USSBE USGEB

Basel, March 2007

Dear USGEB / [BC]^2 participant,

Welcome to the joint USGEB / [BC]^2 conference !

The theme of this meeting, *"From Euler to Computational Biology: integrating mathematics into biological research*," was chosen in honor of the 300th anniversary of the birth of Leonhard Euler, one of Basel's most famous mathematicians. Euler, among other achievements in mathematics, was the first to analyse quantitatively the mortality and multiplication of the human species, publishing this in the mid-1700's.

Now 260 years later the interest in biology as a quantitative science is stronger than ever before, and with over 900 registered participants, we look forward to one of the largest meetings of Swiss scientists in the last 20 years. These two days in Basel are organized jointly by the Basel Computational Biology Conference ([BC]^2) and the Union of Swiss Societies of Experimental Biology (USSBE/ USGEB). While we are here to celebrate a great Basler mathematician, we are here as biologists, and each of the Swiss societies of experimental biology has had an opportunity to organize its own workshop along the theme of the meeting.

Although mathematics has long played a major role in select fields like structure biology or epidemiology, in this post-genomic era mathematical approaches take on unprecedented importance. In biomedical research we deal daily with large data sets from microarray or proteomic analyses, and we attempt through genetics and biochemistry to reconstruct complex living systems. Modelling and predictive algorithms have become important tools in biology, and render the integration of computational approaches essential to every one of us.

These recent developments have also led to the definition of a new discipline called Systems' biology, and Basel is proud to welcome the newly established ETH Department of Biosystems Science and Engineering, led by Renato Paro. In this joint Zürich-Basel effort, we look forward to a new blend of engineering and biology, which will reinforce Basel's existing interests in Nanotechnology and Nanoimaging.

For this year's USGEB/[BC]^2 meeting we welcome as speakers leading biomedical scientists, primarily biologists, who have effectively integrated mathematics into their research. In this same spirit, and on behalf of the organizing committee, I welcome all of you to the lovely city of Basel, and wish you enlightenment as well as a good time.

Susan Gasser, Director of the FMI

Acknowledgements

The Steering Committee of this year's joint [BC]^2/USGEB meeting was as follows:

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We greatly appreciate the dedicated support and invaluable contributions of:

Gabi Gruber	Friedrich Miescher Institute, Basel
Dagmar Baroke	Friedrich Miescher Institute, Basel
Isabella Bogdal	Friedrich Miescher Institute, Basel
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as well as the dedicated help of numerous student volunteers.

We express our gratitude to

Prof. Dr. Hanspeter Kraft, Mathematisches Institut der Universität Basel (Hanspeter.Kraft@unibas.ch) **for his contribution on the Life of Euler**.

Prof. Dr. Antonio Loprieno, Rektor der Universität Basel, **for his welcome address.**

Finally we thank the workshop organizers for assembling interesting speakers for their parts of the programme, as well as the many commercial exhibitors for their presence. We are particularly endebted for financial support to the sponsors listed on the following page.

We thank these sponsoring companies and institutions for supporting this USGEB/[BC]^2 Meeting

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List of Exhibitors

Standn-/Boothno.

Exhibition Layout

Schweizerische Gesellschaft für Biochemie

SWISS SOCIETY FOR BIOCHEMISTRY

Société Suisse de Biochimie

The Swiss Society of Biochemistry has the pleasure to announce the laureate of

THE 2007 FRIEDRICH MIESCHER AWARD

as

Dr DIRK SCHUBELER

Friedrich Miescher Institute for Biomedical Research

For his groundbreaking work in epigenetics on genome-wide analysis of chromatin and DNA modifications

The award will be presented at 16h on Tuesday, March 13, 2007, in the salle Montreal/Singapore. It is followed by the laureate's presentation entitled,

"Genome-wide maps of DNA methylation in mammals"

The FMA award is awarded each year to an outstanding scientist under 40 who is either Swiss or completed a major portion of their prize-winning work within Switzerland. The selection board is composed by the Swiss Society for Biochemistry and includes representatives from the major Swiss research institutes. Nominations should be sent to: Dr Frédéric Lévy at Frederic.Levy@isrec.unil.ch

PROGRAM

Tuesday, 13th March

08.30 Welcome Coffee

08.40 - 09.10 Introductory Remarks
08.40 - Susan M. Gasser, Chair of the Organizing Committee, Director FMI
08.45 - Antonio Loprieno, Rector of the University of Basel
08.50 - Hans-Peter Kraft, Mathematical Institute, University of Basel
The Life of Euler

09.10 - 10.30 Plenary Session 1: Room Montreal/Singapore
Network Theory and Cellular networks

09.10 – 09.50 **Rainer Friedrich**
Friedrich Miescher Institute, Basel, Switzerland
Processing of olfactory information by neuronal circuits in the zebrafish brain

09.50 – 10.30 **Hiroaki Kitano**
The Systems Biology Institute, Tokyo, Japan
Network robustness and drug design

10.30 - 11.00 Coffee Break, Commercial Exhibition

11.00 - 13.00 Workshops 1 – 4 (see speaker lists on pages 12-13)

WS 1 **Potassium channels: molecular biology, pathophysiology, and computational aspects**
Organizer: A. Bärtschi (Swiss Physiology Soc.)
Room: Sydney

WS 2 **Computational Biology**
Organizers: T. Schwede & M.Peitsch (Basel Computational Biology Conference)
Room: Montreal

WS 3 **Stem cells and cancer**
Organizers: H. Walt & G. Christofori (Swiss Soc. for Oncology)
Room: Singapore

WS 4 **Statistics in animal research**
Organizers: W. Zeller & B. Riederer (Swiss Laboratory Animal Science Association)
Room: Rio

13.00 – 13.30 Society Meeting of the Swiss Society for Biochemistry
Room: Rio

13.00 - 14.30 Lunch, Poster session (#1 – #71) and Commercial exhibition

14.30 - 16.00 **Plenary Session 2:** **Room Montreal/Singapore**
Proteomics and genomics

14.30 – 15.15 **Matthias Mann**
Max Planck Institute for Biochemistry, Martinsried, Germany
Quantitative proteomics and phosphoproteomics as a basis for systems biology

15.15 – 16.00 **Renato Paro**
ETH Dept of Biosystems Science and Engineering (BSSE), Basel, Switzerland
Epigenetic networks and transdifferentiation

16.00 - 16.30 Friedrich Miescher Award presentation **Room Montreal/Singapore**

Talk by the 2007 laureate**, Dirk Schübeler**, Friedrich Miescher Institute
Genome-wide maps of DNA methylation in mammals

16.30 - 17.00 Coffee break (Poster Session and commercial exhibition)

17.00 - 18.30 **Plenary Session 3** **Room Montreal/Singapore**

17.00 – 17.45 **Denis Noble**
Oxford University, Oxford, UK
Modeling the heart

17.45 – 18.30 **Svante Pääbo**
Max Planck-Institute for Evolutionary Anthropology, Leipzig, Germany
A genomic view of human origins

21.00 Social Event - Jazz music evening

Volkshaus, Rebgasse 12.
Entry for USGEB/$[BC]^2$ participants only

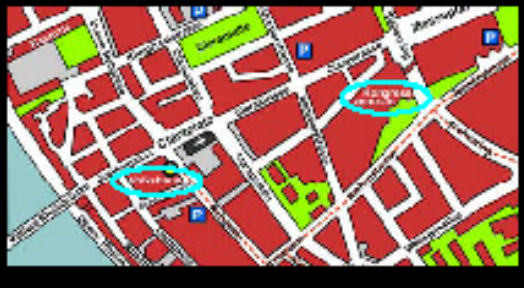
JAZZ EVENING

Tuesday March 13th, 21:00 h

A moment to relax and have a drink.
Meet friends and colleagues
after a day full of talks
and posters.

David Klein – Urs Bachthaler
Quartett

Volkshaus (Grosser Saal)
Rebgasse 12
(a 10 min. stroll from the Congress Center
or take Tram 6 to Claraplatz, 2nd stop)



Workshop Program Day 1 (March 13)

11.00 - 13.00 Workshops 1 - 4

WS 1 Potassium channels: molecular biology, pathophysiology, and computational aspects
Room: Sydney

11.00 – 11.05	**Alex J. Baertschi,** CMU, University of Geneva, Switzerland *Introduction*
11.05 – 11.35	**Ivet Bahar,** School of Medicine, University of Pittsburgh, USA *Gating mechanisms in membrane protein: computational study of the dynamics of potassium channels and glutamate transporters*
11.35 – 12.00	**Richard Warth,** University of Regensburg, Germany *Pathophysiology of epithelial potassium channels in the gastrointestinal tract*
12.00 – 12.20	**Hugues Abriel,** University of Lausanne *IKCNQ1 potassium channel is down-regulated by ubiquitylating enzymes of the Nedd4/Nedd4-like family*
12.20 – 12.45	**Marcus C. Schaub,** University of Zurich, Switzerland *Role of cardiac KATP channels in calcium handling and metabolism*
12.45 – 13.00	General Discussion and Conclusion

WS 2 Computational Biology:
Room: Montreal

11.00 – 11.40	**David Harel,** Weizmann Institute of Science, Rehovot, Israel *In Silico Biology, or On Comprehensive and Realistic Modeling*
11.40 – 12.20	**Shalev Itzkovitz,** Weizmann Institute of Science, Rehovot, Israel *Using genomic variability to reconstruct cell lineage*
12.20 – 13.00	**Alfio Quarteroni,** EPFL, Lausanne, Switzerland *On the mathematical modeling of the human cardiovascular system*
13.00 – 13.10	**Christian von Mering,** University of Zurich, Switzerland *Phylogenetic Assessment of microbial communities through environmental sequencE data*
13.10 – 13.20	**Sven Bergmann,** SIB & University of Lausanne, Switzerland *Pre-steady-sState deconding of the bicoid morphogen gradient*
13.20 – 13.30	**Marco Scarsi,** SIB & Biozentrum University of Basel, Switzerland *A Combined Virtual Screening and Biological Assay Approach*

WS 3 Stem cells and cancer:
Room: Singapore

11.00 – 11.15	**Stephen Ryser,** Geneva University Hospital, Switzerland *Defining the niche of male germinal stem cell in new born rat by* expression profiling
11.15 – 11.40	**Neil J. Harrison,** University of Sheffield, UK *Culture adaptation of embryonic stem cells: models for germ cell tumour progression*
11.40 – 12.05	**Cathrin Brisken,** ISREC, Lausanne, Switzerland *Hormones and paracrine signaling in breast development and breast cancer*
12.05 – 12.20	**Martin Buess,** University of Basel, Switzerland *In vitro analysis of heterotypic cell-cell interaction effects to identify the contribution of tumor-stroma interaction on global gene expression profiles in breast cancer*
12.20 – 12.45	**Andreas Trumpp,** ISREC, Lausanne, Switzerland *Cooperative control of hematopoietic stem cell function by c-Myc and N-Myc.*
12.45 – 13.00	**Damaris Bausch-Fluck,** Swiss Federal Institute of Technology (ETH) Zurich, Switzerland *Cell Surface Capturing as a method of choice for the identification and quantification of relevant plasma membrane antigens of cancer stem cells.*

WS 4 Statistics in animal research
Room: Rio

11.00 – 11.45	**Michael F.W. Festing,** NC3Rs, London, UK *We need to improve the design and statistical analysis of animal experiments.*
11.45 – 12.05	**Robert Greif,** Inselspital Bern, Switzerland *Missing data: what can I do with it?*
12.05 – 12.25	**Javier Fandino,** Inselspital Bern, Switzerland *So what? How do I define relevant outcome parameters in experimental research?*
12.25 – 12.45	**Eva Waiblinger,** Tierversuchskommission Basel, Universität Zürich, Switzerland *Statistics and relevance – How can I convince the local animal welfare committee?*
12.45 - 13.00	Discussion

USGEB ‘08

Next year’s USGEB Meeting will take place in Lausanne, 7 – 9 February 2008

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Wednesday, 14th March

08.30 - 10.00 **Plenary Session 4:** **Room Montreal/Singapore**
Tropical disease and epidemiology

08.30 – 09.15 **Alan Cowman**
The Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia
Antigenic variation and gene silencing in the malaria parasite

09.15 – 10.00 **Klaus Dietz**
University of Tübingen, Germany
Mathematical epidemiology

10.00 - 10.30 Coffee Break

10.30 - 12.30 **Workshops 5 – 7 (see speaker lists on pp 17-18)**

WS 5 **Small RNAs**
Organizers: W. Filipowicz, M. Zavolan (Swiss Soc of Biochemistry)
Room: Sydney

WS 6 **Imaging and image analysis**
Organizers: B. Riederer, T. Vetter (Swiss Soc for Anatomy and Histology)
Room: Rio

WS 7 **Infectious Diseases**
Organizers: S. Bonhoeffer, G. Cornelis
Room: Singapore

12.30 - 13.30 **Lunch & Poster Session** (#72 – #148)

12.30 - 14.00 **Meeting of the Swiss Society for Cell- and Molecular Biology & Genetics (ZMG)** Room: Rio

13.30 - 15.00 **Plenary Session 5** **Room Montreal/Singapore**
Organs and development

13.30 – 14.15 **Olivier Pourquié**
Stowers Institute for Medical Research, Kansas City, USA
Segmental patterning in vertebrate development

14.15 – 15.00 **Eddy DeRobertis**
HHMI University of California, Los Angeles, USA
Self-regulation of embryonic pattern in Xenopus embryos

15.00 - 15.30 Coffee Break (Poster removal)

15.30 - 17.30 **Workshops 8 – 11 (see speaker lists on pp. 18-19)**

WS 8 **Cells to Organs**
Organizers: M. Affolter, P.Matthias, R. Zeller (Swiss Soc. ZMG)
Room: Singapore

WS 9 **Novel approaches in anti-inflammatory drug therapy**
Organizer: H.U. Simon, A. Huwiler (Swiss Soc. of Pharmacology and Toxicology)
Room: Montreal

WS 10 **Computation in heart disease**
Organizers: G. Soldati, T. Moccetti, A. Conti (ASIRB)
Room: Rio

WS 11 **From stem cells to trees**
Organizer: W. Gruissem & C. Kuhlemeier (Swiss Soc. for Plant Physiology)
Room: Sydney

~ 18.00 End of meeting

Please remove your posters by the end of the meeting.

