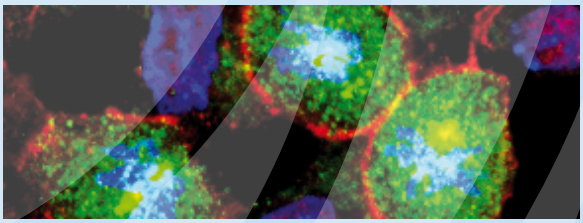

ANNUAL REPORT 2011

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imb
Institut für
Molekulare Biologie
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FOREWORD BY CHRISTOF NIEHRS

"Und jedem Anfang wohnt ein neuer Zauber inne (In all beginnings dwells a magic force)"

This famous quote by the German poet Hermann Hesse also holds true for the newly founded Institute of Molecular Biology (IMB) Mainz, located on the Campus of Johannes Gutenberg University Mainz. IMB was inaugurated in March 2011 and - unusually for a basic research centre - it is privately funded: the Boehringer Ingelheim Foundation has committed a total of 100 million Euro for IMB's operation over the next 10 years. The state of Rhineland-Palatinate provided approximately 50 million Euro for the construction of a state-of-the-art research building, with a net internal area amounting to some 6,000 square metres.

When deciding to found IMB, the Boehringer Ingelheim Foundation aimed to support research in Mainz by strengthening cutting-edge science and increasing its international visibility. This is becoming increasingly important in the face of intensified competition and international rivalry for the 'best brains'. At a time when funding for research is becoming more limited worldwide, a reliable source of institutional funding is key to allowing top scientists to engage in ambitious, long-term projects. In addition to excellent funding, IMB supports its scientists in other ways as well. There are no teaching obligations and a strong management ensures that there is a minimal bureaucratic burden. This allows our scientists to focus on their research. Furthermore, our state-of-the-art Core Facilities provide comprehensive support to all of our researchers. This includes access to the latest equipment as well as training, support and expert advice from dedicated staff. Additionally, IMB has access to the newly built mouse house of Johannes Gutenberg University and will maintain *Xenopus* and zebrafish aquaria in-house.

Research at IMB focuses on three themes: epigenetic gene regulation, DNA repair and developmental biology. Importantly, our groups tend to work at the interfaces of these topics, giving our research a unique angle.

Epigenetics is a burgeoning field which has ties to many biological and medical disciplines, including neurobiology, developmental biology, physiology and cancer. The field has emerged as a sub-discipline within molecular biology and investigates how regulatory states of genes, such as silencing, can be inherited by daughter cells, despite not being fixed in the DNA sequence. Changes in chromatin and DNA methylation as well as the actions of various species of non-coding and small RNAs have all been shown to impact epigenetic gene regulation.

DNA repair is a topic with a long history where scientists analyse how genomic integrity is maintained in the face of replication errors as well as environmental and intrinsic insults, such as radiation and reactive oxygen species, respectively. However, it is becoming increasingly clear that this process is not only involved in genomic homeostasis but is also critically implicated in gene regulation. Furthermore, close links between chromatin biology and DNA repair are emerging. These include the regulation of access for the repair machinery to DNA as a function of the surrounding chromatin and the involvement of DNA repair processes in DNA demethylation.

With the advent of molecular biology enormous progress has been made in the field of developmental biology, most notably in our understanding of the genetic regulation of developmental processes such as patterning, proliferation and differentiation. Developmental biology also has close ties to medicine as developmental control genes continue to act during adult tissue homeostasis and may be important targets in cancer biology. As such, the rich repertoire of processes studied in developmental biology provide the framework within which the role of epigenetic and DNA repair processes can be studied at the level of an entire organism.

"In all beginnings dwells a magic force". For us at IMB, part of that magic has come from witnessing many exciting "first times" this year:

- The official opening of IMB took place on March 11th
- The first phase of construction was finished in record time after only approximately 1½ years, resulting in a modern research building. IMB features spacious and generously equipped laboratories, ample office space, and an inviting science lounge where our staff can meet and interact in a relaxed atmosphere
- IMB's highly effective Administration and Scientific Management were set up by Stephanie Oehl and Ralf Dahm
- Research at IMB began in the summer when the Director of our Core Facilities, Bernhard Korn, and his team moved in and set up the first technology platforms, thus paving the way for our research groups
- In addition to my group, seven more research groups were established by Christoph Cremer (super-resolution microscopy of the cell nucleus), Stefan Legewie (mathematical modelling), George Reid (hormone receptors and gene regulation), Holger Richly (chromatin biology), Jean-Yves Roignant (RNA splicing and chromatin in *Drosophila*), Natalia Soshnikova (mouse development and chromatin) and Vijay Tiwari (signalling and chromatin structure)
- We established a scientific seminar series with renowned external speakers
- The number of employees increased to over 60
- While only in "Year One" of its existence IMB has raised over 6 million Euro in grant funding, including a major 2.4 million Euro grant for an IMB International PhD Programme

More exciting events lie ahead in 2012: On March 16th a high caliber scientific symposium will mark the 'scientific inauguration' of IMB. In October we will hold the first IMB conference on "DNA Demethylation, DNA Repair and Beyond", and towards the end of 2012 the second building phase of IMB will be completed.

To achieve this quick start, we relied on a highly motivated and effective team of administrators, managers, Core Facility experts, technicians, and not least a large number of colleagues from Johannes Gutenberg University Mainz. We are very grateful to all of them for their unfaltering support and enthusiasm. Of course none of this would have been possible without our main sponsor, the Boehringer Ingelheim Foundation, whose commitment to and genuine interest in IMB we gratefully acknowledge.

Starting out from scratch in a brand new institute is a unique opportunity and a daring experience for a Founding Director. I am confident that with the talented Group Leaders, students and postdocs we have on board we will meet the challenge of becoming an internationally known research centre in the molecular life sciences.

Christof Niehrs, Founding Director

"IMB is an exciting place to do research. In our brand-new research building scientists have the resources to pursue ambitious, cutting-edge, projects."

Christoph Cremer

> ***Our microscopes have super-resolution, approaching that of electron microscopes, while maintaining the benefits of light microscopy.***

Education

1970	Diploma in Physics, LMU, Munich
1976	PhD in Biophysics and Genetics, University of Freiburg
1983	Habilitation, University of Freiburg

Positions held

1970 - 1983	Staff Scientist, Institute of Human Genetics, University of Freiburg
1983 - 1999	Managing/Deputy Director, Institute of Applied Physics I, University of Heidelberg
1983 - 2011	Professor of Applied Optics & Information Processing, University of Heidelberg
2005 - 2007	Deputy Director, Kirchhoff-Institute of Physics, University of Heidelberg
Since 2005	Director Biophysics of Genome Structure, Institute for Pharmacy and Molecular Biotechnology, University of Heidelberg
Since 2011	Group Leader, IMB, Mainz

Research Overview

Increasing evidence shows that the functionally compartmentalised organisation of higher order chromatin provides another important level of epigenetic gene regulation. However, a major obstacle to the study of chromatin structure at the nanoscale has been the limits of conventional light microscopy (optical resolution of about 200 nm in the object plane/laterally, 600 nm along the optical axis). To overcome this bottleneck, we have developed and established a variety of super-resolution ("nanoscopy") methods for Light Optical BioSTructure analysis by Enhanced Resolution (LOBSTER). In 2011, we implemented a specific technique of three-dimensional (3D) spectrally assigned localisation microscocopy (SALM) which allowed us to resolve single molecules in nuclear nanostructures down to an optical resolution in the 20 nm range laterally and 30 nm axially, using standard fluorescence proteins/fluorochromes. Our present LOBSTER applications include the quantitative analysis of a variety of nuclear and genome nanostructures.

Research Highlights

Compared with conventional confocal laser scanning microscopy, 3D-SALM now gives an enhancement of up to several thousand times in 3D-structure resolution. This is approaching a resolution range previously reserved to electron microscopy, while maintaining all the advantages of fluorescence microscopy. Applications of this presently studied in the Cremer Lab are the spatial distribution of various histone types in normal/cancer cells before and after ionising radiation exposure; RNA Polymerase II/splicing proteins and nucleosomes; splicing complexes and transcribed DNA. Furthermore, we study the nanostructure of specific heterochromatin domains labelled by Fluorescence *in situ* Hybridisation (FISH) labelled DNA sequences and the formation of individual repair complexes induced by X-rays and single heavy ions in 3D intact cell nuclei. Using a combination of SALM with spatially modulated illumination (SMI) microscopy, we have also studied the expression of breast cancer related membrane proteins on the nanostructural, single molecule level.

Super-resolution microscopy of RNA transcription

In collaboration with the Laboratory of Prof. Thomas Cremer (Biocenter LMU) we quantitatively studied the nuclear topography of RNA transcription in HeLa cell nuclei using SALM. For the first time we were able to resolve the signals of closely adjacent individual antibody labelled Ser5P-Pol II molecules (Figure 1). In transcription clusters, ~10–80 signals (mean value: 33 ± 17 signals per cluster) were detected. In addition, the diameter of these clusters was determined, yielding a size distribution

with a mean value of around 100 nm with a range from 40 to 198 nm. These results are compatible with values obtained by another LOBSTER approach (SMI microscopy) realised in our laboratory and also with recent data from the Cook Laboratory obtained using electron spectroscopic imaging (ESI). However, in contrast to electron microscopy, the SALM/SMI methods allowed the direct analysis of 3D intact nuclei. Furthermore, our SALM data suggest that increased densities of RNA Pol II molecules are associated with decreased densities of H2B, supporting decreased chromatin condensation in the perichromatin region.

Super-resolution imaging of nuclear genome nanostructures

We combined SALM with FISH to analyse the spatial distribution of specific DNA sequences in 3D intact human cell nuclei at the macromolecular optical resolution level. As an example, repetitive DNA sequence DYZ2, located within the heterochromatin region on human chromosome Yq12, was FISH-labelled. Between 300 and 700 single probe molecules were resolved in individual chromatin domains, corresponding to a detected molecule density of around 500/μm^2 with a mean optical resolution in the 50 nm range, i.e. many times higher than resolvable by conventional fluorescence microscopy. These 'proof-of-principle' experiments indicate the potential of SALM-FISH for new perspectives for light microscopic studies of specific chromatin nanostructures in intact cells, and may open a new avenue towards the general analysis of specific DNA sequence copy number in small regions of individual interphase nuclei.

SALM analysis of breast cancer related gene expression

The Her2/neu tyrosine kinase receptor is a member of the epidermal growth factor family. It plays an important role in the tumorigenesis of certain types of breast cancer and its overexpression correlates with distinct diagnostic and therapeutic decisions. We applied localisation microscopy (SALM) to study tumour typical conformational changes of receptor clusters on cell membranes from three different cell lines. This identified differences in clustering of Her2/neu between all the cell lines. Through a combination of SALM with SMI microscopy, a dual colour reconstruction of the 3D spatial arrangement of Her2/neu and Her3 was achieved. These results indicate the usefulness of SALM/SMI super-resolution methods to study gene expression on the single protein level.

Future Directions

By the end of 2011, the research division "Applied Optics and Information Processing" in the Kirchhoff-Institute of Physics (directed 1983 – 2011 by C. Cremer) and the 4Pi/SMI laboratory of C. Cremer in the BioQuant Centre (University Heidelberg) had been terminated. The remaining activities of the Cremer Group are split between a small University of Heidelberg laboratory ("Biophysics of Genome Structure") in the Institute of Pharmacy and Molecular Biotechnology (IPMB) and IMB, to which most of the research activities of C. Cremer will be transferred.

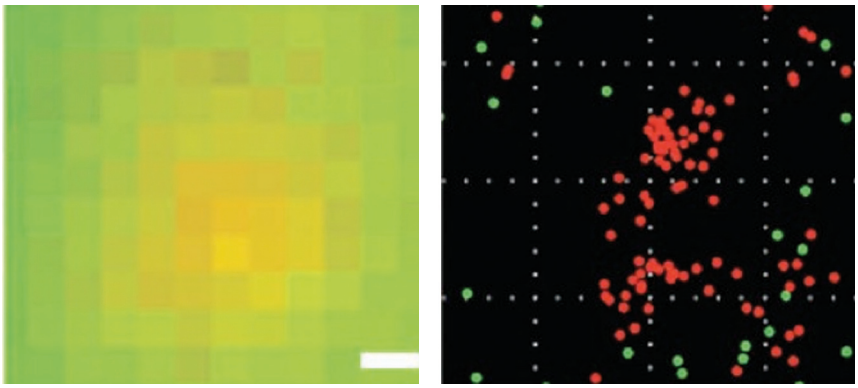


Figure 1. Dual colour super-resolution microscopy (SALM) of RNA Pol II molecules (red) and Histone H2B (H2A) molecules (green) in 3D intact nuclei of HeLa cells. The circles denote positions of single molecules. Scale bar: 100 nm. Left: Conventional microscopy; right: SALM.

➜ Selected Publications

Kaufmann R, Müller P, Hildenbrand G, Hausmann M and Cremer C (2011). Analysis of Her2/neu membrane protein clusters in different types of breast cancer cells using localization microscopy. *J Microsc*, 242, 46-54

Bohn M, Diesinger P, Kaufmann R, Weiland Y, Muller P, Gunkel M, von Ketteler A, Lemmer P, Hausmann M, Heermann DW and Cremer C (2010). Localization Microscopy Reveals Expression-Dependent Parameters of Chromatin Nanostructure. *Biophys J*, 99, 1358-1367

Baddeley D, Batram C, Weiland Y, Cremer C and Birk UJ (2007). Nanostructure analysis using spatially modulated illumination microscopy. *Nat Protoc*, 2, 2640-2646

Stefan Legewie

"Our mathematical models explore the exciting dynamics of biological regulatory networks."

Education

2004	Diploma in Biochemistry, University of Witten/Herdecke
2008	PhD in Biophysics, Humboldt University Berlin

Positions held

2008 - 2009	Postdoctoral Researcher, Institute for Theoretical Biology, Humboldt University Berlin
2009 - 2010	Group Leader 'Theoretical Systems Biology', Department of Theoretical Bioinformatics, German Cancer Research Center (DKFZ), Heidelberg
Since 2010	Group Leader, IMB, Mainz

Group Members

Stephan Baumgärtner / PhD student; since11/2011
Dirk Benzinger / Project student; 03/2011 - 05/2011
Matthias Jeschke / Postdoc; since 07/2011
Tamara Milhaljev / Postdoc; since 11/2010

Research Overview

Many biological processes including animal development are coordinated by cell-to-cell communication. Genome sequencing and high-throughput measurement techniques have led to the identification of hundreds of molecular species involved in sensing external cues. However, the dynamic interplay between signalling proteins is highly complex and cannot be understood by mere intuition. Our group employs mathematical modelling to gain insights into the dynamics of biological regulatory networks. Data-based models are developed in close collaboration with experimental partners and model predictions are verified using wet lab experiments. Our research focuses on cell-to-cell variability in cellular signal transduction and on quantitative modelling of gene expression responses.

