characterised by an accumulation of non-functional proteins and deregulated cellular responses to stress. At the molecular level, aged cells show alterations in the elongation rate of RNA polymerase and increased stalling of ribosomes; however, the physiological mediators underlying these phenomena remain unclear. Moreover, it is poorly understood what cell-protective mechanisms are in place to cope with transcriptional and translational stress, and how these are remodelled during ageing.

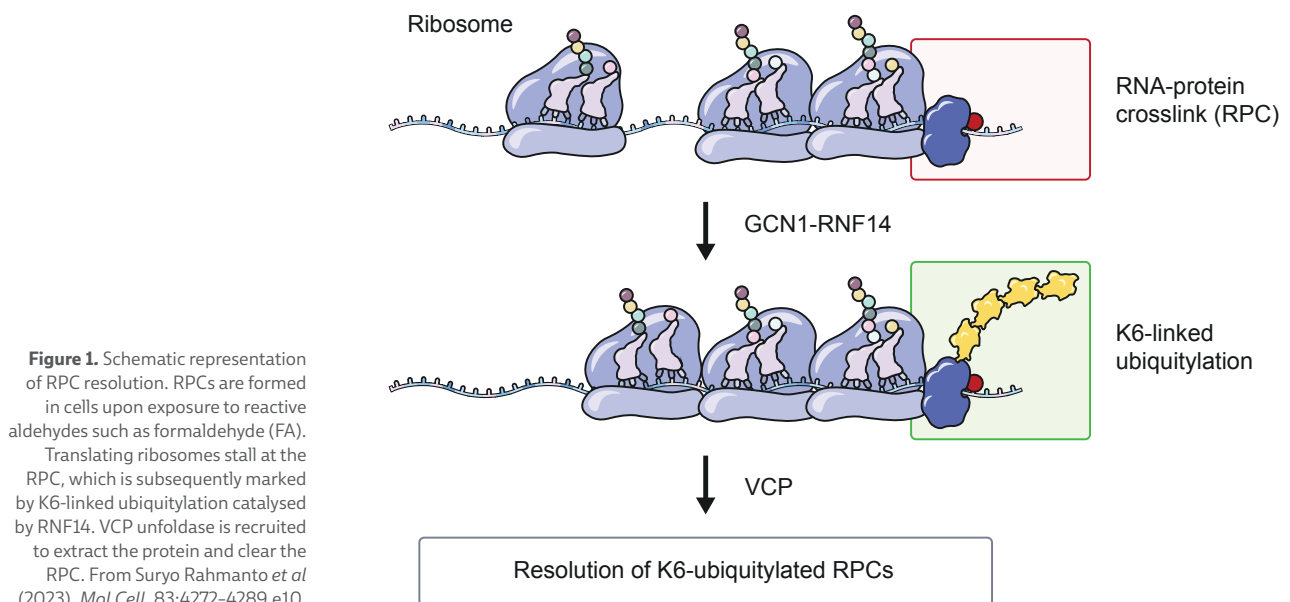
RESEARCH HIGHLIGHTS

Humans are exposed to reactive aldehydes in the environment, as well as those produced in their own bodies. Aldehydes are metabolic genotoxins that cause DNA double-strand breaks and chromosomal aberrations to accumulate in cells. The cytotoxic effects of formaldehyde (FA) are attributed to damage to the genomic DNA and subsequent inhibition of transcription and replication; however, it is not known how FA interferes with other cellular processes and whether dedicated mechanisms are in place to cope with FA-induced RNA and protein damage. In recent collaborative work with the König group, we have demonstrated that FA induces RNA-protein crosslinks (RPCs) that stall the ribosome and inhibit translation. RPCs in mRNA are recognised by translating ribosomes, marked by atypical K6-linked ubiquitylation catalysed by the RING-in-between-RING (RBR) E3 ligase RNF14, and resolved by the ubiquitin-dependent remodeller VCP (also known as p97). In collaboration with the Ulrich group, we found that the RPC stress response

pathway is conserved in budding yeast, in which FA-induced K6-linked ubiquitylation is dependent on the RNF14 ortholog ITT1. Our findings reveal an RPC stress response pathway that is a protective mechanism against reactive aldehydes. Furthermore, they suggest that RPCs contribute to the cellular and tissue toxicity of reactive aldehydes produced in the human body endogenously or after alcohol consumption. The RPC stress response pathway might be particularly pertinent in aged individuals, since expression of the aldehyde-clearing enzymes ALDH2 and ADH5 decreases in different tissues during ageing, possibly causing RPCs to accumulate. In support of this, ribosome pausing and collisions have been reported to increase during ageing in nematodes and yeast. In conclusion, our findings reveal that the RPC stress response pathway is a fundamental co-translational quality control mechanism for coping with RPCs induced by normal metabolism.

FUTURE DIRECTIONS

We are interested in understanding transcription- and translation-coupled quality control mechanisms that maintain the fidelity of gene expression and protein synthesis. We will use quantitative mass spectrometry-based proteomics to investigate cellular responses to stress that cause damage to genomic DNA and transcribed RNA. Our studies will focus on components of the ubiquitin system that regulate cellular responses to stress by catalysing the modification of substrate proteins with different types of ubiquitin chains. We will characterise ubiquitin-based mechanisms and ubiquitin E3 ligases that protect aged cells from the deleterious effects of transcriptional and translational stress.



SELECTED PUBLICATIONS

Suryo Rahmanto A*, Blum CJ*, Scalera C, Heidelberger JB, Mesitov M, Horn-Ghetko D, Gräf JF, Mikicic I, Hobrecht R, Orekhova A, Ostermaier M, Ebersberger S, Möckel MM, Krapoth N, Da Silva Fernandes N, Mizi A, Zhu Y, Chen JX, Choudhary C, Papantonis A, Ulrich HD, Schulman BA, König J and Beli P (2023) K6-linked ubiquitylation marks formaldehyde-induced RNA-protein crosslinks for resolution. *Mol Cell*, 83:4272–4289.e10

Mosler T*, Baymaz HI*, Gräf JF, Mikicic I, Blattner G, Bartlett E, Ostermaier M, Piccinno R, Yang J, Voigt A, Gatti M, Pellegrino S, Altmeyer M, Luck K, Ahel I, Roukos V and Beli P (2022) PARP1 proximity proteomics reveals interaction partners at stressed replication forks. *Nucleic Acids Res*, 50:11600–11618

Mosler T, Conte F, Longo GMC, Mikicic I, Kreim N, Möckel MM, Petrosino G, Flach J, Barau J, Luke B, Roukos V and Beli P (2021) R-loop proximity proteomics identifies a role of DDX41 in transcription-associated genomic instability. *Nat Commun*, 12:7314

*indicates joint contribution

Dorothee Dormann

“*We study the molecular mechanisms that drive age-associated neurodegenerative dementias.*”



POSITIONS HELD

- Since 2021** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Professor of Molecular Cell Biology, Johannes Gutenberg University Mainz (JGU)
- 2014 – 2021** Emmy Noether Group Leader, Ludwig Maximilian University (LMU) Munich, Biomedical Center
- 2007 – 2014** Postdoctoral Fellow, Ludwig Maximilian University (LMU) Munich, Adolf-Butenandt Institute

EDUCATION

- 2007** PhD, Rockefeller University, New York
- 2002** Diploma in Biochemistry, Eberhard Karl University of Tübingen

GROUP MEMBERS

Staff Scientists Bernhard Lieb, Irene Yiallourous

Postdocs Saskia Hutten, Erin Sternberg

PhD Students Lara Gruijs da Silva, Simone Mosna, Emre Pekbilir, Francesca Simonetti, Yongwon Suk, Fatmanur Tiryaki Yildiz, Yelyzaveta Zadorozhna

Lab Manager Nora Knabe

Research Assistant Thomas Schubert

OVERVIEW

We seek to unravel the molecular basis of age-associated neurodegenerative diseases, in particular ALS (amyotrophic lateral sclerosis), FTD (frontotemporal dementia) and Alzheimer’s disease. Existing therapies treat only the symptoms of disease and there are no therapies to slow down or stop disease progression. Our main objective is to obtain a molecular understanding of the mechanisms that drive these devastating disorders. We seek to unravel how RNA-binding proteins (RBPs), in particular TDP-43 and FUS, become mislocalised and aggregated, and how their dysregulation causes a decline in cellular function and eventually neurodegeneration. We previously showed that RBP mislocalisation and aggregation are intimately linked to 1) disturbed nuclear import, 2) aberrant phase separation and molecular ageing processes, and 3) altered post-translational modifications (PTMs). We therefore study how nuclear transport, phase separation and PTMs of disease-linked RBPs are regulated, how they are misregulated in disease and how cellular proteostasis mechanisms prevent this. We also study how disease-linked RBPs interact with other aggregating proteins, such as Tau, to understand how Tau-TDP-43 co-pathology arises in Alzheimer’s patients. By understanding the molecular basis of these processes, we hope to inspire new therapeutic approaches to treat neurodegenerative diseases.

RESEARCH HIGHLIGHTS

The neurodegeneration-linked RBPs TDP-43 and FUS harbour extended intrinsically disordered regions (IDRs) that allow them to self-interact, which leads to their phase separation and partitioning into cellular condensates such as stress granules. Subsequent liquid-to-solid state transition is a molecular ageing process believed to underlie RBP aggregate formation, however such aberrant phase transitions are

normally suppressed by cellular proteostasis mechanisms. We uncovered two important proteostasis mechanisms: suppression of RBP phase transitions by nuclear import receptors and PTMs. Using *in vitro* reconstitution and cellular experiments, we showed that nuclear import receptors (importins) suppress phase separation and stress granule recruitment of FUS, TDP-43 and toxic repeat proteins (poly-GR and -PR), which arise in the most common inherited form of ALS and FTD due to a repeat expansion in the *C9orf72* gene. This suggests that elevating importin levels or enhancing the binding of importins to aggregation-prone proteins could be used to treat protein aggregation disorders.

A second key regulator of RBP phase transitions we uncovered is disease-associated PTMs. PTMs frequently occur in IDRs and influence their phase separation, RNA-binding and RNA-processing functions. Abnormal PTMs often arise in neurodegenerative diseases; for example, we found that FUS arginine methylation is reduced in FTD patients. We previously found that FUS hypomethylation promotes phase separation and stress granule accumulation, suggesting that loss of this PTM may promote FUS aggregation in disease. More recently, we found that arginines in RGG/RG motifs, the sites of arginine methylation, are crucial for proper nuclear localisation, RNA-binding and stress granule recruitment of FUS, highlighting an important regulatory role of these disordered, positively charged motifs, which occur in many nucleic acid-binding proteins.

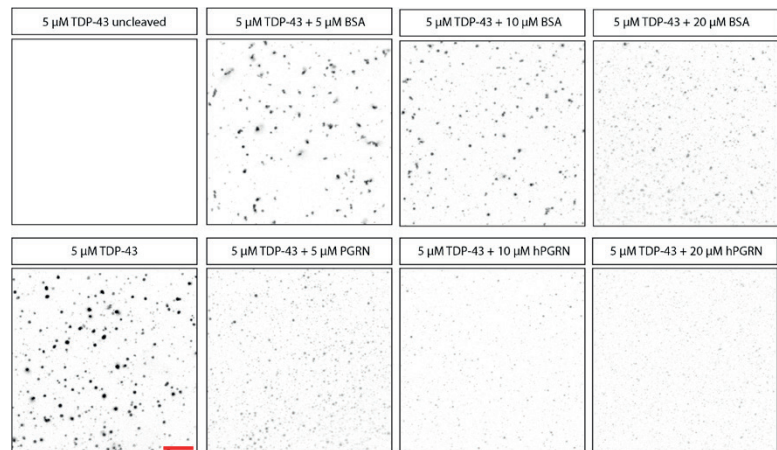
Another disease-associated PTM is C-terminal hyperphosphorylation of TDP-43 in ALS and FTD. We found that C-terminal phosphomimetic substitutions in TDP-43 reduce phase separation and aggregation, render TDP-43 condensates more dynamic and liquid-like, and suppress its recruitment into cellular condensates. TDP-43 phosphorylation may therefore be a protective mechanism for preventing its aggregation and

a physiological mechanism for regulating its condensation. Together with our collaborators in Munich, we showed that antibodies directed against the C-terminal IDR of TDP-43 can suppress TDP-43 phase separation/aggregation. Moreover, we found that the microglial-derived progranulin (PGRN) protein limits TDP-43 condensation and regulates the microglial activation state upon traumatic brain injury.

FUTURE DIRECTIONS

As phase separation is an important pathway towards RBP aggregation, we want to gain a comprehensive understanding of the drivers and regulators of TDP-43 and FUS phase separation. In particular, we plan to systematically decipher the intrinsic sequence features that drive the phase separation and solidification of TDP-43, as well as identify and study new regulators/modifiers of phase separation and molecular ageing. A major focus will be on disease-linked TDP-43 phosphorylation and understanding when and where it is elicited in cells, whether it can dissolve TDP-43 aggregates and how it alters TDP-43's interactome and physiological functions. In addition, we will study the relevance of TDP-43 self-assembly into nanosized clusters or micron-sized condensates for its functions in gene regulation. Finally, we will study the molecular mechanisms of how disease-linked RBPs regulate R-loops and DNA damage repair and how RBP condensates are recognised by the cellular degradation machinery.

Figure 1. Progranulin (PGRN) suppresses TDP-43 condensation *in vitro*. Phase separation of TDP-43 (5 μ M) was induced by TEV protease-mediated cleavage of AI.488-labelled TDP-43-(Tev)-MBP-His6 in the absence or presence of 1x, 2x or 4x BSA (control, upper panels) or purified progranulin (PGRN; lower panels). PGRN but not BSA suppresses TDP-43 condensate formation. Scale bar: 10 μ m.



SELECTED PUBLICATIONS

Grujisi da Silva LA, Simonetti F, Hutten S, Riemenschneider H, Sternburg EL, Pietrek LM, Gebel J, Dötsch V, Edbauer D, Hummer G, Stelzl LS and Dormann D (2022) Disease-linked TDP-43 hyperphosphorylation suppresses TDP-43 condensation and aggregation. *EMBO J*, 41:e108443

Zambusi A*, Novoselc KT*, Hutten S, Kalpazidou S, Kouportidou C, Schieweck R, Aschenbroich S, Silva L, Yazgılı AS, van Bebber F, Schmid B, Möller G, Tritscher C, Stigloher C, Delbridge C, Sirko S, Günes ZI, Liebscher S, Schlegel J, Aliee H, Theis F, Meiners S, Kiebler M, Dormann D* and Ninkovic J* (2022) TDP-43 condensates and lipid droplets regulate the reactivity of microglia and regeneration after traumatic brain injury. *Nat Neurosci*, 25:1608-1625

Hutten S*, Usluer S, Bourgeois B, Simonetti F, Odeh HM, Fare CM, Czuppa M, Hruska-Plochan M, Hofweber M, Polymenidou M, Shorter J, Edbauer D, Madl T and Dormann D* (2020) Nuclear import receptors directly bind to arginine-rich dipeptide repeat proteins and suppress their pathological interactions. *Cell Rep*, 33:108538

*indicates joint contribution, *indicates joint correspondence

Claudia Keller Valsecchi

“*Males and females use different mechanisms to compensate for their X-chromosomal differences.*”



POSITIONS HELD

- Since 2020** Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2013 – 2020** Postdoc, Max Planck Institute of Immunobiology & Epigenetics, Freiburg
- 2012 – 2013** Postdoc, Friedrich Miescher Institute (FMI), Basel

EDUCATION

- 2012** PhD in Biochemistry, Friedrich Miescher Institute (FMI), Basel
- 2008** MSc in Molecular Biology, Friedrich Miescher Institute (FMI), Basel
- 2007** BSc in Molecular Biology, Biozentrum, University of Basel

GROUP MEMBERS

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OVERVIEW

Sexual reproduction facilitates the introduction of genetic diversity within a population. The diploid genetic state serves as a safeguarding mechanism by ensuring development when mutations occur in heterozygosity. Nevertheless, recent large-scale genome sequencing initiatives have uncovered an unexpectedly high number of human genes that exhibit intolerance to heterozygous loss-of-function mutations. Similarly, aneuploidies, characterised by the gain or loss of entire chromosomes, are a prominent cause of miscarriages and pregnancy failures. This suggests that maintaining a precisely two-fold gene dosage is of fundamental importance for the normal progression of organismal development.

Our approach is to understand these pathogenic deviations in gene dosage within the context of natural exceptions to the diploid genetic state. Notably, differentiated sex chromosomes, despite introducing heterozygosity for hundreds of genes, do not confer detrimental effects. This phenomenon can be attributed to dosage compensation (DC), a regulatory mechanism that corrects imbalances in X-chromosomal gene expression between males and females. We study this intriguing paradox surrounding natural gene dosage alterations and their potential deleterious consequences. We investigate how cells effectively manage the interplay between advantageous elements, such as the evolution of sex chromosomes and novel genes, and adverse effects like developmental delays and malignancies.

RESEARCH HIGHLIGHTS

Dosage regulation in sex chromosomes

Sexual dimorphism is a prominent feature in the biology of various species, including the *Anopheles* mosquito, where only females require a blood meal for egg production. Sex

differentiation can be traced back to the sex chromosomes, but they create a gene dosage imbalance between males (XY) and females (XX). Dosage compensation (DC) mechanisms can correct this, but the evolutionary diversity and functional necessity of these mechanisms remain enigmatic, primarily due to limited study in non-model organisms. We studied DC in two related dipterans, *Anopheles gambiae* and *Drosophila melanogaster*. Despite sharing similar genetic content, their X chromosomes evolved independently from a common ancestral autosome. CRISPR knockouts and H4K16ac ChIP-seq experiments revealed that the MSL-H4K16ac pathway, known for DC in model organisms, is not responsible for X chromosome upregulation in mosquitoes.

To unravel the mosquito DC pathway, we constructed an RNA expression atlas at various developmental stages. This data revealed that DC initiates during embryogenesis, with further refinement in later stages. We identified several candidate DC factors with male-biased expression, notably an uncharacterised gene we named *SOA*. Our follow-up work showed that the *SOA* protein is the master regulator of DC in *A. gambiae*. Sex-specific alternative splicing restricts functional *SOA* protein production in females. The male isoform encodes a DNA-binding protein that targets active X chromosomal gene promoters. Expressing male *SOA* induces DC in female cells. Mosquitoes lacking *SOA* in males or ectopically expressing the male isoform in females display X chromosome misregulation, resulting in developmental delay. This milder phenotype differs from the lethality seen in model organisms upon DC loss. Collaborating with theoreticians, we modelled the spread of *SOA* in evolving populations with this mild phenotype. Intriguingly, our model

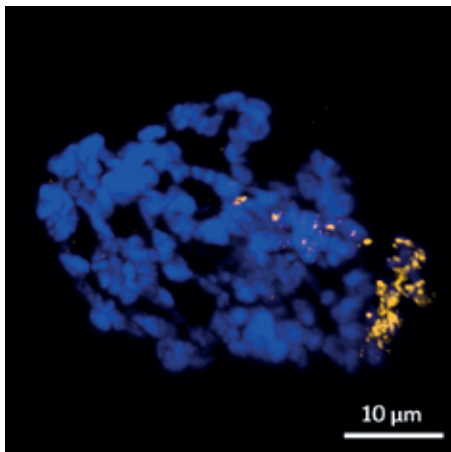


Figure 1. Polytene squash of a third instar *Anopheles gambiae* male larva. In this preparation, the chromosomes are spread and the DNA is detected with DAPI dye (blue). The *SOA* protein responsible for dosage compensation is detected by antibody staining (shown in yellow). *SOA* only binds to one specific chromosome, which is the X chromosome.

predicts that *SOA*-mediated DC may have initially existed as a polymorphism, introducing a novel population-level perspective to the DC field. Our study elucidates the evolutionary progression of a chromosome-specific fine-tuning mechanism through molecular analysis of the first DC master regulator in a non-model organism.

Gene paralogues and dosage-sensitivity of RNA-binding proteins

In this research angle, we explore the molecular mechanism and functional significance of substituting nearly identical proteins. We have focused on the gene paralogues *SNRPB* and *SNRPN*, the latter of which is expressed in mammalian neurons and the heart. Our recent data shows that despite > 90% identity, these paralogues display intrinsic differences in their protein properties. These differences can be narrowed down to posttranslational modifications that differ upon environmental insults. We hypothesise that through these different responses, the two paralogues can control cell-type specific splicing programmes and thus RNA isoforms. The absence of either paralogue can also result in compromised splicing and the formation of harmful chromatin-associated RNA structures like R-loops.

FUTURE DIRECTIONS

Our goal is to characterise DC mediated by *SOA*. Using genomics, we will identify how it regulates the X chromosome and create mutants to understand its relevance for DC. These findings could ultimately inform novel strategies for fighting infectious diseases such as malaria by vector control. In addition to our work with mosquitoes, we also investigate DC in various other non-model organisms. Our research delves into several aspects, including tissue-specific differences, regulatory dynamics throughout an organism's lifespan and adaptability in response to environmental shifts. We aim to elucidate how DC mechanisms operate in crustaceans that exhibit a ZW chromosome system. In parallel, we develop tools to comprehensively identify dosage-sensitive genes and cellular responses in mammals, for example those in *SNRPB/N*. We will also expand our work on the mammalian X chromosome and study the mechanisms of re-activation during development, as well as age-related chromosomal mosaicism during ageing.

SELECTED PUBLICATIONS

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Keller Valsecchi CI*, Basilicata MF*, Georgiev PG, Gaub A, Seyffert J, Kulkarni T, Panhale A, Semplicio G, Dasmeh P and Akhtar A (2021) RNA nucleation by MSL2 induces selective X chromosome compartmentalization. *Nature*, 589:137-142

*indicates joint contribution, *indicates joint correspondence

René Ketting

“*We employ biochemistry and genetics to identify new gene regulatory mechanisms.*”



POSITIONS HELD

- Since 2012** Scientific Director, Institute of Molecular Biology (IMB), Mainz
Professor, Johannes Gutenberg University Mainz (JGU)
- 2010 – 2013** Professor of Epigenetics in Development, University of Utrecht
- 2005 – 2012** Group Leader, Hubrecht Institute, Utrecht
- 2000 – 2004** Postdoc, Hubrecht Institute, Utrecht
- 2000** Postdoc, Cold Spring Harbor Laboratories

EDUCATION

- 2000** PhD in Molecular Biology, Netherlands Cancer Institute, Amsterdam
- 1994** MSc in Chemistry, University of Leiden

GROUP MEMBERS

- Senior Research Associate** Nadine Wittkopp
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- Lab Manager** Yasmin El Sherif
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- Animal Caretaker** Cedric Schmitt
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OVERVIEW

The major focus of my lab is gene regulation by small RNA molecules acting through RNAi-related pathways. Since their discovery at the start of the 21st century, many different RNAi-related pathways have been identified. It is now evident that although all of these pathways depend on proteins from the Argonaute family, each pathway has its own unique characteristics and effects on gene expression. These can range from relatively minor effects on translation (in the case of miRNAs) to full-blown shutdown of loci at the transcriptional level (piRNAs). We focus on the mechanisms related to piRNA and siRNA biology, two species of small RNAs that are particularly abundant in and important for the germline. These small RNA pathways have a major role in maintaining genome integrity by controlling the activity of transposable elements. We use zebrafish and *C. elegans* as model systems to understand the molecular mechanisms governing these pathways and how they contribute to normal development. Questions such as how small RNA pathways distinguish transposable elements from regular genes, how these pathways are organised at a sub-cellular level and how small RNA populations can be inherited across generations are at the heart of our research.

RESEARCH HIGHLIGHTS

Identification of a novel nuclease that helps control transposable elements

Virtually all genomes known to date contain a significant load of so-called transposable elements. These are genetic elements that can multiply themselves, and upon doing so can damage the genome. As such, transposable elements represent a serious threat to genome stability. At the same time, these elements are a strong force in evolution: their activity is known to be a significant factor in the genetic

variability that is essential for evolution. To survive, transposons need to be active in germ cells, and as a consequence germ cells are equipped with unique mechanisms to control the activity of these mobile elements. One of these mechanisms is known as the PIWI-piRNA pathway.

The PIWI-piRNA pathway is based on sequence-specific recognition of transposons, as well as other targets, through the use of small RNA molecules (piRNAs). piRNAs are bound by PIWI proteins, and it is the activity of the PIWI proteins that can silence the activity of transposons. Therefore, the identity of the piRNAs, or in other words, their sequence, is crucial to the success of this mechanism. Interestingly, the way piRNAs are made in different animals appears to vary significantly, likely reflecting the ever-present pressure of the PIWI-piRNA pathway to silence transposons on the one hand, and the selective pressure on transposons to escape the activity of the PIWI-piRNA pathway on the other. As a consequence, studying the molecular mechanisms of the PIWI-piRNA pathway yields a lot of insight into the flexibility of gene regulatory mechanisms in general, and often leads to the identification of completely novel mechanisms.

We studied how piRNAs are made in the nematode *Caenorhabditis elegans*. These small RNAs (also named 21U RNAs in *C. elegans*) are initially made as already-small precursor transcripts roughly 30 nucleotides in length. Following their transcription, they need to be processed at both their 5' and 3' ends. While the 3' end processing steps are known relatively well, the 5' end processing step was unclear. We identified a complex of three subunits that executes this step. This complex, which we named PUCH (Precursor of 21U RNA Cleavage Holoenzyme), is an extremely specific enzyme with thus far unknown activities: it is

extremely sensitive to both the methylation status of the 5' cap of the substrate, as well as the identity of the third base of the substrate. A third key finding was that PUCH is found on mitochondria and that its presence there likely helps to load the cleavage product into a PIWI protein.

The identification of PUCH was interesting for another reason: it is composed of three proteins with a so-called Schlafen fold. Enzymes with such folds are also known in mammals, where they have been linked to innate immunity responses. However, their functions are largely unclear. This work thus forged a link between mammalian innate immunity and small RNA-mediated gene silencing, and suggests that mammalian Schlafen proteins may harbour unexpected activities, which only surface upon forming the right complex.

FUTURE DIRECTIONS

Future work will continue to mechanistically unravel the molecular pathways that are steered by small RNA molecules. One aim will be to further delineate how piRNAs are processed and loaded into PIWI proteins. Other research lines are focusing on the role of biomolecular condensates in small RNA-mediated gene silencing. Such condensates are well known to be required, but their exact functions are unclear. These studies also aim to provide a more generally applicable framework for the roles of condensates in cell biology. Finally, we are zooming into the interfaces between small RNA biology and other aspects of gene regulation. Using genetic screens and immunoprecipitation approaches, we will identify novel factors and then implement these into our current models of gene regulatory mechanisms.

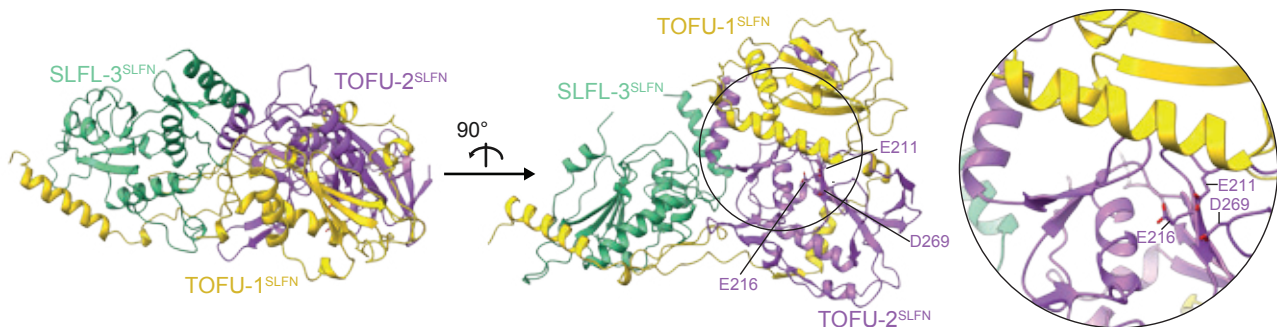


Figure 1. An Alpha-fold model of the PUCH complex. Two different orientations are shown, as indicated by the arrow. The magnified panel shows the catalytic site of the PUCH enzyme.

SELECTED PUBLICATIONS

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Schreier J, Dietz S, Boermel M, Oorschot V, Seistrup AS, de Jesus Domingues AM, Bronkhorst AW, Nguyen DAH, Phillis S, Gleason EJ, L'Hernault SW, Phillips CM, Butter F and Ketting RF (2022) Membrane-associated cytoplasmic granules carrying the Argonaute protein WAGO-3 enable paternal epigenetic inheritance in *Caenorhabditis elegans*. *Nat Cell Biol*, 24:217-229

Placentino M, Jesus Domingues AM, Schreier J, Dietz S, Hellmann S, Albuquerque BF, Butter F and Ketting RF (2021) Intrinsically disordered protein PID-2 modulates Z granules and is required for heritable piRNA-induced silencing in the *Caenorhabditis elegans* embryo. *EMBO J*, 40:e105280

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Anton Khmelinskii

“*We use proteomic approaches to dissect the mechanisms of proteostasis.*”



POSITIONS HELD

- Since 2018** Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2013** Visiting Scientist, Donnelly Centre for Cellular & Biomolecular Research, University of Toronto
- 2011 - 2017** Postdoc, Center for Molecular Biology (ZMBH), University of Heidelberg
- 2011 - 2016** Visiting Scientist, European Molecular Biology Laboratory (EMBL), Heidelberg
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EDUCATION

- 2010** PhD in Biology, University of Heidelberg
- 2005** MSc in Biochemistry, University of Lisbon

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OVERVIEW

The integrity of the proteome is maintained by a complex network that controls the synthesis, folding, transport and degradation of proteins. Numerous quality control systems operate throughout the protein lifecycle to prevent, detect and remove abnormal proteins, thus contributing to proteostasis. Selective protein degradation by the ubiquitin-proteasome system (UPS) plays a key role in proteome turnover and quality control. When degradation is not possible, abnormal proteins can eventually be removed via asymmetric partitioning during cell division. Despite the activity of such systems, proteostasis declines with ageing and in numerous diseases, resulting in the accumulation of abnormal proteins and loss of cell functionality. Working in yeast and human cells, we aim to systematically examine how cells deal with different types of abnormal proteins. We use genetic and proteomic approaches that exploit fluorescent timers to identify UPS substrates and explore the functions of this system in replicative ageing and genome stability. Our goals are to understand the coordination between protein biogenesis and quality control, decipher how abnormal proteins are recognised and elucidate how cells adapt to challenges in proteostasis.

RESEARCH HIGHLIGHTS

Selective protein degradation is involved in most cellular processes and contributes to proteome homeostasis by removing unnecessary or abnormal proteins. The UPS is the key system of selective protein degradation, whereby a cascade of ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-protein ligase (E3) enzymes marks proteins with polyubiquitin chains for proteasomal degradation. Deubiquitinating enzymes (DUBs), which remove ubiquitin marks and replenish the pool of free ubiquitin, are involved

at various stages of the targeting and degradation processes. Despite the central role of the UPS in protein degradation and its association with various diseases and ageing, the functions of many UPS components are unclear and the substrate specificities of E3s and DUBs are not well defined.

Selective protein degradation typically involves substrate recognition via short linear motifs known as degrons. Various degrons can be found at protein termini in species ranging from bacteria to mammals. While degrons located at protein N-termini (N-degrons) have been extensively studied, our understanding of C-terminal degrons (C-degrons) is still limited. To gain a comprehensive understanding of eukaryotic C-degron pathways, we recently performed an unbiased survey of C-degrons in budding yeast (Kong *et al.*, 2023, *bioRxiv*). We identified over 5000 potential C-degrons by stability profiling of random peptide libraries and the yeast C-terminome. Combining machine learning, high-throughput mutagenesis and genetic screens revealed that the SCF (Skp1, cullin, F-box) ubiquitin ligase targets ~40% of degrons using a single F-box substrate receptor, Das1. This is in stark contrast with other C-degron pathways found in human cells, where different degron motifs are recognised by interchangeable substrate receptors of several cullin-RING ubiquitin ligases.

Compared to other ubiquitin ligases targeting C-degrons, Das1 appears to have an exceptionally broad specificity, as determined by the five most C-terminal amino acids (Figure 1). This notion is supported by two observations: 1) the broad spectrum of random degrons and yeast C-terminal degrons targeted by Das1, and 2) that most single amino acid substitutions at the five C-terminal positions have no impact on Das1 degrons. The broad specificity of Das1 towards C-degrons is reminiscent of the broad specificity of Ubr1 towards N-degrons. However, Ubr1 is a large ubiquitin ligase (225 kDa) that recognises a variety of N-degrons and internal degrons using three distinct substrate-binding sites. It remains to be determined whether one or multiple substrate-binding sites in the substantially smaller Das1 (77 kDa) are responsible for its broad specificity.