Workshop Program Day 2 (March 14)

10.30 - 12.30 Workshops 5 - 7

WS 5 Small RNAs
Room: Sydney

10.30 – 11.00	**Mihaela Zavolan,** Biozentrum University of Basel, Switzerland *Computational prediction of ncRNA genes and targets*
11.00 – 11.30	**Elisa Izaurralde,** Max Planck-Institute for Developmental Biology, Tübingen, Germany *Mechanisms of miRNA-mediated gene silencing*
11.30 – 11.45	**Xavier Ding,** Friedrich Miescher Institute, Basel Switzerland *Let-7 microRNA mode of action in vivo: translational effect and role of eif-3*
11.45 – 12.15	**Markus Stoffel,** Institute for Molecular Systems Biology, ETH Zurich, Switzerland *Approaches to study miRNA function in mammals*
12.15 – 12.30	**Jurgi Camblong,** University of Geneva, Switzerland *Anti-sense RNA stabilization in S. cerevisiae induces gene silencing by Hda1/2/3 histone deacetylase complex*

WS 6 Imaging and image analysis
Room: Rio

10.30 – 11.00	**Thomas Vetter,** University of Basel, Switzerland *Statistical shape models for the analysis of human morphology*
11.00 – 11.30	**Jean-Yves Chatton,** University of Lausanne, Switzerland *Image analysis and processing for quantitative cellular imaging*
11.30 – 12.00	**Graham Knott,** University of Lausanne, Switzerland *Exploring brain circuits with serial section electron microscopy; current technology and future directions*
12.00 – 12.15	**Matthias Ochs,** University of Bern, Switzerland *Quantitation of lung structure by stereology: Leonhard Euler and the number of alveoli*
12.15 – 12.30	**Tilman Vogt,** University of Fribourg, Switzerland *The three dimensional reconstruction of motor endplates of the vertebrate skeletal muscle fibres.*

WS 7 Infectious Diseases
Room: Singapore

10.30 – 10.50	**Isabel Sorg,** Biozentrum University of Basel, Switzerland *The Yersinia basal body protein YscU plays a role in recognition of Type III export*
10.50 – 11.10	**Nicolas Maire,** Swiss Tropical Institute, Basel, Switzerland *Stochastic simulation of Malaria epidemiology and control*
11.10 – 11.30	**Laurence Neff,** Geneva University Hospital, Switzerland *Molecular characterization and subcellular localization of macrophage infectivity potentiator, a Chlamydia trachomatis lipoprotein*
11.30 – 11.50	**Christian L. Althaus,** Utrecht University, The Netherlands *Modeling CTL evasion during SIV/HIV infection. Is there a great escape?*

11.50 – 12.10 **Sabine Kuettel,** University of Geneva, Switzerland
Adenosine kinase and glyceraldehyde-3-phosphate dehydrogenase identified as putative CD12001 target(S) in Trypanosoma brucei rhodesiense

12.10 – 12.30 **Christian J. Burckhardt,** Institute of Zoology, University of Zürich, Zürich, Switzerland,
Computational dissection of adenovirus cell surface motion reveals receptor mediated virus drifting on filopodia

15.30 - 17.30 Workshops 8 - 11

WS 8 Cells to Organs
Room: Singapore

15.30 – 16.00 **Lilianna Solnica-Krezel,** Vanderbilt University, Nashville, USA
Apelin and its Receptor Control Heart Field Formation during Zebrafish Gastrulation

16.00 – 16.30 **Bernhard Herrmann,** Max-Planck-Institute for Molecular Genetics, Berlin, Germany
Towards systems biology of organogenesis: deciphering regulatory networks controlling mesoderm development in the mouse

16.30 – 17.00 **Andy McMahon,** Harvard University, Cambridge, MA, USA
From precursor to product: organogenesis of the mammalian kidney.

17.00 – 17.15 **Anne Grapin-Botton,** ISREC/EPFL, Epalinges/Lausanne, Switzerland
Waves of endocrine-cell differentiation in the pancreas

17.15 – 17.30 **Johannes Jaeger,** University of Cambridge, UK
Dynamics control of positional information by the Drosophila gap gene network

WS 9 Novel approaches in anti-inflammatory drug therapy
Room: Montreal

15.30 – 16.00 **Peter Mertens,** University of Aachen, Germany
From inflammation to fibrosis: the Y-box protein-1 as extracellular mediator of fibrogenesis

16.00 – 16.30 **Jürgen Stein,** University Hospital Frankfurt am Main, Germany
Anti-inflammatory mechanisms of histone deacetylase inhibitors

16.30 – 16.45 **Bruno Schnyder,** CNRS, Molecular Immunology and Embryology, Orléans, France
Interleukin-17 is a negative regulator of established allergic asthma

16.45 – 17.00 **Frauke Döll,** University of Bern, Switzerland
Hypoxia regulates the sphingosine kinase-1 activity and expression in the endothelial cell line EA.hy926

17.00 – 17.30 **Josef Pfeilschifter,** University of Frankfurt am Main, Germany
Sphingolipid signaling in inflammation

WS 10 Computation in heart disease
Room Rio

15.30 – 15.50	**General Electrics speaker** *Innovative technology in heart disease*
15.55 – 16.15	**Francesco Faletra** *New approaches in learning cardiac anatomy*
16.20 – 16.40	**Giovanni Pedrazzini** *Cardiac plaque imaging*
16.45 – 17.05	**Stefanos Demertzis** *From Leonardo da Vinci to the operating room via computational simulation: surgical reconstruction of the aortic root*
17.10 – 17.30	**short talks to be assigned**

WS 11 From stem cells to trees
Room: Sydney

15.30 – 16.00	**Henrik Jönsson,** Lund University, Sweden *Computational modelling and live imaging of plant development*
16.00 – 16.30	**Cris Kuhlemeier,** University of Bern, Switzerland *Mathematical models of phyllotaxis*
16.30 – 17.00	**Philipp Zimmermann,** ETH Zürich, Switzerland *Studying transcriptomes using gene and condition meta-profiles*
17.00 – 17.30	**Christian Körner,** University of Basel, Switzerland *From assimilation to growth: carbon limitation in plants*

Speakers Abstracts (Plenary)

Processing of olfactory information by neuronal circuits in the zebrafish brain
Rainer W. Friedrich

Friedrich-Miescher-Institut, Maulbeerstr. 66, 4058 Basel, Switzerland
Rainer.Friedrich@fmi.ch

Although many neurobiological questions concerned with brain function clearly fall within the realm of systems biology, systems neuroscience has not undergone the same rapid development as other biological disciplines in recent years. The reasons for this include technical limitations, the sheer complexity of the brain, and the fact that laws of mass action can often not be applied appropriately to neuronal circuits. To try and overcome these problems, we use a numerically simple vertebrate, the zebrafish, as a model system and established techniques to record spatio-temporal activity patterns across thousands of neurons in the intact brain. Our recent work has been concerned with understanding the function of the olfactory bulb, the first processing center of odor information in the vertebrate brain. The olfactory bulb receives spatially distributed patterns of input activity from sensory neurons in the nose. A comparison of these input patterns with spatio-temporal patterns of output activity revealed that neuronal circuits within the olfactory bulb transform neuronal activity patterns and thereby perform several computations. For example, overlapping patterns of sensory input evoked by structurally similar odorants become decorrelated at the level of olfactory bulb output. This decorrelation enhances the discriminability of sensory stimuli and is a fundamental operation also for other operations and sensory systems. This and other computations were reproduced in realistic computer models that serve as the starting point for the extraction of functional principles by mathematical approaches. This combination of neurophysiological and computational approaches demonstrated that pattern decorrelation can arise from relatively basic features of neuronal circuits consistent with the synaptic architecture of the olfactory bulb.

Network, Robustness and Drug Design
Hiroaki Kitano

The Systems Biology Institute, Tokyo, Japan

Many potential drugs that specifically target a particular protein considered to underline a given disease have been found to be less effective than hoped, or to cause significant side effects. The intrinsic robustness of living systems against various perturbations is a key factor that prevents such compounds from being successful. By studying complex network systems and reformulating control and communication theories that are well established in engineering, a theoretical foundation for a systems-oriented approach to more effectively control the robustness of living systems, particularly at the cellular level, could be developed. Here, I use examples that are based on existing drugs to illustrate the concept of robustness, and then discuss how a greater consideration of the importance of robustness could influence the design of new drugs that will be intended to control complex systems.

Quantitative proteomics and phosphoproteomics as a basis for systems biology

Jesper V. Olsen, Cuiping Pan, Gustavo de Souza, Yanling Zhang, Yong Zhang, Michiel Vermeulen, Tiziana Bonaldi, Jürgen Cox, **Matthias Mann**

Dept. Proteomics and Signal Transduction; Max-Planck Institute for Biochemistry, Am Klopferspitz 18, D-82152 Martinsried; www.biochem.mpg.de/mann

The capabilities of mass spectrometry (MS)-based proteomics have been increasing at an impressive and undiminished pace for the last many years. Here I will summarize the latest technological advances and provide an overview of work being carried out in our group in cell signaling and interaction proteomics.
In cell signaling, we have used the Stable Isotope Labeling by Amino acids in Cell culture (SILAC) technology to quantitatively follow changes in the phosphoproteome at a level of many thousands of phosphopeptides (Olsen et al. Cell, 2006; www.phosida.com). We have now extended the approach to compare disparate signaling pathways and also quantitate differential protein expression changes upon stimulus. It appears that significant parts of signaling networks are shared even for quite distinct stimuli. SILAC-based phosphoproteomics can also be used to 'read out' changes to signaling networks upon treatment with kinase inhibitors, a major class of drugs in the pharmaceutical industry. These experiments show that inhibitors often have effects in other parts of the network - and even upstream - of the intended target.
Quantitative proteomics is a elegant tool in 'interaction proteomics'. This will be illustrated with examples from 'epigenetics', in which we identify interaction partners of modified histones. While histone modifications have been fruitful area for MS-based proteomics for some time, we show here that the function of these modifications – i.e. the identity of recruited proteins – can be deduced by proteomics as well.

Epigenetic networks and cellular reprogramming

Renato Paro*, Tomonori Katsuyama*, Christian Beisel*, Arne Hauenschild[+], Marc Rehmsmeier[+] and Leonie Ringrose[#]

*D-BSSE, ETH Zurich, 4058 Basel, Switzerland, [+]CeBiTec, Bielefeld University, 33594 Bielefeld, Germany, [#]IMBA, 1030 Vienna, Austria.