Research Highlights

Control of cell-to-cell variability in signalling

Cellular signalling networks must function reliably despite noise from intracellular events and fluctuating environments. Molecular noise arises from the stochastic dynamics of signal transduction processes ('intrinsic noise') or from cell-to-cell variability in the copy number of signalling proteins ('extrinsic noise'). Our research focuses on cell-to-cell variability arising from extrinsic noise, since intrinsic fluctuations are typically too fast to affect downstream cell fate decisions.

Embryonic patterning is controlled by self-regulating gradients of extracellular morphogens, including those belonging to the family of bone morphogenetic proteins (BMPs). In collaboration with the Niehrs group, we used mathematical modelling and quantitative experimental analyses to determine how intracellular signalling networks are able to precisely interpret the extracellular BMP gradient. In particular, we focussed on the role of transcriptional negative-feedback regulation. We found that feedback regulators such as BAMBI and SMAD7 are critical for robust morphogen interpretation, since they (i) allow for gradual responsiveness

over a broad BMP concentration range and (ii) efficiently suppress cell-to-cell variability in signalling. Supporting this was the observation that the morphological features of *Xenopus* embryos were significantly more variable when the feedback loops were perturbed *in vivo*. Model analyses showed that signal interpretation over a broad concentration range and suppression of variability were optimised by the functional organisation of feedback regulators and target genes into so-called synexpression groups. Members of the BMP4 synexpression group are transcriptional targets of BMP signalling, show highly conserved promoter architecture and display tight co-expression during vertebrate development. In general, synexpression groups are genetic modules made up of genes which function in the same molecular process and display tight spatio-temporal gene co-expression. Our experimental and theoretical results suggest that synexpression promotes robustness, and may thus explain why organisation in synexpression groups is a design principle common to many growth factor signalling pathways.

In our current research efforts, we are generalising our modelling results of cell-to-cell variability to more complex signalling network architectures. We are applying this theory to interpret live-cell imaging data on mammalian and yeast MAPK signalling networks.

Modelling gene regulatory networks

Our second line of research focuses on quantitative modelling of gene expression dynamics in response to extracellular stimulation. We apply top-down modelling to infer the topology of gene regulatory networks from large-scale data sets. The dynamics of small genetic modules are characterised by a mechanistic bottom-up modelling approach.

External stimuli typically induce the expression of hundreds of genes. These gene expression responses are coordinated at multiple levels including *de novo* synthesis of transcription factors and post-translational control, giving rise to a complex system of regulation. We are currently analysing a medium-scale transcription factor network operating downstream of oncogenic Ras by systematically perturbing and measuring transcription factor expression. Modular response analysis, a top-down reverse engineering approach, has been applied to infer the wiring of the transcription factor network from the data. Subsequent experimental analyses have confirmed that the transcription factor hierarchy predicted by the model is visible at the level of downstream gene expression responses and cell fate decisions including migration and growth. Further model predictions concerning post-transcriptional feed-forward regulation are currently under investigation.

Future Directions

Even single genes are often subject to complex combinatorial control by multiple transcription factors. We are beginning to analyse signal integration by a prototypical human promoter based on systematic promoter mutagenesis and co-stimulation experiments. Thermodynamic models describing combinatorial transcription factor binding to the promoter are being derived to investigate the molecular mechanisms of signal integration. In the near future, we plan to extend our analyses at the single promoter level to the temporal dynamics of transcription in collaboration with the Reid group. Specifically, we are interested in how transcriptional bursts at the single-cell level give rise to population-level cycling dynamics and how these phenomena relate to the transcriptional readout.

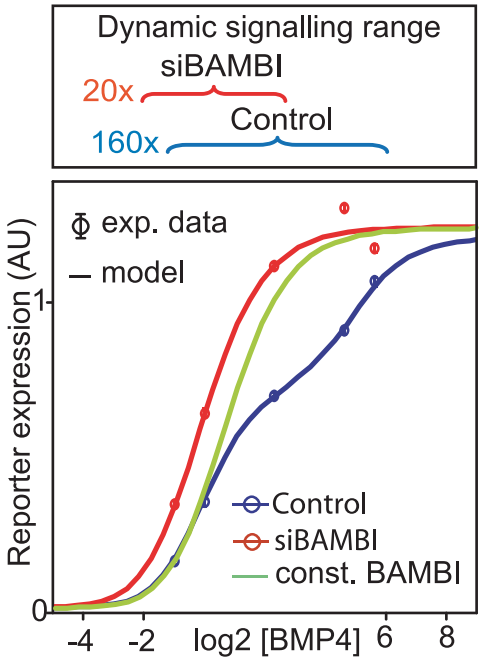


Figure 1. Negative-feedback via BAMBI expands the dynamic range of BMP4 signalling. Simulations and dose-response analysis of a BMP reporter gene in Hek293 cells demonstrate that normal expression of BAMBI is required to respond over a broad (160-fold) range of BMP concentrations (siBAMBI = BAMBI knockdown). Modelling suggests that BAMBI feedback induction is essential for expanding the signalling range, since a feedback-less model with constitutive BAMBI expression fares no better than control (green line). (Paulsen *et al., Proc Natl Acad Sci USA,* 2011)

RESEARCH GROUPS

➜ Selected Publications

Paulsen M#, Legewie S#, Eils R, Karaulanov E and Niehrs C (2011). Negative feedback in the bone morphogenetic protein 4 (BMP4) synexpression group governs its dynamic signalling range and canalizes development. *Proc Natl Acad Sci USA*, 25, 10202-10207 (# joint first authors)

Legewie S, Herzel H, Westerhoff HV and Blüthgen N (2008). Recurrent design patterns in the feedback regulation of the mammalian signalling network. *Mol Syst Biol*, 4, 190

Legewie S, Bluthgen N and Herzel H (2006). Mathematical modeling identifies inhibitors of apoptosis as mediators of positive feedback and bistability. *PLoS Comput Biol*, 2, 1061-1073

Christof Niehrs

"DNA demethylation is one of the big frontiers in epigenetics."

Education

1985	Diploma in Biochemistry, Free University of Berlin
1990	PhD, EMBL, Heidelberg
1997	Habilitation, Faculty of Biology (Zoology), University of Heidelberg

Positions held

1990 - 1993	Postdoctoral Fellow, University of California Los Angeles
Since 1994	Head of Division "Molecular Embryology", German Cancer Research Center (DKFZ), Heidelberg
2000	Professor of Molecular Embryology, DKFZ, Heidelberg
Since 2010	Professor, Faculty of Biology, University of Mainz Founding Director, IMB, Mainz

Group Members

Khelifa Arab / Postdoc; since 11/2011
Mathias Gierl / Postdoc; since 07/2011
Wolfram Gruhn / PhD Student; since 09/2010
Sabine Karl / Postdoc; since 07/2011
Manuel Leichsenring / PhD Student; since 04/2011
Konstantina Marinoglou / Postdoc; since 09/2011
Bernadette Mekker / PhD Student; since 07/2010
Michael Musheev / Postdoc; since 07/2011
Sandra Rölle / Technician; since 04/2011
Andrea Schäfer / Postdoc; since 09/2010
Lars Schomacher / Postdoc; since 07/2011
Dominik Sebastian / PhD Student; since 07/2011
Ulrike Stapf / Technician; since 05/2011
Annika von Seggern / Technician; since 06/2011

Research Overview

In the DNA of many multicellular organisms, DNA methylation is a common epigenetic mark associated with gene silencing. DNA methylation is a dynamic event that can be reversed by enzymatic demethylation, a process which is still incompletely understood. DNA demethylation is a widespread phenomenon in both plants and animals that occurs during development, in adults and during the somatic cell reprogramming of pluripotency genes. We showed that Growth Arrest and DNA Damage 45a (Gadd45a) is a key player in active DNA demethylation and acts via DNA repair. The goal of our research is to analyse the mechanism of DNA demethylation as well as the role played by Gadd45 in development. We study these questions by employing the mouse model as a genetic system and by using molecular biology, biochemistry and cell biology approaches.

Research Highlights

Role of Gadd45 in *Xenopus* embryogenesis

The role of Gadd45 genes during embryonic development is incompletely understood. In mouse we found that Gadd45 genes are expressed both in evolutionary conserved and divergent domains. These domains predominantly encompass areas responsible for cell differentiation; consistent with their established function in growth arrest and DNA demethylation. In frog, we identified Gadd45b, compared Gadd45a, Gadd45b and Gadd45g expression during *Xenopus* embryogenesis (Fig.1), and characterised their gain and loss of function phenotypes. Gadd45a and Gadd45g act redundantly and their double Morpholino knockdown leads to pleiotropic phenotypes, including shortened axes, head defects and misgastrulation. In contrast, Gadd45b, which is expressed at very low levels, shows little effect upon knockdown or overexpression. Gadd45ag double Morphants show reduced neural cell proliferation and down-regulation of pan-neural and neural crest markers. In contrast, Gadd45ag

Morphants display increased expression of multipotency marker genes and down-regulation of neural and mesodermal markers. These results indicate that Gadd45a and Gadd45g are required for early embryonic cells to exit pluripotency and enter differentiation.

Gadd45a is associated with a ribonucleoprotein particle

The stress response gene Gadd45 is part of the L7Ae/L30e/S12e superfamily and acts by recruiting DNA nucleotide excision repair machinery to sites of demethylation. We have investigated Gadd45's properties and found that it is an RNA binding protein that appears to be part of a ribonucleoprotein particle (RNP). This is in line with the function of other members of the L7Ae/L30e/S12e superfamily, which are either ribosomal components or associated with RNPs. Gadd45a displays RNase-sensitive co-localisation with the RNA helicase p68 and the RNA binding protein SC35 in nuclear speckles (Fig. 2). As nuclear speckles are sites of active transcription, RNA splicing and processing, this raises the possibility that Gadd45a RNPs are associated with genes undergoing active DNA demethylation and transcriptional activation.

Future Directions

The discovery that Gadd45 is an RNA binding protein raises new questions which we will address. Which RNAs are physiologically bound to Gadd45? What other proteins are part of the Gadd45 RNP particle? Is the role of Gadd45 bound RNAs purely structural or is RNA involved e.g. for specific targeting to demethylated DNA regions?

To study the biological role of Gadd45 genes, we have obtained Gadd45a, Gadd45b, and Gadd45g mutant mice. We are currently analysing these mice to study their phenotypes and methylation status. We will also analyse what significance ncRNAs may have in Gadd45 mediated DNA methylation by using genome-wide approaches to identify Gadd45 targeted genes.

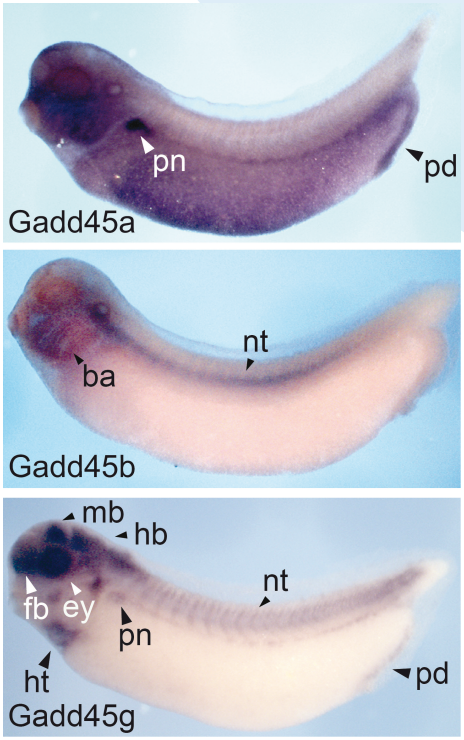


Figure 1. Whole mount *in situ* hybridisation expression analysis of tadpole stage embryos showing differential expression of Gadd45a, Gadd45b and Gadd45g during *Xenopus* embryogenesis. Key: (ba) Branchial arches, (ey) eye, (fb) forebrain, (hb) hindbrain, (ht) heart field, (mb) midbrain, (nt) neural tube, (pd) proctodeum, (pn) pronephros.

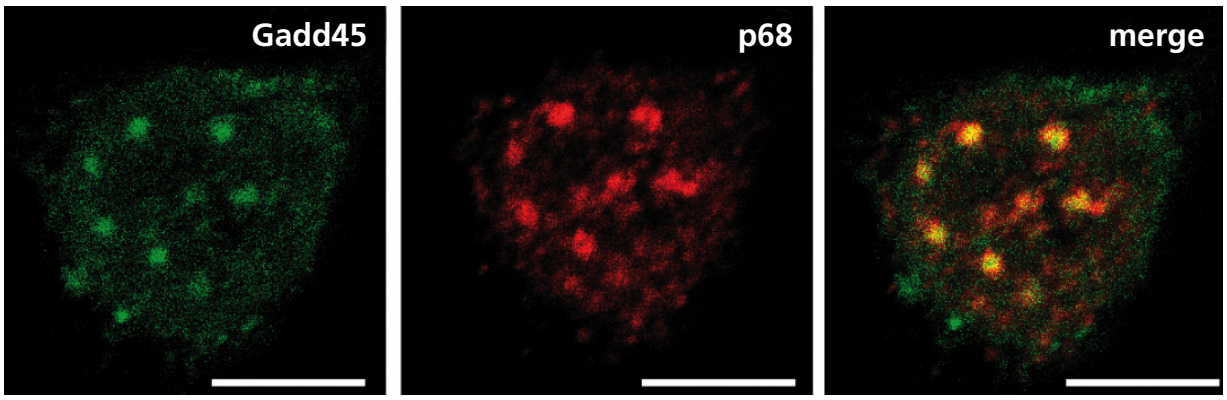


Figure 2. Gadd45a localisation in nuclear speckles demonstrated by immunofluorescence confocal microscopy of detergent-extracted RKO cells showing co-localisation of the nuclear speckle marker p68 RNA helicase with transfected EGFP-Gadd45a.

