Welcome to the 3rd Berlin Summer Meeting

June 24 – 26, 2010

A conference organised by The Berlin Institute for Medical Systems Biology (BIMSB) at the Max Delbrück Center for Molecular Medicine (MDC) Berlin Buch, funded by:

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Der Senat von Berlin

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Berlin-Buch

Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany

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Organisation

Summer Meeting, Secretary:

Michaela Langer / Alexandra Tschernycheff

Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch

Robert-Rössle-Str. 10

13125 Berlin

Phone: +49 30 9406 3720 / 2999
Fax: +49 30 9406 2206 / 3068

E-Mails: langer@mdc-berlin.de / tschernycheff@mdc-berlin.de

Homepage: http://www.berlinsummermeeting.org

Welcome Address

Dear Guests,

Welcome to the 3rd Berlin Summer Meeting! We are delighted that you are participating!

The 'Berlin Summer Meeting' is an annual meeting at the interface of experimental molecular biology and computational approaches. It is designed to create an intense and open atmosphere, aiming at stimulating productive interactions between various branches of biology and bringing together leading scientists and young researchers.

This year's meeting will focus on 'Quantitative Genomics' and on the effects of sequence variation in the transcriptome or proteome. Another focus will be on technologies to characterise phenotypes at the 'omics'-level, on genomics and predictive medicine and on the application of quantitative approaches in different model organisms.

We very much believe that – like in the previous two years – it will be an exciting and highly stimulating get-together.

So, enjoy the interesting talks and fruitful discussions and note that we will also appreciate your direct feedback, since the next Berlin Summer Meeting is expected to take place from June 23 to June 25, 2011!

With best regards,

Wei Chen
Christoph Dieterich
Kris Gunsalus
Norbert Hübner
Markus Landthaler
Nikolaus Rajewsky
(The Organisation Committee 2010)

Program

PROGRAMM SCHEDULE – BERLIN SUMMER MEETING 2010
(long talks: 45 minutes + 15 min discussion, short talks: 15 minutes + 5 min discussion)

Thursday, 24 June 2010

09:00 - Registration + Coffee

09:20 - 09:30 **Nikolaus Rajewsky**
Welcome

Epigenome/genome and environment (Chair: Norbert Hübner)

09:30 - 10:30 **David Gresham, NYU, New York**
Quantitative reverse genetics for call cycle exit, aging and survival

10:30 - 11:00 Coffee Break

11:00 - 12:00 **Andreas Wagner, University of Zurich**
On the origins of evolutionary innovation

12:00 - 13:00 **Jürg Bähler, University College London**
Genome regulation in fission yeast

Lunch break & poster discussion

Genomics and predictive medicine (Chair: Wei Chen)

14:30 - 15:30 **Elaine R. Mardis, Washington University in St. Louis**
Whole genome analysis to compare primary tumors to their metastatic disease

15:30 - 16:00 Coffee break

16:00 - 17:00 **Tim J. Aitman, Imperial College London**
Integrative genomics in the rat model

17:00 – 18:00 **Evan Eichler, University of Washington, Seattle**
Copy number of variation and variability in neuropsychiatric disease

20:00 – 22:00 Dinner for invited speakers, walking distance

Program

Friday, 25 June 2010

09:00 - Registration + Coffee

Model organisms (Chair: Kris Gunsalus)

09:30 - 10:30 **Martha Bulyk, Harvard Medical School, Boston**
Transcription factor-DNA interactions: cis-regulatory codes in genomes

10:30 - 11:30 **Michael Purugganan, NYU, New York**
Adaptive variation in a regulatory network: The case of flowering in Arabidopsis

11:30 - 12:00 Coffee Break

12:00 - 13:00 **Philipp Khaitovich, PICB, Shanghai**
A molecular survey across lifespan: role of developmental timing in human brain evolution and aging

Lunch Break & poster discussion

From phenotypes to omics (Chair: Christoph Dieterich)

14:30 - 15:30 **Michel Georges, Université de Liège**
Deciphering the molecular architecture of complex traits in domestic animal

15:30 - 16:30 **Eric Miska, University of Cambridge**
The complex life of small RNA

16:30 - 17:00 Coffee Break

17:00 - 18:00 **Mihail Sarov, MPI Dresden**
Transgeneomics: A platform for high throughput biology

19:30 - 21:30 Berlin from the Boat: Spree-tour (to be booked separately)

Program

Saturday, 26 June 2010

9:00 - Registration + Coffee

Next-generation Technologies (Chair: Markus Landthaler)

09:30 - 09:50	**Rina Ahmed, Berlin Institute for Medical Systems Biology at the MDC** *miRNA prediction with SOLiD small RNA deep-sequencing data of 10 nematode species*
09:50 - 10:10	**Haoyang Cai, University of Zurich** *Copy number imbalances in human malignancies: A reference data set for systems biology*
10:10 - 10:30	**Tobias Reichenbach, The Rockefeller University, New York** *A ratchet mechanism for low-frequency hearing in mammals*
10:30 - 10:50	**Angelo Valleriani, MPI Potsdam** *Translation of mRNA beyond the steady state*
10:50 - 11:15	Coffee Break
11:15 - 12:15	**Yijun Ruan, Genome Institute of Singapore** *Long-range chromatin interactions and transcription regulation*
12:15 - 13:15	**Jacob Boysen, NYU, New York** *Systematic analysis of the RNA motif 'language' controlling drosophila germ cell specification*
	Lunch

POSTER SESSION WILL TAKE PLACE DURING LUNCH BREAKS.
PLEASE WAIT FOR ANNOUNCEMENTS

Speaker Abstracts

Invited speakers abstracts in alphabetical order

miRNA PREDICTION WITH SOLiD SMALL RNA DEEP-SEQUENCING DATA OF 10 NEMATODE SPECIES

Rina Ahmed, Zisong Chang, Matthias Dodt, Claudia Langnick, Wei Chen, Christoph Dieterich

Berlin Institute for Medical Systems Biology at the Max Delbrück Center for Molecular Medicine Berlin, Germany

Gene expression is regulated at the transcriptional and post-transcriptional level. Key components in post-transcriptional gene regulation are microRNA (miRNA) genes, a large class of small non-coding RNAs. miRNAs (~ 21-24 nt in length) repress protein-coding genes by predominantly binding to the 3 untranslated regions of their target genes. Accordingly, miRNAs play an important role in a broad range of biological processes, such as development of organisms and adult physiology. Determining the miRNAs complement of an organisms genome will lead to a better understanding of the molecular events underlying these biological processes. Current high-throughput sequencing technologies generate small RNA transcriptome data in large batches of millions of short reads. We performed SOLiD SREK multiplex high-throughput sequencing of small non-coding RNAs in 10 different nematodes: *Caenorhabditis elegans*, *Koeneria sudhausi*, *Diplogasteroides magnus* and 7 species belonging to the genus *Pristionchus*. Eight out of these ten species do not have a sequenced genome to date. Adaptor removal is a critical preprocessing step in analyzing deep-sequencing data, especially if a genome sequence is lacking. To this end, we implemented a bioinformatics preprocessing pipeline for SOLiD small RNA colorspace data, including a very fast parallelized adaptor removal software written in C++. The preprocessed transcriptome data were computationally analysed to predict novel miRNA genes. Current state of the art miRNA prediction programs, e.g. miRDeep or miRTRAP, require a reference genome sequence. At present, every available miRNA prediction software depends on a reference genome. To circumvent this, we developed a k-mer based miRNA prediction strategy for species without genome data, based on our ”gold-standard” *C.elegans* small RNA data set. This approach considers biological signatures, such as miRNA star sequences, as well as homology information.

INTEGRATIVE GENOMICS IN THE RAT MODES

Tim Aitman

MRC Clinical Sciences Centre and Imperial College London, UK

Remarkable advances in genomics have occurred in the past 5 years including the advent of whole genome association studies and the ability to re-sequence entire mammalian genomes at a tiny fraction of the cost of the original sequences. Over this period, gene copy number variation (CNV) has also been recognised as a major source of sequence variation in the genomes of humans and other mammals. We have studied the genetics of complex traits in the rat model and, where possible, have translated our findings to an understanding of human disease. We integrated the use of linkage analysis and expression profiling to identify *Cd36* as a cause of insulin resistance in rats and humans. More recently we used this integrated approach to identify expression quantitative trait loci (eQTLs) for thousands of genes across the rat genome. Using these data, we identified *Ogn* as a cause of cardiac hypertrophy in spontaneously hypertensive rats (SHR), and *Fcgr3* and *Jund* as causes of glomerulonephritis and macrophage function in the Wistar Kyoto (WKY) rat. Copy number variation at the rat *Fcgr3* locus provides a molecular basis for susceptibility to glomerulonephritis in the WKY rat, and CNV at the orthologous human *FCGR3B* locus is a cause of autoimmunity in human systemic lupus erythematosus. We have now sequenced the SHR genome at 11x coverage, detecting over three million high-quality single nucleotide polymorphisms between the SHR and Brown Norway (BN) reference sequence, and major coding-sequence variants (stop codons and frameshift variants) in over 600 SHR genes. This near-complete catalogue of genomic differences between the SHR and BN strains provides the starting point for complete elucidation, at the molecular level, of phenotypic differences between these strains.