By screening for full-length substrates, we implicated SCF^{Das1} in the degradation of orphan subunits of various protein complexes (Kong *et al.*, 2023, *bioRxiv*). C-termini of such proteins are, under normal conditions, involved in protein-protein interactions within their respective complexes,

and thus hidden from Das1. We speculate that imbalanced synthesis of protein complex subunits, as seen for example in aneuploidy, can lead to the production of excess subunits, which fail to assemble into complexes and are subsequently recognised via their exposed C-termini and targeted for proteasomal degradation by SCF^{Das1}.

FUTURE DIRECTIONS

On the one hand, we will continue our work on the SCF^{Das1} ubiquitin ligase to define its substrate repertoire and to understand its modes of substrate recognition and physiological functions. On the other hand, despite the general importance of selective protein degradation, the specificity of most ubiquitin ligases remains poorly understood. We will thus expand our systematic search for degrons to all ubiquitin ligases in yeast to uncover the organisation and specificity of the ubiquitin-proteasome system.

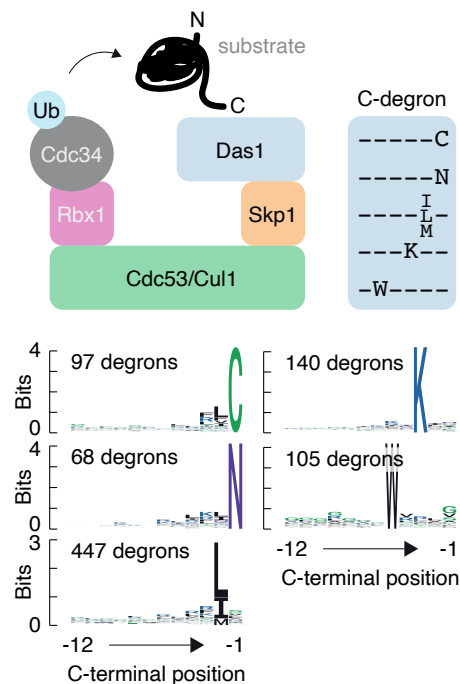


Figure 1. Broad specificity of the SCF^{Das1} ubiquitin ligase towards C-degrons. Top, cartoon of the SCF^{Das1} complex and the putative C-degron motifs targeted by this ubiquitin ligase. Bottom, sequence logos corresponding to the C-degrons matching the five motifs.

SELECTED PUBLICATIONS

Kong KYE*, Shankar S*, Rühle F and Khmelinskii A* (2023) Orphan quality control by an SCF ubiquitin ligase directed to pervasive C-degrons. *Nat Commun*, 14:8363

Schindler N*, Tonn M*, Kellner V, Fung JJ, Lockhart A, Vydzhak O, Juretschke T, Möckel S, Beli P, Khmelinskii A and Luke B (2023) Genetic requirements for repair of lesions caused by single genomic ribonucleotides in S phase. *Nat Commun*, 14:1227

Kong KYE*, Fischer B*, Meurer M*, Kats I, Li Z, Rühle F, Barry JD, Kirrmaier D, Chevyreva V, San Luis BJ, Costanzo M, Huber W, Andrews BJ, Boone C, Knop M* and Khmelinskii A* (2021) Timer-based proteomic profiling of the ubiquitin-proteasome system reveals a substrate receptor of the GID ubiquitin ligase. *Mol Cell*, 81:2460-2476

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Julian König

“*We use quantitative approaches to decipher RNA regulation.*”



POSITIONS HELD

Since 2013 Group Leader, Institute of Molecular Biology (IMB), Mainz

2008 – 2013 Postdoc, MRC Laboratory of Molecular Biology, Cambridge

EDUCATION

2008 PhD in Biology, Max Planck Institute for Terrestrial Microbiology & Philipps University, Marburg

2003 Diploma in Biology, Ludwig Maximilian University (LMU), Munich

GROUP MEMBERS

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PhD Students Miona Corovic, Jasmin Sarah Hallstein, Nadine Körtel, Miriam Mulorz, Cornelia Rückle

Master Students Janine Cathrin Brück, Tim Preißendörfer

Lab Manager Anna Orekhova

OVERVIEW

Posttranscriptional gene regulation plays an important role in neurodegenerative diseases and cancer. The fate of mRNA is regulated by the cooperative action of RNA-binding proteins (RBPs), which recognise specific RNA sequences to form messenger ribonucleoprotein complexes (mRNPs). In addition, epitranscriptomic marks in the form of RNA modifications control mRNA fate. The information in the RNA sequence, RNA modifications and how they are interpreted by RBPs is commonly referred to as the ‘mRNP code’. However, the molecular features that define this code remain poorly understood. My main goal is to significantly contribute to cracking the mRNP code.

RESEARCH HIGHLIGHTS

FUBP1 is a general splicing factor facilitating 3’ splice site recognition and splicing of long introns

Splicing of pre-mRNAs critically contributes to gene regulation and proteome expansion in eukaryotes, but our understanding of the recognition and pairing of splice sites during spliceosome assembly lacks detail. We recently identified the multidomain RNA-binding protein FUBP1 as a key splicing factor that binds a hitherto unknown cis-regulatory motif. By collecting NMR, structural and *in vivo* interaction data, we demonstrated that FUBP1 stabilises U2AF2 and SF1, which are key components at the 3’ splice site, through multivalent binding interfaces located within its disordered regions. Transcriptional profiling and kinetic modelling revealed that FUBP1 is required for efficient splicing of long introns, which is impaired in cancer patients harbouring FUBP1 mutations. Notably, FUBP1 interacts with numerous U1 snRNP-associated proteins, suggesting a unique role for FUBP1 in splice site bridging at long introns. We propose a compelling model for 3’ splice site

recognition of long introns, which represent 80% of all human introns.

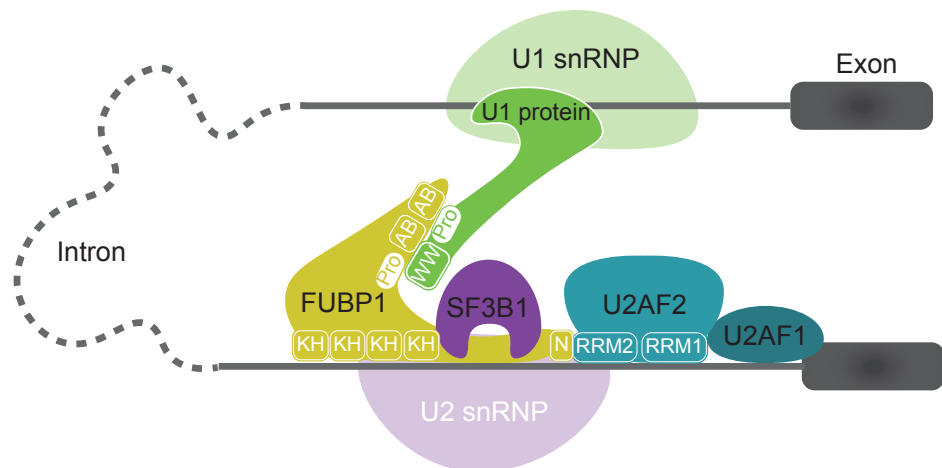
RNA stability controlled by m⁶A methylation drives X-to-autosome dosage compensation in mammals

In mammals, X-chromosomal genes are expressed from a single copy since males (XY) possess a single X chromosome while females (XX) undergo X inactivation. To compensate for this reduction in dosage relative to the two active copies of autosomes, it has been proposed that genes from the active X chromosome exhibit dosage compensation ("Ohno's hypothesis"). However, the existence and mechanism of X-to-autosome dosage compensation are still under debate. We showed that dosage compensation is achieved via differential N⁶-methyladenosine (m⁶A) RNA modification. X-chromosomal transcripts are deficient in m⁶A modifications and more stable compared to their autosomal counterparts. Acute depletion of m⁶A using a small molecule inhibitor selectively stabilised autosomal transcripts across sexes, cell types, tissues and species, resulting in perturbed dosage compensation. We propose that increased stability of X-chromosomal transcripts is directed by lower levels of m⁶A, indicating that mammalian dosage compensation occurs via epitranscriptomic RNA regulation.

FUTURE DIRECTIONS

My research will focus on deciphering the regulatory code of splicing and quality control mechanisms in human physiology and disease. To this end, we will build on the iCLIP technology to map protein-RNA interaction sites throughout the transcriptome. We will use our approaches to predict mutations that cause mis-splicing in cancer and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). We will also take a closer look at critical RNA regulators that are relevant in neurodegeneration. For instance, we recently showed that small alterations in the cellular concentration of the RNA-binding protein HNRNPH can have a strong impact on alternative splicing events in diseases caused by nuclear aggregation. In a parallel project, we will investigate the role of m⁶A modifications in splicing regulation. The aim is to compile a full catalogue of m⁶A-dependent splicing events in the transcriptome and reliably map all m⁶A sites that may impact these events.

Figure 1. Multivalent interactions in disordered FUBP1 regions support spliceosome assembly across introns.



SELECTED PUBLICATIONS

Ebersberger S*, Hipp C*, Mulorz MM*, Buchbender A, Hubrich D, Kang HS, Martínez-Lumbreras S, Kristofori P, Sutandy FXR, Llacsahuanga Allcca L, Schönfeld J, Bakisoglu C, Busch A, Hänel H, Tretow K, Welzel M, Di Liddo A, Möckel MM, Zarnack K, Ebersberger I, Legewie S, Luck K*, Sattler M* and König J* (2023) FUBP1 is a general splicing factor facilitating 3' splice site recognition and splicing of long introns. *Mol Cell*, 83:2653-2672.e15

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Cortés-López M*, Schulz L*, Enculescu M*, Paret C, Spiekermann B, Quesnel-Vallières M, Torres-Diz M, Unic S, Busch A, Orekhova A, Kuban M, Mesitov M, Mulorz MM, Shraim R, Kielisch F, Faber J, Barash Y, Thomas-Tikhonenko A, Zarnack K*, Legewie S* and König J* (2022) High-throughput mutagenesis identifies mutations and RNA-binding proteins controlling CD19 splicing and CART-19 therapy resistance. *Nat Commun*, 13:5570

*indicates joint contribution, *indicates joint correspondence

Nard Kubben

“
Our research aims to put the
brakes on accelerated ageing.
”



POSITIONS HELD

- Since 2021** Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2015 – 2019** NIH Research Fellow, National Cancer Institute, NIH, Bethesda
- 2011 – 2015** NIH Postdoctoral Fellow, National Cancer Institute, NIH, Bethesda

EDUCATION

- 2004 – 2010** PhD in Molecular Biology, Maastricht University
- 2001 – 2004** MSc in Biological Health Sciences, Maastricht University
- 2000 – 2001** BSc in Health Sciences, Maastricht University

GROUP MEMBERS

- PhD Students** Lukas Mann, Felix van der Walt
- Master Student** Tim Müller

OVERVIEW

Ageing is a prime pathological component of most prevalent diseases. At the cellular level, it is characterised by various hallmarks, including epigenetic alterations, genomic instability and loss of protein homeostasis, all of which contribute to an organism-wide decline in function. Unfortunately, our current knowledge of the molecular pathways that drive cellular ageing and the formation of ageing hallmarks is severely limited. We focus on uncovering fundamental biological mechanisms of ageing that can be manipulated to slow down the progression of ageing-related diseases, including the rare and lethal premature ageing disease Hutchinson-Gilford Progeria Syndrome (HGPS). Our group employs unbiased genomics, proteomics and high-throughput microscopy-based screening to i) identify novel pathways that slow down the onset of cellular ageing; ii) investigate cellular pathways that help reverse ageing defects that have already formed, and iii) validate the therapeutic potential of identified ageing mechanisms across various model systems of ageing-related diseases. The overarching goal of our research is to uncover fundamental biological mechanisms of ageing that can help improve human healthspan.

RESEARCH HIGHLIGHTS

A novel model system to identify drivers of ageing

One of the major challenges of ageing research is that ageing manifests as a slow build-up of relatively low percentages of aged cells in our bodies. Molecular techniques that directly compare young and aged biological tissue samples therefore have the disadvantage of only detecting the most robust ageing-correlated changes, many of which turn out to be a consequence rather than a cause of ageing. It is therefore key to establish a technical approach that excludes these passive bystander effects of ageing and focuses directly on

identifying mechanisms that actively drive ageing. We have therefore established an HGPS-based system to functionally screen for events that drive ageing. HGPS is predominantly caused by a silent mutation in the *LMNA* gene, which encodes the nuclear lamina-localised protein lamin A, a key organiser of the mammalian nucleus. The mutation in HGPS results in the accumulation of an alternatively spliced lamin A mutant, termed progerin. A more modest accumulation of progerin also occurs during physiological ageing, suggesting that HGPS and physiological ageing have a common mechanistic basis. Unfortunately, the mechanisms by which progerin exerts its dominant negative effects remain largely unknown. We generated a cellular system in which we can inducibly express progerin and study the formation of many cellular ageing defects within a time frame of only 4 days, using a semi-automated high-throughput microscopy 'QuantitAgeing' pipeline to visualise and quantify ageing defects (Figure 1). This system enables us to investigate if any genetic interventions can prevent ageing upon progerin expression, thereby identifying pathways that are directly involved in driving cellular ageing.

High-throughput screening identifies new anti-ageing targets

We previously provided proof-of-principle that we can use our progerin-inducible cell system for high-throughput identification of pathways that drive progerin-induced ageing. Screening a library targeting 320 human ubiquitin ligases for their capacity to prevent cellular ageing, we identified that progerin entrapment of the proteostatic master

regulator NRF2 partially drives cellular ageing. We similarly performed a kinome (~2000 targets) and genome-wide RNAi screen. The kinome screen revealed Leucine-rich repeat kinase 2 (LRRK2) as a novel regulator of progerin-induced ageing. LRRK2 knockdown prevents progerin from inducing ageing and reverses established ageing defects in primary HGPS patient cells. Interestingly, LRRK2 mutations are a well-known cause of Parkinson's disease (PD). These data suggest that the accelerated ageing in HGPS and PD may have shared pathological roots.

Anti-ageing candidates identified from the genome-wide RNAi screen include a protein complex involved in regulating protein synthesis, suggesting that dysregulated protein turnover may underlie premature ageing in HGPS. Furthermore, we identified a previously uncharacterised zinc finger protein, which upon knockdown not only prevents progerin-induced ageing, but also reverses ageing defects in cells from physiologically aged individuals. These results indicate that understanding the molecular mechanisms that drive accelerated ageing in HGPS is useful for gaining insights into physiological ageing.

FUTURE DIRECTIONS

LRRK2 is a major regulator of the endolysosomal system. We will apply molecular reporter assays and targeted mass spectrometry to evaluate how the endolysosomal system is affected in HGPS and physiological ageing in the context of LRRK2 activity. We will also design SILAC-based mass spectrometry experiments to determine to what extent protein synthesis and degradation are affected in HGPS. We further plan on characterising which pathways are regulated by the zinc finger protein we identified as a strong anti-ageing regulator. Lastly, we will expand our molecular toolbox by creating additional inducible cellular ageing models and determine to what extent the anti-ageing drivers we identified are capable of preventing stressors that drive cellular ageing.

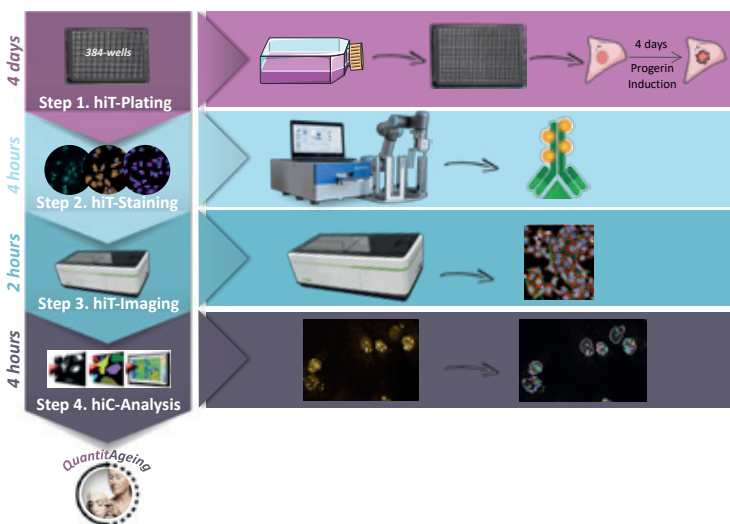


Figure 1. An overview of the "QuantitAgeing" pipeline: Progerin-inducible cells subjected to various genetic experimental interventions are plated in 384-well plates. Four days after induced progerin expression, high-throughput (hiT) immunofluorescent staining is performed for various ageing markers, followed by hiT microscopy imaging and high-content (hiC) image analysis. The effect of genetic interventions on preventing the formation of progerin-induced cellular ageing defects can be quantified through this pipeline in a week.

SELECTED PUBLICATIONS

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Kreienkamp R*, Graziano S*, Coll-Bonfill N*, Bedia-Diaz G, Cybulla E, Vindigni A, Dorsett D, Kubben N, Batista LFZ and Gonzalo S (2018) A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin. *Cell Rep*, 22:2006-2015

Shen Y, Kubben N, Candia J, Morozov A V, Misteli T and Losert W (2018) RefCell: multi-dimensional analysis of image-based high-throughput screens based on "typical cells." *BMC Bioinformatics*, 19:427

*Indicates joint contribution

Edward Lemke

“ We study the role of intrinsically disordered proteins in cellular function & ageing. ”



POSITIONS HELD

- Since 2018** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Professor of Synthetic Biophysics, Johannes Gutenberg University Mainz (JGU)
- 2009 – 2017** Group Leader, European Molecular Biology Laboratory (EMBL), Heidelberg (visiting since 2018)
- 2005 – 2008** Postdoc, The Scripps Research Institute, La Jolla

EDUCATION

- 2005** PhD in Chemistry, Max Planck Institute for Biophysical Chemistry & University of Göttingen
- 2001** Diploma in Chemistry, Technical University of Berlin
- 2001** MSc in Biochemistry, University of Oklahoma

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OVERVIEW

We focus on studying intrinsically disordered proteins (IDPs), which constitute up to 50% of the eukaryotic proteome. IDPs are most famous for their involvement in neurodegenerative diseases of ageing like Alzheimer's, Parkinson's and Huntington's disease. The ability of IDPs to exist in multiple conformations is considered a major driving force behind their enrichment during evolution in eukaryotes, but it also comes with the risk of molecularly 'ageing' into states that ultimately cause disease. Studying biological machineries containing such dynamic proteins is a huge hurdle for conventional technologies. Using a question-driven, multidisciplinary approach paired with novel tool development, we have made major strides in understanding the biological dynamics of such systems from the single molecule to the whole cell level. Fluorescence tools are ideally suited to studying the plasticity of IDPs, as their non-invasive character permits a smooth transition between *in vitro* (biochemical) and *in vivo* (in cell) studies. In particular, single-molecule and super-resolution techniques are powerful tools for studying the spatial and temporal heterogeneities that are intrinsic to complex biological systems. We synergistically combine this effort with cutting-edge developments in chemical and synthetic biology, microfluidics and microscope engineering to increase the throughput, strength and sensitivity of the approach as a whole.

RESEARCH HIGHLIGHTS

Our strong focus on understanding the mechanisms of IDP function and molecular ageing is both driven by and driving novel tool developments for "in-cell/*in situ* structural biology." This comprises a synergistic effort of chemical/synthetic biology and precision fluorescence-based technology/nanoscopy/single-molecule/super-resolution/

microfluidics development. A major technical breakthrough of my lab was the ability to engineer “click”able functionalities into any protein *in vitro* and *in vivo*. This genetic code expansion (GCE) approach has the potential to become a true GFP (fusion protein) surrogate strategy, with the major advantage being that superior synthetic dyes can be coupled with residue-specific precision anywhere in a protein. This opens up new avenues in single-molecule fluorescence and super-resolution microscopy. More recently, we have been able to merge our understanding of protein disorder and synthetic biology to design new membraneless organelles dedicated to protein engineering *in situ*. These custom organelles do not just execute a distinct second genetic code inside the cells; their bottom-up design also enables us to learn how phase separation can be used to generate new functions in eukaryotes. Our findings also have wider implications for understanding gene regulatory and stress-based mechanisms that are carried out by distinct, naturally-occurring organelles and play vital roles in regular cell function, as well as in ageing. These precision tools enable us to make even the most complex molecular machinery visible to our core methodologies, which are based on time-resolved multiparameter and nanoscopy tools. This allows innovative approaches to study the heterogeneity of IDPs *in vitro* and *in vivo*. We discovered a distinct ultrafast protein-protein interaction mechanism that can explain how nuclear pore complexes (NPCs) efficiently fulfil their central role in cellular logistics and how nuclear transport can be both fast and selective at the same time.

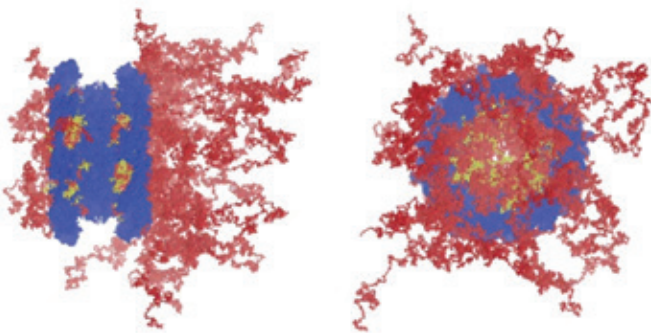


Figure 1. Shown is the top and side view of the nuclear pore complex. The red shows the intrinsically disordered proteins that are not resolved by electron tomography, in contrast to the donut-shaped scaffold structure formed from more folded proteins in blue.

Most recently, all the seemingly different efforts of my lab in chemical/synthetic biology and fluorescence biophysics concluded in a single study that visualised for the first time the permeability barrier of the functional nuclear pore complex *in situ* (Figure 1), which is responsible for regulating all the traffic between the cytoplasm and the nucleoplasm. The key finding that IDPs in this machinery can become a solvent for themselves and that this is accompanied by a giant conformational change in the protein, showcases a genuine example of how knowledge from polymer science can improve our understanding of biological systems.

FUTURE DIRECTIONS

IDPs lack a stable structure and can easily misfold to the amyloid state and aggregate, resulting in their prominent role in many age-related diseases. This intrinsic risk must be outweighed by multiple advantages to explain their enrichment in the evolution of more complex species, but we are only beginning to understand this. IDPs are highly multifunctional and due to their multivalency and large, disordered regions, they can function as dynamic scaffold platforms. We combine chemical and synthetic biology approaches to enable non-invasive, multi-colour high- and super-resolution studies of activity-dependent protein conformation changes in living cells, enabling fluorescence-driven *in situ* structural biology. The key point is that the enhanced spatial and temporal resolution offered by our fluorescent methods will enable us to detect rare events and unexpected behaviours inside cells, which we will then use to identify and understand IDP multifunctionalities that are clearly distinguishable from their normal mode of action. For example, nucleoporins (Nups) normally function in the nuclear pore complex (NPC), but in fact many IDP-Nups have diverse roles, such as in pathogen-host interactions, and can even shuttle away from the NPC to function in gene regulatory processes. Moreover, fusions of *Nup98* with transcription factors are known to be linked to leukaemia. Our work is accompanied by rigorous analysis of the physicochemical properties of IDPs and examines to what extent simple, known polymer concepts such as phase separation can be used to describe the function of IDP biopolymers *in vivo*. Vice versa, we are particularly interested in how disordered proteins play key roles in gene regulation and cellular ageing.

SELECTED PUBLICATIONS

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Reinkemeier CD and Lemke EA (2021) Dual film-like organelles enable spatial separation of orthogonal eukaryotic translation. *Cell*, 184:4886-4903.e21

Reinkemeier CD*, Girona GE* and Lemke EA (2019) Designer membraneless organelles enable codon reassignment of selected mRNAs in eukaryotes. *Science*, 363:eaaw2644

*indicates joint contribution, *indicates joint correspondence

Katja Luck

“*Using AI and experimentation, we work towards a structurally-resolved protein interactome.*”



POSITIONS HELD

- Since 2020** Emmy Noether Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2013 – 2019** Postdoctoral Fellow, Dana-Farber Cancer Institute and Harvard Medical School, Boston
- 2007 – 2008** Research Assistant, EMBL, Heidelberg

EDUCATION

- 2012** PhD in Bioinformatics, University of Strasbourg
- 2007** Diploma in Bioinformatics, Friedrich Schiller University Jena

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Lab Manager Mareen Welzel

OVERVIEW

Cells function because their molecular components (DNA, RNA, proteins) interact with each other. This complex network of molecular interactions mediates all cellular functions and organisation. Genetic and environmental insults perturb these interactions, causing disease. Because of technical limitations, we lack a comprehensive structural and functional understanding of all the protein interactions in human cells, hindering our ability to understand physiological and pathological molecular mechanisms. To tackle this, my lab develops novel computational and experimental methods to identify protein interaction interfaces, and based on this, obtains information on their molecular functions. We use protein interaction interface information to predict the pathogenicity of genetic variants and develop integrative omics data approaches to generate testable mechanistic hypotheses. We apply our approaches to study proteins associated with neurodevelopmental disorders (NDDs), fibroblast growth factor receptors and their role in cancer, proteins involved in mRNA splicing and BAF chromatin remodelling complexes in genome stability.

RESEARCH HIGHLIGHTS

Identification of protein interaction interfaces

Proteins exhibit a modular architecture consisting of folded domains and disordered regions, which can carry short linear motifs. Proteins commonly mediate interactions with each other via domain-domain or domain-linear motif interaction interfaces. We build tools to predict the interfaces in known protein interactions. To this end, we benchmarked the ability of AlphaFold Multimer to accurately predict structures of interacting proteins. We found that AlphaFold (AF) predictions are not very specific and decrease dramatically in sensitivity when using longer protein fragments or

full-length sequences. We therefore developed a prediction pipeline to optimise AF's sensitivity and specificity. Using this pipeline, we predicted interfaces for 62 protein interactions (Luck *et al*, 2020, *Nature*) that link NDD-associated proteins. We obtained highly confident predictions for 18 of these interactions, 7 of which we experimentally validated. We discovered a novel type of interface that mediates binding between the peroxisomal membrane proteins PEX3 and PEX16 and identified a variation of a GYF domain-motif interface type that mediates the interaction between SNRPB and GIGYF1, possibly linking mRNA splicing with posttranscriptional regulation (Lee *et al*, 2023, *bioRxiv*). We also successfully used this prediction pipeline to discover, in collaboration with the Ketting (IMB) and Stelzl (IMB/JGU) labs, a novel interface type that mediates binding between proteins in the piRNA biogenesis pathway (Bronkhorst *et al*, 2023, *EMBO J*).

Experimental mapping of protein interaction interfaces using XL-MS

We explore the use of crosslinking mass spectrometry (XL-MS) to advance the experimental mapping of interfaces in known protein interactions. We are playing with various crosslinkers and selected ~30 interactions with structurally-resolved interfaces to develop and benchmark our XL-MS pipeline. We have almost completed the crosslinking of these PPIs. Initial results suggest that crosslinks are often

not indicative of the crystallised interfaces. We will further analyse the data and repeat the experiments with other crosslinkers to comprehensively assess the ability of XL-MS to discover protein interaction interfaces.

Molecular mechanisms that regulate mRNA splicing

In collaboration with the König (IMB) and Sattler labs (TU Munich), we used our approaches to decipher protein interactions that play a role in mRNA splice site recognition and pairing. We provide strong evidence that FUBP1 is a novel core splice factor that is important for splicing long introns (Ebersberger *et al*, 2023, *Mol Cell*).

Integrative systems biology

Integrating various omics data resources is a powerful strategy for deciphering the systems properties of cells and allows us to employ a data-driven approach to identify new cellular mechanisms. We integrate protein interaction, gene expression and mutation data to predict the molecular mechanisms that mediate brain-specific phenotypes in neurodevelopmental disorders. We also collaborate with the Schick lab (IMB) to gain a systematic understanding of the role of BAF chromatin remodelling complexes in genome stability as part of the Collaborative Research Centre (CRC) 1361.

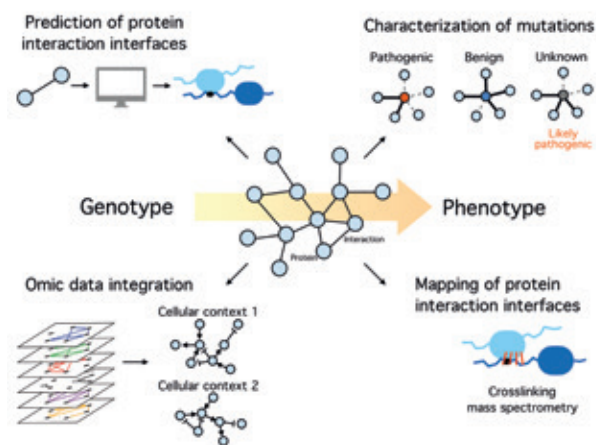


Figure 1. Interactions between proteins are central to cellular function. To improve our ability to predict phenotypes from genotypes, we develop computational and experimental methods to structurally and functionally characterise protein interactions, use interaction profiling to characterise mutations and use omics data integration to predict cellular mechanisms for selected biological processes.

FUTURE DIRECTIONS

We will continue developing tools to predict and experimentally characterise protein interaction interfaces, with the goal of studying interactions involving disordered regions of proteins. Such interactions are often involved in the formation of liquid-like condensates, which we aim to study in the context of viral infections, mRNA splicing and protein homeostasis; the latter is funded as part of the CRC 1551 in collaboration with the Beli lab (IMB) as well as the Kukhareno and Kremer labs (Max Planck Institute for Polymer Research). An intriguing idea is to use critical interaction interfaces to develop proximity-induced drugs to modulate so-far undruggable biological processes.

SELECTED PUBLICATIONS

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Ebersberger S^{*}, Hipp C^{*}, Muloz MM^{*}, Buchbender A, Hubrich D, Kang HS, Martínez-Lumbreras S, Kristofori P, Sutandy FXR, Llacsahuanga Allcca L, Schönfeld J, Bakisoglu C, Busch A, Hänel H, Tretow K, Welzel M, Di Liddo A, Möckel MM, Zarnack K, Ebersberger I, Legewie S, Luck K^{*}, Sattler M[#] and König J^{*} (2023) FUBP1 is a general splicing factor facilitating 3' splice site recognition and splicing of long introns. *Mol Cell*, 83:2653-2672.e15

Luck K^{*}, Kim DK^{*}, Lambourne L^{*}, Spirohn K^{*} ..., Hill DE[#], Vidal M[#], Roth FP[#] and Calderwood MA[#] (2020) A reference map of the human binary protein interactome. *Nature*, 580:402-408

[#]indicates joint contribution, ^{*}indicates joint correspondence

Brian Luke

“*Surprisingly, replicative senescence can even occur when the telomeres are maintained.*”



POSITIONS HELD

- Since 2017** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Heisenberg Professor, Johannes Gutenberg University Mainz (JGU)
- 2014 - 2017** Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2009 - 2014** Group Leader, Centre for Molecular Biology (ZMBH), University of Heidelberg
- 2005 - 2009** Postdoc, Swiss Federal Institute of Technology Lausanne (EPFL)
- 2005** Postdoc, Swiss Federal Institute of Technology Zurich (ETH)

EDUCATION

- 2005** PhD in Biochemistry, Swiss Federal Institute of Technology Zurich (ETH)
- 1999** BSc in Biology, Queen's University, Ontario

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Master Students Tobias Frank, Sophia Sergi

Bachelor Student Franziska Roithner

Technicians Dennis Knorr, Stefanie Reimann

Personal Assistant Christiane Stürzbecher

OVERVIEW

In the soma, telomeres shorten following each round of cell division due to the end replication problem. Shortened telomeres activate the DNA damage checkpoint but avoid repair; as a consequence cells with short telomeres experience stable cell cycle arrest; this is referred to as replicative senescence. Replicative senescence serves as a tumour suppressor by limiting the replicative potential of proliferating cells. Cancer cells, however, replicate indefinitely because they re-activate a telomere maintenance mechanism. The majority of human cancers re-express the telomerase enzyme to maintain telomeres. A subset of cancers employ homology-directed repair (HDR) to lengthen telomeres; this mechanism is frequently referred to as ALT (alternative lengthening of telomeres). Telomerase inhibitors have been unsuccessful in the treatment of human cancer due to their unwanted side effect of inhibiting telomerase in haematopoietic stem cells, which leads to bone marrow failure. The ALT mechanism, on the other hand, has only been observed in cancer cells, making ALT features potential cancer-specific drug targets. We have used budding yeast as a model for ALT to demonstrate that, unexpectedly, these cells undergo a form of replicative senescence, which is regulated by R-loops at telomeres. These results indicate that ALT cancers may be sensitive to senolytic agents.