➜ Selected Publications

Sytnikova YA, Kubarenko AV, Schaefer A, Weber ANR and Niehrs C (2011). Gadd45a is an RNA binding protein and is localized in nuclear speckles. *PLoS One,* 6, e14500

Schaefer A, Schomacher L, Barreto G, Doederlein G and Niehrs C (2010). Gemcitabine functions epigenetically by inhibiting repair mediated DNA demethylation. *PLoS One,* 5, e14060

Barreto G, Schaefer A, Marhold J, Stach D, Döderlein G, Maltry N, Swaminathan SK, Lyko F and Niehrs C (2007). Gadd45a promotes epigenetic gene activation by repair-mediated DNA demethylation. *Nature*, 445, 671-675

George Reid

"Our high-throughput screen has discovered novel small molecules that critically alter dynamic DNA methylation."

Education

1984	BSc in Biochemistry, University of Strathclyde
1988	PhD in Biochemistry, University of Strathclyde

Positions held

1984 - 1985	Research Assistant, Turing Institute, Glasgow
1988 - 1993	Postdoctoral Researcher, MRC Retrovirus Research Laboratory, University of Glasgow
1994 - 1996	Senior Scientist, Pfizer Central Research, Sandwich
1996 - 1998	Postdoctoral Researcher, Beatson Institute for Cancer Research, Glasgow
1999 - 2004	Postdoctoral Researcher, EMBL, Heidelberg
2004 - 2010	Staff Scientist, EMBL, Heidelberg
Since 2006	Co-founder and Executive of Elara Pharmaceuticals, Heidelberg
Since 2010	Group Leader, IMB, Mainz

Group Members

Iryna Charapitsa / Postdoc; since 07/2011
Wolf Henning Gebhardt / Postdoc; since 08/2011

Research Overview

The functional template of gene expression is chromatin. This provides multiple regulatory barriers that have to be overcome prior to the initiation of RNA synthesis. Dynamic methylation of DNA has been demonstrated by us to be an inherent process in the expression of tightly regulated genes. Using oestrogen-mediated gene expression as a model system, we are describing, on a genome-wide scale, changes on the chromatin template that determine the timing and output of transcriptional processes. Moreover, based on our detailed description of these dynamics we have devised a high-throughput screen to discover novel small molecules that impact on dynamic methylation. In addition to being useful biotools with which to further explore transcriptional regulation, they may define new therapeutic approaches for controlling tumour growth by provoking re-expression of silenced tumour suppressor loci.

Research Highlights

Oestrogen-mediated gene expression

As a partner within a pan-European consortium of experimental and computational biologists (SYNERGY), we have generated global profiles of chromatin in oestrogen dependent breast cancer cells following their synchronous release from oestrogen starvation. This massively parallel sequence data set includes time series of RNA expression, polymerase II, oestrogen receptor alpha and variant histone H2AZ occupancy and DNA methylation profiles. Further data will be generated for covalent modifications to histone tails, in particular acetylation and methylation. By combining recent technical improvements in sequencing with state-of-the-art bioinformatics and computational biology with a tightly regulated pathway that signals to chromatin, these integrated and comprehensive data sets provide a wealth of information that promises to provide profound insight into eukaryotic gene regulation.

Small molecular activators of DNA demethylation

Our finding that the proximal promoter DNA of certain genes can undergo rapid DNA demethylation, mediated by base excision repair, suggests that it should be possible to discover small molecules that act to provoke DNA

demethylation. We devised a phenotypic screen where fully methylated plasmid DNA was transfected into cells which were then incubated with test compounds to discover small molecules that could reactivate expression of a reporter gene. Two chemically distinct series of compounds were discovered that induce active demethylation. However, as a cell based screen was employed for their identification, the target of each series could not be inferred directly. Subsequent studies have made progress towards target identification. Genome-wide comparison of RNA profiles between treated and untreated cells shows predominantly up-regulation of a significant number of genes, including a very striking immediate early gene response. For example, Early Growth Response 1 (EGR1), a zinc finger transcription factor that induces differentiation and mitogenesis and which may function as a tumour suppressor, is up-regulated some 50-fold by both compound series. In order to further dissect this effect, we mapped the minimal response element within the EGR1 promoter that conferred induction upon treatment with compound.

Each compound series was found to have distinct response elements upstream of the transcriptional start site of the EGR1 transcript. For one series, exemplified by IMBMZ-744363, the minimal element is 50 base pairs in size and contains a single CREB responsive element which is necessary but insufficient for induction. Six evolutionary conserved and functionally indispensable CpG dinucleotides occur 3' to the CREB element. CREB requires phosphorylation on serine 133 to achieve transcriptional activity; we found that IMBMZ-744363 induced prolonged phosphorylation of CREB on ser133. Furthermore, co-expression of dominant negative versions of CREB, either defective in binding DNA or where ser133 is mutated to valine, abrogated induction of EGR1 promoter activity upon treatment with IMBMZ-744363. Pathway analysis demonstrated a clear induction and response in kinase signalling pathways, and indeed methylation profiling of genomic DNA indicated that phosphorylation cascades can result in active demethylation of DNA containing CREB EGR1 modules. Collectively, these observations suggest that each compound series either acts to stimulate a kinase cascade or to inhibit dephosphorylation events that attenuate signalling to chromatin. Biochemical evaluation of nuclear extracts prepared from cells treated with the compounds has discovered protein bands that are stabilised upon treatment. Additionally, through in-gel refolding of nuclear extracts separated by SDS-poly acrylamide gel electrophoresis, we have determined bands that bind both compound series. Identification of these proteins by mass-spectrometry is in progress.

Reflecting on the potential therapeutic use of approaches that directly target the regulation of gene expression, we observed that one of the two compound series induced re-expression of Dact3, a key regulatory component of wnt/ß-catenin signalling. Deregulated wnt signalling is a key proliferative driver in colon cancer, hepatocellular carcinoma and advanced prostate cancer. Evaluation of IMBMZ-744363 in tumour cell lines dependent on wnt/ß-catenin driven proliferation shows that the compound induces re-expression of Dact3, impacts on ß-catenin signalling and preferentially results in the death of such tumour types.

Future Directions

Our immediate future aims are to determine the mechanism of action for the compounds we have discovered and to further exploit their properties in understanding gene regulation and dynamic DNA methylation.

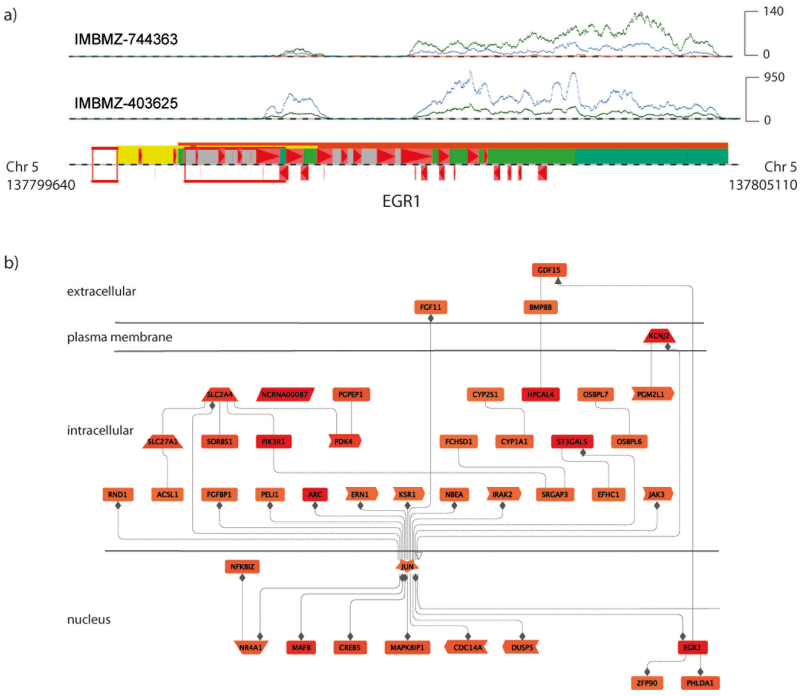


Figure 1. a) Massively parallel mRNA sequence analysis comparing cells after 0, 2 and 6 hours of treatment with IMBMZ-744363 and 403625 demonstrates a rapid induction, up to 50-fold, of EGR1 expression and in addition defines the transcriptional start site used for induction from the many alternative start sites described for EGR1. b) Network analysis of genes upregulated by IMBMZ-744363 describes a coordinated induction of signalling cascades that active AP-1 signalling, represented by Jun. Such bioinformatic analysis, particularly when employed on sequential time series, is useful in suggesting candidate proteins interacting with compounds and in characterising the outcome of exposure to compounds.

RESEARCH GROUPS

➜ Selected Publications

Kangaspeska S, Stride B, Métivier R, Ibberson D, Carmouche RP, Benes V, Gannon F and Reid G (2008). Transient cyclical methylation of promoter DNA. *Nature*, 452:112-115

Métivier R, Gallais R, Tiffoche C, Le Péron C, Jurkowska R, Carmouche R, Barath P, Demay F, Reid G, Jeltsch A, Gannon F and Salbert G (2008). Cyclical DNA methylation of a transcriptionally active promoter. *Nature*, 452:45-50

Holger Richly

"Stem cell differentiation is a hot-spot for epigenetic gene regulation."

Education

2000	Diploma in Biochemistry, Ruhr University, Bochum
2005	PhD in Biochemistry, Ludwig Maximilians University, Munich

Positions held

2005 - 2011	Postdoctoral Researcher, Center for Genomic Regulation (CRG), Barcelona
Since 2011	Group Leader, IMB, Mainz

Group Members

Katerina Gracheva / PhD student; since 08/2011
Jonathan Byrne / PhD student; since 08/2011
Stephanos Papaefstathiou / Research Technician; since 08/2011
Thaleia Papadopoulou / PhD student; since 10/2011
Thomas Wilhelm / PhD student; since 11/2011

Research Overview

Our laboratory is using mouse embryonic stem (ES) cells to study the epigenetic mechanisms underlying stem cell differentiation. Of particular interest are proteins of the Polycomb group family (PRC1 and PRC2), the newly identified switch protein ZRF1 and nuclear RNAs that are important for either pluripotency or during differentiation. Similarly, our laboratory is investigating the role of PRC in the course of DNA repair, especially in the context of skin cancer. Using the nematode *C. elegans* we are also interested in elucidating the role of epigenetic components in the course of ageing. Our research involves chromatin biochemistry, high-resolution microscopy, cell biology and genome-wide RNA and ChIP sequencing techniques.

Research Highlights

Epigenetic mechanisms at the onset of stem cell differentiation

We have previously identified the protein ZRF1 as a switch protein during the differentiation of progenitor cells into neurons (Fig. 1). ZRF1 is important in derepressing Polycomb target genes by a two-step mechanism involving the dislocation of PRC1 and the deubiquitination of histone H2A, which allows for read-through by Polymerase II. Utilising mouse ES cells we are investigating the function of ZRF1 and PRC1 at the very onset of ES cell differentiation. In particular investigating the interplay of PRC1, ZRF1 and other epigenetic components governing differentiation with nuclear RNAs is a major line of our research. We have identified novel RNA binding motifs within some of these protein complexes and are deriving a genome-wide picture of the associated RNA species.

Epigenetic mechanisms during DNA repair

PRC1 and mono-ubiquitination of histone H2A have recently been linked to DNA repair processes. Our laboratory is interested in identifying the molecular mechanism and epigenetic network of PRC1 at chromatin during DNA repair. We have purified several protein complexes in the context of DNA repair and are studying their function at H2AX containing nucleosomes. These data and high-resolution microscopy approaches suggest a concerted action of several epigenetic players to guarantee a full-blown DNA repair response. We are especially interested in studying the molecular mechanisms of novel epigenetic components that have so far not been linked to DNA repair. Moreover, we are linking the action at chromatin during DNA repair with different cell signalling pathways.

The epigenetic code of ageing

Ageing is certainly one of the most interesting but poorly understood phenomena of biology. Tissues of different ages can be easily identified and in the last couple of years cellular pathways and certain factors that act on longevity have been discovered. However, how chromatin is modified during ageing stays enigmatic. Our laboratory is interested in unveiling alterations of the chromatin landscape that occur over the course of ageing. We use the nematode *C. elegans* as a model system and have discovered a specific histone-modification that seems to play a major role during ageing. The focus of this project consists of revealing the enzymes responsible for setting and removing this chromatin mark and the epigenetic readers that transmit the ageing signal. Our research entails classical longevity research but also chromatin biochemistry and mass-spectroscopy approaches. We are also interested in understanding the cross-talk of various epigenetic marks and proteins during ageing. To this end we are utilising a genome-wide sequencing methodology to gain further insight into the intricacies of this well-orchestrated process.

Future Directions

The projects undertaken by our group ultimately aim to delineate the molecular pathways involving ZRF1 and PRC1 that drive stem cells towards differentiation into neurons, and to understand how signalling pathways regulate DNA repair in the context of a sophisticated epigenetic landscape. Furthermore, over the long-term we wish to investigate in stem cells and animal models the ageing processes we identify in *C. elegans*.