Mechanisms of transcriptional memory are required to maintain the differential expression patterns of regulatory genes defining specific cell lineages. This ensures that during proliferation cellular programs are faithfully and heritably transmitted. As transcription programs become stabilized in determined cells by a progressive patterning of chromatin structures, cells lose their plasticity and the ability to freely modify their identity in response to changing developmental cues. In contrast, stem cells maintain this flexibility allowing them to follow different determination pathways. Imaginal discs of Drosophila larvae provide an excellent model system to study maintenance of cell determination prior to the differentiation process. *In vivo* transplantation experiments indicated that imaginal discs are capable of maintaining their determined state over many cell generations in a stem cell-like manner. Fragmented discs are capable to properly regenerate structures upon cultivation in the hemolymph of flies. However, occasionally disc cells loose memory and change their fate, a phenomenon termed „transdetermination".
Proteins of the Polycomb (PcG) and Trithorax (TrxG) groups play a major role in the epigenetic maintenance of gene expression patterns. PcG proteins maintain target genes permanently silence by generating repressed chromatin domains. Conversely, the proteins of the TrxG counteract PcG-repressive chromatin structures, thus, maintaining the genes active. We found that regeneration and transdetermination events are coupled to PcG regulation. PcG function is down-regulated by the Jun N-terminal kinase (JNK) signaling pathway, which is activated in cells undergoing regeneration. Activation of the JNK pathway

is sufficient to reduce PcG gene transcription, and impairing the JNK pathway reduces transdetermination efficiency. However, JNK activation merely potentiates reactivation of previously silenced PcG target genes, and in addition environmental stimuli, like locally restricted signaling networks, are mandatory to revert the epigenetic restrictions that maintain cellular memory. Indeed, we can demonstrate that local activation of the JNK pathway results in a spatially distinct reactivation of PcG target genes.
PcG and TrxG proteins bind differentially to cis-regulatory elements called Polycomb Response Elements (PREs) as we can show in detail in the homeotic clusters using genomic ChIP-on-Chip analyses. Based on the occurrence of specific sequence motifs, we developed an algorithm to identify PREs on a genome-wide scale. The availability of other *Drosophila* genomes now enables a comparative analysis, offering insights into the evolution of PREs. Here we present a comparative analysis of PREs in chosen *Drosophila* species which shows that PRE evolution is extraordinarily dynamic. Using an interdisciplinary combination of computational prediction and experimental verification, we document three kinds of evolutionary plasticity. First, the numbers of predicted PREs differ dramatically between species. This prediction is consistent with cytologically mapped numbers of binding sites. Secondly, sequences homologous to PREs in one species lack PRE features in the other, suggesting that they have lost (or never acquired) PRE functionality. Instead, we can detect PREs in nonhomologous regions nearby that may be functionally analogous. We validated the evolutionary gain and loss of PRE functionality with chromatin immunoprecipitation in both *D. melanogaster* and *D. pseudoobscura.* As a third type of evolutionary plasticity we demonstrate that the motif occurrence in analogous pairs of experimentally validated PREs is independent of sequence conservation. Our analysis indicates that number, position and design of PREs changes rapidly in evolution and suggest that evolutionary changes in the PREs might constitute a rich source of phenotypic diversity.

Modelling the Heart
Denis Noble

University of Oxford, Oxford UK

Biological modelling of cells, organs and systems has reached a very significant stage of development. Particularly at the cellular level, there has been a long period of iteration between simulation and experiment. We have therefore achieved the levels of detail and accuracy that are required for the effective use of models in drug development, in toxicology and in drug development. To be useful in this way, biological models must reach down to the level of proteins (receptors, transporters, enzymes etc) and genes, and they must also reconstruct functionality right up to the levels of organs and systems. I will illustrate these principles with reference to models of the heart and their use in understanding QT prolongation and arrhythmia (Noble, 2002, Noble, 2004, Noble & Noble, 2006). Modelling of the heart at many levels (Crampin et al., 2004) is a good example of the principles of Systems Biology (Noble, 2006).

Crampin, E.J., Halstead, M., Hunter, P.J., Nielsen, P., Noble, D., Smith, N. & Tawhai, M. (2004) Computational Physiology and the Physiome Project, *Experimental Physiology*, 89(1), pp. 1-26.
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Noble, D. (2004) Modeling the Heart, *Physiology*, 19, pp. 191-197.
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A Genomic View of Human Origins
Svante Pääbo

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One approach to understanding what makes humans unique as a species is to perform structural and functional comparisons between the genomes of humans and our closest evolutionary relatives the great apes. Recently, the draft sequences of the chimpanzee and rhesus macaque genomes have opened up new possibilities in this area. I will discuss work that compares functional and structural aspects of the human and ape genomes. I will also discuss the suggestion that a genome-wide analysis of the Neandertal genome would substantially enhance our ability to identify genes that have been of importance during human evolution.

Antigenic variation and gene silencing in the malaria parasite *Plasmodium falciparum*
Alan F. Cowman, Till Voss, Allison Marti, Julie Healer and Brendan Crabb

The Walter & Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia

It has been over a hundred years since the discovery that malaria, a scourge of humanity since antiquity, is caused by infection with the protozoan parasite *Plasmodium*. In humans the most severe form of malaria is caused by *Plasmodium falciparum* and at least a third of the world's population is at risk of infection, with over three hundred million people developing clinical disease each year and at least two million deaths. Virulence, immune avoidance and persistence of *P.falciparum* are underpinned by the expression of variant forms of an immunodominant surface protein termed PfEMP1. The *P. falciparum* genome encodes 60 members of this family but only one member is expressed in any one parasite, a process known as allelic exclusion. It is now recognized that transcriptional regulation of PfEMP1 genes, known as *var* genes, is epigenetic and involves heterochromatic silencing of most family members. Activation of a *var* gene appears to involve physical re-positioning of a locus into a particular site at the nuclear periphery that is permissive for transcription. This site is likely to be a central component of the allelic exclusion program. The nature of this site and/or of proteins responsible for allelic exclusion remain to be defined and is the subject of our current investigations. Additionally, analysis of the sequences required for *var* gene silencing and monoallelic expression has provided important new insights into the regulation of antigenic variation in this important human pathogen.

Mathematical Epidemiology
Klaus Dietz

Department of Medical Biometry, University of Tübingen, Germany

The first application of mathematics to the epidemiology of infectious diseases is due to Daniel Bernoulli in 1760. In the same year Leonhard Euler published his general investigation into the mortality and multiplication of the human species. After a brief historic introduction into mathematical epidemiology a survey will be given of major results. The World Health Organisation launched global eradication programs for malaria (1955), smallpox (1967) and polio (1988). The mathematical contributions to each of these programs will be discussed. In recent years intensive modelling activities are devoted to actual or potential emerging infectious diseases like vCJD or pandemic influenza.

Segmental patterning in vertebrate development
Olivier Pourquié

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The vertebrate body can be subdivided along the antero-posterior (AP) axis into repeated structures called segments. This periodic pattern is established during embryogenesis by the somitogenesis process. Somites are generated in a rhythmic fashion from the paraxial mesoderm and subsequently differentiate to give rise to the vertebrae and skeletal muscles of the body. Somite formation involves an oscillator-the segmentation clock-whose periodic signal is converted into the periodic array of somite boundaries. This clock drives the dynamic expression of cyclic genes in the presomitic mesoderm and requires Notch and Wnt signaling. Microarray studies of the mouse presomitic mesoderm transcriptome reveal that the segmentation clock drives the periodic expression of a large network of cyclic genes involved in cell signaling. Mutually exclusive activation of the Notch/FGF and Wnt pathways during each cycle suggests that coordinated regulation of these three pathways underlies the clock oscillator. Whereas the segmentation clock is thought to set the pace of vertebrate segmentation, the translation of this pulsation into the reiterated arrangement of segment boundaries along the AP axis involves FGF and Wnt signaling. The FGF pathway controls the positioning of the wavefront, which corresponds to the level of the presomitic mesoderm where cells respond to the clock. *fgf8* mRNA is only transcribed in tail bud precursors and it progressively decays in newly formed paraxial mesoderm cells, thus forming a dynamic mRNA gradient. This mRNA gradient is then translated into a graded FGF signaling response used to position the wavefront. This mechanism provides an efficient means to couple the spatio-temporal activation of segmentation to the posterior elongation of the embryo.

Self-regulation of embryonic patterns in *Xenopus* embryos
Eddy M. De Robertis and Jean-Louis Plouhinec

Howard Hughes Medical Institute and University of California, Los Angeles, CA, USA

How do cells at opposite ends of the embryo communicate with each other? We found that dorsal and ventral BMP signals and their extracellular antagonists, expressed under opposing transcriptional regulation, provide a molecular mechanism for embryonic self-regulation. Quadruple knockdown of ADMP and BMP2/4/7 in *Xenopus* embryos caused ubiquitous neural induction throughout the ectoderm. ADMP and Chordin transcription in the Spemann organizer is activated at low BMP levels. When ventral BMP2/4/7 signals are depleted, *Admp* expression increases, allowing for self-regulation. ADMP has BMP-like activity but is unable to signal dorsally because of inhibition by Chordin. Ventrally, high BMP signalling increases transcription of the BMP antagonists Crossveinless-2, Bambi and Sizzled. We are developing an Electronic Frog model to analyze how this network of extracellular proteins works. The model has a single output, the levels of phosphorylation of Smad1 by BMPR. Mathematical modeling provides insights that are not possible by intuition alone.

There are multiple molecular pathways that must be integrated so that a perfect embryonic patter can be generated. We will discuss how three major signaling pathways BMPR, MAPK/RTK and GSK3/Wnt are integrated at the level of the phosphorylation of the Smad 1 transcription factor.

De Robertis, E.M. (2006). Spemann's organizer and self-regulation in amphibian embryos. Nature Reviews Molecular Cell Biology *7*, 296-302.

Speakers Abstracts (Workshops)

Workshop 1 – Potassium channels: molecular biology, pathophysiology, and computational aspects

Room: Sydney

WS1-1

Gating mechanisms in membrane proteins: computational study of the dynamics of potassium channels and glutamate transporters

I. Shrivastava,[1] S. Amara[2] and I. Bahar[1], Departments of Computational Biology[1] and Neurobiology[2], School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, USA.

Membrane proteins play a significant role in a large number of regulatory processes, including the regulation of electro-chemical potential gradients across the cell membrane in potassium channels, or regulating the levels of neurotransmitters at excitatory synapses in glutamate transporters. Despite the critical role of membrane proteins in several microphysiological events and the implication of their dysfunction in several diseases, a molecular understanding of the conformational mechanisms that underlie their biological functions remains to be elusive in many cases, due to the scarcity of structural information on membrane proteins. We have recently examined the dynamics of two groups of membrane proteins, potassium channels and glutamate transporters, using the recently determined structures of these proteins. Computational studies conducted with multiscale models elucidate a wide range of molecular events, occurring at different time scales, which shed light into the intrinsic ability of the proteins to perform their biological function. This ability is directly conferred by the 3-dimensional structure, which is also suggested to result from evolutionary pressure. Potassium channels share a common ion gating mechanism; glutamate transporters also exhibit structure-encoded mechanisms of glutamate binding mediated by the fast motions of helical hairpins. The mechanisms of gate opening elucidated by these different structures provide insights on possible molecular methods for controlling the functional channeling of substrates.

WS1-2

Pathophysiology of epithelial potassium channels in the gastro-intestinal tract

Richard Warth, Institute of Physiology, Regensburg, Germany

Potassium channels are expressed in practically all living cells where they stabilize cell volume and membrane voltage thereby creating the driving force for electrogenic transport processes. From the 75 pore-forming potassium channel genes found in the human genome, some 40-50 are expressed in the epithelial cells of the gastro-intestinal tract allowing adaptation of the cellular function to different needs.

In the stomach, K+ channels play an important role for secretion of gastric acid by parietal cells and probably also for secretion of bicarbonate-rich mucus in surface cells. In parietal cells inactivation of luminal KCNQ1/KCNE2 channels diminishes luminal K+ recycling and thus blocks H+/K+-ATPase activity.

In villus cells of the small intestine, K+ channels are coupled to transport activity during the reabsorption of nutrients. In crypt cells, basolateral K+ channels are a prerequisite for luminal Cl- secretion. In secretory diarrhea, inhibition of basolateral K+ channels could offer a new perspective for the treatment of life-threatening dehydration.

In large intestine, regulated excretion of K+ via luminal K+ channels serves the body K+ homeostasis. Moreover, there is growing evidence for significant changes in K+ channel expression during cell proliferation and cancerogenesis. In the future, investigation of K+ channels in native tissues, their subunit compositions and molecular interactions will form the basis for a better understanding of the physiological relevance and possible clinical implications of epithelial K+ channels.

WS1-3
KCNQ1 potassium channel is down regulated by ubiquitylating enzymes of the NEDD4/NEDD4-like family

Thomas Jespersen[1], Mathieu Membrez[1], Céline Nicolas[2], Bruno Pitard[2], Olivier Staub[1], Søren-Peter Olesen[3], Isabelle Baró[2], and Hugues Abriel[1,4], [1] Department of Pharmacology and Toxicology, University of Lausanne, Switzerland, [2] Inserm, UMR 533, l'institut du thorax, Université de Nantes, Nantes, France, [3] The Danish National Research Foundation Center for Cardiac Arrhythmia, University of Copenhagen, Denmark.[4] Service of Cardiology, CHUV, Lausanne, Switzerland

Background- KCNQ1 potassium channel regulates key physiological functions in a number of tissues. In the heart, KCNQ1 α-subunits assemble with KCNE1 β-subunits forming a channel complex constituting the delayed rectifier current I_{Ks}. In epithelia, KCNQ1 channels participate in controlling body electrolyte homeostasis. Several regulatory mechanisms of the KCNQ1 channel complexes have been reported. However, the mechanisms controlling the membrane density of KCNQ1 channels have attracted less attention.
Methods and Results **-** Here we demonstrate that KCNQ1 expressed in HEK293 cells is down-regulated by Nedd4/Nedd4-like ubiquitin-protein ligases. KCNQ1 and KCNQ1/KCNE1 currents were reduced upon co-expression of Nedd4-2, the isoform among the nine members of the Nedd4/Nedd4-like family displaying the highest expression level in human heart. *In vivo* expression of a catalytically inactive form of Nedd4-2, able to antagonize endogenous Nedd4-2 in guinea-pig cardiomyocytes, increased I_{Ks} significantly, but did not modify I_{K1}. Concomitant with the reduction in current induced by Nedd4-2, an increased ubiquitylation as well as a decreased total level of KCNQ1 proteins were observed in HEK293 cells. Pull-down and co-immunoprecipitation experiments showed that Nedd4-2 interacts with the C-terminal part of KCNQ1. The Nedd4/Nedd4-like-mediated regulation of the KCNQ1 channel complexes was shown to be strictly dependent on a PY motif located in the distal part of the C-terminal domain
Conclusions - These results suggest that KCNQ1 internalization and stability is physiologically regulated by its Nedd4/Nedd4-like-dependent ubiquitylation. This mechanism may thereby be important in regulating the surface density of the KCNQ1 channels in cardiomyocytes and other cell types.

