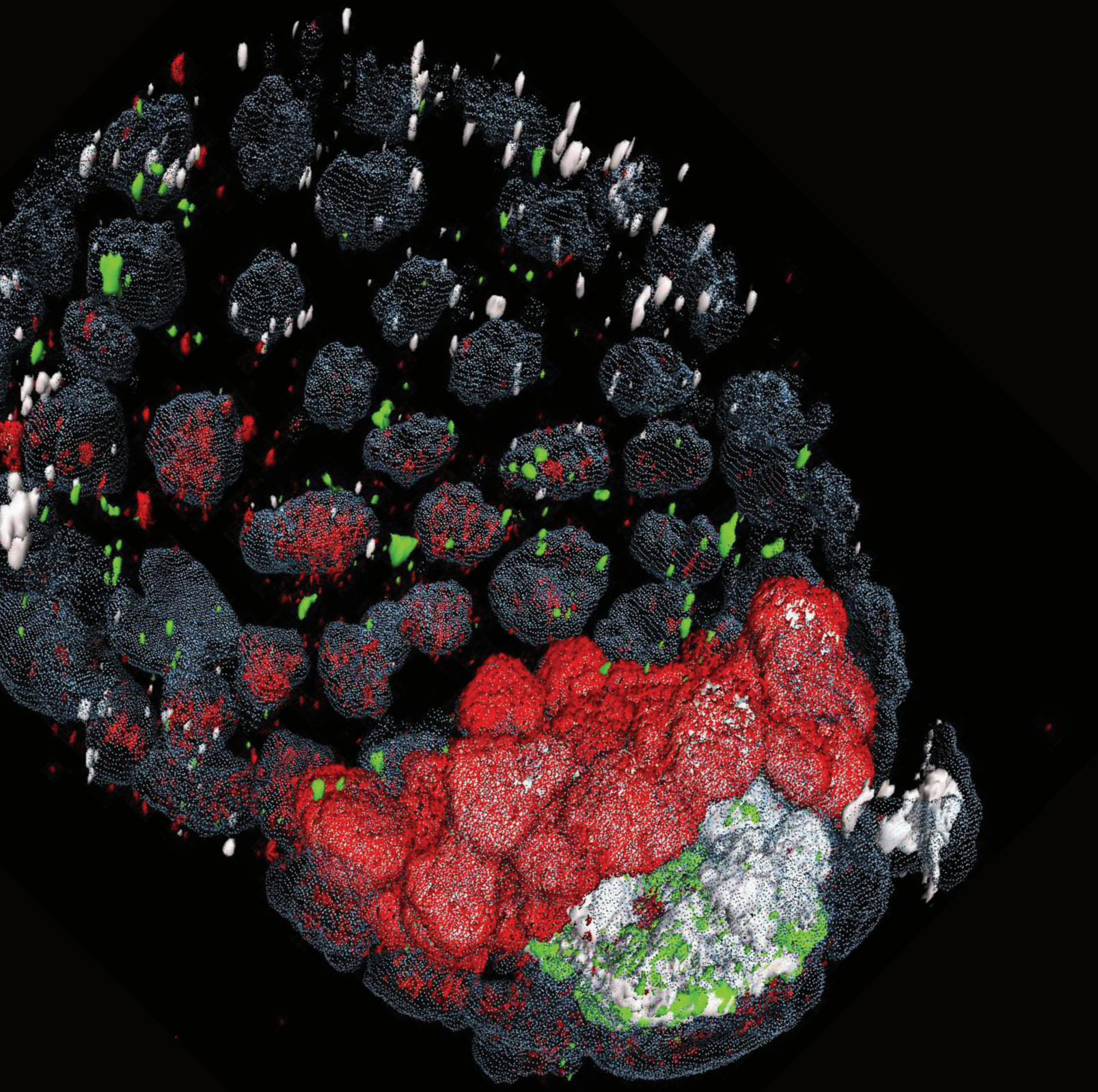
Wellcome Trust - Medical Research Council

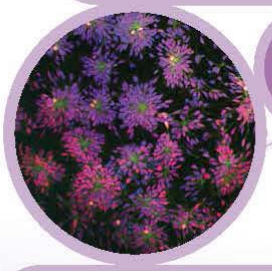
Cambridge Stem Cell Institute

2013

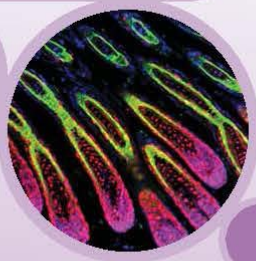


Wellcome Trust - Medical Research Council
Cambridge Stem Cell Institute

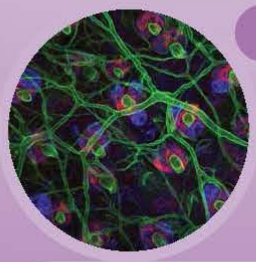
World-leading Institute for stem cell biology and medicine



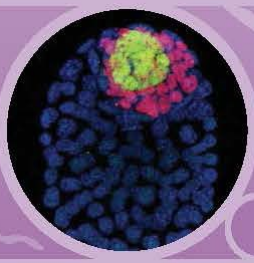
Outstanding researchers from 25 stem cell laboratories in Cambridge



Exploring and defining the properties of stem cells to establish their true medical potential



Cross-disciplinary collaboration



www.stemcells.cam.ac.uk

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Contents

Vision:

"Deep understanding of stem cell biology for prevention and treatment of human disease."

The Institute

Strategy:

Fundamental science of the highest quality and rigour to elucidate the governing principles of stem cell identity and behaviour.

Translational research taking basic science into the clinic to investigate stem cell malfunction in disease, and to define the role of stem cells in regenerative medicine.

Training and mentoring of talented researchers including clinician scientists to implement, spread and evolve the vision.

Collaboration with academia, clinicians and industry in the UK and worldwide to accelerate and enhance understanding of stem cells and their applications.

Communication and public engagement providing reliable information, useful resources, and dialogue opportunities for a range of audiences including schools, policy makers, patient groups, professional bodies, and the media.

Austin Smith
Institute Director

The Institute

Stem Cell Research

Stem cell science is providing a stream of new knowledge about how our bodies are made and maintained. This research brings the promise that better understanding of stem cells will lead to future medical applications. Treatments may come through several routes:

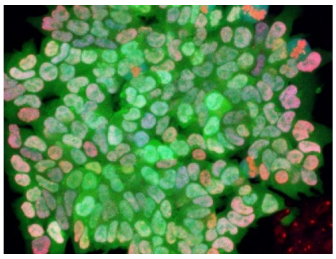
- Human stem cells grown in the laboratory can be used to produce experimental models of diseased tissues and to test therapeutic drugs.
- Some diseases, including forms of cancer, involve abnormal behaviour of stem cells. As we learn how to control stem cells it may become possible to correct these faults.
- Stem cells could be used to renew damaged tissues and replace missing cells in certain disorders.
- Learning how to prevent a decline in numbers and activity of stem cells may help to maintain health during ageing.

Cambridge University has invested in recruiting high quality investigators in mammalian stem cell research at both senior and junior levels. There are currently 26 mainstream stem cell laboratories comprising more than 300 group members including post-doctoral researchers and PhD students.

Leading research scientists, technology specialists and doctors work side by side to create a world-leading centre of excellence in stem cell biology and medicine. The Institute also provides high level training for young researchers from around the world and collaborates with bioindustry.

Research Themes

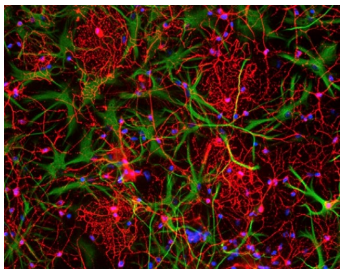
Pluripotency



Pluripotent stem cells can be derived from early embryos, produced by epigenetic conversion of germ cells, or created by transcription factor mediated reprogramming of somatic cells. Our fundamental investigations are directed at the molecular foundations of pluripotency, mechanisms of lineage-specific differentiation and comparative analyses between rodent and human.

Theme Leader: Surani
Principal Investigators: Hendrich, Nichols, Silva, Smith, Vallier, Wutz, Chalut
Affiliate Investigators: Bertone, Bradley, Hemberger, Liu, Martinez-Arias, Reik, Rugg-Gunn, Skarnes

Neural



Concepts regarding cell replacement and regeneration in the adult mammalian central nervous system (CNS) have undergone a radical shift in recent years. This is due in part to the discoveries of continuous neurogenic activity in distinct anatomical regions and of a robust propensity for replacement of oligodendrocytes that myelinate CNS axons. Nevertheless, the loss of neurons remains a major clinical challenge prompting a renewed effort in translational science aimed at prevention as well as replacement. Neuronal loss can occur as a result of (i) inherent defects, (ii) inflammation and (iii) loss of trophic support provided by myelinating cells. In this theme we bring stem cell biology to bear all three causes in an integrated programme of basic and translational research.

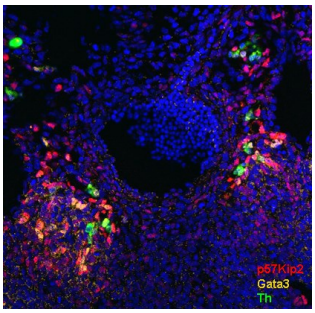
Theme Leader: Franklin
Principal Investigators: Barker, Karadottir, Kotter, Livesey, Pluchino
Affiliate Investigators: Ferguson-Smith, Martin, Stingl, Winton

Core Facilities

The following facilities support the research:

- Bioinformatics
- Flow Cytometry
- Histology
- Imaging
- Next Generation Sequencing Libraries
- Tissue Culture
- Tissue Samples
- Biomedical models

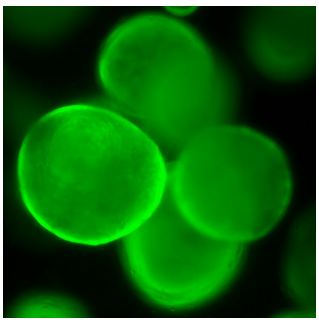
Haematopoiesis



Haematopoiesis represents the best studied adult mammalian stem cell system and provides paradigms for the mechanisms whereby normal stem cells are subverted to form malignancies. The goal of this theme is to delineate the molecular and cellular mechanisms regulating normal and malignant haematopoiesis. A particular focus is our use of complimentary approaches in human and murine systems.

Theme Leader: Green
Principal Investigators: Gottgens, Huntly, Ottersbach, Warren
Affiliate Investigators: Ghevaert, Cvejic

Solid Tissues



Stem cells maintain the lifelong renewal of epithelial tissues throughout the body. SCI investigators are studying the identity and molecular regulation of stem cells in skin, intestine, lung and other epithelia and analysing the dynamics of cell behaviour in healthy and diseased states, including cancers. In contrast stem cells appear to play little or no role in normal physiology of slowly renewing tissues and organs such as the heart, liver and pancreas. However, pluripotent stem cells can be differentiated in vitro from these tissues, providing both a window into human development and the opportunity for cellular disease modelling and drug development. Furthermore, production of tissue progenitors from pluripotent stem cells creates the possibility of future cell replacement therapy for poorly regenerating organs.
In the cardiovascular arena, SCI investigators interact closely with the British Heart Foundation Oxbridge Centre for Regenerative Medicine.

Theme Leader: Frye
Principal Investigators: Jensen, Koo, Pedersen, Rawlins, Simons, Vallier, Ventura.
Affiliate Investigators: Jones, Philpott, Sinha, Stingl, Winton, Watson, Pell

Environment

The Centre for Stem Cell Research (CSCR) in the centre of Cambridge and the Laboratory for Regenerative Medicine (LRM) on the Addenbrooke's Hospital campus presently constitute twin bases for stem cell research and translation. Stem cell groups are also housed in the Cambridge Institute for Medical Research (CIMR), Gurdon Institute, Centre for Brain Repair (CBR) and other Departments. This distribution reflects the intellectual diversity of the Cambridge stem cell community and the breadth of institutional support.

The Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute (SCI) was officially established on 1st July 2012, succeeding the former Wellcome Trust Centre for Stem Cell Biology and the MRC Centre for Regenerative Medicine.
The Institute is supported by a strategic funding partnership between the Wellcome Trust and the Medical Research Council.

Coalescence of basic stem cell research and translational medicine is key to development of clinical applications. The University therefore is constructing a new research building to house the entire Institute on the hospital campus.

2013 Progress Report

"Deep understanding of stem cell biology for prevention and treatment of human disease"

This is the vision of the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute (SCI). To that end the Institute draws together stem cell research groups in Cambridge to constitute a world-leading centre of excellence in the field of stem cell biology and medicine (http://www.stemcells.cam.ac.uk/).

Chair of Stem Cell Medicine

Robin Franklin has been appointed as the first Professor of Stem Cell Medicine at the University of Cambridge. Robin will take up this post in January 2014 and take on the key role of Head of Translational Science in the Stem Cell Institute.

Publications

During the calendar year SCI groups published 152 papers, 100 of these in journals with impact factors greater than 5.0, including Nature, Science, Cell, New England Journal of Medicine, Journal of Clinical Investigation and the Lancet. 30 of these publications are collaborations between two or more SCI groups. Clinicians are authors on 68 papers. SCI PhD students are first authors on 17 (co-authors on 54). In total, 114 (75%) articles were made open access. Considering only the 93 research reports, 85 are open access (91%).

Research Funding

In 2013, SCI held active research grants to a value of £57 million with annual expenditure of £11,668,907. During the year 19 new grants were awarded to SCI investigators, including an ERC consolidator award to Michaela Frye, and a **Wellcome Trust Senior Investigator Award** to Rick Livesey, while Tony Green, Bertie Göttgens and Alan Warren all received programme grant funding from Leukaemia and Lymphoma Research.

SCI responded to the Research Councils' call for hubs in the **UK Regenerative Medicine Platform** by submitting a successful proposal for a Pluripotent Stem Cell Platform (PSCP) in partnership with groups in Sheffield, Loughborough and the National Institute for Biological Standards and Controls. PSCP will focus on technology for manufacturing human stem cells suitable for clinical application, and will include contributions from the Sanger Institute and Babraham with regards to standardising assessment of genetic and epigenetic integrity.

Awards

SCI group leader Kim Jensen was selected for the prestigious EMBO Young Investigator Programme and Jennifer Nichols was honoured at Suffrage Science. Aliaksandra Radzisheuskaya was awarded the Journal of Cell Science "paper of the year" prize for manuscripts with a PhD student as lead author. SCI investigators were invited to speak at major stem cell meetings worldwide, including 4 talks plus a session chair at the International Society for Stem Cell Research Annual Meeting. In addition, several SCI post-docs and students were selected to give talks or awarded poster prizes at international meetings.

New SCI recruit Dr Bon-Kyoung Koo was awarded a **Wellcome Trust Sir Henry Dale Fellowship** to launch his research into homeostatic regulation of adult stem cells. Jose Silva was successful in the competition for a **Wellcome Trust Senior Research Fellowship**.

The Institute received an **MRC Centenary Award** of £30,000 to support innovative studies by PhD students and post-doctoral fellows. The three projects funded all yielded new results that will contribute to publications. In particular, PhD student awardee Rob Fordham visited Tokyo to carry out challenging transplantation experiments that were decisive for a major publication (Fordham et al., Cell Stem Cell).

Career Progression

SCI investigators Brian Hendrich and Michaela Frye were promoted to Principal Research Associate. During the year several SCI scientists progressed to positions in other leading institutions. Anton Wutz was appointed to a Professorship at the ETH in Zurich from April 2012. Kim Jensen took up a Group Leader position at the BRIC in Copenhagen but retains a dual appointment with SCI until 2014. Post-doctoral fellow Joerg Betschinger was successful in application for a group leader position at the FMI in Basel which he began in September 2013, and Gillian Morrison moved to Edinburgh as a Chancellor's Fellow also in September.

PhD Programme

A key challenge for SCI in 2013 was to secure competitive renewal of the Wellcome Trust 4 year PhD Programme in Stem Cell Biology & Medicine. Our application received very positive reviews and we are delighted that the Programme has been funded for a further 5 years. The Wellcome Trust will support 4 studentships per year and the University will fund an additional student every second year.

This year 11 students in SCI laboratories successfully defended their PhD theses.

Resources

The Göttgens group and SCI core bioinformaticians created **HAEMCODE**, a large scale repository for transcription factor binding maps (Ruau D, et al., NATURE METHODS 2013, Building an ENCODE-style data compendium on a shoestring). This database is a valuable tool for harnessing the potential of genome-scale analyses for understanding of both normal and leukaemic blood stem cells and is openly available at http://haemcode.stemcells.cam.ac.uk/. The team has generated a similar repository for pluripotent stem cell transcription factors, the ES cell ChIPseq compendium: http://bioinformatics.cscr.cam.ac.uk/ES_Cell_ChIP-seq_compendium.html

Meetings

The third Cambridge Stem Cell Institute International Symposium on the theme of **"Physical Biology of Stem Cells"** was organised by Ben Simons, Alfonso Martinez-Arias and Austin Smith. The meeting attracted leading international speakers and a broad audience of researchers working at the interface between physical sciences and stem cell biology (http://www.stemcells.cam.ac.uk/news-events/events/physical-biology-stem-cells). Feedback from participants was enthusiastic and Development commissioned a meeting review from Sally Lowell.

The fourth Symposium on 14th/15th July 2014 will be on **"Stem Cells in Medicine"** organised by Robin Franklin, Rick Livesey and Roger Barker.

Communication and Public Engagement

An important role for SCI is to nucleate interest in, and engagement with, stem cell research across the wider Cambridge community.

SCI Affiliates have close research links with SCI. They may also be supervisors in the PhD programme and participate in other institute activities (http://www.stemcells.cam.ac.uk/researchers/affiliate-investigators/). Affiliate investigators in the University and neighbouring Institutes rose to 19 with addition of Dr Jenny Pell (Babraham Institute and Department of Pharmacology), who studies adult muscle stem cells, and Dr Ana Cvejic (Department of Haematology and Sanger Institute), who exploits zebrafish for genetic screens.

The **Cambridge Stem Cell Club** evening meetings comprise 3 short research talks followed by refreshments. This provides a lively and popular forum for scientific interchange and networking and attracts a diverse range of attendees. The series runs on a monthly basis throughout the year. The Presenters are a mixture of SCI principal investigators, affiliates and post-docs plus occasional visiting scientists.

A **quarterly newsletter** has been launched to improve communication at all levels. The newsletter contains details on internal SCI developments, events, funding and achievements by SCI staff. A secure intranet for SCI members enables exchange of data and protocols and is used for core facility bookings. The Intranet is also available for the PhD student and post-doc communities to communicate their own activities.

The Institute produced an **Annual Review** that can be downloaded in Pdf format. This contains a summary of progress and events throughout the past year and provides information on each of the groups, affiliates, core facilities and PhD Programme (http://www.stemcells.cam.ac.uk/about-us/brochure/).

SCI developed a public communication and engagement strategy and supported a range of events in 2013. PhD students organised a stand with various activities during the Cambridge science festival and the SCI Director gave a public talk. SCI members also gave presentations at several local schools and contributed to "Pint of Science" events.

The Stem Cell Institute WEB site (www.stemcells.cam.ac.uk) provides information for both academic and lay audiences, with updates on research progress and listings of seminars and other events. The site attracted over 82,546 visits (1650 visits per week) in 2013, of which 43,000 were unique visitors. SCI also started a twitter feed and currently has 30 followers.

New Stem Cell Institute Building

The University is underwriting the costs for construction of the new building at the Cambridge Biomedical Research Campus. The detailed design phase has been initiated and the building is planned for completion in late 2017. This major development will enable co-location of existing SCI research groups plus expansion through new recruitment. Most importantly, direct proximity to clinician scientists, clinical research facilities and patients will facilitate translational science and clinical trials.

Scientific highlights in 2013:

- Connections between key regulatory genes in blood stem cells revealed by single cell gene expression analysis combined with innovative bioinformatics
  ⇒ Moignard V[S], Macaulay IC, Swiers G, Buettner F, Schütte J, Calero-Nieto FJ, Kinston S, Joshi A, Hannah R, Theis FJ, Jacobsen SE, de Bruijn MF, Göttgens B. Characterization of transcriptional networks in blood stem and progenitor cells using high-throughput single-cell gene expression analysis. NATURE CELL BIOLOGY
  [S] SCI PhD student. Collaboration led by Göttgens with MRC Haematology Unit in Oxford

- Refinement of the transcription factor circuitry governing pluripotent stem cell self-renewal and initiation of differentiation
  ⇒ Betschinger J, Nichols J, Dietmann S, Corrin PD, Paddison PJ, Smith A. Exit From Pluripotency Is Gated By Intracellular Redistribution of the bHLH Transcription Factor Tfe3. CELL
  ⇒ Martello G, Bertone P, Smith A. Identification of the Missing Pluripotency Mediator Downstream of Leukaemia Inhibitory Factor. EMBO JOURNAL
  SCI collaborations led by Smith with Nichols and affiliate Bertone (EBI), supported by lead bioinformatician (Dietmann)

- First characterisation of the effect of a malignant mutation at the level of single stem cells.
  ⇒ Kent DG, Li J, Tanna H[S], Fink J[S], Kirschner K, Pask DC, Silber Y, Hamilton TL, Sneade R, Simons BD, Green AR Self-Renewal of Single Mouse Hematopoietic Stem Cells Is Reduced by JAK2V617F without Compromising Progenitor Cell Expansion. PLOS BIOLOGY
  [S] SCI PhD student. Collaboration between SCI clinician scientist Green and mathematical modeller Simons

2013 Progress Report continued.

- A novel link between an imprinted gene cluster and malignancy, revealing a new pathogenic mechanism associated with acquired regions of genomic loss
  ⇒ Aziz A, Baxter EJ, Edwards C, Ito M, Cheong CY, Bench AŠŠ, Campbell PJ, Ferguson-Smith AC, Green AR. Cooperativity of imprinted genes inactivated by acquired chromosome 20 deletions. JOURNAL OF CLINICAL INVESTIGATION.
  Collaboration between SCI investigator (Green), affiliate (Ferguson-Smith) and Sanger Institute (Campbell)

- A network of three transcription factors controls formation of germ cells in the embryo
  ⇒ Magnúsdóttir E, Dietmann S, Murakami K, Günesdogan U, Tang F, Bao S, Diamanti E, Lao K, Gottgens B, Surani AM. A tripartite transcription factor network regulates primordial germ cell specification in mice. NATURE CELL BIOLOGY
  Collaboration led by Surani with Göttgens and core bioinformaticians Dietmann and Diamanti

- A comprehensive model for tissue maintenance in the skin, whereby each functional compartment is maintained autonomously by stem cells that are lineage restricted during steady state homeostasis but can be broadly recruited upon injury
  ⇒ Page ME[S], Lombard P, Ng F, Gottgens B, Jensen KB. The epidermis is comprised of autonomous compartments maintained by distinct stem cell populations. CELL STEM CELL.
  [S] SCI PhD student. Jensen-lead collaboration with Göttgens and core bioinformatician Lombard

- A source of gut stem cells that can repair inflammatory bowel disease when transplanted into mice, opening a potential route to treatment of diseases such as ulcerative colitis
  ⇒ Fordham RP[S], Yui S, Hannan NR, Soendergaard C, Madgwick A, Schweiger PJ, Nielsen OH, Vallier L, Pedersen RA, Nakamura T, Watanabe M, Jensen KB. Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury. CELL STEM CELL
  [S] SCI PhD student, recipient of an MRC Centenary Award funding to facilitate transplant collaboration in Tokyo. Collaboration led by Jensen involving Vallier and Pedersen.

- Evidence that cell cycle influences cell fate choices in human embryonic stem cells, a key step toward understanding the mechanisms by which stem cells coordinate self-renewal and differentiation
  ⇒ Pauklin S, Vallier L. The cell-cycle state of stem cells determines cell fate propensity. CELL

- A new therapeutic target for remyelination in chronic diseases such as multiple sclerosis
  ⇒ Syed YA, Baer A, Hofer MP, Gonzalez GA, Rundle J, Myrta S, Huang JK, Zhao C, Rossner MJ, Trotter MWB, Lubec G, Franklin RJM, Kotter MR. Inhibition of phosphodiesterase-4 promotes oligodendrocyte precursor cell differentiation and enhances CNS remyelination. EMBO MOLECULAR MEDICINE
  Collaboration between SCI groups of Franklin and clinician scientist Kotter with support from former SCI bioinformatician Trotter

- A direct molecular mechanism by which Nanog functions in the induction of naive pluripotency involving the epigenetic regulators Tet1 and Tet2
  ⇒ Costa Y, Ding J, Theunissen TW, Faiola F, Hore TA, Shliaha PV, Fidalgo M, Saunders A, Lawrence M[S], Dietmann S, Das S, Levasseur DN, Li Z, Xu M, Reik W, Wang J, Silva JCR. NANOG-dependent function of TET1 and TET2 in establishment of pluripotency. NATURE.
  [S] SCI PhD student. Collaboration led by SCI investigator Silva with Wang in New York and affiliate Reik (Babraham), supported by SCI lead bioinformatician Dietmann

Principal Investigators

Roger Barker
Parkinson's and Huntington's disease

Kevin Chalut
Physical Biology of Pluripotency and Differentiation

Robin Franklin
Adult Neural Stem Cells and CNS Regeneration

Michaela Frye
Epithelial Stem Cell Homeostasis and Cancer

Bertie Gottgens
Transcriptional Regulation of Normal & Leukaemic Blood Stem Cells

Tony Green
Haematopoiesis

Brian Hendrich
Transcriptional Control of Stem Cell Fate

Brian Huntly
Leukaemia Stem Cell Biology

Kim Jensen
Epithelial Development, Maintenance & Regeneration

Ragnhildur Thóra Káradóttir
Neurotransmitter Signalling to CNS Progenitor Cells

Bon-Kyoung Koo
Homeostatic Regulation of Adult Stem Cells

Mark Kotter
Neural Stem Cells, Cellular Reprogramming & Regenerative Medicine

Rick Livesey
Human stem cell models of dementia

Jennifer Nichols
Embryonic Pluripotency

Katrin Otterbach
The Developmental Origins of Blood Stem Cells

Roger Pedersen
Mechanics of Mesoderm Differentiation in Mammalian Pluripotent Stem cells

Stefano Pluchino
Central Nervous System Repair

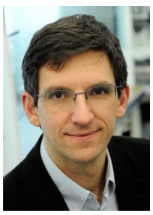
Emma Rawlins
Stem Cell Fate in the Mammalian Lung

José Silva
Biology of Induced Pluripotency

Ben Simons
Tracing stem cell fate in development, maintenance, and disease

Austin Smith
Stem Cell Potency

Azim Surani
Specification & programming of the germline for totipotency & development



Ludovic Vallier
Mechanisms Controlling Differentiation of Pluripotent Stem Cells into Definitive Endoderm

Juan-Jose Ventura
Bronchioalveolar cellular and molecular hierarchy in homeostasis & disease

Alan Warren
Stem cell subversion & bone marrow failure syndromes

Anton Wutz
Epigenetic Regulation & Cell Identity Control

Roger Barker

Roger A. Barker is the Professor of Clinical Neuroscience and Honorary Consultant in Neurology at the University of Cambridge and at Addenbrooke's Hospital. He trained at Oxford and London and has been in his current position for over ten years having completed an MRC Clinician Scientist Fellowship just prior to this. He combines basic research looking at novel therapies to treat chronic neurodegenerative disorders of the brain with clinically based work aimed at better defining them. He is the co-ordinator of the FP7 TRANSEURO project looking at fetal cell grafting in patients with early Parkinson's Disease.

Funding

Butterfield Trust
CHDI Inc
Cure Parkinson's Trust
EC FP7
Swedish Research Council
NIHR
Norfolk and Suffolk NHS Foundation Trust
Parkinson's UK
Rosetrees Trust
The Evelyn Trust
University of Iowa

Fellowships

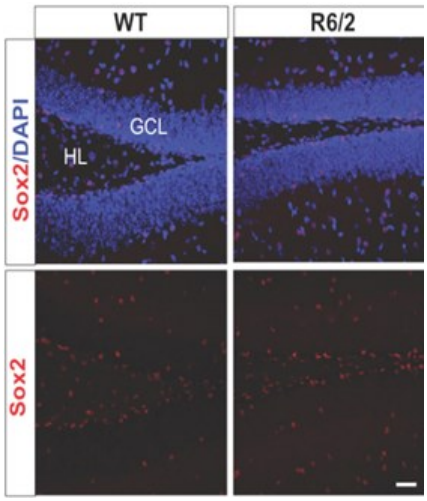
Janelle Ouellet -Drouin	Fonds de Recherche Santé Québec

Parkinson's and Huntington's disease

Our main interests are in the common, chronic neurodegenerative disorders of the nervous system in particular Parkinson's disease (PD) and Huntington's disease (HD).

We are interested in better understanding how these diseases develop and then how they change over time with the idea of better classifying patients into different subtypes of disease. These subtypes can then be used to test new therapies as some types of these diseases may be better suited for one type of experimental whilst others may not: e.g. dopamine cell therapies from stem cells treatment may be better suited to younger PD patients.

These new therapies involve not only cell based treatments as well as other novel approaches that try to stop or modify the disease process itself. This we are now trying to do, using the cells of patients which we collect from the skin and then turn into nerve cells in the lab. Through this we hope that this will recapitulate the disease process that is ongoing in their brains.



Cells proliferating in the mouse hippocampus

Group Members

Wei-Li Kuan	Postdoc Researcher
Alexandra Fragniere	Postdoc Researcher
Romina Vuono	Postdoc Researcher
Fahad Ali	Postdoc Researcher
Simon Stott	Postdoc Researcher
Janelle Ouellet-Drouin	Postdoc Researcher
Alpar Lazar	Postdoc Researcher
Francesca Panin	Postdoc Researcher
Cristina Nombera	Postdoc Researcher
Lucy Collins	Graduate Student
Sarah Mason	Research assistant
Pam Tyers	Research assistant
Xiaoling He	Research assistant
Anna Gerritz	Clinical trial support staff
Danielle Daft	Clinical trial support staff
Natalie V. Guzman	Clinical trial support staff
Su Metcalfe	Senior scientist
Gemma Cummins	Graduate Student
Stevan Wing	Graduate Student
Sarah Moore	Other - Clinical fellow

2013 Publications

Carri AD, Onorati M, Lelos MJ, Castiglioni V, Faedo A, Menon R, Camnasio S, Vuono R, Spaiardi P, Talpo F, Toselli M, Martino G, Barker RA, Dunnett SB, Biella G, Cattaneo E. Developmentally coordinated extrinsic signals drive human pluripotent stem cell differentiation toward authentic DARPP-32^{+} medium-sized spiny neurons. Development. PMID: 23250204

Barker RA, Barrett J, Mason SL, Björklund A. Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease. Lancet Neurology. PMID:23237903

Ali F, Stott SR, Barker RA. Stem cells and the treatment of Parkinson's disease. Experimental Neurology. PMID:23298521

Barker RA, Mason SL, Harrower TP, Swain RA, Ho AK, Sahakian BJ, Mathur R, Elneil S, Thornton S, Hurrelbrink C, Armstrong RJ, Tyers P, Smith E, Carpenter A, Piccini P, Tai YF, Brooks DJ, Pavese N, Watts C, Pickard JD, Rosser AE, Dunnett SB; the NEST-UK collaboration. The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. Journal of Neurology, Neurosurgery & Psychiatry. PMID:23345280

Bianco P, Barker R, Brüstle O, Cattaneo E, Clevers H, Daley GQ, De Luca M, Goldstein L, Lindvall O, Mummery C, Robey PG, Sattler de Sousa E Brito C, Smith A. Regulation of stem cell therapies under attack in Europe: for whom the bell tolls. EMBO Journal. PMID:23644381

Huefner A, Kuan WL, Barker RA, Mahajan S. Intracellular SERS Nanoprobes For Distinction Of Different Neuronal Cell Types. Nano Letters. PMID:23638825

Barker RA, De Beaufort I. Scientific and Ethical Issues Related to Stem Cell Research and Interventions in Neurodegenerative Disorders of the Brain. Progress in Neurobiology. PMID:23665410

Drouin-Ouellet J, Barker RA. The challenges of administering cell-based therapies to patients with Parkinson's disease. NeuroReport. PMID:24145775

Drouin-Ouellet J, Collins LM, Barker RA. Can patient-specific transdifferentiated neuronal cells help us understand the cellular pathology of Parkinson's disease? Future Neurology. November 2013, Vol. 8, No. 6, Pages 605-607 , DOI 10.2217/fnl.13.46.