GENOME REGULATION IN FISSION YEAST

Jürg Bähler

University College London, Department of Genetics, Evolution & Environment and UCL Cancer Institute, London, UK

We study transcriptional and post-transcriptional gene expression control during cellular proliferation, quiescence/ageing, and stress response using *S. pombe* as a model system. We apply multiple high-throughput approaches for systems-level understanding of regulatory networks and complex relationships between genotype, phenotype, and environment, including roles of genome variation and evolution, transcriptome regulation, and non-coding RNAs.

SYSTEMATIC ANALYSIS OF THE RNA MOTIF 'LANGUAGE' CONTROLLING DROSOPHILA GERM CELL SPECIFICATION

Jacob Boysen[1,2,3], Leonard Jones[1,2,3], Samuel Newbold[1,2,3], Ruth Lehmann[1,2,3,4]

[1]Skirball Institute of Biomolecular Medicine, [2]Kimmel Center for Biology and Medicine, [3]NYU, School of Medicine, [4]Howard Hughes Medical Institute, USA

It is now clear that a fundamental component of many biological pathways is the parallel regulation of many different RNA molecules. However, it is not clear how RNA regulation is achieved on a pathway-level scale. Germline development is a well-characterized model of a process that heavily depends on post-transcriptional regulation. For example, in the Drosophila early embryo (and others), the specification of germline progenitor cells depends on the localization, stabilization and translation regulation of a large group of mRNAs in a 3'UTR-dependent manner. These mRNAs are members of a specialized cytoplasm, called germ plasm, that also contains many RNA binding proteins. Most of these RNA binding proteins belong to a network that is required continually during the lifecycle of the Drosophila germline, and this network is conserved throughout vertebrate germline development. Pathway-level mRNA regulation is thought to result from the shared presence of specific motif combinations, as the presence of one motif (such as a microRNA binding site) is rarely sufficient to explain in vivo regulatory patterns. RNA motifs are difficult to decipher on a single-gene level, but if the combinatorial model is correct, then the shared presence of motifs among many co-regulated mRNAs should make identification easier. Our lab has identified greater than 50 germ plasm mRNAs that are co-regulated during germline development. Interestingly, our lab has recently found that germ plasm localization is not sufficient for translation. Rather, germ plasm RNAs are translated in temporally distinct groups. In order to subdivide the set of germ plasm RNAs into co-regulated groups, we are systematically fusing each 3'UTR to GFP and assaying for the timing of fluorescent expression during primordial germline development. In conjunction, we are using computational analysis and functional data to identify co-regulated mRNAs, followed by sequence analysis to identify primary sequence or secondary structure patterns that are common among each group. Our combined analysis aims to produce a germline development 'language' of RNA motif patterns from a pool of recurrin motifs.

TRANSCRIPTION FACTOR-DNA INTERACTIONS: CIS REGULATORY CODES IN GENOMES

Martha Bulyk

Brigham and Women's Hospital/Harvard Medical School, Medicine/Genetics, Boston, USA

The interactions between transcription factors (TFs) and their DNA binding sites are an integral part of the regulatory networks within cells. Identification of the DNA binding specificities of sequence-specific TFs is important for understanding transcriptional regulatory networks, in particular for the prediction of cis regulatory modules (e.g., transcriptional enhancers), inference of cis regulatory codes, and interpretation of *in vivo* TF occupancy data and gene expression data. Using highly parallel *in vitro* technology developed in my group termed universal protein binding microarrays (PBMs), we have characterized the sequence specificities of DNA-protein interactions at high resolution for >500 TFs from a wide range of species. These data have permitted us to identify novel TFs and their functions, to investigate how TFs interact with their target sites *in vivo*, and to identify features of transcriptional enhancers important for driving appropriate gene expression patterns in metazoans. We anticipate that further analyses of closely related TFs and the cis regulatory elements in which their binding sites occur will reveal additional features of cis regulatory codes and how TFs within gene families diverge to acquire new DNA binding specificities and functions.

COPY NUMBER IMBALANCES IN HUMAN MALIGNANCIES: A REFERENCE DATA SET FOR SYSTEMS BIOLOGY

Haoyang Cai, Nitin Kumar, Michael Baudis

Institute of Molecular Life Sciences, University of Zurich, Switzerland

The relevance of genomic copy number aberrations (CNAs) to the development of all forms of human malignancies has been widely recognized. Over the past several years, array comparative genomic hybridization (aCGH) techniques have proven their value for analyzing DNA copy number abnormalities (CNAs) and played an important role in cancer research. By providing an additional layer of information, these data could prove valuable for systems biology approaches to modeling pathways and functional networks involved in oncogenesis. However, no single resource does yet provide a global collection of interpreted ("called") oncogenomic array data. Following it's establishment as main deposition site for gene expression data, the NCBI's Gene Expression Omnibus (GEO) site is increasingly used as genomic data repository, but without emphasis on annotated copy number events or typical cancer associated data qualities. To establish the curated oncogenomic reference data set, we explored GEO for appropriate content. So far, we were able to identify 399 series with approx. 31,000 samples fulfilling our selection criteria (i. e. whole genome arrays of human neoplasias). The majority of array CGH data available has been generated using either spotted large-insert clone DNA (BAC/P1) or in-situ synthesized oligonucleotide arrays. Data is provided in a number of formats, most frequently as normalized probe intensity values. An important obstacle for generating a common reference data set is the necessity to a) determine the genomic positions for the tens to hundreds of thousands array probes with b) reference to a common genome Golden Path edition, c) to perform optimal copy number region segmentation for d) calling regions of copy number gain and loss while dealing with different data resolution and dynamics. For the widely used Affymetrix GenomeWide SNP arrays, we are able to circumvent these issues by currently performing a massive re-analysis of several thousand of raw data sets. So far, we have remapped 4450 arrays from 81 series, comprising 35% of non-Affymetrix arrays for which we were able to obtain normalized probe values. Interestingly, we identified approx. 15,000 Affymetrix GenomeWide arrays in GEO, the majority of which has raw data files suitable for data re-processing. This will allow us to perform quality controlled normalization procedures across thousands of samples, which will allow new insights into the distribution and dynamics of copy number features in human malignancies. Currently, the data sets are prepared for analysis runs with most procedures being in place. After accumulated, the called copy number regions will be included on a per case basis into the Progenetix database (http://www.progenetix.org), making them available to the research community for further oncogenomic data mining. Progenetix presents a case specific overview of chromosomal imbalances for many malignancies. A large, high resolution reference data set of copy number profiles spanning virtually all cancer entities will prove valuable for supporting functional network analysis in cancer research. We believe such systematic analyses will provide invaluable information on the chromosomal mechanisms and will bring tremendous new insights for understanding of disease pathology and new therapeutic approaches.

COPY NUMBER VARIATION AND VARIABILITY IN NEUROPSYCHIATRIC DISEASE

Evan Eichler

University of Washington, USA

Structural variation of the genome is an important aspect in our understanding of the molecular basis of both common and rare disease. Using computational approaches to define the duplication architecture, our lab has focused on 130 genomic regions that we proposed would be hotspots for recurrent rearrangements associated with neurocognitive disease. We have evaluated >4,000 children with a variety of disease phenotypes including developmental delay, idiopathic mental retardation and other cognitive deficits for large-scale copy number change using customized, high-throughput microarrays. Our analysis identified rare microdeletions and microduplications significantly associated with disease for six regions (17q12, 17q21.31, 15q13.3, 15q24, 1q21.1 and 16p12.1) with at least 10 other regions showing enrichment. Comparisons with other studies reveals extreme variability in expressivity for a subset of these recurrent large-scale CNVs suggesting that each molecular lesion may manifest in a variety of pediatric and adult phenotypes, including autism, schizophrenia, mental retardation, and/or epilepsy. We have determined that recurrent CNVs that show the most variability in phenotypic outcome are more likely to be inherited and significantly associated with a secondary CNV insult in cases of severe neurodevelopmental disease. This stands in contrast to CNVs that arise predominantly *de novo* and are more likely to be syndromic. We propose that this two-hit model of rare variants may be more generally applicable to neuropsychiatric disease and help to explain the comorbidity of seemingly diverse neurocognitive and neurobehavioral diseases within families.