RESEARCH HIGHLIGHTS

When telomerase is deleted in budding yeast, the following occur: i) cells lose replicative potential with increased population doublings, ii) they eventually enter a state of senescence, and iii) they re-emerge as survivors using HDR as a telomere maintenance mechanism. It was previously thought that survivors continue to proliferate indefinitely and acquire an immortal status, in a manner equivalent to

their human ALT cancer counterparts. Indeed, it was also previously reported that telomere length was maintained in survivors. We tested the notion that the immortality and telomere length maintenance were an artifact of heterogeneity within the cell culture. Indeed, by isolating single cell clones, we were able to demonstrate that yeast survivors undergo constant telomere shortening with increasing population doublings. At the same time, the cells progressively lose their replicative potential. The clonal populations eventually undergo another round of HDR and the process re-initiates. Therefore, post-senescent survivors also undergo a form of replicative senescence that at first glance is similar to “normal” replicative senescence. We refer to this phenomenon as survivor associated senescence (SAS). We have previously demonstrated that the non-coding RNA TERRA and R-loops are both critical in regulating the rate of replicative senescence. We set out to test whether TERRA and R-loops were also implicated in SAS. We observed that both TERRA levels as well as telomeric R-loops were up-regulated in survivors. This is similar to what has previously been reported in ALT cancer cell lines. We investigated what was responsible for the upregulation of TERRA in survivors, as this is also unknown in ALT cell lines. Strikingly, we were able to show that TERRA is specifically up-regulated when telomeres become critically short during SAS. Hence, the regulation of TERRA and R-loops is identical to what occurs during replicative senescence (Figure 1). Similar to

senescence, either the elimination or hyper-stabilisation of R-loops at telomeres is able to accelerate or reduce the rate of SAS, respectively. The fact that survivors also experience senescence phenotypes may have important therapeutic implications for ALT cancer cells.

FUTURE DIRECTIONS

We would like to fully characterise the SAS phenotype and determine its similarities and differences compared to “normal” replicative senescence. For example, is the gene expression profile associated with senescence identical to that of SAS cells? Furthermore, is the rate of telomere shortening the same, or are SAS cells more likely to bypass senescence at an earlier stage due to their recombinogenic nature? Finally, are the genetic interactions that regulate rates of replicative senescence the same as those that may regulate rates of SAS? The answers to these questions will be critical in understanding how to specifically target and halt the growth of survivors, and eventually ALT cancer cells. We would like to initiate collaborations to determine if ALT cells also experience senescence (SAS) in the same manner as survivors. Finally, it will be interesting to test whether senolytic and senomorphic agents have an inhibitory effect on the growth of ALT compared to telomerase-positive cancer cells.

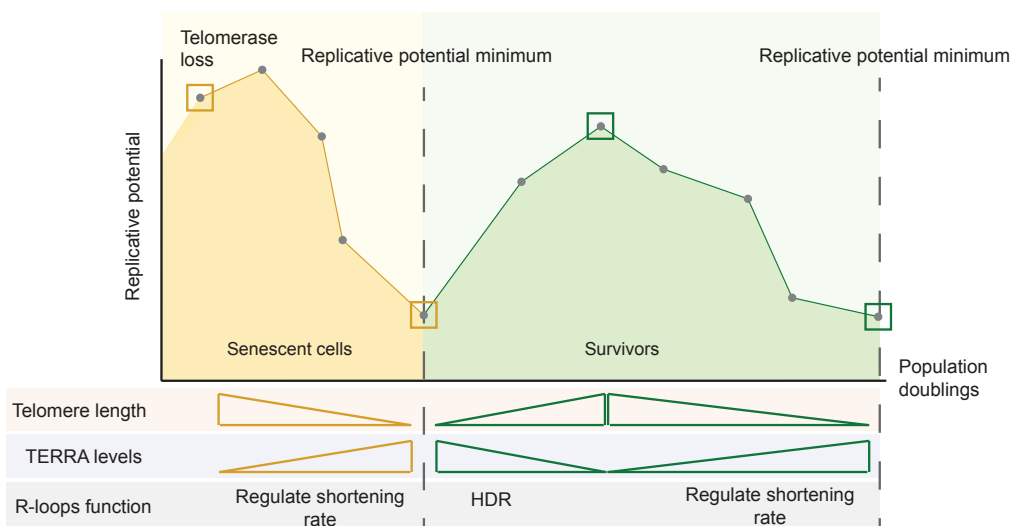


Figure 1. Upon telomerase removal, telomere length decreases and TERRA/R-loop levels increase. Their increase slows the rate of senescence onset by maintaining the length of short telomeres. Eventually survivors arise, telomeres are re-elongated by recombination and TERRA levels drop. Importantly, the cycle continues and telomeres once again shorten, with TERRA and R-loops regulating the rate of SAS. This image was published under a Creative Commons Attribution License. From Misino *et al* (2022), *Nucleic Acids Res.*

SELECTED PUBLICATIONS

Misino S, Busch A, Wagner C, Bento F and Luke B (2022) TERRA increases at short telomeres in yeast survivors and regulates survivor associated senescence (SAS). *Nucleic Acids Res*, 50:12829–12843

Pérez-Martínez L, Wagner T and Luke B (2022) Telomere interacting proteins and TERRA regulation. *Front Genet*, 13:872636

Wagner CB and Luke B (2022) DNA–RNA hybrids at telomeres in budding yeast. *Methods Mol Biol*, 2528:145–157

Christof Niehrs

“ We use frogs as a model to study the epigenetics of ageing. ”



POSITIONS HELD

- Since 2021** Director, Centre for Healthy Ageing (CHA), Mainz
- Since 2010** Founding & Scientific Director, Institute of Molecular Biology (IMB), Mainz
Professor, Johannes Gutenberg University Mainz (JGU)
- Since 2000** Professor of Molecular Embryology, German Cancer Research Center (DKFZ), Heidelberg
- Since 1994** Head of Division “Molecular Embryology”, German Cancer Research Center (DKFZ), Heidelberg
- 1990 - 1993** Postdoc, University of California Los Angeles (UCLA)

EDUCATION

- 1997** Habilitation in Biology, University of Heidelberg
- 1990** PhD in Biology, European Molecular Biology Laboratory (EMBL) & University of Heidelberg
- 1985** Diploma in Biochemistry, Free University of Berlin

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OVERVIEW

Although DNA is commonly perceived as a static molecule, genomic nucleobases are in fact physiologically modified by a variety of chemical modifications. These DNA modifications are deposited in the genome in a site-specific manner and are known or suspected to epigenetically regulate gene expression. Typically, DNA modifications are recognised by specific reader proteins and can be reversed by a variety of enzymatic mechanisms. We study which DNA modifications occur in the mammalian genome, how and where they are deposited, what biological role they play, and how they are recognised and removed. We use ultrasensitive mass spectrometry to identify and quantify DNA modifications in mammalian cells. We employ next-generation sequencing and computational analysis to identify modification sites genome-wide. We characterise the roles of proteins involved in depositing, reading and removing modifications in embryonic stem cells, *Xenopus* embryos and mice. More recently, we have also begun to study DNA methylation-based epigenetic clocks in *Xenopus*.

RESEARCH HIGHLIGHTS

Frog epigenetic clocks

The study of epigenetic ageing has gained attention recently due to its implications for understanding the mechanisms of ageing across species. While much of this research focused on mammals, there is a growing interest in exploring epigenetic ageing in non-mammalian organisms to uncover shared patterns and conserved mechanisms. The African clawed frog (*Xenopus*) is a widely used model system because of its experimental tractability and closer evolutionary relationship with humans compared to fish or invertebrates.

In a collaboration with Steve Horvath (University of California Los Angeles, US), we established the first DNA

methylation clock in *Xenopus* (Zoller *et al*, 2023). First, we developed a technique to measure the amount of methylation in genomic DNA at a sufficient sequencing depth. Our platform of choice was the mammalian methylation array, which allowed us to profile individual CpGs that are highly conserved in mammalian DNA. Because the mammalian methylation array analysis has over a thousand-fold sequencing depth at highly-conserved CpGs, it makes comparative studies across mammals (including humans) easier.

We generated unique DNA methylation (DNAm) data from *X. laevis* and *X. tropicalis* and analysed it using this platform. We examined complete embryos and tadpoles and 6 tissues from animals ranging from 2 days to 19 years of age. We built several DNAm clocks, including *X. laevis* and *X. tropicalis* clocks, as well as a pan-*Xenopus* clock. We also built dual species clocks that apply to both humans and frogs (human-clawed frog clocks), supporting the idea that epigenetic ageing processes are evolutionary conserved outside mammals. Highly conserved, positively age-related CpGs are located in neural-developmental genes such as *uncx* and *tfap2d*, as well as *nr4a2*, which is implicated in age-associated disease. The frog clocks showed epigenetic ageing in embryos and larvae, i.e. before metamorphosis. Many developmental regulators are encoded by *Xenopus* genes associated with positive age-related CpGs, supporting the idea of ‘embryonic ageing’.

We conducted an age-related epigenome-wide association study (EWAS). Positive age-related CpGs were found in developmental gene sets, including embryonic skeletal system development and Polycomb repressive complex 2 (PRC2) target sites. Previous human studies indicated that age-related CpGs are associated with PRC2 target sites, which have more methylation with age, and *Xenopus* replicates this trait. We also discovered enrichments for gene sets in mouse development, such as axial skeleton and rib morphology. Negatively age-related CpGs were less enriched and GO keywords included synaptic transmission and RNA splicing.

In summary, we found that frogs can be used to establish epigenetic clocks and that the underlying ageing markers and CpG features are conserved between humans and frogs. Age-related CpGs are located near genes also found in mammalian clocks and are implicated in age-associated disease. Positive age-related CpGs are associated with PRC2 target sites, just like in mammals. These epigenetic clocks provide the first reliable age indicator in *Xenopus* and allow for the study of ageing in tadpoles and juveniles in this well-established model system. As with human pan-tissue clocks, the *Xenopus* clocks suggest that ageing may be a systemic biological process affecting the entire body.

FUTURE DIRECTIONS

In future, based on the frog DNAm clocks, we will establish a ‘sparse clock’ that allows for higher throughput routine DNAm age determinations. The highly conserved age-related CpGs in neural-developmental genes present an opportunity for functional studies. In-depth investigations into the role of these genes in *Xenopus* neural development and ageing can be conducted. Assessing other age-associated molecular phenotypes in *Xenopus*, such as chromatin changes, can complement the DNAm data. Future experiments will focus on characterising age-related chromatin changes and linking them to specific epigenetic changes and neural genes. To explore potential interventions that mitigate age-related epigenetic changes, experiments involving pharmaceutical or genetic interventions will be designed. Testing the effects on *Xenopus* ageing will provide insights into strategies to modulate epigenetic ageing. These approaches will contribute to the establishment of *Xenopus* as a novel model system for studying the biology of ageing and age-associated diseases.

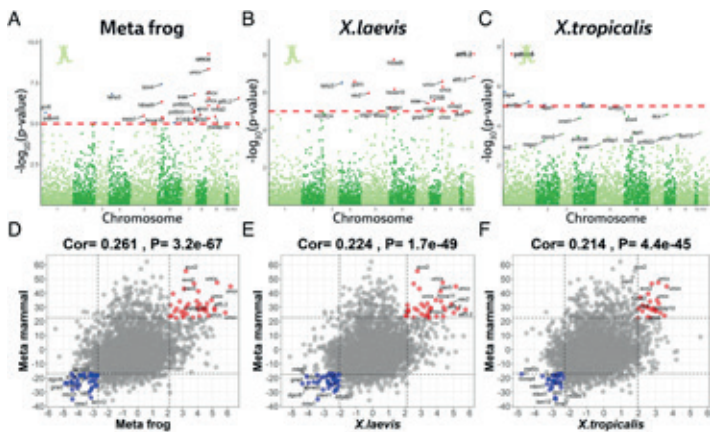


Figure 1. Age-related epigenome-wide association study (EWAS) of age in *Xenopus*. Top, Manhattan plots of A) combined *X. laevis* and *X. tropicalis*, B) *X. laevis*, and C) *X. tropicalis* DNAm across all tissues. Red lines indicate levels of significance. D)-F) Scatter plots between frog EWAS of age and Eutherian EWAS of age. Each point in the scatter plot corresponds to a CpG present in our mammalian array and maps to the *X. tropicalis* genome. CpGs are colored in red or blue for positive or negative age correlations, respectively.

SELECTED PUBLICATIONS

Zoller JA*, Parasyraki E*, Lu AT, Haghani A, Niehrs C* and Horvath S* (2023) DNA methylation clocks for clawed frogs reveal evolutionary conservation of epigenetic aging. *GeroScience*, 46:945-960

Musheev MU*, Schomacher L*#, Basu A*, Han D, Krebs L, Scholz C and Niehrs C* (2022) Mammalian N1-adenosine PARylation is a reversible DNA modification. *Nat Commun*, 13:6138

Musheev MU*, Baumgärtner A, Krebs L and Niehrs C* (2020) The origin of genomic N6-methyl-deoxyadenosine in mammalian cells. *Nat Chem Biol*, 16:630-634

*indicates joint contribution, #indicates joint correspondence

Jan Padeken

“*We link the epigenome to stress and genome stability during ageing and development.*”



POSITIONS HELD

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EDUCATION

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Technician Sheraz Sadouki

Research Assistant Lisa Fol

OVERVIEW

The epigenetic memory of a cell is shaped by pathways that establish, erase and maintain chromatin marks. Lysine 9 methylation on histone H3 (H3K9me) is a defining modification of heterochromatin. In multicellular eukaryotes, heterochromatin has two main functions. First, it silences repetitive sequences to ensure genome stability; second, it maintains the silencing of genes during and post development to ensure a stable differentiated state. The unprogrammed transcription of repetitive sequences leads to an accumulation of toxic R-loops and a dependence on BRCA1 and DNA repair proteins for survival. Thus, it is not surprising that the loss of appropriately targeted heterochromatin is associated with cancer and ageing. In our lab, we are interested in this interface between the mechanisms that establish or alter heterochromatin and the DNA damage response, particularly in the context of premature ageing.

RESEARCH HIGHLIGHTS

How does persistent DNA damage alter heterochromatin after acute exposure and are these changes maintained in old cells?

Rare genetic diseases have been central in linking DNA damage to ageing. Cockayne syndrome (CS) is caused by autosomal recessive mutations in either the *CSA* or *CSB* gene and results in persistent DNA damage. *CSA* and *CSB* are essential for initiating transcription-coupled nucleotide excision repair (TC-NER), a DNA damage response pathway that repairs DNA lesions (e.g. UV-induced pyrimidine dimers) blocking RNA polymerase II at sites of active transcription. CS patients therefore accumulate persistent DNA damage in transcribed genes. This manifests in a complex, multi-organ set of clinical features, including premature ageing, neurodegeneration, dysfunctional mitochondria,

retarded development and loss of subcutaneous fat and muscle function. This progressive, multi-tissue pathology requires a simple but well-characterised model organism such as *C. elegans*, which, in contrast to the mouse, mimics the clinical features of CS patients. Survival of persistent UV damage is tightly linked to genome-wide chromatin changes. Interestingly, the phenotypes observed in CS patients (or the worm model) are mimicked by the loss of H3K9me. Indeed, H3K9me and the histone methyltransferase (HMT) MET-2 are essential in the CS model.

Using our expertise in chromatin biology, we describe the acute and persistent changes in heterochromatin upon persistent UV damage to ultimately answer how H3K9me protects an organism from the persistent DNA damage and premature ageing characteristic of CS.

What are the mechanisms that mediate *de novo* establishment of heterochromatin?

The importance of H3K9me in the stress response, as well as its role in silencing tissue-specific genes and potentially active transposable elements, imply that H3K9me can be highly dynamic. To understand the *de novo* establishment and maintenance of heterochromatin domains on a mechanistic level, we developed a unique system to identify sequences that are sufficient to trigger *de novo* recruitment of the two H3K9-specific HMTs and identify the proteins

that are essential for establishing the H3K9me domain. We will use this to screen for factors essential for the establishment vs. maintenance of heterochromatin and link these pathways to the stress response and premature ageing.

What regulates chromatin compaction and transcriptional noise at heterochromatic genes in parallel to H3K9me?

We previously showed that loss of H3K9me results in cell-type-specific gene derepression (Methot *et al.*, 2021). Interestingly, loss of H3K9me was not sufficient to establish an open, decondensed chromatin state at the promoter and enhancer regions of the derepressed genes. We also observed that this specific form of derepression was characterised by high cell-to-cell transcriptional variability, even between cells of the same tissue. Because this stochasticity in gene expression mirrors the stochastic phenotypes associated with loss of heterochromatin across evolution and has also been repeatedly observed in old or senescent cells, we are currently establishing imaging-based methods to quantitatively screen for mediators of both chromatin compaction and transcriptional noise.

FUTURE DIRECTIONS

Ultimately, the projects above will give us a comprehensive understanding of the pathways that regulate heterochromatin and enable us to ask how these processes are (mis)regulated during ageing and persistent DNA damage. It will also give us a basis to further explore how DNA damage response pathways impact chromatin states beyond the acute response at the site of damage and link this to progeria models such as CS, Hutchinson-Gilford progeria and normal ageing.

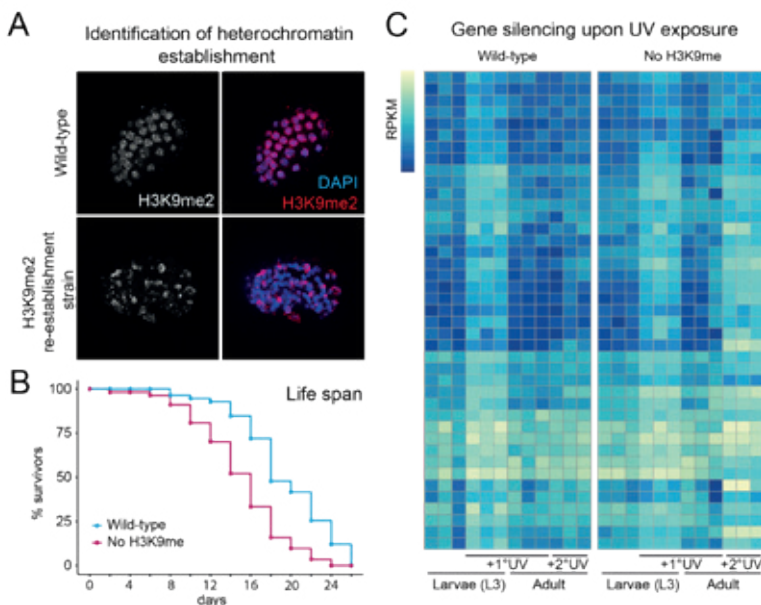


Figure 1. How is epigenetic silencing changed during stress and ageing? A) Example *C. elegans* strain used to identify pathways essential for *de novo* H3K9me establishment. B) Loss of heterochromatin results in a shortened life span and premature ageing. C) Long term, H3K9me-dependent gene silencing induced by UV light.

SELECTED PUBLICATIONS

Delaney CE, Methot SP, Kalk V, Seebacher J, Hess D, Gasser SM and Padeken J (2022) SETDB1-like MET-2 promotes transcriptional silencing and development independently of its H3K9me-associated catalytic activity. *Nat Struct Mol Biol*, 29:85-96

Methot SP*, Padeken J*, Brancati G, Zeller P, Delaney CE, Gaidatzis D, Kohler H, van Oudenaarden A, Großhans H and Gasser SM (2021) H3K9me selectively blocks transcription factor activity and ensures differentiated tissue integrity. *Nat Cell Biol*, 23:1163-1175

Padeken J, Methot S, Zeller P, Delaney CE, Kalk V and Gasser SM (2021) Argonaute NRDE-3 and MBT domain protein LIN-61 redundantly recruit an H3K9me3 HMT to prevent embryonic lethality and transposon expression. *Genes Dev*, 35:82-101

*Indicates joint contribution

Stamatis Papathanasiou

“ We unravel unknown mechanisms of tumorigenesis from errors in mitosis. ”



POSITIONS HELD

- Since 2023** Group Leader, Institute of Molecular Biology (IMB), Mainz
- 2015 – 2023** Postdoc, Harvard Medical School and Dana Farber Cancer Institute, Boston

EDUCATION

- 2015** PhD in Molecular Medicine, National and Kapodistrian University of Athens
- 2008** MSc in Molecular Medicine, National and Kapodistrian University of Athens
- 2005** BSc in Molecular Biology and Biotechnology, University of Crete

GROUP MEMBERS

- PhD Student** Tsung-Lin Tsai
- Research Assistant** Evlambia Parcharidou

OVERVIEW

Proper division of the genomic material is fundamental for cell homeostasis. Although cells have many mechanisms to ensure error-free division, mistakes are common and a hallmark of disease. One consequence of mitotic errors is abnormal nuclear structures such as micronuclei and chromosome bridges – common features of nuclear atypia with a central role in the development of cancer. Micronuclei (“MN”, Figure 1A) are miniature, extra nuclei that form when a chromosome lags during mitosis and recruits its own nuclear envelope. Micronuclei nuclear envelope rupture exposes DNA to the cytoplasm, leading to massive DNA damage. The lesions in the micronucleated chromosome can lead to complex chromosomal rearrangements (“chromothripsis”) and ongoing genome instability. Intriguingly, cells with chromothriptic signatures are extremely penetrant in cancer, showing that they can confer a gain of fitness and even drive tumorigenesis. Although the self-amplifying genetic instability and clinical importance of these nuclear abnormalities are well-recognized, we are missing a detailed understanding of the immediate and long-term, non-genetic, functional consequences of these mitotic errors.

RESEARCH HIGHLIGHTS

Transgenerational inheritance of chromatin defects from mis-segregated chromosomes

We recently proposed a new model of transgenerational epigenetic instability caused by chromosome mis-segregation in mitosis. Specifically, we discovered a phenomenon of heritable chromatin and transcriptional defects mediated by micronuclei (Papathanasiou *et al*, 2023, Nature). The transcriptional and chromatin states of micronucleated chromosomes are extensively altered; these can be inherited by daughter cells, even after the chromosomes are reincorporated into the normal nuclear

environment. Finally, we discovered that persistent transcriptional repression is strongly associated with long-lived DNA damage to these abnormal chromosomes. Taking advantage of this finding, we generated cellular systems to detect and track damaged chromosomes from micronuclei, e.g. fluorescently labelled-MDC1-expressing cells (Figure 1A). We called these structures of reincorporated MN chromosomes with altered chromatin “MN-bodies”. The exact circumstances under which cell division errors lead to massive DNA lesions and other chromatin alterations, how they are inherited in progeny cells and their functional significance all remain a mystery, partly due to a lack of appropriate tools. We develop novel technologies and advanced cellular systems allowing us to approach these questions from a unique angle. For example, we developed a method that combines long-term live-cell imaging and same-cell, direct single-cell RNA sequencing of the whole family of cells after two generations, named “Look-Seq2” (Figure 1B). We are building on this by developing an advanced experimental and computational framework (Simultaneous IMAGING and Direct Isolation for sequencing, “SIMADI-Seq”), which will allow us to directly link observed phenotypes to function by combining imaging and “omics” at the single-cell level. Unravelling the functional properties of abnormal genomes at the single-cell level is fundamental for understanding cellular heterogeneity in disease and developing new therapeutic strategies. Another technology bottleneck was the inability to target specific chromosomes for mis-segregation. We overcame this by developing a novel method to generate “targeted” mis-segregations and micronuclei, with a priori knowledge of the micronucleated chromosome. While doing this, we discovered that micronuclei are a prominent on-target side effect of genome editing, unravelling a previously unknown universal action of CRISPR-Cas9 (Leibowitz*, Papathanasiou* *et al*, 2021,

Nat Genetics). These findings were the basis of one of the first described side effects of genome editing, with fundamental implications for therapeutic applications in clinical trials. We are now further developing these “targeted” approaches and combining them with our cellular systems for tracking mis-segregated chromosomes. Our discovery that micronuclei are a source of transcriptional heterogeneity and epigenetic instability established a new paradigm for how mitotic errors may be inherently coupled to the poorly understood non-genetic, cell-to-cell epigenetic variability in disease (e.g. cancer). Our research follows this new perspective on the functional consequences of mitotic errors and abnormal nuclei, which may impact tumour evolution.

FUTURE DIRECTIONS

We will further develop and combine cutting-edge methodologies with advanced systems to track mis-segregated chromosomes over multiple generations. We aim to identify additional sources of inherited abnormal nuclear structures and characterise their DNA damage/repair dynamics and epigenetic alterations. We will also focus on understanding how transcription dynamics are perturbed in daughter cells upon abnormal mitosis and define chromatin architecture and the higher-order genome organisation of mis-segregated chromosomes. Finally, we will investigate long-term cellular adaptations and assess the tumorigenic potential of abnormal chromosomes. Together, these studies will offer the first comprehensive assessment of non-genetic mechanisms by which errors in mitosis may drive cellular adaptation and tumorigenesis.

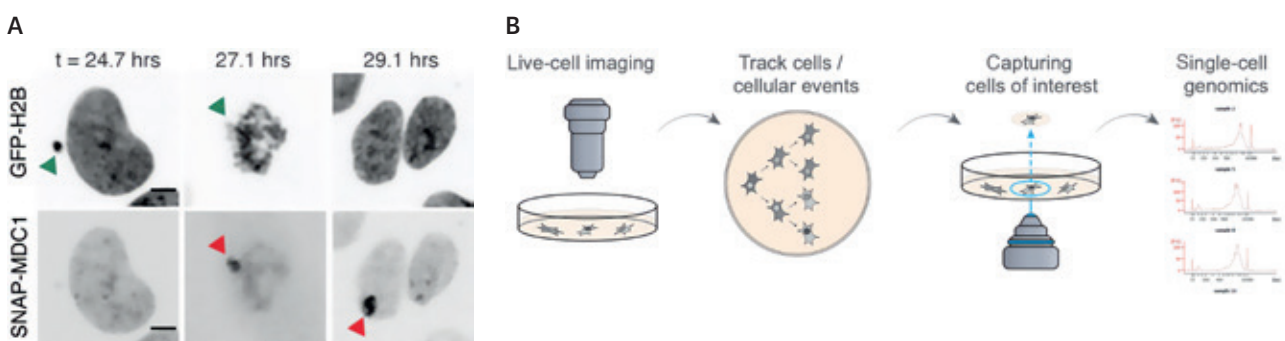


Figure 1. A) Formation of an MN-body (red arrowheads), a type of Mit-body, by reincorporation of a damaged (MDC1) micronucleus (green) into the primary nucleus of a daughter RPE-1 cell (t indicates time after release in mitosis, scale bar = 5 μm). B) Schematic overview of “SIMADI-seq” (based on the previously published “Look-Seq2” method).

SELECTED PUBLICATIONS

Papathanasiou S*, Myhner NA, Liu S, Brunette G, Stokasimov E, Jacob E, Li L, Comenho C, van Steensel B, Buenostro JD, Zhang CZ* and Pellman D* (2023) Heritable transcriptional defects from aberrations of nuclear architecture. *Nature*, 619:184-192

Leibowitz ML*, Papathanasiou S*, Doerfler PA, Blaine LJ, Sun L, Yao Y, Zhang CZ, Weiss MJ and Pellman D (2021) Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing. *Nat Genet*, 53:895-905

Papathanasiou S, Markoulaki S*, Blaine LJ*, Leibowitz ML, Zhang CZ, Jaenisch R and Pellman D (2021) Whole chromosome loss and genomic instability in mouse embryos after CRISPR-Cas9 genome editing. *Nat Commun*, 12:5855

*indicates joint contribution, *indicates joint correspondence

Vassilis Roukos

“*We develop imaging and sequencing methods to study when, where and why chromosomes break.*”



POSITIONS HELD

Since 2022 Assistant Professor, Medical School, University of Patras, Greece

Affiliated Group Leader, Institute of Molecular Biology (IMB), Mainz

2015 – 2022 Group Leader, Institute of Molecular Biology (IMB), Mainz

2013 – 2014 NIH Research Fellow, National Cancer Institute, National Institutes of Health (NIH), Bethesda

2008 – 2013 Postdoc, National Cancer Institute, National Institutes of Health (NIH), Bethesda

EDUCATION

2008 PhD in Molecular Biology & Cytogenetics, University of Patras Medical School

2005 MSc in Applications in Medical Sciences, University of Patras Medical School

2002 BSc in Biology, University of Patras

GROUP MEMBERS

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PhD Student Gabriel Longo

OVERVIEW

The focus of our lab is to understand how cells maintain the integrity of their genome in the context of 3D genome organisation. We are particularly interested in the life cycle of DNA double-strand breaks (DSBs), a very dangerous lesion for cells which if not faithfully repaired can lead to cell death or the formation of tumorigenic genome rearrangements. DSBs can be evoked exogenously upon cancer treatment or the use of programmed nucleases, such as CRISPR/Cas9, which both have important clinical implications, or upon perturbation of intrinsic fundamental cellular processes, such as DNA replication and transcription. A central focus of our work is to understand when, where, why and how chromosomes break across the 3D genome, and to understand how these fragile DNA sites can be turned into persistent breaks that promote the formation of genomic rearrangements. Moreover, we are interested in understanding how programmed nucleases, such as Cas9 and Cas12, generate specific cleavage patterns at different locations across the genome and harness this information to increase the fidelity, precision and predictability of genome editing.

RESEARCH HIGHLIGHTS

Mechanistic insights into the formation of therapy-related oncogenic translocations

Cancers are commonly treated with anticancer drugs called topoisomerase poisons. Treatment with topoisomerase poisons, however, can also cause chromosome translocations in healthy cells that disrupt gene regulation and lead to the development of leukaemia. It is unclear why these leukaemia-promoting translocations are so common after treatment with topoisomerase poisons. We are interested in combining cutting-edge genomics and single-cell imaging methods to determine why these leukaemia-promoting

translocations arise. Our current work has shown that certain sites with highly active genes tend to be close to regions where the DNA folds into chromatin loops and is under more mechanical strain. This makes them susceptible to DNA breaks caused by topoisomerase poisons such as etoposide, producing translocations that drive leukaemia. We have also identified factors involved in the repair of these DNA breaks that actively suppress the formation of translocations. In another direction that may have clinical implications, we are performing unbiased siRNA-based screens to identify factors that suppress these types of translocations while leaving the cytotoxic effect of topoisomerase poisons intact. Our findings highlight how gene activity and the arrangement of DNA within the nucleus can have a profound impact on events that trigger genomic instability and thereby promote cancer.

A novel method to profile Cas nuclease cleavage pattern identified

CRISPR/Cas9 is a powerful genome-editing platform, with immense potential for facilitating gene therapy to treat various diseases. However, Cas9 has a flexible scission profile, which might impact repair outcomes, and it is largely unknown what dictates the type of Cas9 incision that is made. We have developed a sensitive, fast, scalable and cleavage pattern-aware methodology to profile CRISPR/Cas9 on and off-target DSBs, which can be used to identify the determinants of Cas9 incisions. We have found that the target sequence determines how Cas9 cleaves DNA and that the type of incisions made is strongly associated with the repair outcome. Moreover, we identified Cas9 variants

with altered scission profiles and demonstrated that human genetic variation influences Cas9 cleavage and editing outcome, suggesting that patients' genetic backgrounds must be taken into consideration before clinically relevant efforts. Our work illuminates the fundamental characteristics of the Cas9 nuclease and lays the foundation for harnessing the flexible cutting profiles of Cas9 and engineered variants for template-free, precise and personalised genome editing.

FUTURE DIRECTIONS

Central to our focus is shedding light on cellular events that promote DNA fragility intrinsically or upon treatment with cancer therapy and the use of programmed genome-editing nucleases, such as CRISPR/Cas9 (Figure 1). In one of our future directions, we intend to profile endogenous DNA breaks across the genome in various cell types, with the aim of identifying common or cell type-specific signatures of DNA fragility. We will then focus on identifying mechanistically how these endogenous DNA breaks form and evaluate how DNA break repair efficiency is influenced by genomic, chromatin and chromosome organisation context. These studies will directly highlight the link between cell type-specific DNA fragility and repair in the formation of tissue-specific, recurrent oncogenic translocations. In a different direction, we will perform directed evolution and saturation mutagenesis experiments to engineer novel Cas9 variants with higher specificity and predictable editing and will identify the determinants of other Cas9 nucleases, such as Cas12.