Collaborations

Collaborator	Location	From	Nature of Collaboration
Cattaneo	Milan	2008	Striatal development work
Bjorklund	Lund	2011	Alpha synuclein for disease modelling
Arenas	Stockholm	2010	Nigral development and stem cell work
Parmar	Lund	2011	Inducible neuronal work
Austin Smith	SCI	Ongoing	Paper In EMBO Journal
Rick Livesey	SCI	Ongoing	Joint PhD student looking at the dementia of Parkinson's Disease
Anna Philpott	SCI	Ongoing	Looking at better ways to transdifferentiate fibroblasts to neurons
Ludovic Vallier	SCI	Ongoing	iPS work

Public Engagement

Event	Format	Date	Participation	Name
Rotary club	Talk	06/2013	Speaker	Barker
Hills Road Sixth Form College	Talk	04/2013	Speaker	Barker
Open evening for Cambridge Biomedical Research Centre	Talk	03/2013	Speaker	Barker

The Physical Biology of Pluripotency and Differentiation

Kevin Chalut

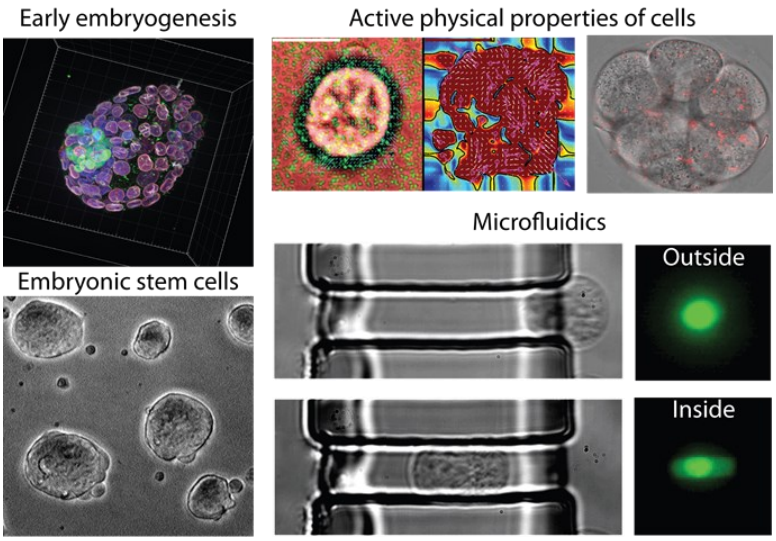
Kevin Chalut is a biophysicist with a PhD in Physics from Duke University, and is currently a Royal Society University Research Fellow (since 2011). His post-graduate background is in biotechnology and imaging, particularly with application to cancer detection and stem cell characterisation. He is currently a group leader both at the Cavendish Laboratory and the Wellcome Trust/Medical Research Council Stem Cell Institute.

His work focuses on developing novel biotechnology to investigate physical states of cells such as mechanics and subcellular structure; in the last years he has focused almost exclusively on the biophysics of embryos and embryonic stem cells. The ultimate goal of his laboratory is to discover the physical mechanisms, and the importance of those mechanisms, to pluripotency, differentiation and reprogramming.

Funding

The Royal Society

The transformation of a stem cell system into mature tissue cells consists of a progression of highly regulated steps. Despite its importance both for bringing comprehension to the formation of the embryo and also for regenerative medicine purposes, the ways in which the process of differentiation are regulated – which have been primarily studied from a biochemical perspective – are not fully understood. We are particularly focused on illuminating differentiation and embryonic development by utilising optical, quantitative microscopy, and microfluidic techniques to probe biophysical aspects. These aspects include system level changes such as cell and nuclear mechanics, subcellular structure, and dynamic processes such as remodeling within cell nuclei. Using this foundation, we have observed broad biophysical changes in embryonic stem cells as they go through the process of differentiation; these changes include a modulation of nuclear substructure and mechanics, among others. Using the biotechnology we develop, we are investigating the meaning of these changes, both in stem cell cultures and in the embryo, and their universality in other developmental niches.



We investigate early embryonic development and embryonic stem cells in order to better understand the physical context in which pluripotency is established.

Group Members

Cynthia Fisher	Postdoc researcher
George Wylde	Graduate Student
Sarra Achouri	Postdoc researcher
Andrew Hodgson	Graduate Student
Chris Revell	Graduate Student
Chibeza Agley	Postdoc researcher (Silva/Chalut)
Christophe Verstrecken	Graduate Student

Key Publications prior to 2013

Chalut K, Höpfler M, Lautenschläger F, Martinez-Arias A, and Guck J. Chromatin decondensation and nuclear softening accompany Nanog downregulation in embryonic stem cells. Biophysical Journal. (2012) PMID: 23200040

Ekpenyong A, Man S, Achouri S, Bryant C, Guck J and Chalut K. Bacterial infection of macrophages induces decrease in refractive index. Journal of Biophotonics. (2012) PMID:22887897

Ekpenyong A, Whyte G, Chalut K, Pagliara S, Lautenschläger F, Fiddler C, Paschke S, Keyser U, Beil M, Chilvers E and Guck J. Viscoelastic properties of differentiating cells are fate- and function- dependent. PLoS One. (2012) PMID:23028868

Collaborations

Collaborator	Location	From	Nature of Collaboration
Ulrich Keyser	Department of Physics, University of Cambridge	2012	Collaborating on a project to develop microfluidic approaches for assessing stem cell fate. This collaboration has resulted in the paper currently in revision for Nature Materials.
Kristian Franze	Department of PDN, University of Cambridge	2011	Investigating physical mechanisms of early embryogenesis
Stefano Pagliara	Department of Physics, Cambridge	2011	Developing microfluidic tools to probe mechanical phenotypes of stem cells
Jose Silva	SCI	Ongoing	Joint paper
Alfonso Marinez-Arias	SCI	Ongoing	Joint paper
Robin Franklin	SCI	Ongoing	Joint paper in revision

Awards & Prizes

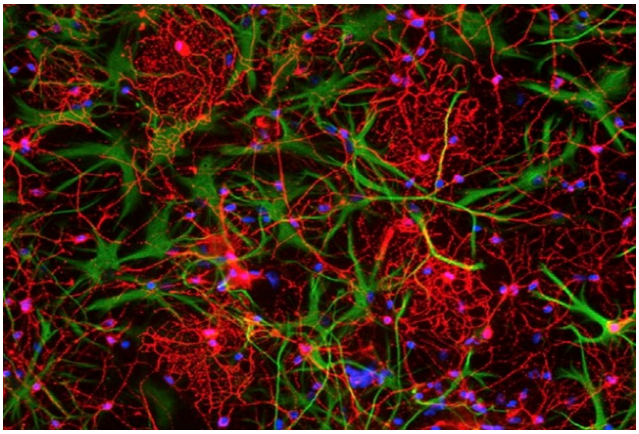
Awardee	Award	Organisation
Cynthia Fisher	ISSF Senior Internship for interdisciplinary research	University of Cambridge
Sarra Achouri	ISSF Senior Internship for interdisciplinary research	University of Cambridge

Public Engagement

Event	Format	Date	Participation	Name
Café de Scientifique at Royal Society science festival	Science Festival	07/2013	Speaker	Chalut
Pint of Science, London	Science Festival	05/2013	Speaker	Agley

Adult Neural Stem Cells and Central Nervous System Regeneration

The Franklin lab studies the mechanisms of Central Nervous System (CNS) regeneration with a particular focus on remyelination, a regenerative process mediated by adult stem/precursor cell called OPCs, in which new myelin sheaths are restored to demyelinated axons. Using a wide range of experimental approaches we are examining extrinsic (environmental) and intrinsic (transcriptional/ epigenetic) factors that govern the responses of adult neural stem/ precursor cells to injury and their differentiation into oligodendrocytes and other glia following CNS injury. The potential medical benefits of this research are to stop nerve cell degeneration and therefore provide a treatment for the currently untreatable secondary progressive phase of multiple sclerosis.



Oligodendrocytes (red) and astrocytes (green) derived from human ES cells at normal physiological oxygen tensions (from Stacpoole et al., Stem Cell Reports 2013)
Image: Sybil Stacpoole

Group Members

Roey Baror	Graduate student
Abbe Crawford	Graduate student
Natalia Deja	Graduate student
Helene Gautier	Postdoc Researcher (Franklin/Karadottir)
Alerie Guzman	Graduate student
Ilias Kazanis	Senior scientist
Dan Ma	Postdoc Researcher
Daniel Morrison	Technician
Muktha Natrajan	Graduate student
Bjoern Neumann	Graduate student
John Parker	Graduate student
Catherine Peacock	Admin
Hartmut Pohl	Postdoc Researcher
Francisco Rivera	Postdoc Researcher
Sybil Stacpoole	Graduate student
Peter van Wijngaarden	Postdoc Researcher
Bowei Wong	Graduate student visitor
Chao Zhao	Senior scientist
Ofra Zidon	Postdoc Researcher

Robin Franklin

Robin Franklin is Professor of Neuroscience and Director of the Neural Stem Cell Programme of the SCI. He obtained his undergraduate degrees in Physiology and Veterinary Medicine and his PhD in Neuroscience. He has worked predominantly on the biology of myelin repair (remyelination) and investigating strategies by which this important regenerative process may be enhanced therapeutically. His lab has focused on the possibility of enhancing remyelination through stimulating endogenous population of adult stem cells. He is at the forefront of studying the cellular and molecular mechanisms of remyelination and describing the mechanisms by which adult stem cells are recruited to areas of demyelination and the extrinsic and intrinsic factors that regulate their differentiation into remyelinating oligodendrocytes.
He is currently Director of the UK MS Society Cambridge Centre for Myelin Repair, a consortium of Cambridge-based scientists and clinicians working towards stem cell -based therapies for myelin repair.

Funding

ARSEP
BBSRC
Fast Forward LLC
Idibell
Medical Research Council
Multiple Sclerosis Society
Queen Mary & Westfield College
Uni of London
Wellcome Trust

2013 Publications

Yuen TJ, Johnson KR, Miron VE, Zhao C, Quandt J, Harrisingh MC, Swire M, Williams A, McFarland HF, Franklin RJ, Ffrench-Constant C. Identification of endothelin 2 as an inflammatory factor that promotes central nervous system remyelination.Brain. PMID: 23518706

Miron VE, Boyd A, Zhao JW, Yuen TJ, Ruckh JM, Shadrach JL, van Wijngaarden P, Wagers AJ, Williams A, Franklin RJ, Ffrench-Constant C. M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. Nature Neuroscience. PMID: 23872599

Syed YA, Baer A, Hofer MP, González GA, Rundle J, Huang JK, Zhao C, Rossner MJ, Trotter MWB, Lubec G, Franklin RJM, Kotter MR. Inhibition of phosphodiesterase-4 promotes oligodendrocyte precursor cell differentiation and enhances CNS remyelination. EMBO Molecular Medicine. PMID:24293318

Coutts DJC, Humphries CE, Zhao C, Plant GW, Franklin RJM. Embryonic-Derived Olfactory Ensheathing Cells Remyelinate Focal Areas of Spinal Cord Demyelination More Efficiently Than Neonatal or Adult-Derived Cells. Cell Transplantation. PMID: 23031825

Stoffels JMJ, De Jonge JC, Stancic M, Nomden A, Van Strien ME, Ma D, Šišková Z, Maier O, Ffrench-Constant C, Franklin RJM, Hoekstra D, Zhao C, Baron W. Fibronectin aggregation in multiple sclerosis lesions impairs remyelination. Brain. PMID: 23365094

van Wijngaarden P, Franklin RJ. Ageing stem and progenitor cells: implications for rejuvenation of the central nervous system. Development. PMID: 23715549

Franklin RJ, Bussey TJ. Do your glial cells make you clever? Cell Stem Cell. PMID: 23472865

Stacpoole SR, Webber DJ, Bilican B, Compston A, Chandran S, Franklin RJ. Neural Precursor Cells Cultured at Physiologically Relevant Oxygen Tensions Have a Survival Advantage Following Transplantation. Stem Cells Translational Medicine. PMID: 23677643

SRL Stacpoole, S Spitzer, B Bilican, A Compston, R Karadottir, S Chandran, RJM Franklin. High Yields of Oligodendrocyte Lineage Cells from Human Embryonic Stem Cells at Physiological Oxygen Tensions for Evaluation of Translational Biology. Stem Cell Reports. PMID: 24286031

Crawford AH, Chambers C, Franklin RJM. Remyelination: The True Regeneration of the Central Nervous System. Journal of Comparative Pathology. PMID: 23831056

Kazanis I, Gorenkova N, Zhao JW, Franklin RJM, Modo M, ffrench-Constant C. The late response of rat subependymal zone stem and progenitor cells to stroke is restricted to directly affected areas of their niche. Experimental Neurology. PMID: 23830949

Lundgaard I, Luzhynskaya A, Stockley J.H, Wang Z, Evans KA, Swire M, Volbracht K, Gautier HO, Franklin RJM, ffrench-Constant C, Attwell D, Káradóttir R. Neuregulin and BDNF induce a switch to NMDA receptor dependent myelination by oligodendrocytes. PLoS Biol. PMID: 24391468

Collaborations

Collaborator	Location	From	Nature of Collaboration
Charles ffrench-Constant	University of Edinburgh	Ongoing	Multiple papers and grants
Catherine Lubetzki	ISERM Paris	Ongoing	Joint grant & paper under consideration
Aurora Pujol	Barcelona	Ongoing	Joint grant
David Lyons	University of Edinburgh	Ongoing	Joint grant
Wia Baron	University of Groningen	Ongoing	Joint papers
David Rowitch/Steve Fancy	UCSF	Ongoing	
Patrizia Casaccia	Mount Sinai, NYC	Ongoing	Paper in preparation
Amy Wagers	Harvard Stem Cell Institute	Ongoing	Joint paper this year; grant in preparation
Jonah Chan	UCSF	Ongoing	Joint papers
Mark Kotter	SCI	Ongoing	Joint paper
Thóra Káradóttir	SCI	Ongoing	Joint paper
Kevin Chalut	SCI	Ongoing	Joint paper in revision

Public Engagement

Event	Format	Date	Participation	Name
Participation in Pint of Science: Addiction & impulse control, The Portland Arms, Cambridge	Public Event	05/2013	Presenter	Gautier
Science Programme with secondary school in Germany: “Planaria: Champions of Regeneration”	Outreach	09/2013	Organiser	Neumann

Epithelial Stem Cell Homeostasis and Cancer

Michaela Frye

Michaela Frye completed her PhD in Frankfurt/Main in Germany in 2000 studying the role of epithelial defensins in Cystic Fibrosis. In 2001 she joined the lab of Fiona Watt as a Postdoctoral Fellow at the CR-UK London Research Institute where she developed her fascination for the question “how stem cells in the skin are regulated”.

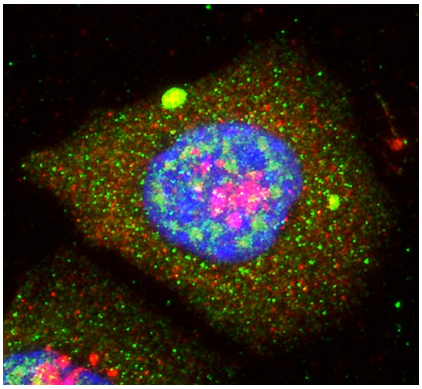
Michaela received a CR-UK Career Development Fellowship in 2007 when she started as a group leader at the WT-MRC Stem Cell Institute. She has renewed this fellowship in 2012 and is now a CR-UK Senior Fellow.

Funding

British Skin Foundation
Cancer Research UK
EC FP7

Stem cells are established during development and remain present in adulthood allowing the body to replace, restore and regenerate dead, damaged or diseased cells. Stem cells continuously maintain their population (self-renewal) while generating progeny (differentiation). During self-renewal stem cells have to avoid cell cycle exit and differentiation; whereas during differentiation stem cells must evade uncontrolled proliferation. Dissecting the regulatory pathways controlling the balance between these two states is fundamental to understanding how stem cell mis-regulation causes human diseases. While transcriptional regulation of stem cells is increasingly understood, virtually nothing is known about how post-transcriptional mechanisms can influence stem cell maintenance. Post-transcriptional modifications are commonly found in non-coding RNA species and our recent studies identified cytosine-5 methylation (m5C) of RNA as a novel mechanism regulating stem cell fate.

To dissect the cellular and molecular functions of cytosine-5 methylated RNA, we are using a combination of system-wide approaches, mouse models and in vitro differentiation assays. Our comprehensive approach will answer how post-transcriptional modification controls stem cell fate in normal tissues and how aberrant cytosine-5 methylation pathways can cause human diseases.



The RNA methltransferase NSun2 (green) changes its localization in response to stress. Red highlights a marker for stress granules and blue delineates the nucleus. Sandra Blanco

Group Members

Sandra Blanco	Postdoc Researcher
Shobbir Hussain	Postdoc Researcher
Jelena Aleksic	Postdoc Researcher
Roberto Bandiera	Postdoc Researcher
Iwona Driskell	Postdoc Researcher
Martyna Popis	Graduate student
Joana Flores	Graduate student
Mahalia Page	Graduate student
Abdul Sajini	Graduate student
Nikoletta Gkatza	Graduate student
Carolin Witte	Master student

2013 Publications

Hussain S, Tuorto F, Menon S, Blanco S, Cox C, Flores JV, Watt S, Kudo NR, Lyko F, Frye M. The mouse cytosine-5 RNA methyltransferase NSun2 is a component of the chromatoid body and required for testis differentiation. Molecular and Cellular Biology. PMID: 23401851

Hussain S, Sajini AA, Blanco S, Dietmann S, Lombard P, Sugimoto Y, Paramor M, Gleeson JG, Odom DT, Ule J and Frye M. NSun2-mediated cytosine-5 methylation of Vault non-coding RNA determines its processing into regulatory small RNAs. Cell Reports. PMID: 23871666

Hussain S, Aleksic J, Blanco S, Dietmann S, Frye M. Characterizing 5-methylcytosine in the mammalian epitranscriptome. Genome Biology. PMID: 24286375

Collaborations

Collaborator	Location	From	Nature of Collaboration
Joseph Gleeson	UCSD	2011	Provided patient cells; impact on grant and publications
Duncan Odom	CI	2007	System-wide approaches; impact on grant and publications
Jernej Ule	UCL	2011	RIP-seq; iCLIP; impact on grant and publications
Frank Lyko	DKFZ	2011	RNA methylases; impact on grant and publications
Mark Helm	Mainz	2012	Mass-spec for RNA modifications; impact on grant and publications
Ana Cvejic	SCI	Ongoing	Loss-of-function studies in epidermis
Austin Smith	SCI	Ongoing	Analysis of NSun2 in neural stem and progenitor cells

Awards & Prizes

Awardee	Award	Organisation
Martyna Popis	Best Poster Prize	Hydra IX - The European Summer School on Stem Cells and Regenerative Medicine

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2013	Volunteer	Aleksic
TReND in Africa	Teaching	08/2013	Lecturer and Organiser	Aleksic
Cambridge Science Festival	Science Festival	03/2013	Co-organiser	Popis
Reach Cambridge Residential Summer School	Teaching	02/2013	Tutor and Demonstrator	Popis
Tour of the SCI for high school students	Tour	07/2013	Organiser	Popis
Cambridge Science Festival	Science Festival	03/2013	Volunteer	Flores

Transcriptional Regulation of Normal and Leukaemic Blood Stem Cells

Bertie Gottgens

First Degree: Biochemistry, Tübingen University, 1992.
Higher Degree: DPhil, Biological Sciences, University of Oxford, 1994.
PostDoc; Haematology, University of Cambridge, 1994-2001.
Leukaemia Research Fund Lecturer Haematology, University of Cambridge, 2002-2007.
University Senior Lecturer, then Reader Haematology, University of Cambridge, 2007-2011.
Professor of Molecular Haematology, University of Cambridge, since Oct 2011.

Funding

BBSRC
EC FP7
Leukaemia & Lymphoma Research
Medical Research Council
Nc3rs
Cancer Research UK
Leukemia & Lymphoma Society

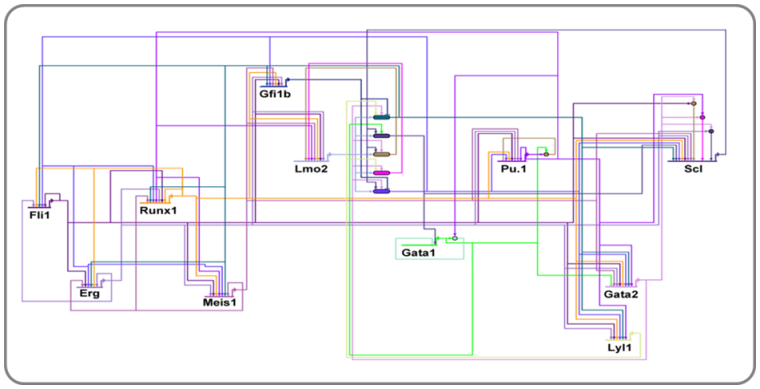
Fellowships

Yosuke Tanaka JSPS Japanese Fellowship

Blood stem cells provide the constant supply of new blood cells throughout a person's lifetime. Their transcriptional regulation, i.e. the fine tuning of which genes should be active at any given time, is critical for their normal function. Moreover, a large number of leukaemias arise, when this fine balance of gene activities is disturbed. Transcription factors are genes responsible for controlling the activity of other genes, and they generally function as components of wider regulatory networks.

The Gottgens group uses a combination of experimental and computational approaches to study transcriptional regulatory networks in blood stem cells; to discover how transcription factor networks control the function of blood stem cells and identify how perturbations of such networks can cause leukaemia.

Through collaboration with other groups within the SCI, the Gottgens group has also been able to apply their integrated experimental / computational approach to other areas of stem cell and regenerative medicine research, which has resulted in several high-profile collaborative publications since 2011.



A regulatory network model for blood stem / progenitor cells. Image generated by B. Gottgens, based on experimental data produced by the entire Gottgens group.

Group Members

Fernando Calero	Postdoc Researcher
Lila Diamanti	Research assistant
Debbie Goode	Postdoc Researcher
Rebecca Hannah	Research assistant
Isabel Jimenez	Research assistant
Viviane Kawata	PhD student
Sarah Kinston	Research assistant
Winnie Lau	Postdoc Researcher
Ana Leal Cervantes	Graduate student
Vicki Moignard	Graduate student
Felicia Ng	Graduate student
David Ruau	Postdoc Researcher
Judith Schütte	Postdoc Researcher
Jonathan Sive	PhD student
Yosuke Tanaka	Postdoc Researcher
Adam Wilkinson	Graduate student
Nicola Wilson	Postdoc Researcher
Steven Woodhouse	Graduate student
Manuel Sanchez-Castillo	Postdoc Researcher

2013 Publications

Moignard V, Macaulay IC, Swiers G, Buettner F, Schütte J, Calero-Nieto FJ, Kinston S, Joshi A, Hannah R, Theis FJ, Jacobsen SE, Bruijn M, Gottgens B. Characterisation of transcriptional networks in blood stem and progenitor cells using high-throughput single cell gene expression analysis. Nature Cell Biology. PMID: 23524953

Bonzanni N, Garg A, Feenstra KA, Schütte J, Kinston S, Miranda-Saavedra D, Heringa J, Xenarios I, Göttgens B. Hard-wired heterogeneity in blood stem cells revealed using a dynamic regulatory network model. Bioinformatics. PMID:23813012

Ruau D, Ng FS, Wilson NK, Hannah R, Diamanti E, Lombard P, Woodhouse S, Göttgens B. Building an ENCODE-style data compendium on a shoestring. Nature Methods. PMID:24076986

Oram SH, Thoms J, Sive JI, Calero-Nieto FJ, Kinston SJ, Schütte J, Knezevic K, Lock RB, Pimanda JE, Gottgens B. Bivalent promoter marks and a latent enhancer may prime the leukaemia oncogene LMO1 for ectopic expression in T-cell leukaemia. Leukemia. PMID: 23302769

Ferreira R, Spensberger D, Silber Y, Dimond A, Li J, Green AR, Gottgens B. Impaired in vitro erythropoiesis following deletion of the Scl/Tal1 +40 enhancer is largely compensated in vivo despite significant reduction in expression. Molecular Cell Biology. PMID: 23319051

Staber PB, Zhang P, Ye M, Welner RS, Nombela-Arrieta C, Bach C, Kerenyi M, Bartholdy BA, Zhang H, Alberich-Jordà M, Lee S, Yang H, Ng F, Zhang J, Leddin M, Silberstein LE, Hoefler G, Orkin SH, Gottgens B, Rosenbauer F, Huang G, Tenen DG. Sustained PU.1 levels balance cell-cycle regulators to prevent exhaustion of adult hematopoietic stem cells. Molecular Cell. PMID: 23395001

Calero-Nieto FJ, Joshi A, Bonadies N, Kinston S, Chan W, Gudgin E, Pridans C, Landry JR, Kikuchi J, Huntly BJ, Gottgens B. HOX-mediated LMO2 expression in embryonic mesoderm is recapitulated in acute leukaemias. Oncogene. PMID: 23708655

Page ME, Lombard P, Ng F, Gottgens B, Jensen KB. The epidermis is comprised of autonomous compartments maintained by distinct stem cell populations. Cell Stem Cell. PMID: 23954751

Magnúsdóttir E, Dietmann S, Murakami K, Günesdogan U, Tang F, Bao S, Diamanti E, Lao K, Gottgens B, Surani MA. A tripartite transcription factor network regulates primordial germ cell specification in mice. Nature Cell Biology. PMID: 23851488

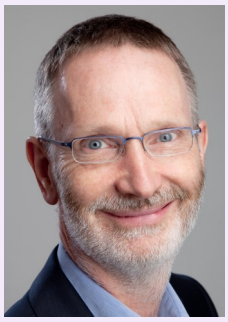
See Appendix 1 for additional publications from the Gottgens group

Collaborations

Collaborator	Location	From	Nature of Collaboration
Marella de Bruijn	Oxford University (WIMM)	2007	Paper in Nature Communications in 2013
Peggy Goodell	Baylor College, Texas	2010	Paper in Nature Genetics in 2013
Len Pennacchio	DOE Joint Genome Institute, LLNBL, USA	2009	Papers in Biology Open & Nature Biotechnology
John Pimanda	UNSW Sydney, Australia	2007	Papers published in 2013 in Blood
Tony Kouzarides	Gurdon Institute, UK	2010	Paper in Leukaemia in 2013
Shai Izraeli	Sheba Medical Center,Tel Aviv, Israel	2005	Paper in 2013 in Blood
Nicola Bonzanni	Vrije Universiteit Amsterdam, Netherlands	2008	Paper in Bioinformatics in 2013
Dan Tenen	Harvard Stem Cell Institute-Cambridge MA, and Singapore	2004	Paper in Molecular Cell in 2013
Tarik Möröy	Montreal, Canada	2010	Paper in Cancer Cell in 2013
Sten Eirik Jacobsen	Oxford (WIMM), UK	2011	Paper in Nature Cell Biology in 2013
Tony Green	SCI	Ongoing	Papers in Molecular Cell Biology & Leukemia
Brian Huntly	SCI	Ongoing	Papers in Oncogene & Leukemia
Kim Jensen	SCI	Ongoing	Paper in Cell Stem Cell
Azim Surani	SCI	Ongoing	Paper in Nature Cell Biology
Austin Smith	SCI	Ongoing	Joint paper
Robin Franklin	SCI	Ongoing	Shared experiments
Emma Rawlins	SCI	Ongoing	Shared experiments

Awards & Prizes

Awardee	Award	Organisation
Victoria Moignard	MRC Centenary Award	Cambridge University Doctoral Training Programme
Nicola Wilson	MRC Centenary Award	Cambridge Stem Cell Institute



Tony Green

Tony Green trained in medicine at the University of Cambridge (1974-77) and University College Hospital London (1977-80) subsequently completing his haematology training at the Royal Free Hospital and the University Hospital of Wales, Cardiff. His scientific training in molecular biology and haematopoiesis was gained at the Imperial Cancer Research Fund, London (1984-87) and the Walter and Eliza Hall Institute, Melbourne (1989-91), the latter as a Hamilton-Fairley Travelling Fellow. He moved to Cambridge in 1991 as a Wellcome Trust Senior Fellow and honorary Consultant and was elected Chair of Haemato-Oncology there in 1999. In 2001 he was elected Fellow of the Academy of Medical Sciences and in 2011 elected Newton Abraham Visiting Professor at the University of Oxford.

Funding

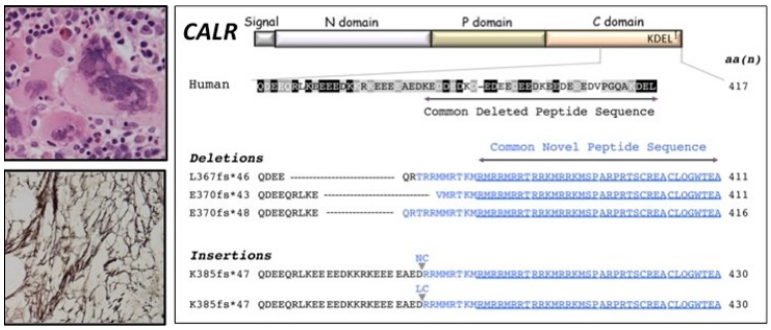
Addenbrooke's Charitable Trust
Cancer Research UK
Guy's & St Thomas's NHS Foundation
Kay Kendall Leukaemia Fund
Lady Tata Memorial Trust
Leukaemia & Lymphoma Research
The Leukaemia & Lymphoma Society

Fellowships

June Park — International Human Frontier Science Program Organisation

Haematopoiesis

Tony Green's research has focused on the mechanisms whereby blood stem cells are subverted during the genesis of haematological malignancies. Over the past decade his lab has increasingly concentrated on JAK/STAT signalling which is dysregulated in many cancers and plays a key role in multiple stem cell systems. His group have focused on the myeloproliferative neoplasms which harbour mutations that activate the JAK/STAT pathway, are experimentally tractable and provide a paradigm for the earliest stages of tumorigenesis, inaccessible in other cancers. His translational studies of MPN pathogenesis have already had direct clinical impact with improved classification, new diagnostic approaches embedded in international guidelines and multiple JAK inhibitors in clinical trials. His more basic research is illuminating the mechanisms whereby the JAK/STAT pathway regulates diverse aspects of cellular function including chromatin biology, DNA replication, genome-wide transcriptional programs and stem cell fate. Most recently, the Green group have identified novel mutations in calreticulin, present in most patients with a JAK2 unmutated MPN.



Mutations in the endoplasmic reticulum chaperone calreticulin (CALR) give rise to a novel C-terminal peptide sequence, and are present in most JAK2 unmutated MPN patients. Images show abnormal megakaryocytes and bone marrow fibrosis in these patients.

Group Members

Athar Aziz	Postdoc Researcher
Danai Dimitropoulou	Research Assistant
Anna Godfrey	Graduate Student
Tina Hamilton	Technician
Radia Johnson	Postdoc Researcher
David Kent	Postdoc Researcher
Kristina Kirschner	Postdoc Researcher
Thorston Kampfl	Postdoc Researcher
Karoline Kollman	Postdoc Researcher
Juan Li	Postdoc Researcher
Stephen Loughran	Postdoc Researcher
Charlie Massie	Postdoc Researcher
Jyoti Nangalia	Graduate Student
Francesca Nice	Graduate Student
June Park	Postdoc Researcher
Dean Pask	Technician
Yvonne Silber	Research Assistant
Rachel Sneade	Research Assistant
Wolfgang Warsch	Postdoc Researcher

2013 Publications

Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, Avezov E, Li J, Kollmann K, Kent DG, Aziz A, Godfrey AL, Hinton J, Martincorena I, Van Loo P, Jones AV, Guglielmelli P, Tarpey P, Harding HP, Fitzpatrick JD, Goudie CT, Ortmann CA, Loughran SJ, Raine K, Jones DR, Butler AP, Teague JW, O'Meara S, McLaren S, Bianchi M, Silber Y, Dimitropoulou D, Bloxham D, Mudie L, Maddison M, Robinson B, Keohane C, Maclean C, Hill1 K, Orchard1 K, Tauro S, Du M-Q, Greaves M, Bowen D, Huntly BJP, Harrison CN, Cross NCP, Ron D, Vannucchi AM, Papaemmanuil E, Campbell PJ and Green AR. Somatic CALR Mutations in Myeloproliferative Neoplasms with Nonmutated JAK2. New England Journal of Medicine. PMID: 24325359

Aziz A, Baxter EJ, Edwards C, Cheong CY, Ito M, Bench A, Kelley R, Silber Y, Beer PA, Chng K, Renfree MB, McEwen K, Gray D, Nangalia J, Mufti GJ, Hellstrom-Lindberg E, Kiladjian JJ, McMullin MF, Campbell PJ, Ferguson-Smith AC, Green AR. Cooperativity of imprinted genes inactivated by acquired chromosome 20q deletions. Journal of Clinical Investigation. PMID:23543057

Kent DG, Li J, Tanna H, Fink J, Kirschner K, Pask DC, Silber Y, Hamilton TL, Sneade R, Simons BD, Green AR. Self-Renewal of Single Mouse Hematopoietic Stem Cells Is Reduced by JAK2V617F Without Compromising Progenitor Cell Expansion. PLoS Biology. PMID:23750118

Ferreira R, Spensberger D, Silber Y, Dimond A, Li J, Green AR, Gottgens B. Impaired In Vitro Erythropoiesis Following Deletion of the Scl/Tal1 +40 Enhancer Is Largely Compensated In Vivo Despite Significant Reduction in Expression. Molecular Cell Biology. PMID: 23319051

Godfrey AL, Chen E, Pagano F, Silber Y, Campbell PJ, Green AR. Clonal analyses reveal associations of JAK2V617F homozygosity with hematologic features, age and gender in polycythemia vera and essential thrombocythemia. Haematologica. PMID:23633544

Harrison CN, Butt N, Campbell P, Conneally E, Drummond M, Green AR, Murrin R, Radia DH, Reilly JT, Mcmullin MF. Diagnostic pathway for the investigation of thrombocytosis. British Journal of Haematology. PMID:23480550

Bench AJ, Baxter EJ, Green AR. Methods for detecting mutations in the human JAK2 gene. Methods in Molecular Biology. PMID:23296725

Wyspianska B, Bannister AJ, Barbieri I, Nangalia J, Godfrey A, Calero-Nieto FJ, Robson S, Rioja I, Li J, Wiese M, Cannizzaro E, Dawson MA, Huntly B, Prinjha RK, Green AR, Gottgens B, Kouzarides T. BET protein inhibition shows efficacy against JAK2V617F driven neoplasms. Leukemia. PMID:23929215

Kollmann K, Heller G, Schneckenleithner C, Warsch W, Scheicher R, Ott RG, Schäfer M, Fajmann S, Schlederer M, Schiefer AI, Reichart U, Mayerhofer M, Hoeller C, Zöchbauer-Müller S, Kerjaschki D, Bock C, Kenner L, Hoefler G, Freissmuth M, Green AR, Moriggl R, Busslinger M, Malumbres M, Sexl V. A Kinase-Independent Function of CDK6 Links the Cell Cycle to Tumor Angiogenesis. Cancer Cell. PMID:23948297

Hobbs CM, Manning H, Bennett C, Vasquez L, Severin S, Brain L, Mazharian A, Guerrero JA, Li J, Soranzo N, Green AR, Watson SP, Ghevaert C. JAK2V617F leads to intrinsic changes in platelet formation and reactivity in a knock-in mouse model of essential thrombocythemia. Blood. PMID:24085768

See Appendix 1 for additional publications from the Green group

Collaborations

Collaborator	Location	Nature of Collaboration
Peter Campbell	WT Sanger Institute	Genomic approaches to myeloid malignancies
Timm Schroeder	ETH Zurich	Linage tracing of MPN stem cells and progenitors
Vernonica Sexl	Vienna	JAK/STAT signalling studies
Cristina Lo Celso	Imperial College	Effect of JAK2 mutation on stem cell localisation
Warren Alexander	WEHI Melbourne	Cooperating mutations and MPN biology
Cedric Ghevaert	NHSBT Cambridge	Megakaryopoiesis and MPN biology
Stein-Erik Jacobsen/Adam Mead	Oxford	Consequences of JAK2 mutation within HSC subsets
Anne Ferguson-Smith	SCI	Targeting of imprinted loci by acquired chromosome deletions
Brian Huntly, Ben Simons, Bertie Gottgens & Cedric Ghevaert	SCI	Joint papers

Awards & Prizes

Awardee	Award	Organisation
Green	Elected Grinberg/Wisch Visiting Professor in Myeloproliferative Disorders	Mount Sinai Medical Center, New York

Public Engagement

Event	Format	Date	Participation	Name
NIHR Cambridge Biomedical Research Centre	Public Open Evening	04/2013	Speaker	Green

Transcriptional Control of Stem Cell Fate

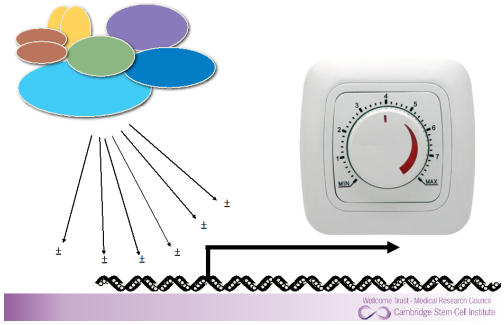
Brian Hendrich

Brian grew up near Seattle, Washington. He got his PhD from Stanford University in 1995 working on X chromosome inactivation with Huntington Willard. In 1995 he joined the lab of Adrian Bird at the University of Edinburgh and participated in the discovery and characterisation of a family of methyl-CpG binding proteins in mammals. In 2001 he started his own laboratory at the University of Edinburgh. In 2008 he moved to the Wellcome Trust Centre for Stem Cell Research in Cambridge.
He is currently a Wellcome Trust Senior Research Fellow in the Basic Biomedical Sciences, and Director of the PhD Programme in Stem Cell Biology for the Cambridge Stem Cell Institute.