DECIPERING THE MOLECULAR ARCHITECTURE OF COMPLEX TRAITS IN DOMESTIC ANIMALS

Michel Georges

Université de Liège, Belgium

QUANTITATIVE REVERSE GENETICS OF CELL CYCLE EXIT, AGING AND SURVIVAL

David Gresham

Center for Genomics and Systems Biology, Department of Biology, NYU, USA

An essential property of all living organisms is the ability to exit from active cell division and persist in quiescent states. For single-celled microbes this most often occurs in response to nutrient deprivation. We have studied the genetic requirements underlying survival of Sachharomyces cerevisiae when starved for two different nutrients: phosphate or leucine. Starvation for phosphate results in a population half-life of 285 hours whereas starvation for leucine results in a half-life of 27 hours. We followed the survival of a complete library of haploid null mutants in populations starved for either phosphate or leucine using a novel high throughput sequencing method to estimate the abundance of each mutant on the basis of frequency of unique molecular barcodes. To determine a quantitative measure of relative fitness in each population we developed a statistical framework that accounts for the multiple sources of variation. We identified unique molecular processes that promote survival of both phosphate and leucine starved cells. We found that genes involved in autophagy and mitochondrial function are required for maintenance of viability in nutrient-starved populations. This study highlights the robustness of networks that respond to nutrient deprivation. Our experimental and analytical methods represent a new approach to characterizing genetic networks with unprecedented resolution. Our findings provide new insight and clarity in the field of aging and quiescence in yeast.

A MOLECULAR SURVEY ACROSS LIFESPAN: ROLE OF DEVELOPMENTAL TIMING IN HUMAN BRAIN EVOLUTION AND AGAIN

Philipp Khaitovich[1,2]

[1]CAS-MPG Institute for Computational Biology, [2]Max Planck Institute for Evolutionary Anthropology, Shanghai

Phenotypically, humans stand out from other primate species in many respects. Here, we focus on two characteristics specific to humans: unique cognitive abilities and extended lifespan. To approach the first question, we surveyed gene expression and metabolic changes taking place during postnatal development in prefrontal cortex and cerebellum of humans, chimpanzees, and rhesus macaques. In prefrontal cortex, but not in cerebellum, we find excess of human-specific changes. Evolutionary, these changes reflect shifts in developmental timing, rather than human innovations. Functionally, these changes predominantly affect calcium signaling, synaptic transmission and long-term potentiation pathways. To approach the second question, we studied lifelong gene expression changes and their regulation in brains of humans and rhesus macaques. We find that in the two species gene expression changes taking place during development continue or reverse in aging. Surprisingly, many expression changes observed in old age, including the down-regulation of neural genes, initiate in early childhood. Both developmental and aging changes appear controlled by miRNA and transcription factors. Thus, difference in the rates of developmental changes might influence the pace of aging in the two species.

WHOLE GENOME ANALYSIS TO COMPARE PRIMARY TUMORS TO THEIR METASTATIC DISEASE

Elaine Mardis

The Genome Center at Washington University School of Medicine, USA

Massively parallel DNA sequencing technology has facilitated new approaches for unbiased characterization of entire genomes to discover genetic changes associated with cancer. We have sequenced matched whole genomes in an effort to discover genomic differences between primary and metastatic breast cancer cases, relative to a normal sample of genomic DNA from that patient. Each sample was sequenced to 30-fold depth, the data were analyzed to discover single nucleotide, indel and structural variants unique to each sample, and then the variation in genomes was compared. Focused PCR and deep read count data were used to validate and establish tumor cell prevalence for each somatic variant. Our data analysis has revealed an emerging picture of metastatic disease progression in the context of the primary tumor genome. I will discuss our results to-date, and next steps that are being pursued toward additional sample sets.

THE COMPLEX LIFE OF SMALL RNA

Eric Miska

University of Cambridge, UK

Post-transcriptional regulation of gene expression by miRNAs is essential for development and has been implicated in a wide range of cellular, developmental and pathological processes. Despite much interest, the mechanism by which miRNAs regulate their target mRNAs is still poorly understood. To take a genetic approach to study the miRNA mechanism, we developed a sensitive assay that gives a quantitative read-out of miRNA activity in live animals (Lehrbach et al. 2009). We have used this assay to screen for miRNA function defective mutants. The mutants isolated include some that map to regions of the genome lacking any known miRNA pathway genes, and so represent new components of the pathway. In addition, we have isolated and characterized an allele of the pash-1 gene; which encodes a factor essential for miRNA biogenesis (Denli et al 2004). pash-1(mj100) mutants have a temperature sensitive defect in miRNA biogenesis. Genetic analysis of miRNA functions using miRNA pathway mutants is difficult because the early and essential functions of miRNAs might mask later roles; a conditional approach using this pash-1ts allele is therefore a powerful means to identify new miRNA functions. We will present new insights into post-developmental miRNA functions derived from this ts allele.

Adaptive variation in a regulatory network: The case of flowering in Arabidopsis

Michael Purugganan

Department of Biology Center for Genomics and Systems Biology, NYU, USA

Several major plant adaptations arise through evolutionary change in developmental programs, resulting in morphological or life history diversification within and between species. We examine the evolution of the developmental regulatory network associated with flowering time variation in the model genetic system Arabidopsis thaliana. Molecular population and quantitative genomic analysis, including mapping analyses using a recently-developed advanced intercross line set, allows us to identify key players in the diversification of this life history transition in Arabidopsis, and we discuss the lessons we have learned about the molecular basis of plant evolution.

TRANSGENOMICS: A PLATFORM FOR HIGH THROUGHPUT BIOLOGY

Mihail Sarov

MPI-CBG, Dresden, Germany

Biological matter at all levels is organized as dynamic and highly interconnected networks of interacting components. Understanding that complexity requires systematic and accurate description of the molecular properties of these components on a large scale. We have previously developed methods for analysis of protein function in metazoans under endogenous expression control using generic tag based localization and purification assays. Extending this approach to systems scale would drastically improve our ability to assign molecular functions to previously unstudied proteins and will reveal new players even in well-understood functional processes relevant to human biology and disease pathways. To address this problem have established a scalable technology platform including an efficient transgenic pipeline, reliable multipurpose tags and sensitive, high-resolution methods for data acquisition. We are currently developing genome scale transgenic resources in several metazoan models, which would permit the localization and biochemical purification of any protein of interest. These tools will also require significant advances in computational biology to deal with new types of data on a massive scale.

A RATCHET MECHANISM FOR LOW-FREQUENCY HEARING IN MAMMALS

Tobias Reichenbach, A. J. Hudspeth

Howard-Huges Medical Institute and Laboratory for Sensory Neuroscience, The Rockefeller University, New York, USA

Hearing employs tuned mechanical amplification to achieve a remarkable sensitivity, frequency selectivity, and wide dynamic range. The mechanism of amplification in the mammalian inner ear is intensely debated, for its mechanoreceptive hair cells exhibit two forms of mechanical activity, active hair-bundle motility and membrane-based electromotility. We show that active hair-bundle motility and electromotility can together implement an efficient mechanism for amplification that functions like a ratchet: sound-evoked forces acting on the elastic basilar membrane are transmitted to the hair bundles while electromotility decouples the active hair-bundle forces from the basilar membrane. This mechanism thereby resembles the operational amplifier from electrical engineering. Through a combination of analytical and computational techniques we demonstrate that the ratchet mechanism can naturally account for a variety of unexplained experimental observations from low-frequency hearing.

TRANSLATION OF mRNA BEYOND THE STEADY STATE

Angelo Valleriani

Dept. of Theory and Bio-Systems, Max Planck Institute of Colloids and Interfaces, Potsdam, Germany

In prokaryotic cells, in certain eukaryotic cells and for certain genes, the mean life time of the messenger RNA is comparable to the time scale of translation. This implies that the mRNAs found in a cell or in a sample of cells cannot be all at steady state concerning ribosomal loading. In particular, very young mRNAs are likely to have less ribosomes than older mRNA. This fact has important consequences for the measurement of the ribosomal profiles because this measurement is, in fact, an average over the age distribution of the mRNAs in the cell. We introduce a simple mathematical theory that deals with two possible processes of non specific mRNA degradation. We derive the age distribution of the mRNA and the profile densities for both processes [1]. Finally, we show that the rate of translation, defined as the mean number of proteins synthesized per mRNA molecule per unit of time, depends on the degradation process and on the length of the mRNA. The theory predicts that the translation rate decreases with increasing length of the mRNA [2].

