2014 LOUIS-JEANTET SYMPOSIUM

October 15 2014
Centre Medical Universitaire (CMU), Geneva
Auditorium 250

Yann Barrandon

Head of laboratory of Stem Cell Dynamics at Ecole Polytechnique Fédérale de Lausanne (EPFL)
Head of Experimental Surgery at Centre Hospitalier Universitaire Vaudois (CHUV)

Wednesday, October 15 2014, 09:00 – 09:25

Microenvironment and stemness

Biography

Yann Barrandon, MD-PhD, is joint professor in Stem Cell Dynamics at the EPFL and at the Lausanne University (Unil), and head of the Department of Experimental Surgery at the CHUV since 2002. He has made major contributions in basic epithelial stem cell biology and in stem cell therapy. YB is a member of the EMBO and the Academia Europaea. He is also a member of the EPFL research committee, EPFL Ethical committee and the Canton de Vaud Ethical committee. He was elected twice best teacher in Life Sciences at EPFL. In 2011, he co-founded gymetrics SA. Since 2012, he is “Initiative director” for the doctoral training cooperation initiative signed between the EPFL and A*Star Singapore.

http://ldcs.epfl.ch/

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October 15 2014
Centre Medical Universitaire (CMU), Geneva
Auditorium 250

Cédric Blanpain

Université Libre de Bruxelles (ULB) – IRIBHM

Wednesday, October 15 2014, 09:25 – 09:50

Mechanisms regulating stemness in skin cancers

For the vast majority of cancers, the cell at the origin of tumor initiation is still unknown. Two epithelial skin cancers are frequent in human populations: the basal cell carcinoma and the squamous cell carcinoma. We developed genetic lineage tracing approaches to identify the cells at the origin of these two types of cancer in mice, isolate these oncogene targeted cells and determined the molecular changes associated with tumor initiation (Youssef NCB 2010, Youssef NCB 2012, Lapouge PNAS 2011).
Cancer stem cells (CSCs) have been described in various cancers including skin squamous cell carcinoma. Using different approaches in mice, we have recently shown that mouse squamous skin tumors contain cancer stem cells characterized by their greater ability to be propagated long term upon transplantation into immunodeficient mice (Lapouge EMBO J 2012) or by their ability to fuel tumor growth using lineage tracing experiments (Driessens Nature 2012).
We transcriptionally profiled and identified genes preferentially upregulated in CSCs. Using state of the art genetic gain and loss of function in mice, we are defining how some of these genes regulate tumor stemness and malignant transition in vivo within their natural environment. I will discuss how the combination of extrinsic factors such as the vascular niche (Beck Nature 2011) and intrinsic factors, such as the expression of Sox2, a transcription factor expressed in a variety of developmental progenitors and adult stem cells, regulate tumor heterogeneity, renewal and invasive properties of CSCs during skin cancer progression (Boumhadi Nature 2014).

Biography

Cédric Blanpain, MD/PhD, is full professor and WELBIO investigator at the IRIBHM, Université Libre de Bruxelles, Belgium. His lab is studying the role of stem cells (SCs) during development, homeostasis and cancer. His lab uncovered stem and progenitors cells in the epidermis, prostate and mammary gland, the cellular origin of the skin cancers, demonstrated the existence of cancer stem cells in skin tumors and the mechanisms regulating their functions.
Cedric Blanpain has been supported by a career development award of the Human Frontier Science Program (HFSP), starting and consolidator grants from the European Research Council (ERC), a research grant from the Foundation Schlumberger for Education and Research (FSER), the Young EMBO investigator program. He received the outstanding young investigator award of the International Society of Stem Cell Research (ISSCR) and the Liliane Bettencourt award for Life Sciences. He is been elected EMBO member in 2012.

http://blanpainlab.ulb.ac.be/index.htm

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Auditorium 250

Margaret Buckingham

Department of Developmental and Stem Cell Biology, CNRS URA 2578, Institut Pasteur, Paris.