Funding

EC FP7
Wellcome Trust

Embryonic stem (ES) cells hold enormous promise for personalised medicine and drug discovery since they can be maintained indefinitely and are pluripotent; that is they have the potential to form any adult cell type. While pluripotency makes ES cells potentially very useful, it also presents a problem: how do you get them to make the cell type you want, and not one you don't? Differentiation of pluripotent cells is exquisitely organised during normal embryogenesis, but controlling differentiation of stem cells in culture presents a major challenge. Since all cells in an organism are genetically identical, the observable differences in their functions and behaviours come down to which genes they express and which genes they don't express. Therefore in order to understand how to direct cellular identity, we seek to understand how cells regulate gene expression during differentiation. We also seek to understand how subtle differences in gene expression patterns in seemingly identical cells influence any subsequent differentiation decisions. To do this we focus on how the DNA is packaged in the cell and study the proteins involved in regulating this chromatin packaging. We use biochemistry, genetics, in vitro stem cell culture and manipulation, single cell analyses, genome-wide analyses and collaborate with bioinformaticians and computer programmers to better understand how control of transcription facilitates decision making in stem cells. By understanding how ES cells make different developmental decisions this work will bring the medical promise of stem cells closer to realisation.



Multiprotein transcriptional 'corepressor' complexes (top left) associate with DNA and, rather than simply turning off genes, act to modulate gene expression. Thus rather than acting in a binary fashion, these chromatin modifying protein activities can fine tune expression levels up or down. This activity allows cells to appropriately respond to developmental cues.
Brian Hendrich

Group Members

Maria Barreira	Postdoc Researcher
Thomas Burgold	Postdoc Researcher
Sarah Gharbi	Research assistant
Antony Hynes-Allen	Research assistant
Anzy Miller	Graduate student
Aoife O'Shaughnessy-Kirwan	Postdoc Researcher
Meryem Ralser	Research assistant
Nicola Reynolds	Senior Scientist
Jason Signolet	Postdoc Researcher

2013 Publications

Reynolds N, O'Shaughnessy A, Hendrich B. Transcriptional repressors: multifaceted regulators of gene expression. Development. PMID:23293282

O'Shaughnessy A, Hendrich B. CHD4 in the DNA-damage response and cell cycle progression: not so NuRDy now. Biochemical Society Transactions. PMID:23697937

Key Publications prior to 2013

Reynolds N, Latos P, Hynes-Allen A, Loos R, Leaford D, O'Shaughnessy A, Mosaku O, Signolet J, Brennecke P, Kalkan T, Costello I, Humphreys P, Mansfield W, Nakagawa K, Strouboulis J, Behrens A, Bertone P and Hendrich B. NuRD suppresses pluripotency gene expression to promote transcriptional heterogeneity and lineage commitment. Cell Stem Cell. (2012) PMID: 22560079

Reynolds N, Salmon-Divon M, Dvinge H, Hynes-Allen A, Balasooriya G, Leaford D, Behrens A, Bertone P and Hendrich B. NuRD-mediated deacetylation of H3K27 facilitates recruitment of Polycomb Repressive Complex 2 to direct gene repression. EMBO Journal. (2011) PMID: 22139358

Collaborations

Collaborator	Location	From	Nature of Collaboration
Ernest Laue	University of Cambridge	2009	Determining the structure and function of chromatin remodelling complexes. This has resulted in the establishment of an EU FP7 Consortium
Saverio Minucci	IEO, Milan	2012	NuRD function in haematopoiesis.
Jeroen Demmers	Rotterdam	2004	Proteomic analysis of the NuRD Complex.
Michiel Vermeulen	Utrecht	2013	Proteomic analysis of the NuRD complex during development
Stephen Emmott	Microsoft Research, Cambridge	2013	Gene expression during cell transitions in single cells. Applied for a joint PhD Studentship
Yong Kim	UCLA	2012	Function of Cdk2ap1 in the NuRD complex
Ryuichi Nishinakamura	Kumamoto, Japan	2012	Function of Sall1 and 4 proteins in ES cells
Tony Green	SCI	Ongoing	NuRD function in haematopoiesis
Jose Silva	SCI	Ongoing	Mechanisms of reprogramming
Kevin Chalut	SCI	Ongoing	Investigation into the physical properties of Chd4-mutant embryos
Paul Bertone	SCI	Ongoing	Bioinformatic analyses of NuRD function in ES cells
Rick Livesey	SCI	Ongoing	Mbd3 function in neurogenesis
Brian Huntly	SCI	Ongoing	CBP-mutant ES cells

Public Engagement

Event	Format	Date	Participation	Name
Cell Science Investigators - 2013	Teaching	01/2013	Presenter	O'Shaughnessy
Summer School - Cambridge Prep Experience	Teaching	06/2013	Presenter	O'Shaughnessy
St. Mary's School	Teaching	01/2013	Organiser & speaker	O'Shaughnessy/ Miller
Perse School	Teaching	05/2013	Organiser & speaker	O'Shaughnessy/ Miller
Oxbridge Summer School	Teaching	07/2013	Organiser & speaker	O'Shaughnessy/ Miller
I'm a Scientist, get me out of here!	Web communication	11/2013	Presenter	O'Shaughnessy/ Miller
Science Week	Science week	03/2013	Presenter	Reynolds
University of Cambridge Science Festival	Science Festival	03/2013	Volunteer	Gharbi
Introduction to Stem Cells Research	Teaching	07/2013	Volunteer	Gharbi
Science Festival—Stem Cell Zone	Science Festival	03/2013	Organiser	Miller
Stem Cell Institute tour	Tour	05/2013	Volunteer	Miller
Microsoft Research Cambridge "Think Computer Science"	Outreach	12/2013	Presenter	O'Shaughnessy/ Miller

Leukaemia Stem Cell Biology

Brian Huntly

Dr Brian Huntly is a clinical academic who combines running a laboratory group with his practice as a Consultant Haematologist in Addenbrooke's Hospital. He studied Medicine at Edinburgh, trained in Haematology in Dundee and Cambridge and is a member of the Royal College of Physicians and a Fellow of the Royal College of Pathologists. He studied for his PhD in Cambridge and performed post-doctoral work at Harvard, prior to returning to Cambridge to set up his own research group.

Funding

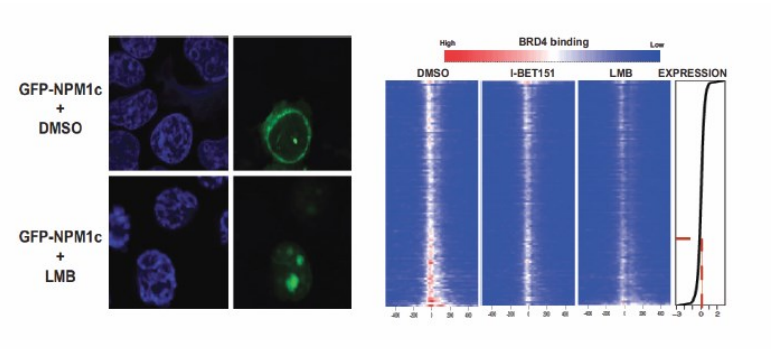
Kay Kendall Leukaemia Fund
Leukaemia & Lymphoma Research
Wellcome Trust

Fellowships

Mark Dawson	Leukaemia Foundation Australia Senior Fellowship
Mark Dawson	VESKI Innovation Fellowship
Mark Dawson	Herman Clinical Fellowship

Leukaemias and many other cancers have recently been demonstrated to be wholly dependent upon a small population of so-called cancer stem cells for their continued growth and propagation. These cells represent the most critical targets for treatment of leukaemia and a greater understanding of their biology and its interface with normal stem cell function is fundamental to improving treatment outcomes in leukaemia.

The focus of the Huntly laboratory is on this interface between normal and malignant haematopoietic stem cell biology. We use a combination of techniques in cell line and animal models as well as confirmatory studies in primary human tissue to dissect stem cell function. Our aim is to understand how normal stem cell function is subverted in cancer and how these processes might be therapeutically targeted to improve the outcome in haematological cancers. As examples of this we are examining the effects of gene mutations, recently documented in Acute myeloid Leukaemia (AML), on haematopoietic stem cell function. Therapeutically, a recent example of our work is the identification of the Bromodomain and extra terminal (BET) proteins as critical mediators of leukaemia stem cells in AML and the development of an inhibitor of these proteins that is about to enter early phase clinical trials in relapsed blood cancers.



Restoration of nuclear NPM1c abrogates BRD4-dependent transcription. The NPMc mutation in AML localises NPM to the cytoplasm (IF left). LMB treatment restores the inhibitory NPM1-BRD4 nuclear interaction, decreasing BRD4 chromatin-binding and gene expression (ChIP-Seq, right)

Group Members

George Giotopoulos	Postdoc Researcher
Mark Dawson	Senior Scientist/Researcher
Sarah Putwain	Graduate student
Sarah Horton	Postdoc Researcher
Eshwar Meduri	Postdoc Researcher
Paolo Gallipoli	Postdoc Researcher
Tonci Sustic	Research assistant
Ester Cannizarro	Research assistant
Faisal Basheer	Graduate student
Chun Fong	Graduate student
Jessica Morrison	Postdoc Researcher
Hikari Osaki	Postdoc Researcher

2013 Publications

Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, Avezov E, Li J, Kollmann K, Kent DG, Aziz A, Godfrey AL, Hinton J, Martincorena I, Van Loo P, Jones AV, Guglielmelli P, Tarpey P, Harding HP, Fitzpatrick JD, Goudie CT, Ortmann CA, Loughran SJ, Raine K, Jones DR, Butler AP, Teague JW, O'Meara S, McLaren S, Bianchi M, Silber Y, Dimitropoulou D, Bloxham D, Mudie L, Maddison M, Robinson B, Keohane C, Maclean C, Hill K, Orchard K, Tauro S, Du M-Q, Greaves M, Bowen D, Huntly BJP, Harrison CN, Cross NCP, Ron D, Vannucchi AM, Papaemmanuil E, Campbell PJ and Green AR. Somatic CALR Mutations in Myeloproliferative Neoplasms with Nonmutated JAK2. New England Journal of Medicine. December 10, 2013DOI: 10.1056/NEJMoa1312542

Dawson MA, Gudgin EJ, Horton SJ, Robson S, Osaki H, Giotopulos G, Putwain S, Cannizarro E, Weiss M, Craig J, Dittmann A, Lugo D, Jeffries P, Drewes G, Prinjha RK, Kouzarides T, Vassiliou GS, Huntly BJP. Recurrent mutations, including NPM1c, activate a BRD4-dependent core transcriptional program in Acute Myeloid. Leukemia. PMID:24220271

Diffner E, Beck D, Gudgin E, Thoms JA, Knezevic K, Pridans C, Foster S, Goode D, Lim WK, Boelen L, Metzeler KH, Micklem G, Bohlander SK, Buske C, Burnett A, Ottersbach K, Vassiliou GS, Olivier J, Wong JW, Göttgens B, Huntly BJ, Pimanda JE. Activity of a heptad of transcription factors is associated with stem cell programs and clinical outcome in acute myeloid leukemia. Blood. PMID:23327922

Calero-Nieto FJ, Joshi A, Bonadies N, Kinston S, Chan W, Gudgin E, Pridans C, Landry JR, Kikuchi J, Huntly BJ, Gottgens B, HOX-mediated LMO2 expression in embryonic mesoderm is recapitulated in acute leukaemias. Oncogene. PMID:23708655

Conte N, Varela I, Grove C, Manes N, Yusa K, Moreno T, Segonds-Pichon A, Bench A, Gudgin E, Herman B, Bolli N, Ellis P, Haddad D, Costeas P, Rad R, Scott M, Huntly B, Bradley A, Vassiliou GS. Detailed molecular characterisation of acute myeloid leukaemia with a normal karyotype using targeted DNA capture. Leukemia. PMID:23702683

Bashford-Rogers R, Palser A, Huntly B, Rance R, Vassiliou G, Follows G, Kellam P. Network properties derived from deep sequencing of the human B-cell receptor repertoires delineates B-cell populations. Genome Research. PMID:23742949

Wyspianska B, Bannister AJ, Barbieri I, Nangalia J, Godfrey A, Calero-Nieto FJ, Robson S, Rioja I, Li J, Wiese M, Cannizzaro E, Dawson MA, Huntly B, Prinjha RK, Green AR, Gottgens B, Kouzarides T. BET protein inhibition shows efficacy against JAK2V617F driven neoplasms. Leukemia. PMID:23929215

Collaborations

Collaborator	Location	From	Nature of Collaboration
GSK	Cambridge	2013	Mechanistic, pre-clinical and clinical investigation of BET inhibitors
Acylin	Cambridge/Seattle	2013	Mechanistic, pre-clinical and clinical investigation of CBP/p300 acetyltransferase inhibitors
George Vassiliou	Cambridge/Wellcome Trust Sanger Institute	2012	Mechanisms of HSC perturbation by AML-specific mutations in epigenetic regulators
Chunaram Choudhary	Cambridge/ Copenhagen	2013	Investigation of the role of acetylation of non-histone proteins in leukaemia stem cell function
Critian Frezza	Cambridge	2013	Characterisation of abnormal metabolism in AML and leukaemia stem cells.
Tony Green	SCI	Ongoing	Joint papers
Bertie Gottgens	SCI	Ongoing	Joint papers
Katrin Ottersbach	SCI	Ongoing	Joint paper
Allan Bradley	SCI	Ongoing	Joint paper

Awards & Prizes

Awardee	Award	Organisation
Dawson	Senior Fellowship	Leukaemia Foundation Australia
Dawson	VESKI Innovation Fellowship	VESKI
Dawson	Herman Clinical Fellowship	Victorian Comprehensive Cancer Centre and University of Melbourne

Policy Briefings

Event	Date	Nature of participation
National Institute of Clinical Excellence (NICE) – single technology appraisal on Ruxolitinib	01/2013	Expert Witness

Kim Jensen

Kim Jensen received his PhD in molecular biology from the University of Aarhus in 2003. He subsequently joined Professor Fiona Watt's group at the London Research Institute, Cancer Research UK, as a post-doctoral fellow. Based on cutting edge technologies and analysis of mouse models he went on to identified Lrig1, a negative regulator of receptor tyrosine kinases, as a novel marker of both human and mouse epidermal stem cells. In 2010 Kim received a Wellcome Trust Career Development Fellowship to establish his own group at the University of Cambridge. Here Kim's group has focused on the role of adult stem cells in tissue homeostasis. In 2013 Kim was awarded an EMBO YIP and also the Lundbeck Fellowship. During 2013 Kim took up a new position as Associate Professor at the BRIC at the University of Copenhagen whilst retaining a part-time appointment at the Cambridge Stem Cell Institute.

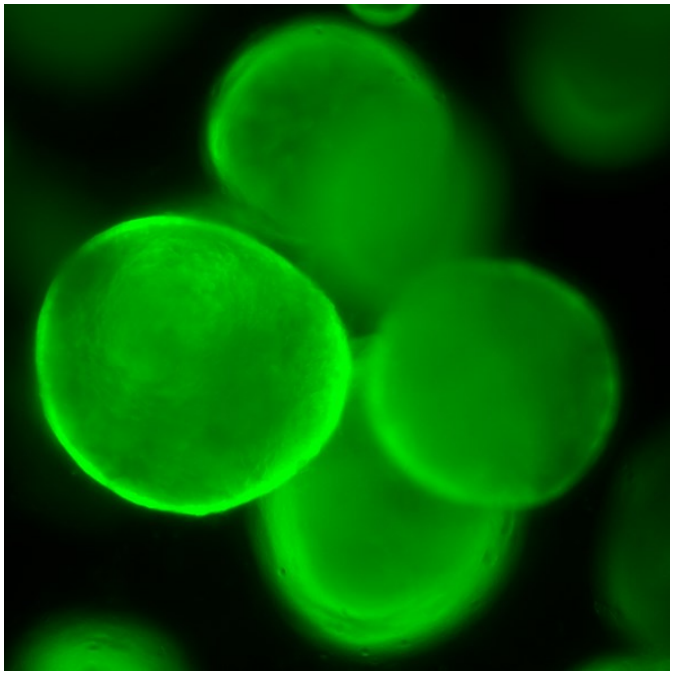
Funding

Wellcome Trust

Epithelial Development, Maintenance and Regeneration

Adult stem cells can be found in most adult tissues. Here they play an important role in tissue maintenance and repair following damage. Stem cells in different organs will behave according to the tissue specific requirements for tissue turnover. Certain tissues like the epithelial lining of the intestine have a high cell turnover, whereas the turnover in the skin is lower. This is however carefully regulated in order to ensure life-long equilibrium of the tissue in question.

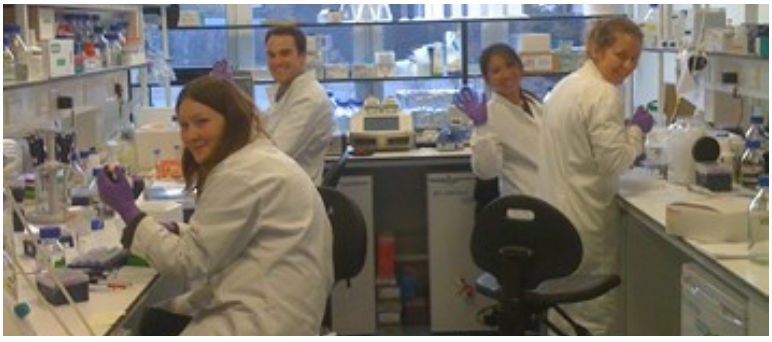
Our work focuses on the epithelium of the skin and the intestine. Stem cells have in both of these tissues been carefully characterised, however, it is still not clear how their behaviour is regulated. We know that their immediate surroundings and neighbours via intrinsic and extrinsic factors play an important role in this regulation. In certain tissue such as the skin, local differences provide the bases for the establishment of multiple distinct populations of stem cells with specific functions. Our goal is to define the functional significance of multiple stem cells compartment and establish how adult epithelial stem cells are regulated during steady state homeostasis. Such regulatory mechanisms are likely to be affected during epithelial disease such as cancer and will constitute prime targets for therapeutic intervention.



Fetal EnteroSpheres from an eGFP mouse model
Image: Robert Fordham

Group Members

Mahalia Page	Graduate student
Robert Fordham	PhD Student



2013 Publications

Hannan NRF, Fordham R, Syed YA, Moignard V, Berry A, Bautista R, Hanley NA, Jensen KB, Vallier L. Generation of multipotent foregut stem cells from human pluripotent cells. Stem Cell Reports. PMID: 24319665

Page ME, Lombard P, Ng F, Gottgens B, Jensen KB. The epidermis is comprised of autonomous compartments maintained by distinct stem cell populations. Cell Stem Cell. PMID:23954751

Fordham RP, Yui S, Hannan NR, Soendergaard C, Madgwick A, Schweiger PJ, Nielsen OH, Vallier L, Pedersen RA, Nakamura T, Watanabe M, Jensen KB. Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury. Cell Stem Cell. PMID:24139758

Tan DW, Jensen KB, Trotter MW, Connelly JT, Broad S, Watt FM. Single-cell gene expression profiling reveals functional heterogeneity of undifferentiated human epidermal cells. Development. PMID:23482486

Lu L, Teixeira VH, Yuan Z, Graham TA, Endesfelder D, Kolluri K, Al-Juffali N, Hamilton N, Nicholson AG, Falzon M, Kschischo M, Swanton C, Wright NA, Carroll B, Watt FM, George JP, Jensen KB, Giangreco A, Janes SM. LRIG1 regulates cadherin-dependent contact inhibition directing epithelial homeostasis and pre-invasive squamous cell carcinoma development. Journal of Pathology. PMID:23208928

Schweiger PJ, Jensen KB. Biological techniques: An embryonic view of tumour development. Nature. PMID:23945591

Collaborations

Collaborator	Location	From	Nature of Collaboration
Mamoru Watanabe	Tokyo	2012	Grafting of FEnS
Ludovic Vallier	SCI	Ongoing	Joint papers
Bertie Gottgens	SCI	Ongoing	Joint paper
Roger Pedersen	SCI	Ongoing	Joint paper

Awards & Prizes

Awardee	Award	Organisation
Kim Jensen	Junior Investigator Award	Danish Cancer Society
Kim Jensen	EMBO YIP member	EMBO
Robert Fordham	Best Poster Prize	First Annual Conference of the German Stem Cell Network, at the Max Delbrück Centre for Molecular Medicine, Berlin
Robert Fordham	MRC Centenary Award	Cambridge Stem Cell Institute

Public Engagement

Event	Format	Date	Participation	Name
Radio programme on public health and IBD	Radio	11/2013	Presenter	Jensen
Seminar for high school students - Copenhagen	School	10/2013	Presenter	Jensen

Ragnhildur Thóra Káradóttir

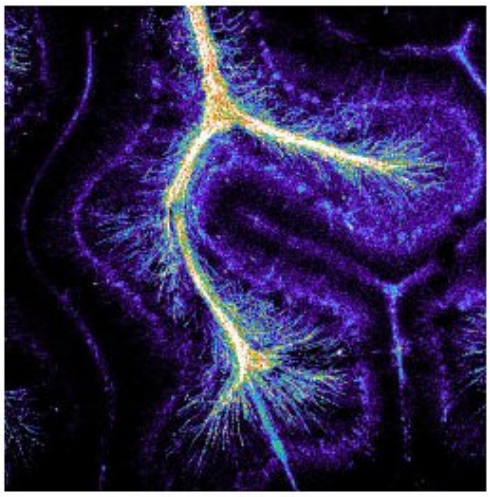
Ragnhildur Thóra Káradóttir graduated with a degree in Biochemistry from the University of Iceland in 2000. Then she did a 4 year Wellcome Trust PhD in Neuroscience at UCL under the supervision of Prof. David Attwell. She continued working with Prof. Attwell as a postdoctoral researcher, before being awarded a Royal Society Dorothy Hodgkin Research Fellowship which she used to work with Prof. Charles ffrench-Constant at the University of Cambridge. In 2008 she established her own independent research group in Cambridge and in 2011 she was awarded the Wellcome Trust Research Career Development fellowship.
She is currently an editor for the journal Brain Plasticity and a guest editor for Neuroscience and for Neuropharmacology.

Funding

EC FP7
Isaac Newton Trust
Wellcome Trust

Neurotransmitter Signalling to Central Nervous System Progenitor Cells

The lab's research interests are neurotransmitter signalling to oligodendrocyte progenitor cells (OPC; a type of CNS stem cell), in both health and disease.
For our brain to work properly, enabling us to feel, move, talk, see, think and learn, fast electrical communication between nerve cells is essential. This is achieved by insulating the nerves with a fatty substance called myelin. In diseases like multiple sclerosis, spinal cord injury and stroke, myelin is lost, while in cerebral palsy myelin fails to develop. Lack of myelin causes physical and mental disability.
Myelin is provided by cells called oligodendrocytes, which develop from oligodendrocyte precursor cells (OPCs). OPCs are 5% of all cells in the adult brain and can turn into most cell types in the brain. Most importantly, OPCs can repair myelin, but this repair often fails.
We have discovered that OPCs express a protein previously only thought to be expressed in neurons, as it is known for being essential for learning. But in OPCs it enables them to sense activity in the neurons. Furthermore, we found that OPCs enter into a dialogue with neurons and this dialogue and neuronal activity, acting on the protein we found, directs OPCs to become myelin-making oligodendrocytes in both health and disease.
We are now investigating how signals in the cells' environment interact with OPCs to instruct them to move to regions where myelin is needed, and to generate myelin-making oligodendrocytes, with special focus on the neuron to OPCs dialogue.
The long-term aim of this work is to understand how OPCs become myelinating cells, and how we can influence them to repair myelin in disease.



Myelinated fibres in the brain, these fibres provide superfast communication between neurons.

Group Members

Kimberly Evans	Graduate student/ Research assistant
Katrin Volbracht	Graduate student
Sylvia Agathou	Graduate student
Sergey Sitnikov	Graduate student
Sonia Spitzer	Graduate student
Moritz Matthey	Graduate student
John Stockley	Postdoc Researcher
Helene Gautier	Postdoc Researcher (Franklin/Karadottir)

2013 Publications

Tailor J, Kittappa R, Leto K, Gates M, Borel M, Paulsen O, Spitzer S, Karadottir RT, Rossi F, Falk A, Smith A. Stem Cells Expanded from the Human Embryonic Hindbrain Stably Retain Regional Specification and High Neurogenic Potency. Journal of Neuroscience. PMID:23884946

SRL Stacpoole, S Spitzer, B Bilican, A Compston, R Karadottir, S Chandran, RJM Franklin. High Yields of Oligodendrocyte Lineage Cells from Human Embryonic Stem Cells at Physiological Oxygen Tensions for Evaluation of Translational Biology. Stem Cell Reports. PMID:24286031

Agathou S, Káradóttir RT, Kazanis I. Niche derived oligodendrocyte progenitors: a source of rejuvenation or complementation for local oligodendrogenesis? Frontiers in Cellular Neuroscience. PMID: 24155691

Spitzer S, Agathou S, Karadottir RT. Clever glia. Stem Cell Research and Therapy. PMID:23998426

Lundgaard I, Luzhynskaya A, Stockley JH, Wang Z, Evans KA, Swire M, Volbracht K, Gautier HO, Franklin RJM, ffrench-Constant C, Attwell D, Káradóttir R. Neuregulin and BDNF induce a switch to NMDA receptor dependent myelination by oligodendrocytes. PLoS Biology. PMID: 24391468

Key Publications prior to 2013

Bakiri Y, Káradóttir R, Cossell L, Attwell D. Morphological and electrical properties of oligodendrocytes in the white matter of the corpus callosum and cerebellum. Journal of Physiology. (2010) PMID: 21098009

Káradóttir R, Hamilton N, Bakiri Y & Attwell D. Spiking and nonspiking classes of oligodendrocyte precursor glia in CNS white matter. Nature Neuroscience. (2008) PMID: 18311136

Bakiri Y, Hamilton N, Káradóttir R & Attwell D. NMDA receptor block as a therapeutic strategy for reducing ischaemic damage to oligodendrocytes. Glia. (2008) PMID: 18046734

Collaborations

Collaborator	Location	From	Nature of Collaboration
David Cavalla	Numedicus	2013	Provides us with licensed drugs known to modulate AMPA receptors to screen for their function on OPCs and potential for MS repair.
Spillantini	BRC, University of Cambridge	2013	Collaborating on a project studing glia and neurons interaction in Alzheimer disease
Klaus Nave and Sandra Gobbles	Max Planck Institute for Experimental Medicine		Regulators of OPC differentiation
Austin Smith	SCI	Ongoing	Joint paper
Robin Franklin	SCI	Ongoing	Joint papers

Public Engagement

Event	Format	Date	Participation	Name
Volunteer for the charity Squeaky Gate. Cambridge Science Festival	Science Festival	03/2013	Volunteer	Gautier

Homeostatic Regulation of Adult Stem Cells

Bon-Kyoung Koo

Bon-Kyoung Koo has the unique experience of studying the role of endosomal E3 ubiquitin ligases in two major signalling pathways, which makes him a leading expert in this field. He is an experienced mouse geneticist with broad experience in the field of E3 ubiquitin ligases.

Bon-Kyoung is part of the Marie Curie Initial Training Network "WntsApp" and was recently awarded with the Sir Henry Dale Fellowship. This Fellowship brings together the Royal Society and the Wellcome Trust to supporting the future leaders of biomedical research.

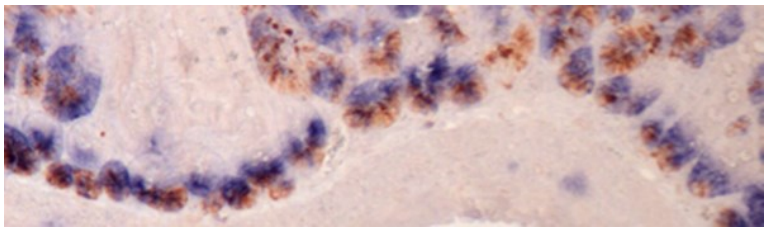
Funding

Wellcome Trust
MRC

Homeostatic turnover in adult tissues is governed by the interplay of a multitude of signalling pathways that are often triggered by niche cells providing diverse ligands to support stem cells. Upon tissue damage, adult stem cells rapidly proliferate to restore the loss and reinstate homeostasis; regulatory signalling that governs proliferation and differentiation of stem cells enable this damage response. De-regulation of these processes on the other hand results in either hyperplasia or loss of stem cells.

An important class of modulators are E3 ubiquitin ligases. Mib1, an E3 for Notch ligands, has a crucial role in Notch ligand activation in niche cells that, in turn, promotes Notch signalling in stem cells. RNF43 and ZNRF3 attenuate Wnt activation in intestinal stem cells by functioning as E3s for Wnt receptors. Thus to date, we have learned about E3 ligases working in the Notch and Wnt pathways in adult stem cells. In light of this, it seems probable that other E3 ligases, with important roles in adult stem cell biology, remain to be identified. Our research focus is on identifying and understanding the role of novel E3 ubiquitin ligases in homeostatic regulation of stem cells.

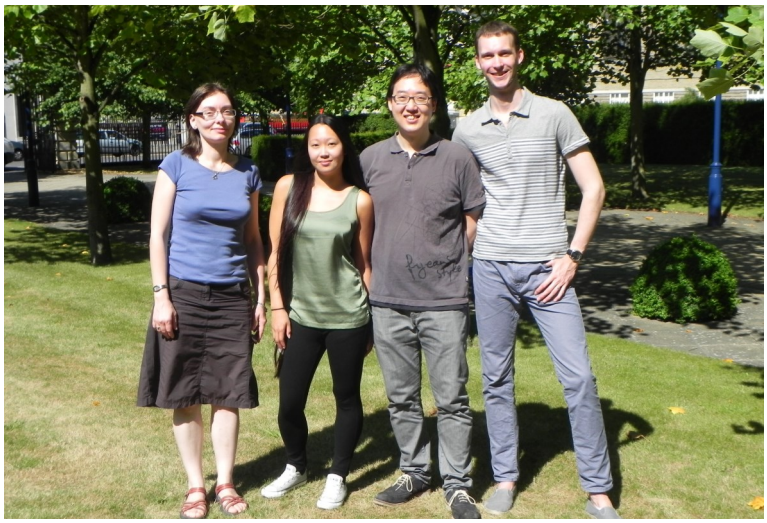
We have identified a novel quiescent Troy+ epithelial stem cell population in the stomach. Upon tissue damage, Troy+ stem cells actively divide to regenerate lost cell types. The discovery of Troy+ stomach stem cells enables us to investigate how an adult tissue can retain its homeostasis after various types of injury. This study will help us understanding how homeostasis is achieved in the adult stomach and in other tissues, which will potentially lead to the development of successful adult stem cell therapy.



