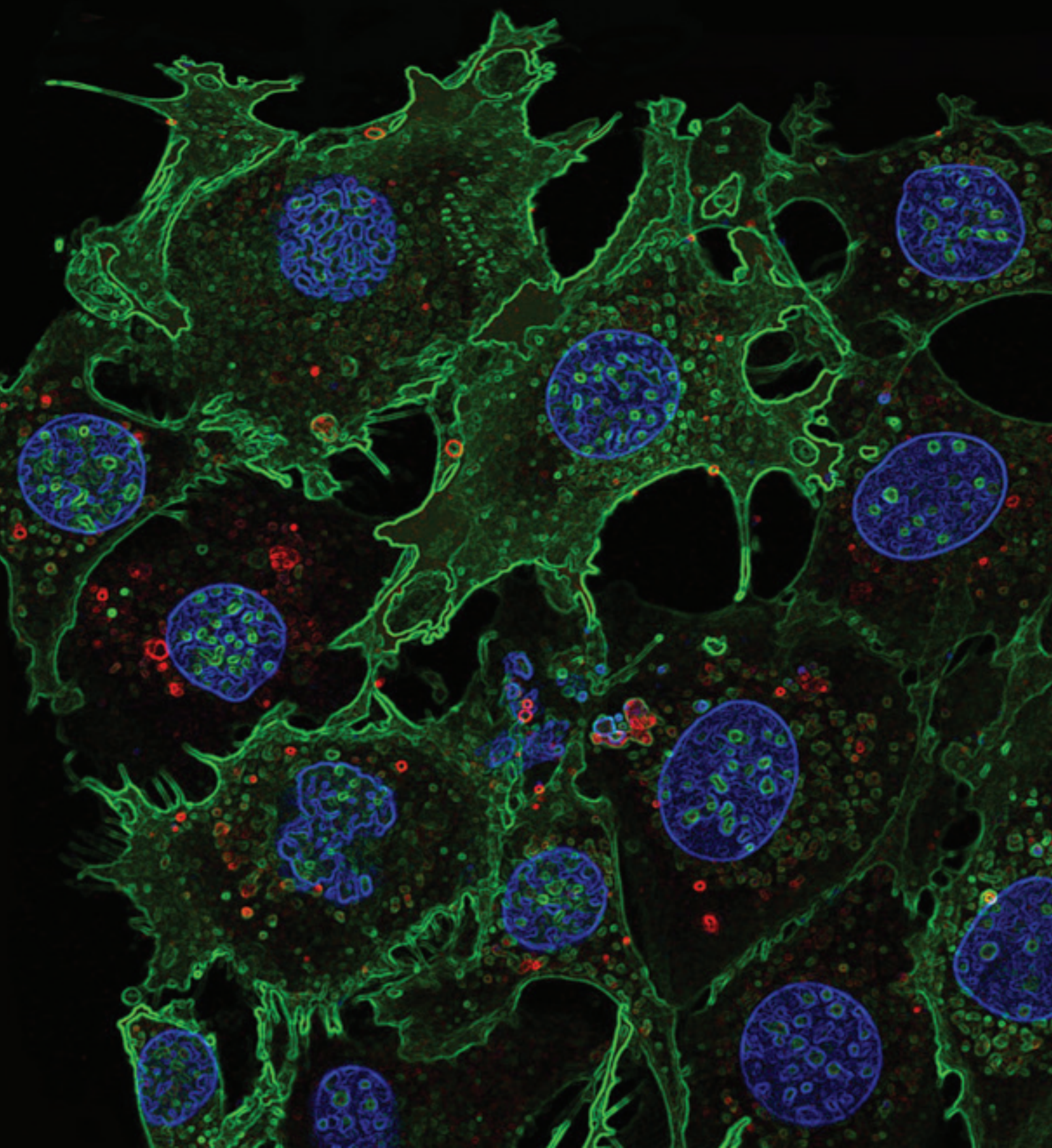
Wellcome Trust - Medical Research Council

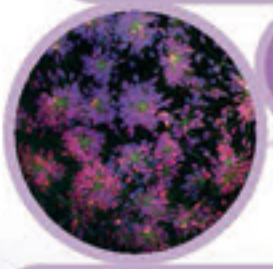
Cambridge Stem Cell Institute

2014

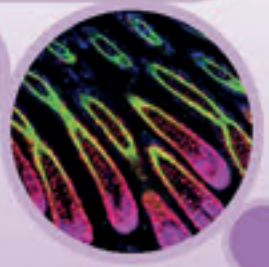


Wellcome Trust - Medical Research Council
Cambridge Stem Cell Institute

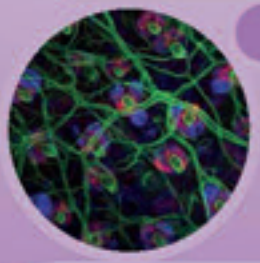
World-leading Institute for stem cell biology and medicine



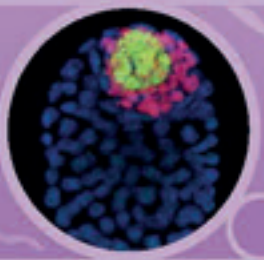
Exploring and defining the properties of stem cells to establish their true medical potential



Cross-disciplinary collaborations between physics, biology and medicine



25 outstanding research teams



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, public engagement and outreach to provide accurate information and valued resources for a range of audiences including schools, patient groups, professional bodies, policy makers and the media.

Austin Smith
Institute Director

The Institute

Stem Cell Research and Medicine

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 prevent or correct these faults.
- Stem cells can be used to renew damaged tissues and replace cells lost in disease.
- Learning how to prevent a decline in numbers and activity of stem cells may help to maintain health during ageing.

Facilities and Resources

Specialist scientists provide cutting edge technology and research resources:

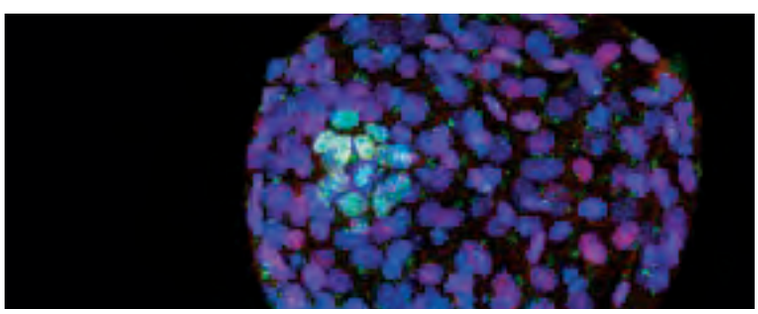
- Bioinformatics
- Flow Cytometry
- Histopathology
- Advanced Light Microscopy
- Next Generation Sequencing Libraries
- Tissue Culture
- Tissue Samples
- Biomedical models

Research Themes

SCI research encompasses both pluripotent (embryonic) stem cells and adult tissue stem cells spanning from fundamental biology to clinical trials. Four research themes correspond to the major stem cell types:

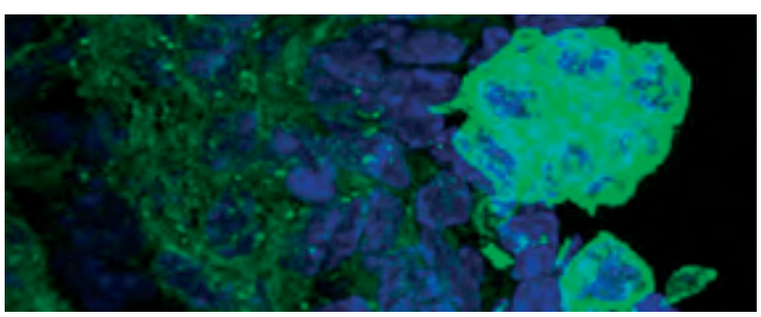
Pluripotent stem cells can be derived from early embryos, produced by epigenetic conversion of germ cells, or created by transcription factor mediated reprogramming of somatic cells. Investigations are directed at the molecular foundations of pluripotency, comparative analyses between rodent and human, and mechanisms of lineage-specific differentiation and cellular reprogramming. This theme intersects with those below, in particular as a source of human cell types derived from both normal subjects and patients.

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



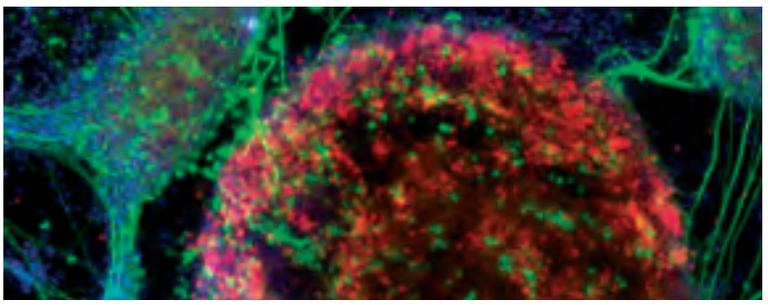
Haematopoietic stem cells represent the best studied adult mammalian stem cell system and provide paradigms for both cell replacement therapies and targeting mechanisms whereby normal stem and progenitor cells are subverted to form malignancies. The goal of this theme is to delineate the molecular and cellular mechanisms regulating normal and malignant haematopoiesis. Complementary use of human clinical genetics and transgenic mouse models is a particular strength.

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



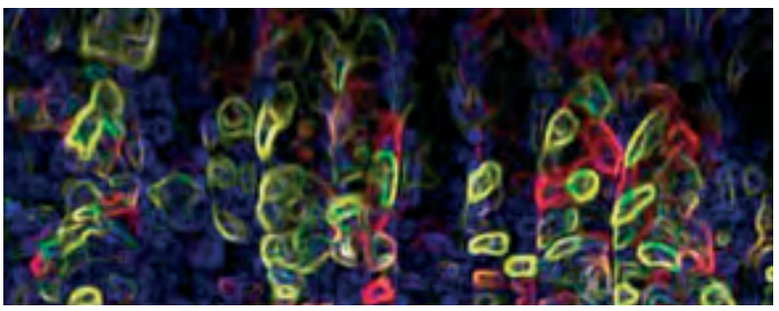
Neural stem cells offer prospects for cell replacement and regeneration in the central nervous system (CNS). Neuronal loss can occur as a result of (i) cell autonomous defects, (ii) inflammation and (iii) loss of trophic support from glial cells. Stem cell biology is brought to bear on all three causes, from basic studies focusing on the homeostasis and recruitment of endogenous stem cells to therapeutic transplantation of stem cell progeny. In addition, reprogramming is exploited to generate patient- and disease-specific neurons and glia and create human cell-based models of neurodegenerative diseases. These models serve as a platform for elucidation of molecular pathomechanisms and for identifying and validating pharmaceutical agents.

