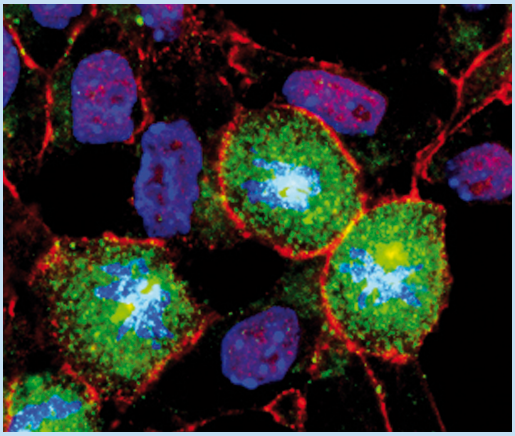
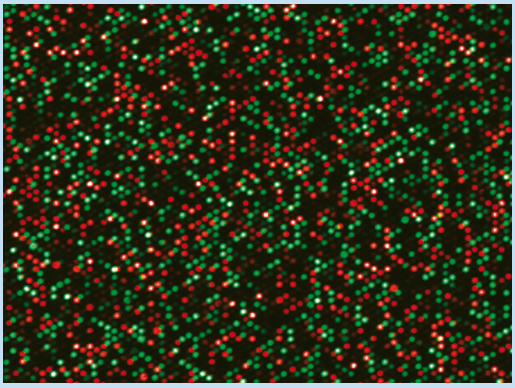
Institute of Molecular Biology

2012 IMB Symposium

Frontiers in Epigenetics and DNA Repair

Mainz, Germany, 16th March 2012





Abstract Book

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Welcome Address

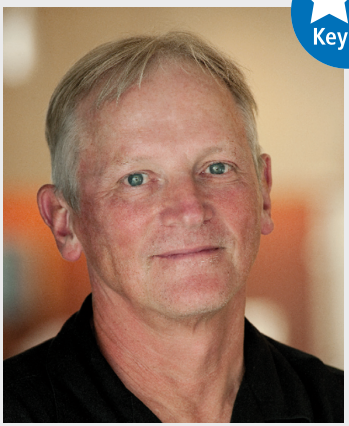
09:00	Christof Niehrs	IMB, Mainz, Germany

Lectures

09:20	Ernst-Ludwig Winnacker	Secretary General, Human Frontier Science Program, Strasbourg, France
10:00	Bradley Cairns	HHMI Huntsman Cancer Institute, Salt Lake City, USA
10:40	Vijay Tiwari	IMB, Mainz, Germany
11:00	*Coffee Break*	
11:20	Alexander Schier	Harvard University, Cambridge, USA
12:00	Josef Jiricny	Institute of Molecular Cancer Research, Zurich, Switzerland
12:40	Natalia Soshnikova	IMB, Mainz, Germany
13:00	*Lunch Break*	
14:30	Stefan Jentsch	Max Planck Institute, Martinsried, Germany
15:10	Renato Paro	D-BSSE, ETH Zurich, Basel, Switzerland
15:50	Ingrid Grummt	DKFZ, Heidelberg, Germany
16:30	*Coffee Break*	
16:50	John Gurdon	The Gurdon Institute, Cambridge, UK
17:30	Rudolf Jaenisch	Whitehead Institute, MIT, Cambridge, USA

Keynote Lecture

18:10	Frederick W. Alt	HHMI & Harvard University Children's Hospital Boston, USA
19:00	Closing Remarks	



Frederick W. Alt

Children's Hospital Boston, USA

Dr Alt received his Ph.D. from Stanford in 1977 with Robert Schimke, where he discovered gene amplification, providing the first evidence for genetic instability in mammalian cells. He did postdoctoral work at MIT with David Baltimore, where he worked out basic principles of immune system recombination and lymphocyte development. He has continued to be a leader in these two general research areas throughout his career. He was Professor of Biochemistry and Biophysics at Columbia University in New York City from 1982-1991, where he also became an Howard Hughes Medical Institute (HHMI) investigator in 1987. In 1991, he became an HHMI Investigator at Boston Children's Hospital and an Investigator at the Immune Disease Institute (IDI), a Harvard affiliated research Institute.

In addition to being an HHMI Investigator, Dr Alt currently is Professor of Genetics and Charles A. Janeway Professor of Pediatrics at Harvard Medical School. He is also Director of the Program in Cellular and Molecular Medicine of Children's Hospital and President of the Immune Disease Institute.