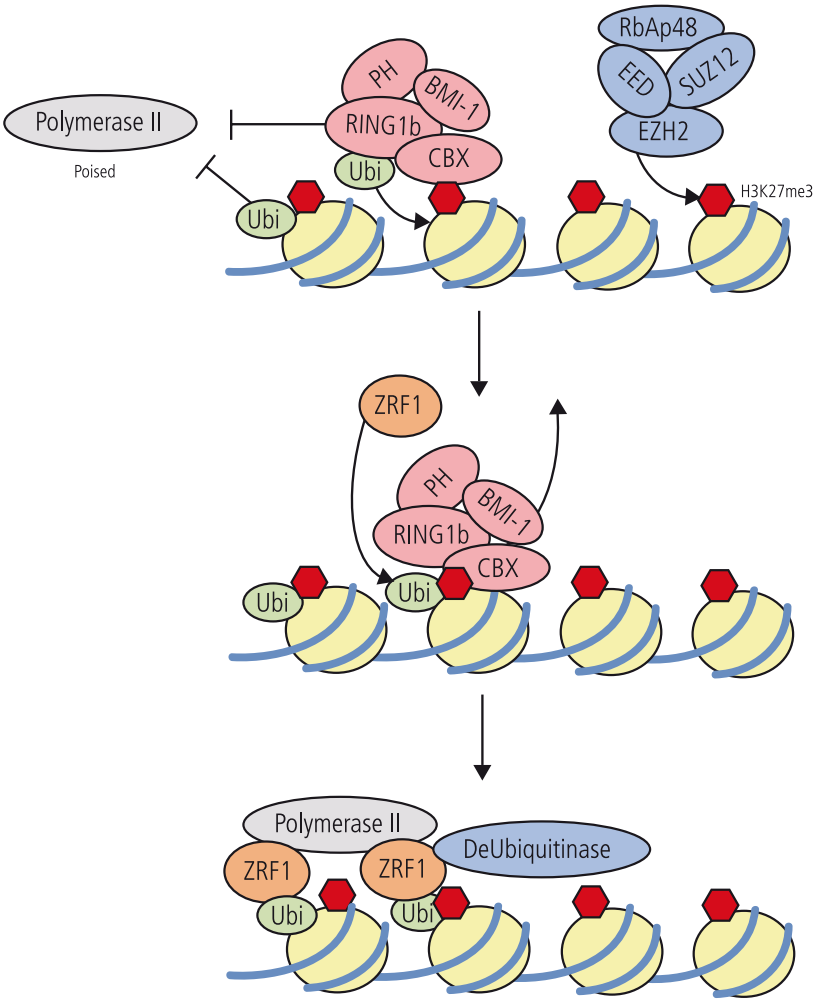


Figure 1. The consecutive action of Polycomb complexes 1 and 2 leads to methylation of H3K27 and subsequently the mono-ubiquitination of histone H2A. Upon recruitment, ZRF1 dislocates PRC1 from chromatin and facilitates the deubiquitination of histone H2A. This leads to an open chromatin conformation that most probably allows for read-through by Polymerase II.

➜ Selected Publications

Richly H, Aloia L and Di Croce L (2011). Roles of the Polycomb group proteins in stem cells and cancer. *Cell Death Dis*, 2, e204

Richly H, Rocha-Viegas L, Ribeiro JD, Demajo S, Gundem G, Lopez-Bigas N, Nakagawa T, Rospert S, Ito T and Di Croce L (2010). Transcriptional activation of polycomb-repressed genes by ZRF1. *Nature*, 468, 1124-1128

Richly H, Lange M, Simboeck E and Di Croce L (2010). Setting and resetting of epigenetic marks in malignant transformation and development. *Bioessays*, 32, 669-679

Jean-Yves Roignant

> ***The interface between chromatin and RNA processing is an exciting unexplored area.***

Education

1997	BSc in Molecular and Cellular Biology, Rennes
2003	PhD in Developmental Biology, Jacques Monod Institute, Paris

Positions held

2003 - 2008	Postdoctoral Fellow, Skirball Institute of Biomolecular Medicine, New York University
2008 - 2011	Research Associate, Skirball Institute of Biomolecular Medicine, New York University
Since 2012	Group Leader, IMB, Mainz

Research Overview

Our laboratory is studying the interplay of chromatin and RNA processing during development in *Drosophila*. Because many RNA processing events such as splicing occur co-transcriptionally, this opens the possibility for chromatin to directly influence the fate of RNAs. Conversely, RNAs can affect the structure of chromatin. One major focus in our lab is to understand how heterochromatic transcripts are processed. We have recently identified a novel function for the exon junction complex (EJC), a crucial regulator of post-transcriptional events, in splicing an important proportion of large heterochromatic introns. We are now investigating the mechanism by which the EJC acts, and more generally, how heterochromatin affects RNA processing.

Research Highlights

The EJC is a highly conserved ribonucleoprotein complex which binds spliced RNAs and remains strongly associated with them following export to the cytoplasm. Once exported, the EJC can then influence the subsequent processing of these bound RNAs. During splicing the EJC is assembled onto mRNAs 20-24 base pairs upstream of exon junctions in a stepwise manner. The DEAD-box RNA helicase eIF4AIII is the first subunit to associate with pre-mRNA. Subsequently, eIF4AIII then recruits Magoh/Mago and Y14, which act to stabilise eIF4AIII binding upstream of the exon junction. Together, these three subunits constitute the pre-EJC; the fourth core subunit, MLN51/Btz, appears to be added after the export of spliced mRNA to the cytoplasm and acts to increase the affinity of eIF4AIII for RNA. Many other accessory proteins can also transiently bind to this core complex and modulate its function.

Role of the pre-EJC is splicing large heterochromatic introns

We have recently uncovered a novel and important function for the EJC in the splicing of a subset of introns. In a screen to identify genes required for photoreceptor differentiation in *Drosophila*, we isolated three alleles of mago based on their EGFR-like phenotype. We showed that Mago is necessary for EGFR signalling due to a specific requirement for maintaining MAPK mRNA levels. To determine whether Mago was acting as a subunit of the EJC to regulate these MAPK mRNA levels, we undertook genetic analysis of the other EJC components. We found that both Y14 and the RNA binding protein eIF4AIII were also specifically required to control MAPK mRNA levels. In contrast, the loss of Btz had no effect. Since Btz is the only component added to the complex in the cytoplasm, this suggested that the three subunits of the pre-EJC might regulate MAPK expression within the nucleus. Indeed, our findings support a novel nuclear function for the pre-EJC in facilitating splicing of MAPK pre-mRNA. Firstly, we showed that

the splicing regulator RnpS1, which associates with the core EJC, is also required to maintain MAPK levels. Secondly, HA-tagged MAPK, expressed from a genomic template containing all the introns and under the control of the exogenous UAS promoter, is also reduced in the absence of mago. This confirms that MAPK is not an indirect transcriptional target of Mago and suggests that the role of Mago is to splice one or more MAPK introns. The MAPK gene has two unusual features: it contains introns of up to 25 kb, much longer than the average size of 1.4 kb for *Drosophila*, and it is expressed despite its location within a region of constitutive heterochromatin. We found in a genome-wide survey of pre-EJC-regulated genes that other genes sharing these features were overrepresented. This indicates that the pre-EJC preferentially controls the expression of large heterochromatic genes. However, the mechanism underlying this specificity remains to be understood.

Future Directions

The ability of the spliceosome to recognise splice sites in the vast ocean of nucleotide sequence has always been quite a conundrum. Now it seems that in addition to specific cis-regulatory elements, nucleosome density and specific patterns of histone modifications may help delineate where the intron-exon junction lies and facilitate exon definition. However, the causal role of chromatin structure in splicing remains poorly documented and controversial. We have found an essential role for the EJC in the splicing of long introns in *Drosophila*. Remarkably, this function appears to be biased towards transcripts encoded by genes located in heterochromatin, suggesting that heterochromatin transcripts might be spliced by a novel mechanism. We plan to determine how heterochromatin transcripts are spliced and the role of the pre-EJC in this process. This will further our understanding of the connection between chromatin and RNA processing.

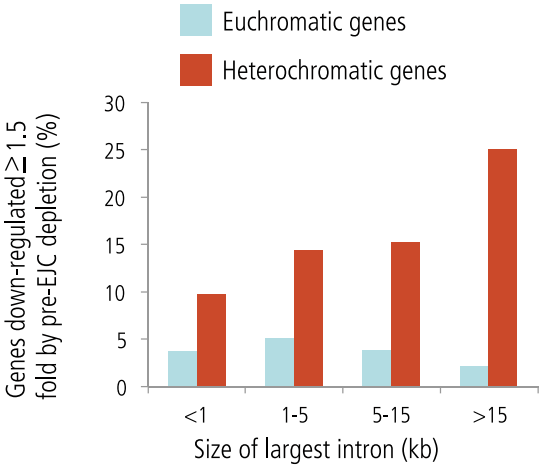


Figure 1. Genes downregulated >1.5-fold in absence of the pre-EJC, broken down by location in euchromatin or heterochromatin and by the size of their largest introns, are shown as a percentage of the total number of genes in each category.

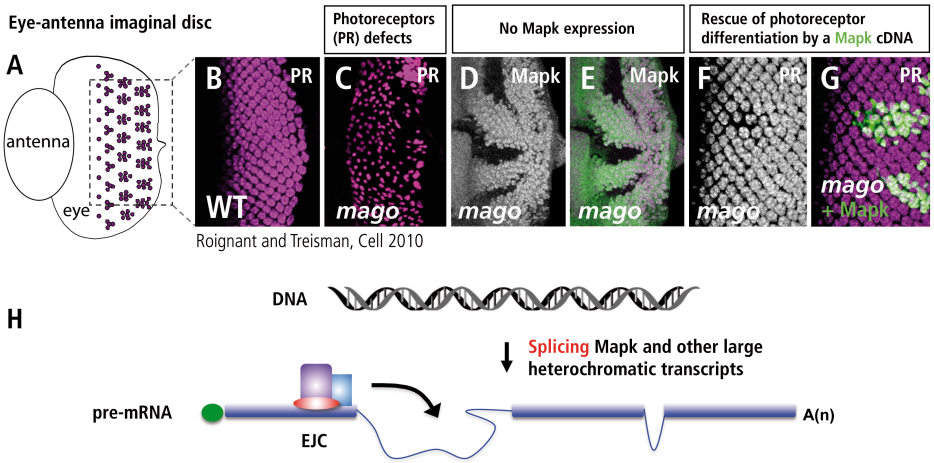


Figure 2. Mago is required for photoreceptor differentiation by controlling the splicing of the large Mapk heterochromatic transcript. Photoreceptors are stained with anti-Elav (purple in B, C, G, white in E). (A) Schematic of a larval eye-antennal imaginal disc. (B) Wild-type eye disc. (C) Eye disc containing large mago mutant clones. Most of the photoreceptors fail to differentiate. (D, E) In mago clones (lack of GFP staining in E), expression of Mapk is strongly reduced (white in D, purple in E). (F, G) Expressing a Mapk cDNA in mago mutant clones (green in G) rescues the photoreceptor differentiation defects. (H) The EJC preferentially affects the splicing of Mapk and other heterochromatic transcripts.

➜ Selected Publications

Roignant JY and Treisman JE (2010). Exon junction complex subunits are required to splice Drosophila MAP kinase, a large heterochromatic gene. *Cell*, 143, 238-250

Roignant JY, Legent K, Janody F and Treisman JE (2010). The transcriptional cofactor Chip acts with LIM-homeodomain proteins to set the boundary of the eye field in Drosophila. *Development*, 137, 273-281

Roignant JY, Hamel S, Janody F and Treisman JE (2006). The novel SAM domain protein Aveugle is required for Raf activation in the Drosophila EGF receptor signaling pathway. *Genes & Dev*, 20, 795-806

Natalia Soshnikova

We explore chromatin in developing embryos to understand epigenetic regulation in an organismal context.

Education

1998	Diploma with honour in Molecular Biology, Novosibirsk State University
2004	PhD in Molecular Biology, Humboldt University, Berlin

Positions held

2004 - 2011	Postdoctoral Researcher, Department of Zoology, University of Geneva
Since 2012	Group Leader, IMB, Mainz

Research Overview

We are interested in the regulatory mechanisms of transcriptional control in both developmental and pathological contexts. Recently, we initiated a programme aimed at the functional analysis of various aspects of chromatin biology *in vivo*. This programme is implementing both mouse genetics techniques and biochemical methods such as ChIP-seq and RNA-seq. This combination of technological approaches should provide a unique opportunity to solve questions regarding the relationships between chromatin structure and gene regulation; questions that have become increasingly important over the last few years.

Research Highlights

Chromatin function and dynamics during cell differentiation

In multicellular organisms, both embryonic development and tissue homeostasis involve the differentiation of pluri- or multi-potent stem cells into a variety of specialised cell types. These various cell types are defined by specific transcriptional programmes that are established and maintained by epigenetic mechanisms. These mechanisms include DNA methylation and the post-translational modification of histones by processes such as methylation, acetylation, phosphorylation and ubiquitination. In particular, the methylation of either H3K4, catalysed by trithorax group proteins (TrxG), or H3K27, catalysed by Polycomb group proteins (PcG), plays an important role in dividing the genome into transcriptionally active and silent areas respectively (Fig.1).

The function of these histone-modifying complexes is essential for the maintenance of stem cell potential and presumably for a stable determination of cell fate. Conversely, dynamic changes in histone modifications at critical gene loci are also required during differentiation of stem cells into more specialised cell types. However, little is known so far about the global pattern of epigenetic reprogramming that takes place during embryogenesis and tissue homeostasis *in vivo*.

We are investigating chromatin function and dynamics in stem cells, both during their maintenance and differentiation, and during neoplastic transformation when healthy multipotent cells become cancer stem cells.

Histone marks at the promoters of target genes faithfully reflect the transcriptional status of cell populations; hence mapping chromatin states is a powerful tool to predict both cell lineage identity and differentiation potential. We are particularly interested in elucidating (i) the relationship between mouse embryonic and adult stem cells, (ii) the molecular mechanisms controlling maintenance and differentiation of stem cells, (iii) the identity of cells prone to neoplastic transformation and (iv) the epigenetic changes taking place in tumour cells.

Future Directions

To perform our studies we are applying genetic and biochemical approaches, including chromatin immunoprecipitation followed by sequencing (ChIP-seq), methylated DNA immuno-precipitation followed by sequencing (MedIP-seq) and RNA-seq using purified cell populations from embryos or adult mice. We expect these approaches to shed light on the epigenetic control of cell identity and lineage commitment and to provide a better understanding of cancer development.