[1] A. Valleriani, Z. Ignatova, A. Nagar, R. Lipowsky, *Turnover of messenger RNA: Polysome statistics beyond the steady state*, Europhys. Lett. **89** (2010) 58003

[2] A. Valleriani, G. Zhang, A. Nagar, Z. Ignatova, R. Lipowsky, *Length dependent translation of messenger RNA by ribosomes*, submitted

LONG-RANGE CHROMATIN INTERACTIONS AND TRANSCRIPTION REGULATION

Yijun Ruan

Genome Institute of Singapore

Genomes are known to be organized into 3D structures in vivo through interactions with protein factors for nuclear process such as transcription, and DNA elements separated by long genomic distances are known to functionally interact. This view has been further emphasized by recent observations that many transcription factors bind remotely to gene promoters. However, it is still largely unknown to us how and to what extent chromatin interactions are involved in transcription regulations on a whole genome scale. To study these questions, we have developed the Chromatin Interaction Analysis using Paired-End-Tag sequencing (ChIA-PET) strategy for de novo detection of genome-wide chromatin interactions, and demonstrated this approach through the comprehensive mapping of chromatin interactions involved in transcription regulations mediated by estrogen receptor á (ERá) in a human genome (Nature 2009 462: 58-64). In order to map all chromatin interactions involved in all transcription regulation networks in the human genome, we have applied the ChIA-PET strategy to active transcriptional marks such as RNA polymerase II (RNAPII) and trimethylation of lysine 4 on histone H3 (H3K4me3) as analysis targets in a number of human cells. Our results have shown that both RNAPII and H3K4me3 are excellent targets for ChIA-PET experiments to detect long-range chromatin interactions between gene promoters and distal regulatory elements, as well as to identify co-localization of remote genes (intra-chromosome and inter-chromosome) in close proximity of nuclear space. Through comprehensive mapping of chromatin interactions and transcriptional activities, we have revealed that a large proportion of actively transcribed genes are involved in extensive chromatin interaction looping structures. The most abundant gene-centric chromatin interactions are appeared to be within local range of megabase genomic span, and nearby genes such as gene family members are organized to share common transcription factories. In addition, we have identified many hot spots of interaction hubs, in which clusters of genes crossing large megabase distance and different chromosomes are co-localized in close proximity. Collectively, our data suggests that long-range chromatin interaction is a primary mechanism for transcription regulation in human genomes. Further analyses of the chromatin interaction and transcription maps will provide deep insights to advance our understanding of transcription regulatory networks and the human genome biology.

THE ORIGINS OF EVOLUTIONARY INNOVATION

Andreas Wagner

University of Zurich, Switzerland

Life can be viewed as a four billion year long history of innovations. These range from dramatic macroscopic innovations like the evolution of wings or eyes, to a myriad molecular changes that form the basis of macroscopic innovations. We know many examples of innovations -- qualitatively new phenotypes that can provide a critical advantage in the right environment -- but have no systematic understanding of the principles that allow organisms to innovate. Most phenotypic innovations result from changes in three classes of systems: metabolic networks, regulatory circuits, and protein or RNA molecules. I will discuss evidence that these classes of systems share two important features that are essential for their ability to innovate.

Poster Abstracts

P1 DETECTION OF SINGLE MOLECULES OF mRNA IN INDIVIDUAL CELLS DURING THE YEAST CELL CYCLE

Aouefa Amoussouvi, Andreas Herrmann

Humboldt-University of Berlin, Institute of Biology/Biophysics, Berlin, Germany

Recently, some single-molecule methods have been designed and they offer an alternative to population approaches for studying the gene expression. The single-molecule techniques revealed an important cell-to-cell variability in the transcription and translation rates among genetically identical populations of cells exposed to the same environment. Also, these recent discoveries give a new direction to many studies: to quantitatively measure the variability of gene expression level in a cells population and to better understand the role of stochastic events in gene expression regulation. The challenging goal of this project is to model the regulatory mechanism of the yeast cell cycle. Firstly, we focus on two genes, Sic1 and Cln2, that drive the transition between the G1 and the S phases in the early stage of the cell cycle. We investigate the influence of randomness on their transcription rates thanks to the MS2-GFP method. This new available technique permits the visualisation of single molecules of mRNA in living yeast cells (Saccharomyces cerevisiae). In this way, we can obtain a quantitative estimation of the transcription rate of individual cells and the transcription noise among a cell population. The strategy is, firstly, to tag the gene with a series of binding sites for the RNA-binding MS2 coat protein (CP), then MS2-CP coupled to a triplet of GFP molecules is expressed in the cells. Finally, when the tagged mRNA is transcript, the MS2-CP-GFP(x3) fuse to the binding sites. The local accumulation of GFP molecules can be observed by fluorescence microscopy and this makes possible the detection of single mRNA molecules. The analysis of the pictures has a primordial importance, as we need to relate the fluorescence intensity levels of the fluorescent dots to the number of mRNA in individual cells. In order to reach this goal, we design a semi automatic algorithm that takes the pictures of bright field and fluorescence as its input, and gives us as its output the transcription level per cell present in the picture. In the final part of the project, we want to use our experimental data to assess a theoretical model. Indeed, in measuring the transcription rate of these specific mRNAs in single cells, we want to obtain quantitative basis of transcript products abundance and variation for developing a model of expression regulation.

P2 MECHANISMS UNDERLYING THE ROBUSTNESS OF CELLULAR OSCILLATIONS

Katharina Baum[1], Antonio Politi[2], Ralf Steuer[3], Jana Wolf[1]

[1]Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch, [2]European Molecular Biology Laboratory, Heidelberg, [3]Humboldt University, Berlin, Germany

Oscillations occur at many different levels of biologic processes, in genetic systems, signaling and as metabolic oscillations. Examples are circadian oscillations, which occur in many organisms from cyano bacteria to mammals, the canonical NFκB-pathway and calcium signaling. The oscillatory mechanisms differ not only in their time-scale, i.e. period length, but also in the intensity of their response towards environmental changes, the so-called robustness or sensitivity. Thereby, calcium oscillations are known to be very sensitive whereas the period of circadian rhythms is very robust; it has to remain nearly unaffected by changes of pH, nutritional conditions and even temperature in order to provide reliable timing. Our goal is to determine which topological principles render the amplitude or period of oscillatory systems robust. We therefore perform sensitivity analyses for mathematical models of the processes in question (calcium oscillations, circadian oscillations) for a great variety of different parameter sets. Additionally, we examine structural properties as type of feedback, existence of flow of matter and kinetics with the help of a core model and deduce structural principles leading to robust systems. In detail, we find that negative feedback, in contrast to positive feedback, leads to oscillations with robust period whereas the existence of flow of matter does not seem to play a role for the sensitivity of oscillations. Contrariwise, enzyme-driven reactions with saturable kinetics decisively decrease period and amplitude robustness of oscillatory systems. The type of robustness analysis applied here may provide a means to determine to which extent an oscillatory system can play a role for signal transduction.

P3 ANALYSIS OF THE β-TrCP2/HOS FEEDBACK IN Wnt/β-CATENIN SIGNALLING

Uwe Benary, Jana Wolf

Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany

The canonical Wnt/β-catenin pathway plays an important role in development and tissue homeostasis. Deregulation of Wnt/β-catenin signalling is associated with various diseases, such as colorectal cancer. In the absence of a Wnt-stimulus, the continuous production of β-catenin is counterbalanced by its continuous proteasomal degradation. The degradation process is initiated by multiple phosphorylations of β-catenin by the destruction complex. In the presence of a Wnt-stimulus, the destruction complex is decomposed, leading to an increase of β-catenin concentration, its nuclear translocation and the induction of target genes. An important target is the F-box protein β-TrCP2/HOS. β-TrCP2/HOS recognises phosphorylated β-catenin and targets it for polyubiquitylation and proteasomal degradation. We use a detailed mathematical model of Wnt/β-catenin signalling to analyse the impact of this feedback on the dynamical properties of the pathway.