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



Epithelial and solid tissue stem cells underpin renewal and repair. Homeostasis is perturbed in disorders such as psoriasis, emphysema and COPD, while epithelial cancers account for 90% of human tumours. In vitro and in vivo approaches are used to identify and characterise stem cells in developing, adult and cancerous epithelia, in particular skin, gut and stomach, and in epithelial organs such as liver and pancreas where they may be obtained from primary tissue or via differentiation of pluripotent stem cells. Bone and cartilage are an additional component of this theme, relevant to joint repair and osteoarthritis.

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



The Stem Cell Institute

The Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute (SCI) was officially established on 1st July 2012. The Institute is supported by a strategic funding partnership between the University of Cambridge, the Wellcome Trust and the Medical Research Council.

World-leading research scientists, technology specialists and doctors work side by side to create one of the world's premiere centres of excellence in stem cell biology and medicine. There are currently 25 mainstream stem cell laboratories led by scientists and clinician-scientists, comprising more than 300 group members including post-doctoral researchers and PhD students.

SCI takes full advantage of the rich intellectual environment in Cambridge by offering affiliate status to collaborating scientists and clinicians in other institutes and departments. SCI also provides high level training for young researchers from around the world and invites collaborations with bioindustry.

Location

The Stem Cell Institute has laboratories at three major locations - the Gleeson Building in the centre of Cambridge, the Ann McLaren Laboratory and the Clifford Allbutt Building at the Cambridge Biomedical Campus (Addenbrooke's hospital site). Stem cell groups are also housed in the Cambridge Institute for Medical Research (CIMR), Gurdon Institute and the Brain Repair Centre (BRC). This distribution reflects the intellectual diversity of the Cambridge stem cell community and the breadth of institutional support. However, coalescence of basic stem cell research and clinical translation is key to development of medical applications. In recognition of this, from 2018 the entire Institute will be housed in a new research building on the hospital campus.

2014 Progress Report

DEEP UNDERSTANDING OF STEM CELL BIOLOGY FOR THE PREVENTION AND TREATMENT OF HUMAN DISEASE

The Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute is a world-leading centre for stem cell biology and medicine formed by drawing research strengths across Cambridge into a single Institute.

New knowledge and understanding of the biology of stem cells provide the potential for developing improved medical diagnostics and treatments. Meeting this challenge is at the heart of the Stem Cell Institute mission. Translation from discovery into application means building collaborative teams with clinicians and with bioindustry. Provision of high-level training for young researchers from around the world and mentoring for junior team leaders is a further key component of our mission.

New Developments during 2014

Robin Franklin took up the University Professorship of Stem Cell Medicine and the post of the Head of Translational Science in the Stem Cell Institute from 1st January 2014. Robin's research is centred on regenerative biology and in particular the role of progenitor cells in remyelination in diseases such as multiple sclerosis. Robin has established his research group in **newly refurbished Stem Cell Institute laboratories in the Clifford Allbutt Building** on the Addenbrooke's biomedical campus.

Joining Robin in the Clifford Allbutt Building is **new Group Leader Elisa Laurenti** who joined SCI in September 2014. Elisa is studying the functional properties and molecular circuits of human blood stem cells in health and disease. Following our annual open call and interviews, further candidates have been selected to join SCI as Group Leaders in 2015.

A **Translational Science Working Group** set up by Robin Franklin convened regularly to oversee and promote clinical translation of SCI research, involving both collaboration within the institute and outreach to the Clinical School, hospital and bioindustry. Following the recruitment of Andrew McCaskie to the University Chair of Orthopaedic Medicine the group recommended the adoption of a new translational programme in **musculoskeletal and orthopaedic regenerative medicine**.

Brian Huntly commenced a **Phase I clinical trial** "A dose escalation study to investigate the safety, pharmacokinetics (PK), pharmacodynamics (PD) and activity of GSK525762 in subjects with relapsed, refractory haematological malignancies". Brian is academic chief investigator for this multi-centre international study sponsored by GSK and involving 4 centres - Cambridge, Imperial (London), Memorial Sloan Kettering Cancer Centre (New York) and the MD Anderson (Houston).

The **Pluripotent Stem Cell Platform (PSCP)** hub of the UK Regenerative Medicine Platform commenced operations in 2014. PSCP is a partnership between SCI, Sheffield University, Loughborough University and the National Institute for Biological Standards and Controls. The hub is focused on technology for manufacturing human stem cells suitable for clinical application. The Project Manager, Dr Philip Driver is based at the SCI along with a team of two post-doctoral scientists and two research assistants (http://www.ukrmp.org.uk/hubs/pscp/).

Publications

During the calendar year 2014, SCI groups published 129 papers. 85 of these papers appeared in journals with impact factors greater than 5.0, including *Nature, Science, Cell, EMBO Journal, Cell Stem Cell, Blood, Development, Nature Medicine and The Lancet Neurology*. Twenty-one of these publications are collaborations between two or more SCI groups. Clinicians are authors on 48 papers. In total, 107 (83%) articles are open access and of the 72 research reports, 64 are open access (89%).

Patents and Licensing

Roger Pedersen and colleagues filed a Patent application: "In Vitro Mesodermal Differentiation", a chemically-defined, 2-dimensional directed differentiation of human pluripotent stem cells into cardiomyocytes and chondrocytes. The Smith Lab filed on: "Resetting pluripotent stem cells"; Guo G, Smith AG, Takashima Y. GB1414992.6; filed August 22nd 2014 and GB1415368.8 filed August 29th 2014. Thora Karadottir licensed through Cambridge Enterprise - MEMO/NEMO/SOS, Media for light stimulations.

Awards and Prizes

Azim Surani was awarded a Jawaharlal Nehru Science Fellowship and the 2014 McEwen Award for Innovation by the International Society for Stem Cell Research. Ben Simons was awarded the Franklin Medal and Prize from the Institute of Physics. Robin Franklin received the International Canine Health Award. Bertie Göttgens was elected as a Fellow of the Academy of Medical Sciences.

Several fellowships were awarded this year to SCI postdoctoral researchers, including a Next Generation Fellowship from the Centre for Trophoblast Research to Sarra Achouri (Chalut lab), BIRAX Fellowship awarded to Ofra Zidon (Franklin lab), Lady Tata Fellowship to Paolo Gallipoli (Huntly Lab) and an EMBO Long-Term Fellowship to Wolfram Gruhn (Surani Lab).

Several SCI post-docs and students were selected to speak at international meetings. Notably at the International Society for Stem Cell Research (ISSCR) Annual Meeting, David Kent, Jan Zylicz and Filipa Soares were invited to give talks.

Career Progression

SCI Group Leader Jenny Nichols was promoted to University Reader. José Silva was promoted to Principal Research Associate. Kim Jensen moved on from SCI to an Associate Professorship in the BRIC at the University of Copenhagen. Juan-Jose Ventura took up a position as Associate Professor at the University of Leuven, Faculty of Medicine.

Among post-docs moving on from SCI, Shobbir Hussain was appointed to a Lectureship in Molecular Genetics of Disease at the University of Bath, Graziano Martello took up a Faculty position at the University of Padua and Mark Dawson moved to the Peter Macallum Centre in Melbourne. Several of our researchers transferred to positions in industry including David Ruau (Astra Zeneca), Iwona Driskell (Axol Bioscience), John Stockley (MedImmune) and Gillian Tannahill (GSK Immunology).

PhD Programme

In 2014 the SCI had a total of 79 students, 16 of those clinically trained. Eight students in SCI laboratories successfully defended their PhD theses. SCI PhD students are authors on 44 published papers, on 21 as first author. The annual PhD Day on 22nd July was organised by the students and in addition to oral and poster presentations of their research, a careers discussion was held with invited guests, including former SCI PhD graduates. The PhD students organise a bi-weekly informal seminar and discussion club where they present to their peers.

Research Funding

In 2014, SCI held active research grants to the value of £72 million with annual expenditure of £13,822,228.
During the year 22 new grants were awarded to SCI investigators. Among these, José Silva received a Wellcome Trust Senior Research Fellow award for £1.8 million and Tony Green a Wellcome Trust Senior Investigator Award for £1.9 million. Roger Barker led a team awarded £1 million by MedImmune, while Alan Warren was awarded a £1.6 million grant from the MRC.

Administration

The SCI Administrator, Lynn Kennedy, retired on the 4th September 2014 and will be sorely missed. Jane Muir has provided temporary cover for this post. Jenny Nelder transferred from the position of SCI Coordinator to Project Manager for the EC FP7 Project PluriMes on 1st February 2014. The Coordinator post was unfilled for the rest of 2014 but an appointment has finally been made to start in February 2015.

Resources

The Göttgens group and SCI core bioinformaticians created **CODEX**, a next-generation sequencing experiment database comprised of haematopoietic (HAEMCODE) and embryonic stem cell (ESCODE) repositories (Sánchez-Castillo M, Ruau D, Wilkinson AC, Ng FS, Hannah R, Diamanti E, Lombard P, Wilson NK, Gottgens B. "CODEX: a next-generation sequencing experiment database for the haematopoietic and embryonic stem cell communities". *Nucleic Acids Research.* PMID: 25270877) - http://codex.stemcells.cam.ac.uk/

The SCI has new live cell high-throughput imaging equipment (Biostation) allowing for detection of morphological parameters and multiple markers in the same cell. In addition an InCell analyser will assist researchers with high-throughput image based cytometry and assay based analysis.