Dr Alt holds elected memberships of numerous organizations including the U.S. National Academy of Sciences and the European Molecular Biology Organization. He has received various cancer research awards including the Clowes Award from the American Association of Cancer Research, the Pasarow Foundation Prize, and the NCI Alfred K. Knudson Award for pioneering contributions to Cancer Genetics. He has also received various prizes for his immunology work including the AAI-Huang Meritorious Career Award and the Novartis Basic Immunology Prize for discoveries on B cell development and antigen responses.

Dr Alt has over 100 trainees, many of whom are leaders in immunology, genetics, or cancer biology and he has received the AAI Excellence in Mentoring Award. The Cancer Research Institute (New York) annually presents the Frederick W. Alt Award for New Discoveries in Immunology and Cancer Immunology.

Genome wide elucidation of mechanisms that promote chromosomal breaks & translocations in mammalian cells

To elucidate mechanisms that generate DNA double strand breaks (DSBs) and chromosomal translocations in mammalian cells, we developed high throughput genome-wide translocation sequencing (HTGTS). We applied HTGTS to activated primary murine B lymphocytes and identified tens of thousands of translocations involving I-SceI meganuclease-generated DNA DSBs within the *c-myc* or *IgH* loci of B lymphocytes and other sequences across the genome. We found that *IgH* or *c-Myc* DSBs translocate widely but that there were clear translocation hotspots. Thus, nearly all endogenous translocation hotspots involved DSBs initiated by Activation Induced-cytidine Deaminase (AID), which initiates DSBs required for IgH class-switching in activated B cells. Most AID independent translocation hotspots were exogenously introduced by I-SceI at numerous cryptic I-SceI target sites in the mouse genome. Comparison of translocation maps with genome-wide nuclear run-ons revealed a marked influence of transcription on translocation targeting, potentially generating DSBs and/or influencing relative spatial proximity between translocation targets.

In this talk, we will describe new studies that extend HTGTS to other cell types and to look in more depth at the role of specific mechanistic factors (e.g. DSBs, spatial proximity, repair pathways) in promoting or suppressing translocations genome wide. One major focus will be on how organization of sequences in the 3-dimensional genome influences their translocation potential genome wide. To address this question, we combined HTGTS and Hi-C analyses to study the influence of genome organization on translocations in G1-arrested pro-B cell lines. In these cells, antigen-receptor loci cleaved by RAG endonuclease are dominant partners for I-SceI DSB translocations regardless of genomic position, reflecting the driving force of high frequency DSBs at these loci and their co-localization in a fraction of cells. This dominance of DSB-driven hotspots obviated direct assessment of spatial proximity contributions to translocation formation. Therefore, we normalized genome wide DSB frequency via ionizing-radiation. Under these conditions, RAG-induced hotspots were minimized and translocations were highly enriched *in cis* along I-SceI breaksite containing chromosomes and within other chromosomes and sub-chromosomal domains in a manner directly related to pre-existing spatial proximity.

We will discuss implications of the relative contribution of DSB frequency and spatial proximity for driving translocations in particular cell types or conditions.

Bradley Cairns

HHMI Huntsman Cancer Institute,
Salt Lake City, USA

Brad Cairns is interested in how chromatin structure helps regulate gene transcription. His lab purifies and characterizes large protein complexes that remodel and modify chromosomal structure. An emerging interest is germline chromatin – how genes are marked (by DNA methylation) and packaged by chromatin in sperm and eggs – to promote proper gene expression in the embryo. The lab also investigates how chromatin regulates RNA Pol III, which synthesizes noncoding RNAs for translational capacity. He and his colleagues use genetic, biochemical, and genomic methods to understand the functions of these chromatin-regulatory complexes in living cells.

Brad was born and raised in Canada, but moved to the United States (Oregon) during 6th grade. He later graduated with a Chemistry Degree from Lewis and Clark College in Portland, Oregon. He attended graduate school at Stanford, receiving a PhD in Cell Biology in 1996, while working on both cell signaling and chromatin remodeling with Nobel Laureate Roger Kornberg. Brad conducted his postdoctoral training with Fred Winston in the Department of Genetics at Harvard Medical School, extending his studies on chromatin remodeling. In 1998, he joined the faculty of the Department of Oncological Sciences and the Huntsman Cancer Institute at the University of Utah School of Medicine. He is currently the Jon and Karen Huntsman Presidential Professor of Cancer Research, co-Chair of the Department of Oncological Sciences, and Senior Director of Basic Science at the Huntsman Cancer Institute. Brad is also and Investigator with the Howard Hughes Medical Institute.