WS1-4
Role of cardiac K(ATP) channels in calcium handling and metabolism

Marcus C. Schaub, Inst. of Pharmacology and Toxicology, University of Zurich, Switzerland

ATP-dependent potassium channels are present in the sarcolemma (sarcoKATP) and in the mitochondria (mitoKATP) of cardiomyocytes. Both channels belong to the inwardly rectifying Kir family. Potassium passes the Kir channels more readily inward than outward. At physiological membrane potential the Kir channels mediate potassium efflux affecting repolarisation and hyperpolarisation. The subfamily Kir6 including the sarco- and the mitoKATP, are typically regulated by magnesium, ATP, ADP and G-proteins. Under physiological conditions the Kir6 channels are mostly closed, but may open during stress such as hypoxia/ischemia. Consequently, the Kir6 channels contribute little to the major features of the action potential. However, by sensing the ATP to ADP ratio their activity is linked to the metabolic state and thus modulates the electrophysiologic properties of the myocytes. Kir6 (~46 kDa) comes in two isoforms from two different genes, Kir6.1 and Kir6.2. Together with four sulfonylurea binding regulatory subunits (SUR ~176 kDa) four Kir6 subunits form a functional hetero-octamer. SUR1 and SUR2 originate from two genes with SUR2 existing in two splice variants, SUR2A and SUR2B. The SUR subunits belong to the ATP-binding cassette protein superfamily. The sarcoKATP comprises Kir6.2/SUR2A, while the molecular identity of the mtoKATP is still unknown (possibly Kir6.1 type). Both sarco- and mitoKATP are involved in intracellular calcium handling. The mitoKATP interacts with the mitochondrial permeability transition pore and plays a key role in cardiac cytoprotective

mechanisms. The involvement of the cardiac sarco- and mitoKATP in pathophysiology and ischemic and pharmacological conditioning will be discussed

Workshop 2 Computational biology Room: Montreal

WS2-1
In silico biology, or on comprehensive and realistic modeling
David Harel, Weizmann Institute of Science, Rehovot, Israel

The talk will discuss the idea of comprehensive and realistic computerized modeling of biological systems. In comprehensive modeling the main purpose is to understand an entire system in detail, utilizing in the modeling effort all that is known about the system, and to use that understanding to analyze and predict behavior in silico. In realistic modeling the main issue is to model the behavior of actual elements, making possible totally interactive and modifiable realistic executions/simulations that reveal emergent properties. I will address the motivation for such modeling and the philosophy underlying the techniques for carrying it out, as well as the crucial question of when such models are to be deemed valid, or complete.

The examples I will present will be from among the biological modeling efforts my group has been involved in: T cell development in the thymus, lymph node behavior, embryonic development of the pancreas, the *C. elegans* reproduction system and a generic cell model.

WS2-2
Using genomic variability to reconstruct cell lineage
Shalev Itzkovitz, Weizmann Institute of Science, Rehovot, Israel

Cell lineage related questions are of vast importance in biology and medicine. They include the understanding of embryonic developmental processes, the maintenance of adult tissue, and the dynamics of cancer progression. Current cell lineage tracing techniques are limited in their invasiveness, non-specificity and limited scope. We have developed a non-invasive cell lineage technique that uses the genomic variability between different cells to reconstruct cell lineage relations. This is based on somatic mutations that occur at micro-satellite loci during mitotic divisions. We have built an automatic robotic-based system that receives DNA samples of cells and outputs the reconstructed lineage relations between them. When analyzing the data we draw parallels between our problem and existing problems in phylogenetics and population genetics, and base our analysis on the vast theory and algorithms that have accumulated over the years in these fields. The talk will present this system, its proof of concept, and the computational challenges of analyzing the data in view of the unique characteristics of the cell lineage data.

WS2-3
On the mathematical modeling of the human cardiovascular system
Alfio Quarteroni, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland
and Politecnico di Milano, Milan, Italy, http://iacs.epfl.ch/cmcs/, Alfio.Quarteroni@epfl.ch

Mathematical investigation of the human circulatory system has drawn increasing attention in recent years, also because cardiovascular diseases represent one of the leading causes of natural death in developed Countries.
One of the most frequent vascular pathologies, the atherosclerotic thickening, typically occurs in preferential sites, such as in outer wall of vessel bifurcations (like in the internal carotid artery), inner wall of curved segments (like in coronary arteries), and anastomotic junctions (e.g. downstream a coronary by-pass). More recently, this was related to peculiar behavior of specific fluid dynamical quantities, notably the wall shear stress, which is defined

as the normal derivative of the tangential flow velocity at the internal vessel walls. More precisely, it has been conjectured that critical flow zones are those where wall shear stress is low but its rate of variation in time is high. This dynamical flow behavior is measured by the so-called oscillatory shear index, whose determination requires solving a truly three dimensional flow problem in real geometries. More generally, mathematical models based upon partial differential equations are nowadays recognized to be the matter of choice if one aims at reproducing the complex features exhibited by blood flow under either physiological or pathological conditions.
Modeling the flow behavior is not the only task to fulfill prior to carry out numerical simulations. Indeed, from one hand one has to construct the computational domain, starting by clinical data such as MRI (magnetic resonance imaging), digital angiography or computed tomography (CT scans). By the same tools the boundary conditions (on fluid velocity and/or fluid pressure) need to be provided at the inlet and outlets of the segment of arteries that we want to address for the numerical simulation.
Another issue that we have to face before carrying out numerical simulations is the modeling of the arterial compliance. Otherwise said, arterial walls deform under blood pressure, precisely they dilate during the systolic phase (when the heart is pumping) by storing elastic energy, and compress during the diastolic phase (when the heart inflates to be refilled by venous blood). This vessel displacement is dimensionally relevant (the increase of the arterial diameter during the systolic phase can reach the 10% of the diameter at rest) and has crucial role in the circulatory functionality, as it contributes to keeping the blood pressure almost uniform from proximal (near the blood) to distal (near peripheries). From the physical viewpoint, wall compliance induces traveling pressure waves which are superimposed to the blood motion that is governed by the Navier-Stokes equations.
However, since blood flow interacts mechanically and chemically with vessel walls producing a complex fluid-structure interaction problem, which is impossible to simulate in its entirety, several reduced models have been developed which may give a reasonable approximation of averaged quantities, such as mean flow rate and pressure, in different sections of the cardiovascular system.
In this talk we address some mathematical issues arising from the modelling of the cardiovascular system through problems of different complexity and show their application to several problems of clinical interest.

WS2-4
Phylogenetic assessment of microbial communities through environmental sequence data
Christian von Mering[1], Hugenholtz P[2], Raes J[3], Tringe SG[2], Doerks T[3], Jensen LJ[3], Ward N[4], Bork P[3], [1]University of Zurich, Institute of Molecular Biology, Winterthurerstrasse 190, 8057 Zurich, Switzerland, [2]DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA, [3]European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, Germany, [4]The Institute for Genomic Research, Rockville, MD 20850, USA

The taxonomic composition of environmental communities is an important indicator of their function and ecology. We discuss how a set of protein-coding marker genes, extracted from large-scale environmental shotgun sequencing data, can provide a more direct, quantitative and accurate picture of community composition than traditional rRNA-based approaches using polymerase chain reaction (PCR). By mapping marker genes from four diverse environmental data sets onto a reference species phylogeny, we demonstrate that certain communities evolve faster than others, determine preferred habitats for entire microbial clades, and provide evidence that such habitat preferences are often remarkably stable over time.

WS2-5

Pre-steady-state decoding of the bicoid morphogen gradient

Sven Bergmann[1,2,3,4], Oded Sandler[1], Hila Sberro[1], Sara Shnider[1,2], Eyal Schejter[1], Ben-Zion Shilo[1], Naama Barkai[1,2*],

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Morphogen gradients are established by the localized production and subsequent diffusion of signaling molecules. It is generally assumed that cell fates are induced only after morphogen profiles have reached their steady state. Yet, patterning processes during early development occur rapidly, and tissue patterning may precede the convergence of the gradient to its steady state. Here we consider the implications of pre–steady-state decoding of the Bicoid morphogen gradient for patterning of the anterior–posterior axis of the *Drosophila* embryo. Quantitative analysis of the shift in the expression domains of several Bicoid targets (gap genes) upon alteration of *bcd* dosage, as well as a temporal analysis of a reporter for Bicoid activity, suggest that a transient decoding mechanism is employed in this setting. We show that decoding the pre–steady-state morphogen profile can reduce patterning errors caused by fluctuations in the rate of morphogen production. This can explain the surprisingly small shifts in gap and pair-rule gene expression domains observed in response to alterations in *bcd* dosage

Citation: Bergmann S, Sandler O, Sberro H, Shnider S, Schejter E, et al. (2007) Pre–steady-state decoding of the Bicoid morphogen gradient. PLoS Biol 5(2): e46. doi:10.1371/journal.pbio.0050046

WS2-6

A combined virtual screening and biological assay approach

Marco Scarsi, Michael Podvinec, Adrian Roth, Hubert Hug, Sander Kersten, Hugo Albrecht, Torsten Schwede, Urs A. Meyer and Christoph Rücker

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Most drugs currently employed in the treatment of type 2 diabetes either target the sulfonylurea receptor stimulating insulin release (sulfonylureas, glinides), or target PPARγ improving insulin resistance (thiazolidinediones). Our work shows that sulfonylureas and glinides additionally bind to PPARγ and exhibit PPARγ agonistic activity. This activity was predicted *in silico* by virtual screening and confirmed *in vitro* in three different biological assays. Among the measured compounds, gliquidone and glipizide (two sulfonylureas), as well as nateglinide (a glinide) exhibit PPARγ agonistic activity at concentrations comparable to those reached under pharmacological treatment. The most active of these compounds, gliquidone, is shown to be as potent as pioglitazone at inducing PPARγ target gene expression. This dual mode of action of sulfonylureas and glinides may open new perspectives for the molecular pharmacology of antidiabetic drugs, since it provides evidence that drugs can be designed which target both the sulfonylurea receptor and PPARγ. Targeting both receptors could increase pancreatic insulin secretion, as well as improve insulin resistance.

Workshop 3 Stem cells and cancer Room: Singapore

WS3-1

Defining the niche of male germinal stem cell in new born rat by expression profiling

Stephan Ryser[1], Philippe Tacchini[2], Philippe Durand[3], Irmgard Irminger-Finger,

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Stem cells have the capacity to self-renew and differentiate along multiples lineages. These stem cell fates are controlled by extracellular signals from the niche and by intrinsic genetic programs within the stem cell. In the germ line, the notion of stem cell niche was intensely studied in *C. elegans* and *Drosophilia* and led to identification of essential genes. However, little is known in mammals. Therefore, functional genomic approaches of spermatogonia stem cells and somatic support Sertoli cells are a valuable tool for characterization of the niche. In prepuberal rat testis (9 dpp) both types of cells proliferate, following a mitotic program initiated during embryogenesis. At puberty, Sertoli cells and spermatogonia have different cell fates. Somatic cells enter into quiescence and form a tight hematotesticular barrier. While germ cells divide to maintain the stem cell pool and produce spermatocytes, which proceed through meiosis. In this study, we compared the transcript profiles of spermatogonia from pre-puberty and post-puberty animals, thus representing pure spermatogonia type A (A_{single}, $A_{aligned}$, A_{1-4}) vs spermatogonia type I and B and preleptotene spermatocytes. Similar comparison was performed for the Sertoli cells from different stages. Interestingly, a large proportion of the gene products, differentially expressed in spermatogonia and Sertolis cells, are involved in contact with the extracellular environment, and include cell adhesion, secreted proteins, extracellular matrix genes, but also receptors, channels and transporters. Identification of new markers in spermatogonia and Sertoli cells will help to define the molecular basis of the germ line stem cell niche in mammals.