The Flow Cytometry facility has equipped the MoFlo cell sorter with fast tuneable infrared femtosecond pulse laser systems that are configured to frequency double. This allows a much bigger spectrum of fluorescent dyes to be detected and sorted, and is highly sensitive. For example, the fluorescent protein mTurquoise expressed in low numbers in a cell line has been detected and positive cells isolated successfully. The Stem Cell Institute MoFlo sorter is unique in this capability, opening up new avenues of fluorescent dye detection for protein/gene expression for our scientists .

The secure intranet for SCI members enables exchange of data and protocols and is used for core facility bookings. The PhD student and post-doctoral communities now have dedicated sections of the website for communicating their activities and matters of interest.

Events

The fourth **Cambridge Stem Cell Institute International Symposium** on the theme of "**Stem Cells in Medicine**" was organised by Robin Franklin, Rick Livesey and Roger Barker. The meeting was organised into three sessions: stem cells and regeneration, stem cells and disease modelling and stem cells and malignancy. Scientists and clinician scientists who are leading experts in their field gave an outstanding series of talks about how they are bringing new tools and insights to stem cell medicine. An emerging theme was how stem cell biology is impacting on the understanding of disease and potential therapies beyond the concept of cell replacement therapy (http://www.stemcells.cam.ac.uk/news-events/events/2014symposium).

The **Cambridge Stem Cell Club** evening meetings continued on a monthly basis throughout the year. The meetings consist of three short research talks followed by refreshments. The Club provides a lively and popular forum for scientific interchange and networking and attracts a diverse range of attendees. The presenters are a mixture of SCI investigators plus occasional visiting scientists. In addition, the SCI seminar series features both internal and

external speakers throughout the year.

SCI group leaders initiated a series of monthly "**chalk talks**" for informal discussion and feedback on their research plans and ideas.

SCI holds a two-day **Annual Meeting** each December for all members and Affiliates. The programme in 2014 included scientific talks, poster presentations, public engagement training, interactive workshops and discussion sessions. The International Scientific Advisory Board, the Wellcome Trust and the MRC attended the meeting as a part of the Institute's annual review.

SCI Affiliates

Affiliates are scientists who have close research links with SCI. They participate in various institute activities and can be supervisors in the Stem Cell Biology and Medicine PhD programme (http://www.stemcells.cam.ac.uk/researchers/affiliate-investigators/). Andrew McCaskie (Professor of Orthopaedics, Department of Surgery) and Meritxell Huch who works on liver stem cells in the Gurdon Institute were welcomed as new affiliates in 2014.
Sadly SCI Affiliate Jenny Pell passed away during 2014.

Research Associate Committee

SCI post-doctoral researchers came together to form a committee aimed at improving networking among the post-docs and supporting professional development. During 2014 the SCI Research Associate Committee organised a range of scientific interdisciplinary seminars, career development events, networking and social activities for post-docs and the whole SCI. These events bring together researchers from different locations of SCI and had a high level of attendance with more than 100 participants at the biggest events, thereby playing a major role in strengthening the SCI community.

Communication and Public Engagement

The Stem Cell Institute website (**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. In 2014 the site attracted over 86,526 visits (1,663 visits per week), of which 48,067 were unique visitors. SCI's Twitter feed now has 180 followers, while its new Facebook page has 377 'Likes'.

Research Horizons, the University of Cambridge publication on current research highlights, featured a spotlight on stem cells with several articles from SCI investigators.

The absence of an **SCI Coordinator** for most of the year reduced capacity for communications and outreach. Nonetheless, a **weekly email bulletin** was launched to supplement the Institute's **bi-monthly newsletter** and improve communication at all levels across SCI. These communications contain information about internal SCI developments, events, funding and achievements by SCI staff and have been well received by staff. A new Coordinator has now been appointed and will start in February 2015.

SCI continued to support a wide range of public engagement events in 2014. The SCI Director and Dr Bertie Göttgens presented at the Cambridge Literary Festival. The Director gave interviews with Time magazine, The Guardian, and Science, among others. Rick Livesey appeared on the BBC's 'Bang Goes the Theory'. Roger Barker and Michaela Frye were invited as expert speakers to a **House of Lords cross-parliamentary meeting** in July 2014. Robin Franklin gave a series of radio interviews for the BBC in October, and gave the keynote lecture at this years MS Life, the annual meeting of members of the MS Society. The Institute also offered four public lectures as part of the Cambridge Science Festival, with talks by Robin Franklin, Kevin Chalut, Roger Barker and José Silva. PhD students organised drop-in activities during this same festival and for the Big Biology Day. The Institute also hosted public tours as part of the University's Science and Alumni Festivals. Furthermore, SCI was successful in applying to the Wellcome Trust for a full-time **Public Engagement Officer**. This post will be filled from end of January 2015.

SCI highlighted its commitment to public engagement by providing a training workshop for all research staff at the 2014 Annual Meeting. This was led by the University's Head of Public Engagement.

New Stem Cell Institute Building - Project Capella

The new building to house all of the SCI groups is on track to open at the beginning of 2018. The architects and construction company have been appointed and Stage 2 of the construction design began in October 2014. The building will be on the Addenbrooke's Hospital biomedical research campus which will facilitate translational interactions.

Athena Swan

The Stem Cell Institute at the Gleeson Building has submitted its application for the Bronze Athena SWAN award in November 2014. We will hear the outcome in Spring 2015.

Scientific Highlights

- Roger Barker took the lead in establishing a global task force to take stem cell therapies to the clinic in Parkinson's disease.

  ⇒ Reported by Alison Abbott in "Fetal-cell revival for Parkinson's". *Nature*. PMID: 24919900.

- Kevin Chalut discovered an unusual mechanical property of the nucleus in embryonic stem cells undergoing differentiation.

  ⇒ Pagliara S, Franze K, McClain CR, Wylde GW[S], Fisher CL, Franklin RJM, Kabla AJ, Keyser UF, Chalut KJ. "Auxetic nuclei in embryonic stem cells exiting pluripotency". *Nature Materials.* PMID: 24747782.
  [S] SCI Student author.

- The Franklin lab in collaboration with the laboratory of Catherine Lubetzki in Paris described how the gene expression profile of neural progenitors changes as these cells convert from a developmental stage to an adult stage and how, on demyelinating injury in the adult, they revert to a developmental state. This work will be published in January 2015 in the Journal of Neuroscience .

- Michaela Frye linked cellular stress responses cause by tRNA cleavage to neurodevelopmental disease in human.

  ⇒ Blanco S, Dietmann S, Flores JV[S], Hussain S, Kutter C, Humphreys P, Lukk M, Lombard P, Treps L, Popis M[S], Kellner S, Hölter SM, Garrett L, Wurst W, Becker L, Klopstock T, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Káradóttir RT, Helm M, Ule J, Gleeson JG, Odom DT, Frye M. Aberrant methylation of tRNAs links cellular stress to neuro-developmental disorders. *The EMBO Journal*. PMID: 25063673

- Bertie Göttgens' team reported genome-wide binding profiles for 10 transcription factors (TFs) in blood progenitors and mast cells, and showed through a combination of experimental and computational modelling approaches that (i) differential binding of shared TFs is predictive of differential gene expression, (ii) cell-type specific TFs may reorganise global binding profiles of shared TFs, and (iii) cell-type specific binding of shared TFs is not predominantly opportunistic.

  ⇒ Calero-Nieto FJ, Ng FS[S], Wilson NK, Hannah R, Moignard V[S], Leal-Cervantes AI[S], Jimenez-Madrid I, Diamanti E, Wernisch L, Göttgens B. "Key regulators control distinct transcriptional programmes in blood progenitor and mast cells". *The EMBO Journal*. PMID: 24760698. The paper was accompanied by a commentary by Eric Davidson: "The uncommon roles of common gene regulatory factors in the genomes of differentiating cells". The EMBO Journal. PMID: 24788410
  [S]SCI Student author.

- Jenny Nichols in collaboration with Paul Bertone showed functional and molecular identity between embryonic stem cells in vitro and newly formed epiblast in the mouse pre-implantation embryo.

  ⇒ Boroviak T, Loos R, Bertone P, Smith A, Nichols J. The ability of inner-cell-mass cells to self-renew as embryonic stem cells is acquired following epiblast specification. *Nature Cell Biology*. PMID: 24859004

- The Silva lab in collaboration with Brian Hendrich demonstrated that the transcriptional regulator NuRD is required for the efficient generation of iPSCs. In addition, its enhanced activity can further boost the generation of iPSCs. This demonstrates that NuRD, an essential DNA regulator for the generation of specialised cells such as skin and brain cells, is also key to the reversion of the specialised cells back into an early embryonic state (iPSCs).

  ⇒ Santos R[S], Tosti L, Radzisheuskaya A, Caballero I, Kaji K, Hendrich B, Silva JCR. Mbd3/NuRD facilitates induced pluripotency in a context dependent manner. *Cell Stem Cell*. PMID: 24835571
  [S] SCI Student author.

- Radial glial progenitors (RGPs) are responsible for generating neurons and glia in the mammalian neocortex. However, the kinetics and division pattern of RGPs remains largely unknown. Ben Simons in collaboration with Luo, Hippenmeyer and Shi showed that RGPs progress through a remarkably orderly deterministic program of proliferation, neurogenesis and gliogenesis. During the neurogenic phase, individual RGPs produce a unitary output of around 8-9 neurons located in both superficial and deep layers, suggesting a

quantal nature of neuronal production in neocortical histogenesis.

⇒ Gao P, Postiglione MP, Krieger TG, Hernandez L, Wang C, Han Z, Streicher C, Papusheva E, Insolera R, Chugh K, Kodish O, Huang K, Simons BD, Luo L, Hippenmeyer S, Shi S-H. Deterministic progenitor behavior and unitary neuron production in the neocortex. *Cell*. PMID: 25417155

- Austin Smith's group collaborated with Microsoft Research to development a powerful new computational modelling method. The successful conjunction of computation and experimentation enabled the authors to identify a potential minimal transcription factor circuitry that determines embryonic stem cell self-renewal.