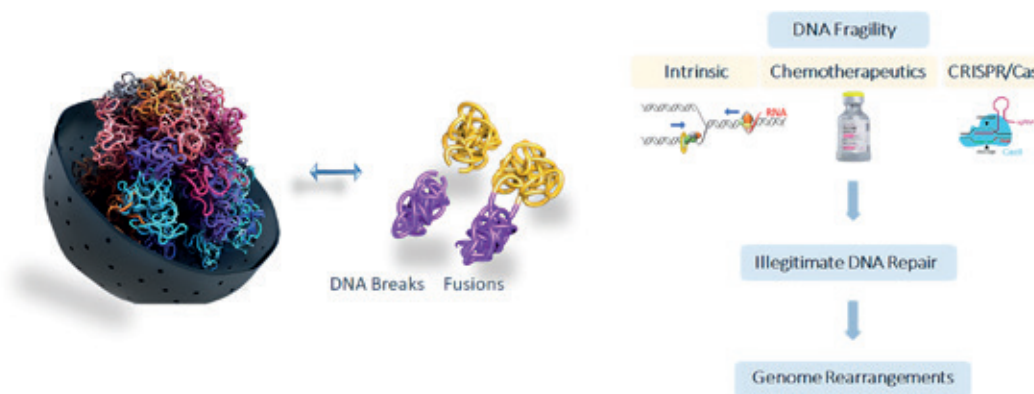


Figure 1. Our research focuses on shedding light on determinants of DNA fragility due to intrinsic cellular processes, treatment with cancer chemotherapeutics or genome editing nucleases, and on cellular pathways that prevent illegitimate repair and the formation of cancerous fusions.

SELECTED PUBLICATIONS

Longo GMC and Roukos V (2021) Territories or spaghetti? Chromosome organization exposed. *Nat Rev Mol Cell Biol*, 22:508-508

Gothe HJ, Bouwman BAM, Gusmao EG, Piccinno R, Petrosino G, Sayols S, Drechsel O, Minneker V, Josipovic N, Mizi A, Nielsen CF, Wagner EM, Takeda S, Sasanuma H, Hudson DF, Kindler T, Baranello L, Papantonis A, Crosetto N and Roukos V (2019) Spatial chromosome folding and active transcription drive DNA fragility and formation of oncogenic MLL translocations. *Mol Cell*, 75:267-283.e12

Piccinno R*, Minneker V* and Roukos V (2019) 53BP1—DNA repair enters a new liquid phase. *EMBO J*, 38:e102871

*indicates joint contribution

Sandra Schick

“*We investigate the role of chromatin remodelling under physiological and pathological conditions.*”



POSITIONS HELD

Since 2020 Group Leader, Institute of Molecular Biology (IMB), Mainz

2016 – 2020 Postdoctoral Fellow, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna

EDUCATION

2016 PhD in Molecular Biology, Institute of Molecular Biology (IMB), Mainz

2012 MSc in Biomedicine and Diploma in Biology, Johannes Gutenberg University Mainz (JGU)

2008 BSc in Molecular Biology, Johannes Gutenberg University Mainz (JGU)

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Master Student Aaron Ottmann

Student Assistants Lena Bonn, Thérèse Koppe, Amy-Sue Sattler, Mara Wolf

OVERVIEW

The condensation of the genome into higher-order chromatin structures requires various dynamic regulatory mechanisms that control the spatiotemporal organisation of genomic processes. These regulatory mechanisms ensure proper gene expression and thus the appropriate execution of all cellular processes. To achieve this, various regulators act in an integrative and coordinated fashion, resulting in a highly complex and fine-tuned system. Therefore, it is not surprising that mutations in genes encoding these regulators are frequently associated with various diseases. To uncover how these regulators integrate and contribute to gene regulation, genome stability and other genomic processes, we employ human cellular model systems and mouse models in combination with genome editing, epigenomics, proteomics and various molecular and biochemical approaches. Moreover, we explore the cellular and molecular consequences of mutations in these regulators to unravel the mechanisms underlying diseases and to identify potential therapeutic approaches.

RESEARCH HIGHLIGHTS

One class of chromatin regulators that is essential for modulating chromatin structure is the BRG1/BRM associated factor (BAF) chromatin remodellers. These remodellers are polymorphic complexes comprised of multiple subunits that are encoded by more than 30 genes and assembled in a combinatorial fashion. There are three subtypes of BAF complexes, each with a few distinct subunits: the canonical BAF complexes (BAF/cBAF), the polybromo-associated BAF complexes (PBAF) and the non-canonical GLTSCR1/1L-BAF complexes (GBAF/ncBAF). These remodellers utilise energy from ATP hydrolysis to slide or eject nucleosomes and thereby modulate DNA accessibility. They control gene

regulatory regions and consequently regulate a multitude of cellular functions. They are also crucial for developmental processes such as lineage specification and differentiation. Moreover, BAF complexes contribute to genomic processes such as the DNA damage response, DNA replication and sister chromatid cohesion, as well as chromatin topology and organisation. The unexpectedly high mutation rate in genes encoding various BAF subunits in cancer and neurodevelopmental disorders further highlights the importance of these remodellers. Therefore, it is of great relevance to elucidate the functions of the diverse BAF complexes and the molecular consequences of mutations in genes encoding BAF complex subunits. These insights will likely enable the development of new targeted therapeutics for BAF-associated diseases.

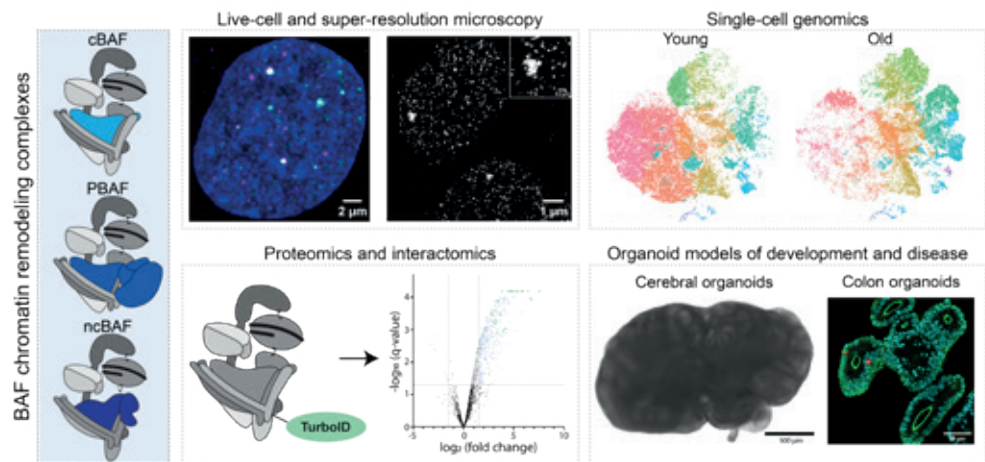
To achieve this, we systematically investigate the role of distinct BAF complexes in different cellular processes in conventional 2D cell lines using a wide variety of experimental approaches, ranging from live-cell and super-resolution microscopy to genomics and proteomics. Using these approaches, we observe BAF subtype-specific regulatory mechanisms, sometimes with opposing effects. In addition, we have established human organoid cultures that closely reflect the development and cellular heterogeneity of organs. These models allow us to investigate the role of BAF complexes in more physiological settings and to unravel their cell type-specific roles. For example, it has been

shown that their composition and function can differ by cell type and changes during development. In addition, these models offer a great opportunity to study diseases that are caused by mutations in BAF complex-encoding genes at the molecular and cellular level *in vitro*. Here, our studies show time- and cell type-dependent phenotypic, cellular and molecular alterations following BAF perturbations, which may mimic disease-related alterations in patients with BAF mutations. In particular, developmental processes and tissue homeostasis are impaired, leading, for example, to altered cell composition. Apart from this, we use mouse models to study the role of BAF complexes in specific cell types and explore alterations that occur during ageing and may promote age-related disorders.

FUTURE DIRECTIONS

We will further explore the molecular function and regulation of BAF complex subtypes, the processes they are involved in and how they integrate with other regulatory mechanisms using a number of different experimental and computational approaches. We will also continue to study context-dependent functions of BAF complexes, including their role in developmental processes, disease and ageing. Ultimately, our research aims to unravel pathogenic mechanisms that can be targeted for therapy.

Figure 1. Interdisciplinary approaches to understand the functions of different BAF complexes in various contexts. BAF chromatin remodellers are divided into three main subtypes: cBAF, PBAF, and ncBAF. Live-cell and super-resolution microscopy allows visualisation of chromatin regulators. Single-cell sequencing enables the study of cell populations under different conditions. Proximity ligation proteomics identifies proteins in the surroundings of BAF complexes. Human organoid models allow *in vitro* studies under more physiological conditions and disease modelling.



SELECTED PUBLICATIONS

Schick S*, Grosche S*, Kohl KE*, Drpic D, Jaeger MG, Marella NC, Imrichova H, Lin JMG, Hofstätter G, Schuster M, Rendeiro AF, Koren A, Petronczki M, Bock C, Müller AC, Winter GE and Kubicek S* (2021) Acute BAF perturbation causes immediate changes in chromatin accessibility. *Nat Genet*, 53:269–278

Varga J, Kube M, Luck K and Schick S (2021) The BAF chromatin remodeling complexes: structure, function, and synthetic lethality. *Biochem Soc Trans*, 49:1489–1503

Schick S, Rendeiro AF, Runggatscher K, Ringler A, Boidol B, Hinkel M, Májek P, Vulliard L, Penz T, Parapatics K, Schmidl C, Menche J, Boehmelt G, Petronczki M, Müller AC, Bock C and Kubicek S (2019) Systematic characterization of BAF mutations provides insights into intracomplex synthetic lethality in human cancers. *Nat Genet*, 51:1399–1410

*indicates joint contribution, *indicates joint correspondence

Lukas Stelzl

“*We predict the morphology of nuclear condensates to understand how dynamic self-organisation regulates biological processes.*”



POSITIONS HELD

Since 2020 Adjunct Group Leader, Institute of Molecular Biology (IMB), Mainz

ReALity Junior Group Leader, Johannes Gutenberg University Mainz (JGU)

2015 – 2020 Postdoctoral Fellow, Max Planck Institute of Biophysics, Frankfurt am Main

EDUCATION

2015 PhD in Biochemistry, University of Oxford

2010 MSc in Molecular and Cellular Biochemistry, University of Oxford

GROUP MEMBERS

PhD Students Ritika Arrgawal, Denis Arribas Blanco, Lucia Baltz, Kumar Gaurav, Cyrille Ngueldjou, Xiaofei Ping, Arya Changiarath Sivadasan, Mahesh Yadav, Emanuele Zippo

Master Student Vasilis Xenedis

Student Assistants Maximilian Mager, Yehor Tuchkov

OVERVIEW

We aim to elucidate how liquid-liquid phase separation and phase-separated condensates of proteins and nucleic acids provide specific regulation and how this is lost in pathologies. We are a computational group that uses chemically detailed multi-scale simulations of biomolecules in our research (Stelzl et al, 2020, Stelzl* & Pietrek*, 2022), bridging atomic-resolution simulations to phase-separated condensates (Grujis da Silva, 2022). The discovery that liquid-liquid phase separation and phase-separated condensates of proteins and nucleic acids are important regulators is revolutionising our understanding of cell biology. Phase separation helps to organise biological functions in time and space. Thus, it not only plays an important role in regulating genes at the transcriptional level, but also at the post-transcriptional level. Dysregulation of liquid-liquid phase separation is hypothesised to be an important driver of ageing and age-related diseases.

RESEARCH HIGHLIGHTS

A major achievement was our work showing that RNA polymerase II CTD forms distinct condensates to regulate transcription initiation and elongation (Changiarath, Padeken, Stelzl, in preparation). We showed in simulations that phosphorylation of RNA polymerase II CTD triggers the formation of two distinct condensates for transcription initiation and elongation, respectively, which could underpin differential recruitment of transcription machinery components. We identified Pro-Tyr interactions, which may be important for recruiting the Mediator complex to the CTD phase for transcription initiation. Intriguingly, the condensate phase remained in contact, with condensates of unphosphorylated CTD being fully and partially engulfed by condensates of phosphorylated CTD and elongation factors. We can explain

this using theories of how liquids behave and the interfacial tensions computed from our simulations. Super-resolution microscopy in *C. elegans* by Jan Padeken (IMB) confirmed the existence of these condensates. Our simulations predicted that CTD condensates would be more stable at higher temperatures, contrary to most protein condensates. In vivo experiments by the Padeken group are in line with our simulations. These results suggest that CTD forms distinct condensates that are different from those of other proteins, explaining how CTD condensates can regulate specific biological processes.

In collaboration with the Ketting lab in the CRC 1551, we are elucidating how different phase-separated condensates specifically recruit proteins (Figure 1). Mutator foci are essential for small RNA biology in *C. elegans* and for suppressing transposable elements. To do this, they recruit proteins with the scaffold protein Mut-16. Mut-16 recruits Rde-2/Mut-7, but how Rde-2 binds to Mut-16 is not understood. Using multi-scale simulations, we resolved how the disordered prion-like domain of Rde-2 binds Mut-16 condensates with atomic resolution. We showed how Tyr residues in the Rde-2 N-terminus are recruited by Arg residues in Mut-16. Lys residues in the same regions of Mut-16 interact with Rde-2 Tyr residues, but less stably. Our simulation suggests that hydrogen bonding between the guanidinium group of Arg with the backbone carbonyl of Rde-2 Tyr residues accounts for the difference in interaction strengths. Based on this, we proposed mutations of seven Arg residues in Mut-16 that would abolish Rde-2 binding. These predictions were experimentally validated by Sebastian Falk (MPFL, Vienna).

In collaboration with Dorothee Dormann (IMB/JGU), we studied TDP-43 phosphorylation. Phosphorylation of TDP-43 is a hallmark of neurodegenerative disease. The paradigm of the field was that phosphorylation induces phase separation and pathological aggregation of TDP-43. However, experiments by the Dormann lab suggested that phosphorylation may be cytoprotective. Our simulations provide a mechanistic basis for this cytoprotective effect, showing how phosphorylation breaks contacts in the C-terminus of TDP-43. Using improved simulation methods, we are elucidating how interactions between different parts of TDP-43 shape this behaviour and how they are influenced by disease-linked phosphorylation. In this way, we will understand whether different phosphorylation patterns or the number of phosphorylated residues governs TDP-43 behaviour and whether TDP-43 phosphorylation always disfavors condensation and aggregation.

FUTURE DIRECTIONS

We will continue to further develop simulation methods to improve our models and better match experimental complexity. We are also developing new simulation methods to study ATP-driven processes in cells (in the CRC/TRR 146). The group is part of the new CRC 1552 “Molecular defects in Soft Matter”, where we focus on the recognition of PTMs and small molecules by proteins. We are also part of the new Carl Zeiss Centre MAINCE, where we are combining simulations with neural networks to understand on- and off-target interactions of small molecules interacting with complex mixtures of proteins. Longer term, our simulation methods will be vital for understanding cellular homeostasis, including the proper functioning of phase-separated condensates.

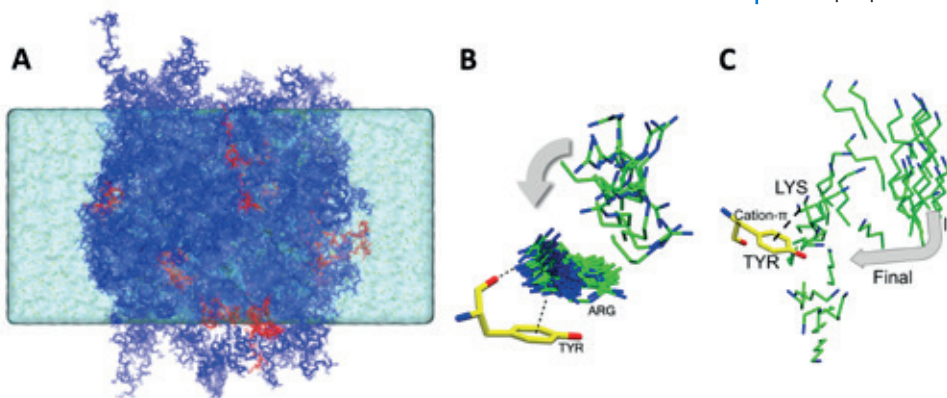


Figure 1. Mut-16 condensates recognise the disordered region of Rde-2. A) Atomistic simulations of a Mut-16 condensate (ca. 900,000 atoms), with Mut-16 in blue and Rde-2 N-terminus (51 aa) in red. B) Arg residues in Mut-16 form long-lived interactions with Tyr residues of Rde-2, with cation- π interactions stabilised by hydrogen bonds between the guanidinium group and the backbone carbonyl of Rde-2 Tyr. C) In contrast, Lys residues form weaker interactions with Rde-2 Tyr residues.

SELECTED PUBLICATIONS

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Stelzl LS, Mavridou DAI, Saridakis E, Gonzalez D, Baldwin AJ, Ferguson SJ, Sansom MSP and Redfield C (2020) Local frustration determines loop opening during the catalytic cycle of an oxidoreductase. *eLife*, 9:e5466

*Indicates joint contribution

Helle Ulrich

“*We study the functions of the actin cytoskeleton in genome maintenance.*”



POSITIONS HELD

- Since 2013** Scientific Director, Institute of Molecular Biology (IMB), Mainz
Professor, Johannes Gutenberg University Mainz (JGU)
- 2004 – 2012** Group Leader, Clare Hall Laboratories, Cancer Research UK London Research Institute
- 2000 – 2004** Group Leader, Max Planck Institute for Terrestrial Microbiology, Marburg
- 1998 – 2000** Postdoc, Max Planck Institute for Biochemistry, Martinsried
- 1997 – 1998** Postdoc, Centre for Molecular Biology (ZMBH), University of Heidelberg

EDUCATION

- 2004** Habilitation in Genetics, Philipps University Marburg
- 1996** PhD in Chemistry, University of California, Berkeley
- 1994** Diploma in Biology, Georg August University Göttingen

GROUP MEMBERS

Staff Scientists Kirill Petriukov, Jie Shi

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Lab Managers Marwah Al-Hushail, Valerie Madsen, Ulrike Seeburg

Student Assistants Claudia Carulla Capdevila, Louis Hammer

Personal Assistant Jutta Karn

OVERVIEW

Genome maintenance mechanisms are important surveillance systems that protect cells against ageing and malignant transformation. Our lab studies the regulatory mechanisms that contribute to the regulation of DNA repair pathways and the management of DNA replication stress, especially as they relate to the posttranslational protein modifiers ubiquitin and SUMO. We aim to understand how cells choose between alternative lesion processing pathways, or between fork-associated and postreplicative modes of DNA damage bypass. One important aspect of replication stress management is the stabilisation of reversed replication forks. Such structures have been postulated to serve as protective measures against fork breakdown in human cells and are processed by factors that include homologous recombination proteins. Work from our lab led by Hans-Peter Wollscheid has implicated an actin-dependent motor protein, myosin VI, in replication fork protection and homology-directed DNA double-strand break repair, thus linking the nuclear actin system to the organisation of the dynamics of the DNA damage and replication stress response. Our progress in elucidating these pathways is revealing new principles of how energy-driven movement may contribute to the maintenance of genome stability.

RESEARCH HIGHLIGHTS

The actin cytoskeleton is best known for its cytoplasmic roles in supporting cell motility and mechanics. Whether actin filaments also form in the nucleus and how they might impinge on genome maintenance has long remained uncertain. Improved tools for the visualisation of nuclear actin filaments have recently revealed a connection between nuclear actin and DNA repair and replication stress management. However, the mechanisms and relevance of myosins as

actin-based motor proteins in these pathways have remained elusive. Myosin VI is one of the few actin-dependent motors reported to have nuclear functions, mainly in transcription. In collaboration with Petra Beli (IMB), we identified novel interaction partners of myosin VI by mass spectrometry. Our follow-up on these interactors has implicated myosin VI in two major genome maintenance pathways: the protection of stalled or reversed replication forks and the homology-directed repair of DNA double-strand breaks (DSBs). Comparing their mechanisms now promises to reveal common principles of how the actin cytoskeleton directly impinges on genome transactions and mobility.

Reversed replication forks form as a protective response to replication stress, which involves reannealing of the parental strands and joining of the newly synthesised strands. The resulting four-way structure requires protection from nuclease-mediated degradation. We found that myosin VI cooperates with the ATPase WRNIP1, a factor that protects stalled or reversed replication forks from nucleolytic attack by DNA2. Via direct interactions that involve the binding of myosin VI to K63-linked polyubiquitin chains, myosin VI promotes the association of WRNIP1 at stalled replication intermediates under conditions of replication stress. The ability of WRNIP1 to also interact with K63-polyubiquitin chains suggests ubiquitin has a scaffolding function in this process (Figure 1A).

In the context of DNA double-strand break repair, we found myosin VI promotes homology-directed repair in a manner that suggests close cooperation with filamentous actin: on the one hand, we showed in collaboration with Alexander Löwer (TU Darmstadt) that depletion of myosin VI interferes with double-strand break mobility – a phenomenon that closely resembles the effects of actin inhibition. On the other hand, myosin VI – like actin – supports the resection of double-strand break ends in preparation for homologous recombination. Here, we observed direct interactions with the ubiquitin-dependent chaperone VCP and the end-binding Ku complex, and we found that myosin VI contributes to VCP-mediated extraction of Ku to allow subsequent resection (Figure 1B). The requirement of myosin VI for correctly localising VCP to double-strand break ends suggests that the motor protein, likely supported by its ubiquitin-binding activity, functions by transporting or anchoring important genome maintenance factors to their sites of action in an actin-dependent manner. The unusual minus end-directed movement of myosin VI would be consistent with a direction of actin filaments emanating from the DNA towards the nuclear periphery.

FUTURE DIRECTIONS

The contributions of myosin VI to replication fork protection and DNA double-strand break repair suggest a broader range of ubiquitin-related activities for this actin-dependent motor in the management of DNA lesions and replication stress. Moreover, further interaction partners identified in the original mass spectrometry screen implicate myosin VI in additional pathways related to DNA replication and chromatin dynamics. We are particularly excited about pursuing the hypothesis that myosin VI might cooperate with VCP in the extraction or resolution of other ubiquitylated complexes involved in genome maintenance. Identifying a more general role of the actin-myosin system in fundamental DNA transactions would provide insight into a new regulatory layer that connects the genetic material to the architecture and dynamics of the nucleus beyond the level of chromatin structure.

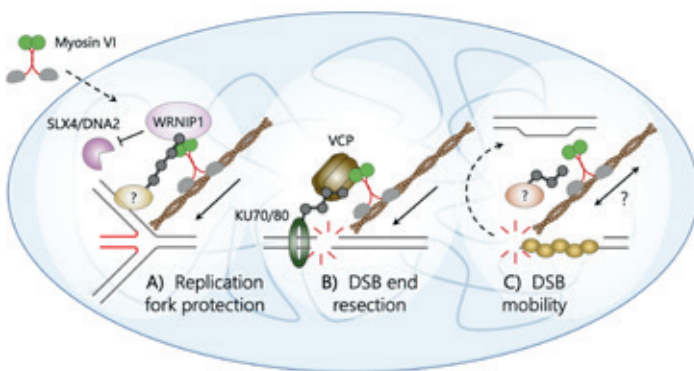


Figure 1. Contributions of myosin VI to DNA replication fork protection and double-strand break (DSB) repair. A) Myosin VI recruits WRNIP1 to stalled or reversed forks via interaction with K63-linked polyubiquitin chains (grey balls) to protect forks from nucleolytic attack by SLX4/DNA2. B) Myosin VI recruits VCP to DSB ends to promote resection via extraction of the ubiquitylated Ku70/80 complex. C) Myosin VI contributes to DSB mobility.

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Wong RP, García-Rodríguez N, Zilio N, Hanulová M and Ulrich HD (2020) Processing of DNA polymerase-blocking lesions during genome replication is spatially and temporally segregated from replication forks. *Mol Cell*, 77:3-16.e4

*indicates joint contribution, *indicates joint correspondence

Sara Vieira-Silva

“*We study the impact of the gut microbiota on human health.*”



POSITIONS HELD

- Since 2022** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Professor, University Medical Center, Johannes Gutenberg University Mainz (JGU)
- 2022** Group Leader, University Medical Center, Johannes Gutenberg University Mainz (JGU)
- 2015 – 2022** Postdoc, Catholic University of Leuven (KU Leuven)
- 2011 – 2015** Postdoc, Free University of Brussels

EDUCATION

- 2007 – 2010** PhD in Genomics, Université Pierre et Marie Curie/Institut Pasteur, Paris
- 2005 – 2006** Postgraduate studies in Computational Biology (PDBC), Instituto Gulbenkian de Ciência, Oeiras
- 2003** Diploma in Biology, University of Lisbon (FCUL)

GROUP MEMBERS

Staff Scientist Gwen Falony

PhD Student Javier Centelles-Lodeiro

OVERVIEW

The human body hosts microbial communities that have an essential role in health. My lab focuses on understanding the ecological dynamics of human gut-associated microbial communities in healthy host-microbiome homeostasis and how their disturbance contributes to the risk of disease onset or progression. We apply quantitative approaches in population cohorts and intervention trials to identify the mechanisms that drive the dynamics of the gut ecosystem in health, what determines its resilience to perturbations, and which alterations contribute to disease (dysbiosis). We focus on tracking the metabolic capacity of these complex communities and their symbiotic or deleterious interactions with the host and its immune system. Our objectives are to identify and quantify the contribution of the gut microbiome as a risk factor for disease development and help develop strategies for microbiota remediation in therapeutic interventions. For this aim, we favour hypothesis-driven experimental design and invest in the development of experimental and computational approaches to study human-associated microbial communities.

RESEARCH HIGHLIGHTS

How the human gut microbiota contributes to anorexia nervosa

Anorexia nervosa (AN) is a severe eating disorder that predominantly affects women and still lacks evidence-based treatments. We explored if the gut microbiota plays a role in AN in a cohort of 147 females. Several bacterial groups, as well as bacterial neuroactive catabolism and the gut virome, were linked to AN, eating patterns and psychological health. Circulating metabolites of microbial origin were also associated with reduced food intake, and causal inference analysis suggested these mediated the impact of the altered gut microbiota on AN behaviour (Figure 1). For mechanistic insight, we performed

faecal microbiota transplantation from AN subjects to germ-free mice under energy-restricted feeding to mirror AN eating behaviour, and found reduced weight gain and altered hypothalamic and adipose tissue gene expression related to aberrant energy metabolism and eating behaviour. Our multi-omics approach and mechanistic studies suggest a disruptive gut microbiome may contribute to AN pathogenesis.

How to identify and quantify causal modifiers of circulating serum metabolites

Trimethylamine N-oxide (TMAO) is a joint product of the host and microbiota metabolism that has been associated with a heightened risk of heart disease. However, the factors controlling its circulating levels in the blood are not fully understood. Using explainable machine learning on the fasting plasma TMAO concentrations of 1,741 adults from the European MetaCardis study, we found that besides age, kidney function is the main predictor of TMAO levels. While the composition of the microbiota and host dietary habits do influence TMAO, their roles are relatively minor. Our data implies a causal relationship between TMAO and kidney health; we validated this in preclinical models, where higher TMAO levels led to increased kidney damage. We also observed that patients on certain glucose-reducing drugs with renoprotective effects had reduced TMAO levels compared to matched controls, suggesting that these drugs could potentially be repurposed to mitigate the cardiovascular risks associated with high TMAO levels.

Which is the highest dietary driver of microbiota and metabolic alteration in obesity?

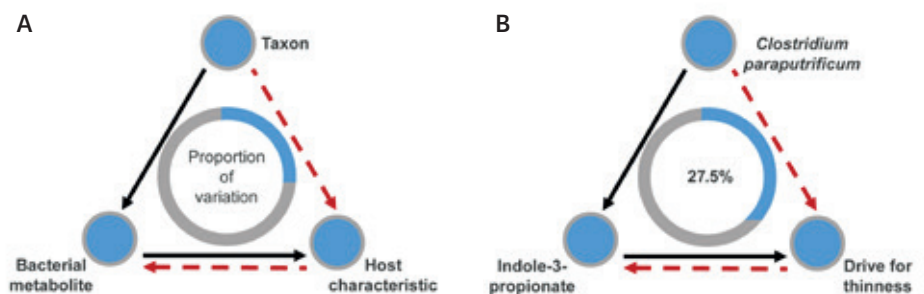
Diet-induced obesity leads to type 2 diabetes, insulin

resistance and organ damage, while also altering the gut microbiota. Although many studies have explored the impact of dietary components like fat and sugar on obesity, their precise roles remain unclear. In our study, C57BL/6J mice were given diets with varying sugar and fat contents for 8 weeks. We assessed obesity, glucose metabolism, inflammation and oxidative and ER stress in several organs. A high-fat (HF) diet led to the most weight and fat gain and altered glucose and insulin levels. Each diet uniquely affected inflammatory stress in different organs and tissues. The different diets all affected gut microbiota composition, but only the HF diet decreased gut microbial load, as observed in obesity in humans. Our findings emphasise that different nutrients distinctly influence obesity, diabetes progression and damage in various organs, and that part of these changes are mediated by alterations of the gut microbiota. Our study indicates that fat, more than sugar, is the primary driver of obesity, diabetes progression and organ inflammation.

FUTURE DIRECTIONS

Our group will continue to study the role of human gut microbiota in health and disease throughout life, diving deeper into its contribution to the risk of cardiovascular disease development in collaboration with clinical partners. We are also exploring how gut microbiota composition modulates therapeutic efficacy and patient outcomes. We will continue to focus on studying the ecological maturation of the gut microbiota under varying conditions, within and outside the boundaries of health, in order to solidify our mechanistic understanding of gut microbiota-host interactions.

Figure 1. Interplay between the gut microbiota composition, serum metabolites and host phenotype in anorexia nervosa. A) Representation of causal inference by bidirectional mediation analysis; B) Serum levels of indole-3-propionic acid – a metabolite originating from gut microbial metabolism – appear to mediate the impact of altered gut microbiota on the anorexia nervosa phenotype (drive for thinness, Eating Disorder Inventory-3).



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*Indicates joint contribution

Siyao Wang

“ We study the transgenerational implications of DNA damage on ageing & longevity. ”



POSITIONS HELD

- Since 2023** Group Leader, Institute of Molecular Biology (IMB), Mainz
- Since 2022** Group Leader, Institute for Genome Stability in Ageing and Disease (IGSAD), University Hospital of Cologne
- 2015 – 2022** Postdoc, CECAD, University Hospital of Cologne

EDUCATION

- 2015** PhD in Molecular Cancer, University of Manchester
- 2010** BMed in Preclinical Medicine, Southern Medical University, Guangzhou

GROUP MEMBERS

- PhD Student** Rose Mary Roshan
- Technician** Neda Bakhshandeh

OVERVIEW

DNA damage poses a major threat to genome stability, chromosomal integrity and cellular function. Defects in transcription-coupled nucleotide excision repair (TC-NER) cause growth and mental retardation, photosensitivity and premature ageing in Cockayne syndrome (CS) patients. To ensure the success of DNA repair, chromatin serves as a platform and is dynamically changed during the DNA damage response (DDR), as described by the Access-Repair-Restore model. As a crucial part of chromatin, histones are post-translationally modified via methylation, ubiquitination and acetylation to regulate DDR-related chromatin functions. Importantly, in contrast to the transient process of DNA repair, many histone modifications can leave a long-term epigenetic memory in cells and be passed down to further generations, raising the question of whether DNA damage could reshape the epigenome in damaged cells and even affect their descendants. My lab uses *C. elegans* as a model to study the role of histone modifications on genome stability, longevity and transgenerational inheritance.

RESEARCH HIGHLIGHTS

Transgenerational inheritance of paternal DNA damage via histone-mediated DNA repair restriction
Epigenetic modifications are well-known for their role in the transgenerational inheritance of several traits, including longevity. However, whether DNA damage-induced epigenetic alterations can lead to a transgenerational effect is still unknown. The transgenerational effect of DNA damage was previously studied mainly via epidemiological and genetic approaches, but contradictory observations were obtained. Interestingly, many studies pointed to a hypothesis that the transgenerational effect is attributed to paternal, but not maternal, DNA damage, although the mechanism

underlying this phenomenon was unclear. Therefore, it raised the question of whether paternal DNA damage can alter the epigenome of offspring and leave a transgenerational effect.

Previously, I identified a novel mechanism underlying the transgenerational genetic and epigenetic effect of paternal DNA damage. Using sex-separated *C. elegans* strains, we found that paternal, but not maternal, ionising radiation (IR) exposure leads to transgenerational embryonic lethality (Figure 1). We also determined that IR-induced paternal DNA double-strand breaks (DSBs) are mainly repaired via maternally-provided error-prone polymerase-theta mediated end joining (TMEJ), while on the other hand, maternal DNA DSBs mainly engage in error-free homologous recombination repair (HRR). Consequently, offspring of irradiated males display various genome instability phenotypes, including chromosomal bridging, chromosomal lagging and DNA fragmentation. This persistent paternal DNA damage in the offspring of irradiated males triggers an alteration in the epigenome during gametogenesis, as increased linker histone H1 levels and excessive heterochromatic regions were detected in the germ cells of the F1 generation. Knockdown of histone H1 or heterochromatin protein HPL-1 can significantly reduce heterochromatin formation in the germline of the F1 generation, activate error-free HRR and consequently rescue the high embryonic lethality observed in the F2 generation. This work identified a novel mechanism for transgenerational inheritance of paternal DNA damage and provided a potential therapeutic target for improving the progeny viability of radiotherapy-treated patients.