Olfm4-positive intestinal stem cells (in purple) reside together with Cryptdin -postive Paneth cells (in brown). Paneth cells tend to locate next to stem cells as nursing niche cells in both normal and tumorigenic glands. Image: Bon-Kyoung Koo

Group Members

Roxana Micsik	Postdoc Researcher
Amanda Andersson-Rolf	PhD Student
Juergen Fink	PhD Student (Koo/Simons)
Emma Martinez Sanchez	Postdoc Researcher



2013 Publications

Koo BK, Stange DE, Huch M, Sibbel G, Basak O, Lyubimova A, Kujala P, Bartfeld S, Koster J, Geahlen JH, Peters PJ, van Es JH, van de Wetering M, Mills JC and Clevers H. Differentiated Troy+ chief cells act as 'reserve' stem cells to generate all lineages of the stomach epithelium. Cell. PMID: 24120136

Schwank G, Andersson-Rolf A, Koo BK, Sasaki N, Clevers H. Generation of BAC Transgenic Epithelial Organoids. PLoS ONE. PMID:24204693

Koo BK, Schwank G, Sasselli V, Dekkers JF, Heo I, Demircan T, Sasaki N, Boymans S, Cuppen E, van der Ent CK, Nieuwenhuis EES, Beekman JM, Clevers H. Functional repair of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients. Cell Stem Cell. PMID: 24315439

Other Key Publications

Heijmans J, van Lidth de Jeude JF, Koo BK, Rosekrans SL, Wielenga MC, van de Wetering M, Ferrante M, Lee AS, Onderwater JJ, Paton JC, Paton AW, Mommaas AM, Kodach LL, Hardwick JC, Hommes DW, Clevers H, Muncan V, van den Brink GR. ER Stress Causes Rapid Loss of Intestinal Epithelial Stemness through Activation of the Unfolded Protein Response. Cell Reports. (2013) PMID:23545496

Koo BK, Spit M, Jordens I, Low TY, Stange DE, van de Wetering M, van Es JH, Mohammed S, Heck AJ, Maurice MM, Clevers H. Tumour suppressor RNF43 is a stem cell E3 ligase that induces endocytosis of Wnt receptors. Nature. (2012) PMID:22895187

Koo BK, Kim HA, Cho JH, Kim YY, Seong J, Chang HJ, Oh YM, Stange DE, Park JG, Hwang D, Kong YY. Notch counteracts Wnt-beta-catenin signaling through chromatin modification in mouse and human colorectal cancer. Journal of Clinical Investigation. (2012) PMID: 22863622

Koo BK, Stange DE, Sato T, Karthaus W, Farin HF, Huch M, van Es JH, Clevers H. Controlled gene expression in primary Lgr5 organoid cultures. Nature Methods. (2011) PMID:22138822

Collaborations

Collaborator	Location	Nature of Collaboration
WntsApp Members	EU based	Marie Curie Initial Training Network
Ben Simons	SCI	Co-supervision of PhD student

Awards & Prizes

Awardee	Award	Organisation
Bon-Kyoung Koo	Sir Henry Dale Fellowship	Wellcome Trust

Neural Stem Cells, Cellular Reprogramming and Regenerative Medicine

Mark Kotter

I am an academic neurosurgeon who undertook postgraduate medical training in Austria (Vienna), Germany (Göttingen), and the UK (Cambridge). During my PhD at the University of Cambridge I have established the importance of macrophages for the regeneration of CNS white matter. I continue to work on extrinsic and extrinsic regulators of CNS remyelination and have developed an interest in mechanisms of direct cellular reprogramming. I am particularly interested in clinical translation with a view to promoting regeneration in a clinical setting.

Funding

UK MS Centre for Myelin Repair
Qatar Science Foundation
Wings for Life
Sir David Walker Fellowship

Fellowships

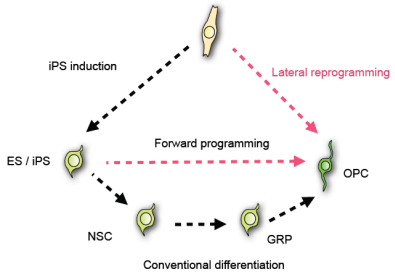
Matthias Pawlowski	German Research Foundation

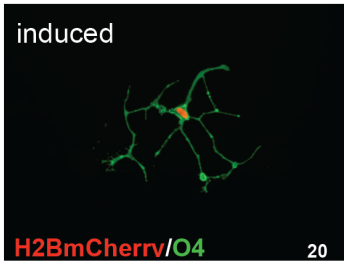
My group is interested in the biology of adult CNS stem and precursor cells. With respect to regeneration in the CNS we are particularly interested in mechanisms of CNS remyelination, a stem/precursor cell-mediated process in which new myelin sheaths are restored to demyelinated nerve fibres (axons). To understand how the differentiation of multipotent oligodendrocyte precursor cells (OPCs) is regulated we use a combination of in vitro and in vivo models.

A second focus of our lab is cellular re-programming techniques. A limited set of transcription factors enables trans-lineage re-programming of somatic cells into distinct neural cell types. We use cellular re-programming techniques to

1. Study transcriptional and epigenetic events that determine the cellular identity of OPCs, NSCs, and differentiated neural cell types,
2. generate patient specific disease models, and
3. develop cellular platforms that can be used for drug discovery and toxicological investigation.

We aim at bedside to bench translation as well as translating our findings into clinical studies.

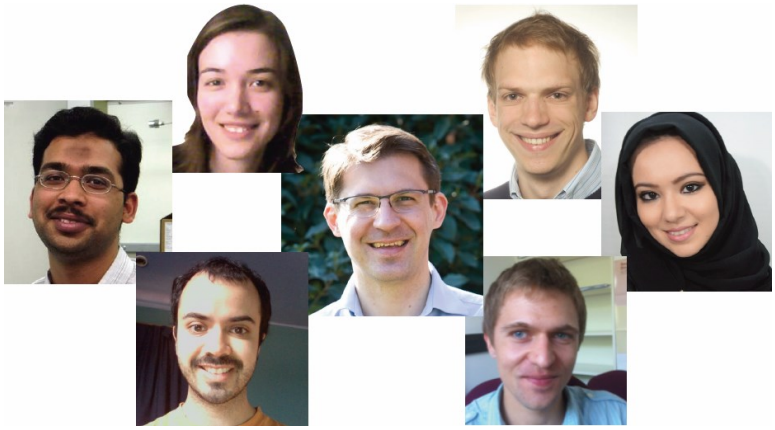




Human induced Oligodendrocyte precursor cell

Group Members

Yasir Ahmed Syed	Postdoc
Ana Amaral	Postdoc
Matthias Pawlowski	Postdoc
Ginez Gonzalez	Graduate student
Sarah Ali Abdulla	Graduate student
Kelly Inthanthon	Graduate student
Saifur Rahman	Graduate student



2013 Publications

Pawlowski M, Kotter M. Generation of Neural Cells by Direct Cellular Reprogramming. Journal of Transplantation and Stem Cell Biology. 2013;1(1): 7.

Syed YA, Baer A, Hofer MP, González GA, Rundle J, Huang JK, Zhao C, Rossner MJ, Trotter MWB, Lubec G, Franklin RJM, Kotter MR. Inhibition of phosphodiesterase-4 promotes oligodendrocyte precursor cell differentiation and enhances CNS remyelination. EMBO Molecular Medicine. PMID: 24293318

Amaral AI, Meisingset TW, Kotter MR, Sonnewald U. Metabolic aspects of neuron-oligodendrocyte-astrocyte interactions. Frontiers in Endocrinology (Lausanne). PMID:23717302

Key Publications prior to 2013

Kotter MR, Stadelmann C, Hartung HP. Enhancing CNS remyelination in disease – can we wrap it up. Brain. (2011) PMID:21507994

Syed YA, Hand E, Möbius M, Zhao C, Hofer M, Nave KA, Kotter MR. Inhibition of CNS remyelination by the presence of Semaphorin. Journal of Neuroscience. (2011) PMID:21389227

Baer AS, Syed YA, Vig R, Hoeger H, ffrench-Constant C, Franklin RJM, Altmann F,Lubec G, Kotter MR. Myelin-mediated inhibition of oligodendrocyte precursor cell differentiation can be overcome by pharmacological modulation of Fyn-RhoA and protein kinase C signalling. Brain. (2009) PMID:19208690

Collaborations

Collaborator	Location	From	Nature of Collaboration
Ursula Sonnewald	University Trondheim, Norway	2013	Joint project studying oligodendrocyte precursor cell metabolism, focus on Glucose metabolism
Klaus-Amin Nave	MPI Göttingen, Germany	2009	Developmental aspects of OPC differentiation
Amparo Acker-Palmer	Mainz University, Germany	2010	Biologial effects of Ephrin on OPC differentation
Bente Finsen	University of Southern Denmark	2013	Transcriptional regulators of OPC differentiation
Robin Franklin	SCI	Ongoing	Joint paper

Public Engagement

Event	Format	Date	Participation	Name
Wings for Life, SCI outreach activity	Lab tour	02/2013	Organiser and Speaker	Kotter
Wings for Life, SCI outreach meeting	Meeting	09/2013	Volunteer	Kotter

Human stem cell models of dementia

Rick Livesey

Rick did his undergraduate and preclinical medical studies in Cork, Ireland before joining the MB/PhD programme at the University of Cambridge Clinical School. He did his PhD at the MRC LMB in Steve Hunt's group and post-doctoral work with Connie Cepko at the Department of Genetics, Harvard Medical School. Rick started his group at the Gurdon Institute in September 2001.

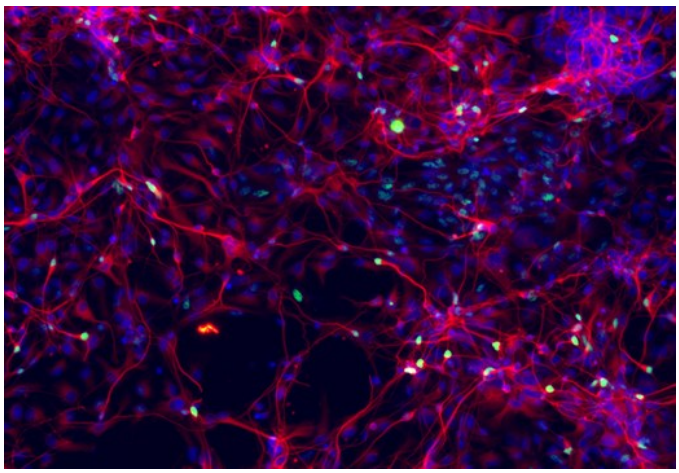
Funding

Wellcome Trust
Alzheimers Research UK
EU Innovative Medicines Initiative (IMI)
Medical Research Council

A major interest of the group is the use of stem cell-based models of Alzheimer's disease to study the initiation and pathogenesis of neurodegeneration in dementia. Developing these models depends on our fundamental research in stem cell biology and neuroscience, together with associated technologies, such as genome engineering and imaging. This background enables us to generate *in vitro* cortical neural networks and to carry out functional studies of Alzheimer's disease biology.

A challenge for modelling Alzheimer's disease (AD), and developing therapies based on those models, is our incomplete understanding of the cell and molecular biology underlying the initiation and progression of the disease. Animal models continue to be critical to understanding the pathogenesis of Alzheimer's disease. However, it is clear that no animal model completely recapitulates AD and there is an ongoing need for tractable systems for studying AD pathogenesis both *in vitro* and *in vivo*.

Building on our previous work using human ES and iPS cells to model Alzheimer's disease pathogenesis in Down syndrome, we are carrying out functional studies of AD initiation and progression in human stem cell models, using genetic forms of dementia and AD.



Human stem cell-derived neurons

Group Members

Peter Kirwan	Postdoc
Tatyana Dias	Postdoc
Steven Moore	Postdoc
Alberto Frangini	Postdoc
Lewis Evans	Postdoc
Manuel Peter	Postdoc
Nathalie Saurat	Grad Student
Tomoki Otani	Grad Student
Teresa Krieger	Grad Student (Simons/Livesey)
Philipp Berg	Grad Student (Barker/Livesey)
James Smith	Research Assistant
Amelia McGlade	Research Assistant
Ayiba Momoh	Research Assistant
Laura Brightman	Research Assistant
Jayne Fisher	Administration

2013 Publications

Saurat N, Andersson T, Vasistha NA, Molnár Z, Livesey FJ. Dicer is required for neural stem cell multipotency and lineage progression during cerebral cortex development. Neural Development. PMID:23895693

Olsson B, Legros L, Guilhot F, Strömberg K, Smith J, Livesey FJ, Wilson DH, Zetterberg H, Blennow K. Imatinib treatment and Aβ42 in humans. Alzheimer's and Dementia. PMID: 24331439

Alsiö JM, Tarchini B, Cayouette M, Livesey FJ. Ikaros promotes early-born neuronal fates in the cerebral cortex. Proceedings of the National Academy of Sciences USA. PMID: 23382203

Key Publications prior to 2013

Shi Y, Kirwan P, Livesey FJ. Directed differentiation of human pluripotent stem cells to cerebral cortex neurons and neural networks. Nature Protocols (2012). PMID: 22976355

Shi Y, Kirwan P, Smith J, MacLean G, Orkin SH, Livesey FJ. A Human Stem Cell Model of Early Alzheimer's Disease Pathology in Down Syndrome. Science Translational Medicine (2012). PMID: 22344463

Shi Y, Kirwan P, Smith J, Robinson HP, Livesey FJ. Human cerebral cortex development from pluripotent stem cells to functional excitatory synapses. Nature Neuroscience (2012). PMID: 22306606

Pereira JD, Sansom SN, Smith J, Dobenecker MW, Tarakhovsky A, Livesey FJ. Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. Proceedings of National Academy of Sciences USA. (2010) PMID: 20798045

Andersson T, Rahman S, Sansom SN, Alsio JM, Kaneda M, Smith J, O'Carroll D,Tarakhovsky A, Livesey FJ. Reversible block of mouse neural stem cell differentiation in the absence of dicer and microRNAs. PLoS ONE. (2010) PMID: 20976144

Subkhankulova T,Yano K, Robinson HP, Livesey FJ. Grouping and classifying electrophysiologically- defined classes of neocortical neurons by single cell, whole-genome expression profiling. Frontiers in Molecular Neuroscience. (2010) PMID: 20428506

Collaborations

Collaborator	Location	From	Nature of Collaboration
John Hardy	Institute of Neurology, UCL	Ongoing	Human stem cell models of familial AD
EU IMI StemBANCC consortium	EU	Ongoing	Stem cell models for drug discovery (Janssen, Roche, Abbvie)
MedImmune		Ongoing	Human stem cell models of neurodegenerative disease
Ben Simons	SCI	Ongoing	Clonal analysis of human cerebral cortex development
Roger Barker	SCI	Ongoing	Modelling Parkinson's disease dementia
Azim Surani	SCI	Ongoing	Epigenetic mechanisms in human neurons in health and disease

Awards & Prizes

Awardee	Award	Organisation
Rick Livesey	Wellcome Trust Senior Investigator Award	Wellcome Trust

Jennifer Nichols

Jenny Nichols began her research career with Professor Richard Gardner at the University of Oxford, where she developed a fascination for early mammalian development. She subsequently moved to Edinburgh to join Austin Smith in his newly formed group at the Centre for Genome Research to focus on investigating how the epiblast lineage is established in the embryo and how pluripotent cells can be captured and propagated efficiently in culture as embryonic stem cell lines.
She obtained her PhD in Edinburgh in 1995 and continued as a post doctoral research fellow in Austin Smith's lab until 2006, when she moved to Cambridge as a group leader in the Stem Cell Institute.

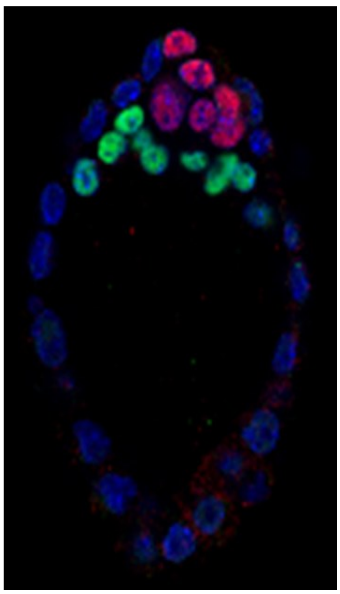
Funding

Wellcome Trust

Embryonic Pluripotency

Unlike most other model organisms, the early mammalian embryo possesses an amazing capacity to regulate its own development. Murine embryos develop a pluripotent epiblast at the late blastocyst stage, which can be propagated in vitro in the form of embryonic stem (ES) cells. The first ES cells were derived directly from mouse blastocysts using culture medium supplemented with serum and a 'feeder layer' of mitotically inactivated fibroblasts. The process by which ES cells emerge was not understood, but their potential applications were immediately realised to be enormous. The purpose of our research is to try to understand how the pluripotent cells are assigned and maintained in the embryo; how they can be harnessed and propagated in culture as ES cell lines and how the process of ES cell derivation can be controlled and improved. Addition of selected inhibitors to the culture medium has obviated the requirement for exogenous cytokines for the maintenance and derivation of murine ES cells, apparently by simply removing the option to differentiate. ES cells can be very efficiently derived from mouse and rat embryos cultured in these conditions. This efficiency is apparently attributable to the ability of the inhibitors both to prevent differentiation and to promote expansion of the epiblast. We have applied this technology to derive ES cells efficiently from hitherto recalcitrant strains of mice, including non-obese diabetic (NOD) mice.

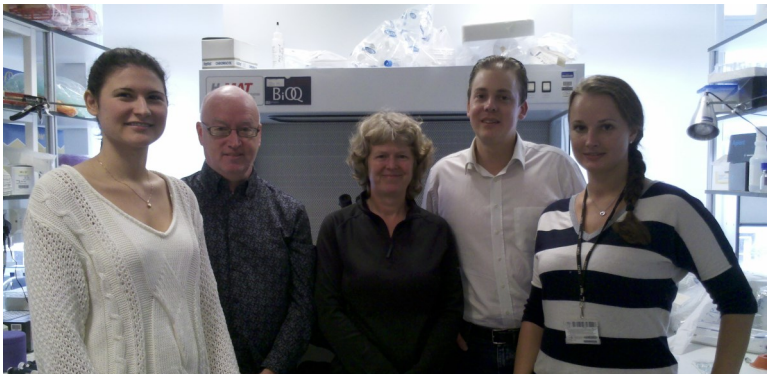
Although pluripotent cell lines have been derived from other mammals, these lines differ from murine ES cells, and are more similar to so called 'epiblast stem cells' (EpiSCs) derived from post-implantation mouse embryos. We are interested in how differences in early embryonic development of various mammalian species influence their subsequent behaviour in culture. We are investigating how the property of naïve pluripotency is established in developing mouse embryos with a view to providing a blueprint for this process. We aim to develop novel strategies to derive non-rodent ES cell lines with properties similar to those of the mouse.



Confocal image of a late blastocyst showing epiblast (pink) and hypoblast (green).

Group Members

Stoyana Alexandrova	Graduate Student
Thorsten Boroviak	Postdoc Researcher
Kenneth Jones	Research Assistant
Agata Kurowski	Graduate Student



2013 Publications

Radzisheuskaya A, Chia Gle B, dos Santos RL, Theunissen TW, Castro LF, Nichols J, Silva JC. A defined Oct4 level governs cell state transitions of pluripotency entry and differentiation into all embryonic lineages. Nature Cell Biology. PMID:23629142

Betschinger J, Nichols J, Dietmann S, Corrin PD, Paddison PJ, Smith A. Exit From Pluripotency Is Gated By Intracellular Redistribution Of The Bhlh Transcription Factor Tfe3. Cell. PMID:23582324

Leitch HG, Nichols J, Humphreys P, Mulas C, Martello G, Lee C, Jones K, Surani MA, Smith A. Rebuilding Pluripotency from Primordial Germ Cells. Stem Cell Reports. PMID:24052943

Morgan MAJ, Muller PSS, Mould A, Newland SA, Nichols J, Robertson EJ, Cooke A, Bikoff EK. The Nonconventional MHC Class II Molecule DM Governs Diabetes Susceptibility in NOD Mice. PLoS One. PMID:23418596

Oliver CH, Nichols J, Watson CJ. The KRAB domain zinc finger protein, Zfp157, is expressed in multiple tissues during mouse embryogenesis and in specific cells in adult mammary gland and skin. Genesis. PMID:23315963

Morgani S, Canham M, Nichols J, Sharov A, Migueles R, Ko MH, Brickman J. Totipotent Embryonic Stem Cells Arise in Ground-State Culture Conditions. Cell Reports. PMID:23746443

Arias AM, Nichols J, Schröter C. A molecular basis for developmental plasticity in early mammalian embryos., Development. PMID:23942513

Livigni A, Peradziryi H, Sharov AA, Chia G, Hammachi F, Migueles RP, Sukparangsi W, Pernagallo S, Bradley M, Nichols J, Ko MS, Brickman JM. A conserved Oct4/POUV-dependent network links adhesion and migration to progenitor maintenance. Current Biology. PMID: 24210613

Collaborations

Collaborator	Location	Nature of Collaboration
Berenika Plusa	University of Manchester	Cell fate and commitment in the early embryo
Joshua Brickman	Danstem, Copenhagen	Stem cell potency and role of Oct4
Anna Katerina Hadjantonakis	Sloan Kettering Institute, New York	Early embryonic lineage decisions
Silvia Munoz Descalzo	University of Bath	Gene regulatory networks in pluripotent lineages in vivo
Erika Sasaki	Keio University, Tokyo	Pluripotency in the marmoset
Harry Moore	University of Sheffield	Human embryo pluripotency
Fabienne Devreker	ULB, Belgium	Human embryo pluripotency
Jose Silva	SCI	Joint paper
Austin Smith	SCI	Joint papers
Azim Surani	SCI	Joint paper
Kim Jensen	SCI	Joint paper
Christine Watson	SCI	Joint paper
Alfonso Martinez-Arias	SCI	Joint paper

Awards & Prizes

Awardee	Award	Organisation
Jennifer Nichols	Suffrage Science Award	Suffrage Science

Public Engagement

Event	Format	Date	Participation	Name
School Pupil (Royal Grammar) work experience	Host	06/2013	Host	Nichols

The Developmental Origins of Blood Stem Cells

Katrin Ottersbach

Katrin Ottersbach obtained her BSc from the University of Edinburgh in 1997 and her PhD from the Beatson Institute for Cancer Research in Glasgow in 2001. She was a postdoc in Elaine Dzierzak's group in Rotterdam 2001-2006.
She set up her own lab at the Cambridge Institute for Medical Research in 2006 and became a PI in the Wellcome Trust – Medical Research Council Cambridge Stem Cell Institute in 2012.

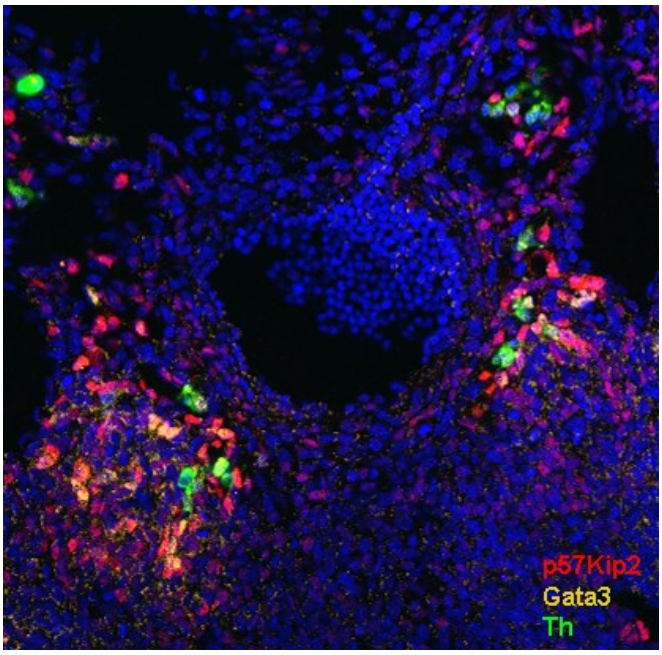
Funding

Isaac Newton Trust
Kay Kendall Leukaemia Fund
Leukaemia & Lymphoma Research

Fellowships

Simon Fitch	Kay Kendall Leukaemia Fund Junior Fellowship

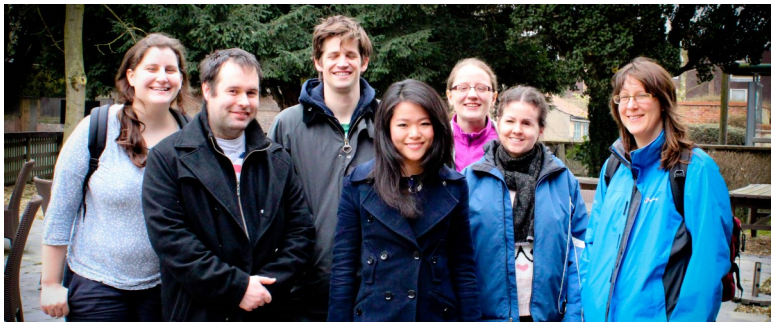
Our work focuses on the emergence and regulation of the first blood stem cells (BSCs) in the mouse embryo in order to identify the basic mechanisms that control their generation from precursor cells and their initial expansion and dissemination. Knowledge of these early regulatory pathways has proven to be invaluable for understanding how adult BSCs can be manipulated for clinical purposes and how interference with these processes may result in blood-related disorders.
We have recently further defined the region of the embryo where BSCs are first detected and have used this information to carry out screening experiments which resulted in the identification of novel regulators of BSC generation. Furthermore, we have unveiled a functional interplay between the embryonic blood and nervous systems and are conducting further research into the microenvironment that regulates BSC emergence. More recently, we have also started focussing on how these pathways are corrupted in infant leukaemia.



Expression of three microenvironmental regulators of blood stem cell emergence around the mouse embryonic dorsal aorta

Group Members

Chrysa Kapeni	Research Assistant and Graduate Student
Maria Mascarenhas	Graduate Student
Neil Barrett	Graduate Student
Wendi Bacon	Graduate Student
Simon Fitch	Postdoc Researcher
Camille Malouf	Postdoc Researcher
Kankan Xia	Graduate Student
Nada Zaidan	Graduate Student



2013 Publications

Diffner E, Beck D, Gudgin E, Thoms JA, Knezevic K, Pridans C, Foster S, Goode D, Lim WK, Boelen L, Metzeler KH, Micklem G, Bohlander SK, Buske C, Burnett A, Ottersbach K, Vassiliou GS, Olivier J, Wong JW, Göttgens B, Huntly BJ, Pimanda JE. Activity of a heptad of transcription factors is associated with stem cell programs and clinical outcome in acute myeloid leukemia. Blood. PMID:23327922

Malouf C, Ottersbach K. The Unconventional Embryo: Immune-Restricted Potential Precedes Multipotentiality. Cell Stem Cell. PMID:24209755

Key Publications prior to 2013

Fitch SR, Kimber G, Wilson NK, Parker A, Mirshekar-Syahkal B, Göttgens B, Medvinsky A, Dzierzak E and Ottersbach K. Signaling from the sympathetic nervous system regulates hematopoietic stem cell emergence during embryogenesis. Cell Stem Cell. (2012) PMID: 23040481

Mascarenhas MI, Parker A, Dzierzak E. and Ottersbach K. Identification of novel regulators of hematopoietic stem cell development through refinement of stem cell localization and expression profiling. Blood. (2009) PMID: 19794138

Ottersbach K. and Dzierzak E. The Murine Placenta Contains Hematopoietic Stem Cells within the Vascular Labyrinth Region. Developmental Cell. (2005) PMID: 15737933

Collaborations

Collaborator	Location	From	Nature of Collaboration
Sten Eirik Jacobsen	Oxford	2012	Sharing of sorting strategy
Tom Milne	Oxford	2013	Sharing of reagents, cloning strategies and disease models
John Pimanda	Sydney	Ongoing	Combined projects
Bertie Gottgens	SCI	Ongoing	Joint paper
Brian Huntly	SCI	Ongoing	Joint paper

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Film showing	03/2013	Presenter; Introduction to documentary film and Q & A session	Ottersbach

Mechanics of Mesoderm Differentiation in Mammalian Pluripotent Stem cells

Roger Pedersen

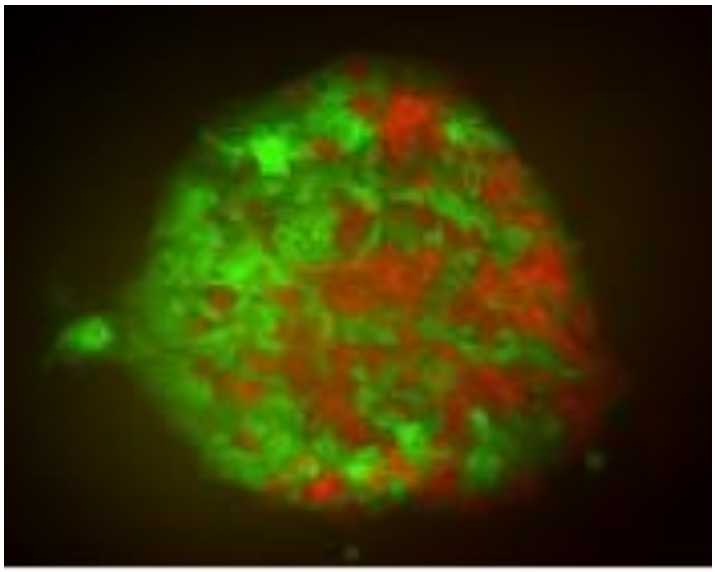
Roger Pedersen is Director of Research in Regenerative Medicine in the Department of Surgery and the Anne McLaren Laboratory for Regenerative Medicine. At UCSF from 1971, he explored developmental potency and cell fate in early mouse development. In 2001 he relocated to Cambridge, where he heads a team devoted to delivering human pluripotent stem cells to clinical use.

Funding

March Of Dimes Birth Defects Foundation
Medical Research Council
N.I.H. (U.S.A.)

Our recent work has focused on the role transforming growth factor family members in the cell fate decision between endoderm and mesoderm, demonstrating that BMP induces hESC and EpiSC differentiation to mesoderm. This work reveals the importance BRACHYURY and CDX2 genes as key mediators of embryonic and extraembryonic lineage differentiation in hESCs and EpiSCs.

Our focus on mesoderm has now led us to study the molecular pathways for early human cardiomyocyte differentiation, with a goal of understanding the transcriptional networks responsible for chamber-specific cardiomyocyte identities and using this to generate more homogeneous cardiomyocyte populations for cell-based therapy and drug discovery. I am also fascinated by the potential opportunities for guiding differentiation of pluripotent human stem cells into other cell types with potential clinical applications.



Migratory behaviour in human embryonic stemcells

Group Members

Sasha Mendjan	Postdoc Researcher
Maria Ortiz	Postdoc Researcher
Daniel Ortmann	Postdoc Researcher
Rob Fordham	Graduate student
Filipa Soares	Graduate student
Victoria Mascetti	Graduate student
Stan Wang	Graduate student

2013 Publications

Lupo G, Novorol C, Smith JR, Vallier L, Miranda E, Alexander M, Biagioni S, Pedersen RA, Harris WA. Multiple roles of Activin/Nodal, bone morphogenetic protein, fibroblast growth factor and Wnt/β-catenin signalling in the anterior neural patterning of adherent human embryonic stem cell cultures. Open Biology. PMID:23576785

Fordham RP, Yui S, Hannan NR, Soendergaard C, Madgwick A, Schweiger PJ, Nielsen OH, Vallier L, Pedersen RA, Nakamura T, Watanabe M, Jensen KB. Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury. Cell Stem Cell. PMID:24139758

Cibelli J, Mascetti VL and Pedersen RA. Epigenetic consequences of somatic cell nuclear transfer and induced pluripotent stem cell reprogramming. Biology and Pathology of the Oocyte.

Key Publications prior to 2013

Bernardo AS, Faial T, Niakan KK, Ortmann D, Gardner L, Senner CE, Callery EM, Trotter MW, Hemberger M, Smith JC, Moffett A, Bardwell L and Pedersen RA. (2011). BRACHYURY and CDX2 mediate BMP-induced differentiation of human and mouse pluripotent stem cells into embryonic and extraembryonic lineages. Cell Stem Cell. (2011) PMID:21816365

Chng Z, Teo A, Pedersen RA, Vallier L. SIP1 mediates cell-fate decisions between neuroectoderm and mesendoderm in human pluripotent stem cells. Cell Stem Cell. (2010) PMID:20074535

Vallier L, Mendjan S, Brown S, Chng Z, Teo A, Smithers LE, Trotter MW, Cho CH, Martinez A, Rugg-Gunn P, Brons G, Pedersen RA. Activin/Nodal signalling maintains pluripotency by controlling Nanog expression. Development. (2009) PMID:19279133

Collaborations

Collaborator	Location	From	Nature of Collaboration
Ludovic Vallier	SCI	Ongoing	Joint papers
Kim Jensen	SCI	Ongoing	Joint paper

Stefano Pluchino

After receiving his MD (1995) and PhD in Neuroscience (2004) from the University of Siena (Italy), Stefano Pluchino completed a residency program in Neurology at the same University (1999) and received additional training at the MRC Brain Repair Centre, Cambridge University, UK (1996-1998). He then completed two subsequent post-doctoral fellowships (2004-2005) at the San Raffaele Scientific Institute, Milan (Italy), where he progressed to the position of Project and then Group leader (2005-2010).
He is currently a University Lecturer in Brain Repair and Honorary Consultant in Neurology within the John van Geest Centre for Brain Repair (2010). He is also a European Research Council (ERC) Starting Independent Researcher and editorial board member for Brain. Dr Pluchino has made significant contributions to the understanding of the mechanisms of therapeutic plasticity of neural stem/precursor cells (NPCs) after systemic transplantation in laboratory animals with experimental inflammatory neurological diseases.