Wednesday, October 15 2014, 10:05 – 10:30

Regulation of muscle satellite cells

Adult skeletal muscle homeostasis and regeneration relies on satellite cells. Unlike muscle stem cells in the embryo, most adult satellite cells have activated the myogenic determination gene, *Myf5*, and thus have acquired muscle identity. However, post-transcriptional mechanisms (1) prevent accumulation of myogenic factors so that satellite cells constitute a reserve cell population which can be mobilized in response to muscle damage. Quiescent satellite cells in their niche on the muscle fibre employ protective strategies against toxins and stress (2). Once activated, satellite cells proliferate and then begin to differentiate into muscle fibres. This process is accompanied by major metabolic changes, as the differentiating cells progress from a glycolytic to an oxidative state with extensive mitochondrial biogenesis. This leads to increased production of reactive oxygen species (ROS). We show that Pitx transcription factors, also present in the quiescent cell, regulate ROS levels by directly activating genes in the antioxidant pathway (3). In *Pitx2;Pitx3* double conditional mutant mice, ROS levels are abnormally high leading to DNA damage, satellite cell senescence and impaired regeneration. In *Pitx3* single mutants, on the other hand, premature differentiation occurs. By manipulating ROS inhibitors in activated satellite cells we show that a moderate level of ROS, acting through the p38 kinase pathway, is necessary for the correct timing of the onset of differentiation. Thus, the physiological enhancement of ROS production and mitochondrial content is an essential regulator of muscle stem cell behaviour.

(1) Crist et al., (2012) Cell Stem Cell **11,** 118; (2) Montarras et al., (2013) FEBS J. **280,** 4036; (3) L'honoré et al., (2014) Dev. Cell **29** 392.

Biography

Margaret Buckingham is an emeritus Research Director in the C.N.R.S. and Professor at the Pasteur Institute in Paris. She is a member of the Académie des Sciences, the Royal Society and the National Academy of Sciences, USA. She graduated in Biochemistry from Oxford University and did postdoctoral work with F. Gros on mRNAs during myogenesis. Using mouse genetics, she has characterised genes that regulate the behaviour of muscle stem cells in the embryo and the adult. Her work on cardiogenesis led to the identification of the second heart field as a major source of cells that form the mammalian heart.

http://www.pasteur.fr/fr/recherche/biologie-du-developpement-cellules-souches/unites-et-groupes/genetique-moleculaire-du-developpement

2014 LOUIS-JEANTET SYMPOSIUM

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Auditorium 250

Tannishtha Reya

Department of Pharmacology, Sanford Consortium for Regenerative Medicine and Moores Comprehensive Cancer Center, University of California San Diego School of Medicine

Wednesday, October 15 2014, 10:30 – 10:55

Stem cell signals in cancer growth and progression

Our research focuses on the signals that control stem cell self-renewal and how these signals are hijacked in cancer.
Using a series of genetic models, we have shown that classic developmental signaling pathways such as Wnt, Hedgehog and Notch play key roles in hematopoietic stem cell growth and regeneration and are dysregulated during leukemia formation. In addition, we have used real-time imaging strategies to show that hematopoietic stem cells have the capacity to undergo both symmetric and asymmetric division, and that shifts in the balance between these modes of division are controlled by the microenvironment and subverted by oncogenes.
Importantly, we have shown that regulators of asymmetric division, including the cell fate determinant Musashi, and the spindle positioning protein Lis1, are critical players in driving progression of solid and liquid cancers and could serve as targets for diagnostics and therapy.
Ongoing studies in the lab also aim to understand mechanisms driving therapy resistance after targeted drug delivery or radiation treatment. Finally, we have developed a high resolution *in vivo* imaging system that has allowed us to begin to map the behavior and interactions of stem cells with the microenvironment within living animals, and to define how these change during cancer formation.