P4 COMPARATIVE TRANSCRIPTOME, PROTEOME AND METABOLOME ANALYSIS OF NEMATODE DAUER LARVAE

Zisong Chang[1], Guido Mastrobuoni[1], Dominic Tolle[1], Hans-Joachim Knölker[2], Stefan Kempa[1], Christoph Dieterich[1]

[1] Berlin Institute for Medical Systems Biology at the Max Delbrück Center for Molecular Medicine, Berlin, [2]TU Dresden, Germany

The life cycle of *Caenorhabditis elegans* proceeds through four larval stages and is usually completed within 3-4 days under laboratory conditions. L2 larvae sense their environment and enter an alternative developmental stage, the Dauer stage, if adverse conditions such as high temperature, low food supply or high population densities prevail. Dauer larvae are non-feeding, stress resistant and long-lived. Dauer larvae morphologically resemble the infective stage of parasitic nematode larvae. Intriguingly, a conserved endocrine mechanism controls the formation of dauer as well as infective larvae in nematodes. We present results of our molecular comparison of dauer and non-dauer stages across three different hermaphroditic nematode species: *C. elegans*, *C. briggsae* and *Pristionchus pacificus*. *Caenorhabditis* species are free-living nematodes whereas *Pristionchus* species show near species-specific associations to scarab beetles (necromenic life style). We have set up an analysis pipeline for relative quantification of thousands of proteins and hundreds of metabolites. To this end, we employ novel techniques (shotgun LC-MS/MS and GCxGC-MS) and a new bioinformatics workflow. Our results highlight profound changes in the proteome and metabolome between conditions and even across species. We will discuss changes in primary metabolism, translation (RNA-binding proteins), signaling and chromatin-related proteins.

P5 APPLYING BAYESIAN NETWORKS COUPLED WITH GAUSSIAN PROCESS REGRESSION FOR THE ANALYSIS OF DRUG RESISTANCE

Sebastian Fröhler, Christoph Dieterich

Berlin Institute for Medical Systems Biology at the Max Delbrück Center for Molecular Medicine Berlin, Germany

Introduction High-throughput technologies in the domain of genotyping, gene product level profiling and imaging help us to characterize any biological model system at an unprecedented level of detail and depth. These data allow us to draw conclusions on the phenotypic outcome of variations at the genotype and/or intermediate levels. Data analysis and functional inference require network-level approaches to obtain a better understanding of component interactions in biological systems. Our Solution We propose to use Bayesian Networks [3] to uncover statistical and possibly biological interactions for the analysis of heritable traits and transcripts influencing drug response. We further argue for replacing Gaussian Regression with Gaussian Process Regression [4], which can be seamlessly integrated into this probabilistic framework. Since an exhaustive bayesian network structure search is NP-hard [2], we perform network structure search by a parallelized multi-step greedy hill-climbing algorithm constraining node ordering and network depth. Results and Conclusions We demonstrate the benefits of our approach by cross-validation on publicly available drug response data on a panel of haploid yeast segregants [1] and compare our results to the ones of Chen et al. [1]. Our software is implemented in JAVA and available upon request. References 1. Bo-Juen Chen, Helen C Causton, Denesy Mancenido, Noel L Goddard, Ethan O Perlstein, and Dana Pe'er. Harnessing gene expression to identify the genetic basis of drug resistance. Mol Syst Biol, 5:310, 2009. 2. David Maxwell Chickering, Christopher Meek, and David Heckerman. Large-sample learning of Bayesian networks is hard. In Proceedings of the Nineteenth Conference on Uncertainty in Artificial Intelligence, Acapulco, Mexico, pages 124–133. Morgan Kaufmann, 2003. 3. Judea Pearl. Probabilistic Reasoning in Intelligent Systems: Networks of Plausible Inference. Morgan Kaufmann Publishers Inc., San Francisco, CA, USA, 1988. 4. Christopher K. I. Williams and Carl Edward Rasmussen. Gaussian processes for regression. In David S. Touretzky, Michael Mozer, and Michael E. Hasselmo, editors, NIPS, pages 514–520. MIT Press, 1995.

P6 GLOBAL ANALYSIS OF WHOLE-GENOME SMALL RNA PROFILES ACROSS 30 HXB/BXH RECOMBINANT INBRED STRAINS USING NEXT-GENERATION SEQUENCING (NGS)

Katharina Grunz[1], Samuel Linsen[2], Matthias Heinig[1], Oliver Hummel [1], Michal Pravenec[3], Edwin Cuppen[2], Norbert Hübner[1]

[1]Max Delbrück Center for Molecular Medicine, Berlin, Germany , [1]Max Delbrück Center for Molecular Medicine, Berlin, Germany , [1]Max Delbrück Center for Molecular Medicine, Berlin, Germany , [2]Hubrecht Institute and University Medical Center Utrecht, Utrecht, NL, [2]Hubrecht Institute and University Medical Center Utrecht, Utrecht, NL, [3]Institute of Physiology and Center for Applied Genomics, Czech Academy of Sciences, Prague, Czech Republic

During the last years several new classes of non-protein coding RNAs (ncRNAs) have been discovered, many of which exert crucial roles as powerful regulators of gene expression. MicroRNAs (miRNA) represent one class of small regulatory RNAs, and it has been shown that miRNA deregulation is involved in the incidence of several pathological traits including metabolic and cardiovascular phenotypes. The advent of state-of-the-art technologies, such as high-throughput, next-generation sequencing (NGS) coupled with computational analyses allows for the global exploration of small regulatory RNAs across genomes to pinpoint deregulated ncRNA-target gene interactions. Here, we present the first global analysis of whole-genome microRNA content across 30 HXB/BXH rat recombinant inbred (RI) strains in heart tissue, derived from a cross of spontaneously hypertensive rat (SHR) and the normotensive BN reference strain, to determine the impact of genetic variation on miRNA abundance, gene expression control, and (patho)physiological traits observed in the RI panel. Our previous studies on heart tissue from SHR and BN parental strains revealed significant strain- and tissue-specific miRNA expression differences. This approach enables us to map *cis*- and *trans*- eQTLs of miRNA gene expression. Further, we integrated information on computationally predicted miRNA targets to identify transcriptional networks that are likely to be regulated directly by the respective targeting miRNAs. Our results will allow to link genomic sequence variation, genotype-dependent, differential microRNA expression, and downstream effects on target gene expression pathways in the context of pathophysiological traits mapped in the SHR.

P7 A CONSERVED TRANS-ACTING REGULATORY LOCUS UNDERLIES AN INFLAMMATORY GENE NETWORK AND SUSCEPTIBILITY TO AUTOIMMUNE TYPE 1 DIABETES

Matthias Heinig[1,2], Enrico Petretto[3,4], Chris Wallace[5], Leonardo Bottolo[4], Maxime Rotival[6], Han Lu[3], Yoyo Li[3], Rizwan Sarwar[3], Sarah R. Langley[3], Anja Bauerfeind[1], Oliver Hummel[1], Young-Ae Lee[1,7], Svetlana Paskas[1], Carola Rintisch[1], Kathrin Saar[1], Herbert Schulz[1], Helge Roider[2], Martin Vingron[2], Stefan Blankenberg[8], Thomas Münzel[8], Tanja Zeller[8], Silke Symczak[9], Andreas Ziegler[9], Laurence Tiret[6], Francois Cambien[6], Deborah J. Smyth[5], Michael Pravenec[10], Timothy J. Aitman[3], David Clayton[5], John A. Todd[5], Norbert Hübner[1], Stuart A. Cook[3,11]

[1]Max-Delbrück-Centrum for Molecular Medicine, Berlin, [2]Max-Planck-Institute for Molecular Genetics, Berlin, [3]Medical Research Council Clinical Science Centre, Faculty of Medicine, Imperial College London, Hammersmith Hospital, [4]Division of Epidemiology, Public Health and Primary Care, Faculty of Medicine, Imperial College London, [5]Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Institute for Medical Research, University of Cambridge, [6]INSERM, Pierre and Marie Curie University and Medical School, Paris, [7]Pediatric Pneumology and Immunology, Charité - Universitätsmedizin Berlin, [8]Medizinische Klinik und Poliklinik, Johannes-Gutenberg Universität Mainz, [9]Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, [10]Institute of Physiology, Czech Academy of Sciences and Centre for Applied Genomics, Prague, [11]National Heart and Lung Institute, Imperial College London