Germline chromatin dynamics

In mature sperm, the genes that encode developmental transcription factors of importance in the embryo are packaged in chromatin with bivalent (H3K4me3 & H3K27me3) nucleosomes that lack DNA methylation - suggesting the pre-packaging and 'poising' of the embryo program in the sperm chromatin. To better understand human germline and developmental epigenetics, we defined multiple epigenome attributes of human sperm, including profiles of many heretofore undetermined histone modifications and variants, as well as cytosine DNA methylation at base-pair resolution. Our analyses are extensive, and reveal new and surprising features of enhancers, spermiogenesis genes, pluripotency factor targets, CpG islands, partially-methylated domains, imprinted loci, repetitive elements and sex chromosome asymmetry. Importantly, enhancers near the genes that will drive embryo development (homeobox and other transcription factors) bear H3K4me1 and H3K27me3 and low DNA methylation, consistent with their poising for future activation, whereas those enhancers near genes active in gametogenesis bear H3K4me1 and H3K27ac/H3K14ac, consistent with current activation. Remarkably, genes for spermiogenesis, but not spermatogenesis, bear H3K4me3 and DNA methylation, a co-incidence not previously observed in mammals. Taken together with other data/regions, the sperm epigenome resembles a mosaic of regions that reflect either a memory of gametogenesis or poising for subsequent embryonic developmental regulation.

Ingrid Grummt

German Cancer Research Center (DKFZ),
Heidelberg, Germany

Ingrid Grummt was born in Dresden in 1943. She studied Biology at the Humboldt-University in Berlin, where she was awarded her Ph.D in 1971. She continued her career as a research assistant from 1972 to 1980 at the German Academy of Sciences in Berlin-Buch and at the Max-Planck-Institute of Biochemistry in Munich from 1972 to 1980. She then was a group leader at the Julius Maximilian University in Würzburg where she worked on the molecular mechanisms that regulate transcription and link ribosome synthesis to cell growth. In 1984 she was appointed Professor at the Institute of Virology and Immunology in Würzburg. Since 1989 she is head of a Research Division at the German Cancer Research Center in Heidelberg. Her lab has deciphered the molecular pathways by which extracellular signals are transferred into the nucleus to modulate transcription of rRNA genes in response to environmental changes and during cell cycle progression. Currently, her work focuses on the molecular mechanisms that control gene expression at the epigenetic level.

Ingrid Grummt serves on a number of scientific advisory boards and has been a member of the European Molecular Biology Organization (EMBO) since 1985, the Academia Europea since 1998 and the German Academy of Sciences Leopoldina since 2008. She was elected to the EMBO Council in 2002 and is an established panel member of European Research Programmes. She is the recipient of numerous awards, including the Science Prize of the Fritz-Winter-Foundation, the renowned Gottfried Wilhelm Leibniz-Prize for German scientists and, most recently, the 2010 EMBO/FEBS Women in Science Award.

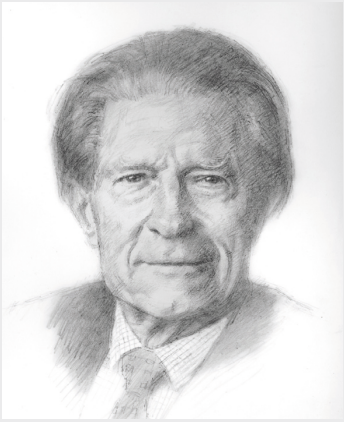
An impressive list of more than 180 peer-reviewed scientific papers and service on editorial boards further enhances her expertise.

Non-coding RNA controls epigenetic processes

Epigenetic mechanisms silence a fraction of rRNA genes (rDNA) by establishing heterochromatic features at the rDNA promoter. Silencing of rDNA is mediated by NoRC, a chromatin remodeling complex that interacts with DNA methyltransferase(s), histone deacetylase(s) and histone methyltransferase(s), thereby targeting enzymes to the rDNA promoter that are required for heterochromatin formation and transcriptional repression. Importantly, NoRC function requires the association with 'pRNA' ('promoter-associated RNA'), a 150-250 nt RNA moiety that is complementary in sequence to the rDNA promoter.

Antisense-mediated depletion of pRNA leads to displacement of NoRC from nucleoli, decrease in rDNA methylation and activation of Pol I transcription. In contrast, overexpression of pRNA mediates heterochromatin formation, *de novo* DNA methylation and transcriptional repression. A 20 nt sequence in the 5'-terminal part of pRNA interacts with the target site of the transcription factor TTF-I, forming a triple-stranded structure that is specifically recognized by the DNA methyltransferase DNMT3b. The results reveal a compelling RNA-based strategy for epigenetic programming, implying that ncRNAs can guide DNA methyltransferase to specific genomic sites to methylate DNA and silence transcription.