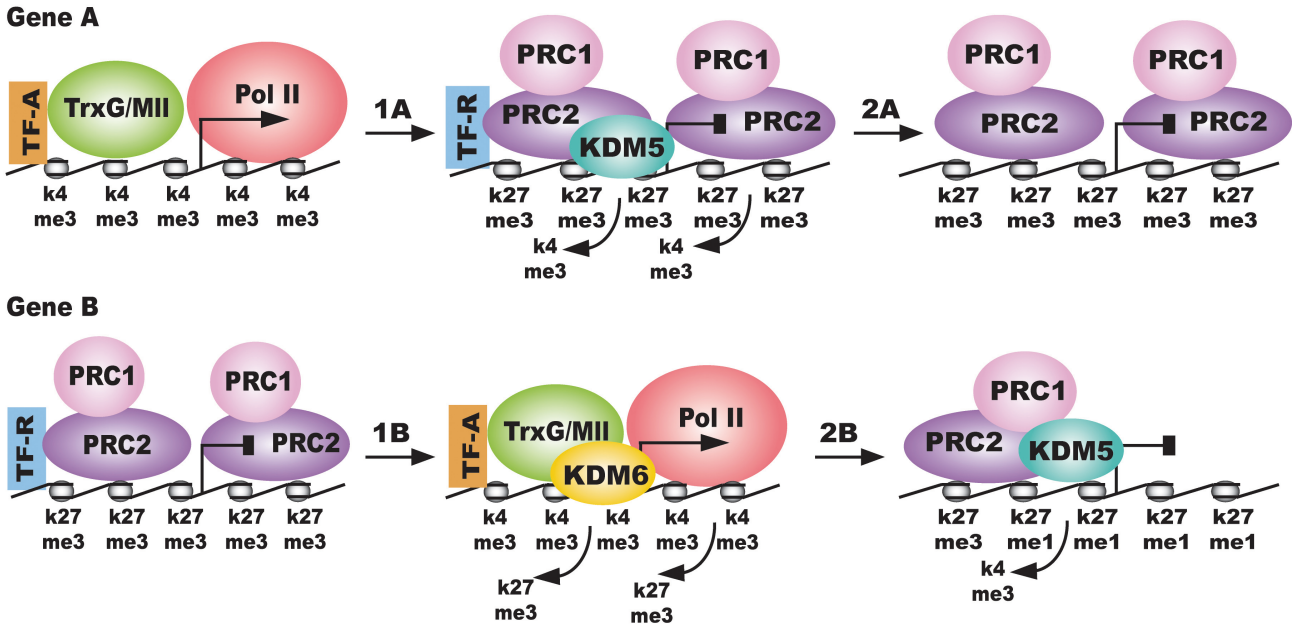


Figure 1. Sequence-specific transcription factors, activators (TF-A) and repressors (TF-R), recruit TrxG/Mll and PRC2-PRC1 to their target genes to activate (gene A) or repress (gene B) them, respectively. The repression (1A) or activation (1B) of the target genes by PRC2-PRC1 and TrxG/Mll is a dynamic process involving both positioning of repressive (k27me3) or activating histone marks (k4me3) and elimination of the concurrent mark by specific lysine demethylases (KDM). (2A) Binding of PRC2-PRC1 to the target promoters establishes the repressed state during many cell generations. (2B) KDM6 leaves the H3K27me1 (k27me1) mark that could possibly recruit PRC2, resulting in gene silencing in the absence of repressive factors of transcription. (Soshnikova, *N Birth Defects Res A Clin Mol Teratol*, 2011)

➜ Selected Publications

Montavon T, Soshnikova N, Mascrez B, Joye E, Thevenet L, Splinter E, de Laat W, Spitz F and Duboule D (2011). A regulatory archipelago controls Hox genes transcription in digits. *Cell*, 147, 132-1145

Soshnikova N, Montavon T, Leleu M, Galjart N and Duboule D (2010). Functional analysis of CTCF during mammalian limb development. *Dev Cell*, 19, 819-830

Soshnikova N and Duboule D (2009). Epigenetic temporal control of mouse Hox genes in vivo. *Science*, 324, 1320-1323

Vijay Tiwari

> *Our research reveals how signalling cascades directly talk to chromatin.*

Education

2002	MSc in Molecular and Human Genetics, Banaras University, Varanasi
2006	PhD in Developmental Biology, Uppsala University

Positions held

2006 - 2008	Postdoctoral Researcher, Johns Hopkins University School of Medicine, Baltimore
2008 - 2011	Postdoctoral Researcher, Friedrich Miescher Institute for Biomedical Research, Basel
Since 2012	Group Leader, IMB, Mainz

Research Overview

Cellular differentiation during mammalian development and disease progression involves the stable resetting of transcriptional programmes. In addition to the involvement of a remarkable variety of transcription factors and co-regulators, the role of chromatin-mediated transcriptional control in this process is being increasingly appreciated. Emerging evidence suggests that the epigenome is modulated by extracellular cues via cell signalling pathways and recent observations have revealed MAP kinases as a novel set of proteins directly binding and functioning on chromatin (Tiwari *et al.*, *Nature Genetics*, 2011). Building on these findings and our expertise in epigenetic gene regulation, my laboratory investigates how chromatin is modulated by MAP kinase pathways to mediate stable transcriptional outputs during cellular differentiation and how this communication is altered in diseases such as cancer. To investigate these questions, we employ a multidisciplinary approach using cutting-edge epigenetics, genomics and proteomics techniques, combined with computational biology tools to produce sophisticated models of cellular differentiation and carcinogenesis.

Research Highlights

A MAP kinase directly binds to promoters

MAP kinase family members are indispensable for embryonic development as well as for embryonic stem cell differentiation *in vitro*. A number of studies have argued for a role of MAP kinase signalling pathways in cellular differentiation. The underlying mechanisms for this have remained unclear though. A generally accepted concept in the field is that rather than by directly influencing transcriptional events, MAP kinases bring about changes indirectly via other downstream effector proteins in a cascade. We recently showed by genome-wide location (ChIP-seq) analysis that a MAP kinase, JNK, directly binds to a large set of active promoters during the differentiation of stem cells to neurons. Furthermore, these targets are enriched for genes involved in developmental pathways (Tiwari *et al*., *Nature Genetics*, 2011). Interestingly, JNK occupied promoters are not enriched for the canonical AP1 target sites, but for binding motifs of the transcription factor NF-Y. ChIP-seq analysis confirmed that NF-Y occupies the JNK target sites genome-wide *in vivo*. Furthermore, overexpression of a dominant-negative form of NF-YA reduced JNK occupancy on chromatin. These data suggested that a MAP Kinase, JNK, is selectively recruited to the promoters of developmental genes during cellular differentiation.

MAP kinase signalling regulates transcription by directly modifying histones

We next searched for a transcriptional regulatory role for chromatin-bound JNK, given the very precise localisation around the transcription site of a large number of active genes. We identified histone H3 serine 10 as a substrate for JNK kinase activity and revealed that JNK-bound promoters are preferentially enriched for histone H3 phosphorylated at this position (p-H3S10). Moreover, chemical inhibition of JNK signalling in post-mitotic neurons reduced this chromatin phosphorylation and specifically down-regulated transcription of JNK target genes. Thus, promoter-bound JNK contributes to the transcriptional activation of target genes by directly modifying chromatin components (Fig. 1). This research has therefore revealed a novel parallel pathway where kinases can regulate genes by acting directly on chromatin.

Future Directions

Our findings have opened a whole new arena of research studying MAP kinases as a novel set of epigenetic modifiers that directly function on gene promoters for transcriptional regulation. We aim to investigate if comparable principles of chromatin binding and activity are utilised by other MAP kinases, especially those with an established function in differentiation and development. We would also like to dissect the molecular mechanisms by which MAP kinase-mediated chromatin modifications contribute to the transcriptional activity of target genes. Furthermore, since a number of these kinases have also been shown to play important roles during carcinogenesis, we will further study how the newly discovered chromatin function of MAP kinases contributes to the transcriptional reprogramming that accompanies the phenotypic alterations required for tissue evasion and metastasis formation during tumour progression.

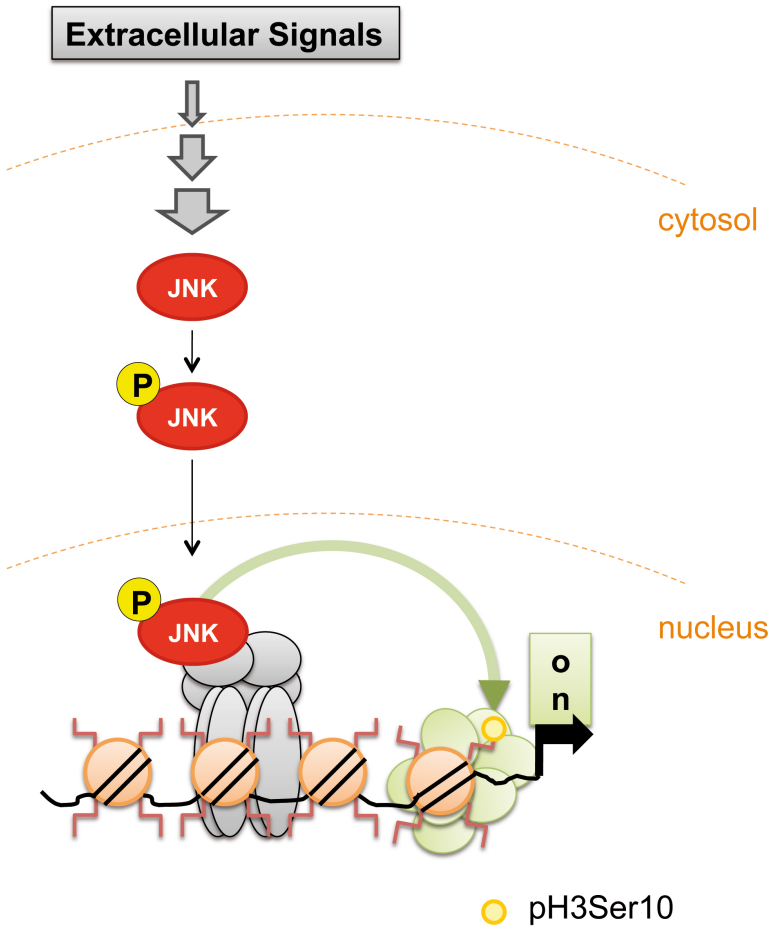


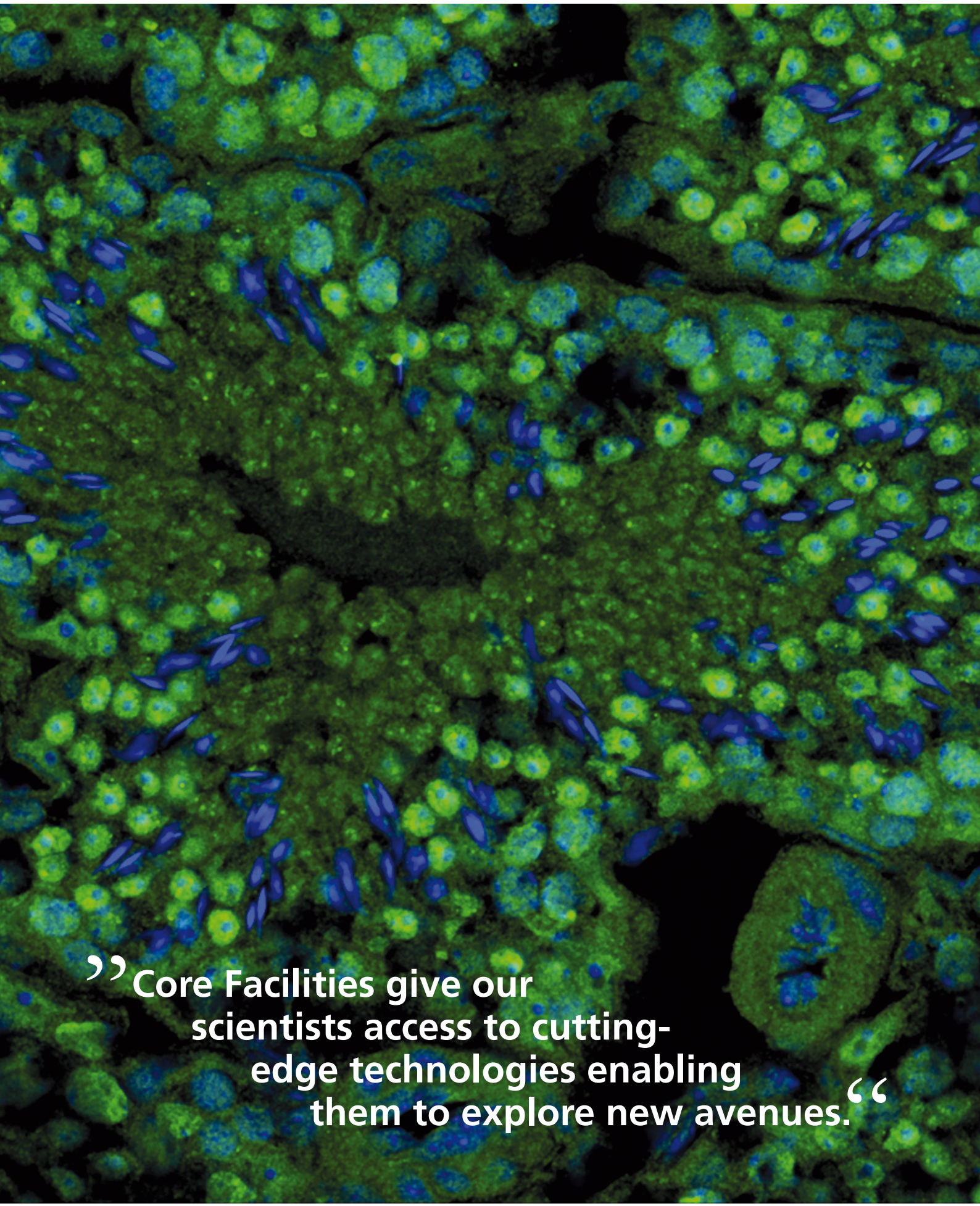
Figure 1. A MAP kinase, JNK, is recruited to gene promoters during stem cell differentiation for the transcriptional regulation of developmental genes via histone phosphorylation.

➜ Selected Publications

Tiwari VK, Stadler M, Wirbelauer C, Paro R, Beisel C and Schübeler D (2011). A Chromatin-modifying Function of JNK during Stem Cell Differentiation. *Nat Genet*, 44, 94-100

Tiwari VK and Baylin SB (2009). Breaching the boundaries that safeguard against repression. *Mol Cell*, 34, 395-397

Tiwari VK, McGarvey KM, Licchesi JD, Ohm JE, Herman JG, Schübeler D and Baylin SB (2008). PcG proteins, DNA methylation, and gene repression by chromatin looping. *PLoS Biol*, 6, 2911-2927


”Core Facilities give our
scientists access to cutting-
edge technologies enabling
them to explore new avenues.“

Bernhard Korn

Director of Core Facilities and Technology

Overview

The Core Facilities (CFs) at IMB are set up to allow IMB Research Groups smooth, fast and economical access to up-to-date technologies that are supported by in-depth expertise from dedicated service personnel. The remit of the Core Facilities is completely driven by demand for in-house research facilities, and they ensure a short turn-around time from initial project discussions to sample supply and the return of data. Service groups are only set up if the highest quality of service and a high demand for the facility can be foreseen. Therefore, we make sure that investments are made in the most efficient way. All Core Facility personnel are dedicated to both service and training. The Core Facilities provide equal access to all IMB members on a first-come-first-serve policy and access is provided as a service or through collaborative research projects.