⇒ Dunn SJ, Martello G, Yordanov B, Emmott S, Smith AG. Defining an essential transcription factor program for naïve pluripotency. *Science*. PMID: 24904165

- Ludovic Vallier and groups at the Sanger Institute provided evidence that transcriptional variability between human Induced Pluripotent Stem Cell lines mainly originates from their genetic background. These results suggest that the phenotypic diversity frequently observed between hIPSC lines could be representative of their genomic diversity. Thus, hIPSCs could provide a unique system to study human genetics in vitro.

⇒ Rouhani F, Kumasaka N, de Brito MC[S], Bradley A*, Vallier L*, Gaffney D* (2104). Genetic background drives transcriptional variation in human induced pluripotent stem cells. *PLoS Genetics*. PMID: 24901476
*joint corresponding authorship
[S] SCI Student author

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
Stem Cell Homeostasis & Disease

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 and Leukaemogenesis

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

Elisa Laurenti
Human Hematopoietic Stem Cells in Health and Disease

Rick Livesey
Human stem cell models of dementia

Jennifer Nichols
Embryonic Pluripotency

Katrin Ottersbach
The Developmental Origins of Blood Stem Cells

Roger Pedersen
Mechanics of Mesoderm Differentiation in Mammalian Pluripotent Stem Cells

Stefano Pluchino
Stem Cell Signalling and Brain 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

Alan Warren
Mechanisms of Ribosome Assembly & Stem Cell Subversion

Roger Barker

Roger 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 since 2000, after completing a MRC Clinician Scientist Fellowship.

Roger combines basic research looking at novel therapies to treat chronic neurodegenerative disorders of the brain with clinically-based work aimed at better defining such disorders. He is the co-ordinator of the FP7 TRANSEURO project looking at fetal cell grafting in patients with early Parkinson's Disease.

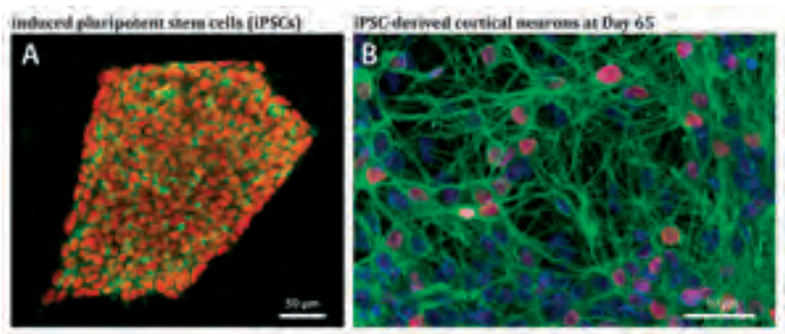
Funding

Swedish MRC
The Evelyn Trust
MRC
EC FP7
MedImmune
NIHR

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.

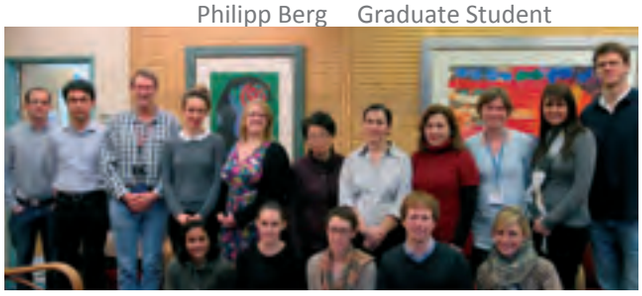
These new therapies involve not only cell based treatments as well as other novel approaches that try to stop or modify the disease process itself. This we are now trying to do, using the cells of patients which we collect from the skin and then turn into nerve cells in the lab. Through this we hope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



Patient-specific induced pluripotent stem cells (iPSCs) allow to capture the genetic background in which a particular disease occurs.

Group Members

Wei-Li Kuan	Postdoc Researcher
Alexandra Fragniere	Postdoc Researcher
Romina Vuono	Postdoc Researcher
Fahad Ali	Postdoc Researcher
Simon Stott	Postdoc Researcher
Janelle Drouin-Ouellet	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
Caroline Williams Gray	Clinical Lecturer
Lindsey Wilkin	Clinic Coordinator
Kirsten Scott	Graduate Student
Ruwani Wijeyekoon	Graduate Student
Katie Hall	Postdoc Researcher
Laetitia Swabb	Graduate Student
Philipp Berg	Graduate Student



2014 Publications

Choi ML, Begeti F, Oh JH, Lee SY, O'Keeffe GC, Clelland CD, Tyers P, Cho ZH, Kim YB, Barker RA. Dopaminergic manipulations and its effects on neurogenesis and motor function in a transgenic mouse model of Huntington's disease. Neurobiology of Disease. PMID: 24561069

Buttery PC, Barker RA. Treating Parkinson's disease in the 21st century: can stem cell transplantation compete? Journal of Comparative Neurology. PMID: 24610597

Moore SF, Guzman NV, Mason SL, Williams-Gray CH, Barker RA. Which Patients with Parkinson's Disease Participate in Clinical Trials? One Centre's Experiences with a New Cell Based Therapy Trial (TRANSEURO). Journal of Parkinson's Disease. PMID: 25170676

Ali FR, Cheng K, Kirwan P, Metcalfe S, Livesey FJ, Barker RA, Philpott A. The phosphorylation status of Ascl1 is a key determinant of neuronal differentiation and maturation in vivo and in vitro. Development. PMID: 24821983

Zhao JW, Dyson SC, Kriegel C, Tyers P, He X, Fahmy TM, Metcalfe SM, Barker RA. Modelling of a targeted nanotherapeutic 'stroma' to deliver the cytokine LIF, or XAV939, a potent inhibitor of Wnt-β-catenin signalling, for use in human fetal dopaminergic grafts in Parkinson's disease. Disease Models & Mechanisms. PMID: 25085990

Cicchetti F, Barker RA. The glial response to intracerebrally delivered therapies for neurodegenerative disorders: is this a critical issue? Frontiers in Pharmacology. PMID: 25071571

Barker RA, Cicchetti F. Neurodegenerative disorders: the Glia way forward. Frontiers in Pharmacology. PMID: 25076908

Barker RA. Developing stem cell therapies for Parkinson's disease: waiting until the time is right. Cell Stem Cell. PMID: 25517462

See page 61 for additional publications from the Barker group

Collaborations

Ernest Arenas	Karolinska Institute - EU FP7 grant DDPD genes- defining genes involved in dopamine differentiation and loss in PD
Tilo Kunath	Centre for Regenerative Medicine - MRC grant to make GMP grade dopamine cells from hES cells
Malin Parmar	Lund University - Disease modelling with iN cells
Anders Bjorklund	Lund University - Neural grafting in PD and disease modelling in PD
Elena Cattaneo	University of Milan - Striatal development in the human and the making of MSNs from hES cells
With SCI Members	
Austin Smith	Multiple projects using fetal tissue for the generation of different types of stem cells
Rick Livesey	Diseases modelling of PD dementia
Ludovic Vallier	iPS cell generation from patients
Anna Philpott	Improved iN generation

Policy Briefings

House of Lords cross party parliamentary meeting, July 2014, Speaker/ Discussant

Public Engagement

Event	Format	Date	Participation	Name
Kings College, London	Public Talk	01/2014	Speaker	Barker
Public Lecture, Bedford School	Public Lecture	02/2014	Speaker	Barker
Newark Parkinson's UK Branch	Public Talk	02/2014	Speaker	Barker
Parkinson's UK	Public Talk	03/2014	Speaker	Barker
Science Festival Talk "What Can Stem Cells Do for Parkinson's	Public Talk	03/2014	Speaker	Barker
Institute of Neurology Stem Cell	Public Talk	03/2014	Speaker	Barker
Open Day for Patients	Public Talk	10/2014	Presenter	Barker, Collins
The Naked Scientist	Radio show & Podcast	09/2014	Speaker	Metcalfe

The Physical Biology of Pluripotency and Differentiation

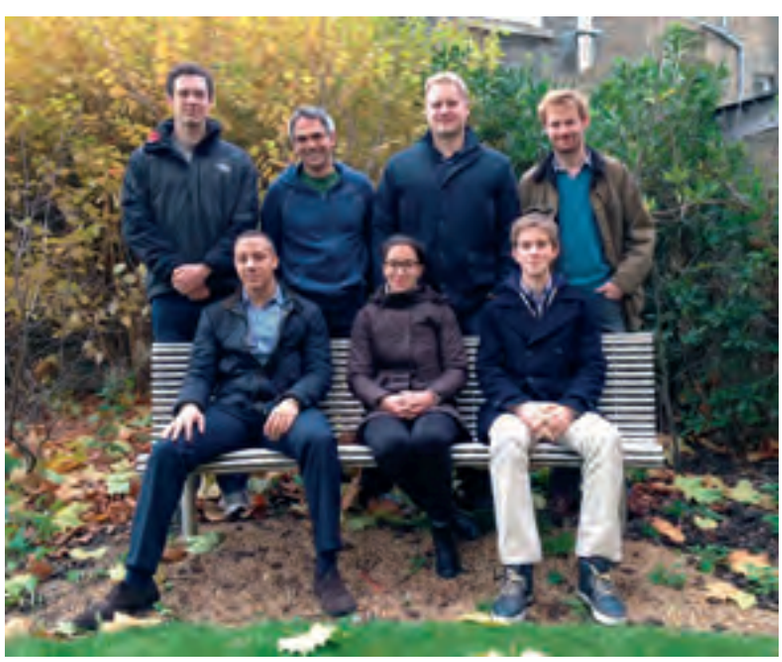
The transformation of a stem cell system into mature tissue cells consists of a progression of highly regulated steps. Despite its importance both for bringing comprehension to the formation of the embryo and also for regenerative medicine purposes, the ways in which the process of differentiation are 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 remodelling 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 are investigating the role of cell-cell adhesion and cell-matrix adhesion in cellular reprogramming

Image: Chibeza Agley

Group Members

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
Cynthia Fisher	Postdoc Researcher