Data will be presented showing that DNA:RNA triplex-mediated targeting of DNMTs is not restricted to rDNA but has the potential to act on other genes that are silenced by DNA methylation.



John Gurdon

Gurdon Institute of Cancer
and Developmental Biology,
University of Cambridge, UK

Educated at Eton College, where he did Classics, having been advised that he was unsuited for science, and Christ Church, Oxford (Zoology). PhD with Michael Fischberg, on nuclear transplantation in *Xenopus*. Obtained the first clone of genetically identical adult animals. Demonstrated genetic totipotency of somatic cell nuclei by obtaining sexually mature frogs from the nuclei of intestinal epithelium. Did postdoctoral work at Cal-Tech, on bacteriophage genetics. Moved to MRC Molecular Biology Laboratory in Cambridge (Chairman Max Perutz), subsequently becoming Head of Cell Biology Division. In 1983, accepted John Humphrey Plummer Professorship of Cell Biology in University of Cambridge, in Zoology Department. Initiated, with Prof R Laskey, Cancer Research Campaign unit of Molecular Embryology in Zoology Department Cambridge. In 1990 moved to new Wellcome CRC Institute of Cancer and Developmental Biology in Cambridge, and served as Chairman 1990-2001. From 2001, the Institute was renamed The Gurdon Institute. Master of Magdalene College, Cambridge 1995 to 2002, and Governor (= Trustee) of the Wellcome Trust 1995 to 2000. Chairman of the Company of Biologists from 2001 to 2011.

Main directions of research have been:

(i) nuclear transplantation and mechanisms of reprogramming of somatic cell nuclei;

(ii) the use of *Xenopus* eggs and oocytes for mRNA microinjection, and hence gene overexpression;

Dr Gurdon has received various recognitions (see Who's Who) including, most recently, the Albert Lasker Award for Basic Medical Science.

Interests: skiing, tennis, horticulture, Lepidoptera.

Nuclear reprogramming by oocytes and eggs

Oocytes and eggs of mammals and amphibia have a remarkable capacity to reprogram the nucleus of adult differentiated cells towards embryonic gene expression. Somatic cell nuclei injected into the germinal vesicle of an oocyte are reprogrammed with high efficiency so that a high proportion of injected nuclei undergo reprogramming and extensive re-initiation of transcription takes place for some pluripotency genes. This situation makes it possible to analyse the mechanisms by which reprogramming takes place.

Current work aims to identify the reprogramming components of eggs and oocytes and the time course with which the various steps in this process take place. A major part of the reprogramming activity of oocytes and eggs includes a massive decondensation of chromatin accompanied by exchange and modification of histones. This seems to result in a global activation of transcription of many genes not normally associated with the germ cells or with early embryos. We have determined the absolute number of transcripts synthesized per gene per day in this reprogramming system and this helps us to identify the sequence of events during the reprogramming process.

An equally interesting aspect of nuclear reprograming concerns the resistance of somatic cell chromatin to the gene activating conditions of oocytes. This resistance reflects the normal stability of the differentiated state of specialized cells. Mechanisms of resistance to reprogramming will be discussed.

Rudolf Jaenisch

Whitehead Institute, MIT,
Cambridge, USA

Dr Rudolf Jaenisch is Professor of Biology at the Whitehead Institute and the Department of Biology, Massachusetts Institute of Technology. He has generated the first transgenic mice carrying exogenous DNA in the germ line and was the first to use insertional mutagenesis for identifying genes crucial for embryonic development.

Perhaps his most fundamental contributions have been in the study of epigenetic processes during development. In particularly he showed that methylation of DNA plays important roles in gene expression, imprinting and X-inactivation as well as in diseases such as cancer and mental retardation.

His work has focused on mammalian cloning and has defined some of the molecular mechanisms that are crucial for the nuclear reprogramming. Most recently he is using direct reprogramming of somatic cells to generate "induced Pluripotent Stem" (iPS) cells in the culture dish. These cells are relevant to establish *in vitro* system to study major human diseases and eventually to derive cells that could be used for "customized" therapy.

iPS cell technology and disease research: Issues to be resolved

The recent demonstration of *in vitro* reprogramming using transduction of 4 transcription factors by Yamanaka and colleagues represents a major advance in the field. Direct reprogramming of somatic cells into induced pluripotent stem (iPS) cells can be achieved by over-expression of the Oct4, Sox2, Klf4 and c-Myc transcription factors. This approach will allow the generation of patient specific iPS cells that can be used to study complex human diseases in the Petri dish. Progress in using iPS cells for therapy and for the study of complex human diseases will be summarized. The presence of reprogramming vectors in the iPS cells and the inefficiency of gene targeting represent two important impediments for realizing the potential of ES and iPS cells to study human diseases. We have designed strategies that efficiently allow the generation of vector-free iPS cells. In addition, we have used Zn finger and TALEN mediated genome editing to establish efficient protocols to target expressed as well as silent genes in human ES and iPS cells.