Biography

Tannishtha Reya received her B.A. from Williams College and her Ph.D. from the University of Pennsylvania. Subsequently she completed her postdoctoral training at UCSF and Stanford University. Dr. Reya joined the Duke University faculty in 2001 and served as the Co-Director of the Stem Cell Biology and Regenerative Medicine Program.
She was recruited to the University of California San Diego in 2010 where she is a Professor of Pharmacology, and co-director of the Stem Cell Research Program at the Moores Comprehensive Cancer Center.
Her awards include the Presidential Early Career Award for Scientists and Engineers and the Pioneer Award.

http://www.reyalab.org

FONDATION LOUIS-JEANTET

2014 LOUIS-JEANTET SYMPOSIUM

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Centre Medical Universitaire (CMU), Geneva
Auditorium 250

Freddy Radtke
Swiss Institute for Experimental Cancer Reserach (ISREC),
Ecole Polytechnique Fédérale de Lausanne

Wednesday, October 15 2014, 11:10 – 11:35

Indirect regulation of stem cell fate by inflammation

The corneal epithelium is a self-renewing epithelium that is responsible for maintaining the integrity of the ocular surface. Maintenance of this tissue is mediated by corneal epithelial stem cells that are located predominantly at the limbus. Interestingly, corneal epithelial stem cells are endowed with a high degree of plasticity and can adopt different epithelial cell fates depending on the microenvironment they are exposed to. Related to this, chronic inflammatory diseases of the cornea are closely associated with squamous cell metaplasia, where the corneal epithelium adopts an epidermal-like fate resulting in blindness.
We have elucidated the cellular and molecular events that promote corneal squamous cell metaplasia by using conditional Notch1 knockout mice, in which the corneal epithelium adopts an epidermal fate in response to injury. We demonstrate that the epidermal fate switch in Notch1 deficient corneal epithelial cells results from a chronic inflammatory response that is initiated during repair by the immediate early response factor c-jun/AP-1. In response to chronic inflammation, Wnt signaling is elevated in the corneal epithelium and is essential for promoting epidermal fate conversion; genetic ablation of ß-catenin is sufficient to maintain normal corneal differentiation even in the presence of a chronic inflammatory environment. Moreover we show that chronic inflammation, results in increased ECM deposition in close proximity of limbal stem cells, causing changes in tissue stiffness, and activation of mechano transduction pathways which leads to increased b-catenin mediated wnt signaling and squamous cell metaplasia.

Biography

Freddy Radtke graduated from University of Zürich in molecular biology 1994, a postdoctoral fellowship at Genentech Inc. USA 1995-1996 was followed by a postdoctoral position at ISREC Switzerland 1997-1999; Assistant Member of the Ludwig Institute for Cancer Research 1999-2004 promoted to Associate Member in 2004; joined ISREC as Senior Scientist in 2006, before joining EPFL in August 2006 as associate professor and promoted to full professor in 2012.

http://radtke-lab.epfl.ch/

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Paolo Bianco
Department of Molecular Medicine, Sapienza University of Rome

Wednesday, October 15 2014, 11:35 – 12:00

Bone marrow, the skeleton and stem cells

The bone marrow harbors multipotent, clonogenic progenitors for multiple lineages (bone, cartilage, adipocytes, fibroblasts). These cells are able to self-renew in vivo, reside at the abluminal surface of bone marrow sinusoids, can be identified and isolated based on phenotype both in humans and in mice (CD146, Leptin receptor) and represent a pivotal component of the hematopoietic “niche” and microenvironment. Heterotopic transplantation represents the mainstay of the experimental investigation of human stromal (skeletal, aka “mesenchymal”) stem cells in the bone marrow. Recent development of this classical approach have extended their significance in multiple directions: the comparative use in similar assays of cells isolated from multiple sources reveals the existence of perivascular postnatal progenitors endowed with distinct potential in different tissues; refined versions of heterotopic grafts allow for quantitative assessment of the hematopoietic “niche” and microenvironment; and transplantation of genetically abnormal stromal progenitors from patients with genetic diseases provide a unique way of modeling human diseases with stem cells in vivo. Originally shaped conceptually on the blueprint provided by hematopoiesis, the stromal system has unique biological features. A measure of plasticity of differentiated phenotypes links to one another “lineages” commonly seen as sharply distinct (e.g., bone and fat, bone and cartilage), and multiple cell types in the system play functions in the assembly and regulation of microvascular networks, directly amenable to in vivo assay. Understanding the regulatory circuitries that underpin these properties, and identifying the evolutionarily selected function(s) that the stromal system plays in the organism are important challenges ahead.