Kevin Chalut

Kevin Chalut is a biophysicist with a PhD in Physics from Duke University. Since 2011 he has been a Royal Society University Research Fellow. Kevin's post-graduate background is in biotechnology and imaging, particularly with regards to detecting cancer and characterising stem cells. He is currently a group leader at both 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 few years he has focused almost exclusively on the biophysics of embryos and embryonic stem cells. The ultimate goal of his laboratory is to discover physical mechanisms and their importance to pluripotency, differentiation and reprogramming

Funding

The Royal Society
Leverhulme Trust
Medical Research Council
Newton Trust

Fellowships

Sarra Achouri — Centre for Trophoblast Research Next Generation Fellowship

2014 Publications

Pagliara S, Franze K, McClain CR, Wylde GW, Fisher CL, Franklin RJ, Kabla AJ, Keyser UF, Chalut KJ. Auxetic nuclei in embryonic stem cells exiting pluripotency. Nature Materials. PMID: 24747782

Chalut KJ, Janmey PA. Clamping down on tumor proliferation. Biophysical Journal. PMID: 25418157

Key Publications prior to 2014

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

Ulrich Keyser	University of Cambridge - Developed microfluidics for stem cell analysis, recent paper in Nature Materials, submitted BBSRC research grant
Kristian Franze	University of Cambridge - AFM analysis of stem cells, recent paper in Nature Materials, collaborator for Leverhulme Trust grant
Berenika Plusa	University of Manchester - Physical biology of early embryogenesis, collaboration on Leverhulme Trust research grant
Stefano Pagliara	University of Exeter - Developed microfluidics for stem cell analysis, recent paper in Nature Materials
With SCI Members	
Jose Silva	Co-supervisor of Chibeza Agley, collaboration on MRC research grant
Robin Franklin	Analysing cell mechanics of oligodendrocyte progenitor cells, collaboration on submitted BBSRC research grant
Jenny Nichols	Physical biology of early embryogenesis, collaboration on Leverhulme Trust research grant and Newton Trust research grant
Austin Smith	Working together to develop microfluidic techniques for single cell live cell analysis for embryonic stem cells

Awards & Prizes

Awardee	Award	Organisation
Chibeza Agley	Tadion Rideal Prize for leading research in molecular science	King's College London
Sarra Achouri	Centre for Trophoblast Postdoctoral Research Fellowship	Centre for Trophoblast Research

Public Engagement

Event	Format	Date	Participation	Name
Science Festival Talk: "Using Physics and Engineering Principles in Stem Cell Research"	Public Talk	03/2014	Speaker	Chalut
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Achouri, Fisher

Adult Neural Stem Cells and Central Nervous System Regeneration

Robin Franklin

Robin Franklin is Professor of Stem Cell Medicine and Head of Translational Science at 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 also 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.

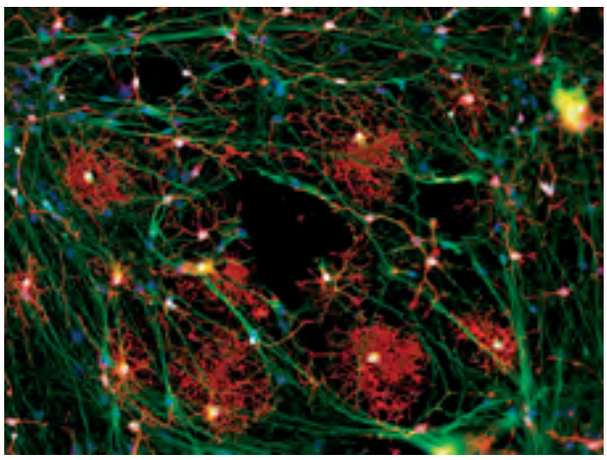
Funding

BBSRC
Multiple Sclerosis Society
Wellcome Trust
MRC Confidence in Concepts
Action Medical Research
MRC

Fellowships

Ofra Zidon BIRAX Fellowship

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



Oligodendrocytes (red) and astrocytes (green) generated in tissue culture from human embryonic stem cells
Image: Sybil Stacpoole

Group Members

Roey Baror	Graduate student
Abbe Crawford	Graduate student
Ludovica di Canio	Graduate student
Sarah Foerster	Graduate student
Joseph Guy	Graduate Student
Alerie Guzman	Postdoc researcher
Myfanwy Hill	Research assistant
Ilias Kazanis	Senior scientist
Dan Ma	Postdoc researcher
Chris McMurran	Graduate student
Daniel Morrison	Technician
Muktha Natrajan	Graduate student
Bjoern Neumann	Graduate student
John Parker	Graduate student
Michael Segal	Graduate student
Chao Zhao	Senior scientist
Natalia Deja	Graduate student

2014 Publications

Mei F, Fancy SP, Shen YA, Niu J, Zhao C, Presley B, Miao E, Lee S, Mayoral SR, Redmond SA, Etxeberria A, Xiao L, Franklin RJ, Green A, Hauser SL, Chan JR. Micropillar arrays as a high-throughput screening platform for therapeutics in multiple sclerosis. Nature Medicine. PMID: 24997607

Pagliara S, Franze K, McClain CR, Wylde GW, Fisher CL, Franklin RJ, Kabla AJ, Keyser UF, Chalut KJ. Auxetic nuclei in embryonic stem cells exiting pluripotency. Nature Materials. PMID: 24747782

Franklin RJ, Gallo V. The translational biology of remyelination: past, present, and future. Glia. PMID: 24446279

Crawford AH, Stockley JH, Tripathi RB, Richardson WD, Franklin RJ. Oligodendrocyte progenitors: adult stem cells of the central nervous system? Experimental Neurology. PMID: 24800913

Sawcer S, Franklin RJ, Ban M. Multiple sclerosis genetics. The Lancet Neurology. PMID: 24852507

Tyzack GE, Sitnikov S, Barson D, Adams-Carr KL, Lau NK, Kwok JC, Zhao C, Franklin RJ, Karadottir RT, Fawcett JW, Lakatos A, Tyzack GE, Sitnikov S, Barson D, Adams-Carr KL, Lau NK, Kwok JC, Zhao C, Franklin RJ, Karadottir RT, Fawcett JW, Lakatos A. Astrocyte response to motor neuron injury promotes structural synaptic plasticity via STAT3-regulated TSP-1 expression. Nature Communications. PMID: 25014177

Granger N, Franklin RJ, Jeffery ND. Cell Therapy for Spinal Cord Injuries: What Is Really Going on? Neuroscientist. PMID: 24415275

Miron VE, Franklin RJ. Macrophages and CNS remyelination. Journal of Neurochemistry. PMID: 24601941

Stoffels JM, Hoekstra D, Franklin RJ, Baron W, Zhao C. The EIIIA domain from astrocyte-derived fibronectin mediates proliferation of oligodendrocyte progenitor cells following CNS demyelination. Glia. PMID: 25156142

See page 61 for additional publications from the Franklin group

Collaborations

Charles ffrench-Constant	University of Edinburgh - Several publications and grants
Catherine Lubetzki	INSERM Paris - Joint paper
Aurora Pujol	Institut d'Investigacio Biomedica de Bellvitge (IDIBELL) - Joint grant
David Lyons	University of Edinburgh
Wia Baron	University of Groningen - Joint papers
David Rowitch/ Steve Fancy	University of California (SF) - Joint papers
Patrizia Casaccia	Mount Sinai Hospital, NY - Joint paper
Jonah Chan	University of California (SF) - Joint papers
With SCI Members	
Mark Kotter	Joint publications
Thora Karadottir	Joint publications
Kevin Chalut	Joint paper
Ben Simons	

Awards & Prizes

Awardee	Award	Organisation
Robin Franklin	International Canine Health Award	The Kennel Club Charitable Trust
Ofra Zidon	BIRAX Fellowship	The British Council
Muktha Natrajan	Best poster in Neuroscience Award	NIH Graduate Student Symposium

Public Engagement

Event	Format	Date	Participation	Name
Science Festival Talk: "Stem Cells and Repairing Brains"	Public Talk	03/2014	Speaker	Franklin
Cambridge Alumni Festival Talk	Public Talk	09/2014	Speaker	Franklin
Pint of Science "Repairing Ageing Brains"	Science Festival	05/2014	Speaker	Franklin
Canterbury Festival "Repairing the Brain"	Science Festival	10/2014	Speaker	Franklin
Interview on BBC Radio Cambridge	Radio Interview	10/2014	Interviewee	Franklin
Interview on BBC Radio Wales	Radio Interview	10/2014	Interviewee	Franklin
Interview on BBC TV News	TV Interview	10/2014	Interviewee	Franklin
MS Life - Myelin Repair	Public Talk	04/2014	Speaker	Franklin
Big Biology Day	Science Festival	10/2014	Volunteer	Foerster

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 Fiona Watt's lab 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 SCI. She renewed this fellowship in 2013 and is now a CR-UK Senior Fellow.

Funding

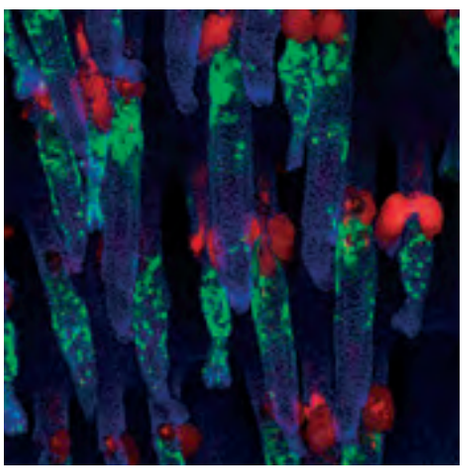
British Skin Foundation
Cancer Research UK
Worldwide Cancer Research
ERC

Stem Cell Homeostasis and Disease

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 and cancer.

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 including cancer.