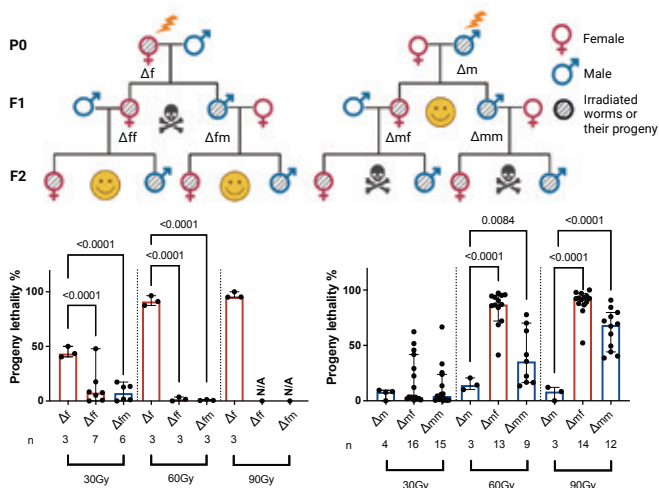


Figure 1. Paternal, but not maternal, exposure to IR leads to transgenerational embryonic lethality.

H3K4me2 regulates the recovery of protein biosynthesis and homeostasis following DNA damage

How DNA damage reshapes the epigenome and influences ageing is a fascinating question. I previously identified a specific role for histone 3 lysine 4 (H3K4me2) di-methylation in the recovery of protein biosynthesis and homeostasis following UV-induced TC-NER. Upon UV treatment, H3K4me2 deposition is transiently increased in the somatic tissues of *C. elegans*. Blocking the deposition of H3K4me2 by removing the H3K4 methyltransferase complex MLL/COMPASS results in developmental arrest and lifespan shortening after UV treatment. In contrast, elevating H3K4me2 by depleting the histone demethylase SPR-5 can accelerate development and extend lifespan upon UV damage. Specifically, we have shown that UV-induced H3K4me2 facilitates the transcriptional recovery of protein biosynthesis and homeostasis genes. Repressing protein biosynthesis by treating worms with the translational inhibitor cycloheximide can reverse the beneficial effect of elevating H3K4me2 deposition upon UV treatment. This study highlights the importance of H3K4me2 in the regulation of development and ageing in somatic tissues following transcription-blocking DNA damage.

FUTURE DIRECTIONS

Our future work will explore the long-term and transgenerational effects of DNA damage on the epigenome and protein homeostasis. We will use the well-established ChIP-seq technique and SILAC proteomics analysis to monitor the deposition of epigenetic modifications and proteome alterations at different time points and generations following DNA damage. Meanwhile, to understand the transgenerational effect of paternal DNA damage, we will use RNA-seq, ATAC-seq and Hi-C techniques to examine transcriptional regulation and chromatin conformation in the subsequent generations following paternal radiation exposure. In addition, we will measure *de novo* mutations, DNA fragmentation and chromosomal rearrangements in the subsequent generations through whole-genome sequencing, karyotype analysis and comet assay. Importantly, by screening mutants deficient in different epigenetic modifications, we will be able to identify the role of epigenetic regulation in paternally inherited genome instability and find potential therapeutic targets for paternal hereditary disorders.

SELECTED PUBLICATIONS

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Wang S, Meyer DH and Schumacher B (2020) H3K4me2 regulates the recovery of protein biosynthesis and homeostasis following DNA damage. *Nat Struct Mol Biol*, 27:1165-1177

*indicates joint contribution

Sina Wittmann

“ We dissect how transcription factors form condensates that affect gene activation. ”



POSITIONS HELD

Since 2023 Group Leader, Institute of Molecular Biology (IMB), Mainz

2017 - 2023 Postdoc, Max Planck Institute of Molecular Cell Biology & Genetics, Dresden

EDUCATION

2017 PhD in Biochemistry, University of Oxford

2012 MSc in Biochemistry, University of Regensburg

2009 BSc in Biochemistry, University of Regensburg

GROUP MEMBERS

PhD Student Felizitas Stiehler

Technician Franziska Roth

Research Assistant Rhadika Khatter

OVERVIEW

In my group, we are trying to understand the molecular mechanisms by which gene activation is regulated. Many decades of intricate work have identified hundreds of proteins that participate in the gene activation process, as well as their roles. Traditionally, transcriptional research focused on structured protein regions, which elucidated in the highest molecular detail how RNA is synthesised. However, the development of structure predictors and the emergence of AlphaFold have shown us that structured regions constitute only a small part of the transcriptional proteome. DNA-binding transcription factors were shown to be particularly disordered; these are the main focus of my research group. Using a combination of *in vitro* biochemistry and biophysics, we are trying to characterise how transcription factors use their intrinsically disordered regions to communicate with each other and different transcriptional proteins. This communication involves the formation of small liquid-like droplets directly on DNA. These droplets could also be observed inside cells, but their function is not well understood. By using the knowledge that we gain from our *in vitro* studies to design cellular experiments, we aim to understand why these droplets form and how they affect gene activation.

RESEARCH HIGHLIGHTS

Formation of transcription factor droplets on DNA

Gene activation plays a major role during development and needs to be precisely regulated for different cell types to form. If this regulation breaks down, the cell loses control of its transcriptional programme, which can result in cancerous transitions.

One of the first steps in gene activation is the binding of transcription factors (TFs) to regulatory DNA regions. For this, TFs use DNA-binding domains that allow them to

recognise short target sequences. However, computational prediction of TF binding in the genome is very poor, demonstrating that the presence of the motif alone is insufficient to determine localisation.

In addition to the DNA-binding domain, TFs typically contain large, disordered regions. Previous work indicates that transcriptional proteins can use these regions to interact with each other, thereby forming little condensates on the genome. However, the function of these condensates remains elusive. The hope is that by understanding how TF condensates are regulated, we will be able to control their activity in diseases such as cancer, where they are unusually big and drive the expression of oncogenes.

In my research, we visualised the interaction of the TF Klf4 (Krüppel-like factor 4) with individual DNA molecules *in vitro*. This protein plays a major role in keeping cells in a pluripotent state during embryonic development. My research showed that Klf4 is able to form little condensates on its own but only at high protein concentrations. Interestingly, DNA enables this condensation to occur at much lower - or physiological - concentrations and specifically at sites that contain Klf4 recognition motifs.

Given that Klf4 can also bind in a sequence-specific manner in the absence of condensation, we were wondering what the advantage of forming condensates is. To this end, we repeated the above experiment with a variant of Klf4 that is unable to condense. As expected, the protein did not form droplets but instead covered the entire DNA at physiological concentrations. By performing the DNA binding experiment at many different concentrations with both variants and carefully quantifying the resulting images, we were

able to demonstrate that sequence-specific binding in the absence of condensation can only be obtained at extremely low protein concentrations. However, sequence-specific localisation in the physiological concentration range required the Klf4 variant that is able to condense.

These data are very intriguing as they show a potential new role of condensation for finding regulatory DNA regions in the genome. Our results were surprising because up until now only the DNA-binding domain was thought to determine DNA localisation. We speculate this can explain why computational prediction of TF binding is so poor. In contrast, we could show that condensation via the disordered region is also important. While the exact motif is indeed identified by the DNA-binding domain, the larger sequence context in which the motif occurs is read out by the cooperative action of hundreds of Klf4 molecules acting together inside a condensate. This mechanism allows regulatory regions to be identified and distinguished from randomly-occurring recognition sites elsewhere in the genome.

FUTURE DIRECTIONS

While these results are very intriguing, the work was limited to *in vitro* experiments and does not give direct insight into the role of condensates inside cells. Future research will therefore focus on the characterisation of condensate formation, which will allow us to manipulate droplet formation *in vivo*. In this way, we can test what their role is inside cells and how altered condensate properties affect transcription.

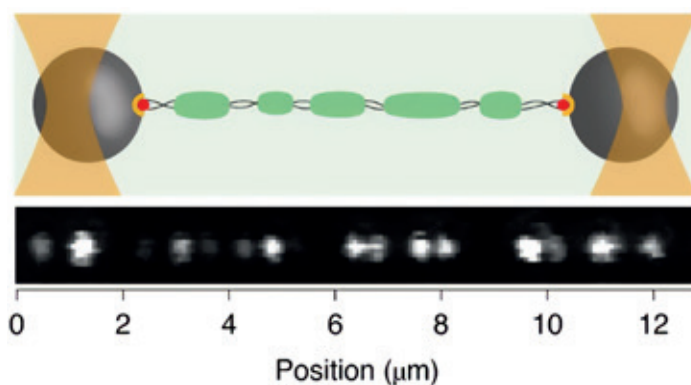


Figure 1. Optical tweezers were used to image the condensation of the transcription factor Klf4 on single molecules of DNA. The top shows a schematic of the experimental setup: individual DNA molecules can be captured via optical traps that can hold the ends. Condensation of the protein of interest (green) can then be studied by fluorescence microscopy. A representative image of Klf4 condensates is shown at the bottom. From Morin *et al.*, 2022 (*Nature Physics* 18:271-276). This image was published under a Creative Commons Attribution License.

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Wittmann S and Alberti S (2019) ERα condensates: chronic stimulation is hard to ignore. *Nat Struct Mol Biol*, 26: 153-154

Wittmann S, Renner M, Watts BR, Adams O, Huseyin M, Baejen C, El Omari K, Kilchert C, Heo DH, Kecman T, Cramer P, Grimes JM and Vasiljeva L (2017) The conserved termination factor Seb1 bridges RNA polymerase II and nascent RNA. *Nat Commun*, 8:14861

*indicates joint contribution

Eva Wolf

“ We use structural biology to dissect the molecular mechanisms of circalunar clocks. ”



POSITIONS HELD

- Since 2013** Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Professor of Structural Biology, Johannes Gutenberg University Mainz (JGU)
- 2012 – 2013** Group Leader, Ludwig Maximilian University (LMU), Munich
- 2009 – 2011** Group Leader, Max Planck Institute for Biochemistry, Martinsried
- 2000 – 2009** Group Leader, Max Planck Institute for Molecular Physiology, Dortmund
- 1996 – 2000** Postdoc, Rockefeller University, New York

EDUCATION

- 2007** Habilitation in Biochemistry, Ruhr University, Bochum
- 1996** PhD in Biology, European Molecular Biology Laboratory (EMBL), Heidelberg
- 1991** Diploma in Biology, University of Heidelberg

GROUP MEMBERS

- Postdoc/Lab Manager** Torsten Merbitz-Zahradnik
- PhD Students** Baris Cakilkaya, Marcel Conrady, Florian Hof, Hong Ha Vu
- Bachelor Students** Marius Müller, Sophia Remers
- Personal Assistant** Ruth Schaupt

OVERVIEW

Many marine organisms, including corals, brown algae, fish, turtles and bristle worms, time their maturation and reproduction according to the phases of the moon. These monthly (~29.5 days) circalunar rhythms are essential to ensure their successful reproduction, which is crucial in maintaining the marine ecosystem. In recent years, anthropogenic disturbances (e.g. nocturnal light pollution and climate change) have increasingly endangered the survival of marine organisms by desynchronising their moon-controlled reproduction cycles. However, despite these ecological threats, the molecular architecture of circalunar timing systems is still completely unknown. The marine bristle worm *Platynereis dumerilii* possesses an inner monthly calendar (referred to as circalunar clock or circalunar oscillator) to control its monthly reproduction cycles. We found that a light-sensitive cryptochrome called L-Cry can discriminate between moonlight and sunlight and even between different moon phases, which enables the marine worm to synchronise its reproduction to the full moon. By determining the 3D structures of the dark-adapted and fully light-activated L-Cry protein, we have provided important molecular and mechanistic insights into L-Cry's light receptor functions.

RESEARCH HIGHLIGHTS

To gain molecular-mechanistic insights into circalunar oscillators, we characterised the light-sensitive cryptochrome L-Cry from *Platynereis dumerilii* (*Pdu*) using a combination of protein biochemistry, UV-VIS spectroscopy, 3D structural analyses and cell biology. We found that L-Cry can form three distinct states, which differ in their cellular localisation, oligomeric state and the redox state of its light-sensitive cofactor flavin adenine dinucleotide (FAD). In darkness, L-Cry forms a dimeric, mostly nuclear dark state with fully oxidised FAD_{ox}.

In the presence of sunlight, L-Cry forms a monomeric, more cytosolic sunlight state with a fully reduced anionic FAD radical (FAD^{•-}), while very dim moonlight leads to the formation of a mostly nuclear moonlight state where only about half of the FAD molecules are photoreduced (Pöhn, Krishnan *et al*, 2022). These three distinct molecular states allow L-Cry to distinguish moonlight from sunlight and recognise the full moon as the moon phase to which the worms synchronise their reproduction.

We recently determined the cryo-electron microscopy (Cryo-EM) structures of the dark-state L-Cry dimer and the light-activated monomer (collaboration with Prof. Elmar Behrmann, University of Cologne; Vu, Behrmann *et al*, 2023; Figure 1). Structural and functional data from this study revealed a novel cryptochrome dimer arrangement in darkness, with a mechanistic coupling between the light-sensing FAD chromophore, the dimer interface and the regulatory C-terminal tail, which leads to light-induced monomerisation of L-Cry. Mutations in the dimer interface and the C-terminal tail region of L-Cry disrupted the L-Cry dimer in darkness as determined by Size Exclusion Chromatography (SEC), revealing a functional role of the non-conserved L-Cry tail in dimer formation and light signalling.

Interestingly, the L-Cry dimer interface is very different from the dimer interfaces of light-sensitive plant cryptochromes. Moreover, plant cryptochromes form higher oligomeric states after light illumination, whereas in L-Cry intense illumination induces dimer disruption. Hence, L-Cry exhibits an inverse photo-oligomerisation mechanism with respect to its plant Cry homologs. Dimer disruption by intense illumination (such as sunlight) also explains our earlier observation that sunlight state L-Cry cannot directly be converted into the half-reduced moonlight state, as moonlight state formation has to start from the dark state L-Cry dimer (Pöhn, Krishnan *et al*, 2022). We further hypothesise that monomer formation at high flux rates explains the enhanced cytosolic localisation of sunlight state L-Cry compared to its dimeric dark state, assuming that only the monomer is targeted for nuclear export. Monomerisation, nuclear export and subsequent cytosolic degradation could therefore be mechanistically coupled to enable downstream cytosolic signalling pathways triggered by sunlight. Interestingly, the light-sensitive cryptochrome of *Drosophila melanogaster* (dCry), to

which L-Cry is most closely related, does not respond to moonlight (Zurl *et al*, 2022). dCry is a monomer under dark and light conditions and has critical amino acid substitutions in the L-Cry dimer interface preventing its oligomerisation. Moreover, we found that a tyrosine residue in L-Cry, which is not conserved in dCry, enhances the light sensitivity of L-Cry compared to dCry. Together, our study has important implications for our understanding of how L-Cry discriminates moonlight from sunlight and how it gains its exceptionally high light sensitivity.

FUTURE DIRECTIONS

Our long-term goal is to elucidate the molecular mechanism of the circalunar oscillator that generates monthly rhythms of reproduction and behaviour in animals and synchronises these biological rhythms to the lunar cycle. Following up on our molecular-mechanistic characterisation of the L-Cry protein, we will now clarify L-Cry's signalling to the circalunar clock. To this end, we will search for L-Cry interactors in worm tissues using pulldown and mass spectrometry approaches under dark, moonlight and sunlight conditions. Putative L-Cry interactors will then be analysed *in vivo* and *in vitro*. Furthermore, we will elucidate the molecular properties of L-Cry's enigmatic moonlight state via 3D structural and biochemical analyses. We will also employ mutations that are designed based on our dark-state L-Cry structure to further characterise L-Cry's distinct light responses to very dim moonlight and sunlight.

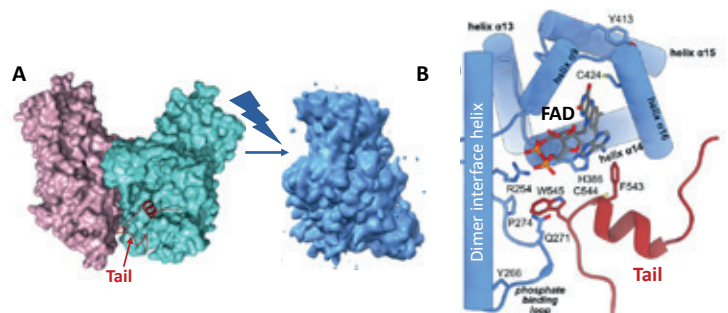


Figure 1. A) Cryo-EM structures of the dark-state L-Cry dimer (left) and the light-activated L-Cry monomer (right). B) Close-up view showing the connection between the light-sensitive FAD cofactor, the dimer interface and the regulatory C-terminal tail.

SELECTED PUBLICATIONS

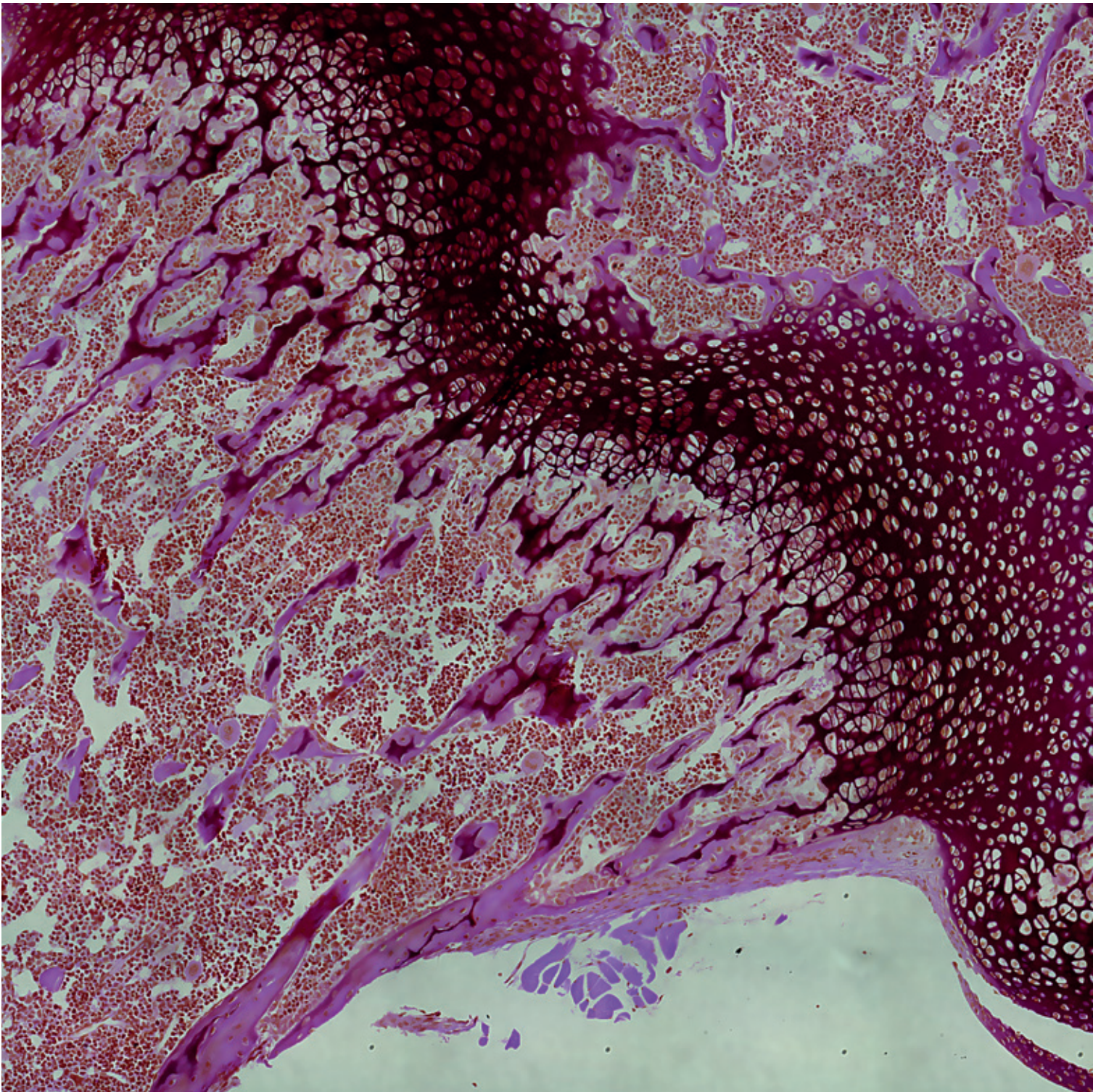
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*indicates joint contribution, *indicates joint correspondence

Adjunct Clinicians

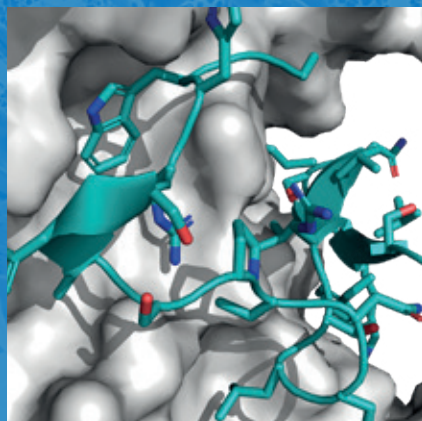


Stephan Grabbe 56

Oliver Tüscher 60

Susann Schweiger 58

Philipp Wild 62



Stephan Grabbe

“ We study the immunoregulatory functions of β_2 integrins to develop therapies for cancer. ”



POSITIONS HELD

- Since 2022** Adjunct Clinician, Institute of Molecular Biology (IMB), Mainz
- Since 2007** Director, Department of Dermatology, University Medical Center (UMC), Mainz
- 2003 – 2007** Director, Department of Dermatology, University of Essen Medical Center
- 2000 – 2003** Professor of Dermatology & Dermato-Oncology, University of Münster
- 1998 – 1999** Heisenberg Scholarship Visiting Scientist, Skin Disease Research Center, Brigham and Women’s Hospital, Harvard University, Boston
- 1992 – 1998** Research Associate, University of Münster
- 1989 – 1992** Postdoctoral Research Fellow, Wellman Laboratories of Photomedicine and MGH-Harvard Cutaneous Biology Research Center, Massachusetts General Hospital, Harvard University, Boston
- 1987 – 1989** Research Associate, University of Münster

EDUCATION

- 1996** Habilitation, University of Münster
- 1996** Dermatology, Allergology & Phlebology National Boards (Germany)
- 1987** MD, University of Münster
- 1987** Medical School, University of Münster

RESEARCH HIGHLIGHTS

Within my research group, we pursue several aspects of cutaneous and general immunology research. Our projects centre on cellular immunology, with a focus on dendritic cells and regulatory T cells. The group is tightly embedded into two DFG-funded collaborative research centres: the CRC 1066 on “Nanoparticle-mediated tumour immunotherapy”, of which I am the Speaker, and the CRC TRR156 on “The skin immune system”, of which I am the Site Coordinator for Mainz. Moreover, we are part of the JGU “Research Center for Immunotherapy (Forschungszentrum für Immuntherapie, FZI)” (Speakers: Stephan Grabbe and Tobias Bopp).

Dendritic cells: master controls of adaptive immunity

Dendritic cells (DCs) play a central role in maintaining self-tolerance by presenting self-antigens and harmless environmental antigens (peptides) in the absence of stimulatory signals to T cells. T cells that bind to these antigens are inactivated or reprogrammed to so-called (immuno) regulatory T cells (Treg). In addition, DCs that phagocytose a pathogen or pathogen-infected cell play a role in activating antigen-specific effector T cells. Activated cytotoxic T cells (CTL) can directly kill infected cells and tumour cells, while other activated T cells exerts helper functions (Th cells) and promote CTL activation.

Due to their versatile role, DCs are interesting targets for immunotherapeutic strategies to treat autoimmune and allergic diseases, or to mount profound and sustained anti-tumour responses. We work to test multi-functionalised nano-vaccines for their ability to activate DC and stimulate DC-mediated T cells, as well as testing candidate vaccines in tumour mouse models. In addition, we study where immunotherapeutic nanoparticles travel in the body after intravenous injection, and elucidate the mechanisms by which they are retained in the liver.

β_2 integrins: leukocyte adhesion molecules with multiple immune functions

β_2 integrin receptors are expressed specifically by leukocytes. They have many functions in the immune system; some bind ICAMs, providing a scaffold for interactions between immune cells, while others enable leukocytes to roll along the endothelium in search of inflammation sites or function as phagocytic receptors for complement-opsonised pathogens and immune complexes.

We study the roles that β_2 integrins play in maintaining tolerance and how their dysregulation contributes to autoimmune disease, with the goal of discovering therapeutic treatments. For this purpose, we recently generated a mouse strain with a floxed CD18 gene locus, which will enable us to study the distinct roles of β_2 integrins in DC, Treg and neutrophil cells.

Tumour immunotherapy

Tumours can be recognised and destroyed by the immune system, but often manage to escape destruction. Using murine melanoma models and patient-derived tumour samples, we work to understand key elements of the interaction between the immune system and tumours and develop anti-cancer immunotherapeutic strategies using nanoparticle-based approaches or by modulating the tumour microenvironment with β_2 integrins.

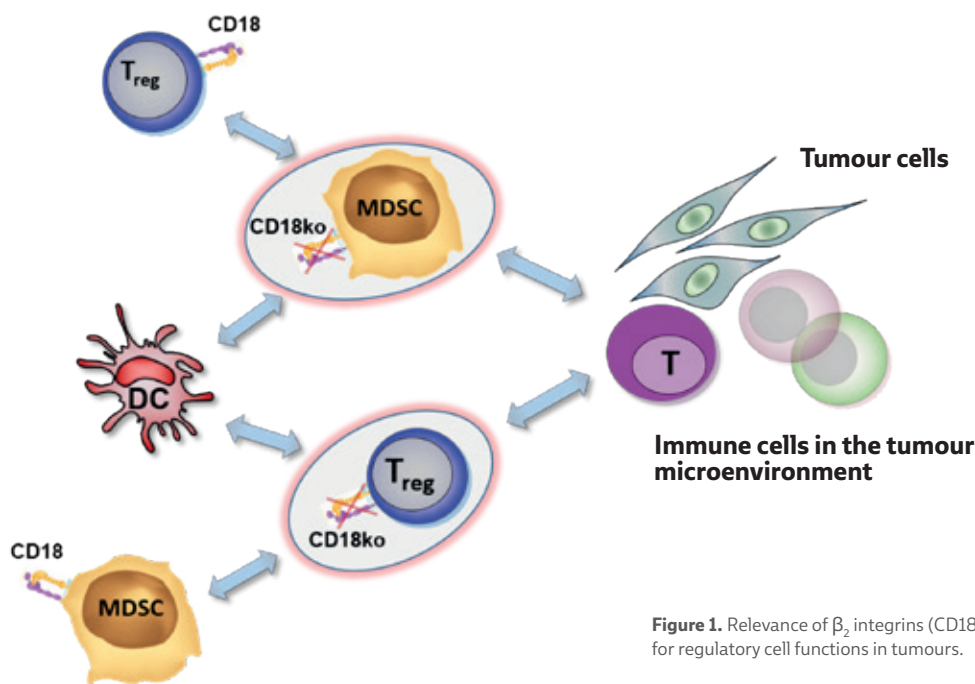


Figure 1. Relevance of β_2 integrins (CD18) for regulatory cell functions in tumours.

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*indicates joint correspondence

Susann Schweiger

“*We work to understand the clinical variability of Mendelian disorders of the CNS.*”



POSITIONS HELD

- Since 2022** Adjunct Clinician, Institute of Molecular Biology (IMB), Mainz
- Since 2020** Group Leader, Leibniz Institute for Resilience Research (LIR), Mainz
- Since 2012** Director, Institute of Human Genetics, University Medical Center (UMC), Mainz
- 2007 - 2012** Professor of Molecular Medicine, Dundee Medical School
- 2010 - 2012** Vice Chair, Wellcome Trust Center for Molecular Medicine, Dundee
- 2005 - 2010** Lichtenberg Professor, Charité-Berlin
- 2001 - 2005** Group Leader, Max Planck Institute for Molecular Medicine, Berlin

EDUCATION

- 2006** Board Certificate in Human Genetics, Charité-Berlin
- 1993** MD in Biochemistry, University of Freiburg
- 1993** Medical School, University of Freiburg
- 1989** Medical School, University of Innsbruck

RESEARCH HIGHLIGHTS

In our genetics clinic, we see a large variety of patients with rare diseases, with a particular focus on neurodevelopmental and neurodegenerative disorders. We study the mutations in our patients in combination with their phenotypes in order to understand gene function in humans. We also use reprogramming of patients' cells and differentiate induced pluripotent stem cells into neural precursor cells, neurons and cerebral organoids to study gene function and the mechanisms of disease. We put a particular emphasis on understanding the molecular mechanisms that underlie variability in clinical phenotypes. Mouse models and analysis in patient cohorts complete our methodological repertoire. With all these attempts, we aim to develop experimental therapies for patients with rare disorders.

Early processes in Huntington's Disease

Huntington's Disease (HD) is a late-onset and devastating neurodegenerative disorder that is very hard to detect in the early stages. However, once the disease has reached the symptomatic phase, neurodegeneration is already far advanced and therapy is likely to be too late. Using mouse models of HD, we have found aberrations in the cortical network at a very early stage before disease onset; these were associated with subtle behavioural abnormalities. We found that the synthesis of disease-causing protein in Huntington's Disease is driven by a protein complex that contains the mTOR kinase (mammalian target of rapamycin). Metformin inhibits the formation of this complex and, as we can show, substantially reduces the production of disease-causing protein in an animal model of Huntington's Disease. Currently, we are following the hypothesis that Huntingtin RNA and proteins assemble in a condensate with the mTOR kinase and protein phosphatase 2A through phase separation, and that metformin and other small compounds might interfere

with this. Furthermore, we are investigating whether early treatment with metformin can improve later disease progression in the mouse and have put together a clinical trial for patients before disease onset.

Premature cognitive decline in a mouse model for tuberous sclerosis

Little is known about the influence of (impaired) neurodevelopment on cognitive ageing. We are using a mouse model of tuberous sclerosis (TS) carrying a heterozygous deletion of the *Tsc2* gene. Loss of *Tsc2* function leads to mTOR hyperactivity in mice and patients. In a longitudinal behavioural analysis, we found a premature decline of hippocampus-based cognitive functions, together with a significant reduction of immediate early gene (IEG) expression. While we did not detect any morphological changes in hippocampal projections and synaptic contacts, molecular markers of neurodegeneration were increased, and the mTOR signalling cascade was downregulated in hippocampal synaptosomes. Injection of IGF2, a molecule that induces mTOR signalling, could fully rescue cognitive impairment and IEG expression in ageing *Tsc2*^{-/-} animals.

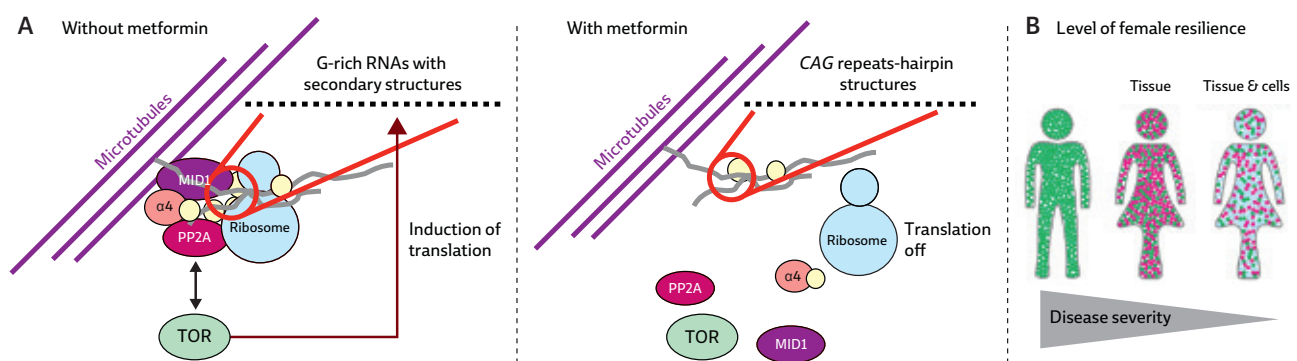
This data suggests that TS causes erosion of the mTOR pathway over time. IGF2 might be a novel avenue for treating age-related degeneration in mTORopathies. We are looking longitudinally along the disease trajectory for vulnerable windows of disease development in which treatment would most make sense and looking at possibilities for early intervention.