Funding

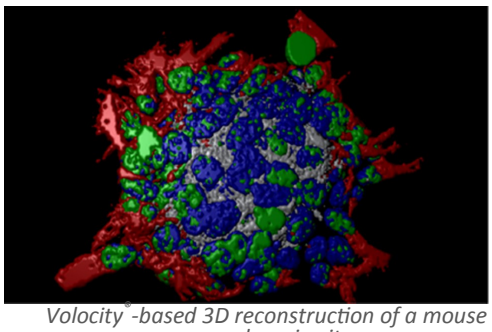
EC FP7
International Foundation For Research In Paraplegia-Irp
The Evelyn Trust

Central Nervous System Repair

The development of cell-based therapies aimed to promote tissue repair in central nervous system (CNS) diseases, represents one of the most challenging areas of investigation in the field of regenerative medicine. Several cell-replacement strategies have been developed in the last few years. Recent evidence from our own and other laboratories indicates that undifferentiated neural stem/precursor cells (NPCs) might very efficiently protect the CNS from chronic degeneration induced by inflammation both in small rodents as well as in primates. However, before envisaging any potential human applications of such innovative therapies we need to confront with some preliminary and still unsolved questions:

The ideal stem cell source for transplantation, whether it has to be from pluripotent or multipotent sources;
2. The ideal route of cell administration, whether it has to be focal or systemic;
3. The ideal balance between differentiation and persistence of stem cells into the targeted tissue;
4. The ideal mechanism of tissue repair to foster, whether it has to be cell replacement or tissue protection (rescue).

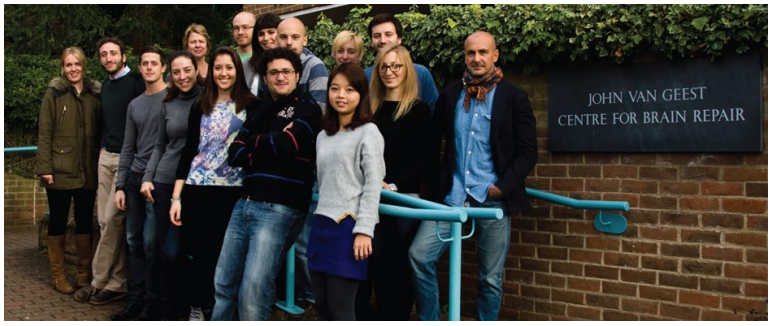
Current projects in the laboratory are further exploring the cellular and molecular mechanisms regulating the therapeutic plasticity of NPCs in complex CNS diseases such as multiple sclerosis, and spinal cord injury. Besides some classical experimental cell therapy approaches with pluripotent stem cell-derived precursors/progenitors, we are devoting special attention to the different modalities by which NPCs engage programs of horizontal cell-to-cell communication with cells in the microenvironment.



Volocity® -based 3D reconstruction of a mouse neurosphere in vitro.

Group Members

Elena Giusto	Postdoc Researcher
Nunzio Iraci	Postdoc Researcher
Jayden A. Smith	Postdoc
Matteo Donega'	Graduate student
Bing Huang	Graduate student
Tommaso Leonardi	Graduate student
Silvia Basilico	Undergraduate
Luca Peruzzotti-Jametti	Research assistant
Giulia Mallucci	Graduate student
Gillian Tannahill	Postdoc
Jeroen Verheyen	Graduate student
Joshua Bernstock	PhD student
Beatriz Vega-Blanco	Research assistant
Joan Pidgeon	Admin



2013 Publications

L'episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Impagnatiello F, Pluchino S, Marchetti B. Aging-Induced Nrf2 -ARE Pathway Disruption in the Subventricular Zone Drives Neurogenic Impairment in Parkinsonian Mice via PI3K-Wnt/β-Catenin Dysregulation. Journal of Neuroscience. PMID:23345222

Marchetti B, Pluchino S. Wnt your brain be inflamed? Yes, it Wnt! Trends in Molecular Medicine. PMID:23312954

Pluchino S, Cossetti C. How stem cells speak with host immune cells in inflammatory brain diseases. Glia. PMID:23633288

Giusto E, Donegà M, Cossetti C, Pluchino S. Neuro-immune interactions of neural stem cell transplants: From animal disease models to human trials. Experimental Neurology. PMID:23507035

Marchetti B, L'Episcopo F, Morale MC, Tirolo C, Testa N, Caniglia S, Serapide MF, Pluchino S. Uncovering novel actors in astrocyte-neuron crosstalk in Parkinson's disease: the Wnt/β-catenin signaling cascade as the common final pathway for neuroprotection and self-repair. European Journal of Neuroscience. PMID:23461676

Drago D, Cossetti C, Iraci N, Gaude E, Musco G, Bachi A. Pluchino S. The stem cell secretome and its role in brain repair. Biochimie. PMID:23827856

Pluchino S, L Peruzzotti-Jametti L. Rewiring the ischemic brain with human induced Pluripotent Stem Cell (iPSC)-derived cortical neurons. Brain. PMID: 24335051

Hill AF, Pegtel DM, Lambertz U, Leonardi T, O'Driscoll L, Pluchino S, Ter-Ovanesyan D, Nolte-'t Hoen EN. ISEV position paper: extracellular vesicle RNA analysis and bioinformatics. Journal of Extracellular Vesicles. PMID: 24376909

Collaborations

Collaborator	Location	From	Nature of Collaboration
Robin Franklin	SCI	Ongoing	Study of the myelinogenic potential of induced neural stem cells in vitro and in vivo
Keith Martin	SCI	Ongoing	Study of the restorative capacities of neural stem cells after transplantation in experimental glaucoma models

Public Engagement

Event	Format	Date	Participation	Name
Patients' Discovery Day at the University of Cambridge	Public Event	11/2013	Speaker	Pluchino

Stem Cell Fate in the Mammalian Lung

Emma Rawlins

Emma Rawlins is an MRC Career Development Fellow. She obtained her PhD in developmental biology from the University of Edinburgh where she worked with Prof Andrew Jarman. Her postdoctoral training was at Duke University Medical School, North Carolina, USA in the lab of Prof Brigid Hogan. This was where she first worked on mouse lung stem cells. She was one of the first people to use modern genetic techniques to study mouse lung stem cells and has been instrumental in identifying several stem cell populations.

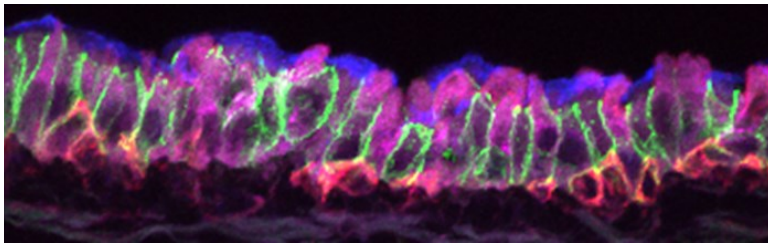
Funding

Addenbrooke's Charitable Trust
March Of Dimes Birth Defects Foundation
Medical Research Council
Wellcome Trust

From first breath to last gasp, our lungs are an essential organ. Lung architecture is complex and must be maintained throughout life. If things go wrong with lung maintenance, the resulting changes can contribute to multiple different lung diseases. Many of these are degenerative diseases – such as Chronic Obstructive Pulmonary Disease – and are associated with ageing. Consequently, they are increasing in prevalence worldwide. In common with other organs, the lung is maintained by the function of tissue-specific stem cells which must act on demand to replace old or dying cells. Specifically, the stem cells must do two things:

- produce new daughter cells when required to do so: either too few or too many cells can be disastrous for lung function.
- produce the correct types of daughter cells: changes to cell identity can also disrupt lung function.

The Rawlins lab investigates the mechanisms which control stem cell behaviour in the lungs. We are most interested in how the stem cells in the normal adult lung know which type of daughter cell they need to make and when. Our approach is to use the power of mouse genetics to understand the control of lung stem cell behaviour at the single cell level. This allows individual cells to be analysed quantitatively in vivo, or by live-imaging in organ culture systems. One current interest is the characterization of a new stem cell population in the airways of the adult mouse lung which is already committed to produce a specific type of daughter cell.



Mouse tracheal epithelium

Group Members

Gayan Balasooriya	Graduate student
Christoph Budjan	Graduate student
Jo-Anne Johnson	Graduate student (MD)
Usua L. Garay	Postdoc Researcher
Marko Nikolic	Graduate student (MD)
Chandika Rao	Technicians

Key Publications prior to 2013

Onaitis M, D'Amico TA, Clark C, Guinney J, Harpole DH, Rawlins EL. A 10-gene progenitor cell signature predicts prognosis in lung adenocarcinoma. (2011) Annals of Thoracic Surgery. PMID: 21353202.

Rawlins EL, Clark CP, Xue Y, Hogan BLM. The Id2+ distal tip lung epithelium contains individual multipotent embryonic progenitor cells. (2009) Development. PMID: 19855016

Rawlins EL, Okubo T, Xue Y, Brass DM, Auten R L, Hasegawa H, Wang F, Hogan BLM. The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. (2009) Cell Stem Cell. PMID: 19497281

Rawlins EL, Hogan BLM. Ciliated epithelial cell lifespan in the mouse trachea and lung. (2008) American Journal of Physiology: Lung Cell Molecular Physiology. PMID: 18487354

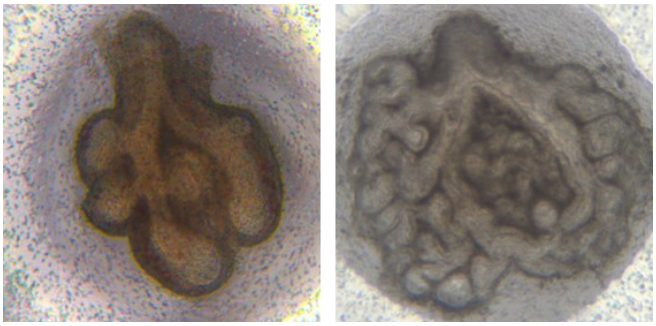
Rawlins EL, Ostrowski LE, Randell SH, Hogan BLM. Lung development and repair: contribution of the ciliated lineage. (2007) Proceedings of the National Academy of Sciences USA. PMID: 17194755

Collaborations

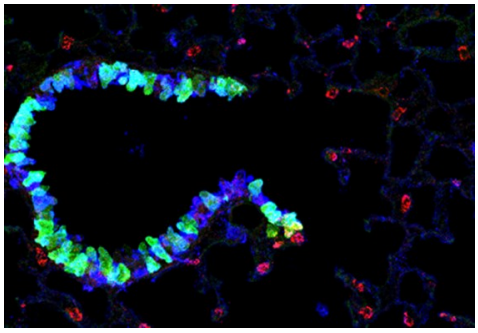
Collaborator	Location	From	Nature of Collaboration
Albert Basson	Kings College London	2010	Shared reagents/samples and experiments
Bertie Gottgens	SCI	Ongoing	Lab experiments

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival 2013	Science Festival	03/2013	Gurdon Institute	Garay
European Researchers Night at the Natural History Museum	Public Event	2013	Gurdon Institute	Garay
Cambridge University Summer Schools outreach programme	Talk	2013	Speaker	Watson



Lung development: differentiated cell identity



Adult lung stem cells: cell lineage and control

José Silva

José received his first degree in Biology from the University of Porto, in Portugal. He joined the GABBA graduate program from University of Porto and then went on to do his PhD studies at Imperial College under the supervision of Professor Neil Brockdorff on heritable silencing mechanisms during mouse development.

In 2003 and following his PhD, José moved to Professor Austin Smith's laboratory at the University of Edinburgh as an EMBO post-doctoral fellow to investigate factors involved in nuclear reprogramming. This work has led to the identification of Nanog as the first defined gene with nuclear reprogramming capacity in the conversion of a somatic cell into pluripotency.

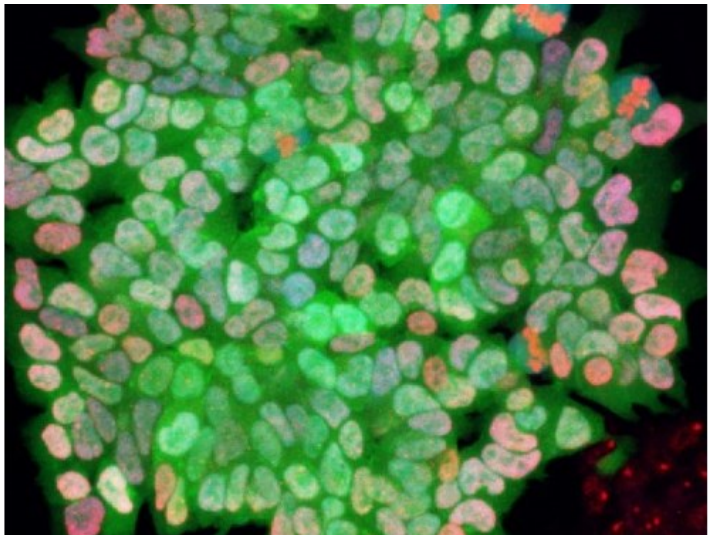
In 2008 José started as a group leader at the CSCR investigating the underlying biology of the process of induced pluripotency. His work was initially supported by a Next Generation Award (2008) and subsequently by a Wellcome Trust Career Development Fellowship Award (2009).

Funding

Wellcome Trust
Newton Trust

Biology of Induced Pluripotency

The aim of our lab is to understand the underlying biology of the conversion of a somatic epigenome back into a pluripotent epigenome, a process known as induced pluripotency. We are particularly interested in determining the molecular mechanisms by which the key players in this process work. Fully understanding induced pluripotency and better characterising iPS and ES cells is indispensible before these can be used in biomedical applications.



A colony of stem cells reprogrammed to a pluripotent state from adult brain cells. Inhibitors of the Mek/Erk and GSK3 pathways (2i) in the absence of serum promote the generation of induced pluripotent stem (iPS) cell colonies, shown here. These cells show expression of a pluripotency reporter (green) and reactivation of the silent X chromosome, as demonstrated by the lack of the nuclear red staining body (trimethyl H3K27). For comparison, a cluster of non-reprogrammed cells (non-green) displaying a silent X chromosome (red nuclear body) is shown in the bottom right-hand corner. Image: Jose Silva

Group Members

Yael Costa	Postdoc Researcher
Moyra Lawrence	PhD student
Aliaksandra Radzisheuskaya	Postdoc Researcher
Rodrigo Santos	PhD student
Hannah Stuart	PhD student
Lawrence Bates	Research assistant
Chibeza Agley	Postdoc Researcher (Silva/Chalut)

2013 Publications

Costa Y, Ding J, Theunissen TW, Faiola F, Hore TA, Shliaha PV, Fidalgo M, Saunders A, Lawrence M, Dietmann S, Das S, Levasseur DN, Li Z, Xu M, Reik W, Wang J, Silva JCR. NANOG-dependent function of TET1 and TET2 in establishment of pluripotency. Nature. PMID:23395962

Radzisheuskaya A, Chia Gle B, dos Santos RL, Theunissen TW, Castro LF, Nichols J, Silva JC. A defined Oct4 level governs cell state transitions of pluripotency entry and differentiation into all embryonic lineages. Nature Cell Biology. PMID:23629142

Radzisheuskaya R and Siva JC. Do all roads lead to Oct4? The emerging concepts of induced pluripotency. Trends in Cell Biology. PMID: 24370212

Key Publications prior to 2013

Radzisheuskaya A, Pasque V, Gillich A, Halley-Stott RP, Panamarova M, Zernicka-Goetz M, Surani MA, Silva JCR. Histone variant macroH2A marks embryonic differentiation in vivo and acts as an epigenetic barrier to induced pluripotency. Journal of Cell Science. (2012) PMID: 23077180

Collaborations

Collaborator	Location	From	Nature of Collaboration
Jianlong Wang	Black Family Stem Cell Institute, New York	2011	To benefit from his lab's complimentary expertise - namely proteomic assays.
Jennifer Nichols	SCI	Ongoing	Joint paper
Kevin Chalut	SCI	Ongoing	Interdisciplinary research
Wolf Reik	SCI	Ongoing	Joint paper
Austin Smith	SCI	Ongoing	Role of STAT3 in reprogramming
Brian Hendrich	SCI	Ongoing	Role of Mbd3 in nuclear reprogramming

Awards & Prizes

Awardee	Award	Organisation
Jose Silva	Wellcome Trust Senior Research Fellowship	Wellcome Trust
Aliaksandra Radzisheuskaya	Outstanding Poster Award	CiRA International Symposium
Aliaksandra Radzisheuskaya	Award for Young Scientists 2012	Journal of Cell Science

Public Engagement

Event	Format	Date	Participation	Name
Pint of Science festival	Talk	05/2013	Speaker	Silva
University of Cambridge Science Festival	Science festival	03/2013	Organiser	Dos Santos
Cambridge Science Festival	Science festival	03/2013	Volunteer	Lawrence

Tracing stem cell fate in development, maintenance, and disease

Ben Simons

Ben has a background in theoretical condensed matter physics. Having obtained his PhD at the Cavendish Laboratory in Cambridge researching high temperature superconductivity, he undertook post-doctoral research in mesoscopic physics at MIT and NEC Research Inc. in Princeton. In 1994 he transferred to a Royal Society Research Fellowship and was appointed to a Lectureship at Imperial College before moving to the Cavendish Laboratory in 1995. In 2002, he was promoted to a Chair in Theoretical Condensed Matter Physics. In 2011, Ben was appointed to the Herchel Smith Chair in the Physics of Medicine.

His research is supported by grant income from EPSRC, MRC, and the Wellcome Trust with whom he holds a Senior Investigator Award.

Funding

EPSRC
Wellcome Trust

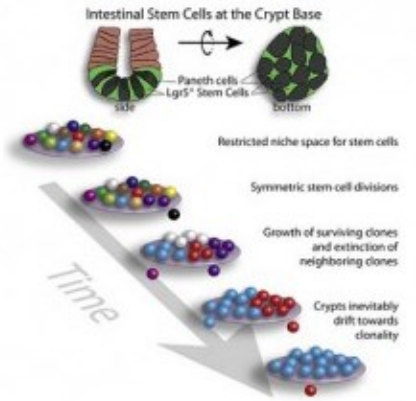
Fellowships

Philip Greulich	German Academic Exchange Service

Theories of tissue maintenance place stem cells at the apex of proliferative hierarchies, possessing the lifetime property of self-renewal. In homeostasis the number of stem cells remains fixed imposing an absolute requirement for fate asymmetry in the daughters of dividing stem cells, such that only half are retained as stem cells. In recent years, much emphasis has been placed on resolving the extrinsic factors controlling stem cell fate and the spatial organization associated with the stem cell niche. Guided by the paradigm of invariant asymmetry, many studies have sought to identify factors that provide proliferative control, and ensure stem cell longevity. However, by addressing long-term lineage tracing studies involving several adult tissue types, from interfollicular epidermis and intestine to germ line, we have found that stem cell loss, leading to population asymmetric renewal, is central to homeostasis.

By drawing upon concepts from statistical physics and mathematics, we have shown that tissue homeostasis permits just three classes of stem cell behaviour, discriminated by universal patterns of long-term clonal evolution. As well as achieving a functional classification of tissue stem cell types, this identification provides a general framework that we are using to interpret lineage tracing and mosaic-chimera studies, and to explore mechanisms of dysregulation.

In a separate but closely related programme of research we are also using these general concepts and lineage tracing methodologies to elucidate patterns of progenitor cell fate in the late stage development of tissues, from retina and cortex to pancreas and heart.



In intestinal crypt, stem cells (marked by Lgr5 expression) lie intercalated between Paneth cells at the base of the crypt. In homeostasis, the frequent and stochastic loss of stem cells is compensated by the self-renewal of neighbours. As a result, the clonal progeny of stem cells undergo a pattern of neutral drift dynamics in which clonal loss is compensated by the expansion of others until the crypt becomes fully clonal.

Group Members

Juergen Fink	Graduate Student (Koo/Simons)
Philip Greulich	Postdoc Researcher
Teresa Krieger	Graduate Student (Simons/Livesey)
Crystal McClain	Postdoc Researcher
Steffen Rulands	Postdoc Researcher
Hinal Tanna	Graduate Student

2013 Publications

Kent DG, Li J, Tanna H, Fink J, Kirschner K, Pask DC, Silber Y, Hamilton TL, Sneade R, Simons BD, Green AR. Self-Renewal of Single Mouse Hematopoietic Stem Cells Is Reduced by JAK2V617F Without Compromising Progenitor Cell Expansion. PLoS Biol. PMID:23750118

Blanpain C, Simons BD. Unravelling stem cell dynamics by lineage tracing. Nature Reviews Molecular Cell Biology. PMID:23860235

Teixeira VH, Nadarajan P, Graham TA, Pipinikas CP, Brown JM, Falzon M, Nye E, Poulsom R, Lawrence D, Wright NA, McDonald S, Giangreco A, Simons B, Janes SM. Stochastic homeostasis in human airway epithelium is achieved by neutral competition of basal cell progenitors. eLife. PMID:24151545

Simons BD. Getting your gut into shape. Science. PMID:24115430

Simons BD. Stem Cell Renewal Theory Turns 60. Nature Reviews Molecular Cell Biology. PMID:24263358

Driskell RR, Lichtenberger BM, Hoste E, Kretzschmar K, Simons BD, Charalambous M, Ferron SR, Herault Y, Pavlovic G, Ferguson-Smith AC, Watt FM. Distinct fibroblast lineages determine dermal architecture in skin development and repair. Nature. PMID: 24336287

Snippert HJ, Schepers AG, van Es JH, Simons BD, Clevers H. Biased competition between Lgr5 intestinal stem cells by oncogenic K-ras induces clonal expansion. EMBO Reports. PMID: 24355609

Collaborations

Collaborator	Location	From	Nature of Collaboration
Erika Back	NYU Medical School	2012	Dynamics and fate behaviour of germ line stem cells in drosophila
Cedric Blanpain	Brussels	2011	Development, maintenance and disease (cancer) of mouse epidermis; Development of heart, prostate, mammary epithelium.
Hans Clevers	Hubrecht Institute	2010	Maintenance of the intestinal epithelium and on the maintenance of the subventricular zone
Song-hai Shi	Memorial Sloan-Kettering	2013	Development of mouse neocortex
Hongjun Song	Johns Hopkins Medical School	2012	Maintenance of mouse hippocampus
William Harris	PDN	2011	Development of zebrafish retina
Jacco van Rheenen	Hubrecht Institute	2013	Maintenance of the intestinal epithelium
Shosei Yoshida	Okazaki	2009	Maintenance of male germ line in mouse
Jochen Wittbrodt	Heidelberg	2012	Maintenance of the ciliary marginal zone of zebrafish retina
Samuel Janes	UCL	2012	Maintenance of human airways
Peter Dirks	Toronto	2013	Dynamics of tumor propagating cells in medullablastoma
Tony Green	SCI	Ongoing	Joint paper
Anne Ferguson-Smith	SCI	Ongoing	Joint paper

Austin Smith

Austin Smith was captivated by pluripotency as a student in Oxford. He pursued this through PhD studies in Edinburgh and postdoctoral research back in Oxford. He returned to Edinburgh as a Group Leader in 1990 and from 1996 was Director of the Centre for Genome Research, later the Institute for Stem Cell Research.

In 2006 he moved to Cambridge where he is Director of the Stem Cell Institute. Professor Smith is a Medical Research Council Professor, an EMBO Member, and a Fellow of the Royal Societies of Edinburgh and of London. In 2010 he was awarded the Louis Jeantet Prize.

Funding

BBSRC
EC FP7
Japan Science & Technology Agency
Medical Research Council
Wellcome Trust

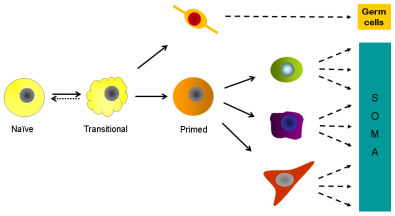
Fellowships

Martin Leeb	Schrödinger
Meng Amy Li	Henry Wellcome
Graziano Martello	HFSP
Yasuhiro Takashima	Herchel-Smith

Stem Cell Potency

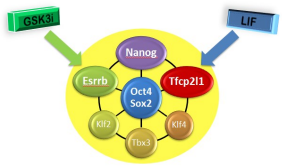
We study embryonic stem (ES) cells. These are pluripotent cells, meaning they can generate all other types of cell. Our goal is to understand how they maintain this broad potency and how they decide which cell types to make when they begin to differentiate. We also analyse the degree of conservation between pluripotent cells from different mammalian species in order to find common principles underlying embryonic stem cell properties. Our long-term goal is to control the growth and differentiation of human stem cells for better understanding of human embryo development and for applications in drug discovery and regenerative medicine.

Embryonic Stem Cell Path to Differentiation



Schematic of possible differentiation pathway of pluripotent embryonic stem cells and their in vivo counterparts in the pre-implantation epiblast.

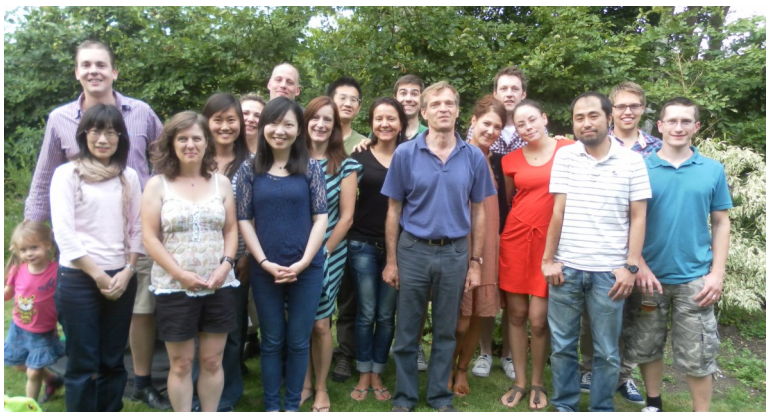
Embryonic Stem Cell Self-Renewal Circuit



Naïve ES cell self-renewal is sustained by a select group of transcription factors that are highly interconnected; conferring stability, robustness and flexibility

Group Members

Joerg Betschinger	Postdoc Researcher
Yaoyao Chen	Postdoc Researcher
James Clarke	Technician
Rosalind Drumond	Technician
Ge Guo	Postdoc Researcher
Tuzer Kalkan	Postdoc Researcher
Masaki Kinoshita	Postdoc Researcher
Raja Kittappa	Postdoc Researcher
Martin Leeb	Postdoc Researcher
Meng Amy Li	Postdoc Researcher
Graziano Martello	Postdoc Researcher
Gillian Morrison	Postdoc Researcher
Carla Mulas	Graduate student
Melanie Rittirsch	Technician
Rika Takashima	Admin
Yasuhiro Takashima	Postdoc Researcher
Elena Tzouanacou	Postdoc Researcher
Mariya Rostovskaya	Postdoc Researcher
Meryem Ralser	Bioinformatician
Harry Leitch	Visiting Researcher



2013 Publications

Betschinger J, Nichols J, Dietmann S, Corrin PD, Paddison PJ, Smith A. Exit From Pluripotency Is Gated By Intracellular Redistribution Of The bHLH Transcription Factor Tfe3. Cell. PMID:23582324

Tailor J, Kittappa R, Leto K, Gates M, Borel M, Paulsen O, Spitzer S, Karadottir RT, Rossi F, Falk A, Smith A. Stem Cells Expanded from the Human Embryonic Hindbrain Stably Retain Regional Specification and High Neurogenic Potency. Journal of Neuroscience. PMID:23884946

Martello G, Bertone P, Smith A. Identification of the Missing Pluripotency Mediator Downstream of Leukaemia Inhibitory Factor. EMBO Journal. PMID:23942233

Leitch HG, McEwen KR, Turp A, Encheva V, Carroll T, Grabole N, Mansfield W, Nashun B, Knezovich JG, Smith A, Surani MA, Hajkova P. Naive pluripotency is associated with global DNA hypomethylation. Nature Structural & Molecular Biology. PMID: 23416945

Chen Y, Blair K, Smith A. Robust self-renewal of rat embryonic stem cells requires precise tuning of glycogen synthase kinase-3 inhibition. Stem Cell Reports. PMID: 24319657

Stricker SH, Feber A, Engström PG, Carén H, Kurian KM, Takashima Y, Watts C, Way M, Dirks P, Bertone P, Smith A, Beck S, Pollard SM. Widespread resetting of DNA methylation in glioblastoma-initiating cells suppresses malignant cellular behavior in a lineage-dependent manner. Genes & Development. PMID:23512659

Leitch HG, Nichols J, Humphreys P, Mulas C, Martello G, Lee C, Jones K, Surani MA, Smith A. Rebuilding Pluripotency from Primordial Germ Cells. Stem Cell Reports. PMID:24052943

Danovi D, Folarin A, Gogolok S, Ender C, Elbatsh AM, Engström PG, Stricker SH, Gagrica S, Georgian A, Yu D, U KP, Harvey KJ, Ferretti P, Paddison PJ, Preston JE, Abbott NJ, Bertone P, Smith A, Pollard SM. A high-content small molecule screen identifies sensitivity of glioblastoma stem cells to inhibition of polo-like kinase 1. PLoS One. PMID:24204733

Mohsen-Kanson T, Hafner AL, Wdziekonski B, Takashima Y, Villageois P, Carrière A, Svensson M, Bagnis C, Chignon-Sicard B, Svensson PA, Casteilla L, Smith A, Dani C. Differentiation of human induced pluripotent stem cells into brown and white adipocytes: Role of Pax3. Stem Cells. PMID:24302443

Bianco P, Barker R, Brüstle O, Cattaneo E, Clevers H, Daley GQ, De Luca M, Goldstein L, Lindvall O, Mummery C, Robey PG, Sattler de Sousa E Brito C, Smith A. Regulation of stem cell therapies under attack in Europe: for whom the bell tolls. EMBO Journal. PMID:23644381

Leitch HG, Smith A. The mammalian germline as a pluripotency cycle. Development. PMID:23715543

Smith A. Nanog heterogeneity: tilting at windmills? Cell Stem Cell. PMID:23827703

Collaborations

Collaborator	Location	Nature of Collaboration
Hitoshi Niwa	RIKEN Center for Developmental Biology	Systems biology of pluripotent stem cells.
Yves Barde,	Swiss National Science Foundation	SINERGIA, Swiss National Science Foundation
Clare Blackburn	University of Edinburgh	EC FP7: Eurostemcell
Francis Stewart	Technische Universitaet, Dresden	EC FP7: SyBoSS
Daniel Pipeleers	Center for Beta Cell Therapy in Diabetes	EC FP7: BetaCell Therapy
Tom Burdon	Roslin Institute, Edinburgh	BBSRC: Gene Targeting in the Rat
Norbert Hubner	MDC, Berlin	EC FP7: EuraTrans
Steven Emmott and Sara-Jane Dunn	Microsoft Research	Computational Modelling
Paul Bertone	European Bioinformatics Institute (EBI)	Deep Sequence Analysis
Wolf Reik	Babraham	Methylation analyses
Henk Stunnenberg and Hendrik Marks	Nijmegen Centre for Molecular Life Sciences	Deep Sequencing
Christian Dani	University of Nice	Mesenchymal differentiation
Peter Andrews	University of Sheffield	UK Regenerative Medicine Platform
David Williams	University of Loughborough	UK Regenerative Medicine Platform
Jennifer Nichols	SCI	Joint papers
Thóra Káradóttir	SCI	Joint paper
Azim Surani	SCI	Joint paper
Roger Barker	SCI	Joint paper

Awards & Prizes

Awardee	Award	Organisation
Martin Leeb	FWF Erwin Schroedinger fellowship	Austrian Science Fund

Public Engagement

Event	Format	Date	Participation	Name
Science Festival Talk – Stem Cells: Hope or Hype	Talk	03/2013	Speaker	Smith

Specification and programming of the germline for totipotency and development

Azim Surani

Born in Kenya and received PhD in 1975 at Cambridge University under Professor Sir Robert Edwards FRS (Nobel Laureate, 2010). Joined the Babraham Institute in 1979 and discovered Genomic Imprinting in 1984 and subsequently, novel imprinted genes and their functions, with mechanisms through establishment and erasure of DNA methylation. He was elected the Marshall-Walton Professor (1992), and Director of Germline and Epigenomics Research (2013) at Cambridge University.
He has recently established the genetic basis for germ cell specification and epigenetic programming.
He was elected a Fellow of the Royal Society (1990) and Fellow of the Academy of Medical Sciences (2001) He was awarded a Royal Medal in 2010.