WS3-2

Culture adaptation of embryonic stem cells: models for germ cell tumour progression

Neil J. Harrison and P.W.Andrews, University of Sheffield, UK

Human embryonic stem cells (hESC) are derived from the inner cell mass of the blastocyst stage embryo, and have pluripotent potential which may be utilized in regenerative medicine. The genetic stability of hESC is not assured however, as reports have emerged detailing karyotypic abnormalities arising during extended culture. The abnormal cells tend to overtake the normal cells in the population, indicative of a growth advantage for these cells. As such, the abnormal hESC must be better suited to *in vitro* expansion, and we have termed them 'culture adapted'

The karyotypic abnormalities observed in the culture adapted hESC are mostly non-random, involving gain of material from chromosomes 12, 17 and X. These changes are also frequently seen in germ cell tumours (GCT), and more particularly embryonal carcinoma (EC) cells, the stem cells of these tumours. The balance between self-renewal, differentiation and apoptosis is critical in EC proliferation, and these behaviours are also likely to be affected during hESC culture adaptation. Hence, we propose culture adaptation as a model for tumour progression, and believe a better understanding of the abnormal hESC will provide insights into germ cell malignancy.

WS3-3

Hormones and paracrine signaling in breast development and breast cancer

Cathrin Brisken, ISREC, Lausanne, Switzerland

Life time exposure to reproductive hormones, affects breast cancer risk. Studies in my laboratory focus on the cellular and molecular mechanisms by which systemic hormones control breast proliferation and morphogenesis *in vivo* and how they contribute to breast carcinogenesis using the mouse as a model system. We have used tissue recombination techniques to show that estrogens induce mammary epithelial cell proliferation during puberty via epithelial estrogen receptor α (ERα). When ER$\alpha^{-/-}$ mammary epithelial cells are in close vicinity to ERα wt cells, they proliferate and contribute to all aspects of mammary gland development, indicating that estradiol, like progesterone, orchestrates proliferation and morphogenesis by a paracrine mechanism, affecting nearby cells in the mammary epithelium. Epidermal growth factor receptor (EGFR) signaling has long been implicated downstream of ERα signaling and several EGFR ligands have been described as estrogen target genes in tumor cell lines. We have found that amphiregulin is the unique EGF family member to be transcriptionally induced by estrogen, in the mammary glands of puberal mice at a time of exponential expansion of the ductal system and provide evidence that amphiregulin is an important paracrine mediator of estrogen function specifically required for puberty-induced ductal elongation.

WS3-4

In vitro analysis of heterotypic cell-cell interaction effects to identify the contribution of tumor-stroma interaction on global gene expression profiles in breast cancer

Martin Buess[1,3], Dimitry S.A. Nuyten[2], Trevor Hastie[3], Michal Rajski[1], Richard Herrmann[1], Christoph Rochlitz[1] and Patrick O. Brown[3], [1]Division of Medical Oncology, Department of Research, Basel University, Basel, Switzerland, [2] Netherlands Cancer Institute, Amsterdam, The Netherlands, [3]Stanford University, Stanford, CA,USA.

Background:Communication between different cell types is central to multi-cellular organisms and perturbations in cell-cell interaction are a key feature of cancer. However, the systematic effects of cell-cell interaction on global gene expression in cancer are largely unexplored. We hypothesized that gene expression signatures induced by cell-cell interaction might be of clinical relevance.
Methods: We simulated tumor-stroma interaction *in vitro* by systematically co-cultivating breast cancer cells with stromal fibroblasts and determined associated gene expression changes with cDNA microarrays. A dataset of pre-treatment gene expression profiles from 295 early stage breast cancers with a follow-up of 12.6 years allowed evaluating *in vitro* effects *in vivo*.
Results: The picture of heterotypic interaction effects that emerged from this analysis is complex reflecting the variation in signaling capacities and responsiveness of the involved cells. A frequent and prominent response to epithelial-mesenchymal interaction was an up-regulation of interferon-response genes (IRG), which was detected in estrogen receptor negative breast cancer cell lines in co-culture with fibroblasts, but not in normal mammary epithelial cells. Upon close cell–cell contact fibroblasts produce type I interferons, which induce a strong up-regulation of the IRG in the epithelial cells. In parallel to this in vitro finding, immunohistochemical staining for STAT1, an IRG, demonstrated preferential expression in breast cancer cells having close contact to the stroma. In vivo, the IRG showed an extraordinary coordinated behavior and segregated the breast cancers into two groups. Tumors with high expression levels (n=161) of IRG had a significantly shorter distant metastasis free survival (p=0.0014) (58 % at 10 years) and overall survival (p=0.000926) (59 % at 10 years) than tumors with low expression levels (n=134) (metastasis free survival: 74 % at 10 years overall survival: 80% at 10 years). Immunohistochemical staing of STAT1 protein in a case series of 353 primary breast cancers paralleled these results.

Conclusions: Our data suggest that interferon signaling results as an effect of tumor-stroma interaction and is associated with more aggressive tumor behavior in breast cancer. The mechanisms of additional specific heterotypic interaction effects in our *in vitro* model are currently under investigation. A more comprehensive understanding of these mechanisms will hopefully provide new therapeutic strategies for breast cancer.

WS3-5

Cooperative control of hematopoietic stem cell function by c-Myc and N-Myc.

Elisa Laurenti[1], Anne Wilson[2], Paul S. Knoepfler[3], Robert N. Eisenman[3], H. Robson MacDonald[2] and Andreas Trumpp[1], [1]Genetics and Stem Cell Laboratory, Swiss Institute for Experimental Cancer Research (ISREC), CH-1066 Epalinges, and Ecole Polytechnique Fédérale de Lausanne (EPFL), School of Life Sciences, CH-1015 Lausanne, Switzerland, [2]Ludwig Institute for Cancer Research, Lausanne Branch, University of Lausanne, CH-1066 Epalinges, Switzerland, [3] Fred Hutchinson Cancer Research Center, Seattle, USA.

Hematopoietic stem cells (HSCs) are defined by their ability to self-renew while concomitantly producing a defined set of differentiated progeny for life-long replenishment of all blood cell types. The proto-oncogenes encoding c-Myc and N-Myc have been implicated in various important biological functions such as cellular division, growth, differentiation and apoptosis. We have recently demonstrated a key role for c-Myc in HSC function by using conditional gain- and loss- of function studies in the mouse. HSCs (defined as $lin^-ckit^+Sca1^+CD34^-Flk2^-$), in which c-Myc is conditionally deleted, accumulate in the bone marrow due to their failure to undergo normal differentiation. Our data suggest that levels of c-Myc control the balance between HSC self-renewal and differentiation by controlling their entry and exit from the stem cell niche via the regulation of cell adhesion molecules such as N-cadherin (1;2). Surprisingly, the intrinsic self-renewal/proliferation program is undisturbed in c-Myc mutant HSCs, raising the possibility that these functions may be controlled by N-Myc alone or by both proteins together. In order to study HSCs lacking both c-Myc and N-Myc, we bred *Mx-Cre;c-myc$^{flox/flox}$;N-myc$^{flox/flox}$* mice, and eliminated both proto-oncogenes in the bone marrow of 4 week old animals. Double mutant mice rapidly develop severe pan-cytopenia and subsequently die as early as 14 days after Cre recombinase induction. The individual and cooperative effects of c-Myc and N-Myc on HSC quiescence, self-renewal, survival and niche-dependent differentiation will be discussed.

(1) Wilson A., et al. (2004). c-Myc controls the balance between hematopoietic stem cell self-renewal and differentiation. Genes&Dev 18;2747-2763.
(2) Wilson A. and Trumpp A. (2006). Bone marrow hematopoietic stem cell niches. Nature Reviews Immunology, 6:93-106.

WS3-6

Cell surface capturing as a method of choice for the identification and quantification of relevant plasma membrane antigens of cancer stem cells

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Cell surface-exposed proteins embedded in the plasma membrane (PM) are crucial for cell-cell communication, interaction with pathogens and responding to environmental perturbations. The identification of the PM subproteome is hampered by inherent problems in isolating PMs, the limited relative abundance of PM proteins compared to cytoplasmic proteins and the difficulty in resolving and identifying hydrophobic polypeptides. A three step protocol circumvented these problems.

This involved a tandem affinity labeling strategy employing chemical labeling of carbohydrate-containing proteins on living cells, combined with a specific enzymatic peptide release step that allowed systematic and selective identification of glycosylated peptides derived from cell surface proteins via reversed phase LC-MS/MS.
The recently emerged concept of cancer stem cells describes the percentage of cells within a solid tumor capable of unregulated self-renewal as well as of the generation of progenitor cells. Unfortunately, there are no conclusive data available for specifically expressed proteins on cancer stem cells, that would allow the detection, enrichment and further functional studies of these cells. In preliminary experiments, cells from melanoma biopsies were expanded in neurospheres, sorted according to their expression of the p75 neurotrophin receptor, and subjected to the CSC technology. In summary, 166 PM proteins covering a broad spectrum of biological function were identified. Several receptors, for example for insulin growth factor, transferrin, VEGF and PLGF, receptor tyrosin kinases erbB as well as 38 cell differentiation antigens were found. The next step will be the quantitation of specific differences in the expression level of melanoma stem cell PM proteins.

Workshop 4 Statistics in animal research

Room: Rio

WS4-1
We need to improve the design and statistical analysis of animal experiments

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Animal experiments are frequently poorly designed and incorrectly analysed. This leads to a waste of resources and can have serious additional consequences as the experiments may fail to predict human responses. Scientists often violate basic principles such as that treated and control groups should be as similar as possible.
The first step is to define the purpose of the experiment, the animal model must then be chosen, including species strain, genotype and any experimental preparation. Failure to identify correctly the “experimental unit” is common. It is that entity which can be assigned at random to a treatment. It may be an animal or a cage of animals. Treatments and outcomes themselves must be defined. Where possible outcomes should be measured “blind” with respect to treatments. Appropriate formal experimental designs such as completely randomised and randomised block designs need to be appropriately chosen. Methods of randomisation must be specified and sample size needs to be determined. All too often group sizes are determined by tradition. Finally, the results need to be statistically analysed and correctly interpreted. Guidelines [1], books[2] and web sites (www.isogenic.info) are available to help the scientist.
1. Festing M.F.W. & Altman D.G. (2002) Guidelines for the design and statistical analysis of experiments using laboratory animals. *ILAR Journal* 43, 233-243.
2. Festing M.F.W., Overend P., Gaines Das R., Cortina Borja M., & Berdoy M. (2002) *The Design of Animal Experiments*, 1-112. Laboratory Animals Ltd., London.

WS4-2
"Missing data: what can I do with it?"

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Background: No study is perfect. Missing data is a common problem but often ignored, underestimated and seldom reported. If more then 5% of data are missed a Missing Data Diagnosis should be performed

Types of missing data: (1) Missing Completely At Random (MCAR): no relation between data e.g. blood probe tube accidentally broken (2) Missing Not at Random Missing (MNAR): systematic error or bias e.g. missing data always with male (3) Missing At Random (MAR): most missing data, some kind of association e.g. height and weight
Possible Solutions: (1) List wise deletion: one variable missing – study subject is deleted, resulting in a new population and compromised analytic power. Used in nearly all software packages for multiple regressions (2) Pair wise deletion: All possible comparisons performed except those with missing data. Not all data lost if 1 is missing resulting in a subgroup analysis (3) Substitution of the mean: mean of available data used for imputation. Artificial homogenisation
Modern Handling of Missing Data: (1) Expectation Maximization Algorithm; Estimation algorithm to generate single missing values - study population not reduced; Suitable for up to 30% of missing data (2) Multiple Imputation; Several sets of data constructed, statistically analysed and averaged to a pooled estimate. Available in standard software packages.
Conclusion: Identifying causes of missing data is an inherent part of data analysis. Missing data may bias your results. Overall mean imputation does not work. Appropriate assumptions and multiple imputation correctly estimates data. Prevent loss of data and consult a statistician early

WS4-3

Javier Fandino, Inselspital Bern, Switzerland

Abstract not available

WS4-4

Statistics and relevance - how can I convince the local animal welfare committee?

Eva Waiblinger, Tierversuchskommission BS; Animal Behaviour, University of Zurich, Switzerland

In Switzerland, both the cantonal veterinary office and the animal experimentation committee have to approve of animal experimentation applications before a license can be granted. It is their task to judge whether biometric planning, i.e. experimental design, group sizes and intended statistical methods are appropriate to reach the scientific goals proposed in the application and whether animal numbers have been minimised as the law and the 3R principles require. In practice, the information given by the applicants is incomplete, thus the committee is often unable to correctly review the application. Very rarely the applicants show that they use previously acquired data to roughly assess data variability and estimate animal numbers in follow-up experiments. Where there are no former experimental results to base this decision on, and where distribution and variability of the results are unclear yet, pilot studies and power analyses should be integrated into the licence application from the start. Usually very scant information is given on statistical methods. A priori most applicants intend to use parametric tests without checking first whether their data fulfil the requirements, i.e. whether they will need to be transformed or analysed using non-parametric tests. Since such information is often not given, the committee cannot know whether the applicants are just ignorant of the important statistical requirements or too lazy to give all the details. In the workshop presentation, some anonymised examples from applications are given which demonstrate how the paragraph “biometric planning” should be filled in to satisfy the needs of animal experimentation committees.