The set-up of strong in-house Core Facilities allows all IMB groups to undertake ambitious projects with high-throughput designs. Project support is provided from the initial phase of grant applications (e.g. feasibility studies, consulting, application support), via experimental design and experimentation, to data management and analysis. Core Facility support is provided in various ways. Full service is given for next-generation-sequencing (NGS), microarray analysis and cell sorting. In these cases IMB members provide samples, which are quality controlled by the Core Facilities, and a complete service is then provided up to the point of data production. Basic data analysis is also conducted to ensure a good quality and accuracy of the information being returned to the in-house user. To be able to offer this type of cutting-edge service, we have entered into cooperations with other academic institutes such as EMBL, the German Cancer Research Center (DKFZ) and Johannes Gutenberg University, Mainz. Public-private partnerships have also been initiated such as the establishment of IMB as a reference centre for high-resolution microscopy with Leica microsystems. A very strong part of the Core Facilities covers informatics of various flavours, from basic front-end IT support, server administration and intranet provision, to bioinformatics, statistics and on-demand programming.

Whenever possible, IMB outsources services provided that sufficient quality and a fast turn-around time can be guaranteed by external providers. However, for strategic reasons we keep certain technologies and their development in-house, so that we can provide sufficient outreach, training and education to IMB students and personnel in these areas. We also provide assisted access to equipment and facilities within IMB. In this respect the Cytometry, Genomics, Histology and Microscopy Core Facilities provide specific training and assistance in the use of their equipment. Furthermore, Core Facility personnel provide training courses for the use of any other Core Equipment that is available at IMB, e.g. plate readers, ultra centrifuges etc. Finally, the Core Facilities provide a wide range of additional support, encompassing a media kitchen, animal care, management of in-house enzymes and clone/vector/cell line storage.

Core Facility Overview

Bioinformatics Team

Emil Karaulanov
Holger Klein
Joern Toedling

The Bioinformatics Core Facility provides different levels of advanced data analysis tools and support to IMB scientists; this support ranges from experimental design to data evaluation. The Facility is committed to finding and providing optimal solutions for bioinformatics issues that arise in the course of research projects. The rapidly changing landscape of biomedical research and the ever increasing flow of high-throughput data sets necessitate dedicated and flexible bioinformatic support for the many projects at IMB. The Facility enables researchers to analyse experimental data themselves by providing access to state-of-the-art software tools with workflows for standard analyses that can be utilised and adapted to specific problems. Additionally, the Facility offers long-term support and analytical expertise for individual research projects on a collaborative basis. The Facility operates a 48-CPU compute server, a file server and several IT systems with exclusive access; it also has shared access to the HPC cluster and other IT infrastructure of the Johannes Gutenberg University in Mainz.

Services Offered

The Bioinformatics Core Facility provides assistance on two levels:

1. General support to the IMB user base:
   - Assistance with experimental design of high-throughput assays such as ChIP-Seq, RNA-Seq or Bisulfite-Seq
   - In-house training and tutorials on bioinformatic tools and databases to facilitate data access and analysis
   - Implementation and adaptation of open-source tools and commercial software solutions for "omics" data interpretation
   - Setup and development of analysis pipelines for sequencing, microarray, cytometry and microscopy data
   - Quality assessment and pre-processing of raw data coming from the sequencing instruments
2. In-depth assistance for individual projects:
   - Comprehensive high-throughput data analyses, interpretation and presentation of results
   - Development of custom tools to address specific bioinformatic needs
   - Exploration and implementation of novel analysis methods and pipelines
   - Data mining of "omics" databases and published high-throughput data sets

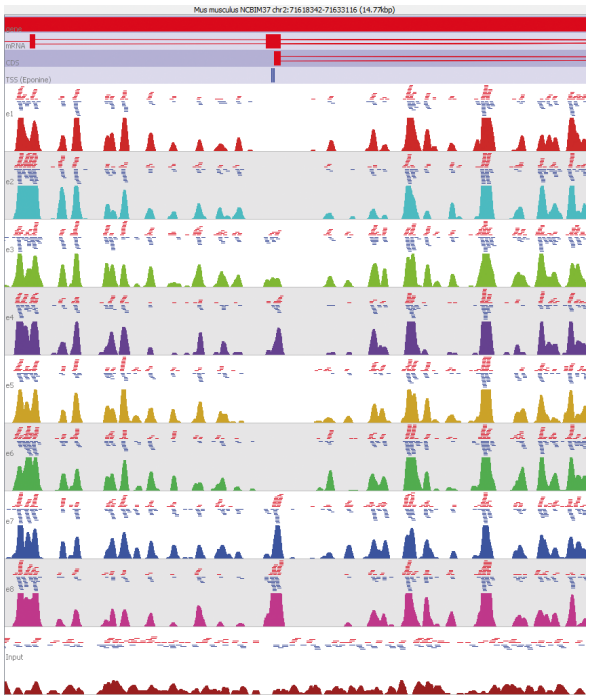


Figure 1. Data from genome-wide methylation profiling (MBD-seq) of mouse embryonic fibroblasts of different genotypes. Differentially methylated regions were identified through comparative and statistical analyses and then visualised using the SeqMonk genome browser.

The following bioinformatic resources were established at IMB in 2011:

- GALAXY: open-source environment for genomics data analysis, including next-generation-sequencing data (Fig. 1)
- GENOMATIX: commercial software for performing standard next-generation-sequencing data mapping and analysis tasks
- OMERO: open-source environment for visualisation, storage and annotation of microscopy images
- CHIPSTER: open-source data analysis platform for various types of microarrays

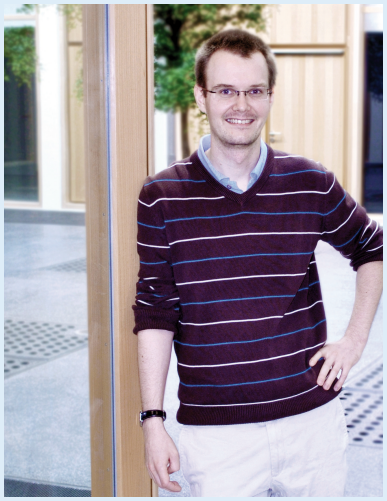
➜ Selected Publications

Hallen L, Klein H, Stoschek C, Wehrmeyer S, Nonhoff U, Ralser M, Wilde J, Roehr C, Schweiger MR, Zatloukal K, Vingron M, Lehrach H, Konthur Z and Krobitsch S (2011). The KRAB-containing zinc-finger transcriptional regulator ZBRK1 activates SCA2 gene transcription through direct interaction with its gene product, ataxin-2. *Hum Mol Genet*, 20, 104-114

Corpet A, De Koning L, Toedling J, Savignoni A, Berger F, Lemaître C, O'Sullivan RJ, Karlseder J, Barillot E, Asselain B, Sastre-Garau X and Almouzni G (2011). Asf1b, the necessary Asf1 isoform for proliferation, is predictive of outcome in breast cancer. *EMBO J*, 30, 480-493

Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M and Niehrs C (2010). Requirement of prorenin receptor and vacuolar H+-ATPase-mediated acidification for Wnt signaling. *Science*, 327, 459-463

Malte Paulsen



Education

2006	Diploma in Biology (Biochemistry) University of Konstanz
2011	PhD, German Cancer Research Center (DKFZ), Heidelberg

Positions held

Since 2011	Head of Cytometry, Core Facilities and Technology, IMB, Mainz

Core Facility Overview

The mission of the Cytometry Core Facility is to provide state of the art services for IMB personnel and collaborating institutions. The facility provides assisted access to the newest generation of high-end FACS analysers and cell sorters operated by dedicated staff. The Facility operates in its own laboratory facilities providing bench and cell culture space for all users in an equal opportunity environment.

Services Offered

The cytometer and sorter are both optically identical and harbour a five laser excitation suite and 18 parameter detector bench (Excitation Lasers 355/405/488/561/640 nm; Emission Detection (PMTs):2/5/3/5/3) providing the users with the broadest range of usable dye and application choices. Routine checking and servicing of the cytometers and laboratory equipment ensures that scientists perform experiments with reliable and up-to-date instruments.

Levels of staffing within the Facility allow for the proper training of users, help with experimental design and hands-on support during measurements. The Facility offers IMB scientists cell sorting possibilities with high flexibility in experimental planning and very short waiting periods. Along with user support, the Facility also provides a full-service for routine analyses and sorts to ease the workload of scientific personnel. Among the laboratory support, the head of the Facility offers dedicated help planning and analysing experiments based on flow cytometry and performs extensive reagent research to ensure cost-effective choices.

In cooperation with research groups from IMB and JGU, the Facility aims to develop new methods applicable for their respective studies. This technology developing service has already resulted in a manuscript being prepared (under review in 'Methods') for a novel flow cytometry method now used by the laboratory of Prof. Thomas Efferth from the Pharmaceutical Department of the Johannes Gutenberg University.

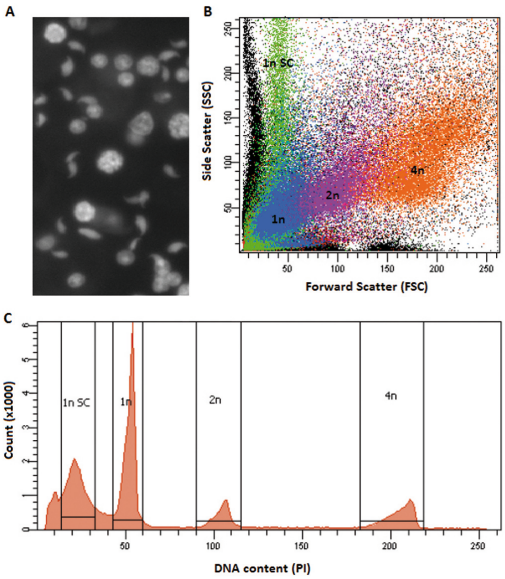


Figure 1. (A) Microscopy of a whole mouse testis preparation stained with DNA dye PI showing differently matured sperm. (B) and (C) FACS analysis of mouse spermatogenesis serves as a test sample for benchmarking optical precision and sorting efficiencies when analysing DNA content and light scatter; functional sperm (1n SC), spermatids (1n), regular cells (2n) and cycling cells (4n).

➜ Selected Publications

Paulsen M#, Legewie S#, Eils R, Karaulanov E and Niehrs C (2011). Negative Feedback in the bone morphogenetic protein 4 (BMP4) synexpression group governs its dynamic signalling range and canalizes development. *Proc Natl Acad Sci USA*, 25, 10202-10207 (# joint first authors)

Bernhard Korn

Education

1989	Diploma in Biology and Biochemistry, University of Kaiserslautern
1994	PhD in Genomics, German Cancer Research Center (DKFZ), Heidelberg

Positions held

1994	Postdoctoral Researcher, Imperial Cancer Research Fund, Genome Analysis Laboratory, London
1995	Postdoctoral Researcher, DKFZ, Heidelberg
1996 - 2000	Head of Contract Research, German Resource Center for Genome Research, DKFZ, Heidelberg
2000 - 2005	CSO Head of Heidelberg node of the German Resource Center for Genome Research, gGmbH, Berlin
2006 - 2010	Head of Division, Genomics and Proteomics Core Facilities, DKFZ, Heidelberg
Since 2010	Director of Scientific Core Facilities and Technology, IMB, Mainz

Core Facility Overview

The Genomics Core Facility provides a full service for next-generation-sequencing (NGS) and microarray technologies. We primarily provide NGS services using the 454/Roche and Illumina platforms. In terms of microarrays we offer Agilent and some Illumina services. Moreover, the Facility provides hands-on training and access to central quality control (QC) systems such as qPCR, Bioanalyser and Nanodrop.

Services Offered

The Facility has been established according to the needs of the current research groups at IMB. As not all groups have started yet, spare capacity is provided to the wider Mainz scientific community.

All genomics services start with a mandatory project discussion between the user, Facility staff and associated bioinformatic support. This ensures optimal experimental design and adaptation to any given project. All services have a defined start and end point for Facility support. This typically starts with nucleic acids of a given quality and quantity and finishes with the provision of raw data (that has passed all predefined QC measures) to the user or a member of the Bioinformatics Core Facility.

In terms of NGS, we perform all applications available on the 454/Roche platform, but with a clear focus on amplicon sequencing of human and mouse, including methylation analyses of promoters. In addition, we have set up a method pipeline for Illumina sequencing, namely, RNA-seq, ChIP-seq, MeDIP-seq, and genome sequencing. With this technology, all library preparation and QC steps are performed in-house, and the final sequencing is carried out in collaboration with EMBL, the German Cancer Research Center (DKFZ) or Johannes Gutenberg University. These institutes all have up-to-date Illumina HiSeq2000 systems and spare capacity. This ensures Illumina services can be provided to IMB Research Groups with very short turn-around times.

As many microarray applications have started to be migrated to NGS, the Facility decided to establish microarray technology at a basic level, using a platform that allows for the highest flexibility. To do so, the Agilent inkjet pipeline was chosen due to its ability for very cheap customisation and its support of the variety of model organisms that are used at IMB (e.g. human, mouse, frog, fish, fly, worm, yeast). In this initial phase, expression profiling of mRNA and miRNA has been established and applied for Facility users.

➜ Selected Publications

Bartholomae CC, Arens A, Balaggan KS, Yáñez-Muñoz RJ, Montini E, Howe SJ, Paruzynski A, Korn B, Appelt JU, Macneil A, Cesana D, Abel U, Glimm H, Naldini L, Ali RR, Thrasher AJ, von Kalle C and Schmidt M (2011). Lentiviral vector integration profiles differ in rodent postmitotic tissues. *Mol Ther*, 4, 703-710

Breitling LP, Yang R, Korn B, Burwinkel B and Brenner H (2011). Tobacco-smoking-related differential DNA methylation: 27K discovery and replication. *Am J Hum Genet*, 88, 450-457

Meder B, Haas J, Keller A, Heid C, Just S, Borries A, Boisguerin V, Scharfenberger-Schmeer M, Stähler P, Beier M, Weichenhan D, Strom TM, Pfeufer A, Korn B, Katus HA and Rottbauer W (2011). Targeted next-generation sequencing for the molecular genetic diagnostics of cardiomyopathies. *Circ Cardiovasc Genet*, 2, 110-122

Andreas Vonderheit

Education

2000	Diploma in Molecular Biology, ZMBH, University of Heidelberg
2004	PhD in Biochemistry, ETH, Zürich

Positions held

2005 - 2008	Postdoctoral Researcher, Institute of Nanotechnology, ETH, Zürich
2008 - 2011	Screening Scientist at the RNAi Image-based Screening Center (RISC) at the Light Microscopy Centre (LMC), ETH, Zürich
Since 2011	Head of Microscopy, Core Facilities and Technology, IMB, Mainz

Core Facility Overview

The Microscopy Core Facility provides hands-on training and access to various state-of-the-art microscopes, ranging from stereo and confocal microscopes to super-resolution microscopes. Furthermore, the facility provides image processing stations, bench space and cell culture facilities for transient sample preparation. With the available equipment a variety of microscopic techniques can be achieved. These include live microscopy, TIRF, FRET, FRAP, FLIM, FCS, 3D-reconstruction, screening, and super-resolution.