One of the key questions for using the iPS technology for disease research is how to define what a good ES or iPS cell is. I will summarize our efforts to characterize different states of pluripotency in the mouse system and how to stabilize corresponding states in human ES and iPS cells.

Stefan Jentsch

Max Planck Institute of Biochemistry, Martinsried/Munich, Germany

Stefan Jentsch is director at the Max Planck Institute of Biochemistry, Martinsried, Germany. He obtained his Ph.D. in biology at Free University Berlin and Max Planck Institute for Molecular Genetics and was postdoctoral fellow at MIT, Cambridge, USA. After periods at the Friedrich-Miescher Laboratory (Max Planck Society, Tübingen) and the University of Heidelberg (ZMBH), he is since 1998 director of the Department of Molecular Cell Biology.

Stefan Jentsch pioneered studies on protein modifications by ubiquitin and related proteins. Modification of proteins by ubiquitin usually targets the proteins for degradation. However, Stefan Jentsch's research revealed that ubiquitin plays non-proteolytic roles as well. In particular, he discovered the importance of the ubiquitin system for genome maintenance and DNA repair. He and his group identified the "PCNA switch", a ubiquitin/SUMO-controlled mechanism that governs genome stability and mutagenesis. The current focus in the lab is on regulatory functions of ubiquitin family proteins, in particular for DNA transactions and splicing, and general mechanisms of DNA repair.

Stefan Jentsch is EMBO member since 1995 and elected member of the German National Academy of Sciences Leopoldina. His honors include the Otto Klung Prize (1992), Leibniz Preis (1993), Otto Bayer Award (1996), Max-Planck Research Award (2003), honorary professorship of Fudan University Shanghai, and Louis-Jeantet Prize for Medicine (2011).

Regulatory roles of ubiquitin family proteins

Covalent modification of proteins by ubiquitin and related proteins (ubiquitin-like modifiers, UBLs) often critically alters substrate activity by influencing metabolic stability, binding behavior or localization. Ubiquitin is best known for its role in selective protein degradation by the proteasome. However, equally important are ubiquitin's non-proteolytic functions e.g. in protein sorting, signaling and DNA repair.

In my talk I will discuss two examples of regulation by ubiquitin family proteins. The first example is the regulation of DNA repair by ubiquitin and SUMO. I will discuss how these proteins - through modification of PCNA - function as decision makers. The second example is the regulation of splicing by Hub1, an unusual member of the ubiquitin family. Hub1 does not form covalent conjugates with other proteins, but modifies proteins only through non-covalent interactions. I will report that Hub1 controls 5'-splice site usage and alternative splicing in yeast by binding to the spliceosome. Our study suggests a novel mechanism for splice site utilization that is guided by non-covalent modification of the spliceosome by an unconventional ubiquitin-like modifier.

Josef Jiricny

Institute of Molecular Cancer Research, University of Zurich, Switzerland

Josef Jiricny was born in Prague in 1951. In 1969 he emigrated to England, where he studied chemistry, first in Birmingham, then in London. He obtained his PhD in 1977. His postdoctoral studies at King's College, London, were devoted to studying the chemical synthesis of DNA. In 1980 he moved to the Imperial Cancer Research Fund laboratories in London, where he began to study DNA repair mechanisms. In 1983 he joined the Friedrich Miescher Institute (FMI) in Basel, where he became Senior Group Leader in 1989. In 1990 he helped found Istituto di Ricerche di Biologia Molecolare (IRBM) as Senior Director of Biochemistry. In 1996 he joined the medical faculty of the University of Zurich as Professor (ordinarius) and Director of the Institute of Molecular Cancer Research (IMCR). IMCR currently houses ~60 scientists investigating links between DNA repair malfunction and cancer.

Josef Jiricny co-founded the Functional Genomics Center Zurich (FGCZ, www.fgcz.uzh.ch), a state-of-the art "-omics" technology platform. He is also Chairman of the University Research Priority Program in Functional Genomics/Systems Biology (www.sysbio.uzh.ch), of the Cancer Network Zürich (www.cnz.uzh.ch), and of the Cancer Biology PhD program of the Life Science Zurich Graduate School (www.lifescience.uzh.ch).