WS5-1
Computational prediction of ncRNA genes and targets

Dimos Gaidatzis, Alain Sewer and Mihaela Zavolan, Division of Bioinformatics, Biozentrum, University of Basel

Small RNA molecules have emerged as important regulators of gene expression. The most studied among them are the microRNAs (miRNAs), which are conserved over evolutionary distances as large as from worm to human, and are involved in many developmental and physiological processes, such as cell lineage decisions and proliferation, apoptosis, morphogenesis, fat metabolism, and hormone secretion. The number of miRNAs has grown continuously since the discovery of the evolutionarily conserved let-7 miRNA, due to many studies that used various combinations of experimental and computational approaches. Our group has developed computational methods to support ncRNA gene identification in several ways. We have developed a small RNA annotation tool that has been used to identify the small RNAs that originate in a set of known classes of RNA genes. One output of this annotation is the count of molecules of each type of miRNA that has been observed in a given sample. These counts can be used as a measure of the expression levels of each miRNA in the sample, and we have developed a Bayesian model for comparing and clustering miRNA expression profiles of different samples. Novel classes of ncRNAs (such as rasiRNAs and piRNAs) can be sometimes identified in the subset of cloned sequences that are not annotated during the steps described above.
The discovery of miRNA targets has lagged behind the discovery of miRNA genes. Recently, high-throughput approaches based on the observation that miRNAs can induce partial degradation of their mRNA targets, are used to define miRNA targets. Here I will discuss our work on miRNA target identification using computational predictions and analyses of microarray expression data.

WS5-2
Mechanisms of miRNA-mediated gene silencing

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MicroRNAs (miRNAs) represent a novel class of genome-encoded eukaryotic regulatory RNAs that silence gene expression post-transcriptionally. Although the proteins mediating miRNA biogenesis and function have been identified, the precise mechanism by which miRNAs regulate the expression of target mRNAs remains unclear. We have recently shown that miRNAs silence gene expression by at least two independent mechanisms: by repressing translation and/or by promoting mRNA degradation. In *Drosophila,* both mechanisms require Argonaute 1 (AGO1) and the P-body component GW182. Moreover, mRNA degradation, but not translational repression, by miRNAs is inhibited in cells depleted of the CAF1:CCR4:NOT1 deadenylase complex, the decapping DCP1:DCP2 complex or of several decapping co-activators, which also localize to P-bodies. Our findings suggest a model for miRNA function in which AGO1 associates with miRNA targets through miRNA:mRNA base-pairing interactions. GW182 interacts with AGO1 and recruits deadenylases and decapping enzymes, leading to mRNA degradation. However, not all miRNA-targets are degraded: some stay in a translationally silent state, from which they may eventually be released. We propose that the final outcome of miRNA regulation (i.e. degradation versus translational repression) is influenced by other RNA-binding proteins interacting with the targeted mRNA.

WS5-3

let-7 microRNA mode of action _in vivo_: translational effect and role of eif-3

Xavier Ding & Helge Grosshans, Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

MicroRNAs (miRNAs) are a large class of ~22 nucleotide long non-coding RNAs that negatively regulate many genes at the posttranscriptional level. MiRNAs base-pair to imperfectly complementary elements in the 3' untranslated region of their targets, which ultimately prevents their expression. It has been reported that miRNA may regulate their targets by translation inhibition, mRNA destabilization, or cotranslational polypeptide degradation. None of these mechanisms have yet been estbalished *in vivo* and their relative importance is currently not clear.

Using an RNAi-mediated genetic screen in *C. elegans*, we identified the eukaryotic translation initiation factor 3 (*eif-3*) as a potential mediator of *let-7* miRNA. We hypothesize that *let-7* may function by negatively affecting eIF3 activity, thereby preventing translation initiation of its targets.

We observed that the phenotype induced by knocking-down *eif-3* is opposed to the *let-7* mutant phenotype, which is consistent with negative regulation of *eif-3* by *let-7*. Moreover, we found that reducing eIF3 activity in *let-7* mutants specifically downregulates a *let-7* target reporter. Using sucrose density gradient centrifugation, we are currently investigating the translational profile of *let-7* targets to verify that *let-7* represses translation at the initiation level *in vivo*.

WS5-4

Approaches to study miRNA function in mammals

Markus Stoffel, Institute for Molecular Systems Biology, ETH Zürich, Switzerland

MicroRNAs (miRNAs) are an abundant class of short non-coding RNAs that have been identified in the genomes of a wide range of multi-cellular life forms as well as viruses. Like conventional mRNAs, miRNAs are transcribed by polymerase II as long primary transcripts that are capped, polyadenylated and spliced. Unlike mRNAs, miRNAs are processed into 19-22-nt duplexes by a two-step process involving nuclear and cytosolic RNase III-type endonucleases, known as Drosha and Dicer, to yield the 'mature' miRNA. In a final step, this RNA duplex is loaded into the RNA-induced silencing complex (RISC), one of the strands is eliminated, and the remaining strand engages in imperfect base pairing with specific sequences in target mRNAs. This induces either degradation of the target mRNA or translational repression. This mechanism resembles the process of RNA interference triggered by double-stranded RNA and utilizes similar molecular machinery. The elucidation of the mechanism of miRNA function in the regulation of gene expression suggests an elegant gene regulatory model: Nuclear encoded genetic information is not only transcribed and translated into proteins but at the same time regulates these processes through non-coding miRNA via sequence-guided interactions with the cognate mRNA. This paradigm adds a new level of regulation and fine-tuning of gene expression that is likely to be important for the maintenance of many, if not all, cellular functions.

In spite of our ability to identify miRNAs, elucidate their biogenesis and basic mechanisms of action, there is still very little known regarding miRNA function in animals. Genetic studies in *Caenorhabditis elegans*, *Drosophila melanogaster* and *Danio rerio* have identified important functions of specific miRNAs in the coordination of cell proliferation and death during development, stress resistance, fat metabolism, and brain morphogenesis. Relative to lower model organisms, our knowledge of miRNA function in mammals is much more limited. For the past few years, one primary focus of the investigators studying mammalian miRNAs has been to identify and catalogue the complete miRNA inventory and its expression pattern using both cloning, bioinformatics, and gene expression approaches.

With these efforts nearing completion in the near future, the focus is shifting to the rapid elucidation of miRNA function. Several technological advances including bioinformatic prediction algorithms, reporter assays, in situ hybridizations, overexpression and silencing technologies, have been developed to deduce miRNA function. I will address current and future technologies to study miRNA function in mammals, discuss their limitations, and point out their relevance to modern medicine and potential as therapeutic targets for small-molecule inhibitors.

WS5-5

Anti-sense RNA stabilization in S. cerevisiae induces gene silencing by Hda1/2/3 histone deacetylase complex

Jurgi Camblong, Nahid Iglesias, Céline Fickentscher and Françoise Stutz*, Dept. of Cell Biology, Sciences III, 30 Quai E. Ansermet, 1211 Geneva 4, Switzerland.

Recent genome wide studies in the yeast S. cerevisiae show that the transcriptome includes intergenic transcripts, regulated by the exosome component Rrp6, but also numerous anti-sense transcripts. The role of most of these transcripts is still unclear, although evidence suggests they may affect gene expression. We observed that Rrp6 function is affected in aging yeast cells, resulting in the accumulation of PHO84 anti-sense transcripts and the repression of PHO84 sense transcription. Epistasis and chromatin immunoprecipitation experiments support the view that loss of Rrp6 function and stabilization of anti-sense RNAs lead to the recruitment of Hda1 histone deacetylase to PHO84 and neighboring genes. However histone deacetylation and gene repression is restricted to PHO84, suggesting that Hda1 activity is dependent on anti-sense RNA. Together, our data indicate first that the stabilization of PHO84 anti-sense transcripts participates in PHO84 gene repression via a mechanism distinct from transcription interference and second that modulation of Rrp6 function contributes to gene regulation by inducing RNA dependent epigenetic modifications.

Workshop 6 - Imaging and image analysis Room: Rio

WS6-1
Statistical shape models for the analysis of human morphology
Thomas Vetter, University of Basel, Switzerland, http://gravis.cs.unibas.ch

In medical data analysis many questions require the knowledge of the normal or physiological state of an anatomical structure. Often conditions are characterized as a deviation from the norm.
Here we present statistical shape models for an automated analysis of the variability of anatomical structures of a certain class (e.g. faces, skulls or femur). These models derive prior knowledge on possible shape variations from prototypical exemplar data-sets.
By exploiting the correspondences between all the examples, these models introduce a vector space structure on the examples that allows to model and synthesize novel instances of that class.
Data analysis can be performed by fitting such a flexible model to novel data with an optimization process. Then, the model parameters yielding the optimal reconstruction are used to code or analyze the data presented.
The main challenge in this process is the standardized comparison of the data-sets. This problem is known as the registration problem. The focus of this talk is on recent developments on non parametric surface registration as well as on applications for the reconstruction and prediction of missing data in surgical planning.

WS6-2
Image analysis and processing for quantitative cellular imaging
Jean-Yves Chatton, Dept. Physiology & Dept. Biol. Cell Morphology, University of Lausanne

Fluorescence microscopy has become a multifaceted approach that encompasses the most advanced technologies of optics, photonics, electronics, and computer science. Today's microscopes are capable of simultaneously recording images of several fluorophores as two- and tree-dimensional image data sets. Spectral information on each recorded pixel may be readily obtained yielding spectral images of samples. All these acquisition modes can be combined and repeated over time at high speed potentially leading to massive image data sets to be processed, analyzed, and archived. We will discuss specific issues related to digital images recorded on optical microscopes, and review some of the approaches available to analyze, process, and display the images, as well as to extract useful quantitative information. We will then present examples depicting how image processing combined with image analysis procedures may be applied to dynamic imaging of cellular functions.

WS6-3

Exploring brain circuits with serial section electron microscopy; current technology and future directions

Graham Knott , Christel Genoud, University of Lausanne, Switzerland, / Gatan UK, Abingdon, UK

For several decades the electron microscope has explored the detailed structure of the brain. With its subnanometer resolution it is the only tool available today capable of visualizing all synaptic contacts between neurons. Painstaking analyses over many years, using serial section transmission electron microscopy (ssEM) of labeled and unlabeled brain tissue, have provided a wealth of information about how the cortex is wired. In recent years, the appearance of multi-photon imaging has extended the neurobiologist's explorations into the brain's circuits. With its ability to make optical recording hundreds of microns inside tissue, this technique can be used to image subcellular events occurring in living cells. Recently, studies of dendrite dynamics in the rodent somatosensory cortex show that dendritic spines grow and retract on a daily basis. However, interpreting these structural changes in terms of an alteration in the neuronal connectivity requires ssEM. Combining these techniques shows how dendritic spines form and over what time period their synaptic connection develops[1]. These studies underlie the importance of the electron microscope for researching the brain, also highlighted by the advances being made to transform the serial sectioning and imaging technique into one that is fully automated, occuring within a scanning EM[2]. These developments in EM technology will bring us closer to understanding not just the function of several neurons, but entire cortical circuits. 1, Nat Neurosci 9, 1117-24 (2006). 2, PLoS Biol 2, e329 (2004).

WS6-4

Quantitation of lung structure by stereology: Leonhard Euler and the number of alveoli

Matthias Ochs, Institute of Anatomy, Experimental Morphology, University of Bern, Switzerland

Quantitative microscopy is essential in experimental morphology and pathology, including the phenotyping of genetically altered organisms. The gold standard to obtain accurate and precise quantitative data in microscopy is stereology. In the mammalian lung, the smallest gas exchange unit is the alveolus. Therefore, the number of alveoli is a key structural determinant of parenchymal architecture and lung function. In principle, an assumption-free stereological method to estimate alveolar number has to use a 3-dimensional test system, i.e. disectors. However, alveoli have incomplete boundaries due to their openings, which makes a rigorous topological definition for the appearance of an alveolus in a disector necessary. With their entrance rings formed of strong fiber tracts in the free edges of the alveolar septae, alveolar openings form a 2-dimensional network in 3-dimensional space. As a measure of connectivity, and thus the number of "holes" in this network, the Euler number χ can be estimated using physical disectors at the light microscopic level. This makes direct quantification of alveolar development and remodeling possible. Using this approach in adult human lungs, we estimated a mean of 480 million alveoli, with a close correlation to total lung volume (Ochs et al. 2004: Am J Respir Crit Care Med 169:120-124). Important applications of this method include the analysis of transgenic mouse models that develop emphysema-like pathology characterized by a loss of alveoli, e.g. gene-targeted mice deficient in surfactant proteins (Ochs et al. 2004: Am J Physiol 287:L1333-L1341; Jung et al. 2005: Anat Rec 286:885-890; Ochs 2006: J Microsc 222:188-200).

WS6-5

The three dimensional reconstruction of motor endplates of the vertebrate skeletal muscle fibres.