Services Offered

The Facility can be used by the whole scientific community in Mainz. After an introduction and training on the specific systems by Facility staff, users can book and use the microscopes and image processing stations. Currently the Facility provides hands-on training and access to various ultramodern confocal laser scanning microscopes, motorised fast fluorescence microscopes for live-microscopy, super-resolution microscopes, and PCs for image processing equipped with software for deconvolution and 3D-rendering. The following microscopic equipment, a large part of which was financed by DFG, is available:

- M80 Demonstration Stereo Microscope, equipped with a camera and a 24"monitor for teaching
- M205 FA Fluorescence Stereo Microscope, equipped with a camera and a fluorescence light source and three filters for UV, green, and red fluorophores
- DM 2500 Fluorescence Upright Microscope, equipped with a colour camera and a fluorescence light source and three filters for UV, green, and red fluorophores and with five air objectives (this microscope is perfectly suited for histology)
- AF7000 Widefield Fluorescence Microscope, this widefield microscope is equipped with an incubator box for live-microscopy and fast filter wheels and a fast camera
- TCS LSI Macro Zoom Confocal, this microscope combines a stereo microscope with a confocal. Organisms like *C. elegans* or *Drosophila* larvae can be scanned as a whole or zoomed down to single cell level in confocal mode
- TCS SPE Confocal Microscope, an upright confocal microscope with one detector
- TCS SP5 Confocal Microscope, a confocal with an inverse microscope stand, four PMTs, four laser lines, five objectives, and a resonance scanner
- TCS STED CW Super-Resolution Microscope, a super-resolution microscope, equipped with an incubator box and three normal PMTs and two HyD detectors, resonance scanner and FCS module
- SR GSD Super-Resolution Microscope, a super-resolution microscope based on the localisation method, TIRF mode possible

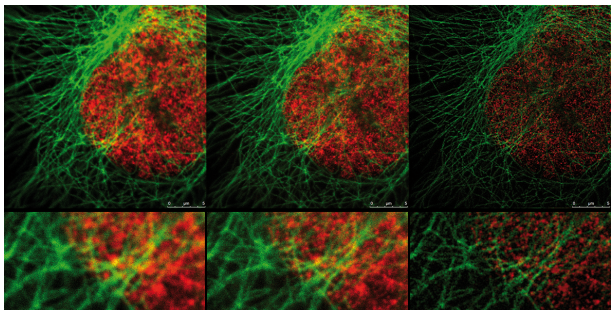


Figure 1. Image of microtubules (labelled with OregonGreen) and nuclear pores (labelled with BD Horizon V500). Left: conventional confocal image, middle: STED image, right: deconvolved STED image. The depletion beam (592 nm) was used at 100%, a pixel size of 25 nm was applied. For the deconvolution the Point Spread Function (PSF) of the STED image was calculated using the Lorenz-function and a full-width-half-maximum (FWHM) of 70 nm was used. Ten iterations and the Signal Energy mode with a value of 0.02 were used. The images have been recorded at IMB's Leica TCS STED CW by A. Vonderheit.

A Brief History of IMB

imb Institute of Molecular Biology

Feb 2009	Establishment of a new Research Centre of Excellence for Mainz announced by the Boehringer Ingelheim Foundation
Dec 2009	Construction of the new institute begins
May 2010	Christof Niehrs announced as IMB's Founding Director
Sep 2010	Official topping-out ceremony of the IMB building
Mar 2011	IMB officially inaugurated
Jul 2011	First five Group Leaders start work at IMB: Christoph Cremer, Stephan Legewie, Christof Niehrs, George Reid and Holger Richly
Dec 2011	IMB obtains €2.4 million for its new International PhD Programme on "Dynamics of Gene Regulation, Epigenetics and DNA Damage Response"
Jan 2012	Three new Group Leaders join IMB: Jean-Yves Roignant, Natalia Soshnikova and Vijay Tiwari
Jan 2012	IMB announces its International Summer School for undergraduate, Masters and PhD students

2011 in Numbers

Institute of Molecular Biology

€100 million

Core funding provided to IMB by the Boehringer Ingelheim Foundation

10

Number of grants awarded to IMB

64

Number of staff working at IMB 6 months after moving in

10 years

Duration of IMB's first period of funding from the Boehringer Ingelheim Foundation

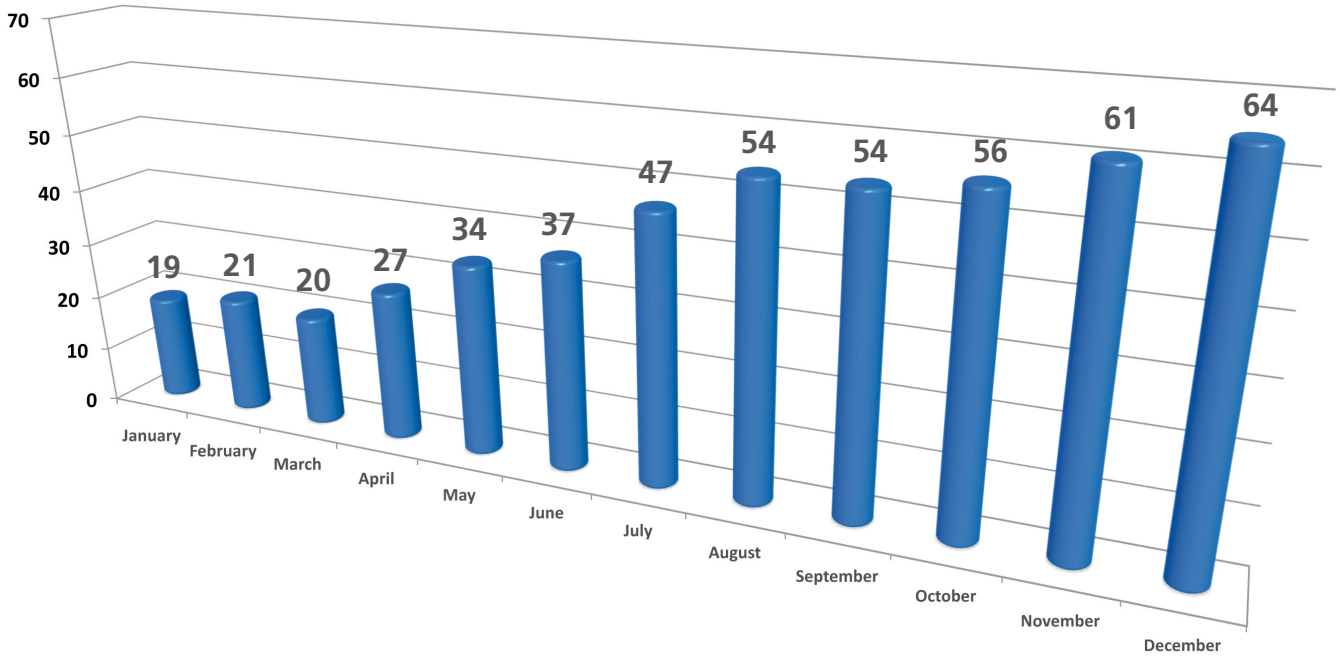
€6.2 million

Value of grants awarded by various funding bodies to IMB

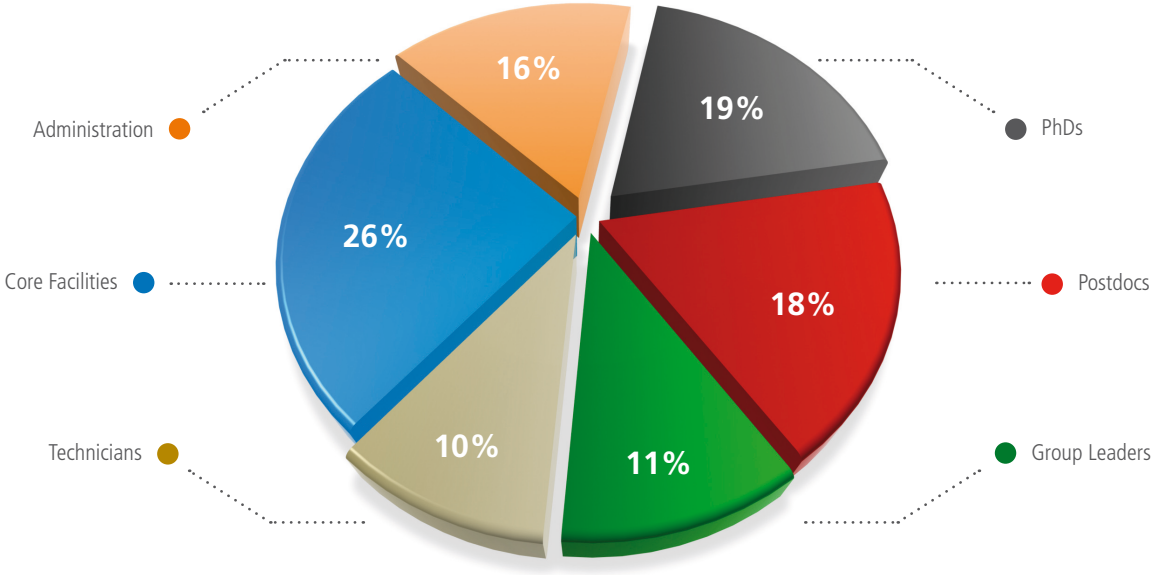
8

Number of Group Leaders at IMB, half of whom hail from abroad

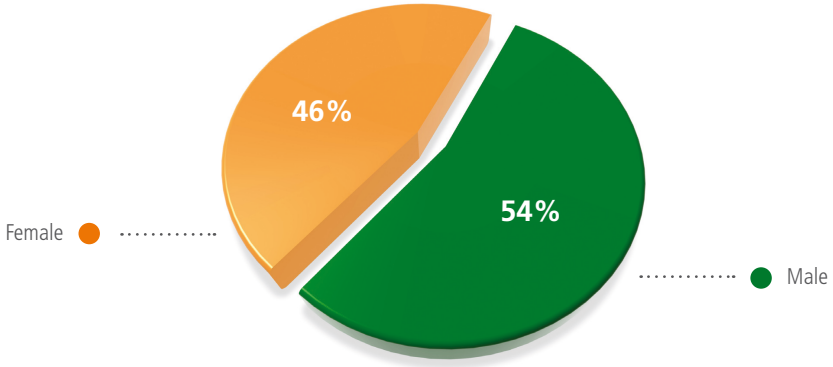
Personnel Development January 2011 to December 2011



Employees by Staff Category

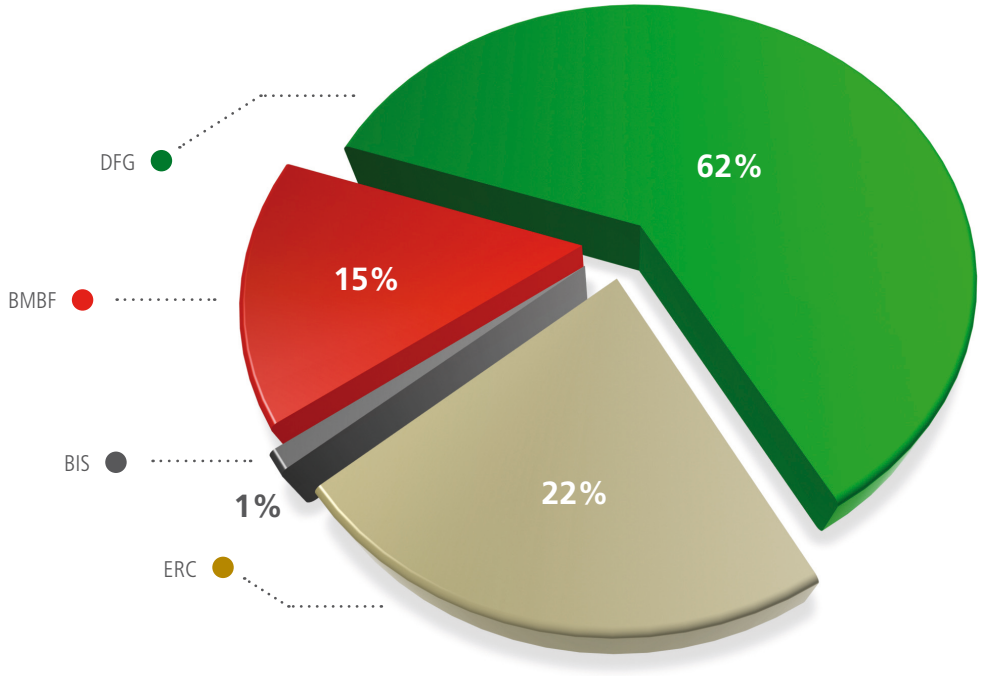


Gender Distribution



Research Grants

Funds granted for the year 2011
(excl. core funding)



Sources of Funding

At IMB our activities are supported by a number of different sponsors to which we are very grateful.
These sponsors include the following funding bodies and organisations:

Boehringer Ingelheim Stiftung
Boehringer Ingelheim Foundation

DFG
Deutsche Forschungsgemeinschaft

European Research Council
erc
European Research Council

Federal Ministry of Education and Research
Fedral Ministry of Education and Research

universitätmainz NMFZ
Naturwissenschaftlich-Medizinisches Forschungszentrum

ptj Projektträger Jülich Forschungszentrum Jülich
Projektträger Jülich

Articles published by IMB scientists in 2011

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6. Best G, Amberger R, Baddeley D, Ach T, Dithmar S, Heintzmann R and Cremer C (2011). Structured illumination microscopy of autofluorescent aggregations in human tissue. *Micron,* 42, 330-335
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LEGEWIE