Labelling of hair follicle stem cells (green) in mouse tail skin. Blue: DNA staining; Red: Sebaceous Glands
Image: Iwona Driskell

Group Members

Sandra Blanco	Postdoc Researcher
Jelena Aleksic	Postdoc Researcher
Roberto Bandiera	Postdoc Researcher
Martyna Popis	Graduate student
Mahalia Page	Graduate student
Abdul Sajini	Graduate student
Nikoletta Gkatza	Graduate student
Tommaso Selmi	Postdoc Researcher
Feride Oeztuerk-Winder	Postdoc Researcher
Rosana Cortes Garrido	Erasmus student
Joana Flores	Graduate Student

2014 Publications

Blanco S, Dietmann S, Flores JV, Hussain S, Kutter C, Humphreys P, Lukk M, Lombard P, Treps L, Popis M, Kellner S, Hölter SM, Garrett L, Wurst W, Becker L, Klopstock T, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Káradóttir RT, Helm M, Ule J, Gleeson JG, Odom DT, Frye M. Aberrant methylation of tRNAs links cellular stress to neuro-developmental disorders. EMBO Journal. PMID: 25063673

Blanco S, Frye M. Role of RNA methyltransferases in tissue renewal and pathology. Current Opinion in Cell Biology. PMID: 25014650

Driskell I, Oeztuerk-Winder F, Humphreys P, and Frye M. Genetically induced cell death in bulge stem cells reveals their redundancy for hair and epidermal regeneration. Stem Cells. PMID: 25447755

Hussain S. Developing a PPI inhibitor-based therapy for STXBP1 haploinsufficiency-associated epileptic disorders. Frontiers in Molecular Neuroscience. PMID: 24550774

Collaborations

Ducan Odom	Cancer Research UK CI - Shared reagents and computational advice, led to publications and grant applications
Frank Lyko	German Cancer Research Centre (DKFZ) - Shared reagents, led to publications and grant applications
Mark Helm	Johannes Gutenberg University, Mainz - Support performing specific techniques, led to publications
Jernej Ule	University College London - Shared reagents and computational advice, led to publications and grant applications
John Marioni	EMBL - EBI - Computational support
With SCI Members	
Austin Smith	Shared reagents
Ana Cvejic	Shared reagents

Awards & Prizes

Awardee	Award	Organisation
Jelena Aleksic	£1k CUE business competition	Cambridge University Entrepreneurs
Jelena Aleksic	Project/ Initiative Award	Cambridge-Africa Alborada Research Fund

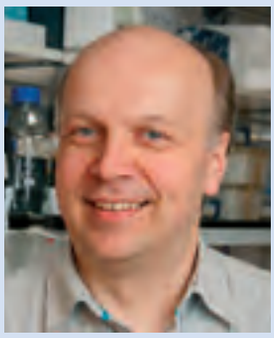
Policy Briefings

All-Party Parliamentary Group on Stem Cell Transplantation and the All-Party Parliamentary Group on Medical Research, “Harnessing stem cells for patients and economic growth”, July, as expert witness

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Popis, Gkatza, Aleksic, Flores
Pint of knowledge (Society of Spanish Researchers in the UK-SRUK)	Public Talk	09/2014	Speaker & Organiser	Blanco

Transcriptional Regulation of Normal and Leukaemic Blood Stem Cells



Bertie Göttgens

Bertie Göttgens graduated from Tübingen University in 1992 with a degree in biochemistry. He received his DPhil in biological sciences from the University of Oxford in 1994 and then proceeded to a post-doc position in the Department of Haematology, University of Cambridge, between 1994-2001.

Between 2002-2007 he was a Leukaemia Research Fund Lecturer in the Department of Haematology, Cambridge. He was then a University Lecturer, and subsequently a Reader in Haematology, between 2007-2011.

Since October 2011, Bertie has been Professor of Molecular Haematology, University of Cambridge.

Funding

BBSRC
Leukaemia & Lymphoma Research
Cancer Research UK
Leukemia & Lymphoma Society
Wellcome Trust

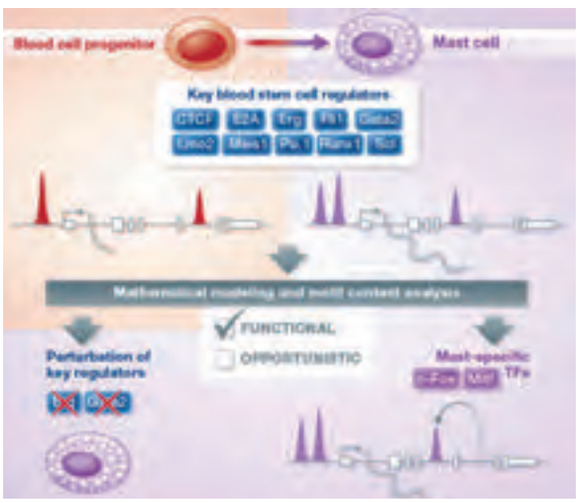
Fellowships

Yosuke Tanaka JSPS Fellowship

Blood stem cells provide the constant supply of new blood cells throughout a person's lifetime. Transcription factors are critical regulators of normal blood stem cell function, and their perturbation represents a common cause of leukaemia development.

Transcription factors 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.



Key regulators control distinct transcriptional programs in blood progenitor and mast cells
Image credit: Felicia Ng

Group Members

Silvia Basilico	Graduate student
Fernando Calero	Postdoc Researcher
Debbie Goode	Postdoc Researcher
Rebecca Hannah	Research assistant
Wajid Jawaid	Graduate student
Isabel Jimenez	Research assistant
Sarah Kinston	Research assistant
Vasilis Ladopoulos	Postdoc Researcher
Winnie Lau	Postdoc Researcher
Ana Leal Cervantes	Graduate student
Vicki Moignard	Postdoc Researcher
Felicia Ng	Graduate student
Jonathan Sive	Graduate student
Yosuke Tanaka	Postdoc Researcher
Adam Wilkinson	Graduate student
Nicola Wilson	Postdoc Researcher
Steven Woodhouse	Graduate student
Manuel Sanchez-Castillo	Postdoc Researcher
Chee Lim	Graduate Student

2014 Publications

Calero-Nieto FJ, Ng FS, Wilson NK, Hannah R, Moignard V, Leal-Cervantes AI, Jimenez-Madrid I, Diamanti E, Wernisch L, Göttgens B. Key regulators control distinct transcriptional programmes in blood progenitor and mast cells. EMBO Journal. PMID: 24760698

Sánchez-Castillo M, Ruau D, Wilkinson AC, Ng FS, Hannah R, Diamanti E, Lombard P, Wilson NK, Gottgens B. CODEX: a next-generation sequencing experiment database for the haematopoietic and embryonic stem cell communities. Nucleic Acids Research. PMID: 25270877

Wilkinson AC, Kawata VK, Schütte J, Gao X, Antoniou S, Baumann C, Woodhouse S, Hannah R, Tanaka Y, Swiers G, Moignard V, Fisher J, Hidetoshi S, Tijssen MR, de Bruijn MF, Liu P, Göttgens B. Single-cell analyses of regulatory network perturbations using enhancer-targeting TALEs suggest novel roles for PU.1 during haematopoietic specification. Development. PMID: 25252941

Moignard V, Göttgens B. Transcriptional mechanisms of cell fate decisions revealed by single cell expression profiling. Bioessays. PMID: 24470343

Dickel DE, Zhu Y, Nord AS, Wylie JN, Akiyama JA, Afzal V, Plajzer-Frick I, Kirkpatrick A, Göttgens B, Bruneau BG, Visel A, Pennacchio LA. Function-based identification of mammalian enhancers using site-specific integration. Nature Methods. PMID: 24658141

Sun D, Luo M, Jeong M, Rodriguez B, Xia Z, Hannah R, Wang H, Le T, Faull KF, Chen R, Gu H, Bock C, Meissner A, Göttgens B, Darlington GJ, Li W, Goodell MA. Epigenomic profiling of young and aged HSCs reveals concerted changes during aging that reinforce self-renewal. Cell Stem Cell. PMID: 24792119

Buettner F, Moignard V, Göttgens B, Theis FJ. Probabilistic PCA of censored data: accounting for uncertainties in the visualization of high-throughput single-cell qPCR data. Bioinformatics. PMID: 24618470

Mahata B, Zhang X, Kolodziejczyk AA, Proserpio V, Haim-Vilmovsky L, Taylor AE, Hebenstreit D, Dingler FA, Moignard V, Göttgens B, Arlt W, McKenzie AN, Teichmann SA. Single-cell RNA sequencing reveals T helper cells synthesizing steroids de novo to contribute to immune homeostasis. Cell Reports. PMID: 24813893

Pooley C, Ruau D, Lombard P, Gottgens B, Joshi A. TRES predicts transcription control in embryonic stem cells. Bioinformatics. PMID: 24958811

See page 61 for additional publications from the Gottgens group

Collaborations

Jasmin Fisher	Microsoft Research - Joint research paper
Marella de Bruijn	Weatherall Institute of Molecular Medicine, University of Oxford - Joint research paper
Peggy Goodell	Baylor College of Medicine, Houston - Joint research paper
Len Pennacchio	DOE Joint Genome Institute - Joint research paper
John Pimanda	University of New South Wales - Joint research paper
Shai Izraeli	Sheba Medical Centre - Joint research paper
Nicola Bonzanni	Vrifje University of Amsterdam - Joint research paper
Daniel Tenen	Harvard Stem Cell Institute - Joint research paper
With SCI Members	
Tony Green	Joint research paper
Brian Huntly	Joint research paper
Azim Surani	Joint research paper
Austin Smith	Joint research paper
Robin Franklin	Joint research paper
Emma Rawlins	Joint research

Awards & Prizes

Awardee	Award	Organisation
Adam Wilkinson	Bill Wood Prize for best presentation	18th Globin Switching Conference in Oxford
Jonathan Sive	Abstract Achievement Award	Annual Meeting of the American Society of Hematology
Felicia Ng	Highlight Talk	European Conference on Computational Biology 2014

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Literary Festival- "The promise of Stem Cells"	Public Talk	04/2014	Speaker	Gottgens
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Leal Cervantes