Josef Jiricny is a member of EMBO since 1996 and of Academia Europea since 2000. In 2001, Josef Jiricny was elected member of the Faculty of Natural Sciences (MNF) of the University. In 2003 he was awarded the Gregor Mendel Medal of the Czech Academy of Sciences. In the same year, he was elected to the Bonizzi-Theler Chair of Functional Genomics at the ETH Zurich. He won the Swiss Bridge Award (2003), the San Salvatore Prize (2006) and the International Award of the Slovak Academy of Sciences (2006).

Josef Jiricny is the author of more than 150 peer-reviewed publications, and of a number of editorials and reviews.

Mismatch repair: Error-free or error-prone

In this presentation, I shall discuss recent advances in our understanding of the molecular mechanisms of canonical mismatch repair (MMR), which improves replication fidelity by removing misincorporated nucleotides from the nascent DNA strand. I shall also discuss the role of MMR in other pathways of DNA metabolism, in particular somatic hypermutation (SHM). In this process, MMR and base excision repair contradict their roles as guardians of genomic integrity. Instead, they contribute towards antibody diversity through locus-specific mutagenesis, which has been postulated to require mismatch repair (MMR) proteins, monoubiquitylated PCNA and the error-prone DNA polymerase-η (pol-η).

In this presentation, I shall describe non-canonical MMR (ncMMR), a hitherto uncharacterized process of DNA metabolism that is activated by a variety of lesions. ncMMR is largely independent of DNA replication, lacks strand directionality, triggers PCNA monoubiquitylation and promotes recruitment of pol-η to chromatin. Importantly, our findings show that ncMMR is limited neither to SHM, nor to B cells. In addition, we demonstrate a role for ncMMR in mutagenesis induced by alkylating damage. Thus, whereas MMR increases the fidelity of DNA replication by several orders of magnitude, activation of ncMMR by DNA damage may give rise to mutations and thus contribute to genetic diseases and cancer.

Renato Paro

D-BSSE, ETH Zurich,
Basel, Switzerland

Renato Paro studied and received his Ph.D. at the Biozentrum of the University of Basel. After post-docs at the University of Edinburgh and Stanford University, he continued his career at the Center for Molecular Biology of the University of Heidelberg (ZMBH) in Germany. He was Professor at the Faculty of Medicine and Faculty of Biosciences of the University of Heidelberg and between 2001 und 2004 acting director of the ZMBH. In 2006 he became founding director of the new Department of Biosystems Science and Engineering (D-BSSE) of the ETH Zurich in Basel and Professor of Biosystems at the University of Basel.

The major research areas of his laboratory focus on mechanisms of epigenetic gene control and cellular signaling. Key contributions concern the role of the Polycomb and Trithorax proteins in epigenetic regulation, including their part in development and disease. Chromatin controls the activity of genes in a eukaryotic cell and maintains gene expression patterns epigenetically stable and heritable during cell division. In the past the laboratory was the first to identify and describe at the molecular level the transgenerational inheritance of epigenetic traits in a complex organism.

His group generates systems-level comprehensive descriptions of chromatin structures to provide tissue specific epigenetic typing of cells. The aim is to be able to alter specifically the fate of cells towards the needs required for tissue engineering and regenerative medicine. Additionally, the laboratory has continuously developed new technologies, the best known being chromatin immunoprecipitation (ChIP) now used worldwide to detect and map the in vivo distribution of chromatin and DNA-associated proteins.

Chaperoning epigenetic regulation

Environmental epigenetics attempts to understand how environmental cues interact with cellular epigenetic networks affecting gene expression, and possibly leading to an inheritance of altered gene activity. Our study focuses on one such interaction between heat shock protein 90 (Hsp90) and the cellular memory system controlled by the Polycomb and Trithorax chromatin proteins (PcG/TrxG). While the former mediates stress response, the latter are involved in maintenance of gene expression crucial for development and homeostasis.

By mapping chromatin-binding sites of Hsp90 at high resolution across the *Drosophila* genome, we uncover an unexpected mechanism by which this chaperone orchestrates cellular physiology. It localizes near promoters of many coding and non-coding genes including miRNAs.

Using computational and biochemical analyses we find that Hsp90 regulates many PcG/TrxG target genes by affecting RNA polymerase II pausing, via stabilizing the Negative Elongation Factor complex. Hsp90 is required for optimal activation of paused genes in *Drosophila* and mammalian cells in response to environmental stimuli. This raises questions pertaining to possible effects of environmental stress on gene regulation, linking cellular exterior to epigenetic gene regulation via Hsp90 and PcG/TrxG.