Biography

Paolo Bianco, MD is currently a Professor and Director of Anatomic Pathology, and Director, Stem Cell Lab, Department of Molecular Medicine at Sapienza University of Rome. His work focuses on stem cells for skeletal tissues in the bone marrow, aka mesenchymal stem cells, their biology, role in disease and significance in therapies and medicine. His contributions include the direct identification of such cells in the human bone marrow, prospective isolation, identity as perisinusoidal cells, role in the hematopoietic niche and proof of their self-renewal in vivo.

http://www.accademiamedicadiroma.it/
http://www.eurostemcell.org/biography/paolo-bianco

2014 LOUIS-JEANTET SYMPOSIUM

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Auditorium 250

Hans Clevers

2004 Louis-Jeantet prize-winner

Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences & University Medical Centre, Utrecht

Wednesday, October 15 2014, 12:00 – 12:25

Keynote lecture: Wnt signaling, Lgr5 stem cells and cancer

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined *Lgr5* as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of *Lgr5* in cycling, columnar cells at the crypt base. Using lineage tracing experiments in adult mice, we found that these *Lgr5*$^{+ve}$ crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific and almost 'generic' marker for stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear tongue and stomach epithelium.
Single sorted *Lgr5*$^{+ve}$ stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the *Lgr5*$^{+ve}$ stem cells of stomach, liver, pancreas and kidney.
Intestinal cancer is initiated by Wnt pathway-activating mutations in genes such as APC. As in most cancers, the cell of origin has remained elusive. Deletion of APC in stem cells, but not in other crypt cells results in progressively growing neoplasia, identifying the stem cell as the cell-of-origin of adenomas. Moreover, a stem cell/progenitor cell hierarchy is maintained in early stem cell-derived adenomas, lending support to the “cancer stem cell”-concept.

Biography

Hans Clevers obtained his MD-degree in 1984 and his PhD-degree in 1985 from the University Utrecht, the Netherlands. He worked as postdoc (1986-1989) with Cox Terhorst at the Dana-Farber Cancer Institute of the Harvard University, Boston, USA.
From 1991-2002 he was Professor in Immunology at the University Utrecht and, since 2002 in Molecular Genetics. From 2002-2012 he was director of the Hubrecht Institute, Utrecht. Since 2012 he is President of the Royal Netherlands Academy of Arts and Sciences (KNAW).
He is the recipient of multiple awards and Chevalier de la Legion d'Honneur (2005) and Knight in the Order of the Netherlands Lion (2012).

http://www.hubrecht.eu/research/clevers/index.html

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Jennifer Nichols

Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute, Department of Physiology, Development and Neuroscience, University of Cambridge

Wednesday, October 15 2014, 13:40 – 14:05

Embryo origin of pluripotency

The mammalian embryo's ability to orchestrate the production of specific tissues in the correct time and place depends upon specification and control of a pool of pluripotent cells. We are interested in how these cells are segregated and the process by which they can be captured to produce naïve pluripotent embryonic stem (ES) cell lines capable of forming all the tissues in the body. We have generated transcriptional and functional data demonstrating that embryonic cells acquire the properties of naïve pluripotent ES cells during blastocyst expansion, and that the closest molecular counterpart to ES cells in the embryo is the epiblast just before blastocyst implantation. We use embryos in which specific core pluripotency factors are genetically deleted to investigate how the pluripotency network is established in the blastocyst inner cell mass. Our findings suggest that the majority of pluripotency-associated genes examined so far are activated normally, even when Oct4 or Nanog is completely deleted. This surprising observation is somewhat at odds with the widely accepted assumption prompted by *in vitro* analysis of ES cells that assembly of the wider network is dictated by the core pluripotency factors. Furthermore, it leaves open the question of the exact causes of subsequent developmental collapse in these mutant embryos. We propose that establishment of pluripotency *in vivo* is initiated by a robust mechanism, independent of these core pluripotency factors, and that acquisition of naïve pluripotency is a secondary step dependent upon interplay between pluripotency factors and the environmental cues within the developing embryonic niche.