Combined analyses of gene networks and DNA sequence variation have the potential to provide new insights into the aetiology of common diseases. We used integrated genome-wide approaches across seven tissues in a panel of rat recombinant inbred strains to identify gene networks and the loci underlying their regulation. We defined a gene network centred on the interferon response transcription factor Irf7, which is regulated in multiple rat tissues by a single locus on chromosome 15q25. At this locus, Epstein-Barr virus induced gene 2 (Ebi2), which we localised to macrophages and controls B cell migration, directly regulates the Irf7 network that represents a molecular biomarker for macrophages in tissues. Monocyte-derived macrophages and lymphocytes are central to the pathobiology of pancreatic islet destruction in autoimmune type 1 diabetes (T1D). The IRF7 network is conserved in human monocytes and network genes were significantly more likely to associate with T1D than randomly selected genes ($p = 2.9 \times 10^{-8}$). The human chromosome 13q32 locus that is orthologous to the rat region controlling the network was associated with risk of T1D at SNP rs9585056 in two independent large cohorts (combined $p = 7.0 \times 10^{-10}$, odds ratio = 1.15). This SNP is located 60kb from EBI2, the human orthologue of rat Ebi2, which is cis-regulated in monocytes in two human cohorts and represents a candidate gene for T1D susceptibility. Our data implicate IRF7 network genes and their regulatory locus in the pathogenesis of T1D and demonstrate how integration of gene networks and genome-wide association analyses can advance knowledge of disease pathogenesis.

P8 DETECTING DIFFERENTIAL TRANSCRIPT EXPRESSION FROM RNA-SEQ EXPERIMENTS

Oliver Stegle[2,3], Philipp Drewe[1], Regina Bohnert[1], Karsten Borgwardt[2,3], Gunnar Rätsch[1]

[1]Friedrich Miescher Laboratory of the Max Planck Society, Tübingen [2]Max Planck Institute for Developmental Biology, Tübingen, [3]Max Planck Institute for Biological Cybernetics, Tübingen, Germany

As a fruit of the current revolution in sequencing technology, transcriptomes can now be analyzed at an unprecedented level of detail. These technological advances have already been exploited in diverse ways. Examples of such applications include the detection of differentially expressed genes across biological samples, and the quantification of the abundances of various RNA transcripts within single genes. A natural next step is now to extend the detection of differential abundance, focusing on individual transcripts within one gene. However, explicit strategies to solve this problem have not yet been defined. This task is particularly challenging, if the transcript annotation is incomplete or incorrect. In this work, we present two novel statistical tests to address this important methodological gap: a ‘gene-structure-sensitive’ Poisson test for detecting differential expression when the transcript structure of the gene is known, and a non-parametric kernel-based test, called Maximum Mean Discrepancy (MMD), when the transcripts expressed in a region are yet unknown. Both approaches directly use the read alignments and do not rely on previous quantifications of transcripts that are often inaccurate. We analyzed both proposed methods on simulated read data from two artificial samples as well as on factual reads generated by the Illumina Genome Analyzer for four *C. elegans* samples. Our analysis shows that the Poisson test identifies genes with differential transcript expression considerably better than approaches based on RNA transcript quantification. Even more striking, the MMD test is able to detect a large fraction (75%) of true differential cases in the absence of any knowledge of the annotated transcripts. This method is therefore very well suited to analyze RNA-Seq experiments where other approaches are doomed to fail, namely when the genome annotations are incomplete, false or entirely missing. As part of our empirical evaluation we also investigated the MMD test on the data from Waterston et al. (2009), comparing to a second study Barberan-Soler and Zahler (2009) of 352 genes with splicing event in the early development stages of *C. elegans*. Although our test does not make use of transcript annotation, the method was able to detect between 40% and 85% of the transcripts that exhibited at least one log fold change between developmental stages in Waterston et al. These overlaps are significantly greater than expected by chance, indicating that differentially expressed transcripts detected by MMD are indeed of biological significance. When taking the transcript annotation into account, the Poisson test can be applied, which yields an even sharper overlap picture. Here, we proposed two novel approaches to test for differential expression on the level of transcripts. While the Poisson test exploits existing transcript annotation, the MMD test can be used in settings where details about transcripts are not available. On simulated reads and investigation of real data, we achieved promising results using these methods, highlighting their potential as discovery and statistical testing tool. It is current work to extend both the Poisson model and the non-parametric MMD test to cope with multiple replicates in order to better account for technical and biological variation. We will expand on our preliminary analysis of a recent *C. elegans* development study Waterston et al., comprehensively investigating differential transcript expression in settings where current methodology cannot be applied.

P9 INFERENCE OF FUNCTIONAL GENE NETWORKS IN NON-PATHOGENIC SIV INFECTION

Brice Targat[1], Béatrice Jacquelin[2], Steven Bosinger[3], Nicolas Tchitchek[1], Jose Felipe Golib Dzib[1], Christophe Bécavin[1], Françoise Barré-Sinoussi[2], Guido Silvestri[3], Michaela Müller-Trutwin[2], Arndt Benecke[1]

[1]Institut des Hautes Etudes Scientifiques, Bures sur Yvette, France, [2]Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France., [3]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, USA

Several independent functional genomics studies have recently characterized innate immune responses to SIV infection in different non-progressor primate species such as *C. Sabaeus* and *C. Atys* [1-3]. Comparative studies indicate that SIV triggers a strong and rapid innate response in these non-progressors similar to progressor species such as *M. Mulatta*. Since *C. Sabaeus* and *C. Atys* cells are able to produce IFN-I, the transient ISG response in these animals is likely the result of active regulatory mechanisms that are lacking or are inhibited in SIV-infected *M. Mulatta*. The mechanisms responsible for the attenuation of the IFN-I pathway in the post-acute phase of SIV infection of natural hosts are now the focus of intense studies, as these mechanisms of active attenuation might play a major role in protection against harmful chronic immune activation observed in pathogenic HIV and SIV infections. Required for the elucidation of the positive and negative control of the innate immune responses and the differences between the non-progressing and progressing species is the identification of the functional gene regulatory networks, possibly including epigenetic regulatory events. Using novel methodology from algebraic geometry and probability theory [4-5], we have dissected the kinetics and topographics [6] of the transcriptome profiles from the different non-progressing and progressing species. Correlation analysis within and across topographic gene expression groups identifies additional gene expression patterns allowing to better understand the positive and negative regulatory control. Inter-species comparisons also identify conserved and species specific elements of the innate immune responses to SIV infection. Due to higher statistical power the combined datasets permit the use of methodology from statistical mechanics for functional network inference [7]. These works highlight the need to decipher the networks of immune responses, and make a compelling case for meta-analysis of functional genomics data across species. Elucidation of the attenuation mechanisms in non-progressing natural hosts may lead to the identification of novel candidates for strategies aimed at blocking the harmful chronic immune activation that is associated with progression to AIDS in HIV infected individuals. Keywords: non-pathogenic SIV infection, innate immune response, regulatory control and attenuation, transcriptome profiling, gene network inference PACS classification: 02.40.Dr 02.50.Sk 02.60.Cb 02.70.Ns 02.70.Rr Acknowledgments. *This work was funded by the Centre National de la Recherche Scientifique (C.N.R.S., to A.B.), the Agence Nationale pour la Recherche contre le SIDA et les hépatites virales (A.N.R.S., to F.B.S., M.M.T., A.B.), the Agence Nationale pour la Recherche (A.N.R., to A.B.), the Institut Pasteur (to F.B.S., M.M.T.), the Genopole Evry (to A.B.), and NIH grants AI-66998 and HL-75766 (to G.S.) and P51 RR00165 to the Yerkes National Primate Research Center. C.B. is recipient of a Ph.D. fellowship from the A.N.R.S., S.B. holds a Canadian Institutes of Health Research HIV/AIDS Research Initiative Fellowship (HFE-85139), J.F.G.D. is a CONACYT-Mexico Ph.D. fellow.* References: 1. Lederer S, Favre D, Walters KA, Proll S, Kanwar B, Kasakow Z, Baskin CR, Palermo R, McCune JM, Katze MG (2009) *Transcriptional profiling in pathogenic and non-pathogenic SIV infections reveals significant distinctions in kinetics and tissue compartmentalization.* PLoS Pathog. 5(2):e1000296. 2. Jacquelin B, Mayau V, Targat B, Liovat AS, Kunkel D, Petitjean G, Dillies MA, Roques P, Butor C, Silvestri G,

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List of Participants

Adamidi, Catherine
Robert-Rössle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 2973
E-Mail: catherine.adamidi@ mdc-berlin.de