Alexander Schier

Harvard University,
Cambridge, USA

Alexander Schier obtained his PhD from the Biocenter in Basel, Switzerland, where he studied the transcriptional regulation of homeobox genes in Walter Gehring's lab. He spent his postdoc in Wolfgang Driever's lab in Boston, where he performed a large-scale screen for mutations affecting zebrafish development. He started his lab in 1996 at the Skirball Institute of the New York University School of Medicine and joined Harvard University in 2005. Dr Schier's lab has contributed to the understanding of the molecular basis of vertebrate embryogenesis, focusing on Nodal morphogens and microRNAs, and to the development of zebrafish as a model system. More recently, he has begun to study complex behaviors, with the long-term goal to identify molecules and neural circuits that modulate sleep and nociception.

Nodal morphogen interpretation

Morphogens are long-range signaling molecules that pattern developing tissues in a concentration-dependent manner. The graded activity of morphogens within tissues exposes cells to different signal levels and leads to region-specific transcriptional responses and cell fates.

To determine how morphogen gradients are established and interpreted, we study morphogens belonging to the Nodal family. Nodal signals induce and maintain cell fates in embryos and embryonic stem cells. It is poorly understood how dynamic Nodal signaling is interpreted by responding cells to generate different cell types.

I will discuss our recent studies that determine how signal concentration, signaling duration, and cellular history underlie the interpretation of Nodal signals.

Natalia Soshnikova

IMB, Mainz, Germany

Natalia Soshnikova was born in Turkmenabad, Turkmenistan in 1976. She studied Biology at the Novosibirsk State University, Novosibirsk, Russia. She joined the group of Prof. Walter Birchmeier at the Max-Delbrueck Centre for Molecular Medicine (Berlin, Germany) where she obtained her Ph.D in 2004. After receiving an EMBO long term fellowship she continued her career as a postdoc from 2004 to 2011 in the group of Prof. Denis Duboule at the University of Geneva (Geneva, Switzerland). Since January 2012 she is now a Group Leader at the Institute of Molecular Biology (IMB) in Mainz. Her work focuses on the regulatory mechanisms of transcriptional control, in both developmental and pathological contexts.

Epigenetic control of *Hox* genes expression during embryogenesis

Hox family homeodomain-containing transcription factors play an essential role in the patterning of many structures along the anterior-posterior axis. In bilaterians, *Hox* genes are organized in clusters. During development, *Hox* genes are activated both in time and space according to their physical order within the cluster. Dynamic changes in chromatin marks are important parameters in the temporal regulation of the *Hox* gene family. Furthermore, fixed and stable chromatin domains divide active and repressed genes into distinct 3D territories during their spatial regulation.

Vijay Tiwari

IMB, Mainz, Germany

Dr Tiwari obtained an MSc in Molecular & Human Genetics at Banaras University, a Centre of Excellence in the Life Sciences in India. He then moved to the epigenetics lab of Prof. Rolf Ohlsson at Uppsala University in Sweden for his doctoral studies where he completed a thesis with distinction. His research continued very successfully as a postdoc with Prof. Stephen Baylin, a pioneer in cancer epigenetics, at Johns Hopkins University School of Medicine in Baltimore and then with Prof. Dirk Schübeler, who is a European leader in epigenomics, at the Friedrich Miescher Institute (FMI) in Basel.

Dr Tiwari's PhD studies revealed how an antisense RNA can control the functional properties of a regulatory region in the genome and he elucidated how regulatory factors organize higher order structures in chromatin to regulate gene expression. As a postdoc, his work provided evidence that epigenetic mechanisms regulate chromatin compaction and accessibility for gene regulation. Furthermore, his research found that epigenetic machineries mediate physical proximity between distant chromosomal elements that further serves to simultaneously regulate co-expressed genes.

His recent work provided the first evidence that a MAP kinase directly binds to development-specific gene promoters during cellular differentiation for transcriptional regulation via epigenetic mechanisms. Dr Tiwari has received numerous awards and fellowships including a Junior Research Fellowship from the Government of India Council of Scientific and Industrial Research, funding from Zoologiska foundation, Sweden, a Johns Hopkins postdoctoral fellowship, an European Molecular Biology Organization (EMBO) fellowship and a Marie Curie International Incoming Fellowship (IIF).

A chromatin function for MAP kinases during stem cell differentiation

Signalling mediates cellular responses to extracellular stimuli. The c-Jun NH2-terminal kinase (JNK) pathway exemplifies one sub-group of mitogen-activated protein (MAP) kinases, which besides established functions in stress response, also contribute to development by an unknown mechanism. We show by genome-wide location analysis that JNK binds to a large set of active promoters during differentiation of stem cells to neurons. JNK-bound promoters are not enriched for binding motifs for AP-1 but for the transcription factor NF-Y. Furthermore, NF-Y occupies these predicted sites and overexpression of dominant-negative NF-YA reduces JNK presence on chromatin. We find Histone H3 Serine 10 to be a substrate for JNK and JNK-bound promoters are enriched for this particular phosphorylation. Inhibition of JNK signalling in postmitotic neurons reduces this modification as well as expression of target genes. These results establish MAP kinase binding and function on chromatin as a novel class of target genes during stem cell differentiation.