Dynamic X-chromosomal reactivation enhances female brain resilience

Sexual dimorphism is well-documented in neurodevelopmental disorders, but the underlying molecular mechanisms are not well understood. One of the most important differences between male and female mammals is the sex chromosomes. In order to allow dosage compensation between the sexes, large parts of one X chromosome are randomly inactivated in females. Using induced pluripotent stem cells, neural precursor cells, neurons and brain organoids as models, we have found that expression of X-chromosomal genes can be dynamically reactivated from the inactive X-chromosome during neurodevelopment, thereby allowing facultative escape of selected genes. This substantially influences the phenotype and development of X-linked neurodevelopmental diseases in females, adding an extra layer of resilience in the female brain.

In collaboration with the ReALity community and with Claudia Keller Valsecchi (IMB), Felicia Basilicata (IMB), Joan Barau (IMB) and Peter Baumann (IMB/JGU), we also plan to study X chromosomal gene reactivation in the developing immune system and work to understand the molecular mechanisms underlying X chromosomal reactivation.

Figure 1. A) Synthesis of aberrant protein in Huntington's Disease is induced by an mTOR-containing protein complex that binds to a hairpin made by the RNA containing the expanded CAG repeat. Metformin destroys this complex and thereby inhibits the synthesis of aberrant proteins in Huntington's Disease. B) In females with random X-inactivation, mutations in X-chromosomal genes are expressed in 50 % of cells (resilience on the tissue level). Through reactivation of the wildtype allele on the inactive X-chromosome, the phenotype in those cells expressing the mutant allele becomes milder (second level of resilience in females).



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*indicates joint contribution, *indicates joint correspondence

Oliver Tüscher

“ We unravel the mechanisms of resilience that enable healthy human ageing. ”



POSITIONS HELD

- Since 2022** Adjunct Clinician, Institute for Molecular Biology (IMB), Mainz
- Since 2020** Founding Member, Research Group Leader & Head of the Clinical Investigation Center (CIC), Leibniz Institute for Resilience Research (LIR), Mainz
- Since 2016** Professor of Mental Health & Cognitive Resilience in Old Age, University Medical Center (UMC) & German Resilience Center (DRZ), Mainz
- Since 2015** Vice-chair, Department of Psychiatry, UMC, Mainz
- Since 2013** Attending in Psychiatry & Psychotherapy, UMC, Mainz
- 2010 – 2013** Residency in Psychiatry & Psychotherapy, UMC, Mainz
- 2009 – 2010** Residency in Psychiatry & Psychotherapy, University of Freiburg
- 2006 – 2010** Head of the Emotion Regulation & Impulse Control Imaging Group (ERIC), Freiburg Brain Imaging, University of Freiburg
- 2006 – 2009** Residency in Neurology, University of Freiburg
- 2003 – 2006** Postdoc, Weill Medical College Cornell University, New York
- 2001 – 2003** Residency in Neurology, UKE, University of Hamburg

EDUCATION

- 2013** Board Certification for Psychiatry and Psychotherapy
- 2010** Board certification for Neurology
- 2011** Habilitation in Neurology, University of Freiburg
- 2002** MD/PhD in Neurobiology, University of Heidelberg
- 2000** Medical School, University of Heidelberg
- 1995** Medical School, University of Bochum

RESEARCH HIGHLIGHTS

Our research focus on “Healthy ageing, neurodegeneration and neuropsychiatry” at the Department of Psychiatry and Psychotherapy is led by Kristina Endres, Katharina Geschke/ Isabel Heinrich and myself. We make use of a broad methodological spectrum spanning from preclinical lab work to clinical studies to investigate the mechanisms of healthy ageing, and resilient ageing in particular. Based on these findings, we aim to develop preventive, disease-modifying and therapeutic interventions. Our interdisciplinary research group includes biologists, chemists, psychologists, physicians and computer scientists, enabling us to implement findings from research on molecular mechanisms to clinical use. The results of our investigations are evaluated using a translational cycle, with the ultimate goal of fostering an ageing process that is as cognitively healthy and free of ailments as possible.

We work in close cooperation with the Centre for Healthy Ageing (CHA) to identify and investigate biomarkers and mechanisms of (healthy) ageing in neuronal tissues. Intervention strategies are tested on animal models ranging from *C. elegans* to mice. Using neuroimaging techniques, we translate this research to the human brain and study neural network mechanisms of resilient ageing – a conceptual framework we recently developed to explicitly understand and target those biological mechanisms which protect the brain and body against functional loss caused by ageing and ageing-related diseases. Studies in our lab include the following areas:

Resilient ageing: ReALizing healthy body & brain ageing (ReALity HBBA)

We are investigating the mechanism(s) conveying resilience to body and brain ageing by comprehensively assessing the (epi)genomic, proteomic, cellular-immunologic and cardiovascular phenotypes of participants in the AgeGain study

(with the Bopp Lab, FZI/UMC and the Wild Lab, CTH/UMC & IMB). On the methylome level, we have been able to show that resilient ageing is associated with having a significantly younger biological age (PhenoAge epigenetic clock) compared to “normal agers” (in collaboration with the Wild/Niehrs ReALity Project EpiHF). Intriguingly, PhenoAge correlates with the volume and the connectivity of memory-related brain structures (see Figure 1). We will further uncover the genetic and cellular senescence mechanisms related to this by comparing resilient and non-resilient participants (in collaboration with the Baumann Lab, JGU/IMB).

Gut-brain axis in ageing

Recent studies suggest that certain bacterial commensals may cause accelerated or diseased ageing. We study the gastrointestinal system in mouse models of Alzheimer’s disease and accelerated ageing (together with the Baumann (IMB/JGU) and Schick labs (IMB) through the CHA and SHARP initiative) to identify pathways that can serve as new therapeutic treatment options to ameliorate cognitive decline in ageing (Nguyen *et al*, 2023, *Int J Mol Sci*).

Signatures of vulnerability in the ageing brain

Certain brain regions maintain function throughout ageing and even diseased ageing, while others are highly

vulnerable. Together with the Dormann (JGU/IMB), Gerber (UMC) and Bopp (UMC) labs, we analyse how different brain areas and cellular subpopulations in the brain are affected by normal and accelerated ageing. With the Krämer-Albers lab (JGU), we also analyse neuronal extracellular vesicles (EVs) in humans to unravel novel biomarkers of cognitively healthy ageing (Brahmer *et al*, 2023, *Cell Commun Signal*).

Anti-brain ageing therapeutics

We are evaluating the use of sarcopenia (the progressive loss of strength and functionality of skeletal muscles) as an external measure of healthy ageing in rodent models and humans, and are using it to assess the efficacy of therapeutic interventions for Alzheimer’s disease and preventing cognitive decline in normal and accelerated ageing. We have just shown that 5xFAD mice (which are used as models of neurodegeneration) had significantly lower quantities of *Bacteroides* spp. in their gut microbiota when only considering frailty, and lower levels of *Bacteroidetes* when considering both frailty and chronological age compared to their wild-type littermates. Thus, the quality of ageing—as assessed by frailty measures—should be taken into account to unravel potential changes in the gut microbial community in Alzheimer’s disease (Kapphan *et al*, 2023, *Microorganisms*).

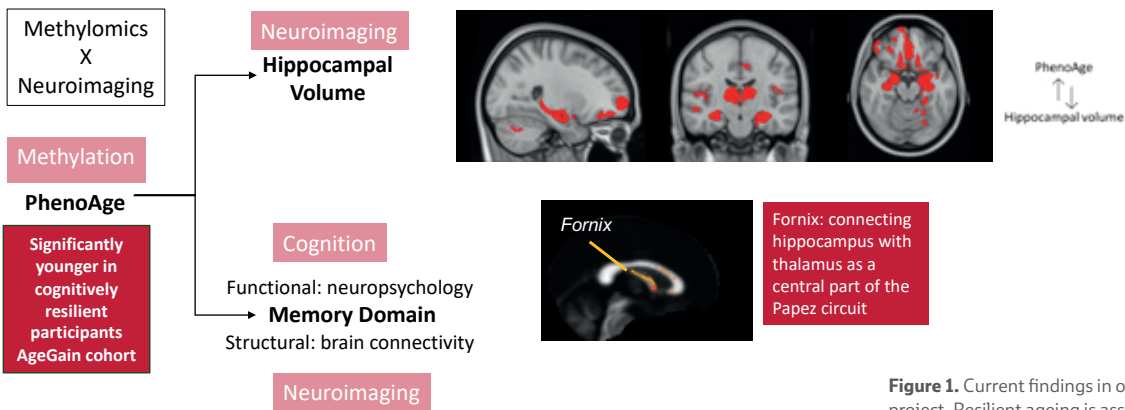


Figure 1. Current findings in our ReALity HBBA project. Resilient ageing is associated with younger biological age as measured by the PhenoAge biological clock, which is in turn related to hippocampal volume and connectivity – central brain regions of the brain’s memory system (unpublished results of the ReALity HBBA project).

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Schaum M, Pinzuti E, Sebastian A, Lieb K, Fries P, Mobascher A, Jung P, Wibrall M* and Tüscher O* (2021) Right inferior frontal gyrus implements motor inhibitory control via beta-band oscillations in humans. *eLife*, 10:e61679

*indicates joint correspondence

Philipp Wild

“*We use systems medicine to understand the pathomechanisms of age-related disease.*”



POSITIONS HELD

- Since 2022** Adjunct Clinician, Institute of Molecular Biology (IMB), Mainz
- Since 2020** Rhine-Main Deputy Site Speaker, German Center for Cardiovascular Research (DZHK)
- Since 2015** Head of Liquid Biobank, University Medical Center (UMC), Mainz
- Since 2015** Speaker, Research Center for Translational Vascular Biology (CTVB), UMC, Mainz
- Since 2013** Head of Preventive Cardiology and Preventive Medicine, Center for Cardiology, UMC, Mainz
- Since 2012** Professor of Clinical Epidemiology, Center for Thrombosis & Hemostasis Mainz (CTH), UMC, Mainz
- Since 2012** Head of Clinical Epidemiology & Systems Medicine, Center for Thrombosis & Hemostasis (CTH), UMC, Mainz
- Since 2011** Coordinating Principal Investigator & Steering Committee Member of the Gutenberg Health Study (GHS), UMC, Mainz
- 2010 - 2012** Senior Physician, UMC, Mainz

EDUCATION

- 2022** Board certification in Cardiology
- 2012** MSc in Epidemiology, IMBEI, UMC, Mainz
- 2009** Board certification in Internal Medicine
- 2004** MD, Philipps University Marburg
- 2002** Medical School, University Leipzig and Medical School, Philipps University Magdeburg

RESEARCH HIGHLIGHTS

Systems medicine – a holistic approach to promoting healthy ageing

The Systems Medicine Group has comprehensive experience in molecular epidemiology and systems medicine research. We focus on investigating complex common diseases, which are strongly driven by the ageing process. Our research themes range from cardiovascular diseases, such as thrombotic disease and heart failure, to cardiometabolic conditions like obesity and type 2 diabetes mellitus, as well as infectious diseases with system-wide sequelae (SARS-CoV-2 and COVID-19) and cancers. The study of how the ageing process induces pathological changes is highly clinically relevant and a key priority for our group.

Developing tailor-made therapeutic treatments for disease

By using artificial intelligence (AI) methods and state-of-the-art high-throughput omics profiling techniques, we holistically integrate multi-omics data with environmental exposures, (sub)clinical parameters and advanced imaging data to discover new biomarkers and biosignatures, detect diseases at an earlier stage and predict their further progression. This is the basis for the development of tailor-made therapies, diagnostics, prognostics and therapy monitoring tools to determine a patient's response to therapy. A key strength of our group is our large multidisciplinary team, spanning expertise from molecular biology, biomedicine and clinical and molecular epidemiology to bioinformatics, biostatistics/AI and disciplines critical to maintaining a large clinical research infrastructure (e.g. IT, biobanking, regulatory affairs).

Exemplary highlights

2023 was marked by several milestones for our group: the BMBF-funded cluster of excellence *curATime* (curatime).

org; funding for the first 3 of 9 years: €15 million) was launched, which I was significantly involved in coordinating and managing as Principal Investigator and the group was involved in implementing. This was accompanied by an influx of new team members, many recruited through the IMB International PhD Programme (IPP). In this consortium, we collaborate with basic researchers, drug developers (TRON, BioNTech), large and medium-sized pharmaceutical companies, as well as small and medium enterprises. Our aim is to identify and evaluate new therapeutic targets for the treatment, diagnosis, monitoring and prognosis of atherothrombosis, and to translate these into actionable interventions, particularly using innovative RNA-based immunotherapies.

We have also significantly expanded our multi-omics resources: we successfully established the newly launched Olink Explore HT platform (Olink Proteomics, Uppsala, Sweden; now acquired by Thermo Fisher Scientific). This platform uses dual antibodies, oligonucleotide barcoding and a combination of real-time PCR and next-generation sequencing to sensitively and specifically quantify more than 5,400 proteins, making it the most advanced high-coverage proteomics platform on the market. The Targeted Proteomics Laboratory in the Systems Medicine Group is one of the first in the world to be certified for this platform and has measured over 3,000 samples for use in large-scale human studies. This has resulted in a unique new set of

several thousand plasma protein measurements in multiple biodatabases, with unprecedented resolution over the systems-wide protein profile (i.e. the measurement of organ-based microvesicles). In addition to these measurements, we have further expanded our clinical epigenetics resources by expanding DNA methylation measurements (Illumina MethylationEPIC 850k array). With a combined sample size of more than 5,000 individuals with DNA methylation measurements, this dataset is one of the five largest cohorts of its kind in the world. The project builds on the existing EpiHF project (collaborators: Christoph Niehrs, IMB, and Steve Horvath, Altos Labs, USA), a collaboration of the ReALity/SHARP network.

In addition to several exciting new publications in the areas of thrombosis, heart failure and epigenetics, in 2023 we also explored the emerging field of autoantibodies as regulatory mechanisms in both physiological and pathophysiological states. A landmark publication by our team in the *European Heart Journal* (Müller *et al*, 2023) was described by the journal as a “game changer in epidemiological studies”. The paper showed that autoantibodies to chemokine receptor 3 (CXCR3) were detectable in unselected individuals from the general population without autoimmune disease or cancer, and that these were modulated by characteristics such as age, cardiovascular disease, chronic lung disease and declining renal function. They were also

associated with structural and functional changes in the heart and could predict all-cause death and cardiovascular outcomes up to 14 years in advance. In a translational collaboration with the team of Gabriele Riemekasten (University Medical Center Schleswig-Holstein Campus, Lübeck), active and passive immunisation experiments in mice confirmed that CXCR3 plays a critical role in the development of atherosclerotic lesions, and further data from humans showed that CXCR3 expression is increased in unstable atherosclerotic plaques. We are currently involved in several other projects to further explore the role of the autoantibodiome in health and disease – a promising new direction.

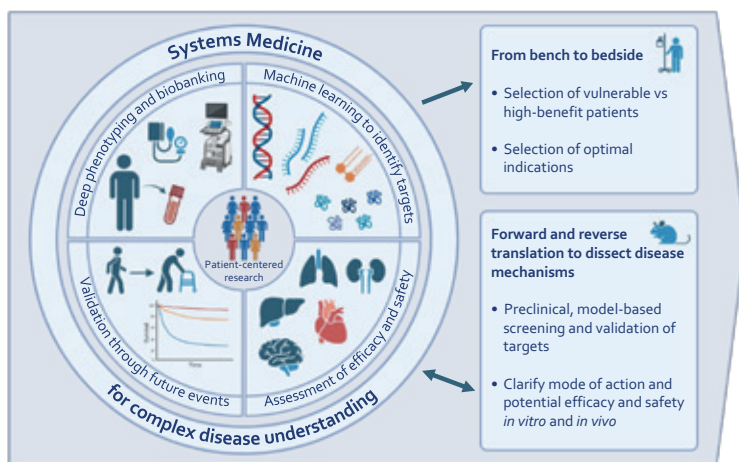


Figure 1. Research focuses of the Systems Medicine group.

SELECTED PUBLICATIONS

Müller FS, Aherrahrou Z, Grasshoff H, Heidorn MW, Humrich JY, Johanson L, Aherrahrou R, Reinberger T, Schulz A, Ten Cate V, Robles AP, Koeck T, Rapp S, Lange T, Brachaczek L, Luebber F, Erdmann J, Heidecke H, Schulze-Forster K, Dechend R, Lackner KJ, Pfeiffer N, Ghaemi Kerahodi J, Tüscher O, Schwarting A, Strauch K, Münzel T, Prochaska JH, Riemekasten G and Wild PS (2023) Autoantibodies against the chemokine receptor 3 predict cardiovascular risk. *Eur Heart J*, 44:4935-4949

Tröbs SO*, Prochaska JH*, Schwuchow-Thonke S, Schulz A, Müller F, Heidorn MW, Göbel S, Diestelmeier S, Lerma Monteverde J, Lackner KJ, Gori T, Münzel T and Wild PS (2021) Association of global longitudinal strain with clinical status and mortality in patients with chronic heart failure. *JAMA Cardiol*, 6:448-456

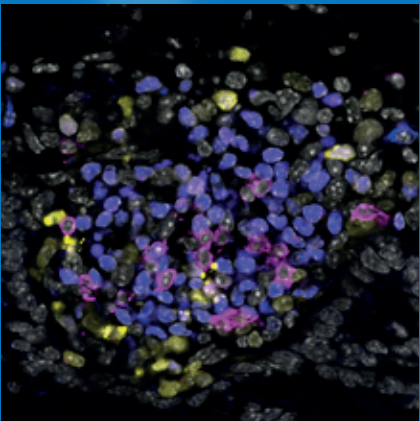
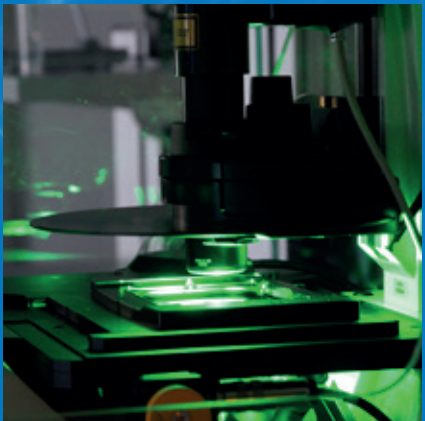
Ten Cate V, Prochaska JH, Schulz A, Koeck T, Pallares Robles A, Lenz M, Eggebrecht L, Rapp S, Panova-Noeva M, Ghofrani HA, Meyer FJ, Espinola-Klein C, Lackner KJ, Michal M, Schuster AK, Strauch K, Zink AM, Laux V, Heitmeier S, Konstantinides SV, Münzel T, Andrade-Navarro MA, Leineweber K and Wild PS (2021) Protein expression profiling suggests relevance of noncanonical pathways in isolated pulmonary embolism. *Blood*, 137:2681-2693

*indicates joint contribution

Core Facilities



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Overview

“*The Core Facilities provide access to key technologies, as well as support & training by experts.*”



IMB has seven Core Facilities (CFs): Bioinformatics, Flow Cytometry, Genomics, Microscopy/Histology, Proteomics, Protein Production and a Media Lab. The Bioinformatics, Genomics and Proteomics CFs provide a “full service”, encompassing experimental design and quality control to the generation, analysis and presentation of data. The Flow Cytometry and Microscopy/Histology CFs provide an “assisted service”, where researchers work independently on CF equipment after introductory training by CF staff. The CFs’ staff are available for consultation and troubleshooting for all users, whether they receive a full or assisted service. Furthermore, CF staff can collaborate with researchers to provide customised or specialised services. IMB researchers have access to all seven CFs. In addition, the Flow Cytometry, Genomics, Microscopy/Histology and Proteomics CFs are open to external users in Mainz.

CF services are adjusted based on user demand. Each facility has a user committee that provides feedback on the equipment and user experience. This also helps determine the implementation of new CF services. The overall CF functions as a service axis by aligning and combining individual

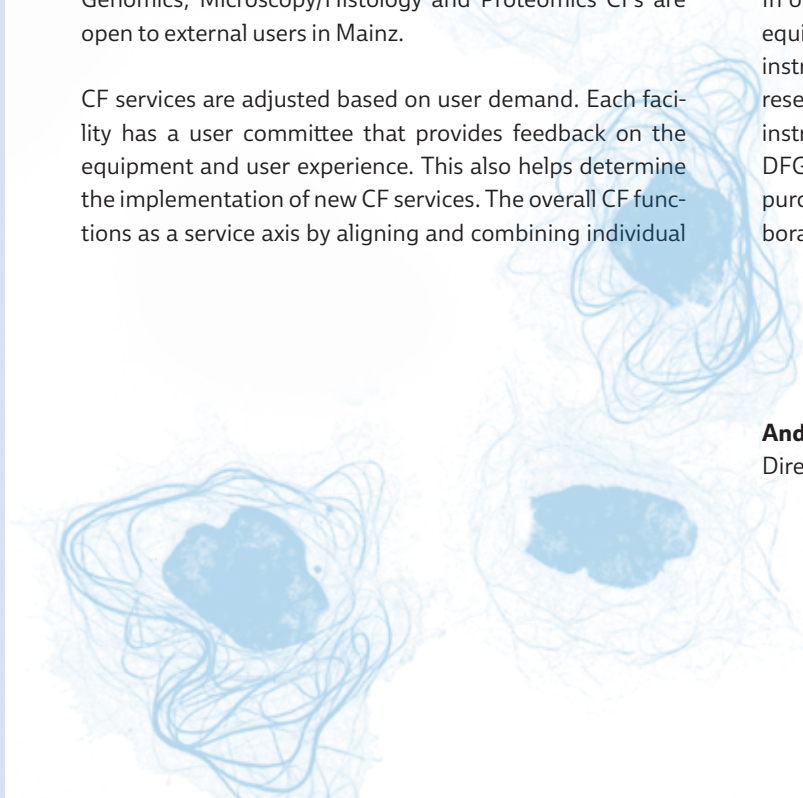
services to create new, innovative workflows (e.g. single-cell sequencing, which requires an overlap between Flow Cytometry and Genomics). The CFs also offer lectures and practical courses on new techniques and instrumentation, experimental design, statistics and data acquisition, processing and analysis to allow researchers to keep up-to-date with current and emerging technologies. Lectures are open to everyone, including those outside of IMB.

The CFs also maintain and provide training for IMB’s core equipment and are responsible for managing the radioactivity lab, the S2 lab and IMB’s in-house animal facilities (mouse, zebrafish and *Xenopus*).

In order to offer users the best and most modern research equipment, several CFs purchased new state-of-the-art instrumentation this year. These acquisitions will benefit researchers by replacing older instruments and adding new instruments to increase the pool of available devices. The DFG provided partial funding for some larger equipment purchases. In addition, many CFs take part in different collaborative research initiatives.

Andreas Vonderheit

Director of Core Facilities and Technology



Bioinformatics

The Bioinformatics Core Facility (BCF) supports researchers with computing infrastructure, software training, experimental design, biostatistics and data analysis. We offer tailored bioinformatics solutions for next-generation sequencing (NGS) and other omics methods.



MEMBERS

Head Emil Karaulanov

Bioinformaticians Anke Busch,
Antonella di Liddo, Patrick Hüther,
Sivarajan Karunanithi, Nastasja Kreim,
Michal Levin, Giuseppe Petrosino,
Frank Rühle, Sergi Sayols Puig

Biostatistician Fridolin Kielisch

SERVICES OFFERED

BCF staff offer support at different levels depending on project needs, ranging from basic bioinformatics services to full-scale scientific collaborations in the context of “big data” research projects.

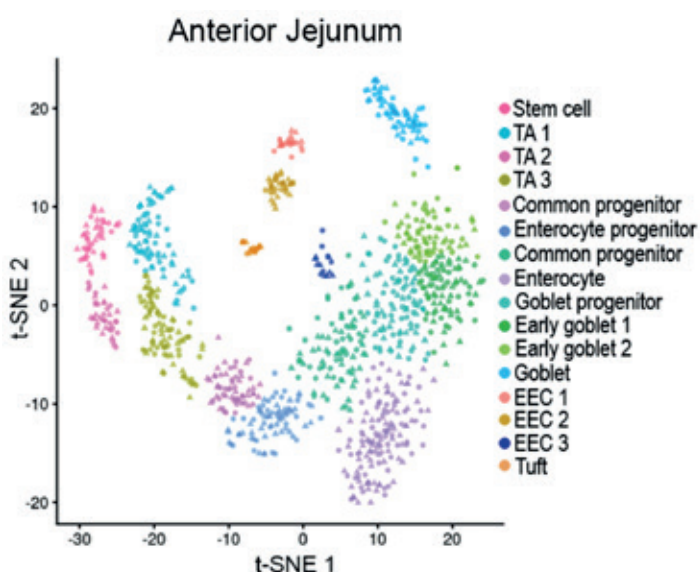
Services include:

- Consulting on biostatistics and the experimental design of genomics projects
- Data quality assessment, processing, analysis, visualisation and interpretation
- Implementation of NGS pipelines and customising them for individual projects
- Development of novel tools and custom methods for specific analysis tasks
- Testing, implementation and customisation of software tools and services
- Data mining of published datasets, correlation and integration of results
- Assistance with preparing manuscripts, presentations and grant proposals
- Bioinformatics and biostatistics courses to facilitate data access and analysis

The facility maintains GitLab and GitHub repositories (<https://gitlab.rlp.net/imbforge> & <https://github.com/imbforge>) with software tools and pipelines for advanced NGS data analysis. These are also used by many computational biologists embedded within IMB's research groups. In addition to standard tools and pipelines, the BCF offers customised bioinformatics solutions and long-term analytical support for numerous data-intensive omics projects that require expert handling for optimal results.

The BCF also provides bioinformatics expertise to the CRC 1361 on “Regulation of DNA Repair & Genome Stability” and the “Science of Healthy Ageing Research Programme” (SHARP).

Figure 1. Single-cell transcriptome profiling of epithelial cells from the adult mouse gut depicting a t-distributed stochastic neighbour embedding (t-SNE) plot, with single cells coloured by cluster annotation (published in Zinina *et al*, 2022, doi:10.1111/apha.13773).





Flow Cytometry

The Flow Cytometry Core Facility (FCCF) offers high-throughput measurements, analysis and separation of biological units using a large particle sorter, two cell sorters and two analysers. With this equipment, the FCCF can analyse and sort particles from 0.5 μm to 1,000 μm in diameter.

SERVICES OFFERED

The FCCF offers a full service for sorting and an assisted service with training for the analysers. Additionally, staff members are available for collaborations to analyse flow cytometry data and prepare samples. During the past year, the FCCF has performed various types of experiments, including multicolour measurements, cell separation for next-generation sequencing, sorting isolated neuronal nuclei, classical enrichments for subsequent cell culture, qPCR analysis, mass spectrometry and microscopy. The FCCF works with many different types of material, including nuclei, stem cells, yeast, *C. elegans*, *Arabidopsis* seeds, autophagosomes and lipid droplets, as well as various cultured cell lines and primary cells from humans, mice, zebrafish and *Drosophila*. To educate and train users, the FCCF offers three different lectures, an annual practical course for basic flow cytometry analysis and an advanced practical course for cell sorting.

The latest addition to the facility, the Bigfoot cell sorter, is a full-spectrum jet-in-air instrument with an integrated biosafety cabinet and allows cell sorting under biosafety level 2 conditions. The Bigfoot is especially suited for sensitive cell types like embryonic stem cells or primary cells and shows superior survival rates for single-cell clones.

MEMBERS

Head Stefanie Möckel

Staff Scientist Stephanie Nick

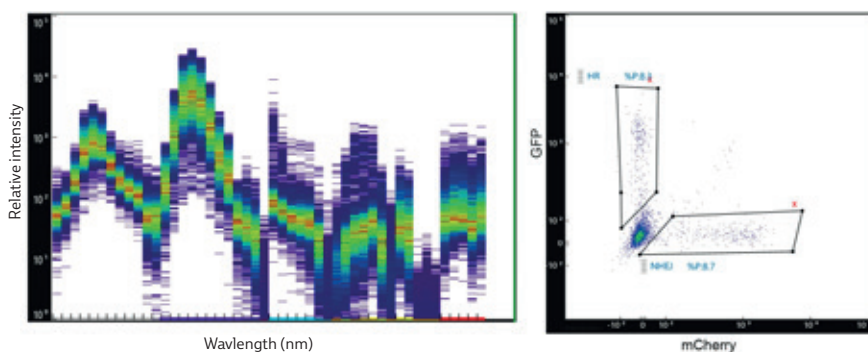


Figure 1. Left: First spectral detection of DNA repair pathways by Traffic Light Reporter assay. A full spectrum plot is shown on the left. Data of unmixed GFP (homologous recombination, HR) versus mCherry (non-homologous end-joining; NHEJ) is shown on the right. Measurement was performed on an Invitrogen Bigfoot using SQS software (above).

Genomics

The Genomics Core Facility (GCF) offers next-generation sequencing (NGS) services based on the Illumina NextSeq 2000, MiniSeq and MiSeq platforms. A MinION sequencer (Oxford Nanopore Technologies) is also available.



MEMBERS

Head Maria Mendez-Lago

Staff Scientists Annabelle Dold,
Pablo Llavana, Robert Pyne

Technicians Hanna Lukas,
Ramona Rohde, Joshua Wachlin,
Regina Zimmer

SERVICES OFFERED

The GCF provides a full service for NGS, beginning with the experimental design of the project and continuing to the generation of sequencing data. In addition, the GCF also sequences self-prepared libraries from researchers at IMB, Mainz University and the University Medical Center, as well as others from outside Mainz.

After submission of RNA or DNA samples, the GCF performs initial quality control of the samples, library preparation, quality control of the prepared libraries, sequencing and raw data generation. In 2023, the GCF supported library preparation for 20 applications as a standard service. New protocols were also implemented to accommodate users' needs for their specific projects.

RNA:

- Strand-specific mRNA-Seq with poly-A selection
- Strand-specific total RNA-Seq with rRNA depletion
- Low input RNA-Seq
- Small RNA-Seq
- RIP-Seq
- STARR-Seq
- QuantSeq
- eTAM-Seq

DNA:

- Whole genome sequencing
- Single-stranded DNA-Seq
- ChIP-Seq
- DIP-Seq
- DRIP-Seq
- Amplicon-Seq
- GLOE-Seq
- dl-Seq

Single-cell sequencing:

- SmartSeq2 scRNA-Seq
- 10 x genomics scRNA gene expression
- 10 x genomics sc Multiome (ATAC & gene expression)
- 10 x genomics multiplex RNA-Seq (Fixed RNA profiling)

User-prepared libraries:

- Amplicon-Seq
- ATAC-Seq
- ATAC-DIP
- Cut&Tag
- Cut&Run
- GLOE-Seq v1 & v2
- iCLIP-Seq v1 & v2
- miCLIP
- sBLISS
- RAD-Seq
- TTchem-Seq

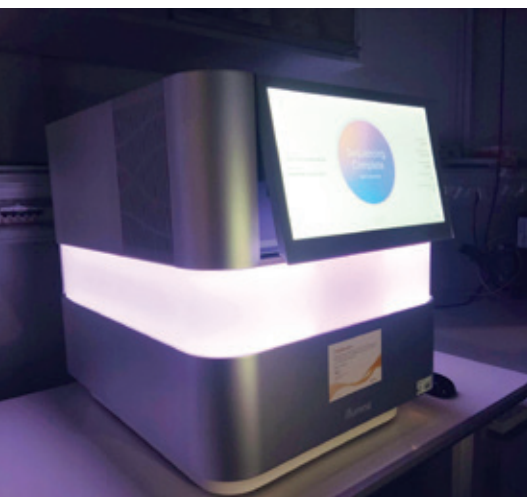


Figure 1. NextSeq 2000 benchtop high-throughput sequencer from Illumina



Microscopy & Histology

The Microscopy and Histology Core Facility (MHCF) provides state-of-the-art microscopes and histology instruments, as well as expertise in sample preparation and data post-processing. Users benefit from lectures and hands-on training and can choose from an independent, assisted or full service.

SERVICES OFFERED

The MHCF has 14 instruments ranging from stereo and widefield to confocal, high-content screening and super-resolution microscopes. Eight (three widefield, one holotomography, two scanning confocal and three spinning disk confocal microscopes) are equipped for live-cell imaging.

In 2023, MHCF acquired three new microscopes: a bench-top spinning disk system (BC43, Andor), a laser microdissection system (PALM MicroBeam, Zeiss) and a super-resolution microscope for single-molecule localisation microscopy (Nanolmager, ONI). The spinning disk microscope is easy to use and has excellent image quality. The laser microdissection microscope can combine spatial information using omics-analytics to detect RNA, DNA or proteins. Specific areas in tissue sections (cryo or paraffin), single cells (fixed or living) or even single nuclei can be isolated for further analyses like single-cell sequencing. The super-resolution microscope can resolve fluorescently labelled subcellular structures at nanometer resolution and detect up to three colours in 3D, enabling users to colocalise, track and analyse molecule clusters.