Ahmed, Rina
Robert-Rössle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 4261
E-Mail: rina.ahmed@ mdc-berlin.de

Aitman, Timothy
Du Cane Road
W12 0NN
UK
Fon: +44 208 383 4253
E-Mail: t.aitman@ csc.mrc.ac.uk

Amoussouvi, Aouefa
Invalidenstr. 42
10115 Berlin
Germany
Fon: +49 30 2093 8487
E-Mail: aouefa.amoussouvi@ staff.hu-berlin.de

Anders, Gerd
Robert-Rössle-Straße 10
16341 Berlin
Germany
Fon: 030-9406 3537
E-Mail: gerd.anders@ mdc-berlin.de

Andreotti, Sandro
Takustrasse 9
14195 Berlin
Deutschland
Fon: 030 838-75137
E-Mail: andreott@ inf.fu-berlin.de

Aßmus, Heike
Robert-Rössle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 2405
E-Mail: heike.assmus@ mdc-berlin.de

Avila Ospina, Liliana
Robert Rossle Str 10
13092 Berlin
Germany
Fon: 030-9406 2972
E-Mail: liliana.avila@ mdc-berlin.de

Ayoub, Salah
Robert-Rössle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 2973
E-Mail: salah.ayoub@ mdc-berlin.de

Babic, Ana
Robert-Rössle-Str
13125 Berlin
Germany
Fon: 030-9406 3041
E-Mail: ana.babic@ mdc-berlin.de

Baethge, Kerstin
Robert-Roessle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 3528
E-Mail: kerstin.baethge@ mdc-berlin.de

Bahler, Jurg
Gower Street
WC1E 6BT London
U.K.
Fon: 0203-1081602
E-Mail: j.bahler@ ucl.ac.uk

Baltz, Alexander
Bornholmerstr. 17
10439 Berlin
Germany
Fon: 0176 4202 3120
E-Mail: alexander.baltz@ mdc-berlin.de

Bauerfeind, Anja
Robert-Rössle-Straße 10
13125 Berlin
Deutschland
Fon: 030-9406 2930
E-Mail: a.bauerfeind@ mdc-berlin.de

Baumgrass, Ria
Chariteplatz 1
10117 Berlin
Germany
Fon: 030-28460 732
E-Mail: baumgrass@drfz.de

Benary, Uwe
Roebert-Roessle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 2465
E-Mail: uwe.benary@mdc-berlin.de

Benecke, Arndt
35, route de Chartres
91440 Bures sur Yvette
France
Fon: 33160926665
E-Mail: arndt@ihes.fr

Bertrams, Wilhelm
Augustenburger Platz 1
13353 Berlin
Deutschland
Fon: 030-4505 53536
E-Mail: wilhelm.bertrams@charite.de

Bockmayr, Alexander
Arnimallee 6
14195 Berlin
Germany
Fon: 030-838 75867
E-Mail: Alexander.Bockmayr@fu-berlin.de

Böhm, Siegfried
Karl-Marx-Alle 51
10178 Berlin
Germany
Fon: 030-241 2102
E-Mail: si-boehm@t-online.de

Boysen, Jacob
SKI lab 4-13 540 First Ave
10016 New York City
USA
Fon: 001-2122838082
E-Mail: jacob.boysen@med.nyu.edu

Bulyk, Martha
77 Avenue Louis Pasteur NRB 466D
02115 Boston
USA
Fon: 001-617-525-4725
E-Mail: mlbulyk@receptor.med.harvard.edu

Busse, Dorothea
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-94062405
E-Mail: dorothea.busse@mdc-berlin.de

Cai, Haoyang
Winterthurerstrasse 190
8057 Zurich
Switzerland
Fon: 041 0767037729
E-Mail: haoyang.cai@imls.uzh.ch

Chang, Zisong
Robert-Rössle-Straße 10. Haus 87
13125 Berlin
Germany
Fon: 030-9406 3529
E-Mail: zisong.chang@mdc-berlin.de

Chen, Wei
Robert-Roessle-str. 10
13125 Berlin
Germany
Fon: 030-9406 2995
E-Mail: wei.chen@mdc-berlin.de

Diesbach, Julia
Robert-Rössle-Strasse 10
13125 Berlin
Germany
Fon: 030-94063527
E-Mail: julia.diesbach@mdc-berlin.de

Dixon, Rick
14 Whitemoors Close
CV13 6EQ Warwickshire
UK
Fon: +44 7720 276 899
E-Mail: rick.dixon@lifetech.com

Eichler, Evan
1705 NE Pacific ST S413C
98195-5065 Seattle
USA
Fon: 001-206-543-9526
E-Mail: eee@ gs.washington.edu

Ferlinz, Astrid
Calvinstr. 14
13467 Berlin
Germany
Fon: 030-4005 7862
E-Mail: Astrid.Ferlinz@ lifetech.com

Georges, Michel
1, avenue de l'Hopital - B34
4000 Liege
Belgium
Fon: 032 4366 4157
E-Mail: michel.georges@ ulg.ac.be

Gong, Maolian
Robert-Roessle-Str. 10
13125 Berlin
Germany
Fon: 030-9406 3430
E-Mail: maolian@ mdc-berlin.de

Gresham, David
100 Washington Square East, 1009 Silver Center
10003 New York
USA
Fon: 001 212-998-3879
E-Mail: dgresham@ nyu.edu

Gruen, Dominic
Rosenthaler Weg 10
51465 Bergisch Gladbach
Germany
Fon: 0179 1073 352
E-Mail: dominic.gruen@ mdc-berlin.de

Gunsalus, Kris
1009 Silver Center, 100 Washington Sq. E.
10003 New York
USA
Fon: 001 212-998-8236
E-Mail: kcg1@ nyu.edu

Fang, Zhuo
Robert-Roessle str. 10
13125 Berlin
Germany
Fon: 030-9406 4248
E-Mail: f.zhuo@ mdc-berlin.de

Fröhler, Sebastian
Robert-Rössle-Strasse 10
13125 Berlin
Germany
Fon: 030-9406 4262
E-Mail: sebastian.froehler@ mdc-berlin.de

Gogol-Döring, Andreas
Robert-Rössle-Straße 10
13125 Berlin-Buch
Germany
Fon: 030-9406 4260
E-Mail: andreas.doering@ mdc-berlin.de

Gregersen, Lea Haarup
Robert-Rossle Str. 10
13125 Berlin Buch
Germany
Fon: 030-9406 3528
E-Mail: lea.gregersen@ mdc-berlin.de

Grosswendt, Stefanie
Rhapsodieweg 11
13158 Berlin
Deutschland
Fon: 0041 762415688
E-Mail: grosswes@ student.ethz.ch

Grunz, Katharina
Robert-Rössle-Straße 10
13125 Berlin
Deutschland
Fon: 030-9406 2531
E-Mail: k.grunz@ mdc-berlin.de

Hatzigeorgiou, Artemis
34th Alexander Fleming
16672 Vari, Attica
Greece
Fon:
E-Mail: skouloudis@ fleming.gr

Hu, Haiyang
320 Yueyang Road
200031 Shanghai
China
Fon: (86)-21-54920218
E-Mail: oceanhu@126.com

Hu, Hao
Lützelsteiner Weg 26
14195 Berlin
Germany
Fon:
E-Mail: hu@molgen.mpg.de

Hübner, Norbert
Robert-Rössle-Str. 10
13125 Berlin
Deutschland
Fon: 030-9406 3512
E-Mail: kdokup@mdc-berlin.de

Hummel, Oliver
Robert-Rössle-Straße 10
13125 Berlin
Deutschland
Fon: 030-9406 4385
E-Mail: o.hummel@mdc-berlin.de

Jens, Marvin
Eylauer Str. 14
10965 Berlin
Germany
Fon: 0151 1035 4154
E-Mail: marvin.jens@mdc-berlin.de

Julia, Freund
Tatzberg 47/49
01307 Dresden
Germany
Fon: 0351 463 40169
E-Mail: julia.freund@crt-dresden.de

Jungkamp, Anna-Carina
Robert-Roessle Str.10
13125 Berlin
Deutschland
Fon: 030-9406 2973
E-Mail: anna-carina.jungkamp@mdc-berlin.de

Kempa, Stefan
RR
13125 Berlin
Germany
Fon:
E-Mail:

Khaitovich, Philipp
320 Yue Yang Rd
200031 Shanghai
China
Fon: 0086 21 5492 0454
E-Mail: khaitovich@eva.mpg.de