T. Voigt, Dept. Medicine, Unit of Anatomy, University of Fribourg, CH-1700 Fribourg, Switzerland

According to electrophysiological model simulations of the motor endplate (MEP) of frog and mammalian skeletal muscle fibres the subsynaptic folds supply a contribution to the strengthening of the praesynaptic signal. Simplified morphological assumptions which were derived from ultra thin sections were taken as a basis for the computations.
By means of three dimensional reconstructions of serial ultra thin sections through parts of motor endplates of lanthanum incubated frog and mammalian skeletal muscle fibres we tried to elucidate morphological ideas about the fold structure. Our efforts show that the morphological assumptions from single ultra thin sections represent an extreme simplification of the fold structure. Rather the reconstruction shows that these are impressions of the sarcolemma with finger- to flat ramifications which rather suggests a seaweed-like figure. In addition the reconstructions indicate that the subsynaptic folds are opened in T-tubules of the T-system. In its structure these openings resemble the bent openings of T-tubules to the myofibrillar sarcolemma outside the motor endplate. In analogy to the function of the T-tubules outside the motor endplate we assume that the endplate potential of the subsynaptic membrane could directly propagate to the postsynaptic sarcolemma around the sole plate nuclei.

WS7-1

The *Yersinia* basal body protein YscU plays a role in recognition of Type III export substrates

Isabel Sorg, Stefanie Wagner, Marlise Amstutz and Guy R. Cornelis, Biozentrum University of Basel, Switzerland

The *Yersinia* injectisome enables direct translocation of effector proteins from the bacterial cytosol into the cytoplasm of the eukaryotic target cell (Type-III secretion). It consists of a basal body spanning the two bacterial membranes topped by a hollow needle. The assembly occurs in an ordered manner using two different export systems. Basal body components are inserted in a Sec-dependent manner, while proteins needed at later steps of the assembly process, are sequentially exported by the type-III apparatus in the basal body.
The needle length is controlled by the molecular ruler YscP exported itself during needle assembly. When the needle has reached its final length YscP switches the substrate specificity of export substrates from early to late substrates. The first exported proteins after the substrate specificity switch are most likely the translocators YopB/YopD/LcrV, required for pore formation in the eukaryotic cell membrane. After pore formation effector proteins are translocated into the host cytoplasm. The current model suggests that upon termination of needle assembly YscP transmits a signal to the transmembrane protein YscU. This changes the conformation of the cytoplasmic domain of YscU, which finally results in the substrate specificity switch.
The cytoplasmic domain of YscU is cleaved auto-catalytically into two parts, which remain associated. Here we investigate the importance of the YscU cleavage for its function. A mutant with changed cleavage properties was still able to control needle length but revealed defects in the export of some substrates suggesting that YscU is involved in their recognition.

WS7-2

Stochastic simulation of malaria epidemiology and control

Nicolas Maire, Swiss Tropical Institute Malaria Modeling Team, Basel, Switzerland

Malaria may account for as much as 40% of public health expenditure in developing countries. Many different malaria control strategies are possible, but rational choice among them is difficult. To decide on how to allocate resources for malaria control, predictive models are needed to assess their likely impact. We have embarked on a project to generate such predictions using an individual-based discrete- time simulation approach. It is not sufficient to have a general idea of the effect of interventions if the models are to be used for resource allocation, and the uncertainty inherent in disease modeling needs to be minimized by ensuring that all elements of the model fit as well as possible to data. We therefore fit different components of the models to datasets from many different ecologic and epidemiologic settings. The simulation approach leads to implicit statistical models requiring many iterations in order to make approximate parameter estimates. This strategy leads to the need for many millions of individual-based simulation runs, each of which requires in the order of a few hours of CPU time on current mid-range PC. We use a volunteer computing approach to access the necessary computing power. We now present predictions of the impact of different types of malaria vaccines on the clinical epidemiology of malaria.

WS7-3

Molecular characterization and subcellular localization of macrophage infectivity potentiator, a *Chlamydia trachomatis* lipoprotein

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Macrophage infectivity potentiator (MIP) was reported to be a chlamydial lipoprotein from its ability to be radiolabeled by palmitic acid, soluble in Triton X-114 and posttranslationally processed in a globomycin-sensitive step but the detailed structural characterization of its lipidic moiety was never undertaken. To this aim, bioinformatics and mass spectrometry analysis as well as labeling and immunochemical experiments were conducted to provide information about MIP structure and subcellular localization. In silico analysis showed that MIP is conserved among five different species of the Chlamydiale order. Its probable signal sequence with its lipobox were determined. A recombinant variant was prepared with the probable lipobox cysteine substituted by an alanine. Incorporation of radiolabeled glycerol and palmitic acid as well as post-translational processing, inhibitable by globomycin, were observed in wild type recombinant MIP but not in the C20A recombinant MIP variant. Fatty acid content of native and recombinant MIP was analyzed by gas chromatography-mass spectrometry. Presence of amide-linked fatty acids was investigated by alkaline methanolysis. Results demonstrated a lipid modification of MIP similar to that of other procaryotic lipoproteins. In addition, MIP was detected in outer membrane preparation, shown to be surface biotinylable and surface immunoprecipitable, data that argue for a presence of MIP at the surface of bacteria.

WS7-4

Modeling CTL evasion during SIV/HIV infection. Is there a great escape?

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Several studies have shown that cytotoxic T lymphocytes (CTL) play an important role in controlling SIV/HIV infection, e.g. the association of human HLA types with disease progression and the occurrence of escape mutants. However, it proves difficult to assess the definite role of the cellular immune response. We present a new mathematical model of SIV/HIV infection including a broad cellular immune response targeting different viral epitopes. These CTL clones are stimulated by viral antigen and interact with the virus population through cytotoxic killing of infected cells. Consequently, the virus population reacts through the acquisition of CTL escape mutations, a stochastic process that in combination with the responding CTL clones leads to a complex behavior of the system. With our model we are able to reproduce several observations of virus and CTL dynamics. Furthermore, we show that even though the total killing induced by the CTL response is high, escape rates against single CTL clones are often low and difficult to estimate by sequence measurements over time. Finally, our simulations show that immunodominance and compensatory mutations affect the virus population on different time scales during the infection, which highlights the different impact of CTL responses during acute and chronic SIV/HIV infection.

WS7-5

Adenosine kinase and glyceraldehyde-3-phosphate dehydrogenase identified as putative CD12001 target(S) in *Trypanosoma brucei rhodesiense*

Sabine Kuettel, Scapozza L., Perozzo R., University of Geneva, Quai Ernest-Ansermet 30, 1211 Geneva, Switzerland

Compound 4-[5-(4-phenoxy-phenyl)-2*H*-pyrazol-3-yl]-morpholine (CD12001), was found to exhibit antitrypanosomal activity with 50% growth inhibition at 0.98µM on *Trypanosoma brucei rhodesiense*, the causative agent of the acute form of Human African Trypanosomiasis or Sleeping Sickness. Three derivatives of this compound, each containing an additional amine, were synthesized and immobilized on epoxy-activated agarose to perform affinity chromatography. [1], [2], [3]

After successfully coupling the compounds to the resin, *T. b. rhodesiense* cell lysate was incubated with the ligand-bound matrices. The matrices were washed extensively and the bound proteins were separated by SDS-PAGE, detected by silver staining and identified by trypsin digestion followed by LC/ESI/MS/MS-QTOF mass spectrometry.

Using this chemical proteomics approach, adenosine kinase and glyceraldehyde-3-phosphate dehydrogenase of *T. b. rhodesiense* were identified as two putative targets. The identified enzymes have been cloned and expressed as soluble proteins to elucidate the inhibition mechanism at the molecular level.

Literature:

[1] Tomisawa K, *Chem. Pharm. Bull.* **1986**, *34*, 701-712. [2] Mahata P K, *Tetrahedron* **2003**, *59*, 2631-2639. [3] Chauhan S M S, *Synthesis Comm.* **1975**, 798-801

WS7-6

Computational dissection of adenovirus cell surface motion reveals receptor mediated virus drifting on filopodia

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The earliest steps of virus host cell interactions are incompletely understood. In the case of human adenoviruses type 2 (Ad2), they involve viral attachment to the coxsackie virus B adenovirus receptor CAR, and alpha v integrins followed by endocytic uptake and infection. How the virus finds the appropriate domain on the plasma membrane to engage in endocytosis is unknown. Here we are using live fluorescence imaging at high temporal resolution together with single particle tracking algorithms to systematically map the motion of adenoviruses on filopodia of human epithelial cells. Surprisingly, the individual trajectories are of considerable heterogeneity. To unravel the information contained within these trajectories, we developed a novel trajectory segmentation approach based on neural networks. This approach revealed three distinct patterns, drifts, diffusion and confined motions. Upon attachment to filopodia, viruses were mostly randomly diffusive, before they processively drifted towards the cell body. Ad2 drifts required filamentous actin and myosin2. The absence of CAR reduced Ad2 drifts whereas alpha-V-integrin depletion increased the drifts, suggesting a competition between CAR and integrins in viral surface motions. Deletion of the PDZ binding motif in the cytosolic domain of CAR reduced Ad2 drifts on filopodia, suggesting that PDZ domain-bearing protein(s) link CAR to actin filament flow. Together, our combination of live fluorescence imaging and computational analyses reveals new features of the adenovirus receptor CAR, which are important for virus-host interactions on the cell surface.

WS8-1

Apelin and its receptor control heart field formation during zebrafish gastrulation

Xin-Xin I. Zeng, Thomas P. Wilm, Diane S. Sepich, and Lilianna Solnica-Krezel, Department of Biological Sciences, Vanderbilt University, Nashville, TN, USA

The vertebrate heart arises during gastrulation as cardiac precursors converge from the lateral plate mesoderm territories toward the embryonic midline and extend rostrally to form bilateral heart fields. G-protein coupled receptors (GPCRs) mediate functions of the nervous and immune systems, however, their roles in gastrulation remain largely unexplored. We show that the zebrafish homologs of the Agtrl1b receptor and its ligand, Apelin, implicated in physiology and angiogenesis, control heart field formation. Zebrafish gastrulae express *agtrl1b* in the lateral plate mesoderm, while *apelin* expression is confined to the midline. Reduced or excess Agtrl1b or Apelin function caused deficiency of cardiac precursors and subsequently heart. In Apelin deficient gastrulae, the cardiac precursors converged inefficiently to the heart fields and showed ectopic distribution, whereas cardiac precursors overexpressing Apelin exhibited abnormal morphology and rostral migration. Our results implicate GPCR signaling in movements of discrete cell populations that establish organ rudiments during vertebrate gastrulation.

WS8-2

Towards systems biology of organogenesis: deciphering regulatory networks controlling mesoderm development in the mouse.

Philipp Grote, Markus Morkel, Lorenz Neidhardt, Ralf Spörle, Martin Werber, Lars Wittler, and Bernhard G. Herrmann
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Mesoderm formation is a fundamental process of embryonic development. Mouse mutants affecting mesoderm formation show premature arrest of axial development and die during midgestation. A number of genes involved in mesoderm formation have been identified and analysed in the last 15 years. Nevertheless, our understanding of the molecular mechanisms controlling mesoderm formation and patterning is still vague.
We have set out to investigate mesoderm formation in a systematic manner. Large-scale gene expression analysis by whole mount in situ hybridization has been carried out in order to identify the players in this process. To date we have analysed appr. 8000 genes for expression in mid-gestation embryos. Some 600 genes showing a restricted expression in the caudal region of the embryo have been identified. In order to place them in regulatory networks we have started to analyse their promoters, produce and analyse knock-out and knock-down alleles using vector based RNA interference, and use ChIP-on-chip technology to identify targets of transcription factors acting in mesoderm development. The hierarchy of regulators controlling presomitic mesoderm formation, maturation and segmentation, has been established. The combined approaches will provide verified regulator-target relation

WS8-3
From precursor to product: organogenesis of the mammalian kidney.
Andy McMahon

Harvard University, Cambridge, MA, USA

The functional unit of the mammalian kidney is the nephron. Many hundreds of thousands of nephrons make up an adult human kidney. Nephrons arise from an epithelial precursor the renal vesicle. Our research has focused on understanding the molecular and cellular mechanisms that establish the renal vesicle from a mesenchymal progenitor pool, and maintain a competent progenitor cell population throughout the extensive period of kidney development.

WS8-4
Waves of endocrine-cell differentiation in the pancreas
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All pancreatic endocrine cells, producing glucagon, insulin, somatostatin or PP, differentiate from $Pdx1^+$ progenitors that transiently express Neurogenin3. To understand whether the competence of pancreatic progenitors changes over time, we generated transgenic mice expressing a tamoxifen-inducible Ngn3 fusion protein under the control of the *Pdx1* promoter and backcrossed the transgene into the $Ngn3^{-/-}$ background, devoid of endogenous endocrine cells. Early activation of $Ngn3ER^{TM}$ almost exclusively induced $glucagon^+$ cells, while depleting the pool of pancreas progenitors. As from E11.5, $Pdx1^+$ progenitors became competent to differentiate into $insulin^+$ and PP^+ cells. $Somatostatin^+$ cells were generated from E14.5 while the competence to make $glucagon^+$ cells was dramatically decreased. Hence pancreas progenitors, similar to retinal or cortical progenitors, go through competence states that each allow the generation of a subset of cell types. We further show that the progenitors acquire the competence to generate late-born cells in a mechanism that is intrinsic to the epithelium. We are currently investigating whether pancreas progenitors can execute the competence change in a cell-autonomous manner and what are the molecular mechanisms underlying these events.