Biography

Jennifer Nichols first studied early mouse development under the supervision of Richard Gardner in Oxford, and subsequently joined Austin Smith's lab in Edinburgh to concentrate on investigating how the pluripotent lineage is specified during early mouse development and how embryonic stem (ES) cell lines can be captured *in vitro*. She is now a group leader at the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute. The group studies entry, maintenance and departure of pluripotency in several mammalian model systems. These include embryos with specific and inducible deletions in key pluripotency factors, embryonic diapause and live imaging of ES cell chimaeras.

http://www.stemcells.cam.ac.uk

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Hendrik G. Stunnenberg

Head of Department of Molecular Biology, Science faculty, Radboud University, Nijmegen

Wednesday, October 15 2014, 14:05 – 14:30

Genomics and epigenomics of pluripotency

Deciphering the human genome sequence has provided critical insight in genome function in relation to biological processes in health and diseases. Recent technological improvements have opened up the analysis of the epigenetic regulation of the information embedded in the genome. Epigenetic regulation takes place at many levels including histone modifications, positioning of histone variants, nucleosome remodeling and DNA accessibility. Together with DNA modifications, transcription factors and other DNA-binding proteins this information provides an epigenetic blueprint. The epigenetic features of each cell type in the body (>250) are distinct and once established during development and differentiation need to be maintained. Hence, the study of epigenetic processes go beyond DNA-stored information and provide essential insight in the manual of the genome, in deciphering derailed processes in disease. I will discuss mechanisms and modeling of DNA demethylation in embryonic stem cells.

Biography

Henk Stunnenberg is full professor and head of the Department of Molecular Biology since 1996. He is a member of EMBO.
He obtained his PhD in 1981 in Biology, was post-doc in Zurich and Basel Switzerland from 1981-1985 and was group leader at the EMBL in Heidelberg from 1985-1996. He is coordinator of the EU FP7 High Impact Project BLUEPRINT-epigenome (www.blueprint-epigenome.eu) and chair of the scientific steering of the International Human Epigenome Consortium (IHEC) (www.ihec-epigenomes.org).

http://www.ncmls.nl/molbio/home.htm

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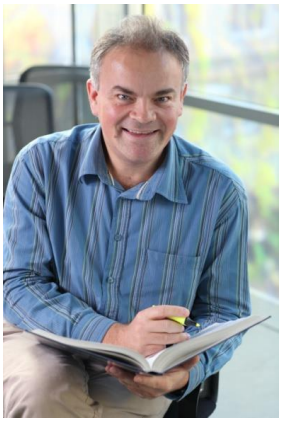

Juergen A. Knoblich
Institute of Molecular Biotechnology of the Austrian Academy of Science (IMBA), Vienna

Wednesday, October 15 2014, 14:45 – 15:10

Modeling human brain development and disease in 3D culture

The human brain is highly unique in size and complexity. While many of its characteristics have been successfully studied in model organisms, recent experiments have emphasized unique features that cannot easily be modeled in animals. We have therefore developed a 3D organoid culture system derived from human pluripotent stem cells that recapitulates many aspects of human brain development. These cerebral organoids are capable of generating several brain regions including a well-organized cerebral cortex. Furthermore, human cerebral organoids display stem cell properties and progenitor zone organization that show characteristics specific to humans. Finally, we use both RNAi and patient specific iPS cells to model microcephaly, a human neurodevelopmental disorder that has been difficult to recapitulate in mice. This approach reveals premature neuronal differentiation with loss of the microcephaly protein CDK5RAP2, a defect that could explain the disease phenotype. Our data demonstrate an *in vitro* approach that recapitulates development of even this most complex organ, which can be used to gain insights into disease mechanisms.

Biography

Juergen Knoblich did his PhD in the laboratory of Christian Lehner at the Friedrich Miescher Institute of the Max Planck Society in Tübingen. After a postdoctoral period in the laboratory of Yuh Nung Jan at UCSF, San Francisco, he joined the IMP in 1997 as a junior group-leader. In 2004, he moved to IMBA where he is now senior scientist and deputy director.