Krek, Azra
1275 York Ave
10065 New York
USA
Fon: 001 646-888-2613
E-Mail: azra.krek@gmail.com

Kretschmer, Simon
Gabelsbergerstr. 99
80333 Munich
Germany
Fon: 089-23717667
E-Mail: simon.kretschmer@campus.lmu.de

Kretschmer, Julia
Robert-Roessle-Str.10
13125 Berlin
Germany
Fon: 030-9406 3530
E-Mail: julia.kretschmer@mdc-berlin.de

Kröger, Stefan
Chariteplatz 1
10117 Berlin
Germany
Fon: 030-2846 0697
E-Mail: s.kroeger@drfz.de

Kuntzagk, Andreas
Robert Rössle Str. 10
13029 Berlin
Germany
Fon: 030-9406 2997
E-Mail: andreas.kuntzagk@mdc-berlin.de

Langer, Michaela
Robert Rössle Str 10
13125 Berlin
Germany
Fon: 030-9406 3720
E-Mail: langer@mdc-berlin.de

Li, Na
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 3043
E-Mail: na.li@mdc-berlin.de

Mackowiak, Sebastian
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 2992
E-Mail: sebastian.mackowiak@mdc-berlin.de

Mardis, Elaine
4444 Forest Park Blvd
St Louis MO
United States
Fon: 001 314 286-1800
E-Mail: jgrigsby@wustl.edu

Menssen, Adriane
Robert-Rössle-Str.10
13125 Berlin
Germany
Fon: 030-9479 3256
E-Mail: menssen@fmp-berlin.de

Mothes, Janina
Robert-Rössle-Str 10
13125 Berlin
Germany
Fon: 030-9406 2465
E-Mail: janina.mothes@mdc-berlin.de

Oenal, Pinar
Robert-Roessle Str. 10
13125 Berlin
Germany
Fon: 030-9406 2973
E-Mail: pinar.oenal@mdc-berlin.de

Lebedeva, Svetlana
Robert-Roessle-Str 10
13125 Berlin
Germany
Fon: 030-9406 2972
E-Mail: lebedeva@mdc-berlin.de

Maaskola, Jonas
Robert Roessle Str 10
13125 Berlin
Germany
Fon: 030-94 06 2991
E-Mail: jonas.maaskola@mdc-berlin.de

Mardis, Elaine
4444 Forest Park Pkwy., Campus Box #8501
63108 St. Louis, Missouri
United States
Fon: 001 314 286-1805
E-Mail: emardis@wustl.edu

Mastrobuoni, Guido
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 3045
E-Mail: guido.mastrobuoni@mdc-berlin.de

Miska, Eric
Tennis Court Rd
CB2 1QN Cambridge
United Kingdom
Fon: +44-1223-334 088
E-Mail: eam29@cam.ac.uk

Munschauer, Mathias
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 3530
E-Mail: mathias.munschauer@mdc-berlin.de

Overall, Rupert
Augsburger Strasse 45
01309 Dresden
Germany
Fon: 0351 4634 0095
E-Mail: rupert.overall@crt-dresden.de

Pietzke, Matthias
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 3031
E-Mail: matthias.pietzke@ mdc-berlin.de

Polak, Paz
Ihnetsr 63
14195 Berlin
Germany
Fon: 0175 7587078
E-Mail: polak@ molgen.mpg.de

Pollok, Ilona
Augustenburger Platz 1
13353 Berlin
Germany
Fon: 030-450 553536
E-Mail: ilona.pollok@ charite.de

Purugganan, Michaela
29 Washington Square West
10011 New York
USA
Fon:
E-Mail:

Rajewsky, Nikolaus
Robert-Rössle-Strasse 10
13125 Berlin
Germany
Fon: 030-9406-2999
E-Mail: rajewsky@ mdc-berlin.de

Rätsch, Gunnar
Spemannstr. 39
72076 Tübingen
Germany
Fon:
E-Mail: Gunnar.Raetsch@ tuebingen.mpg.de

Reichenbach, Tobias
1230 York Avenue
10065 New York
U.S.A.
Fon: 001 212 327-8885
E-Mail: tobias.reichenbach@ rockefeller.edu

Reinert, Knut
Steinmetzstrasse 14
12207 Berlin
Germany
Fon: 030-8387 5222
E-Mail: knut.reinert@ fu-berlin.de

Rüschendorf, Franz
Robert-Rössle-Straße 10
13125 Berlin
Deutschland
Fon: 030-9406 3378
E-Mail: fruesch@ mdc-berlin.de

Rybak, Agnieszka
Robert-Rössle-Str. 10
13125 berlin
Germany
Fon: 030-9406 2973
E-Mail: agnieszka.rybak@ mdc-berlin.de

Saar, Kathrin
Robert-Rössle-Straße 10
13125 Berlin
Deutschland
Fon: 030-9406 3534
E-Mail: ksaar@ mdc-berlin.de

Sarov, Mihail
Pfotenhauerstrasse 108
01307 Dresden
Germany
Fon: 0351-210 2617
E-Mail: sarov@ mpi-cbg.de

Scheel, Tobias
Chariteplatz 1
10117 Berlin
Deutschland
Fon: 030-2846 0697
E-Mail: scheel@ drfz.de

Schmeck, Bernd
Augustenburger Platz 1
13353 Berlin
Germany
Fon: 030-450 553052
E-Mail: bernd.schmeck@ charite.de

Schulz, Christine
Augustenburger Platz 1
13353 Berlin
Germany
Fon:
E-Mail: christine.schulz@charite.de

Schulz, Herbert
Robert-Rössle-Straße 10
13125 Berlin
Deutschland
Fon: 030-9406 4384
E-Mail: heschulz@mdc-berlin.de

Small, Stephen
100 Washington Square East
10003 New York
USA
Fon: 001-212 998 8244
E-Mail: sjs1@nyu.edu

Somel, Mehmet
Yue Yang Lu 320
200031 Shanghai
China
Fon: +86-21-54920487
E-Mail: somel@eva.mpg.de

Stegle, Oliver
Spemannstrasse 38
72076 Tübingen
GERMANY
Fon: 07071-601 582
E-Mail:

Steinkötter, Jutta
Robert-Rössle-Str. 10
13125 Berlin-Buch
Germany
Fon: 030-9406 2990
E-Mail: jutta.steinkoetter@mdc-berlin.de

Thierfelder, Nadine
Robert-Rössle-Str. 10
13125 Berlin
Germany
Fon: 030-94062972
E-Mail: n.thierfelder@mdc-berlin.de

Tolle, Dominic
Robert-Rössle-Str. 10
13092 Berlin
Germany
Fon: 030-9406 4234
E-Mail: dominic.tolle@mdc-berlin.de

Valleriani, Angelo
Wissenschaftspark Golm
14424 Potsdam
Germany
Fon: 0331-5679616
E-Mail: valleriani@mpikg.mpg.de

Vasile, Alexandra
Robert-Rössle-Str. 10
13092 Berlin
Germany
Fon: 030-9406 3528
E-Mail: alexandra.vasile@mdc-berlin.de

Vasquez-Kool, Jorge
9101 Fayetteville Road
NC 27603 Raleigh
USA
Fon: 001-919 866 5641
E-Mail: jvasquezkool@waketech.edu

Vischi Winck, Flavia
Rostockerstraße 50
10553 Berlin
Germany
Fon: 030-3319772812
E-Mail: vischi@mpimp-golm.mpg.de

von Oertzen, Lena
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 2973
E-Mail: lena.oertzen@mdc-berlin.de

Wagner, Andreas
Winterthurerstrasse 190
8057 Zürich
Schweiz
Fon: +41 44 635 61 41
E-Mail: aw@bioc.uzh.ch

Wang, Yongbo
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 3043
E-Mail: yongbo.wang@mdc-berlin.de

Weese, David
Takustraße 9
14195 Berlin
Deutschland
Fon: 030-8387 5246
E-Mail: weese@inf.fu-berlin.de

You, Xintian
Robert-Rössle-Straße 10
13125 Berlin
Germany
Fon: 030-9406 3043
E-Mail: xintian.you@mdc-berlin.de

Wanker, Erich
Robert-Roessle-Strasse 10
13125 Berlin
Germany
Fon: 030-9406 2157
E-Mail: ewanker@mdc-berlin.de

Ruan, Yijun
60, BIOPOLIS STREET, #02-01 GENOME
138672 SINGAPORE
SINGAPORE
Fon: +65 6808 8073
E-Mail: ruanyj@gis.a-star.edu.sg