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

The Leukaemia and Lymphoma Society

Cancer Research UK

Kay Kendall Leukaemia Fund

Wellcome Trust

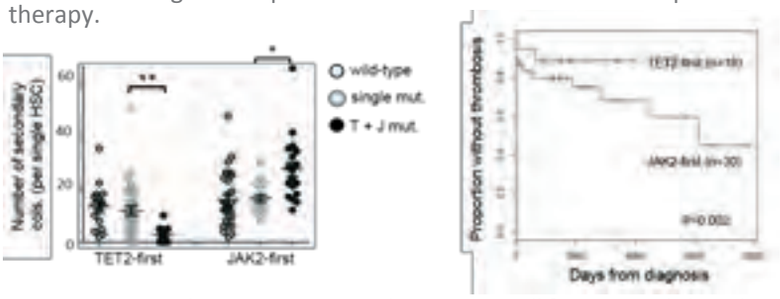
Leukaemia & Lymphoma Research

Fellowships

June Park	International Human Frontier Science Program Organisation
Jyoti Nangalia	Kay Kendall Leukaemia Fund
Jacob Grinfeld	Leukaemia & Lymphoma Research Clinical Training Fellowship
Wolfgang Warsch	Austrian Science Fund: Schroedinger Fellowship

Haematopoiesis

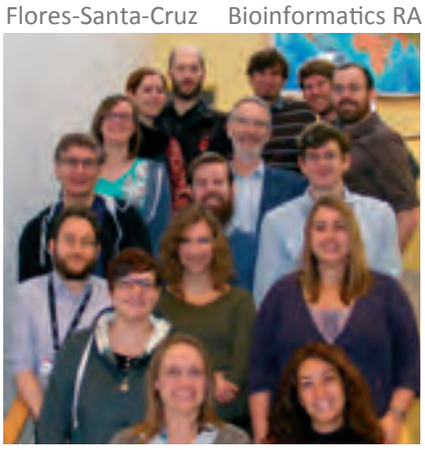
Tony Green's research has focused on the mechanisms whereby blood stem cells are subverted during the genesis of haematological malignancies. Over the past decade his lab has increasingly concentrated on JAK/STAT signalling which is dysregulated in many cancers and plays a key role in multiple stem cell 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. Recent highlights include: identification of calreticulin mutations in most patients with a JAK2-unmutated MPN, thus establishing an unexpected link with endoplasmic reticulum biology; and the first demonstration in any cancer that mutation order affects stem and progenitor behaviour, thus influencing clinical presentation thrombosis risk and response to therapy.



Mutation order impacts stem and progenitor cell function and clinical course of disease in myeloproliferative neoplasms: HSCs from patients who acquire a TET2 mutation first make fewer progenitors compared to those that acquire JAK2V617F first (left). JAK2-first patients also presented in clinic >10 years earlier and had an increased number of thrombotic events (right). Image: David Kent

Group Members

Danai Dimitropoulou	Research Assistant
Anna Godfrey	Graduate Student
Tina Hamilton	Technician
David Kent	Postdoc Researcher
Kristina Kirschner	Postdoc Researcher
Thorsten Klampfl	Postdoc Researcher
Karoline Kollman	Postdoc Researcher
Juan Li	Senior Scientist/ Researcher
Stephen Loughran	Postdoc Researcher
Jyoti Nangalia	Graduate Student
Francesca Nice	Graduate Student
June Park	Postdoc Researcher
Dean Pask	Technician
Rachel Sneade	Research Assistant
Wolfgang Warsch	Postdoc Researcher
Jacob Grinfeld	Graduate Student
David Flores-Santa-Cruz	Bioinformatics RA



2014 Publications

Chen E, Ahn JS, Massie CE, Clynes D, Godfrey AL, Li J, Park HJ, Nangalia J, Silber Y, Mullally A, Gibbons RJ, Green AR. JAK2V617F promotes replication fork stalling with disease-restricted impairment of the intra-S checkpoint response. Proceedings of the National Academy of Sciences USA. PMID: 25288776

Kollmann K, Nangalia J, Warsch W, Quentmeier H, Bench A, Boyd E, Scott M, Drexler HG, Green AR. MARIMO cells harbor a CALR mutation but are not dependent on JAK2/STAT5 signalling. Leukemia. PMID: 25249012

Li J, Kent DG, Godfrey AL, Manning H, Nangalia J, Aziz A, Chen E, Saeb-Parsy K, Fink J, Sneade R, Hamilton TL, Pask DC, Silber Y, Zhao X, Ghevaert C, Liu P, Green AR. JAK2V617F homozygosity drives a phenotypic switch in myeloproliferative neoplasms, but is insufficient to sustain disease. Blood. PMID: 24692758

Guglielmelli P, Nangalia J, Green AR, Vannucchi AM. CALR mutations in myeloproliferative neoplasms: hidden behind the reticulum. American Journal of Hematology. PMID: 24458922

van Galen P, Kreso A, Mbong N, Kent DG, Fitzmaurice T, Chambers JE, Xie S, Laurenti E, Hermans K, Eppert K, Marciniak SJ, Goodall JC, Green AR, Wouters BG, Wienholds E, Dick JE. The unfolded protein response governs integrity of the haematopoietic stem-cell pool during stress. Nature. PMID: 24776803

Prick J, de Haan G, Green AR, Kent DG. Clonal heterogeneity as a driver of disease variability in the evolution of myeloproliferative neoplasms. Experimental Hematology. PMID: 25201757

Girardot M, Pecquet C, Chachoua I, Van Hees J, Guibert S, Ferrant A, Knoops L, Baxter EJ, Beer PA, Giraudier S, Moriggl R, Vainchenker W, Green AR, Constantinescu SN. Persistent STAT5 activation in myeloid neoplasms recruits p53 into gene regulation. Oncogene. PMID: 24681953

Godfrey AL, Nangalia J, Baxter EJ, Massie CE, Kent DG, Papaemmanuil E, Campbell PJ, and Green AR. Non-genetic stochastic expansion of JAK2V617F-homozygous subclones in polycythemia vera. Blood. PMID: 25414437

Jones AV, Ward D, Lyon M, Leung W, Callaway A, Chase A, Dent CL, White HE, Drexler HG, Nangalia J, Mattocks C, Cross NC. Evaluation of methods to detect CALR mutations in myeloproliferative neoplasms. Leukemia Research. PMID: 25499808

Collaborations

Timm Schroeder	ETH Zurich - Video imaging in JAK2 V617F HSCs (manuscript in preparation)
Veronika Sexl	University of Veterinary Medicine, Vienna - JAK/STAT transcriptional programs
Cristina Lo Celso	Imperial College London - Manuscript in preparation
Warren Alexander	Walter and Eliza Hall Institute of Medical Research - Mouse models for MPN transformation
Sten Eirik Jacobsen/ Adam Mead	University of Oxford - Role of MuRD in haematopoiesis: mouse models for MPN transformation
John Marioni	EBI - Role of JAK2 in splicing
With SCI Members	
Ben Simons	Joint paper
Bertie Gottgens	Multiple joint papers
Brian Hendrich	Role of NuRD in haematopoiesis
Anne Ferguson-Smith	Joint paper
Cedric Ghevaert	Joint paper

Awards & Prizes

Awardee	Award	Organisation
David Kent	TRTH Scholar	EHA - ASH
Thorsten Klampfl	Wilhem Turk Award	Austrian Society of Haematology
Karoline Kollmann	OGMBT/ Biomin Research Award	OGMBT
Jyoti Nangalia	Johnstone & Florence Stoney Studentship	British Federation of Women Graduates

Public Engagement

Event	Format	Date	Participation	Name
Canadian Stem Cell Network Signals Blog	Blog	2014	Contributor	Kent

Transcriptional Control of Stem Cell Fate

Brian Hendrich

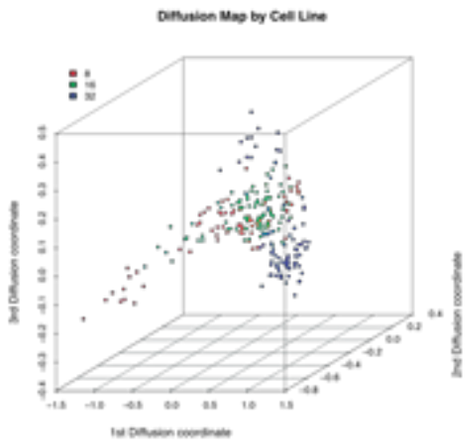
Brian Hendrich grew up near Seattle, Washington. He got his PhD from Stanford University in 1995 working on X chromosome inactivation with Huntington Willard. In 1995 he joined the lab of Adrian Bird at the University of Edinburgh and participated in the discovery and characterisation of a family of 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.



Diffusion plot of single cell gene expression analysis. Red spots represent cells from 8-cell embryos, green spots are cells from 16-cell embryos, and blue spots are cells from 32-cell embryos. Once can see a temporal maturation in gene expression patterns through the time course, with the first cell fate decision visualised as a bifurcation in the blue signal: cells adopt either an inner cell mass (lower blue spots) or trophectoderm fate at the 32-cell stage.