WS8-5
Dynamic control of positional information by the *Drosophila* gap gene network
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Segment determination in *Drosophila melanogaster* is based on periodic prepatterns of gene expression produced by the segmentation gene network at the blastoderm stage of early development. The gap gene network constitutes the topmost of three hierarchical regulatory layers in the segmentation gene network. The establishment of spatially localized gap gene expression domains is thought to rely on threshold-dependent interpretation of positional information provided by maternal morphogen gradients. However, quantified gene expression patterns (http://urchin.spbcas.ru/flyex) show significant shifts in gap domain boundaries after their initial establishment. We have used the gene circuit method, a data-driven modeling approach to study the dynamical regulatory interactions underlying these domain boundary shifts. Our analysis suggests a regulatory mechanism based on asymmetric repressive feedback among gap genes.

This mechanism relies exclusively on gap-gap cross-regulatory interactions and does not require diffusion of gap proteins. In addition, we present a gene circuit analysis of the establishment of gap mRNA domains in the early blastoderm, which suggests that known maternal gradients are not able to position initial gap boundaries in the middle of the embryo. Our results imply that maternal gradients are not sufficient to determine positional information in the *Drosophila* blastoderm, and suggest that Wolpert's concept of positional information as a static embryonic coordinate system may be inadequate to explain pattern formation in the early *Drosophila* embryo.

WS9-1

From inflammation to fibrosis: the Y-box protein-1 as extracellular mediator of fibrogenesis

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The Y-box (YB) protein-1 is a prototypic member of the cold shock protein family with pleiotropic regulatory functions in gene transcription and mRNA translation. Recent findings indicate active secretion of this protein by different model cell systems after challenge with inflammatory cytokines (PDGF-BB, TGF-beta, IFN-gamma) and under oxidative stress. Given the extracellular occurrence we focused at defining extracellular roles of this protein. By means of *two hybrid* screening extracellular domains of the Notch receptor protein family were determined as interacting partner. In-depth analyses of the interaction of YB-1 with the extracellular aspects of cells and especially the Notch receptor indicate direct signaling of YB-1 via this receptor in cell model systems as well as experimental models of renal inflammation. Furthermore, human spot urine samples from patients with the most common glomerular disease, IgA nephritis, were tested for the presence of YB-1 protein. In a cohort of 21 patients the presence of YB-1 protein fragments was the best prognostic marker indicating adverse clinical course and progressive renal fibrosis over a 2 year follow-up period.
The roles of extracellular YB-1 in conveying profibrogenic effects and the promotion of proliferative diseases, e.g. cancer, will be discussed.

Workshop 9 - Novel approaches in anti-inflammatory drug therapy
Room: Montreal

WS 9-2

Jürgen Stein, University Hospital Frankfurt am Main, Germany
Anti-inflammatory mechanisms of histon deacetylase inhibitors

Abstract not available

WS9-3

Interleukin-17 is a negative regulator of established allergic asthma

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Th17 cells producing IL-17 play a role in autoimmune and allergic inflammation. Here, we show that IL-23 induces IL-17 in the lung and IL-17 is required during antigen sensitization to develop allergic asthma, as shown in IL-17R deficient mice. Since IL-17 expression increased further upon antigen challenge, we addressed its function in the effector phase. Most strikingly, neutralization of IL-17 augmented the allergic response in sensitized mice. Conversely, exogenous IL-17 reduced pulmonary eosinophil recruitment and bronchial hyperreactivity, demonstrating a novel regulatory role of IL-17. Mechanistically, IL-17 down-modulated eosinophil-chemokine eotaxin (CCL11) and Thymus- and Activation-Regulated Chemokine (TARC/CCL17) in lungs *in vivo* and *ex vivo* upon antigen restimulation. *In vitro*, IL-17 reduced TARC production in dendritic cells, the major source of TARC, as well as antigen uptake by dendritic cells, and IL-5 and IL-13 production in regional lymph nodes. Furthermore, IL-17 is regulated in an IL-4 dependent manner since mice deficient for IL-4Rαsignaling showed a marked increase in IL-17 concentration with inhibited eosinophil recruitment. Therefore, endogenous IL-17 is controlled by IL-4 and has a dual role. While it is essential during antigen sensitization to establish allergic asthma, in sensitized mice IL-17 attenuates the allergic response by inhibiting dendritic cells and chemokine synthesis.

WS9-4

Hypoxia regulates the sphingosine kinase-1 activity and expression in the endothelial cell line EA.hy926

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Sphingosine 1-phosphate (S1P) is a potent mitogenic signal generated from sphingosine by the action of sphingosine kinases (SKs). Hypoxia induces transcription of genes which are activated to facilitate cell survival and restore O_2 homeostasis.
In this study, we show that in the human arterial endothelial cell line EA.hy 926 chronic hypoxia induces a time-dependent up regulation of the SK-1 mRNA and protein expression which is followed by increased SK-1 activity. In contrast, SK-2 activity is not affected by hypoxia. The increased SK-1 protein expression is due to stimulated de novo synthesis since cycloheximide inhibited the delayed SK-1 protein up regulation. Moreover, the increased SK-1 mRNA expression results from increased promoter activation. The SK-1 promoter contains two putative hypoxia response elements (HRE). Deletion of the first HRE leads to a complete suppression of hypoxia-induced SK-1 promoter activity, whereas the second HRE has no influence on promoter activity. EMSA studies confirm that only one element is able to bind the hypoxia inducible factor (HIF). The induction of Sk-1 is dependent on HIF1α and HIF2α, as experiments with HIF inhibitors and small interfering RNA (siRNA) shows. Parallel to the induction of SK-1, hypoxia stimulates an increased migration of endothelial cells, which is prevented by depletion of the SK-1 by siRNA.
In summary, these data show that hypoxia induced HIF1a and HIF2a expression activates SK-1 in endothelial cells which, in turn, is critically involved in the mechanism of endothelial cell migration.

WS9-5

Sphingolipid signaling in inflammation

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The sphingolipid sphingosine 1-phosphate (S1P) has attracted a lot of interest during the last years because of its capability to trigger various important cellular responses including cell proliferation and differentiation, cell survival and cell migration. These cell responses are mainly mediated by S1P binding extracellularly to specific cell surface receptors, the S1P receptors of which 5 subtypes have been identified ($S1P_{1-5}$).Exposure of renal mesangial cells to S1P leads to a rapid activation of various protein kinase cascades including the TGFβ/Smad signalling cascade. Since TGF-β is considered as a potent anti-inflammatory cytokine in mesangial cells able to block cytokine-induced pro-inflammatory genes such as the inducible nitric oxide synthase (iNOS) and the secreted group IIA phospholipase A_2 ($sPLA_2$), a similar anti-inflammatory effect of S1P may be envisioned. Indeed, S1P leads to a reduction of cytokine-stimulated $sPLA_2$ expression and subsequent PGE_2 formation. Similarly, the therapeutically used FTY720, originally described as a immunosuppressive agent with S1P-receptor agonistic activity, also down-regulates cytokine-stimulated $sPLA_2$ expression and activity and PGE_2 formation. These suppressive effects of S1P and FTY720 were owing to a transactivation of the TGFβ/Smad pathway and to a Smad-mediated inhibition of $sPLA_2$ promoter activity.

In summary, these data suggest that the cellular regulation of S1P levels may be an important determinant of an inflammatory reaction.

Workshop 10 - Computation in heart disease Room: Rio

Abstracts not available, will be provided by the workshop organizers

WS11-1

Computational modelling and live imaging of plant development

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The aboveground development of plants is to a large extent determined by the shoot apical meristem (SAM) where differentiation from stem cells to differentiated organ tissue is initiated. One of the unique features of SAM function is its ability to maintain its structure and particular patterns of gene expression over the lifetime of the plant, despite the constant flow of cells away from the SAM and into organs or stem tissue. Important for SAM development is the maintenance of the "stem cell niche", a region of *CLV3*-expressing cells at the plant apex. While *CLV3* expression is induced by the transcription factor WUS, which is expressed in cells below the CLV3 region, CLV3 mediates repression of WUS activity. An important goal of our research (http://www.computableplant.org) is to incorporate this negative feedback system into a mathematical description of SAM development. Such a mathematical description, or model, would ideally include gene regulation, molecular interactions and hormone transport as well cellular growth and division. By utilizing confocal microscope-based live imaging techniques these types of data can now be obtained at high temporal and spatial resolution enabling the reverse engineering of molecular interactions as well as optimization of model parameters. Here we show how this approach is used to address questions related to stem cell regulation via the CLV3/WUS feedback system. Model hypotheses that spontaneously lead to robust spatial expression domains will be presented.

WS11-2

Mathematical models of phyllotaxis

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Within the variety of phyllotactic patterns found in nature, the most intriguing, and at the same time the most prevalent, is the spiral phyllotactic pattern. It is characterized by the arrangement of organs into conspicuous spirals (parastichies), where the numbers of parastichies are consecutive elements of the Fibonacci series. This pattern is related to the divergence angle between organs approximating the golden angle of 137.5 degrees. In the entire world of developmental biology, phyllotaxis is perhaps the most striking example of a phenomenon that can only be described using quantitative notions of geometry. Our molecular-genetic experiments indicate that active transport of the plant hormone auxin is the key process regulating phyllotaxis. A conceptual model based on these experiments provides an intuitively plausible interpretation of the data, but raises the question of whether the proposed mechanism is in fact capable of producing the observed temporal and spatial patterns. Moreover, is this mechanism robust, can it start de novo, and can it account for phyllotactic transitions, for instance, the frequently observed transition from decussate to spiral phyllotaxis? To answer these questions, we created a computer simulation model that reproduces, within the standard error, the divergence angles measured in Arabidopsis seedlings and reproduces the effects of selected experimental manipulations. It also reproduces distichous, decussate, and tricussate patterns. The model thus offers a plausible link between molecular mechanisms of morphogenesis and the geometry of phyllotaxis.

References

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2. Smith, R., Guyomarc'h, S., Mandel, T., Reinhardt, D., Kuhlemeier, C. and Prusinkiewicz, P. A plausible model of phyllotaxis. Proc. Natl. Acad. Sci. USA 2006 103: 1301-1306

WS11-3
Studying transcriptomes using gene and condition meta-profiles
Philip Zimmermann, Stefan Bleuler, Tomas Hruz, Oliver Laule, and Wilhelm Gruissem, ETH Zürich, Switzerland

Organisms grow and survive in their environment by activating different sets of transcriptional programs. The study of these programs requires the availability of genome-wide expression data sets from numerous developmental stages, treatments, and genetic modifications. While a single experiment allows to study a limited number of variables (e.g. time-course of a drug treatment), the compilation and simultaneous analysis of thousands of arrays allows to derive so-called meta-profiles and study multiple variables in a single run. A gene meta-profile is an average expression vector for a single gene across the time, space and response dimensions of a transcriptome. A condition meta-profile is the average expression vectors for a single condition across a set of genes.
Genevestigator® is a multi-organism gene expression database and web-based discovery tool for life scientists that uses both expression profiles and expression meta-profiles. Innovative tools facilitate the systematic exploration of gene expression across hundreds of tissues, developmental stages, stimuli, drug treatments, or mutations. This presentation will deal with the question whether and how meta-profiles can be used to study different transcriptional networks, with special focus on the model organisms mouse and *Arabidopsis*.

WS11-4
From assimilation to growth: carbon limitation in plants
Christian Körner, Institute of Botany, University of Basel

Since Theodore de Saussure's classical experiment in Geneva (1804), we know that plants assimilate carbon from the atmosphere rather than from soil, as was believed before. Since then it is taken as self-evident that photosynthesis drives plant growth. While it is unquestioned that plant dry matter and energy ultimately come from photo-assimilates, the functional relationship is the reverse in most situations: growth drives photosynthesis. Except for deep shade, where photon flux density is limiting, the rate of photosynthetic CO2 uptake is controlled by the capacity of the plant to invest carbon compounds into structural growth or storage. In turn, the activity of these C-sinks is driven by developmental stage and the availability of resources other than C. Because sink (meristem) activity is the predominant driver of carbon uptake 'on demand', and because it is against plausibility that all chemical elements required for plant life other then C are unlimited, we have to view plant growth as primarily controlled by stoichiometric rules and by the rate at which mineral nutrients are released from the substrate by microbes. Such a view at plant growth makes it easier to understand why there is no correlation between crop productivity and leaf photosynthetic capacity, puzzling crop breeders for 30 years, and why elevated atmospheric CO2 concentrations hardly stimulates plant growth, unless nutrients are added or the soil is disturbed (thus periodically activated). This insight also underpins, why any attempt at engineering the photosynthetic machinery for higher rates is unlikely to affect crop production. Under current ambient CO2-concentrations, it is sink activity and its developmental and nutrient control which matters. Textbooks do not yet reflect this rather basic wisdom of crop breeders. References: Körner C (2003) J Ecol 91:4ff; Körner C et al (2005) Science 309:1360ff; Körner C (2006) New Phytol 172:393ff.