<u>Preliminary Program</u>, Bioinformatics Satellite of the 2nd Int'l Congress on Stem Cells and Tissue Formation, 10.7.2008, BioTec, Dresden. For Registration, etc, see

http://project.informatik.uni-osnabrueck.de/stemcell-bioinformatics/

9:30-10:00	I. Roeder: *Analysis of Cellular Genealogies*
10:00-10:30	L. Royer: *Identifying candidate genes and pathways for neural-like stem cell differentiation using networks and textmining*
10:30-11:00	H. Schulz: *Genomic Analysis of Self-Renewal and Differentiation in Mouse Embryonic Stem Cells*
Coffee	
11:30-12:00	E. Tanaka: *Genetic profiling of regenerating tissue*
12:00-12:30	M. Arauzo: *Integration of gene expression and proteomics data for disentangling regulatory networks in toti- and pluripotent cells*
12:30-13:00	G. Fuellen: *Pluripotency Players and Networks*
Lunch	
14:15- 15:00	H. Meinhardt: *Models for regeneration from a pattern-formation perspective*
15:00-15:30	D.Onichtchouk & F.Geier: *A multi-scale modelling approach of Oct4/Pou5f1 – dependent state changes in the transcriptomes of zebrafish pluripotent blastomers, neural precursors, and neural stem cells.*
15:30- approx 16:30	Informal Get-Together

<u>Abstracts</u>:

Analysis of Cellular Genealogies

Ingo Roeder

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The analysis of individual cell fates within a population of stem and progenitor cells is still a major experimental challenge in stem cell biology. However, new monitoring techniques, such as high-resolution time lapse video microscopy, facilitate the tracking and the quantitative analysis of single cells and their progeny. Information on cellular development, divisional history, and differentiation are naturally comprised into a pedigree-like structure, denoted as cellular genealogy. However, to extract reliable information about effecting variables and control mechanisms underlying cell fate decisions, it is necessary to analyse large numbers of cellular genealogies, which calls for the application of automatic cell tracking algorithms. In the talk I will present methods that allow for the automatic reconstruction of cellular genealogies from time lapse video data of cultured hematopoietic stem cells. Furthermore, I will discuss a set of statistical measures that are specifically tailored for the analysis of cellular genealogies and I will show how these measures can be applied to characterize and compare cellular fates under different conditions.

Idenfying candidate genes and pathways for neural-like stem cell differentiation using networks and textmining

Loic Royer, Alexander Storch, Michael Schroeder

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The differentiation of Mesenchymal Stem Cells (MSCs) into Neural like Stem Cells (NSC) is still a poorly understood mechanism. We present a bioinformatics analysis of deregulated genes involved in the differentiation from MSC to NSC. Combining gene expression data with high quality interactions and textmining, we identify key candidate pathways and genes such as the hypoxia inducible factor and STAT signalling pathways.

Genomic Analysis of Self-Renewal and Differentiation in Mouse Embryonic Stem Cells

Herbert Schulz

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The FunGenES consortium has performed a collective analysis of extended expression datasets containing 258 expression arrays. The consortium comprising 20 researchers was established to study the transcriptome of ES cells during growth towards ectodermal, endodermal and mesodermal lineages. The general cross-project data analysis using different clustering, principle component, and functional enrichment approaches was feasible because of standardized experiment conditions and allowed the exploration of the genetic programs controlling self-renewal and differentiation. The study provides an entry point to unlock the regenerative potential of stem cells.

Genetic profiling of regenerating tissue

Dunja Knapp, Eugen Nacu, Elly Tanaka

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A number of animals have the remarkable capability to regenerate whole body structures after injury. Among vertebrates, members of the salamander family can regenerate their appendages, the spinal cord, tissues of the eye and the lower jaw. During this process, tissue amputation causes the mature tissue to produce of field of embryonic-like progenitors that regenerate all of the missing tissues. We are interested in the injury-initiated signals that start the process of regeneration, and the intracellular responses that reprogram the adult tissue to generate the stem cells for regeneration. Regeneration is a complex process involving the coordinated response of many tissue types. It is particularly challenging in this complex landscape to disentangle the genetic networks controlling progenitor cell formation. Which genetic networks underlie simply wound healing versus direct reprogramming of adult cells into progenitors? Are the genetic networks for reprogramming each tissue similar or distinctive? To address these questions, we are undertaking an expression analysis of regenerating salamander limb tissue using a custom designed microarray. To identify the genetic networks underlying regeneration, we are performing a dense time-course of regeneration, as well as expression profiling specific cell types such as dermis and Schwann cells during regeneration. We would like to understand which gene modules are common to dedifferentiating cell types, and which ones are cell-type specific.