Ernst-Ludwig Winnacker

Human Frontier Science Program (HFSP), Strasbourg, France

Professor Ernst-Ludwig Winnacker was appointed Secretary General of the Human Frontier Science Program Organization (HFSPO) in July 2009. He studied chemistry at the Swiss Federal Institute of Technology (ETH Zurich) where he obtained his Ph.D. in 1968. After postdoctoral work at the University of California in Berkeley and the Karolinska Institute in Stockholm from 1968 to 1972, he became assistant and then DFG Visiting Professor at the Institute for Genetics at the University of Cologne. In 1977 he was appointed Associate Professor at the Institute of Biochemistry at the Ludwig Maximilians University of Munich where he was made full professor in 1980. From 1984 to 1997, he was Director of the Laboratory of Molecular Biology, the University of Munich Gene Center.

He served as President of the German Research Foundation (DFG) from 1998 to 2006. From 2003 to 2004 he also chaired the European Heads of Research Councils (EUROHORCs) and from 2000 to 2004 was member of the European Life Science Group established by Commissioner for Research, Philippe Busquin. He served as first Secretary General of the European Research Council (ERC) from 2007 to 2009. He is a member of the National Academy of Germany (Leopoldina) and the Institute of Medicine (IOM) of the US National Academies of Sciences.

He received honorary doctoral degrees from the Veterinary University of Vienna and the University of Wuerzburg, as well as numerous awards, including the Order of the Rising Sun, Gold and Silver Star from Japan and the International Science and Technology Cooperation Award from the People's Republic of China. Professor Winnacker's main fields of research are virus/cell interaction, the mechanisms of gene expression in higher cells and prion diseases.

Opening the doors for Frontier Research

My lecture will address some thoughts on the paradox that science/research is international, yet the public institutions which support it are either national or even only regional. The resulting fragmentation which is particularly obvious in Europe can breed a false impression of excellence, may lead to undue duplication and a subcritical availability of scientific instrumentation and other infrastructure. Apart from efforts dedicated to very specific and applied issues, like the IPCC or the International Polar Year, only two agencies in the world have addressed this issue, the Human Frontier Science Program and the new European-level funding agency for basic research, the ERC. My presentation will discuss strengths and weaknesses of such structures, based on experience in running both of them.

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IMB 2012 Conference
DNA Demethylation, Repair and Beyond

Mainz, Germany 18th - 21st October 2012

Speakers

Geneviève Almouzni
CNRS Institut Curie, Paris, France

Thomas Carell
CIPSM, Ludwig Maximilians University, Munich, Germany

Jean-Marc Egly
Institute of Genetics and Molecular and Cellular Biology (IGBMC), Illkirch-Graffenstaden, France

Bernd Epe
Johannes Gutenberg University, Mainz, Germany

Óscar Fernández-Capetillo
CNIO, Madrid, Spain

Robert Fischer
University of California, Berkeley, USA

Nicole Francis
Harvard University, Cambridge, USA

Jan Hoeijmakers
Erasmus Medical Center, Rotterdam, The Netherlands

Penny Jeggo
University of Sussex, Brighton, UK

Bernd Kaina
Johannes Gutenberg University Medical Center, Mainz, Germany

Markus Löbrich
Technical University Darmstadt, Germany

Wolf Reik
Babraham Institute, Cambridge, UK

Primo Schär
University of Basel, Switzerland

Wim Vermeulen
Erasmus Medical Center, Rotterdam, The Netherlands

Jörn Walter
Saarland University, Saarbrücken, Germany

Guoliang Xu
Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, Shanghai, China

Yi Zhang
University of North Carolina, Chapel Hill, USA

Keynote Speakers

Azim Surani
Gurdon Institute, University of Cambridge, UK

Anjana Rao
La Jolla Institute for Allergy & Immunology, USA

Scientific Organisers

Helle Ulrich
CRUK London Research Institute, UK

Christof Niehrs
IMB, Mainz, Germany

George Reid
IMB, Mainz, Germany

Holger Richly
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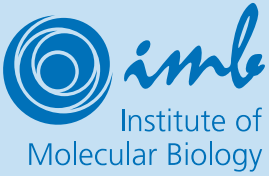
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