Image analysis is performed on five high-power workstations with licensed software for deconvolution (Huygens Essential, SVI), 3D visualisation and analysis (Imaris, Harmony, Vision 4D, LAS-X, VisiView) or fluorescence lifetime analysis (e.g. via phasor plots). We develop custom solutions for users with open source software (e.g. Fiji, ImageJ, or ilastik) or by assembling predefined building blocks in Columbus, a database and analysis software designed for high-content imaging data. Most of these software tools can analyse images using artificial intelligence. We support image analysis requests from users and train them in the annual "Image Analysis and Processing" course.

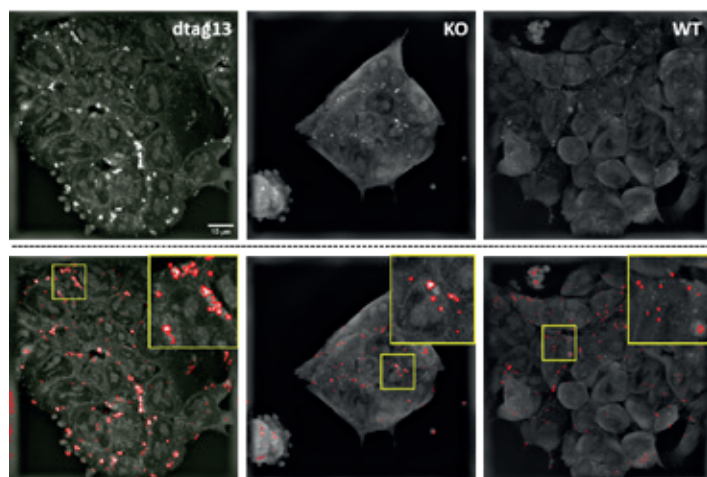
The MHCF also provides histology techniques: in addition to semi-automated fixation and paraffin embedding, machines for sectioning paraffin-embedded tissue (microtome), frozen tissue (cryotome) and gelatine/agarose embedded or fresh tissue (vibratome) are available. We offer optimised protocols for immunodetection and tissue clearing, as well as solutions for classical tissue staining.

MEMBERS

Head Sandra Ritz

Staff Scientists Márton Gelléri,
Rossana Piccinno, Petri Turunen

Figure 1. Lipid droplet analysis in genetically engineered mESCs with degron-tagged chromatin regulator (image provided by Felicia Basilicata, Claudia Keller Valsecchi). Upon addition of dtag13 compound, the tagged protein is targeted for degradation and lost from the system. Wild-type (WT) cells are untreated. In the knockout (KO), the chromatin regulator is chronically removed from the cells. Top row: snapshot of the first frame of time-lapse. Second row: lipid droplet segmentation using random forest-based pixel classification (Ilastik).



Protein Production

The Protein Production Core Facility (PPCF) provides support with the design, expression, purification and development of assays for recombinant proteins used in IMB's research. The facility also offers a variety of common protein tools routinely used by IMB researchers on a day-to-day basis.



MEMBERS

Head Martin Möckel

Staff Scientist Sabine Heinen

Technical Assistant Kanish Siddarth

Ravi Chandran

SERVICES OFFERED

The PPCF supports researchers throughout the process of protein production. This includes screening suitable expression systems and vectors, optimisation of purification steps, upscaling of protein production and purification, as well as functional analysis and assay development with the purified products. The facility is equipped with five automated chromatography systems, which enable the use of the latest chromatographic methods for state-of-the-art protein purification strategies.

Another key task of the PPCF is to generate and perform functional quality control of routine laboratory enzymes and affinity probes for IMB researchers. The PPCF currently offers 26 products to IMB scientists, matching the most frequently used protein tools at the institute.

The demand by IMB's research groups for PPCF support in producing recombinant proteins and developing assays has been steadily increasing over the years. In 2023, the PPCF purified approximately 150 recombinant proteins and antibodies for IMB groups. The facility has a head and a full-time staff scientist who assist researchers with their project needs and offer services tailored to specific user requests.

Since January 2023, the PPCF has been part of the newly-founded CRC 1551 on "Polymer Concepts in Cellular Function", where a support project is managed together with the Polymer Analysis Group at the Max Planck Institute for Polymer Research to support researchers in the production of intrinsically disordered proteins. In order to meet the additional demands of the CRC 1551's research projects, we hired a technical assistant in April (covered by CRC 1551 funds).

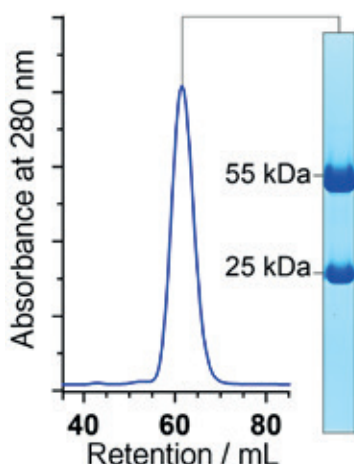
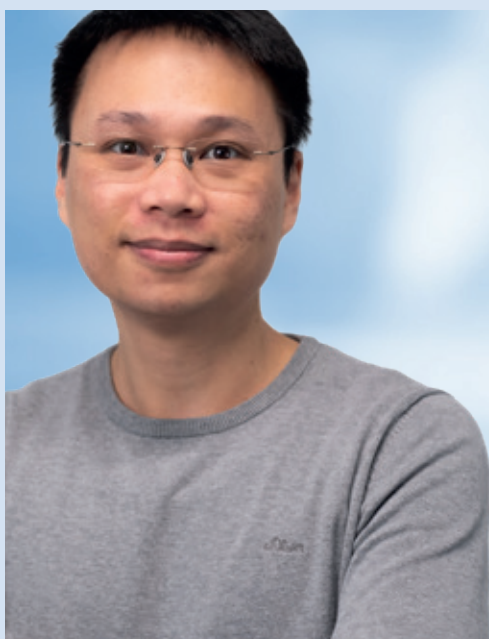


Figure 1. Left: Elution profile of a monoclonal antibody during the final gel filtration step. Plotted is the absorbance at 280 nm over the column volume (retention). The heavy and light chains of the antibody are visualised by Coomassie-stained SDS-PAGE next to the elution profile. Right: Various affinity and ion exchange chromatography columns used in the Core Facility.



Proteomics

The Proteomics Core Facility (PCF) operates high-resolution mass spectrometers (Q Exactive Plus and Exploris 480) coupled to nanoflow ultra-high performance liquid chromatography (UHPLC) systems (EASY-nLC 1000 and 1200) and provides services to the entire scientific research community in Mainz. The PCF is staffed by both wet- and dry-lab scientists with a broad range of research experience and technical expertise.

SERVICES OFFERED

The PCF actively participates in the experimental design of each user project and offers tailored services ranging from simple gel band identification to quantitative analysis of complex samples. The PCF currently supports label-free, dimethyl-labeled, TMT and SILAC-based quantitative proteomic experiments, as well as detection of post-translational modifications. The PCF also works closely with users on downstream bioinformatic data analysis to support users in making discoveries from the data. As part of the annual Modern Techniques in Life Sciences lecture series offered by the Core Facilities, the PCF delivers a theoretical lecture on proteomics technologies. Additionally, the PCF offers an annual practical training course on proteomics sample preparation and related bioinformatic data analysis.

MEMBERS

Head Jiaxuan Chen
Staff Scientist Amitkumar Fulzele
Technician Jasmin Cartano
Bioinformatician Mario Dejung

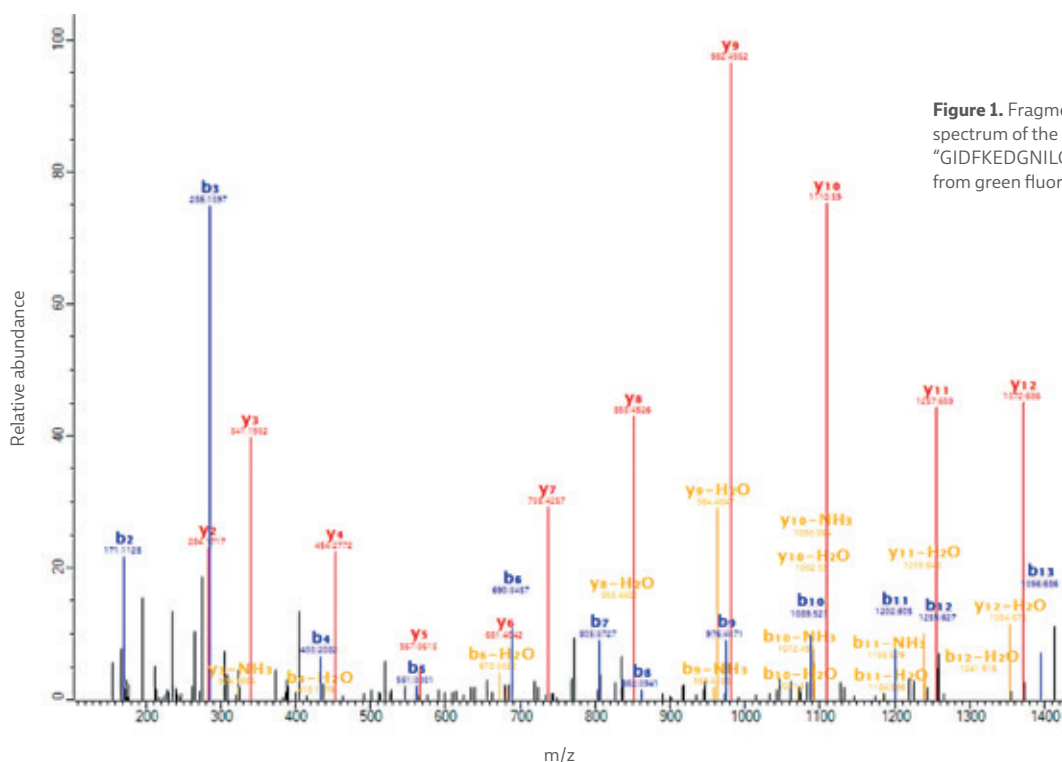


Figure 1. Fragment mass spectrum of the peptide "GIDFKEDGNILGHK", derived from green fluorescent protein.

Media Lab

The Media Lab primarily supports scientific groups and other Core Facilities by producing media, buffers and agar plates. In addition, the Media Lab is responsible for the administration of three supply centres, S1/S2 waste management and cleaning and sterilising glassware. Furthermore, the Media Lab is managing a human ORF cDNA clone collection.



MEMBERS

Head Andrea Haese-Corbit

Assistants Doris Beckhaus, Alwina Eirich,
Pascal Hageböiling, Annette Holstein,
Marion Kay, Abraham Welday Gebre

SERVICES OFFERED

The Media Lab provides the following services:

- 24/7 supply of routinely used buffers, solutions, liquid media and agar plates for molecular biology research and for culturing bacteria, yeast, insect cells and *C. elegans*
- Production of made-to-order media
- Management of three supply centres for enzymes, kits and cell culture media
- Administration of a human ORF clone collection
- Overnight cultures for plasmid preparation
- Sterilisation of solutions/media
- Cleaning and sterilisation of glassware and lab equipment
- Autoclaving of S1/S2 waste
- Maintenance of the in-house transport system

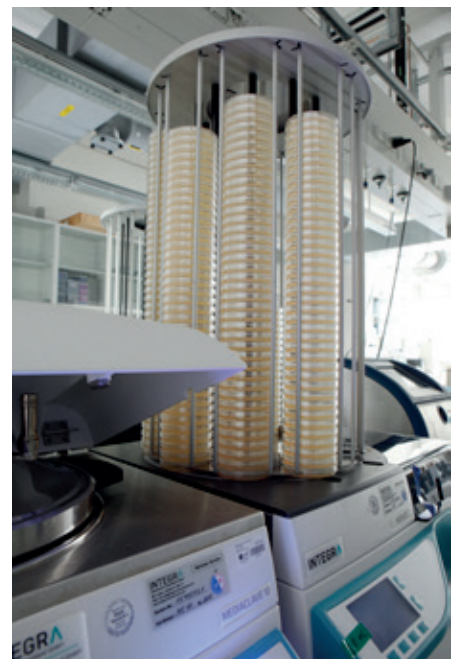
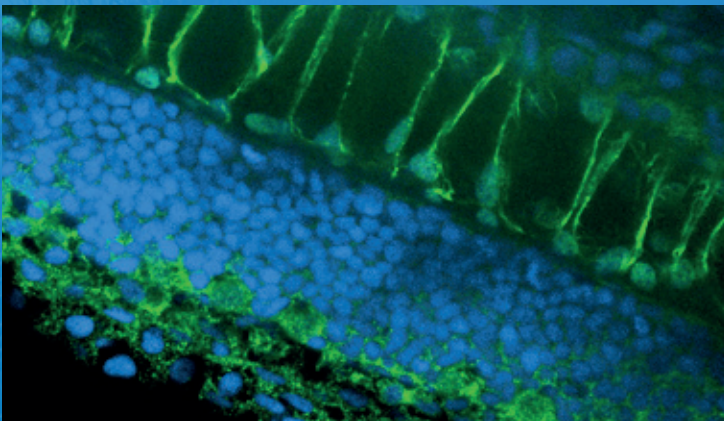


Figure 1. Top: The Media Lab produces 120L of buffers and media per week. Right: The Media Lab produces agar plates for different experimental setups with an output of about 1,700 plates per week.

Facts & Figures



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IMB Staff

European **78 %**



22 % Rest of the world

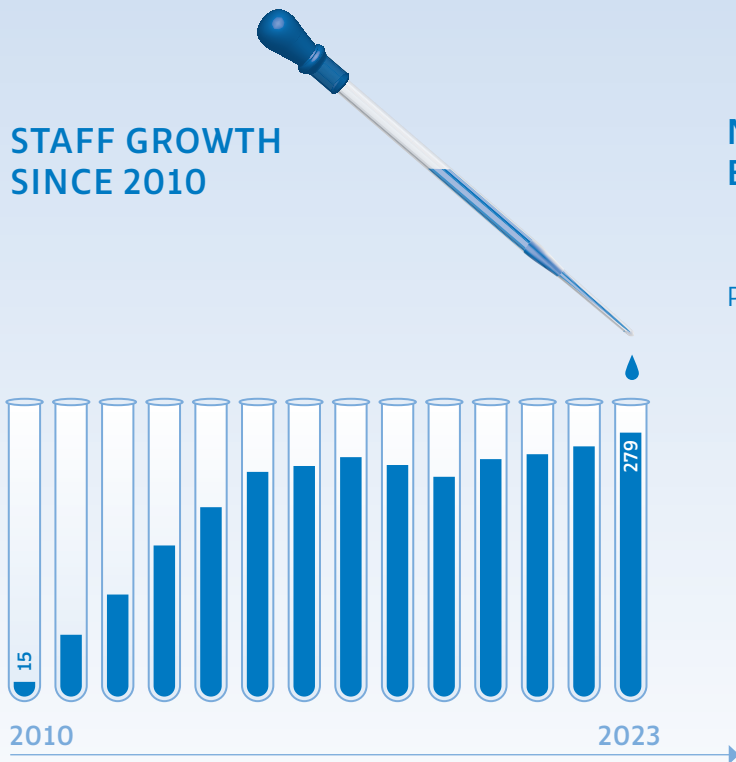


from Germany **39 %**

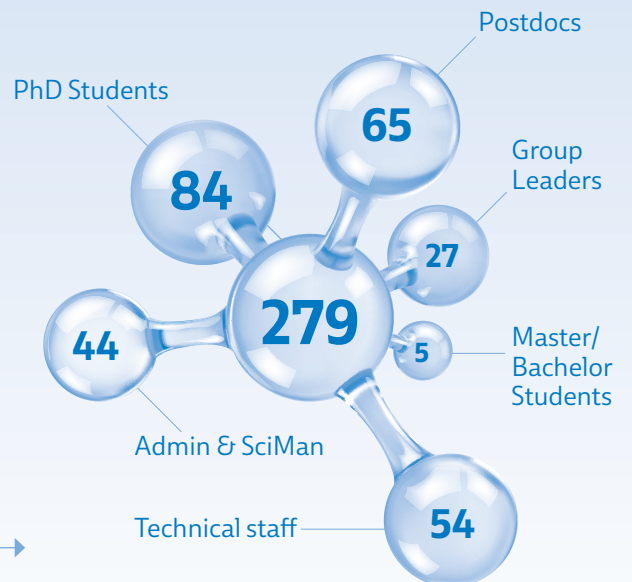


61 % from abroad

STAFF GROWTH SINCE 2010



NUMBER OF STAFF BY CATEGORY



Scientific Advisory Board

IMB is grateful to the members of our Scientific Advisory Board for the insight, guidance and advice that they have provided in order to help us continue to be a leading research centre.

Peter Becker (CHAIR)

Biomedical Center Munich,
Ludwig Maximilian
University (LMU), Munich,
Germany



Bradley Cairns

Huntsman Cancer Institute,
University of Utah, Salt Lake
City, USA



Rudolf Jaenisch

The Whitehead Institute
for Biomedical Research,
Cambridge, USA



Malene Hansen

Buck Institute for Research
on Aging, Novato, USA



Ian Hickson

Center for Chromosome
Stability and Center for
Healthy Aging,
University of Copenhagen,
Denmark



Ruth Lehmann

The Whitehead Institute
for Biomedical Research,
Cambridge, USA



Marina Rodnina

Max Planck Institute for
Biophysical Chemistry,
Göttingen, Germany



Scientific Management

“
We support our scientists across a range of areas so they can focus on their research.
”

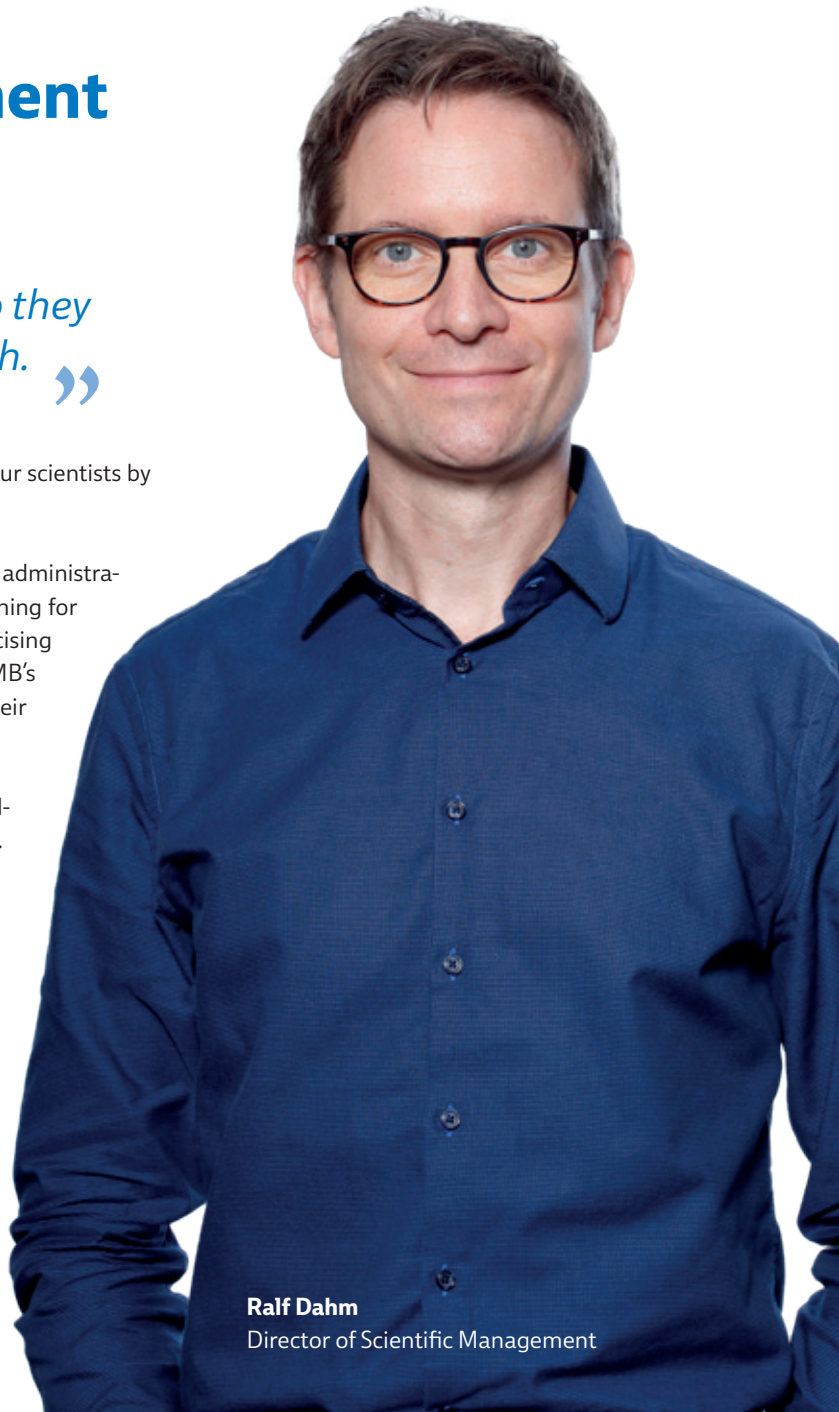
IMB's Scientific Management team fosters the success of our scientists by providing the best environment for their research.

We know that research involves a lot of time-consuming administrative work, from screening job applications, organising training for students and writing reports to managing funds and publicising key achievements. To relieve our scientists of these tasks, IMB's Scientific Management takes on these duties, freeing up their time for quality research.

Another important way we support our scientists is by building a friendly atmosphere where scientists enjoy working. This encourages collaborations to spark innovative ideas and build a strong community spirit. Through a wide range of scientific events, we also give our scientists the chance to engage with outstanding leaders in research from around the world.

We offer a range of services in, for example:

- Communications & Outreach
- Events Management
- Scientific Writing
- Fundraising & Grant Management
- Recruitment, Training & Career Development
- Technology Transfer
- Reporting, Research Evaluations & Strategic Planning



Ralf Dahm
Director of Scientific Management



Communications & Events

Building a strong collaborative spirit and encouraging frequent social interactions between our scientists are key for productive scientific exchange. To facilitate this, we organise a wide range of events for our scientists to share their research with each other, the scientific community, and the general public. We also invite top experts from all over the world to speak about their work in Mainz. Events we organise include:

- Seminars, conferences, workshops & symposia
- Public outreach activities & social media posts
- Institutional reviews
- Social events & retreats

We also maintain connections between current staff and IMB's alumni by keeping them informed of the latest developments via newsletters and IMB's social media channels.



Fundraising & Grant Management

Getting funding is essential for scientists to embark on ambitious projects and advance their careers. The Grants Office maximises our scientists' chances of getting funded by helping them find, obtain and manage extramural funding. Our services include:

- Screening & informing scientists of calls for grants & fellowships
- Supporting scientists in the application process
- Administering existing project grants

Science Writing

For junior scientists, it is extremely important that their breakthroughs are seen by the scientific community. We increase the visibility of our scientists' work to a broad audience by producing and distributing scientific and general texts about IMB's research. We help with writing texts for:

- Press releases and IMB's website
- Annual Reports
- Institutional grant applications



Coordination of Research Initiatives

IMB Group Leaders contribute as spokespersons and principal investigators in six major research initiatives in Mainz, including two Collaborative Research Centres, two Research Training Groups and two training programmes in ageing research. To ensure they run smoothly on a day-to-day basis, they are overseen by dedicated coordinators in Scientific Management, who manage and organise aspects such as recruitment, scientific training activities, events and finances, as well as support the students and communicate relevant news to all members.



Recruitment, Training & Career Development

IMB has a vibrant and international population of young scientists who are the driving force behind our exciting research. New students and postdocs are recruited through the Professional Development Office. We work to attract talented young researchers and manage IMB's training programmes, ensuring that each provides a comprehensive range of courses, lectures and career events to target the needs of our scientists and prepare them for the next step of their career. IMB's programmes include:

- The International Summer School (ISS) for undergraduate students
- The International PhD Programme (IPP) for graduate students
- The IMB Postdoc Programme (IPPro) for more experienced scientists
- The Career Development Programme for Junior Group Leaders
- The IMB Internships Programme for undergraduate students

Extramural Funding

In addition to core funding from the Boehringer Ingelheim Foundation and the State of Rhineland-Palatinate, IMB is grateful for funding from the following:



Awards

RAJANYA BHATTACHARJEE

PhD Student (Lemke lab)

Junior Member of the Gutenberg Academy Honors Program

DOROTHEE DORMANN

ERC Consolidator Grant

AGATA KALITA

PhD Student (Keller Valsecchi lab)

Honourable mention for the International Birnstiel Award for Doctoral Research in Molecular Life Sciences

JULIAN KÖNIG

Selected as a member of the Heisenberg Programme

STAMATIS PAPATHANASIOU

ERC Starting Grant

Rising Star Award (European Association for Cancer Research, the Mark Foundation for Cancer Research and the Fondazione Pezcoller)

JAN SCHREIER

PhD Student (Ketting lab)

Elisabeth Gateff Prize (*Gesellschaft für Genetik* [Genetics Society])

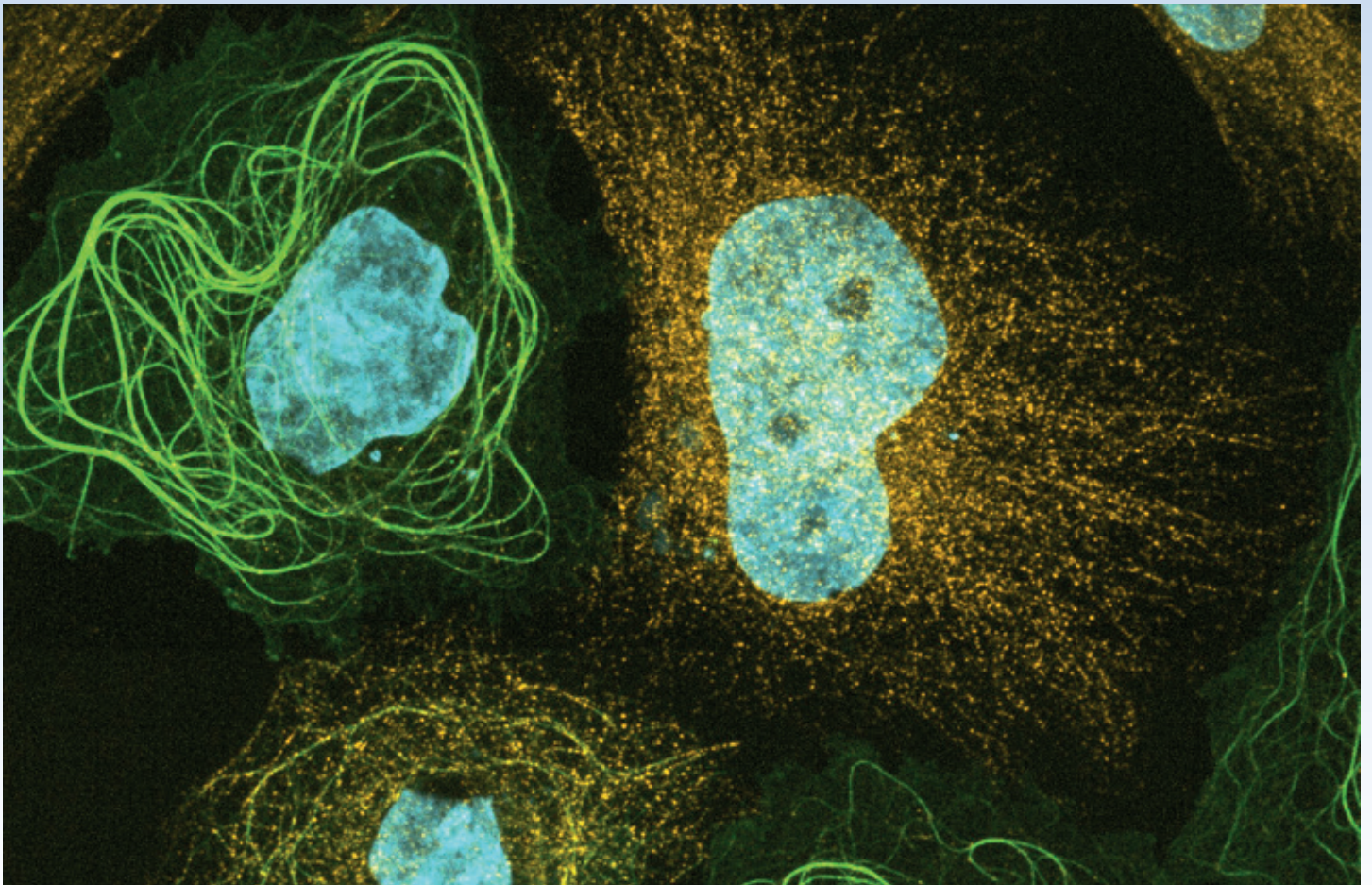
SARA VIEIRA-SILVA

Nominated to 2023 Outstanding Women Academics on AcademiaNet

MIAO YU

Postdoc (Lemke lab)

1000 Talent Investigator Award



Professional Development & Training

As a thriving international research centre, IMB focuses on giving our researchers the best possible environment in which to do their science.

Our scientists work at the forefront of their fields to answer key questions in how organisms grow, age and develop disease. Through the discoveries already made at IMB, we are beginning to transform our understanding of gene regulation, epigenetics and genome stability.

[IMB Postdoc Programme \(IPPro\)](#)

[International PhD Programme \(IPP\)](#)

[International Summer School \(ISS\)](#)

[Advanced Training & Career Programme](#)





We actively support our scientists as their careers develop by providing comprehensive training in scientific, technical and complementary skills, including:

- **Scientific & technical training** in state-of-the-art equipment by experts, as well as technical support in implementing the latest techniques
- **Professional skills training** in presentation, scientific writing, project management, fundraising, career development, negotiation and leadership by qualified trainers

Through this dedicated training, our scientists gain a competitive edge at all stages of their career in both academic and commercial settings.

IMB's scientists produced **370** publications in the last 5 years, with **111** in 2023 (of which 35 % had an impact factor of 10 or higher)

IMB POSTDOC PROGRAMME (IPPro)

The IPPro was established to meet the specific needs of our postdoctoral community. The programme provides ambitious, early-career scientists with the skills and guidance necessary to develop into future scientific leaders.

The IPPro actively supports our young professionals as their careers develop.



www.imb.de/postdocs

WE PROVIDE:

- Advanced training in **scientific methods** and **transferable skills** through a range of lectures, focused workshops and tailored events
- **Guidance** from leading scientists and **mentoring** from IMB's structured Mentoring Programme for Junior Scientists
- Networking at **career events** and **symposia** with leading external scientists from industry and academia

As well as offering fully funded positions, we also support our postdocs to raise funds for their research to help them become more independent. Collectively, the IPPro ensures that our postdocs have access to the training and technology needed to effectively carry out their research projects and advance their prospects in building successful careers.

INTERNATIONAL PHD PROGRAMME (IPP)

PhD students are key to our research at IMB. To provide the structure, training and supervision necessary to excel during a PhD, IMB created the IPP with the help of funding from the Boehringer Ingelheim Foundation.

Within this programme, our students tackle ambitious research projects, receive a broad and diverse education and have easy access to the expertise and equipment needed to drive their projects forward.



www.imb.de/PhD

THIS TRAINING INCLUDES:

- **Regular supervision** from 3 or more experts
- Training in **scientific, professional & technical skills**
- **Networking** opportunities at symposia, retreats & seminars

With the comprehensive scientific and technical training the IPP provides, our students are prepared for successful careers in the quickly evolving field of life sciences.

In 2021, a panel of independent reviewers representing leading PhD programmes at German and international institutions considered the IPP **"a model for a structured PhD programme, which is on par with the most prominent schools in Europe"**

INTERNATIONAL SUMMER SCHOOL (ISS)

IMB's ISS is a 6-week programme on "Epigenetics & Genome Stability of Health, Ageing & Disease" that brings talented undergraduate and Masters students from around the world to Mainz every summer. Through the ISS, enthusiastic students get the chance to work on their own hands-on project at the forefront of biological research.

The informal and international environment of the ISS gives participants an excellent framework in which to develop their practical and professional skills.



www.imb.de/ISS

THIS INCLUDES:

- **Training by leading experts** in scientific and transferable skills needed as a scientist
- **Lectures** to learn comprehensive insights into the latest research
- **Networking** with leading international researchers

The ISS teaches students to identify key open questions in the fields of gene regulation, epigenetics and genome stability and prepares them to tackle ambitious Master or PhD projects. This gives our ISS alumni a head start in their careers, with many going on to study and work at prestigious institutions around the world.