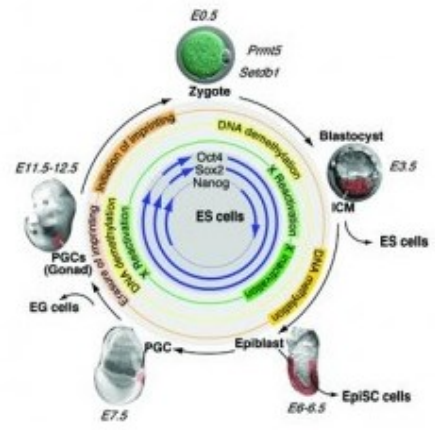
Funding

British Council Israel
EC FP7
Human Frontier Science Programme
Wellcome Trust

Fellowships

Ufuk Gunesdogan	EC Marie Curie Postdoctoral Fellowship
Toshihiro Kobayashi	JSPS Postdoctoral Fellowship for Research Abroad
Julia Tischler	Austrian Academy of Science Fellowship (APART)

Specification of primordial germ cell (PGC) occurs after development of equipotent epiblast cells following their exit from naïve pluripotent state. These epiblast cells can give rise to both somatic and germ cells in vivo and in vitro. Recent studies show that BLIMP1, PRDM14 and AP2g are necessary and sufficient for PGC specification. This mutually interdependent tripartite genetic network is involved in the repression of the somatic program, the initiation of the germ cell program and re-expression of pluripotency genes in early germ cells. The network also initiates sequential, orderly and dynamic epigenetic changes in histone modifications, reactivation of the X chromosome and comprehensive global DNA demethylation and imprints erasure. These epigenetic changes are essential towards imprinting of functional differences between parental genomes and the establishment of the totipotent state, which follows after fertilisation and establishment of the zygote. Whereas a repressive complex maintains unipotency of germ cells, dedifferentiation of unipotent PGCs to pluripotent stem cells in vitro is accompanied by the reversal of the PGC specification process. Early germ cells also exhibit unprecedented genome-wide DNA demethylation and chromatin remodelling, which are essential towards the establishment of totipotency. We are gathering insight into the mechanisms involved in epigenetic programming in germ cells, and continuing to identify the key factors that are crucial at these times. We are interested in exploiting the knowledge gained from studies on germ cells by creating in vitro models for induced epigenetic reprogramming, and using these models towards attempts at rejuvenation of somatic cells.



Mouse germline cycle and the origin of primordial germ cells. The figure depicts key stages of early development and the origin of pluripotent stem cells.

Group Members

Delphine Cougot	Postdoc Researcher
Vinh Dang Do	Postdoc Researcher
Lynn Froggett	Administration
Wolfram Gruhn	Postdoc Researcher
Ufuk Günesdogan	Postdoc Researcher
Jamie Hackett	Postdoc Researcher
Yun Huang	Graduate Student
Naoko Irie	Postdoc Researcher
Elena Itskovich	Graduate Student
Shinseog Kim	Postdoc Researcher
Toshihiro Kobayashi	Postdoc Researcher
Caroline Lee	Technician
Roopsha Sengupta	Postdoc Researcher
Walfred Tang	Graduate Student
Julia Tischler	Postdoc Researcher
Jan Zylicz	Graduate Student

2013 Publications

Grabole N, Tischler J, Hackett JA, Kim S, Tang F, Leitch HG, Magnúsdóttir E, Surani MA. Prdm14 promotes germline fate and naive pluripotency by repressing FGF signalling and DNA methylation. EMBO Reports. PMID:23670199

Magnúsdóttir E, Dietmann S, Murakami K, Günesdogan U, Tang F, Bao S, Diamanti E, Lao K, Gottgens B, Surani MA. A tripartite transcription factor network regulates primordial germ cell specification in mice. Nature Cell Biology. PMID:23851488

Leitch HG, McEwen KR, Turp A, Encheva V, Carroll T, Grabole N, Mansfield W, Nashun B, Knezovich JG, Smith A, Surani MA, Hajkova P. Naive pluripotency is associated with global DNA hypomethylation. Nature Structural & Molecular Biology. PMID:23416945

Hackett JA, Surani MA. DNA methylation dynamics during the mammalian life cycle. Philosophical Transactions of the Royal Society Biological Sciences. PMID:23166392

Barrios F, Irie N, Surani MA. Perceiving signals, building networks, reprogramming germ cell fate. International Journal of Developmental Biology. PMID:23784822

Leitch HG, Tang WW, Surani MA. Primordial germ-cell development and epigenetic reprogramming in mammals. Current Topics in Developmental Biology. PMID:23587241

Leitch HG, Nichols J, Humphreys P, Mulas C, Martello G, Lee C, Jones K, Surani MA, Smith A. Rebuilding Pluripotency from Primordial Germ Cells. Stem Cell Reports. PMID:24052943

Hackett JA, Surani MA. Beyond DNA: Programming and inheritance of parental methylomes. Cell. PMID:23663772

Gillich A, Bao S, Surani MA. Reversion of mouse postimplantation epiblast stem cells to a naïve pluripotent state by modulation of signalling pathways. Methods in Molecular Biology. PMID:23975802

Surani MA. Genomic Reprogramming, Handbook of Stem Cells 1:393-398 2013

Hackett JA, Dietmann S, Murakami K, Down TA, Leitch HG, Surani MA. Synergistic Mechanisms of DNA Demethylation during Transition to Ground-State Pluripotency. Stem Cell Reports. PMID: 24371807

Collaborations

Collaborator	Location	From
Jacob Hanna	Weizmann	2012
Michael Elowitz/Uri Alon	Caltech/Weizman	2012
Bertie Gottgens	SCI	Ongoing
Austin Smith	SCI	Ongoing
Jennifer Nichols	SCI	Ongoing

Mechanisms Controlling Differentiation of Pluripotent Stem Cells into Definitive Endoderm

Ludovic Vallier

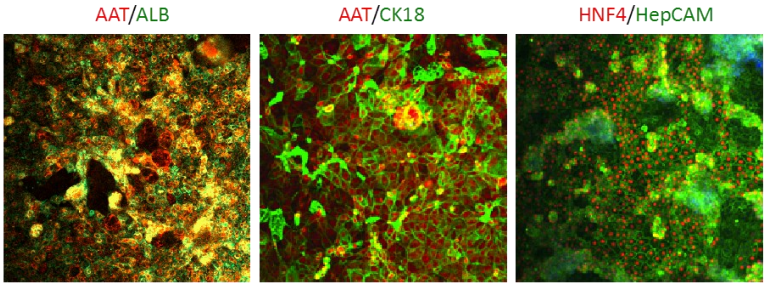
Ludovic graduated in Molecular biology and Immunology from the University Claude Bernard Lyon I in 1997. In 2001, he earned his PhD at Ecole Normale Superieur of Lyon in the group of Jacques Samarut, under the supervision of Pierre Savatier, studying mechanisms that control the cell cycle in mouse embryonic stem (ES) cells. Following a year in the biotechnology industry, Ludovic joined Professor Pedersen's group at the University of Cambridge Department of Surgery. In 2008 he joined the newly opened Anne McLaren Laboratory for Regenerative Medicine (LRM) as a Principal Investigator.

Ludovic holds a joint appointment between the University of Cambridge and the Wellcome Trust Sanger Institute where he is respectively Reader in Stem Cells and Regenerative Medicine and Senior Faculty. He is also the director of the Cambridge National Institute for Health Research (NIHR)/Biomedical Research Centre HiPSC (human induced pluripotent stem cell) core facility.

Funding

ERC
EC FP7
EPSRC
Medical Research Council
The Evelyn Trust

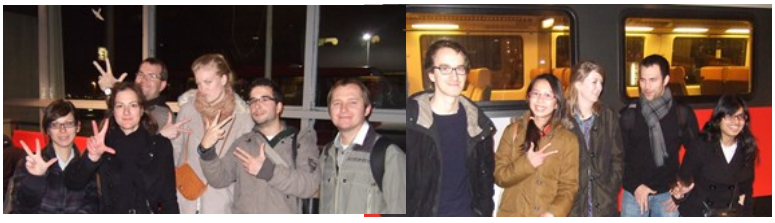
Understanding the mechanisms controlling early cell fate specification in human development has major importance for regenerative medicine. Indeed the generation of fully functional cell types from stem cells may only be achievable by recapitulating a normal succession of cell fate decisions. The first event of differentiation of the embryo proper occurs at the stage of gastrulation with the specification of the three primary germ layers ectoderm, mesoderm and endoderm, from which all the cells of adult tissues are derived. The main objective of our group is to define the molecular mechanisms controlling the specification of the endoderm germ layer and also its subsequent differentiation into pancreatic, hepatic, lung and gut progenitors. For that, we use human puripotent stem cells (hESCs and hIPSCs) as in vitro model of development to study the transcriptional networks orchestrating organogenesis and epigenetic modifications associated with differentiation. The resulting knowledge allows the development of new culture system to drive differentiation of pluripotent stem cells into hepatocytes and pancreatic Islet cells. These cells are then used to model disease in vitro and we have a specific focus on metabolic disorders affecting the liver and the pancreas. Furthermore, we are currently investigating how similar mechanisms could regulate adult stem cells self-renewal /differentiation during organ regeneration. Overall, our objective is not only to differentiate human pluripotent stem cells (hESCs/hIPSCs) into cell type relevant for clinical applications but also to acquire the knowledge necessary to differentiate any cell types into pancreatic and hepatic progenitors.



hIPSCs differentiated into hepatocytes expressing markers specific of their in vivo counterparts
Image: Miguel Cardoso de Brito

Group Members

Stephanie Brown	Research Assistant
Sapna Vyas	Research Assistant
Imbisaat Geti	Research Assistant
Nicholas Hannan	Postdoc Researcher
Siim Pauklin	Postdoc Researcher
Mariya Chhatriwala	Postdoc Researcher
Pedro Madrigal	Postdoc Researcher
Kasia Tilgner	Postdoc Researcher
Fiona Docherty	Graduate student
Charis-Patricia Segeritz	Graduate student
Filipa Soares	Graduate student
Morteza Jalali	Graduate student
Miguel Cardoso-de-Brito	Graduate student
Alessandro Bertero	Graduate student
Fotis Sampaziotis	Graduate student
Trey Gieseck	Graduate student
Crystal Chia Ying	Graduate student
Rana Khairi	Graduate student



2013 Publications

Pauklin S, Vallier L. The cell-cycle state of stem cells determines cell fate propensity. Cell. PMID:24074866

Hannan NR, Segeritz CP, Touboul T, Vallier L. Production of hepatocyte-like cells from human pluripotent stem cells. Nature Protoc. PMID:23424751

Hannan NRF, Fordham R, Syed YA, Moignard V, Berry A, Bautista R, Hanley NA, Jensen KB, Vallier L. Generation of multipotent foregut stem cells from human pluripotent cells. Stem Cell Reports. PMID:24319665

Dianat N, Steichen C, Vallier L, Weber A, Dubart-Kupperschmitt A. Human pluripotent stem cells for modelling human liver diseases and cell therapy. Current Gene Therapy. PMID:23444872

Lupo G, Novorol C, Smith JR, Vallier L, Miranda E, Alexander M, Biagioni S, Pedersen RA, Harris WA. Multiple roles of Activin/Nodal, bone morphogenetic protein, fibroblast growth factor and Wnt/β-catenin signalling in the anterior neural patterning of adherent human embryonic stem cell cultures. Open Biology. PMID:23576785

Fordham RP, Yui S, Hannan NR, Soendergaard C, Madgwick A, Schweiger PJ, Nielsen OH, Vallier L, Pedersen RA, Nakamura T, Watanabe M, Jensen KB. Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury. Cell Stem Cell. PMID:24139758

Yang G, Si-Tayeb K, Corbineau S, Vernet R, Gayon R, Dianat N, Martinet C, Clay D, Goulinet-Mainot S, Tachdjian G, Tachdjian G, Burks D, Vallier L, Bouillé P, Dubart-Kupperschmitt A, Weber A. Integration-deficient lentivectors: an effective strategy to purify and differentiate human embryonic stem cell-derived hepatic progenitors. BMC Biology. PMID:23870169

Weedon MN, Cebola I, Patch AM, Flanagan SE, De Franco E, Caswell R, Rodríguez-Seguí SA, Shaw-Smith C, Cho CH, Allen HL, Houghton JA, Roth CL, Chen R, Hussain K, Marsh P, Vallier L, Murray A; International Pancreatic Agenesis Consortium, Ellard S, Ferrer J, Hattersley AT. Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis Nature Genetics. PMID:24212882

Collaborations

Collaborator	Location	From	Nature of Collaboration
Neil Hanley	Manchester	2010	Science/paper
Jorge Ferrer	London	2010	Science/paper
Steve Dalton	University of Georgia	2012	Science/paper
Andrew Hatersley	University of Exeter	2010	Science/paper
Dan Gafney	WTSI	2012	Science/paper
David Lomas	London UCL	2010	Science/paper
Oliver Bilker	WTSI	2012	Science/paper
Gordon Dugan	WTSI	2012	Science/paper
Paolo decopi	London UCL	2011	Science/paper
Darel Koton	Harvard	2013	Science/paper
Kim Jensen	SCI	Ongoing	Joint papers
Roger Pedersen	SCI	Ongoing	Joint papers

Awards & Prizes

Awardee	Award	Organisation
Trey Gieseck	Poster and Image Competition Prizewinner	Cambridge University Graduate School of Life Sciences

Public Engagement

Event	Format	Date	Participation	Name
Publication in Bluesci Students Magazine Cambridge University	Magazine	03/2013	Author	Bertero
BHF Fundraising Event	Public event	10/2013	Demonstrator	Bertero
Cambridge Science Festival	Science Festival	03/2013	Volunteer	Segeritz
BHF fund raising	Public event	10/2013	Speaker	Vallier
Night in the museum	Public event	01/2013	Speaker	Vallier
National Science Week	Public event	03/2013	Speaker	Chhatriwala
Stem cells Lecture, Colchester Royal Grammar School - Colchester	Talk	03/2013	Speaker	Chhatriwala

Bronchioalveolar cellular and molecular hierarchy in homeostasis and disease

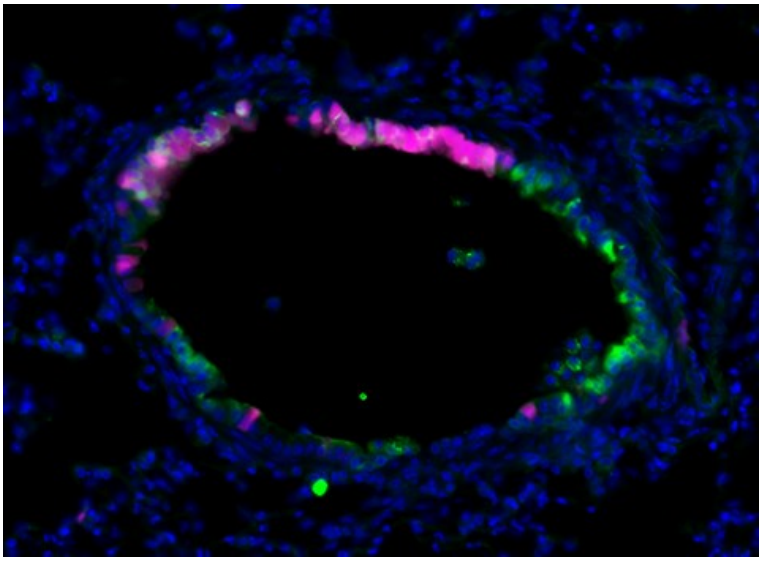
Juan-Jose Ventura

Juan started his PhD studies in Molecular Biology at the University Complutense of Madrid focusing his work on the role of inflammatory signals in liver development.
Following his interest in MAPKs, he moves to Roger Davis group at the HHMI/UmassMed school in Worcester, MA. After that period, Juan moved back to Madrid with a Ramon y Cajal contract to work at the CNIO with Angel Nebreda. In this group, they uncover a novel role for the p38a/MAPK in lung homeostasis and cancer.
Juan's growing interest in this topic led him to become a PI and start his own group at the newly established CSCR in the University of Cambridge. He is studying lung bronchioalveolar regulation.

Funding

Medical Research Council

The Ventura lab is interested in deciphering the ways used by the lung to replenish its damaged tissue in normal conditions and how that can go wrong in disease, and especially in lung cancer. Using animal models and human samples we are trying to determine the existence of specific groups of cells with a potential to differentiate and regenerate any other cell types that can have died, allowing the maintenance of lung functionality. Defining molecules that specifically can be targeted for distinct populations will allow the tracking, isolation, study and potential use as cellular therapy to regenerate damaged areas. Knowing the intracellular mechanisms involved in regulating when those progenitors should differentiate and into what cell type will be essential to understand the process of regeneration and any possible used in the clinic. We have uncovered some molecular targets that target progenitor populations with diverse differentiation potential and mechanisms involved in maintaining the proper process of regeneration. Failure of the mechanisms regulating these cell populations results in lung diseases as lung fibrosis or cancer.
Combining in vivo experiments with the optimization of lab methods, we are increasing our knowledge on lung physiology and the possibility to manipulate it to combat disease.



Lineage tracing shows Lrig1 cells repairing damaged bronchioles after naphthalene injury (dTomato, red). Clara cells (green).

Group Members

Feride Oeztuerk-Winder	Senior Scientist/Researcher
Anna Guinot	Graduate student
Josue Ruiz Medina	Postdoc Researcher

2013 Publications

Voisset E, Oeztuerk-Winder F, Ruiz EJ, Ventura JJ. p38a negatively regulates survival and malignant selection of transformed Bronchioalveolar stem cells. PLoS One. PMID: 24265727

Key Publications prior to 2013

Oeztuerk-Winder F, Guinot A, Ochalek A and Ventura J-J. Regulation of Human Lung Alveolar multipotent cells by a novel p38a MAPK/miR-17-92 axis. EMBO Journal. (2012) PMID: 22828869

Oeztuerk-Winder F and Ventura J-J. The many faces of p38 mitogen-activated protein kinase in progenitor/stem cell differentiation. Biochemical Journal. (2012) PMID:22702973
22702973

Ventura J-J, Tenbaum S, Perdiguero E, Guerra C, Barbacid M, Pasparakis M, and Nebreda AR. p38 MAP kinase is essential in lung stem and progenitor cell proliferation and differentiation. Nature Genetics. (2007) PMID: 17468755

Collaborations

Collaborator	Location	Nature of Collaboration
Kim Jensen	SCI	Paper in revision in Nature Cell Biology

Stem cell subversion and bone marrow failure syndromes

Alan Warren

Alan Warren obtained his undergraduate degrees in Biochemistry (1983) and Medicine (1986) at the University of Glasgow. He completed his PhD in Molecular Biology in 1995 in the laboratory of Dr. Terry Rabbitts at the MRC Laboratory of Molecular Biology where he discovered that the LIM-only protein Lmo2 is required for haematopoiesis.

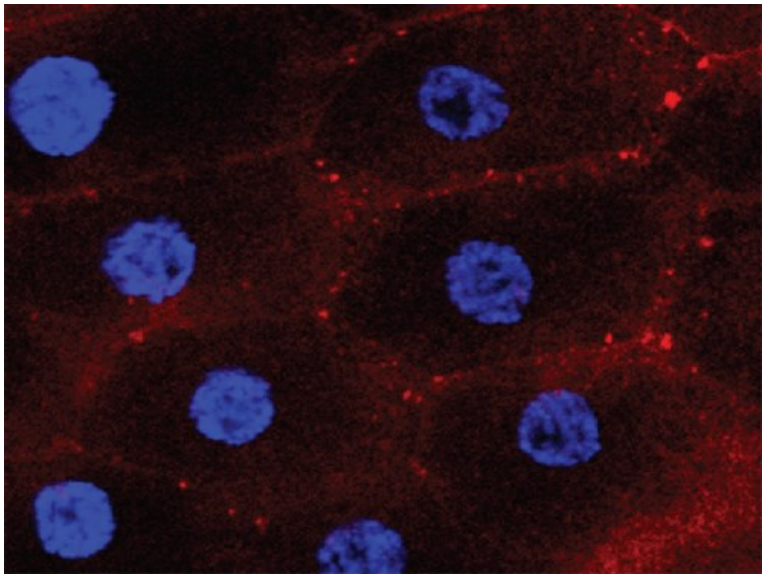
He is currently Professor of Haematology at the University of Cambridge, UK.

Funding

Leukaemia & Lymphoma Research
Medical Research Council

Our long-term goal is to elucidate the molecular mechanisms of ribosome assembly and to understand how defects in this process subvert haematopoietic stem cell function to cause bone marrow failure and leukaemia predisposition.

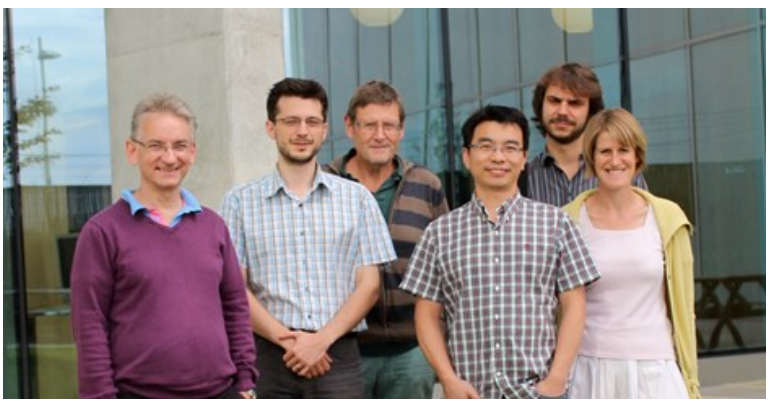
The Warren lab previously made the surprising discovery that the inherited leukaemia predisposition disorder Shwachman-Diamond syndrome is a “ribosomopathy”, caused by impaired maturation of the large ribosomal subunit. This work is providing fundamental new insights into the process of ribosome assembly. However, key questions remain about the molecular mechanisms involved and how defects in ribosome assembly subvert haematopoietic stem cell function to cause bone marrow failure and cancer predisposition



Drosophila ovarian follicle cells showing cytoplasmic Sbds (red) and DAPI stained nuclei (blue).
Image: Shengjiang Tan

Group Members

Mark Churcher	Postdoc Researcher
Tobias Fleischmann	Postdoc Researcher
Christine Hilcenko	Postdoc Researcher
Shengjiang Tan	Postdoc Researcher
Félix Weis	Postdoc Researcher



Key Publications prior to 2013

Hilcenko C, Simpson PJ, Finch AJ, Bowler FR, Churcher MJ, Jin L, Packman LC, Shlien A, Campbell P, Kirwan M, Dokal I, Warren AJ. Aberrant 3' oligoadenylation of spliceosomal U6 small nuclear RNA in poikiloderma with neutropenia. Blood. (2012) PMID: 23190533

Wong CC, Traynor D, Basse N, Kay RR, Warren AJ. Defective ribosome assembly in Shwachman-Diamond syndrome. Blood. (2011) PMID: 21803848

Finch AJ, Hilcenko C, Basse N, Drynan LF, Goyenechea B, Menne TF, González Fernández Á, Simpson P, D'Santos CS, Arends MJ, Donadieu J, Bellanné-Chantelot C, Costanzo M, Boone C, McKenzie AN, Freund SM, Warren AJ. Uncoupling of GTP hydrolysis from eIF6 release on the ribosome causes Shwachman-Diamond syndrome. Genes and Development. (2011) PMID: 21536732

Menne TM, Goyenechea B, Sánchez-Puig N, Wong CC, Tonkin LM, Ancliff P, Brost RL, Costanzo M, Boone C and Warren AJ. The Shwachman-Bodian-Diamond syndrome protein mediates translational activation of ribosomes in yeast. Nature Genetics. (2007) PMID: 17353896

Collaborations

Collaborator	Location	Nature of Collaboration
Sjob Scheres	MRC - LMB	Electron microscopy cryo-EM
Mark Byroft	MRC - LMB	NMP Nuclear Magnetic Resource Spectroscopy
Charlie Brone	University of Toronto	Yeast genetics
Minmin Yu	MRC - LMB	X-ray crystallography
Ludovic Vallier	SCI	Generation of iPS cells for patients with Shwachman-Diamond syndrome

Awards & Prizes

Awardee	Award	Organisation
Shengjiang Tan	Trainee Awards	7th International congress on Shwachman-Diamond Syndrome
Felix Weis	Trainee Awards	7th International congress on Shwachman-Diamond Syndrome

Public Engagement

Event	Name
International Congress on SDS - involved families and medical/nursing staff	Warren
Chairman of SDS Medical Advisory Board	Warren

Anton Wutz

Anton Wutz received his PhD from the Technical University of Graz in 1997 based on his work performed at the Research Institute of Molecular Pathology in Vienna, Austria. After postdoctoral work with Rudolf Jaenisch at the Whitehead Institute for Biomedical Research in Cambridge (USA) he joined the Research Institute of Molecular Pathology as a group leader in 2001.
In 2009 he moved to the Wellcome Trust Centre for Stem Cell Research at the University of Cambridge. His research activities focus on nuclear mechanisms that regulate changes of cellular identity during stem cell differentiation and specify the diverse cell types of the body. His laboratory has also contributed to the development of genetic strategies for studying mammalian pathways.
Anton moved to the Institute of Molecular Health Sciences in Zurich as Professor of Genetics in April 2013.

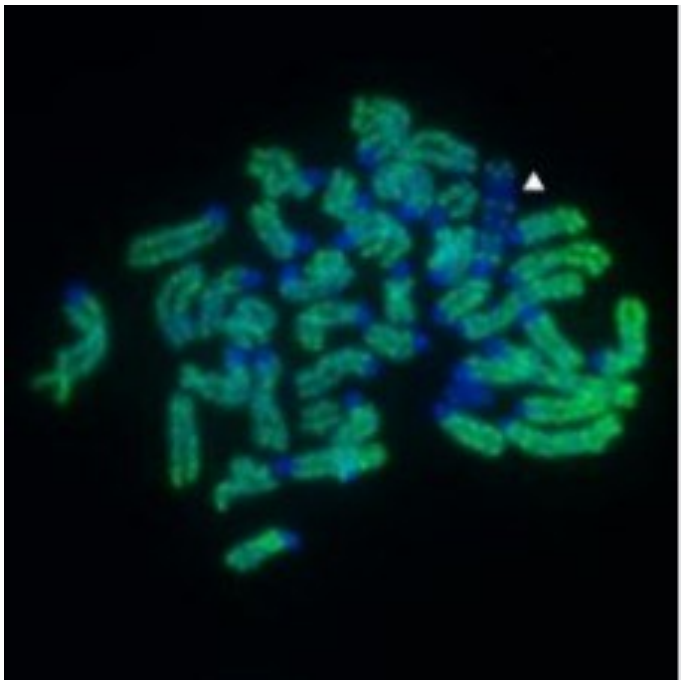
Funding

Wellcome Trust

Epigenetic Regulation and Cell Identity Control

For successful development, the information stored in the genome needs to be precisely regulated. During differentiation, each individual cell uses an ever-changing repertoire of epigenetic mechanisms to achieve proper control of gene expression. Our research focuses on understanding how the cell nucleus specifies the identities of the different cell types in the body, and how changes of cell identity are regulated in development.

Our group's interest is in nuclear mechanisms that regulate changes of cellular identity during stem cell differentiation and specify the diverse cell types of the body. Previously, we have used the mammalian dosage compensation process, X inactivation, as an experimentally tractable system for studying the developmentally regulated establishment of silent chromatin. This has put us in a position to apply previously generated tools for studying aspects in stem cell biology.



Separation of epigenetic modifications and gene silencing

Group Members

Asun Monfort	Postdoc
Agata Kurowski	Graduate Student
Deborah McGee	Technician

2013 Publications

Boudadi E, Stower H, Halsall JA, Rutledge CE, Leeb M, Wutz A, O'Neill LP, Nightingale KP, Turner BM. The histone deacetylase inhibitor sodium valproate causes limited transcriptional change in mouse embryonic stem cells but selectively overrides Polycomb-mediated Hoxb silencing. Epigenetics Chromatin. PMID: 23634885

Agrelo R, Kishimoto H, Novatchkova M, Peraza V, Paolino M, Souabni A, Wutz A. SATB1 collaborates with loss of p16 in cellular transformation. Oncogene. PMID: 23686316

Bock C, Wutz A. DNA methylation: a matter of culture. Nature Structural & Molecular Biology. PMID: 23463307

Monfort A, Wutz A. Breathing-in epigenetic change with vitamin C. EMBO Reports. PMID: 23492828

Wutz A. Noncoding roX RNA Remodeling Triggers Fly Dosage Compensation Complex Assembly. Molecular Cell. PMID: 23870139

Wutz A. Epigenetic regulation of stem cells : the role of chromatin in cell differentiation. Advances in Experimental Medicine and Biology. PMID: 23696364

Key Publications prior to 2013

Leeb M, Walker R, Mansfield B, Nichols J, Smith A, Wutz A. Germline potential of parthenogenetic haploid mouse embryonic stem cells. Development. (2012) PMID: 22912412

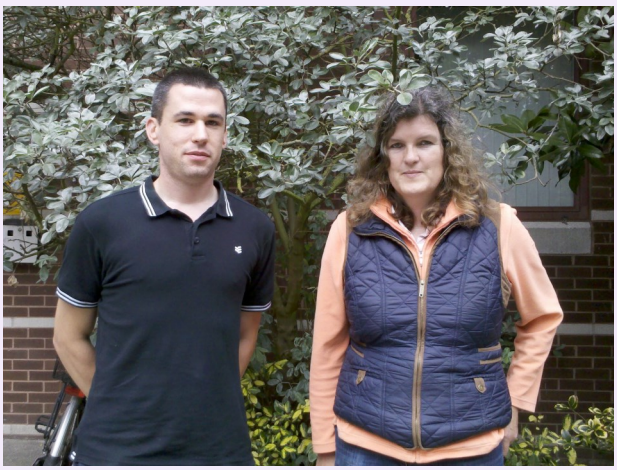
Leeb M, Wutz A. Derivation of haploid embryonic stem cells from mouse embryos. Nature. (2011) PMID: 21900896

Ohhata T, Senner C, Hemberger M, Wutz A. Lineage-specific function of the noncoding Tsix RNA for Xist repression and Xi reactivation in mice. Genes and Development. (2011) PMID: 21852535

Collaborations

Collaborator	Location	Nature of Collaboration
Jennifer Nichols	SCI	Joint paper
Austin Smith	SCI	Joint paper

Bioinformatics



Sabine Dietmann & Patrick Lombard

Bioinformatics is an interdisciplinary field which addresses biological questions with computational and statistical methods. A major activity in bioinformatics is to develop and adapt software tools to generate useful biological knowledge in close collaboration with experimentalists. Bioinformatics has become an integral part of many research projects in stem cell biology. It plays a role in the analysis and interpretation of gene and protein expression and regulation. It aids in sequencing and annotating transcription and chromatin factor binding sites and epigenetic profiles. It plays a role in the textual mining of biological literature and the development of biological and gene ontologies to organize and query biological data. Bioinformatics tools aid in the comparison of genetic and genomic data and more generally in the understanding of evolutionary aspects of molecular biology. At a more integrative level, it helps analyze and catalogue the biological pathways and networks that are an important part of systems biology. In structural biology, it aids in the simulation and modeling of DNA, RNA, and protein structures as well as molecular interactions.

Services and Equipment

Computational resources comprise an integrated storage and computing infrastructure, with additional access to wider University computing facilities. The facility provides terabyte-level distributed data storage with reciprocal back-up of information stored at different sites, a secure data-exchange and online results display facility, and server-based multi-core computing facilities for use by core bioinformaticians. Data-handling and downstream analyses are implemented via the combination of custom and third-party, open-source and commercial software. The provision of licenses for popular commercial bioinformatics software to SCI members is in development.

Training

Training for experimentalists is provided in PERL scripting, R/Bioconductor statistical computing and applications of open-source software platforms, such as Galaxy.