The Knoblich lab uses Drosophila and mouse genetics to identify the molecular mechanisms that control asymmetric cell division and the balance between proliferation and differentiation in neural stem cell lineages.

http://www.imba.oeaw.ac.at/research/juergen-knoblich/

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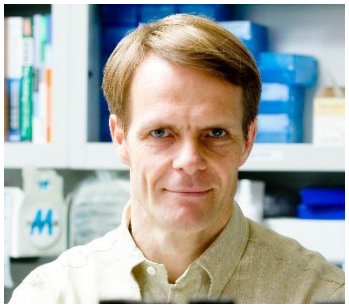

Lorenz Studer

Memorial Sloan Kettering Cancer Center, New York

Wednesday, October 15 2014, 15:10 – 15:35

Disease modelling with induced pluripotent stem cells

The discovery of induced pluripotent stem (iPS) cells offers novel stem cell based therapeutic opportunities. In addition to developing patient-matched cell therapies, a particularly promising approach is the use of iPS cells for modeling human genetic disease. Our group has demonstrated that iPS cell based disease modeling can yield novel insights into disease mechanisms and serve as platform for drug discovery. Some of the most successful examples for modeling disease in vitro have been for early onset monogenic disorders such as familial dysautonomia (FD) or primary Herpes Simplex encephalitis (HSE). In both cases, we were able to use iPSC technology to gain novel mechanistic insights into pathogenesis of those disorders. Recent studies in the lab also address Hirschsprung's disease, another early-onset genetic disease affecting the enteric nervous system where both disease modeling and cell therapy strategies are being pursued. Modeling late-onset disorders such as Parkinson's disease (PD) using iPS cells present additional challenges such as the question on how to model the age-component of the disease. To address this issue, we have developed methods to manipulate aspects of cellular age that in combination with patient-specific iPSC technology can reveal late-onset phenotypes of disease. Advances in human genetics, human iPS cell technology, directed differentiation and cell based screening platforms are key elements towards harnessing the full potential of in vitro human disease modeling efforts in the future.

Biography

A native of Switzerland, Lorenz Studer graduated from medical school in 1991 and received his doctoral degree in Neuroscience at the University of Bern in 1994. As a postdoctoral fellow he joined the laboratory of Ron McKay at the NIH in Bethesda where he demonstrated the first successful use of in vitro derived dopamine neurons in an animal model of Parkinson's disease. In 2000, he started his own research program at the Memorial Sloan-Kettering Cancer Center (MSKCC) in NYC. His lab pioneered strategies for the directed differentiation of pluripotent stem cells. He also developed some of the first iPS cell-based disease models and is currently leading a large effort towards the clinical application of human pluripotent stem cells in Parkinson's disease. Studer is Director of the Sloan-Kettering Center for Stem Cell Biology, a Member of the MSKCC Developmental Biology Program and a Professor in Neuroscience at Weill-Cornell.

http://www.mskcc.org/research/lab/lorenz-studer

2014 LOUIS-JEANTET SYMPOSIUM

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Thomas Graf

Senior Scientist and ICREA professor
Centre for Genomic Regulation, Barcelona

Wednesday, October 15 2014, 15:50 – 16:15

Learning about differentiation from forced cell fate changes

How do stem cells differentiate to generate the large variety of specialized cells in our body? How are stem cells generated in the first place? Major insights into these processes have come from perturbation experiments with transcription factors that result in cell reprogramming.
In my talk I will discuss how the enforced expression of the macrophage restricted transcription factor C/EBPa can direct B lymphocytes to become macrophages. I will also discuss recent data showing that the same transcription factor can facilitate the transition of B cells into induced pluripotent stem cells by the Yamanaka factors. These two highly efficient and rapid reprogramming systems permit to study the early events required for cell differentiation and the generation of stem cells, and to determine whether they are based on common principles. One such principle that has emerged is the activation of a DNA modifying enzyme (Tet2), which is required for both the fully efficient induced conversion of B cells into both macrophages and iPS cells.