Currently **32** postdocs from **12** countries



Alumni work in industry, academia and beyond as:

Assistant Professors, Lab Heads, Senior Research Scientists, Managers, Policy & Governance Officers, Consultants, Start-up Founders

Currently **211** PhD students from **44** countries in **74** research groups, located at IMB, Johannes Gutenberg University Mainz (JGU), its University Medical Center and TU Darmstadt

132 graduates since **2011**

IPP STUDENT NATIONALITIES



188 ISS participants from **38** countries since 2012



Rated as **“excellent”** or **“very good”** by **98 %** of participants

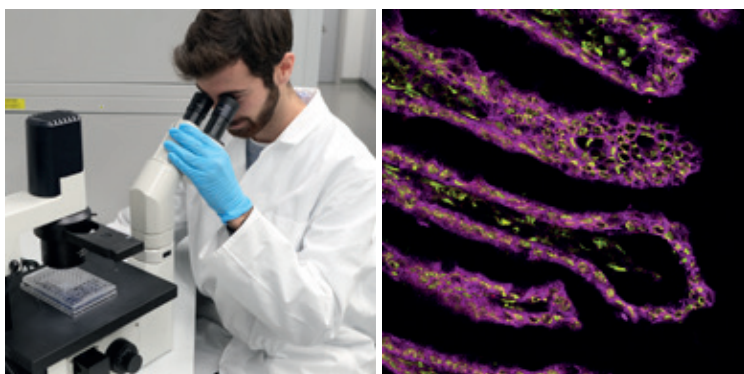
Core Facilities Training

IMB's Core Facilities staff provide our scientists with training in key scientific techniques and a wide range of cutting-edge methodologies to ensure they can consistently perform top-quality research. In 2023, IMB offered the following training courses:

LECTURES

CORE FACILITY	DATES	TITLE
GENERAL	17 Apr	Molecular & biochemistry techniques
BIOINFORMATICS	05 Jun	Databases in bioinformatics
	26 Jun	Design & analysis of NGS experiments
FLOW CYTOMETRY	02 Mar	Flow cytometry: Introduction I
	07 Mar	Flow cytometry: Introduction II
	18 Apr	Advanced flow cytometry: Principles of cell sorting
	03 Jul	Flow cytometry
GENOMICS	19 Jun	Genomics (NGS)
MICROSCOPY & HISTOLOGY	08 May	Introduction to microscopy
	15 May	Microscopy: F-techniques & super-resolution
	22 May	Histology & fluorescent labelling
	10 Jul	Electron microscopy
PROTEIN PRODUCTION	24 Apr	Protein production & crystallography
PROTEOMICS	12 Jun	Proteomics





PRACTICAL COURSES

CORE FACILITY	DATES	TITLE
BIOINFORMATICS	19 Apr	Bioinformatics: Introduction to biostatistics
	26 Apr	Bioinformatics: Introduction to biostatistics
	03 May	Bioinformatics: Introduction to biostatistics
	10 May	Bioinformatics: Introduction to biostatistics
	17 May	Bioinformatics: Introduction to biostatistics
	24 May	Bioinformatics: Introduction to biostatistics
	05 Jun	Bioinformatics: Introduction to R (Part I)
	07 Jun	Bioinformatics: Introduction to R (optional exercise session)
	12 Jun	Bioinformatics: Introduction to R (Part II)
	14 Jun	Bioinformatics: Introduction to R (Part III)
	19 Jun	Bioinformatics: Plotting with R (Part I)
	21 Jun	Bioinformatics: Plotting with R (Part II)
	07 Nov	Bioinformatics: Introduction to biostatistics
	14 Nov	Bioinformatics: Introduction to biostatistics
	21 Nov	Bioinformatics: Introduction to biostatistics
	28 Nov	Bioinformatics: Introduction to biostatistics
	05 Dec	Bioinformatics: Introduction to biostatistics
	12 Dec	Bioinformatics: Introduction to biostatistics
	13 Nov	Bioinformatics: Introduction to RNA-seq analysis (Part I)
	15 Nov	Bioinformatics: Introduction to RNA-seq analysis (Part II)
27 Nov	Bioinformatics: Introduction to ChIP-seq and related NGS assays (Part I)	
29 Nov	Bioinformatics: Introduction to ChIP-seq and related NGS assays (Part II)	
07 Dec	Bioinformatics: Efficient HPC usage and version control with GitLab	
FLOW CYTOMETRY	08 - 09 Mar	Basic flow cytometry practical course
	15 - 16 Mar	Basic flow cytometry practical course
	22 - 23 Mar	Basic flow cytometry practical course
	29 - 30 Mar	Basic flow cytometry practical course
	19 - 20 Apr	Advanced flow cytometry practical course: Principles of cell sorting
MICROSCOPY	26 - 30 Jun	Image processing & analysis
PROTEOMICS	01 Mar	Proteomics data analysis
	18 - 20 Sep	Proteomics practical course

Scientific & Transferable Skills Training

We provide our scientists with comprehensive training spanning both scientific and non-scientific skills. This ensures they have the expertise to perform top-quality research and succeed in their careers.

LECTURES

DATES	TITLE
18 Apr - 04 Jul	CRC 1361 lecture series on "DNA Repair & Genome Stability"
18 Jul - 16 Nov	Advanced lectures on "Gene Regulation, Epigenetics & Genome Stability"
06 Jul	Good scientific practice - protecting research integrity
31 Jul	Good scientific practice
31 Jul	Project management in big pharma
27 Nov	Risk, research and (scientific) responsibility: ethical considerations in bioscience

PRACTICAL COURSES

DATES	TITLE
18 & 19 Jan	Successful leadership in research and industry
07 & 08 Feb, 08 & 09 Mar	Project management ■
06 & 07 Mar	Presentation skills
14 & 15 Mar	Think before you write (Scientific writing)
16 Mar & 26 May	Dealing with imposter syndrome ▲
20 Apr	Adobe Illustrator (Beginner level)
11 & 12 May	Scientific writing
15 & 16 May	Presentation skills
04 Jul	Adobe Illustrator (Beginner level)
04 Jul	Adobe Illustrator (Intermediate level)
10 Jul	Proposal writing ■
03 & 04 Aug	How to make your next job application a success
12 & 13 Sep	Presentation skills
25 & 28 Sep	Data visualisation ■
10 & 11 Oct	Scientific writing
16 & 17 Oct	Critical reasoning & logic
13 - 15 Nov	Mastering your PhD, managing your project ■
11 - 13 Dec	Career crafting

Scientific Events

Scientific events organised by IMB in 2023:

08-10 May

Meeting of the FOR2333 Research Unit

Scientific organisers: Dierck Niessing (Ulm University), Julian König (IMB)

17 May

DKFZ-IMB Ageing & Cancer Workshop

Scientific organisers: Dorothee Dormann (IMB/Mainz University), Maja Funk (DKFZ), Mick Milsom (DKFZ), Christof Niehrs (IMB)



27 June

Public Lecture & Podium Discussion

“Rejuvenation is possible. The newest findings in cell biology”

Scientific organiser: Christof Niehrs (IMB)



11-12 October

Gutenberg Workshop

“Longitudinal Cohorts in Healthy Ageing and Disease Prevention”

Scientific organisers: Christof Niehrs (IMB), Annette Peters (Ludwig-Maximilians-University Munich & Helmholtz Munich), Philipp Wild (IMB/University Medical Center Mainz)



Invited Speakers

IMB hosts regular talks by renowned scientists & other professionals on cutting-edge topics.



DATE	EVENT	SPEAKER	INSTITUTION	TITLE
11 Jan	IMB Green Seminar	Elmar Uherek	Office of Environment and Climate Protection, Rüsselsheim, DE	Rethinking our daily energy consumption
19 Jan	CRC 1361 Seminar ▲	Martijn Luijsterburg	Leiden University Medical Center, NL	Molecular mechanisms in transcription-coupled DNA repair
26 Jan	CRC 1361 Seminar ▲	Stephanie Panier	Max Planck Institute for Biology of Ageing, Cologne, DE	The good, the bad and the ugly: SLX4IP-dependent regulation of the Alternative Lengthening of Telomeres pathway
16 Feb	CRC 1361 Seminar ▲	Patrick Matthias	The Friedrich Miescher Institute for Biomedical Research, Basel, CH	Role of the deacetylase HDAC6 and ubiquitin chains in the stress response and viral infection
09 Mar	CRC 1361 Student-Hosted Seminar ▲	Tomoyuki Tanaka	University of Dundee, Scotland, UK	How chromosomes become prepared for segregation in mitosis
23 Mar	IPP Student-Hosted Seminar ■	Wolf Reik	Altos Labs, Cambridge Institute of Science, UK	Single-cell multi-omics landscape of development and ageing
13 Apr	CRC 1361 Seminar ▲	Günter Schneider	University Medical Center Göttingen, DE	Frameworks for novel pancreatic cancer therapies
20 Apr	IMB Green Seminar ▲	Pamela Ornelas	Max Planck Institute of Biophysics, Frankfurt, DE	Can we make wet labs sustainable?
09 May	RTG GenEvo Seminar	Buck Triple	Harvard University, Cambridge, US	The molecular basis of caste development and evolution in ants
16 Jun	CRC 1361 & CRC 1551 Seminar ▲	Matthias Altmeyer	University of Zurich, CH	Dynamics and functions of DNA repair compartments
29 Jun	IMB Seminar ▲	Lucía Chemes	Universidad Nacional de San Martín (UNSAM), Buenos Aires, AR	Evolution of SLiM-mediated interactions and their hijack by viral pathogens
25 Jul	RTG GenEvo Seminar	Yun Ding	University of Pennsylvania, Philadelphia, US	The cellular and neural origin of species-specific mating behaviours
11 Sep	CRC 1361 Seminar ▲	Taekjip Ha	Harvard Medical School, Boston, US	Light, CRISPR and DNA repair



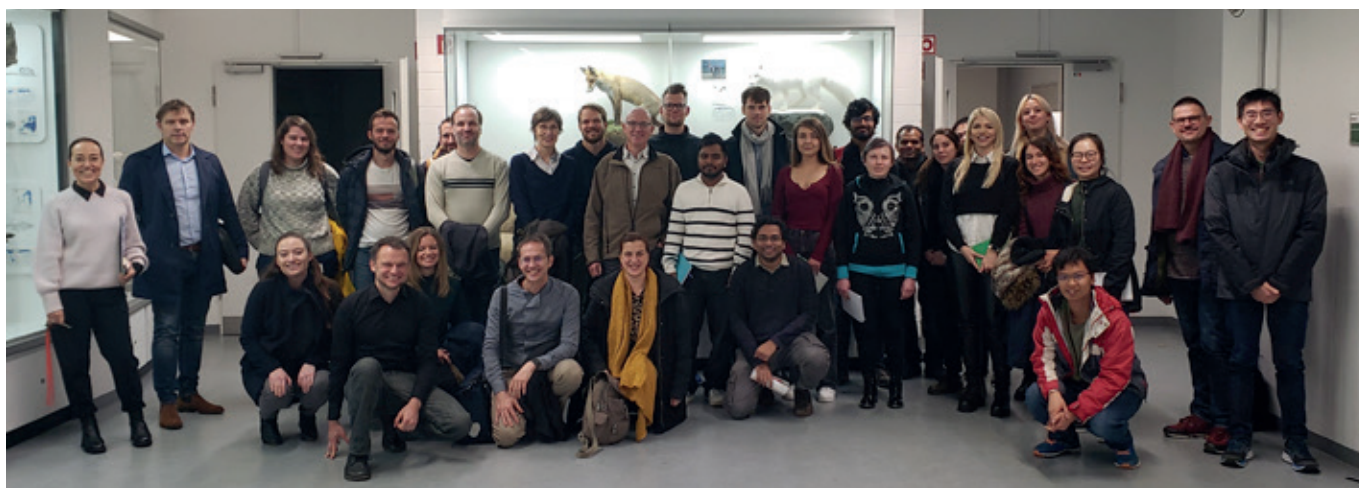
DATE	EVENT	SPEAKER	INSTITUTION	TITLE
14 Sep	Ad Hoc Seminar	Simon Hippenmeyer	Institute of Science and Technology Austria (ISTA), AT	Principles of neural stem cell lineage progression
18 Sep	Ad Hoc Seminar	Kay Hofmann	Institute for Genetics, University of Cologne, DE	Here be clippases! Searching for unusual deubiquitinases in uncharted territory
28 Sep	CRC 1361 Student-Hosted Seminar ▲	Noel Lowndes	University of Galway, IR	Novel roles for kinases and kinesins in the maintenance of genome stability
18 Oct	RTG 4R Seminar	Benoit Palancade	Institut Jacques Monod, Université Paris Cité, FR	R-loop-dependent genetic instability: a matter of time and place
26 Oct	CRC 1361 Seminar ▲	Timothy Humphrey	University of Oxford, UK	Chromosome breaks, chromatin and cancer
31 Oct	RTG GenEvo Seminar	Qiaowei Pan	University of Lausanne, CH	Sex determination from fish to ants
09 Nov	IMB Seminar ▲	Sebastian Glatt	Malopolska Centre of Biotechnology, Jagiellonian University Krakow, PL	tRNAslational control of eukaryotic gene expression
09 Nov	RTG GenEvo Seminar	Romain Libbrecht	University of Tours, FR	Factors and mechanisms controlling phenotypic specialisation in insect societies
23 Nov	CRC 1361 Seminar ▲	Jaqueline Jacobs	Netherlands Cancer Institute, Amsterdam, NL	Genome stability maintenance at broken DNA, telomeres and stalled replication forks
06 Dec	IMB Seminar ▲	Stefan Mundlos	Charité & Max Planck Institute for Molecular Genetics, Berlin, DE	Gene regulation in restructured genomes - Lessons from development, disease and evolution
07 Dec	CRC 1361 Seminar ▲	Claus Azzalin	Instituto de Medicina Molecular, Lisbon, PO	The interplay between telomere transcription and shelterin at human telomeres
13 Dec	RTG 4R & CRC 1361 Seminar	Andrés Aguilera	CABIMER, Sevilla, ES	Insights into chromatin remodelling and RNA biogenesis in genome integrity

Research Initiatives

IMB is a driver of six major research initiatives in Mainz, which bring together scientists from multiple centres across Germany.



CRC 1361 "REGULATION OF DNA REPAIR & GENOME STABILITY"
Spokesperson: Helle Ulrich (IMB)



The CRC 1361 launched in January 2019. During its first funding period, it was funded by the DFG with €12.4 million. In 2022, the CRC was evaluated by an external review board and received excellent reviews. As a result, the DFG granted the CRC another €13.1 million until December 2026.

This initiative consolidates 22 projects from investigators across 6 institutions (IMB, Johannes Gutenberg University Mainz and its University Medical Center, Darmstadt Technical University, Ludwig Maximilian University Munich and Goethe University Frankfurt) to understand the molecular mechanisms that modulate genome maintenance activities.

Supported by two dedicated service projects and centralised management, the network comprises experts in structural biology, organic chemistry, biochemistry, molecular & cell biology, genetic toxicology and clinical sciences. The CRC's Integrated Research Training Group ensures that participating students receive the best possible training and career development.

In 2023, CRC 1361 researchers published 17 papers from projects funded by this initiative and organised 13 seminars. A key event was the public lecture in German by Nina Ruge on "Rejuvenation is possible: the latest findings in cell biology", co-organised with IMB, the Centre for Healthy Ageing (CHA) and the CRC 1551. This was followed by a panel discussion with Clemens Hoch (Minister for Science and Health of the State of Rhineland-Palatinate), Peter Baumann (CRC 1361), Dorothee Dormann (CRC 1551), and Nina Ruge. Other events included the 6th German-French DNA Repair Meeting (co-organised by CRC 1361 investigators and co-funded by the consortium) and a joint Christmas Colloquium with the CRC 1551, GenEvo and 4R RTG featuring Prof. Hanna Kokko, recipient of the 2023 Alexander von Humboldt professorship.

www.sfb1361.de





CRC 1551 "POLYMER CONCEPTS IN CELLULAR FUNCTION" Spokesperson: Edward Lemke (IMB/JGU)

The CRC 1551 launched in January 2023 and is funded by the DFG with €12 million. The initiative brings together polymer and life scientists to understand the dynamic interplay between different biopolymers and how they govern cellular function. The CRC includes 33 PIs, as well as 5 associate group leaders, from the fields of polymer physics, macromolecular chemistry, bioinformatics, molecular and cell biology, biochemistry, organismal biology and ageing research.

Members come from Johannes Gutenberg University's (JGU) Faculty of Biology, Physics and Chemistry, as well as IMB, the University Medical Center Mainz, the Max Planck Institute for Polymer Research, the Max Planck Institute for Biophysics and the University of Stuttgart. Together, they work on 13 interdisciplinary projects on transcription, protein aggregation and proteostasis and the formation of higher-order complexes and organelles. The CRC 1551 also has

service projects on biopolymer visualisation and production/ analytics. Its Integrated Research Training Group (IRTG) provides interdisciplinary training at the interface of the polymer and life sciences and career development for PhD students and postdocs. In 2023, 22 PhD students and 5 postdocs, as well as 11 associated PhD students and 12 associated postdocs, were enrolled in the IRTG.

Highlights this year include the Gutenberg workshop on "Multivalent interactions in Ageing" held at Kloster Wasem in Ingelheim, and the CRC 1551 retreat at Kloster Höchst, where CRC members presented their research and had many lively discussions. The CRC was acknowledged in 11 papers in 2023 in journals such as *Nature*, *Nature Methods*, *Nature Chemistry*, *Nature Synthesis* and *Molecular Cell*.

crc1551.com



RTG GENEVO: "GENE REGULATION IN EVOLUTION" Spokespersons: Susanne Foitzik (JGU) & René Ketting (IMB)



GenEvo launched in June 2019 and is funded by the DFG with €5.8 million over its first four-and-a-half year funding period. This initiative was a collaboration between Johannes Gutenberg University's (JGU) Faculty of Biology and IMB. GenEvo is centred around the core question of how complex and multi-layered gene regula-

tory systems have both evolved and driven evolution. Mixing both junior and senior researchers, GenEvo brings together outstanding scientists in 14 projects, fusing expertise in evolutionary and molecular biology. The Research Training Group (RTG) focuses on training PhD students to work on ambitious research projects at the interface of these two

themes, while also receiving a broad, interdisciplinary education. In 2023, two new PIs joined GenEvo: Hanna Kokko, a Humboldt professor and evolutionary theoretician, and Meret Huber, an Emmy Noether group leader and professor of evolutionary ecology in plants.

In August, GenEvo was evaluated by a DFG review board for a second round of funding, and in November, we were rewarded the excellent news that the DFG had approved GenEvo for a second funding period, with €7 million until June 2028.

To date, there have been 26 papers published with GenEvo PhD students as authors, including some in *Science*, *Molecular Cell* and *Nature Communications*.

www.genevo-rtg.de

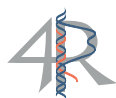


SCIENCE OF HEALTHY AGEING RESEARCH PROGRAMME (SHARP)
Steering Committee: Peter Baumann (IMB/JGU), Stephan Grabbe (UMC/IMB) & Christof Niehrs (IMB)

SHARP was launched in 2021 as a joint PhD training programme between IMB, Johannes Gutenberg University Mainz (JGU) and the University Medical Center Mainz (UMC). The goal of SHARP is to strengthen cooperation between research groups at IMB and UMC in projects focusing on ageing and longevity. This programme brings together 25 group leaders, including clinical/preclinical researchers from the fields of stem cell biology, epidemiology, immunology, cardiology, neurobiology and cancer biology together with basic molecular biology researchers in the fields of epigenetics, proteomics, telomere biology, RNA biology, DNA repair and autophagy.

By combining the complementary skills of basic and clinical/translational researchers, SHARP gains new insights into the underlying causes of ageing and discovers new ways to successfully prevent them. SHARP is funded with €1.8 million by Rhineland-Palatinate's Ministry of Science, Education and Culture until 2024. As of 2023, there are 11 PhD students in SHARP and two papers have been published from projects in this programme.

www.cha-mainz.de/SHARP



4R RTG: "R-LOOP REGULATION IN ROBUSTNESS & RESILIENCE"
Spokespersons: Brian Luke (IMB/JGU) & René Ketting (IMB)

In May 2023, the DFG awarded €8.3 million in funding for the 4R Research Training Group (RTG) on "R-loop Regulation in Robustness and Resilience". The core focus of the 4R RTG lies in its innovative training programme that delves into the profound impact of R-loops on the orchestration of complex cellular processes promoting robustness and resilience. The biological processes that will be comprehensively explored include DNA repair, telomere maintenance, gene regulation and RNA processing. The 4R RTG brings together 14 research groups drawn from IMB, Johannes Gutenberg Uni-

versity Mainz (JGU) and the University Medical Center Mainz. The 4R-associated research groups offer 24 PhD projects over 5 years and each project is funded for 48 months. As of late 2023, 11 new PhD students have already joined the 4R RTG. In addition to fully funded PhD positions, our students will have the opportunity to attend highly specialised seminar series, tech talks and training courses to develop both scientific and complementary skills.

4r-rtg.de



CHA PROGRAMME FOR CLINICIAN SCIENTISTS (CHANCE)
Spokespersons: Wolfram Ruf (UMC), Klaus Lieb (UMC) & Christof Niehrs (IMB)

Clinician Scientists are practising medical doctors who balance the treatment of patients with the pursuit of innovative research. CHANCE was established in 2023 as a joint programme between IMB, Johannes Gutenberg University Mainz and the University Medical Center Mainz (UMC). CHANCE aims to strengthen translational ageing research in the framework of the Centre for Healthy Ageing (CHA) by fostering collaborations between the participating institutions. Starting in January 2024, CHANCE will enable three Clinician Scientists and two Advanced Clinician Scientists to establish independent research programmes in ageing with

a strong translational focus by offering them research funds and protected time dedicated to research.

CHANCE will further strengthen interactions between clinicians and basic researchers within the CHA and promote collaborative research on key topics of ageing research and research in the context of age-related diseases. CHANCE is funded by Rhineland-Palatinate's Ministry of Science and Health with €1.2 million from 2023 to 2026.

www.cha-mainz.de/CHANCE

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*indicates joint contribution, **indicates joint correspondence

Research Environment

IMB is embedded in a strong and dynamic research environment. It is located on the leafy campus of Johannes Gutenberg University, just west of the Mainz city centre.





With 10 departments, more than 150 institutes and 32,000 students, Johannes Gutenberg University is one of the largest German universities. In biomedical research, the university has built strong, interdisciplinary centres dedicated to neuroscience, cardiovascular medicine, immunology and oncology.

The University Medical Centre, which is located near the main university campus, has a strong focus on clinical and translational research and has researchers who also work in close contact with IMB. In addition to the University, IMB has two Max Planck Institutes (the Max Planck Institute for Chemistry and the Max Planck Institute for Polymer Research), the Leibniz Institute for Resilience Research and Mainz's University of Applied Sciences as immediate neighbours.

Mainz is also surrounded by a number of towns and cities with extensive research activities. For instance, Frankfurt is only 35 km away and is home to Goethe University, which has over 46,000 students and 10 research institutes within the Biochemistry, Chemistry and Pharmacy Department alone. Furthermore, there are several Max Planck Institutes in Frankfurt (including the Max Planck Institute for Biophysics, the Max Planck Institute for Brain Research and the Ernst Strungmann Institute for Cognitive Brain Research).

In addition to Frankfurt, nearby Darmstadt is home to both a Technical University, whose Department of Biology has a focus on synthetic biology and the biology of stress responses, and a University of Applied Sciences that includes a focus on biotechnology.

In addition, there is an extensive industry R&D presence, with, for example, the headquarters of Boehringer Ingelheim, BioNTech, Translational Oncology (TRON) and the Merck Group in close vicinity.

WHERE WE ARE

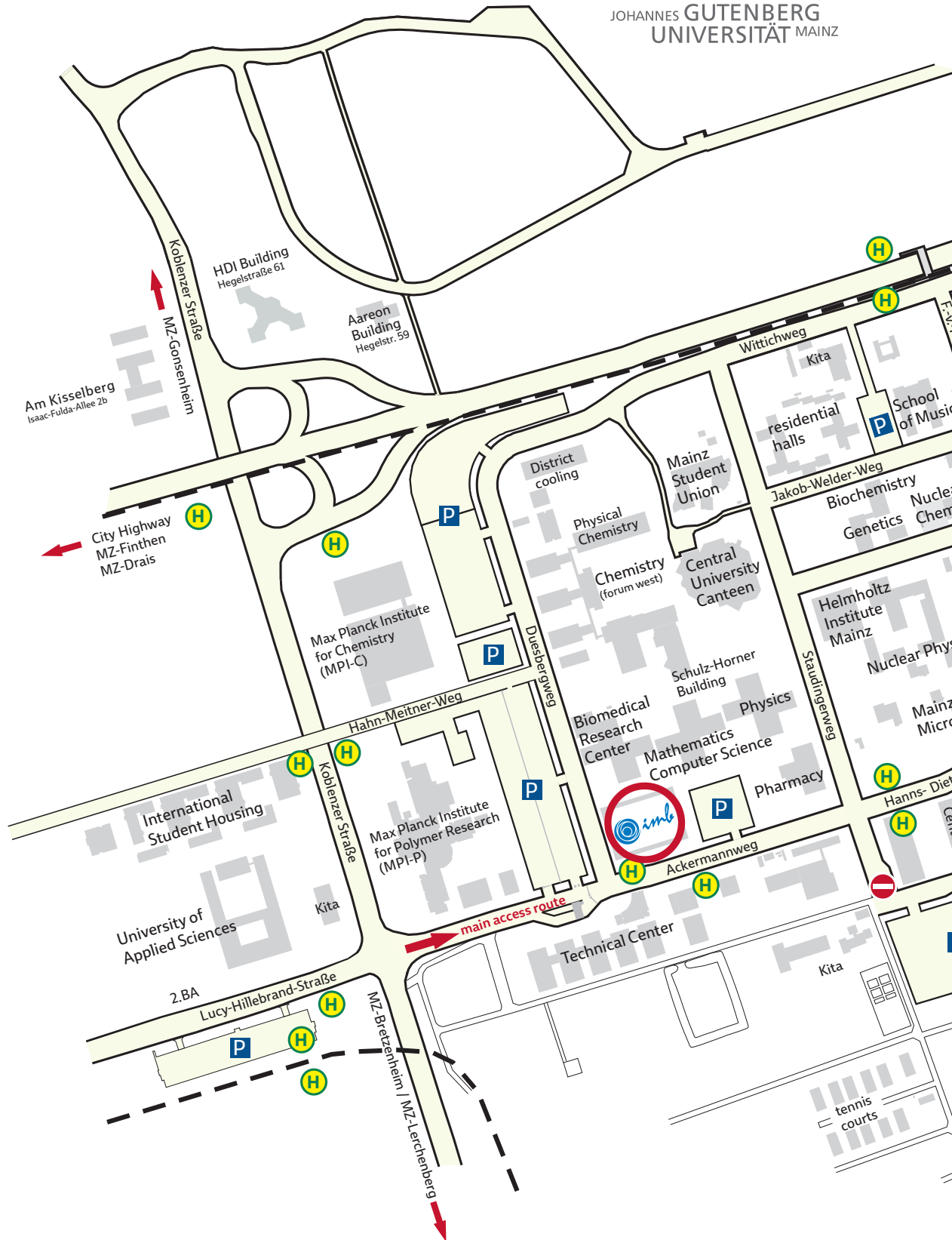
IMB is located in Mainz, a charming, open-minded city that dates back 2,000 years to Roman times and still has a historic centre with a magnificent medieval cathedral. It was also here, in 1450, that Johannes Gutenberg invented modern book printing. The city is located at the confluence of two of the most important rivers in Germany, the Rhine and the Main, and has spectacular esplanades. Mainz is within easy reach of both cosmopolitan Frankfurt, with its famous opera house, avant-garde museums and glass-and-steel banking district, and the Rhine valley region with its castles, vineyards and nature reserves that offer great outdoor activities. With Frankfurt airport - one of the largest airports in Europe - only 25 minutes away, countless European and overseas destinations are within easy reach.

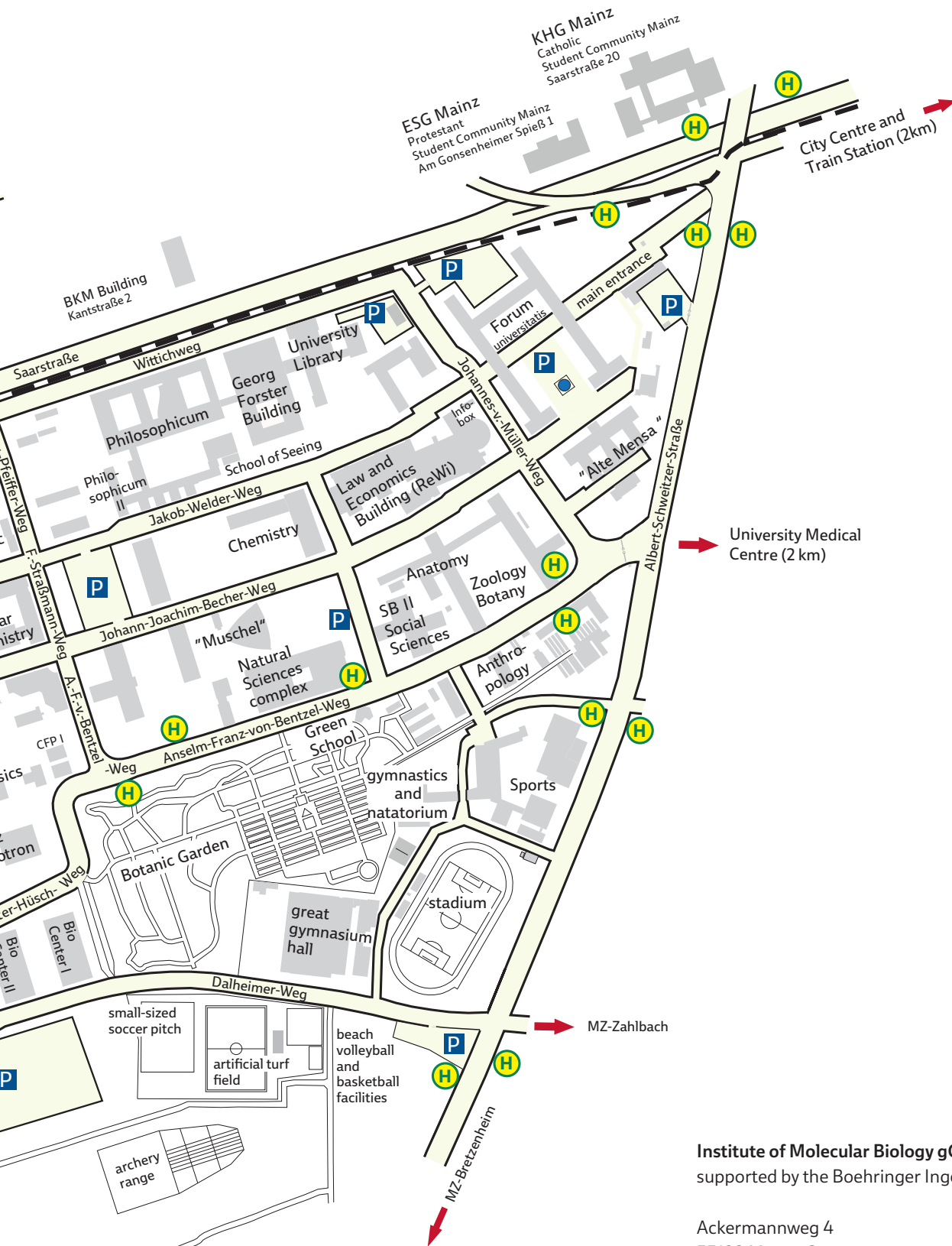


Campus Map & Contact



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(p4) Structural model generated with AlphaFold Multimer, suggesting a trimeric complex between the peroxisomal proteins PEX3, PEX16, and PEX19. Image credit: Katja Luck.

(p6) Monolayer section of whole murine colon after DNA damage. Image credit: Konrad Gronke (Charité, Berlin) & IMB Microscopy Core Facility.

(p54) Giemsa staining of bone epiphyses from Scurfy mice (FoxP3+ Treg depletion). Image credit: Mia de Haas.

(p55 & 81) HeLa cells stained with β -tubulin and transfected with various isoforms of MID1-GFP protein. Image credit: Marco Bertin.

(p55) Structural model generated with AlphaFold Multimer, suggesting a trimeric complex between the peroxisomal proteins PEX3, PEX16, and PEX19. Image credit: Katja Luck.

(p65) Centre: Image credit: Konrad Gronke (Charité, Berlin) & IMB Microscopy Core Facility. Background: DNA fibers of A549 cells visualised using the DNA Fiber Spreading technique to visualise individual DNA replication forks. Image credit: Srijana Maharjan (Ulrich group).

(p75) Notochord of a zebrafish embryo at 1 day post fertilisation. Image credit: Carisa Goh Sho Yee (Butter group).

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