Core Bioinformatics Staff

Sabine Dietmann
Lila Diamanti
Patrick Lombard

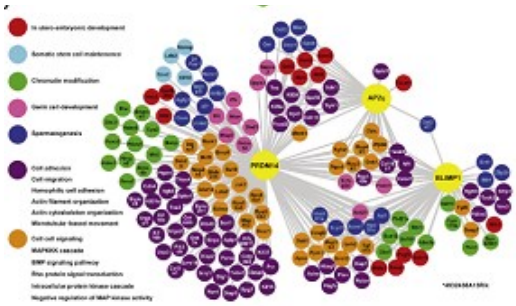
Examples of publications in 2013

Hussain S, Sajini AA, Blanco S, Dietmann S, Lombard P, Sugimoto Y, Paramor M, Gleeson JG, Odom DT, Ule J, and Frye M. NSun2-mediated cytosine-5 methylation of Vault non-coding RNA determines its processing into regulatory small RNAs. Cell Reports. PMID: 23871666

Ruau D, Ng FS, Wilson NK, Hannah R, Diamanti E, Lombard P, Woodhouse S, Göttgens B. Building an ENCODE-style data compendium on a shoestring. Nature Methods. PMID:24076986

Betschinger J, Nichols J, Dietmann S, Corrin PD, Paddison PJ, Smith A. Exit From Pluripotency Is Gated By Intracellular Redistribution Of The Bhlh Transcription Factor Tfe3. Cell. PMID: 23582324

Magnúsdóttir E, Dietmann S, Murakami K, Günesdogan U, Tang F, Bao S, Diamanti E, Lao K, Gottgens B, Surani AM. A tripartite transcription factor network regulates primordial germ cell specification in mice. Nature Cell Biology. PMID: 23851488

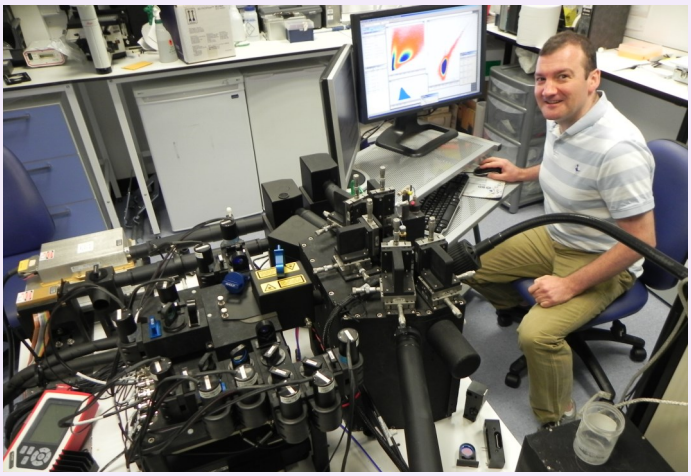


Transcription factor network for PGC specification

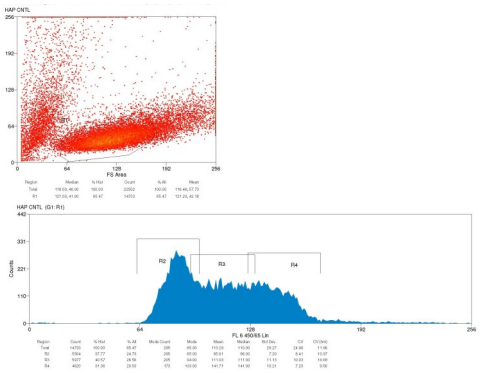
Other SCI Bioinformaticians

Meryem Ralser (Smith & Hendrich Labs)
Jelena Aleksic (Frye Lab)
Tommaso Leonardi (Pluchino Lab)
Felicia Ng, Rebecca Hannah, Manuel Sanchez-Castillo, David Ruau (Gottgens Lab)
Eshwar Meduri (Huntly Lab)

Flow Cytometry



Andy Riddell



Flow cytometry is a laser-based, biophysical technology employed in cell counting, cell sorting, biomarker detection and protein engineering, by suspending cells in a stream of fluid and passing them by an electronic detection apparatus. It allows simultaneous multiparametric analysis of the physical and chemical characteristics of thousands of particles every second. Flow cytometry is routinely used in the diagnosis of health disorders but has many other applications in basic research, clinical practice and clinical trials. A common variation is to physically sort particles based on their properties, so as to purify populations of interest.

Services

We have a multi-site facility comprising of expert-led high-speed cell sorters and self-use sorter/analyser equipment. Our services include sorting, assay design and training.

Equipment

Sorters:

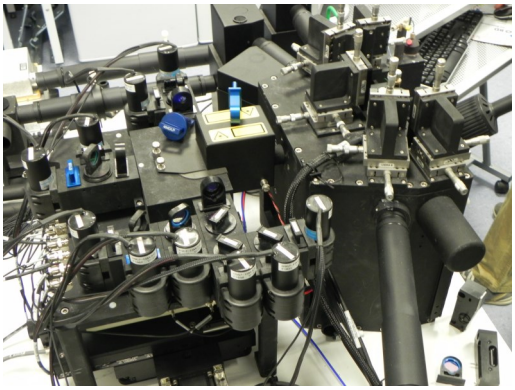
Beckman Coulter MoFlo 3 laser system with up to 12 parameters.
BioRad S3 Bench to sorter with 2 lasers and 7 parameters.
A BD Aria IIu sorter with 3 lasers and up to 12 parameters.

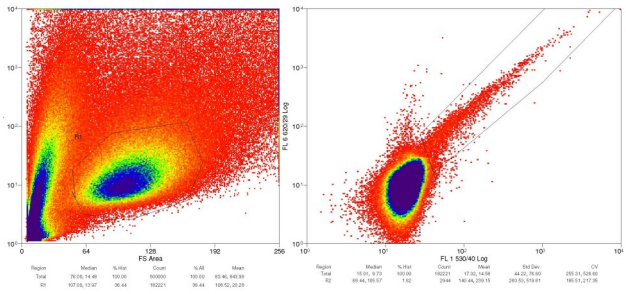
Analysers:

A BD Fortessa with 4 lasers and 20 parameters.
A Beckman Coulter CyAn with 3 lasers and 10 parameters

Training

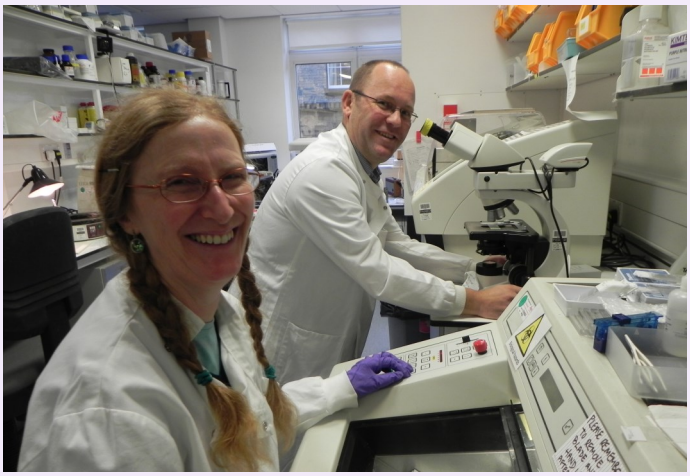
Training is given on the systems by request.





Staff
Andy Riddell

Histology



John Brown and Helen Skelton

Histopathology is the study of the microscopic anatomy of tissue and associated diseases. It is performed by slicing and staining pieces of tissue followed by examination under a light microscope or electron microscope. Histological studies may be conducted via tissue culture, where live cells can be isolated and maintained in a proper environment outside the body. The ability to visualize or differentially identify microscopic structures is frequently enhanced through the use of histological stains.

Services

Our histopathology facility provides a service for paraffin processing and embedding of fixed samples, paraffin section cutting and cryostat sectioning of samples frozen in OCT blocks. Routine haematoxylin and eosin staining of slides is also available.

Specialised services

The histopathology facility has extensive expertise in immunohistochemical techniques and can provide a range of automated or manual procedures for both chromogenic and immunofluorescence protocols. Our experts are willing to offer advice and training in protocol design.
Tissue microarrays are a research tool that enables multiple samples to be tested and sectioned onto a single slide which can provide statistically relevant sample numbers. The histopathology service provides both design and manufacture of TMAs.
The facility can also offer DNA and RNA extraction from tissues for downstream genomic analysis and in-situ techniques for morphological identification of DNA sequences.

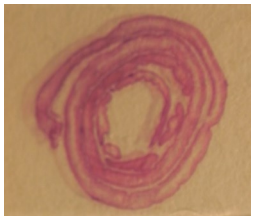
Equipment

The facility is well equipped with a Leica tissue processor and embedding centre, two rotary microtomes for paraffin work, and a cryostat for frozen section work. A Leica Autostainer provides automated H&E staining or dewaxing for paraffin sections prior to other methods and a microwave oven is provided for antigen retrieval techniques. A Ventana Benchmark immunohistochemical stainer is also available.

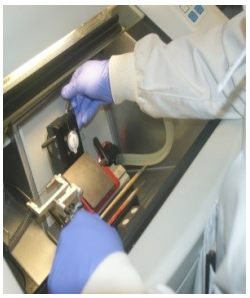
Training

Training is available for all SCI members in cryosectioning and microtomy, immunohistochemical techniques and TMA manufacture.

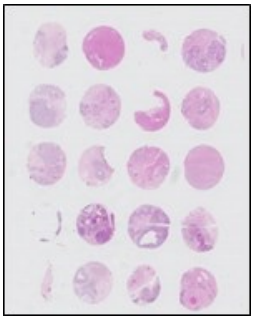
Staff
Peter Humphreys John Brown Helen Skelton

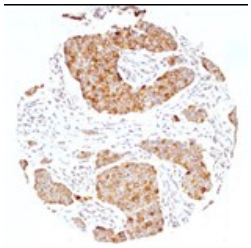


H&E stained section



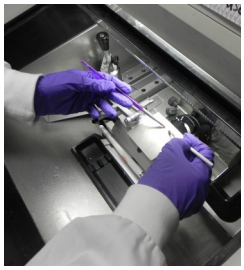
Cryosectioning

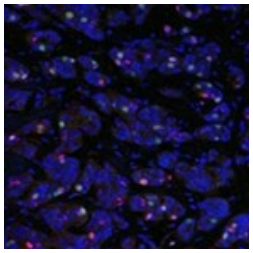


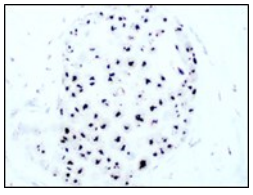


Tissue microarrays

Microdissection for DNA extraction

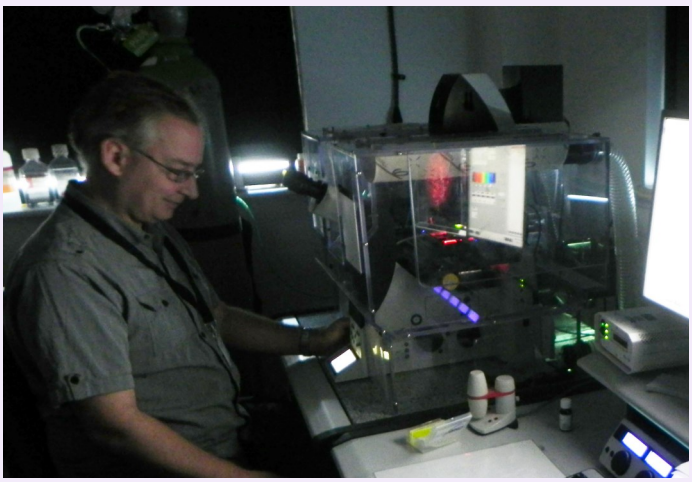




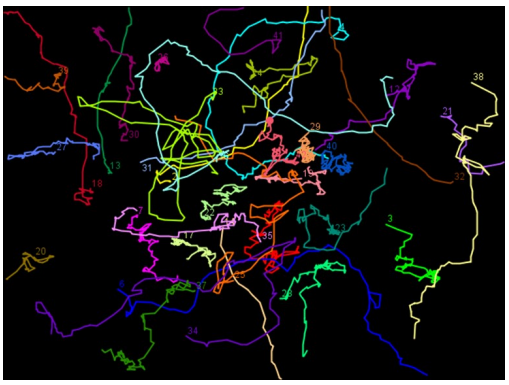


In-situ hybridisation

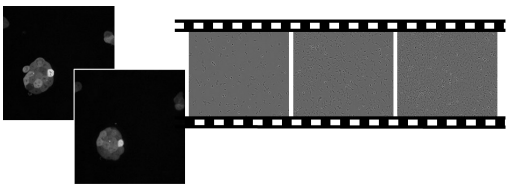
Imaging



Peter Humphreys



Cell Tracking



Live cell timelapse

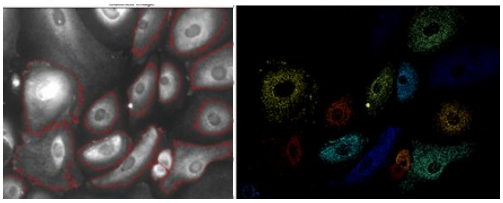
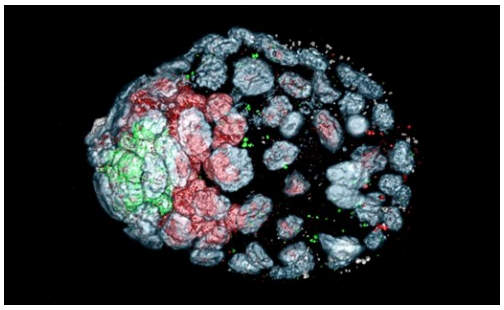


Image analysis



3D reconstruction

Our advanced multi-user imaging facility provides SCI members with resources including confocal microscopy, live cell imaging, high content screening and colony analysis, image analysis and reconstruction.

Equipment

- Leica SP5 Confocal Microscopes
- Andor Revolution XD Spinning Disk Confocal microscope
- Leica Matrix High Content screening/live cell imaging microscope
- Nikon Biostation IM
- Essen Incucyte HD
- Zeiss Imager structured illumination & transmitted light (H&E)
- Tissue Culture Microscopes & research grade fluorescence microscopes.
- Fluorescence Correlation Spectroscopy/ lifetime imaging

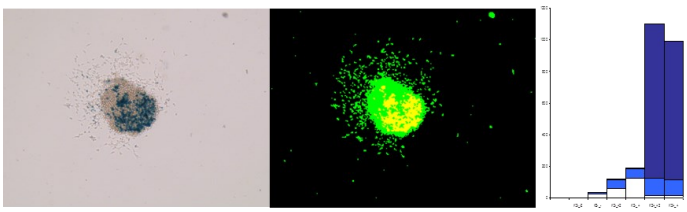
Training

Expert advice, assistance and training are able for the following:

- All aspects of imaging for researchers
- Image analysis and custom analysis tools
- Processing of image volumes (deconvolution, 3D reconstruction)
- Creation of figures for publication

Data Analysis

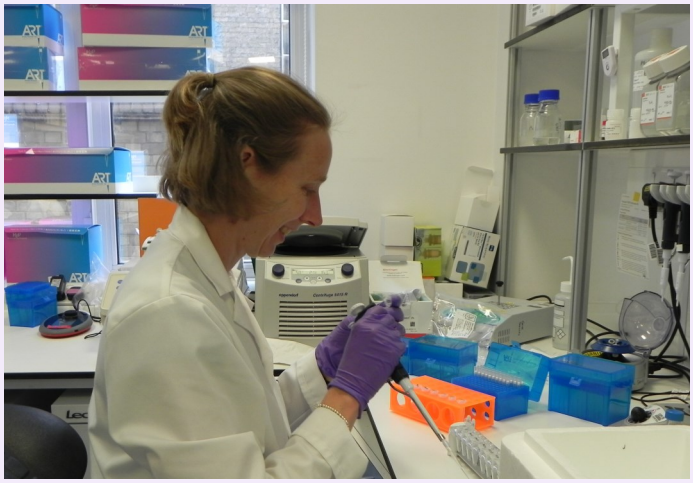
- Workstations for 3d Reconstruction, volumetric measurement and analysis.
- High content analysis and cell tracking.



Colony analysis

Staff
Peter Humphreys

Next Generation Sequencing Libraries

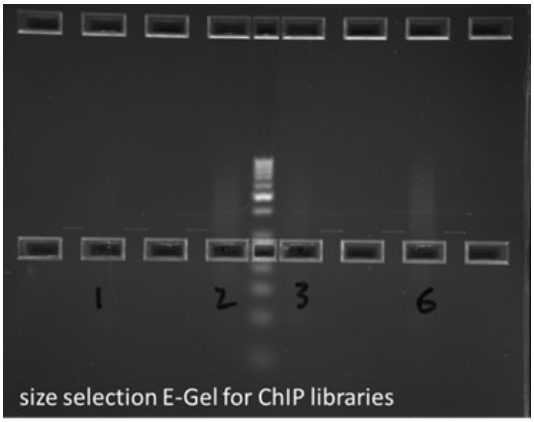


Maike Paramor

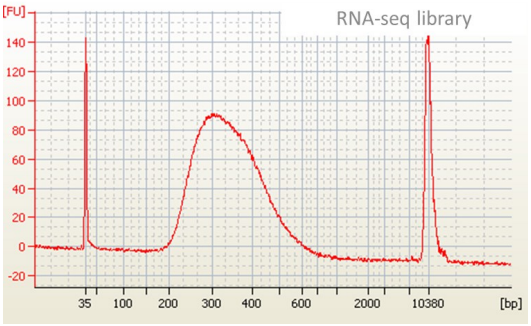
This facility provides the preparation of DNA/RNA libraries for Next Generation Sequencing (NGS) projects to support SCI scientists.

In recent years, the demand for high throughput sequencing methods has increased rapidly in the field of stem cell research. However, the technical challenge of library production is often daunting and time-consuming, and forms the major bottleneck for many projects.
To accommodate this, the Institute has created a state-of-the-art facility which produces NGS libraries on demand.

This facility provides a fast turnaround for standard library preparation. Moreover, individual and non-standard methods are being developed as well.
We strive to provide a local and flexible service to anybody within the Institute.



size selection E-Gel for ChIP libraries



Services

- Help and advice with project planning
- Transcriptome/RNA-seq libraries
- Small RNA libraries
- ChIP-seq libraries
- DNA/amplicon libraries
- individual projects and non-established methods will be considered

Moreover, we offer the use of our Covaris for shearing of DNA/RNA samples or chromatin samples. Training can be provided on request.

Sequencing

The SCI has purchased a share in a HiSeq2500 sequencing machine housed in the Cancer Research UK Cambridge Institute. With this, all groups in the SCI will have direct internal access to high throughput sequencing runs from the beginning of 2014. In addition to this, access to a MiSeq and a Roche 454 is provided by the Biochemistry DNA sequencing facility.

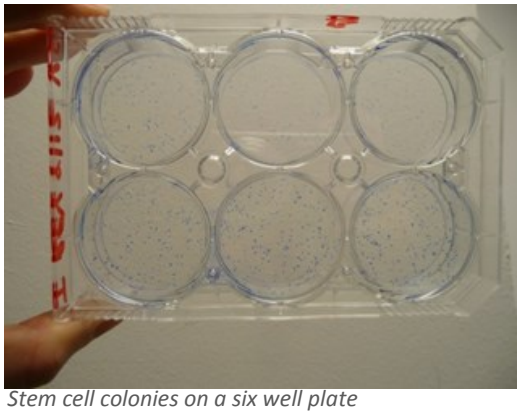
Currently available preparations/kits:

- Illumina small RNA library kit
- Nextflex directional RNA seq kit (Illumina)
- Nextflex adapters for multiplexing up to 24 samples (Illumina)
- NEBNext reagents for standard Illumina
- DNA libraries and ChIP libraries
- Covaris S2 instrument for DNA/RNA shearing and chromatin shearing

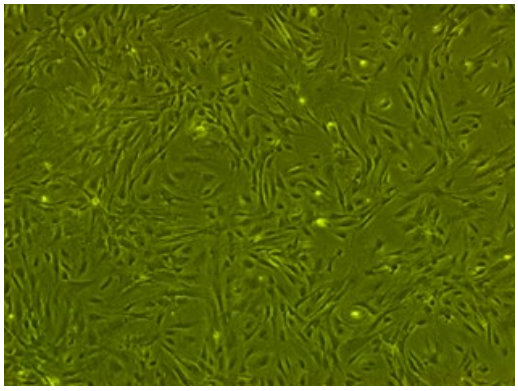
Staff
Maike Paramor

Tissue Culture

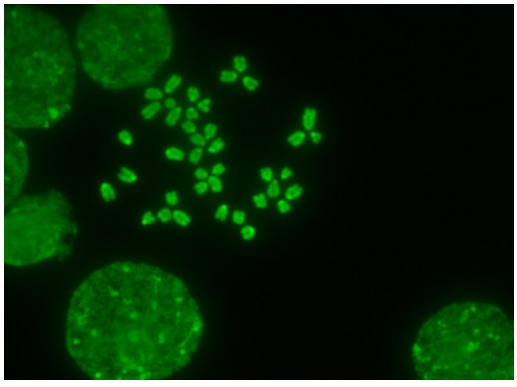
Sally Lees and Emma Harkness



Stem cell colonies on a six well plate



MEFs



Chromosome spread

Tissue culture is the growth in an artificial medium of cells derived from living tissue. This is typically facilitated via the use of a liquid, semi-solid, or solid growth medium, such as broth or agar allowing cells to be grown on petri dishes. Tissue culture is an important tool for the study of the biology of cells enabling stem cells to be cultured, manipulated and assessed in an in-vitro state. Our facility includes fully managed designated primary, derivation and cell culture rooms.

Services

Cell banks: Cell banks of WT Mefs, DS red Mefs and DR4 Mefs are produced for use as feeder cells. Banks of other popular cell lines such as HEK293, 293FT, Cos-7 and E14 cells are also available.

Growth factors/proteins: Quality assured proteins that are produced within the University are available at a fraction of the cost of commercial products. These include growth factors such as mLIF, huLIF, FGF2, actavin, and BMP4.

Serum: Variation in the quality of serum and its suitability for particular applications in cell culture can have a dramatic effect on experiments. To ensure this variability is kept to a minimum all serum is batch tested and large stocks held to provide consistency in the cell culture, so making the results obtained more consistent.

Mycoplasma Screening: Mycoplasma infections may induce cellular changes, including chromosome aberrations, changes in metabolism and cell growth, having a huge detrimental effect on research. All laboratories and cell lines are routinely screened to ensure the Institute remains mycoplasma free.

Quality assurance: Variation in batches of reagents, specifically those used in serum free media can have major impact on the down stream processing of differentiation assays and cell culture, assays that can take several months to perform. To reduce this impact reagents are subjected to a barrage of assays to determine their suitability for the culture of cells and application in specific assays.

Training

As cell culture is a fundamental skill used by all scientists working with stem cells, training is available to all staff to ensure they have a solid foundation in cell and ES culture.

Staff
Sally Lees Emma Harkness Kathryn Cook Diana Breitmaier

IT

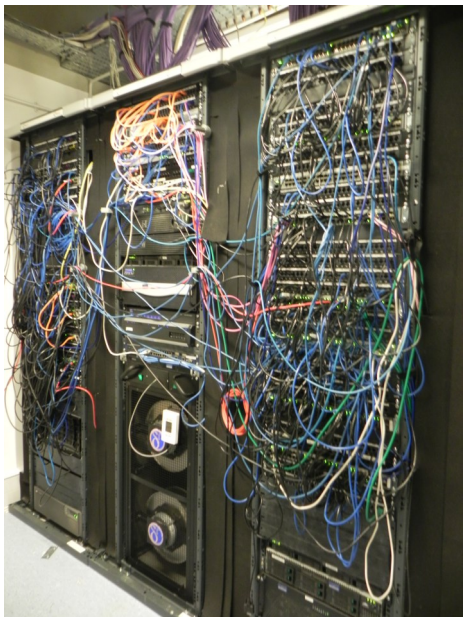
Paul Sumption and Paul Barrow

The IT facility plans, develops, maintains and manages the whole IT infrastructure for the staff located at the Centre for Stem Cell Research as well as some servers and services located at some other Stem Cell Institute sites. In addition they are responsible for the migration and planning of the IT infrastructure when the Stem Cell Institute relocates to its new building in 2017.

Services:

- Hosting and running websites for the Bioinformatics service
- Bioinformatic server management and installation / advice on Bioinformatic packages
- Hardware and software purchases
- Development and day to day maintenance of the IT systems used within the CSCR building
- General computer support and advice to the research, teaching and administrative occupants of the CSCR building
- Liaising with the University Computing Service concerning support and security issues to ensure the security and correct use of up to 400 computing resources
- Monitoring and improving network performance and security
- Co-ordinating and liaising with other IT staff that are part of the SCI
- VoIP phone system
- Wireless access
- Managed printing and data storage
- Offsite data storage and server replication in liaison with the Clinical School Computing Service

The IT team have a help desk system, the core hours for this are 9am - 4.30pm. Users submit a support request and are issued a 'ticket' which then tracks progress on their request.



Staff

IT Technician - Paul Barrow
The SCI's primary help desk contact, his areas of speciality are Windows Server 2008, Windows 7 and general desktop support

Computer Officer - Paul Sumption
Runs the SCI's core infrastructure (servers, switches and storage) and his areas of speciality are Debian / Ubuntu Linux and large storage systems

Other Resources

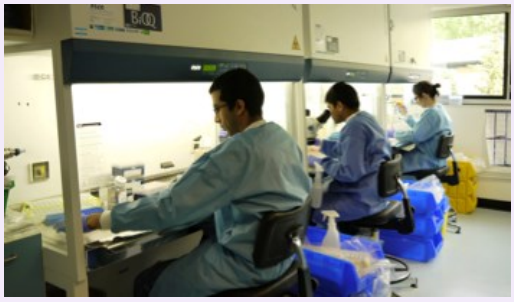
Human Tissue Samples

SCI provides support for collection and banking of donated human tissues with appropriate ethical approval.

Biomedical Models

A world-class transgenic core facility with state of the art equipment and expertise. This service generates models for basic and translational biomedical research across the Stem Cell Institute .

Cambridge Biomedical Research Centre (BRC) hIPSCs core facility

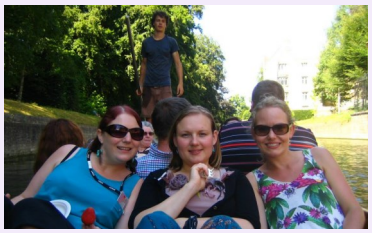


The Cambridge Biomedical Research Centre (BRC) hIPSCs core facility was created in 2009 to promote the clinical applications of human Induced Pluripotent Stem Cells (hIPSCs) and to answer the increasing need for deriving new lines for disease modelling in vitro. During the past two years, this platform has derived and characterised more then 400 hIPSC lines from 70 patients suffering from neurodegenerative diseases, cardiovascular syndromes, metabolic and blood disorders. These projects have been directed by clinicians associated with diverse departments of University of Cambridge, including Neurosciences, Metabolic Science, Cardiovascular Medicine, Haematology, Surgery and Hepatology/Thoracic Medicine.

The main objective of this platform is the production of hIPSC lines on demand for the development of in vitro models of disease, compatible with drug development and basic mechanistic studies. In addition, a growing activity of the BRC hIPSCs core facility will be in training clinicians and basic scientists to derive, grow and differentiate hIPSC lines. Located in the Anne McLaren Laboratory for Regenerative Medicine (LRM), the BRC hIPSC core facility benefits from state of the art environment for stem cell research and also from the broad expertise of research groups on the Addenbrookes Biomedical Campus.

http://www.cambridge-brc.org.uk/

Administration and Support Services



The SCI administrative and support staff run the day to day operations of the Institute. They support the scientists in activities including HR, finance/grants, building and equipment maintenance, PhD programme, cleaning, glass washing and organizing conferences and public engagement.

The team is led by the Institute Administrator, Lynn Kennedy.

General Administration

Institute Administrator: Lynn Kennedy
Principal Assistant: Mark Hammond
SCI Coordinator: Jenny Nelder
Senior Clerical Assistant: Jo Jack
Principal Sec./Austin Smith's PA: Genevieve Blais
Administrative Assistant (Data): Susana Camacho
Administrative Assistant (HR): Edita Paralova
Receptionist: Klara Cichovska
LRM Lab Manager: Morgan Alexander

Finance Team

Senior Grants/Accounts Clerk: Louise Carter
Accounts Clerk: Thomas Jeffrey
Accounts Clerk: Laura Spong

Building Maintenance Team

Snr. Chief Building Services Tech.: Alistair Finlayson
Chief Building Services Technician: Paul Vaes
Custodian: Jim Bagstaff
Assistant: Andrew Ayling
Cleaner: Roy Pelegrin
Cleaner: Amjadali Khan
Glasswash and media Technicians

Affiliate Members

SCI Affiliates are individuals invited by the Steering Committee to engage with the Institute. They are independent group leaders whose research intersects with, or who have emerging programmes in, stem cell biology and medicine. They may be based in the University of Cambridge or in neighbouring research institutes such as the Wellcome Trust Sanger Institute, the Babraham Institute, or the European Bioinformatics Institute.

Affiliates and their lab members are encouraged to participate in seminars, retreats and networking activities of SCI and to develop collaborations with SCI Principal Investigators. In addition affiliates:

- have access, for collaborative studies, to SCI core platforms that are not available in their host department/ institute.
- are eligible to be partners in cross-disciplinary seed-funding proposals
- may offer projects on the 4-year PhD programme (unless they participate in another Wellcome Trust PhD Programme).
- may be asked to contribute to critical discussion sessions with PhD students.
- may enrol students in the critical discussion series and their students can participate in SCI student events.

In 2013 the Institute welcomed two new Affiliate members:

- Dr Ana Cvejic - Department of Haematology, University of Cambridge
- Dr Jenny Pell - Department of Pharmacology, University of Cambridge

Dr Paul Bertone
Stem Cell Transcriptomics

EMBL-EBI

Professor Allan Bradley
Genome Engineering

wellcome trust sanger institute

Dr Ana Cvejic
Developmental Haematopoesis

UNIVERSITY OF CAMBRIDGE
Dept of Haematology

Professor Anne Ferguson -Smith
Stem cells and the epigenetic programme

UNIVERSITY OF CAMBRIDGE
Dept of PDN

Dr Cedric Ghevaert
In vitro production of platelets for transfusion in humans from pluripotent stem cells

UNIVERSITY OF CAMBRIDGE

CIMR

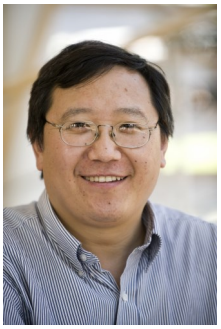
Dr Myriam Hemberger
Trophoblast Stem Cells

Babraham Institute

Dr Phil Jones
Epidermal Stem Cells

MRC Cancer Unit

MRC Cancer Unit
UNIVERSITY OF CAMBRIDGE



Dr Pentao Liu
Human iPS Cells

wellcome trust sanger institute

Professor Keith Martin
Neuroprotection and repair of the visual system
UNIVERSITY OF CAMBRIDGE
Centre for Brain Repair

Professor Alfonso Martinez-Arias
The structure and function of living matter
UNIVERSITY OF CAMBRIDGE
Dept of Genetics

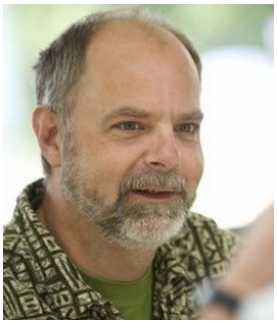
Dr Jenny Pell
Regulation of adult muscle stem cell behaviour
UNIVERSITY OF CAMBRIDGE
Dept of Pharmacology

Dr Anna Philpott
Co-ordination of proliferation and differentiation in stem and progenitor cells
UNIVERSITY OF CAMBRIDGE
Dept of Oncology

Professor Wolf Reik
Epigenetics
Babraham Institute

Dr Peter Rugg-Gunn
Stem Cell Research
Babraham Institute

Dr Sanjay Sinha
Regulation of vascular smooth muscle cell development and disease
UNIVERSITY OF CAMBRIDGE
Dept of Medicine



Dr Bill Skarnes
Stem Cell Genetics
wellcome trust sanger institute

Dr John Stingl
Mammary Stem Cells
UNIVERSITY OF CAMBRIDGE
CANCER RESEARCH UK | CAMBRIDGE INSTITUTE

Professor Christine Watson
Stem cell and lineage determining factors in mammary glands
UNIVERSITY OF CAMBRIDGE
Dept of Pathology

Dr Doug Winton
Intestinal Stem Cells
UNIVERSITY OF CAMBRIDGE
CANCER RESEARCH UK | CAMBRIDGE INSTITUTE

Committees

Steering Committee

Austin Smith
Institute Director
Chair

Robin Franklin
Theme Leader:
Neural

Michaela Frye
Theme Leader:
Solid Tissue

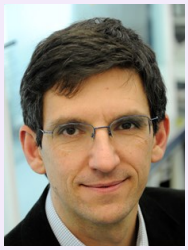
Tony Green
Theme Leader:
Haematopoiesis

Brian Hendrich
Postgraduate
Training Director

Katrin Ottersbach
Junior Group
Leader

Ben Simons
Physical Sciences

Azim Surani
Theme Leader:
Pluripotency



Ludovic Vallier
Laboratory for
Regenerative
Medicine

Lynn Kennedy
Institute
Administrator

Jenny Nelder
SCI Coordinator

International Scientific Advisory Board

Prof Janet
Rossant , **Chair**
Hospital for
Sick Children,
Toronto

Prof Cédric
Blanpain
Université
Libre de
Bruxelles

Dr Meinrad
Busslinger
Vienna
Biocenter

Dr Shin-Ichi
Nishikawa

Prof Maarten
van Lohuizen
Netherlands
Cancer
Institute

Dr Ruth
McKernan
Pfizer

Prof David
Rowitch
UCSF
Children's
Hospital

Governance Committee

The role of this Committee is to ensure University oversight of and support for the joint Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute. This includes communication with the sponsors regarding recruitment, funding arrangements, commitments and other strategic issues.

The committee will normally meet twice per year with sponsor representatives invited as observers.

Patrick Maxwell
Head of the School of Clinical Medicine.

Duncan Maskell
Head of the School of Biological Sciences

Austin Smith
Institute Director

Robin Franklin
Stem Cell Institute

Tony Green
Stem Cell Institute

Ben Simons
Physical Sciences

Lynn Gladden
Pro-Vice Chancellor for Research.