Biography

Thomas Graf did his PhD at the University of Tuebingen and postdoc at Duke University. After working as a Group Leader at the Max Planck Institute in Tuebingen and the DKFZ in Heidelberg he served as a Programme Coordinator at EMBL in Heidelberg. Following work for 8 years in New York at the Albert Einstein College of Medicine he is now a Senior Scientist at CRG in Barcelona.
Graf co-discovered several viral oncogenes and showed that they co-operate in causing leukemia. More recently he demonstrated that cell type-restricted specific transcription factors can transdifferentiate blood cells and facilitate reprogramming of pluripotent stem cells.

http://www.crg.eu/en/programmes-groups/hematopoietic-stem-cells-transdifferentiation-and-reprogramming

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Auditorium 250

Sarah-Jane Dunn
Biological Computation, Computational Science Laboratory
Microsoft Research, Cambridge

Wednesday, October 15 2014, 16:15 – 16:40

Biological computation in pluripotent stem cells

The culture conditions required to sustain embryonic stem (ES) cells *in vitro* have been progressively refined. It is understood that a homogeneous population of ES cells can be established solely under '2i' (CH and PD), but that the addition of the cytokine leukaemia inhibitory factor (LIF) is optimal. Moreover, it is possible to maintain and propagate ES cells using any two of these three components, suggesting a flexible transcriptional program. But how does an ES cell process the information that it receives from these input signals? What is the biological computation that determines pluripotency?

To address this question, we adapted formal methods traditionally applied to probe and verify safety-critical engineered systems to reason automatically about biological data and models. We developed a data-constrained, computational approach to tackle and reduce the complexity of a potentially vast interactome to derive a set of functionally validated components and gene interaction combinations sufficient to explain observed ES cell behaviour. The minimal set, which comprises only 16 interactions, 12 components, and three inputs, satisfies all prior specifications for self-renewal and furthermore predicts unknown and non-intuitive responses to compound genetic perturbations. Utilising this pluripotency program, we ask whether it is possible to predict conditions under which naïve pluripotency can be induced, and interrogate the efficiency of this process – the results of which could be applied both to understand and to derive protocols for cellular reprogramming.

Biography

I studied Mathematics at the University of Oxford, graduating in 2007. I remained at Oxford as a postgraduate student, joining the Computational Biology group within the Department of Computer Science. My DPhil focused on the development of a computational model of the intestinal crypt, to investigate the initial stages of carcinogenesis in colorectal cancer. I joined Microsoft Research in 2011 as a postdoctoral researcher within the Computational Science laboratory. Here I migrated my research interests towards the fundamental concepts of biological computation, with particular emphasis on computation in stem cells. In June 2014 I became a permanent scientist at Microsoft.

http://research.microsoft.com/en-us/groups/science/

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Austin G. Smith

2010 Louis-Jeantet prize-winner

Medical Research Council Professor & Director, Wellcome Trust – Medical Research Council, Cambridge Stem Cell Institute, University of Cambridge

Wednesday, October 15 2014, 16:40 – 17:05

***Keynote lecture*: Ground state of pluripotency**

Pluripotency may be defined as the capacity of individual cells to initiate all lineages of the mature organism in response to signals from the embryo or cell culture environment. A pluripotent cell has no predetermined programme; it is a ground state. This is the foundation of mammalian development and of embryonic stem (ES) cell biology. What are the design principles of this primitive cell state? How is naïve pluripotency acquired and maintained. Suppressing activation of extracellular signal regulated kinases (Erk) is critical to establishing and sustaining true embryonic stem cells. Inhibition of glycogen synthase kinase-3 (Gsk3) reinforces this effect. We review the effect of selective kinase inhibitors on pluripotent cells and consider how these effects are mediated.

Biography

Professor Smith, obtained his Ph.D. from the University of Edinburgh in 1986. Following postdoctoral research at the University of Oxford, he joined the Institute for Stem Cell Research at the University of Edinburgh in 1990 as a group leader. In 1996, he was appointed Director of the Centre. He was appointed MRC Research Professor in 2003. He took up the post of Director of the Cambridge Stem Cell Institute in 2006. Professor Smith's expertise is in the field of stem cell biology and has pioneered key advances in the field of Embryonic Stem Cell research. His research focuses on the molecular and cellular controls of embryonic and somatic stem cells, and on interconversion between pluripotent and tissue-restricted states.

http://www.stemcells.cam.ac.uk/