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2. Kober AM#, Legewie S#, Pforr C, Fricker N, Eils R, Krammer PH, Lavrik IN (2011). Caspase-8 activity has an essential role in CD95/Fas-mediated MAPK activation. *Cell Death Dis,* 2, e212 (# joint first authors)
3. Legewie S, Koenig R and Schmidt-Glenewinkel H (2011). Cellular Systems Biology. *An Introduction to Molecular Biotechnology - Fundamentals, Methods and Applications* (Ed. Wink M), Wiley-VCH

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3. Kaufmann LT, Gierl MS and Niehrs C (2011). Gadd45a, Gadd45b and Gadd45g expression during mouse embryonic development. *Gene Expr Patterns,* 8, 465-470
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RICHLY

1. Richly H, Aloia L and Di Croce L (2011). Roles of the Polycomb group proteins in stem cells and cancer. *Cell Death Dis,* 2, e204
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SOSHNIKOVA

1. Montavon T, Soshnikova N, Mascrez B, Joye E, Thevenet L, Splinter E, de Laat W, Spitz F and Duboule D (2011). A Regulatory Archipelago Controls Hox Genes Transcription in Digits. *Cell,* 147, 1132-1145
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TIWARI

1. Tiwari VK, Stadler M, Wirbelauer C, Paro R, Beisel C and Schübeler D (2011). A Chromatin-modifying Function of JNK during Stem Cell Differentiation. *Nat Genet,* 44, 94-100
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CORE FACILITIES

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3. Meder B, Haas J, Keller A, Heid C, Just S, Borries A, Boisguerin V, Scharfenberger-Schmeer M, Staehler P, Beier M, Weichenhan D, Strom TM, Pfeufer A, Korn B, Katus HA and Rottbauer W (2011). Targeted Next-Generation Sequencing for the Molecular Genetic Diagnostics of Cardiomyopathies. *Circ Cardiovasc Genet,* 4, 110-122
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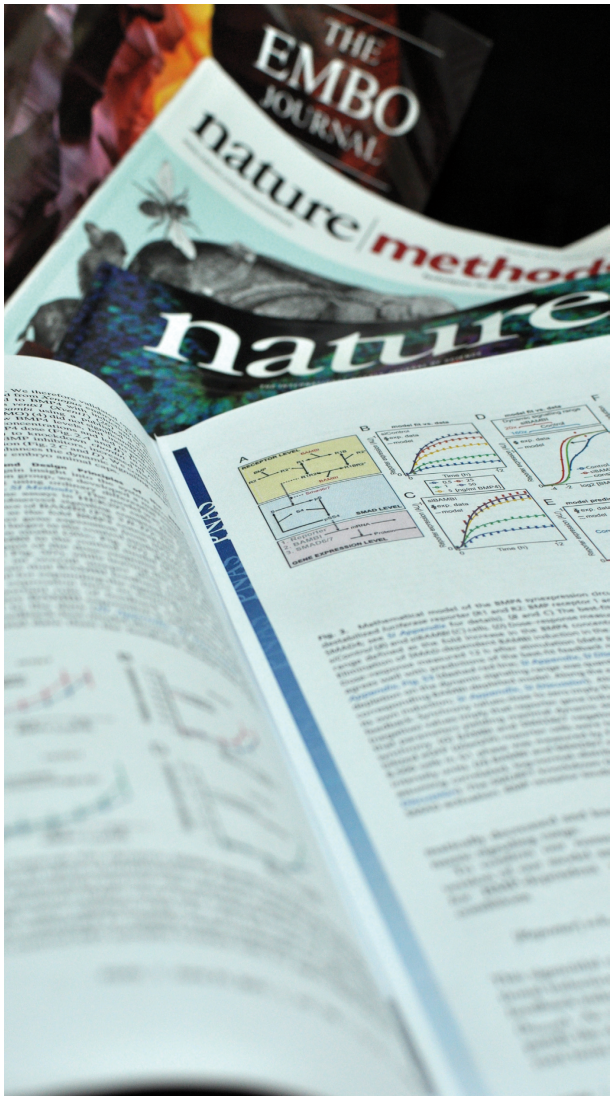
External speakers at IMB in 2011

- 5th August, **Helle Ulrich**, CRUK London Research Institute, UK, *"Ubiquitin, SUMO and Genome Maintenance"*
- 6th September, **Joanna Wysocka**, Stanford University, USA, *"Making a face: what epigenomics can teach us about human development"*
- 19th September, **Jonas Korlach**, Pacific Biosciences, *"Single-Molecule, Real-Time (SMRT™) Monitoring of Biomolecules: DNA Sequencing and Beyond"*
- 29th September, **Karolin Luger**, Colorado State University, USA, *"Structural Transitions in Chromatin"*
- 6th October, **Markus Löbrich**, Technical University Darmstadt, Germany, *"The complexity of repairing DNA double-strand breaks"*
- 13th October, **Simone Di Giovanni**, University of Tübingen, Germany, *"Epigenetics control of axonal outgrowth and regeneration"*
- 10th November, **Cristina Cardoso**, Technical University Darmstadt, Germany, *"Chromatin dynamics and remodelling in differentiation and disease"*
- 15th November, **Rainer Ebel**, Sigma-Aldrich, *"Targeted Genome Editing in Mammalian Cells Using Engineered Zinc Finger Nucleases"*
- 8th December, **Heinrich Leonhardt**, Ludwig Maximilians University, Germany, *"Reprogramming with designer TALEs: Green tools controlling red genomes"*



Research and Training at IMB

IMB is the place to be for scientists who want to carry out cutting-edge research in the fields of epigenetics, developmental biology, DNA repair and the interfaces between these fields. The research conducted by our multinational team of Group Leaders, postdocs and PhD students is vital to IMB's work in addressing key questions within these areas.

PhD students and postdocs at IMB are a key part of our research team and work on projects of fundamental biological importance or of relevance to human disease. Their research is conducted in a vibrant and highly interdisciplinary environment with leaders in the fields of epigenetics, DNA repair, developmental biology and systems biology.

At IMB we make sure our scientists can work productively. A key part of the support we offer comes from our state-of-the-art Core Facilities. They provide services in bioinformatics, cytometry, histology, microscopy and sequencing, and are staffed by experts who are there to advise and assist our scientists during each step of their experiments: from the initial conception to the analysis of data. As part of the dynamic and collaborative spirit at IMB, all key equipment is shared between research groups and looked after by trained staff in the Core Facilities. This means our scientists will always have access to the most up-to-date and well maintained equipment that is required for their experiments.

In addition to the training available through our Core Facilities, IMB has training programmes for both specialist scientific techniques and key transferable skills. The scientific training we provide includes courses on key topics such as statistics, the analysis of large data sets (including those generated by microarrays and next-generation-sequencing methods) and advanced live and super-resolution microscopy. We also make sure our junior scientists learn the soft skills required for a successful career in an increasingly competitive scientific world both within and outside of academia. Courses we offer cover topics such as presentation skills, scientific writing and project management, as well as conflict management and leadership skills.

International PhD Programme

Our International PhD Programme on the *"Dynamics of Gene Regulation, Epigenetics and DNA Damage Response"* gives talented and enthusiastic students the opportunity to undertake PhD research at the cutting edge of modern biology.

Our groups cover a broad range of expertise and include leading biochemists; geneticists; cell and developmental biologists who study the molecular mechanisms of embryonic development, ageing and disease; bioinformaticians and systems biologists who analyse high-throughput data sets and model regulatory gene networks; and applied physicists who develop ground breaking super-resolution microscopes. This range of expertise and the open and vibrant atmosphere within the Programme encourages multidisciplinary collaborations and innovative research.

The International PhD Programme therefore has a clearly defined and unique profile that provides students with interdisciplinary education in the following fields:

- Epigenetics
- Gene Regulation
- DNA Repair
- Functional Morphology of the Nucleus
- Systems Biology and Bioinformatics

The Programme is coordinated by IMB and participating groups are located at the:

- Institute of Molecular Biology
- Johannes Gutenberg University
- University Medical Center
- Max Planck Institute for Polymer Research

www.imb-mainz.de/PhD

International Summer School

The IMB International Summer School (ISS) is a six-week programme for outstanding and enthusiastic undergraduate, Masters and PhD students who want to acquire excellent practical skills and hands-on training from leading scientists in molecular biology. Research Groups participating in the ISS include Group Leaders at IMB, Johannes Gutenberg University and Mainz's University Medical Centre.

The International Summer School offers an attractive framework to improve the training of prospective scientists in an informal and international atmosphere. This includes theory modules (lectures and discussion groups) and practical research projects. Lectures by Group Leaders and external speakers give students comprehensive insight into the latest research findings and identify key open questions in Gene Regulation, Epigenetics and DNA Damage. Furthermore, the ISS teaches students the complementary skills, such as presentation and communication techniques, that are required for a successful career as a scientist.

Beyond these specific events, ISS participants are also fully integrated into scientific life at IMB by participating in Lab Meetings and Journal Clubs. Furthermore, students work on a cutting-edge research project within the lab of one of the participating research groups.

www.imb-mainz.de/ISS

IMB's Research Environment

IMB is embedded in a strong and dynamic research environment. It is located within the leafy campus of the Johannes Gutenberg University (JGU), just west of Mainz city centre. With 10 departments, 150 institutes and 36,000 students, the JGU is one of the largest German universities. In biomedical research, the University has built strong, interdisciplinary centres dedicated to cardiovascular medicine, neuroscience, immunology and oncology.

The University Medical Centre, which is located less than a mile from the main campus, with its strong focus on clinical and translational research, also works in close contact with IMB. In addition to the University, IMB has two Max Planck Institutes (Max Planck Institute for Chemistry, Max Planck Institute for Polymer 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 a total of 38,000 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 Strüngmann 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.

Furthermore, there is an extensive industry R&D presence, with the headquarters of Boehringer Ingelheim and the Merck Group both in close vicinity.

Where We Are

IMB is located in the city of 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 – the largest airport in mainland Europe – only 20 minutes away, countless European and overseas destinations are within easy reach.

SCIENTIFIC ADVISORY BOARD

IMB is extremely thankful

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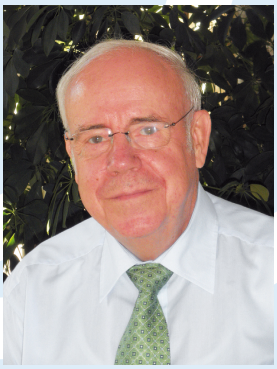

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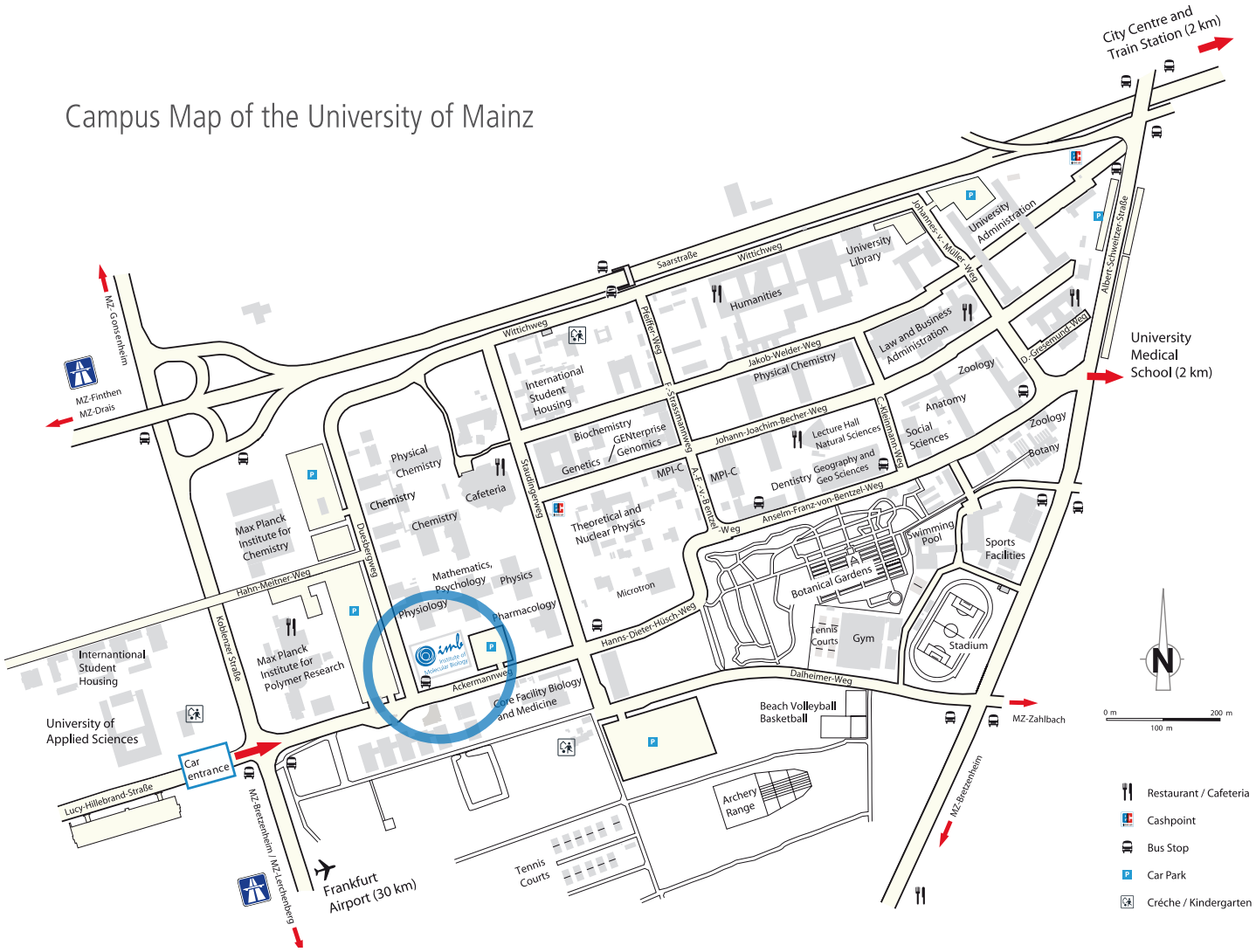
Campus Map of the University of Mainz



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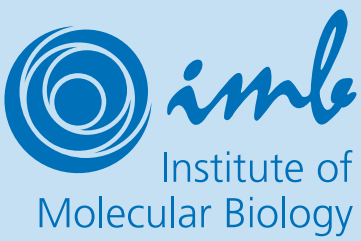

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