Paul Luzio
Deputy Head of the Clinical School

Anne Fergusson-Smith
SBS

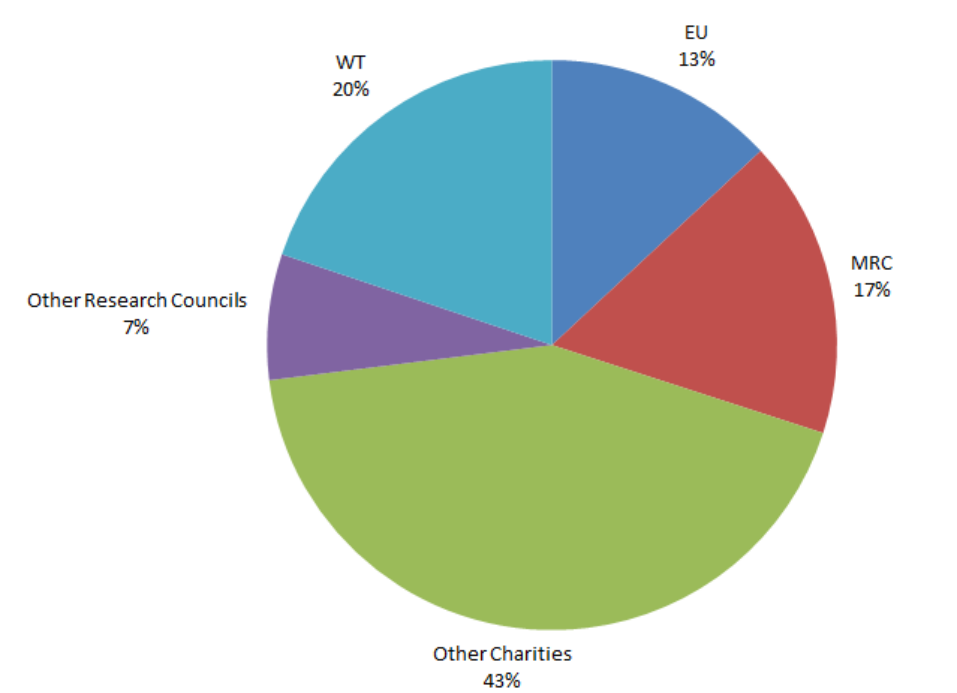
Funding

2013 SCI Budget

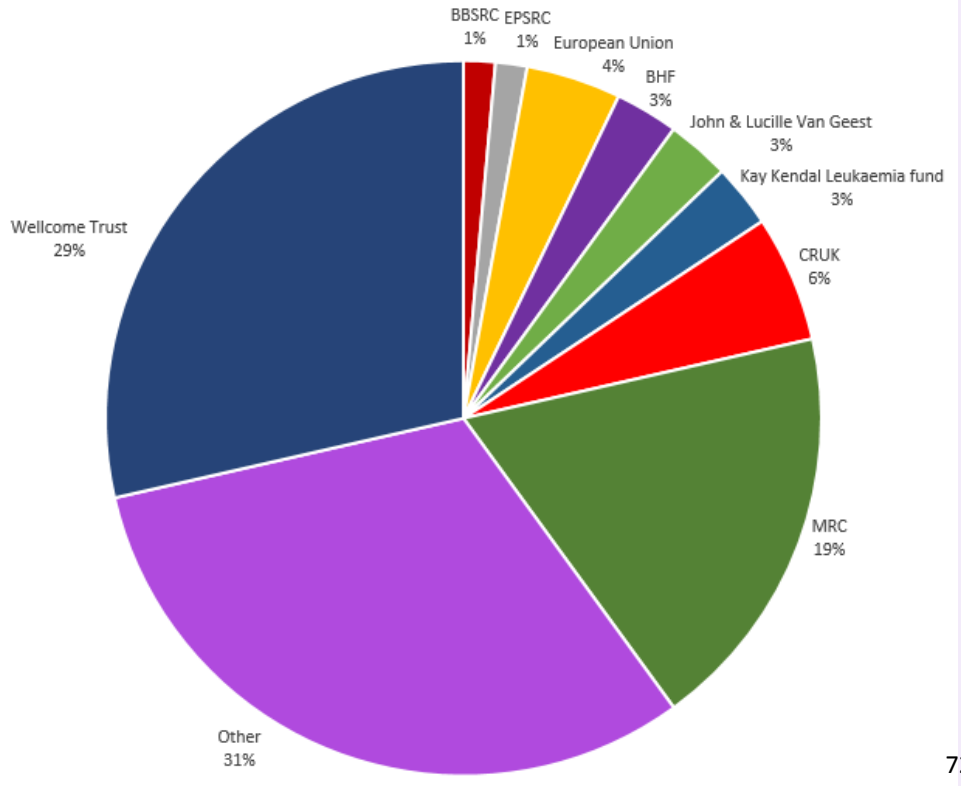
The Institute is funded by the University of Cambridge and also a core grant from the Wellcome Trust and Medical Research Council. In addition to this funding researchers secure individual research grants from a variety of funding sources. In 2013:

- SCI held active research grants to a value of £57 million (excluding Wellcome Trust/MRC Core Funding)
- 19 new grants were awarded to SCI investigators.
- Research grant expenditure from January to November 2013 was £11,668,907 (excluding Wellcome Trust/ MRC Core Funding)

Research Grant Expenditure in 2013



Student Funding



Funding Bodies and Sponsors

The Stem Cell Institute would like to thank the following organisations for their continuing support.

Highlights of 2013

New Stem Cell Institute Building

Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute

The University is underwriting the costs for construction of a new building at the Cambridge Biomedical Research Campus. The detailed design phase has been initiated and the building is planned for completion in late 2017.

This major development will enable co-location of existing SCI research groups plus expansion through new recruitment. Most importantly, direct proximity to clinician scientists, clinical research facilities and patients will facilitate translational science and clinical trials.

wellcome trust

MRC Medical Research Council

UNIVERSITY OF CAMBRIDGE

Wellcome Trust Sir Henry Dale Fellowship

Bon-Kyoung Koo

Suffrage Science 2013

Jenny Nichols

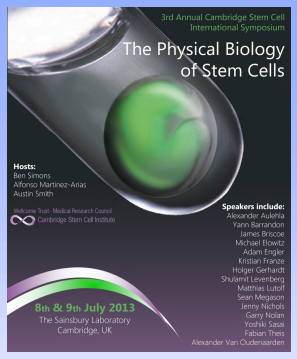
Chair of Stem Cell Medicine

Robin Franklin has been appointed Professor of Stem Cell Medicine with effect from 1st January 2014.

A key part of his role will be as Head of Translational Science for the Wellcome Trust-MRC Cambridge Stem Cell Institute, with responsibility for promoting and coordinating research aimed at turning scientific discoveries into medical applications.

3rd Annual Cambridge Stem Cell Symposium

"The Physical Biology of Stem Cells"



Organised by Ben Simons, Alfonso Martinez-Arias and Austin Smith.

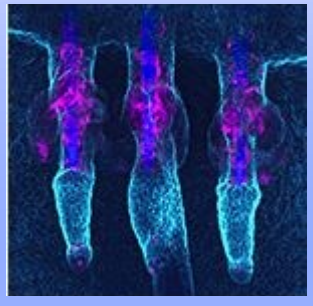
It attracted 101 participants from 10 countries. Talks were presented by 16 invited speakers and 5 short talks selected from abstracts. 28 posters were presented by the delegates.

Feedback from participants was enthusiastic and Development commissioned a meeting review from Sally Lowell.

Public Engagement

Members of the Stem Cell Institute took part in 51 events in 2013, including **Cambridge Science Festival events "Stem Cell Generation".**

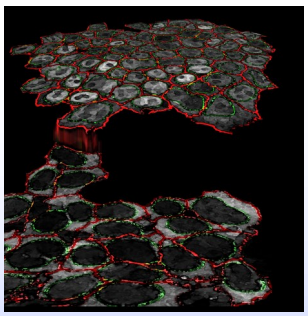
Shining stem cells reveal how our skin is maintained



The epidermis is the outer layer of our skin and protects our body against the hostile environment. Stem cells carry out the life-long maintenance of the epidermis, which is a requirement for life. This study shows that all stem cells in the skin are essentially equal, but that local signals instruct their behaviour both normally, in response to injury and tumour formation. The researchers marked the early skin stem cell with shining proteins in order to map stem cell behaviour in the outer layer of the skin. The stain is inherited by the daughter cells, so that they can trace their origin and make a family tree. The fine details of the family tree can be used to infer the stem cell's role in normal maintenance of the skin, as well as in wound healing.

Page ME, Lombard P, Ng F, **Göttgens B**, **Jensen KB**. The epidermis comprises autonomous compartments maintained by distinct stem cell populations. Cell Stem Cell. PMID: 23954751

Displacement of pluripotency factor Tfe3 from nucleus to cytoplasm precedes differentiation



Embryonic stem cells (ESCs) have the ability to develop into any tissue or organ. To do this they must first lose their stem cell identity which in turn allows formation of specific cell types, such as nerve or muscle. Understanding how ESCs change their identity is a fundamental challenge that can improve our ability to use stem cells in medical application. Joerg Betschinger tested thousands of genes to identify those that control the loss of ESC identity. He found a new mechanism involving genes called Folliculin and Tfe3 that were not previously known to act in ESCs. Intriguingly, these genes cause kidney cancer in humans, pointing to a link between stem cells and tumour formation.

Betschinger J, **Nichols J**, Dietmann S, Corrin PD, Paddison PJ, **Smith A**. Exit from pluripotency is gated by intracellular redistribution of the bHLH transcription factor Tfe3. Cell. PMID: 23582324

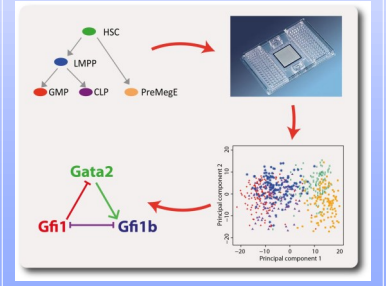
Wellcome Trust Senior Research Fellowship

José Silva

Wellcome Trust Senior Investigator Award

Rick Livesey

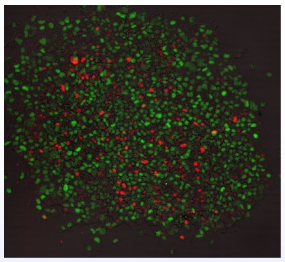
Revealing regulatory codes in individual blood cells



Transcription factor proteins are known to regulate cellular decision-making, but how they function in individual cells to regulate cell fate transitions is not well understood. Taking advantage of state of the art microfluidics technology, this study determined the gene expression of a network of 18 key transcription factors in 600 cells from five primary blood stem and progenitor populations. Computational analysis demonstrated that each population is characterised by a distinct network activity state, and importantly revealed for the first time that single cell gene expression information can be used to predict previously unknown interactions between transcription factors .

Moignard V, Macaulay IC, Swiers G, Buettner F, Schütte J, Calero-Nieto FJ, Kinston S, Joshi A, Hannah R, Theis FJ, Jacobsen SE, de Bruijn MF, **Göttgens B**. Characterization of transcriptional networks in blood stem and progenitor cells using high-throughput single-cell gene expression analysis. Nature Cell Biology. PMID: 23524953

The cell-cycle state of stem cells determines cell fate propensity



Stem cells can divide to maintain the source of new cells or can commit irrevocably to becoming a specialised cell, such as a liver or pancreas cell. Now, researchers describe for the first time the switches that determine how stem cells make that crucial decision. Their work might enable stem cells to be converted into a range of adult tissues more efficiently and more homogeneously.

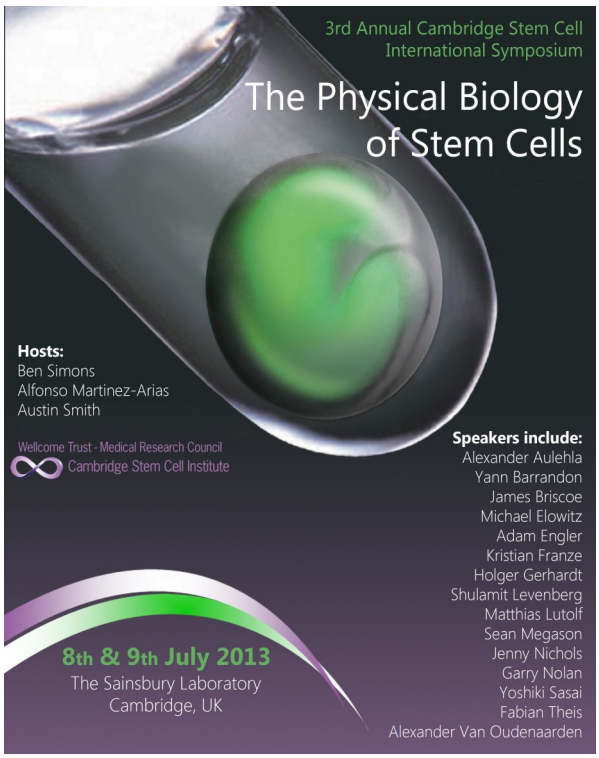
The team looked at the activity of key genes and proteins during the cell cycle - the processes by which a cell divides - in human pluripotent stem cells. They found that the molecular decision to continue to divide or to differentiate - to commit to a pathway towards a defined tissue type - is made during a restricted phase of the cell cycle

Pauklin S, **Vallier L**. The cell-cycle state of stem cells determines cell fate propensity. Cell. PMID: 24074866

EMBO Young Investigator Programme

Kim Jensen

2013 SCI International Symposium: The Physical Biology of Stem Cells



Our 3rd annual Symposium was organised by Ben Simons, Alfonso Martinez Arias and Austin Smith. The Symposium attracted 101 participants from 10 countries. Talks were presented by 16 invited speakers and 5 short talks selected from abstracts. 28 posters were presented by the delegates.

Session 1: Stem Cell Dynamics

Alexander Van Oudenaarden
Hubrecht Institute / University Medical Center Utrecht, THE NETHERLANDS
"Controlling gene expression fluctuations during development"

Fabian Theis
Helmholtz Zentrum München / Technische Universität München, GERMANY
"Quantifying single-cell anog-protein dynamics in mouse embryonic stem cells"

Julia Tischler
Gurdon Institute, University of Cambridge, UK
"Investigating transitions through transcriptional states at single-cell-resolution"

James Briscoe
MRC National institute for Medical Research, UK
"Gene regulatory logic of sonic hedgehog morphogen interpretation"

Sean Megason
Harvard Medical School, USA
"Physical control of developmental robustness: specification by strain, patterning by sorting, and size control by pressure"

Sara-Jane Dunn
Microsoft Research, UK
"A formal approach to uncovering the pluripotency network in embryonic stem cells"

Session 2: The Physics of the Niche

Daisuke Nanba
Ehime University, JAPAN
"Impact of temperature on human epidermal stem cells behaviour"

Matthias Lutolf
EPFL, SWITZERLAND
"Dissecting micro-environmental effectors of pluripotent stem cell fate in 3D"

Ana Teixeira
Karolinska Institutet, SWEDEN
"Ephrin nano-callipers tune Eph receptor function"

Edward Morrissey
Cancer Research UK
"Stem cell dynamics defined in intestinal epithelium and adenomas by use of continuous clonal labelling"

Adam Engler
UC San Diego / Sanford Consortium for Regenerative Medicine, USA
"Intrinsic matrix properties and the molecular mechanisms that regulate stem cell fate"

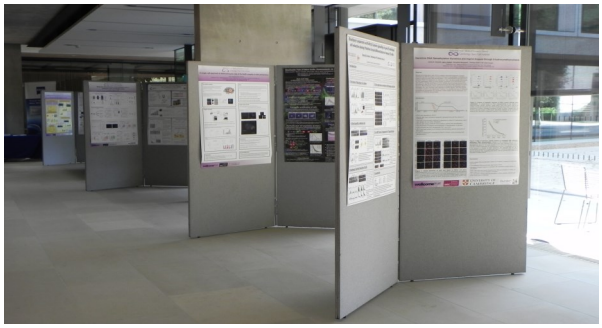
Garry Nolan
Stanford University School of Medicine, USA
"Single cell systems structure view of stem cells and cancer"

Shulamit Levenberg
Biomedical Engineering, Technion, ISRAEL
"The physical environment of embryonic stem cells in 3D can direct early differentiation and germ layer specification"

Kristian Franze
Department of PDN, University of Cambridge, UK
"Mechanics in the development of neurons"

Yoshiki Sasai

Our Stem Cell Symposium Series



Session 3: Self-organisation

Yoshiki Sasai
RIKEN Center for Developmental Biology, JAPAN
"Cytosystems dynamics in neural structure self-organisation in ES cell culture"

Sally Lowell
MRC Centre for Regenerative Medicine, University of Edinburgh, UK
"Too many choices? Variability and unpredictability during differentiation of pluripotent cells"

Alexander Aulehla
EMBL, Heidelberg, GERMANY
"Self-organisation of coupled genetic oscillators during mesoderm patterning and scaling"

Kevin Chalut
WT-MRC Cambridge Stem Cell Institute, UK
"Pre-committed state of embryonic stem cells defined by an auxetic nucleus"

Holger Gerhardt
Cancer Research UK
"Notch signalling dynamics in vascular patterning"

Jenny Nichols
WT-MRC Cambridge Stem Cell Institute, UK
"Control of pluripotency within and without the developing embryo"

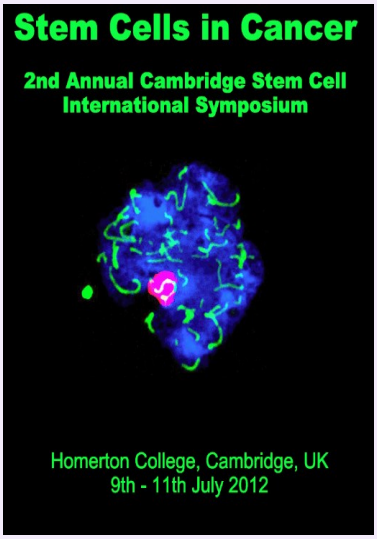
Michael Elowitz
Caltech, USA
"Cell signaling at the single-cell level"

Development commissioned a meeting review from Sally Lowell:

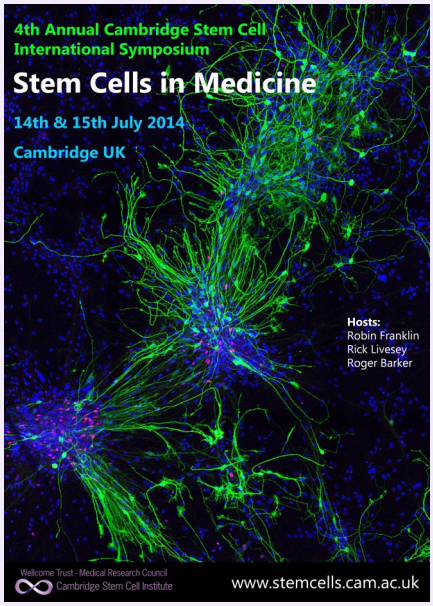
http://dev.biologists.org/content/140/20/4125

Michael Elowitz

Previous:



Future:



Seminars and Public Engagement Events

Stem Cell Club Seminar Series

Date	Title	Speaker
14/02/13	Integration of signalling and transcription factor activity in a developmental lineage decision switch	Christian Schroeter
	Shared transcription factors contribute to stage-specific transcriptional programmes during blood cell differentiation	Felicia Ng
	The role of Oct4 in early development: fence or gateway?	Jenny Nichols
27/03/13	The ability of inner cell mass cells to self-renew as embryonic stem cells in acquired upon epiblast specification	Thorsten Boroviak
	IGF2 and the regulation of stem cells in adult neurogenesis	Anne Ferguson-Smith
	Strange material properties of the embryonic stem cell nucleus during differentiation	Kevin Chalut
24/04/13	Genetics dissection of mammalian cell commitment using haploid embryonic stem cells	Martin Leeb
	Whole genome sequence analysis of human iPS cells	Kosuke Yusa
	The chromatin remodeller Me-2beta is required for early embryonic cell development	Aoife O'Shaughnessy
16/05/13	The UK Human IPS Cell Initiative (HipSci) project	Richard Durbin
	Mesodermal patterning is defined by the exit mechanism from human pluripotency	Sasha Mendjan
	Extracellular signal convergence on Oct4 regulates ES cell self-renewal and differentiation	Tuzer Kalkan
06/06/13	Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of Wnt receptors.	Bon-Kyoung Koo
	A fine balance: Self-renewal and differentiation of single stem cells amidst tumour heterogeneity	David Kent
	NuRD, the complex life of a transcriptional repressor	Remco Loos
18/07/13	New insights into skin stem cell aging and cancer	Bill Keyes
	The life of breath: Stem cells of the adult lung	Brigid Hogan
24/10/13	Unraveling neurodegenerative diseases using patient-specific iPSCs	Haruhisa Inoue
	Intestinal progenitor cell plasticity in homeostasis and cancer	Simon Buczacki
21/11/13	Myeloproliferative neoplasms - resetting the rheostat for haematopoiesis	Tony Green
	Generation of Multipotent Foregut Stem Cells from Human Pluripotent Stem Cells	Nick Hannan
	How neural stem cells speak with immune cells	Stefano Pluchino

The Stem Cell Club Seminar series catering was kindly sponsored by:

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Major Public Engagement Events

Date	Title
14/01/2013	Cell Science Investigator - Lesson at St Mary's School
16 & 17/3/2013	Cambridge Science Festival: "Stem Cell Generation"
21/3/2013	Public Talk: "Stem Cells: Hope or Hype", Austin Smith
26/3/2013	Film: Stem Cell Revolutions: A vision of the Future

The Stem Cell Institute also contributes to a large number of other public engagement events throughout the year which range from public talks to teaching in schools as well as radio broadcasts and tours of the Institute.

Seminars by External Speakers

Date	Title	Speaker(s)
14/02/13	Heterogeneity of skeletal progenitors in mouse bone marrow	Maria Rostovskaya, Dresden
21/02/13	Functional architecture of the nuclear genome; from cell populations to single molecule analysis of chromosome structure	Peter Fraser, Babraham Institute
28/02/13	The mammalian piRNA pathway, from epigenetic transposon silencing to germ line maintenance	Donal O'Carroll, EMBL
20/03/13	Modulation of gene expression via overlapping binding sites exerted by ZNF143, Notch1 and THAP11	Patryk Ngondo-Mbongo, University of Strasbourg
04/04/13	Aurora B kinase and Ring1B cooperate to regulate transcription in resting lymphocytes	Alberto Frangini, Imperial College London
30/05/13	Too many choices? - Variability and unpredictability during the differentiation of pluripotent cells	Sally Lowell, Centre for Regenerative Medicine, Edinburgh
20/06/13	The role of inflammation in progenitor cell mediated liver repair and carcinogenesis	Luke Boulter, Centre for Regenerative Medicine
01/08/13	Physiological and Forced Neurogenesis in the Adult Brain	Benedikt Berninger, University Medical Center
13/08/13	Transcriptional status of CpG islands determines PRC2 recruitment	Eva Riising, University of Copenhagen
05/09/13	Towards the role of 5-hydroxymethylcytosine in neuronal DNA	Skirmantas Kriaucionis, University of Oxford
14/10/13	In vivo clonal analysis of hematopoietic stem and progenitor cells unveils a process of non-stepwise specification in lineage commitment	Hiromitsu Nakauchi, University of Tokyo
24/10/13	Allosteric calcium sensors and signalling switching	Nicolas Le Novere, Babraham Institute

Internal Seminar Series

The Stem Cell Institute also has a vibrant programme of internal seminars on a weekly basis at which SCI members present seminars and receive feedback on their ongoing research.

PhD Programme in Stem Cell Biology and Medicine

The Institute offers a unique environment for high-level research training in stem cell biology. The University of Cambridge is exceptional in the depth and diversity of its research in this area, and has a dynamic and interactive research community that is ranked amongst the foremost in the world. Our PhD programme enables students to take full advantage of the strength and breadth of stem cell research available in Cambridge. Our studentships are funded from a variety of sources including the Wellcome Trust, MRC and CRUK. Additional studentships funded by other sponsors are regularly available within the Institute. We also welcome applications from self-funded students.

Brian Hendrich, Postgraduate Training Director

The Wellcome Trust 4-Year PhD Programme

The Wellcome Trust generously funds our highly competitive 4-Year PhD Programme in Stem Cell Biology and Medicine. The programme has been run annually since 2007 and provides students with an opportunity to spend time in three different labs during their first 'rotation' year before making a decision about where they would like to undertake their thesis work for years 2-4.

In year one students receive practical research training through rotation projects; overviews of current basic and translational stem cell research through interactive critical discussion sessions and specialist workshops; and learn scientific writing via assessed rotation reports and a written PhD proposal. Students on this programme are awarded an MRes qualification at the end of this year. At the end of year one the students choose a supervisor and topic for their full PhD and spend the next three years embedded in that laboratory.

Current 4-Year 'Stem Cell Biology' Programme Students

2010 Starters

Joana Flores | Moyra Lawrence | Ana Leal Cervantes | Victoria Moignard * | Hinal Tanna * | Jan Zylicz

"The programme is perfect for shaping future scientists and helping them find the exact research field they want to work in."

2011 Starters

Anne-Louise Miller | Martyna Popis | Agnieszka Wabik

2012 Starters

Philipp Berg | Juergen Fink | Elena Itskovich | Moritz Matthey

2013 Starters

Amanda Andersson Rolf * | Sarah Förster | Riina Lampela | Anna Osnato | Loukia Yiangou

* Students funded by the MRC

In 2013, SCI students were co-authors on 54 papers, of which 17 of these were first authored by students.

Other Current SCI Students

All of our PhD students have the opportunity to participate in the critical discussion sessions with the Wellcome Trust students. The following students are funded from a variety of sources, and supervised by SCI members.


Sarah Ali Abdulla


Stoyana Alexandrova


Wendi Bacon


Gayan Balasooriya


Neil Barrett
C


Alessandro Bertero


Christoph Budjan

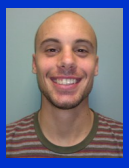

Wesley Chua


Lucy Collins


Abbe Crawford


Gemma Cummins


Natalia Deja
C


Matteo Donegà


Krista Farrell


Julia Frede


Nikoletta Gkatza


Anna Godfrey


Ginez Gonzalez


Anna Guinot Aguado


Douglas Hall


Yun Huang
MB /C


Morteza Jalali
C


Jo-Anne Johnson
C


Fatima Junaid
MB


Chrysa Kapeni


Kai Kretzchmar


Agata Kurowski


Tommaso Leonardi


Victoria Mascetti


Carla Mulas


Jyoti Nangalia
C


Muktha Natrajan


Bjoern Neumann


Felicia Ng


Marko Nikolic
C


Mahalia Page


Matthias Pawlowski
C


Abdul Sajini


Rodrigo Santos


Nathalie Saurat

Charis-Patricia Segeritz

Jonathan Sive
C

Greta Skrupskelyte

Filipa Soares

Sonia Spitzer

Hannah Stuart

Magdalena Sznurkowska

Stan Wang

Adam Wilkinson

Stevan Wing
C

Steven Woodhouse

George Wylde

Crystal Chia Ying

Nada Zaidan

C = Clinicians
MB = MB PhD students

Alumni

Fiona Watt

Fiona moved to Kings College London in 2012 as Director of the Centre for Stem Cells and Regenerative Medicine.

Anton Wutz

Anton moved to the Institute of Molecular Health Sciences in Zurich as Professor of Genetics in April 2013.

Kim Jensen

In 2013 Kim took up a new position as Associate Professor at the BRIC at the University of Copenhagen whilst retaining a part-time position at the Cambridge Stem Cell Institute

Joerg Betschinger

In 2013 Joerg became a Junior Group Leader at the Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland.

Gillian Morrison

In 2013 Gillian became a Chancellor's Fellow at the Centre for Regenerative Medicine, University of Edinburgh.

Career Progression - Students

The Stem Cell institute is dedicated to ensuring the success of our students. Students work alongside world-class scientists in an enriching and stimulating learning environment. We are committed to helping our students to pursue a career in academic research. Our PhD Students are some of the best, brightest and most ambitious, aspiring scientists. We actively encourage students to publish papers, to attend conferences, to engage with the public and to make the connections which will lead to successful scientific careers.

The following data about our Wellcome Trust PhD students demonstrates the success of our programme:

Name & Date	Funder	Next destination
Aryna Luzhynskaya (2007)	WT	Associate at L.E.K. Consulting, UK
Astrid Gillich (2007)	WT	Postdoctoral Fellow, Stanford University, USA
Thor Theunissen (2007)	WT	Prof. Rudolf Jaenisch's Lab, M.I.T. USA (sponsored by Sir Henry Wellcome Post-doc Fellowship)
Mila Roode (2007)	WT	Research Scientist at Crescendo Biologics, Ltd, Cambridge, UK
Ornella Barrandon (2007)	Self-funded	Post-doc in Prof. Douglas Melton's Lab, Harvard University, USA
Kathryn Blair (2007)	Gates Foundation	Bench Biologist at Seven Bridges Genomics, Massachusetts
Alexander Goncharevich (2008)	WT	Posdoctoral researcher in Robin Franklin's lab at the University of Cambridge
Gloryn Chia (2008)	WT	Applying for post-doc positions
Jamie Trott (2008)	WT	Postdoctoral Felllow, Institute of Molecular Biology, Singapore
Nils Grabole (2008)	WT	Postdoctoral Fellow, Roche, Basel, Switzerland
Claire Cox (2008)	MRC	Postdoc Fellow in Professor Connie Eaves lab, BC Cancer Agency, Vancouver, Canada
Hayley Frend (2009)	WT	PhD extension until March 2014
Nicola Love (2009)	WT	Applying for post-doc positions
Paulina Chilarska (2009)	WT	Applying for post-doc positions
Robert Fordham (2009)	MRC	Research Scientist/Postdoctoral Research Fellow in Prof. Owen Sansom's lab at The Beatson Institute for Cancer Research, Glasgow (starting Jan-2014)
Jason Signolet (2009)	MRC	Research assistant, Brian Hendrich's lab at the Stem Cell Institute, Cambridge
Jignesh Tailor (2009)	BRC	Specialty Registrar in Neurosurgery in London
Marta Lesko (2009)	MRC	Research Associate in Prof Fiona Watts' lab, King's College London
Aliaksandra Radzisheuskaya (2010)	Darwin Trust	Post-doc in Jose Silva's lab at the Stem Cell Institute, Cambridge
Sarah Putwain (2010)	WT	Veterinary Clinical Pathologist at PTDS Ltd., UK
Harry Leitch (2011)	Merck, Sharp & Dohme	Clinical Medicine

2013 Publications

Research Reports

Oram SH, Thoms J, Sive JI, Calero-Nieto FJ, Kinston SJ, Schütte J, Knezevic K, Lock RB, Pimanda JE, Gottgens B. Bivalent promoter marks and a latent enhancer may prime the leukaemia oncogene LMO1 for ectopic expression in T-cell leukaemia. Leukemia. PMID:23302769

Leitch HG, McEwen KR, Turp A, Encheva V, Carroll T, Grabole N, Mansfield W, Nashun B, Knezovich JG, Smith A, Surani MA, Hajkova P. Naive pluripotency is associated with global DNA hypomethylation. Nature Structural & Molecular Biology. PMID:23416945

Costa Y, Ding J, Theunissen TW, Faiola F, Hore TA, Shliaha PV, Fidalgo M, Saunders A, Lawrence M, Dietmann S, Das S, Levasseur DN, Li Z, Xu M, Reik W, Wang J, Silva JCR. NANOG-dependent function of TET1 and TET2 in establishment of pluripotency. Nature. PMID:23395962

Ferreira R, Spensberger D, Silber Y, Dimond A, Li J, Green AR, Gottgens B. Impaired In Vitro Erythropoiesis Following Deletion of the Scl/Tal1 +40 Enhancer Is Largely Compensated In Vivo Despite Significant Reduction in Expression. Molecular and Cellular Biology. PMID:23319051

Diffner E, Beck D, Gudgin E, Thoms JA, Knezevic K, Pridans C, Foster S, Goode D, Lim WK, Boelen L, Metzeler KH, Micklem G, Bohlander SK, Buske C, Burnett A, Ottersbach K, Vassiliou GS, Olivier J, Wong JW, Göttgens B, Huntly BJ, Pimanda JE. Activity of a heptad of transcription factors is associated with stem cell programs and clinical outcome in acute myeloid leukemia. Blood. PMID:23327922

L'episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Impagnatiello F, Pluchino S, Marchetti B. Aging-Induced Nrf2 -ARE Pathway Disruption in the Subventricular Zone Drives Neurogenic Impairment in Parkinsonian Mice via PI3K-Wnt/β-Catenin Dysregulation. Journal of Neuroscience. PMID:23345222

Sharma NL, Massie CE, Ramos-Montoya A, Zecchini V, Scott HE, Lamb AD, MacArthur S, Stark R, Warren AY, Mills IG, Neal DE. The Androgen Receptor Induces a Distinct Transcriptional Program in Castration-Resistant Prostate Cancer in Man. Cancer Cell. PMID:23260764

Carri AD, Onorati M, Lelos MJ, Castiglioni V, Faedo A, Menon R, Camnasio S, Vuono R, Spaiardi P, Talpo F, Toselli M, Martino G, Barker RA, Dunnett SB, Biella G, Cattaneo E. Developmentally coordinated extrinsic signals drive human pluripotent stem cell differentiation toward authentic DARPP-32^{+} medium-sized spiny neurons. Development. PMID:23250204

Barker RA, Mason SL, Harrower TP, Swain RA, Ho AK, Sahakian BJ, Mathur R, Elneil S, Thornton S, Hurrelbrink C, Armstrong RJ, Tyers P, Smith E, Carpenter A, Piccini P, Tai YF, Brooks DJ, Pavese N, Watts C, Pickard JD, Rosser AE, Dunnett SB; the NEST-UK collaboration. The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. Journal of Neurology, Neurosurgery and Psychiatry. PMID:23345280

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Diapause blastocyst

Image: Jenny Nichols/ Peter Humphreys

SCI Review created by:
SCI Coordinator: sci-coordinator@stemcells.cam.ac.uk
SCI Records: sci-records@stemcells.cam.ac.uk