Integration of gene expression and proteomics data for disentangling regulatory networks in toti- and pluripotent cells

Marcos J. Arauzo-Bravo, Kinarm Ko, Jeong Beong Kim, Johannes Graumann, David Ruau, Matthias Mann, Martin Zenke, Hans Schöler

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Embryonic stem cells (ESCs) have the capacity for self-renewal and the potential to form all the cell types of the body. This brings the possibility to exploit the ESC populations as cellular therapies for medical situations where tissue damage is irreversible. To make this potentials a reality, a better understanding of the interplay of the transcription factors (TFs), and their binding sites involved in the regulation of the transcription network that determine the ability of ESCs to maintain their self-renewal and pluripotency, is necessary. To elucidate the regulation pathways, we performed an integrating approach. We predicted stemness genes using as an experimental base the mouse embryonic stem cells, spermatogonial stem cells (SSCs), neural stem cells (NSCs) and mouse embryo fibroblasts (MEFs). We categorized as possible candidates for stemness those genes that were expressed in the stem cells populations, (ESC, SSC and NSC) but not in the control non-stemness population (MEFs). To measure the gene level of expression, we used Affymetrix microarrays and integrated and validated the results using a whole-proteome approach through protein abundance quantification using non-labelling mass spectrometer data.

Pluripotency Players and Networks

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A sketch of the interaction/regulation network underlying pluripotency was derived from reviews, original papers and databases. Possibilities to further enhance the network, to keep it up to date, and to put it into use, are discussed. The network is one cornerstone of the bioinformatics support to be supplied to the DFG-SPP "Pluripotency and Cellular Reprogramming". Multi-species comparison of 'pluripotency networks' and network data integration & filtering issues will be discussed.

Models for regeneration from a pattern-formation perspective

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The generation of primary embryonic axes, the formation of sub-patterns such as legs and wings, the formation of the proximodistal pattern during limb outgrowth or the formation of vascular structures are based, of course, on different molecular mechanisms. Therefore, also the mechanisms that allow compensating a partial loss of existing structures are expected to be different. By introducing models for the generation of these structures during normal development it will be shown that these mechanisms have strong self-regulatory components, which account for the reformation of signals that allow replacement the removed parts. Computer simulations will demonstrate that these models describe essential steps in regeneration rather precisely when compared with experimental observations.

A multi-scale modelling approach of Oct4/Pou5f1 – dependent state changes in the transcriptomes of zebrafish pluripotent blastomers, neural precursors, and neural stem cells.

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The early phase of vertebrate development is characterized by establishment and maintenance of a pluripotent stem cell population, from which progenitor cell populations for the various specific tissues successively segregate by patterning and induction mechanisms. Oct4/Pou5f1 is a transcription factor that has been associated with pluripotency and counteracts differentiation in blastomeres and ES cells in mammals. However, Oct4/Pou5f1 also functions in development of specific tissues, including endoderm specification and brain patterning. How Oct4/Pou5f1 contributes to regulatory networks involved in maintenance of embryonic blastomere pluripotency as well as in tissue specification is not well understood.

We characterized transcriptional targets of Oct4/Pou5f1 in early zebrafish development by microarray-based comparison of wild type and Pou5f1 mutant embryos at 9 selected developmental stages. Direct Pou5f1 targets were distinguished in additional experiments by suppression of translation of primary target gene mRNAs. One third of the direct targets are transcription factors. Nearly half of these are expressed in the earliest neural system primordia. Several of the direct (i.e. Sox2, Her3) as well as indirect (hesx1) targets were previously characterized as implicated in neural stem cell maintenance. In contrast, a subset of transcription factors indirectly (down-) regulated by Pou5f1 is known to be involved in promoting differentiation (Sox21, Pax6). This analysis has led us to identify genetic regulatory modules which are likely to define different cellular states from pluripotent blastomers to neural stem cells on one side, and differentiating cells on the other. Using a multi-scale modeling approach we aim to describe the formation of these different cell types on a population level as well as at individual cell level. The cell population level is reflected phenomenologically by a partial differential equation based model that describes the dynamics of each cell population on spatial and temporal axes taking cell differentiation and cell mobility into account. The characteristics of individual cells are controlled by genetic regulatory modules, implemented as ordinary differential equations, which enable cells to adopt different properties and fates depending on their environment and regulatory state. This complementary modeling approach will utilize quantitative time series analysis of expression levels as well as cell population sizes to establish data based dynamic models linking cell population characteristics and the involved genetic regulatory modules. These models should aid to predict crucial regulatory features of state changes from pluripotent to neural stem cell as well as maintenance of the pluripotent state.