Image: Patrick Lombard

Group Members

Maria Barreira-Gonzalez	Postdoc Researcher
Thomas Burgold	Postdoc Researcher
Julie Cramard	Research Assistant
Robin Floyd	Technician
Sarah Gharbi	Research assistant
Anzy Miller	Graduate student
Meryem Ralser	Research assistant
Nicola Reynolds	Senior Scientist
Pedro da Silva	Graduate Student
Aoife O'Shaugnessy	Postdoc Researcher

2014 Publications

dos Santos RL, Tosti L, Radzisheuskaya A, Caballero IM, Kaji K, Hendrich B, Silva JC. MBD3/NuRD facilitates induction of pluripotency in a context-dependent manner. Cell Stem Cell. PMID: 24835571

Signolet J, Hendrich B. The function of chromatin modifiers in lineage commitment and cell fate specification. The FEBS Journal. PMID: 25354247

Key publications prior to 2014

Reynolds N, O'Shaughnessy A, Hendrich B. Transcriptional repressors: multifaceted regulators of gene expression. (2013) Development. PMID:23293282

O'Shaughnessy A, Hendrich B. CHD4 in the DNA-damage response and cell cycle progression: not so NuRDy now. (2013) Biochemical Society Transactions. PMID:23697937

Collaborations

Ernest Laue	University of Cambridge - Joint EU FP7 grant, ongoing technology development
Kathryn Lilley	University of Cambridge - Collaborative research
Juan Mata	University of Cambridge - ES cell experiments
Stephen Emmot	Microsoft Research - Joint PhD Studentship
Jessica Downs	University of Sussex - Investigating DNA repair function of CHD4
Adrian Bird	University of Edinburgh - Joint research efforts, discussing grant options
Saverio Minucci	European Institute of Oncology - Collaborative small molecule screen; joint EU FP7 grant
Jeroen Demmers	Erasmus University Medical Centre, Proteomics Centre - Joint paper and others in preparation
Michiel Vermeulen	University Medical Centre Utrecht - Collaborative investigation into protein complex structure; joint EU FP7 grant
Imre Berger	EMBL, Grenoble - Collaboration on NuRD structure; joint EU FP7 grant
Ryuichi Nishinakamura	University of Kumamoto
With SCI Members	
Tony Green	Joint research project
Jose Silva	Joint paper and another in revision
Paul Bertone	Close collaboration; Joint papers and joint PhD supervision
Rick Livesey	Paper under review

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Barreira-Gonzalez
STEM event at IWM Duxford	Outreach	06/2014	Organiser	Barreira-Gonzalez, O'Shaugnessy, Miller
Science Uncovered at the National History Museum	Outreach	09/2014	Volunteer	Barreira

Brian Huntly

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, for his PhD in Cambridge and performed post-doctoral work at Harvard, prior to returning to Cambridge to set up his own research group.

He is also a member of the Royal College of Physicians and a Fellow of the Royal College of Pathologists.

Funding

Wellcome Trust
Kay Kendall Leukaemia Fund
Leukaemia & Lymphoma
Worldwide Cancer Research
Medical Research Council

Fellowships

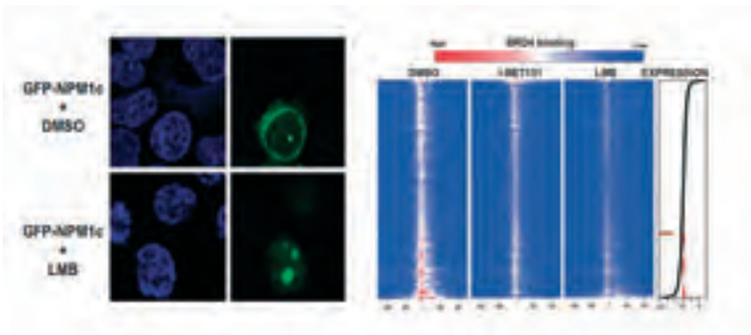
Mark Dawson	Leukaemia Foundation Australia Senior Fellowship
Mark Dawson	VESKI Innovation Fellowship
Faisal Basheer	Wellcome Trust Fellowship for Clinicians
Paolo Gallipoli	Academy of Medical Sciences Starter Grant
Paolo Gallipoli	Lady Tata Fellowship

Leukaemia Stem Cell Biology and Leukaemogenesis

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

The focus of the Huntly laboratory is on this interface. 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. We are examining the role of mutations that occur in and alter the role of haematopoietic stem and progenitors as early events before leading to the subsequent development of leukaemias and lypmphomas (pre-leukaemic stem cells). As examples of this we are examining the effects of gene mutations, recently documented in Acute myeloid Leukaemia (AML), and in the progression of chronic myeloid malignancies to AML.

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
Sarah Horton	Postdoc Researcher
Eshwar Meduri	Postdoc Researcher
Paolo Gallipoli	Postdoc Researcher
Faisal Basheer	Graduate student
Hikari Osaki	Postdoc Researcher
Haiyang Yun	Postdoc Researcher
Ann Sophie Bach	Postdoc Researcher
Mark Dawson	Senior Scientist/Researcher

2014 Publications

Dawson MA, Gudgin EJ, Horton SJ, Giotopoulos G, Meduri E, Robson S, Cannizzaro E, Osaki H, Wiese M, Putwain S, Fong CY, Grove C, Craig J, Dittmann A, Lugo D, Jeffrey P, Drewes G, Lee K, Bullinger L, Prinjha RK, Kouzarides T, Vassiliou GS, Huntly BJ. Recurrent mutations, including NPM1c, activate a BRD4-dependent core transcriptional program in acute myeloid leukemia. Leukemia. PMID: 24220271

Placke T, Faber K, Nonami A, Putwain SL, Salih HR, Heidel FH, Krämer A, Root DE, Barbie DA, Krivtsov AV, Armstrong SA, Hahn WC, Huntly BJ, Sykes SM, Milsom MD, Scholl C, Fröhling S. Requirement for CDK6 in MLL-rearranged acute myeloid leukemia. Blood. PMID: 24764564

Pellicano F, Scott MT, Helgason GV, Hopcroft LE, Allan EK, Aspinall-O'Dea M, Copland M, Pierce A, Huntly BJ, Whetton AD, Holyoake TL. The antiproliferative activity of kinase inhibitors in chronic myeloid leukemia cells is mediated by FOXO transcription factors. Stem Cells. PMID: 24806995

Collaborations

George Vassiliou	Wellcome Trust Sanger Institute - Generation of mouse models
Chuna Ram Choudhary	University of Copenhagen - Generation of acetylation target
Christian Frezza	MRC CU - Academic collaboration
Peter Tumino	GSK Cancer Epigenetics DPU - Translational collaboration in experimental therapeutics
Kevin Lee	Pfizer - Translational collaboration in experimental therapeutics
Ed Kiesicki	Acylin - Translational collaboration in experimental therapeutics
Cameron Osbourne	King's College London - Academic collaboration
With SCI members	
Tony Green	Academic collaboration
Bertie Gottgens	Academic collaboration
Katrin Ottersbach	Academic collaboration
Allan Bradley	Academic collaboration

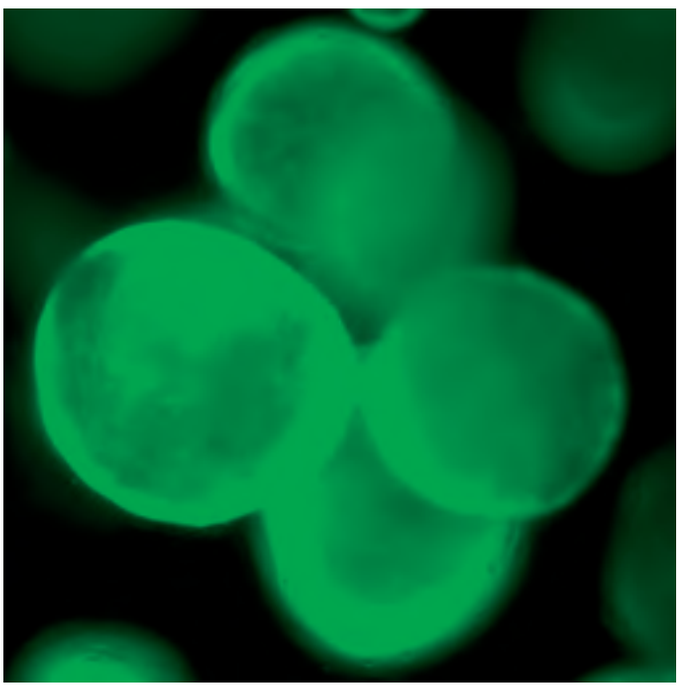
Awards & Prizes

Awardee	Award	Organisation
Paolo Gallipoli	Lady Tata Fellowship Award	Lady Tata Memorial Trust
Faisal Basheer	Sims Fellowship	University of Cambridge
Paolo Gallipoli	Academy of Medical Sciences Starter Grant for Lecturers	Academy of Medical Sciences
Paolo Gallipoli	Thomas and Margaret Smellie Prize - Cancer	Senate of the University of Glasgow

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.



Foetal Enterospheres derived from the mouse small intestine
Image: Robert Fordham

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 until May 2014.

Funding

Wellcome Trust

Group Members

Mahalia Page Graduate student

2014 Publications at the SCI

Schepeler T, Page ME, Jensen KB. Heterogeneity and plasticity of epidermal stem cells. Development. PMID: 24961797

Key Publications prior to 2014

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. (2013) 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. (2013) 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. (2013) Cell Stem Cell. PMID:24139758

Collaborations

Clare Blackburn	Centre for Regenerative Medicine, University of Edinburgh
Mamaru Watanabe	Tokyo Medical and Dental University
Takahiro Nakamura	Research Centre for Inflammation and Regenerative Medicine, Doshisha University
With SCI Members	
Ludovic Vallier	

Ragnhildur Thóra Káradóttir

Ragnhildur Thóra Káradóttir graduated with a degree in Biochemistry from the University of Iceland in 2000. She then completed a four-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.

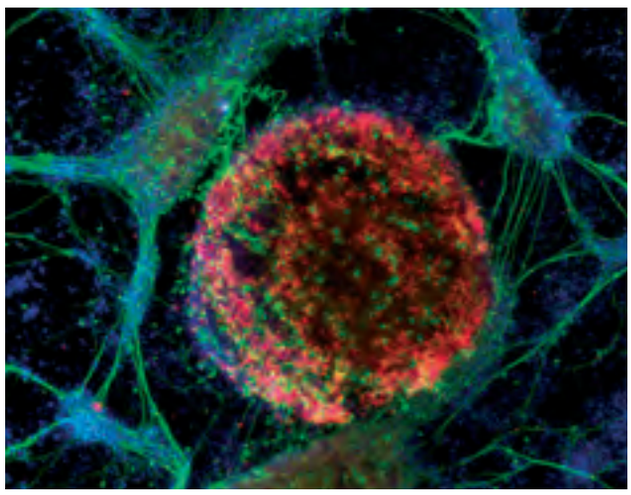
She is currently an editor for the journal *Brain Plasticity* and a guest editor for *Neuroscience* and for *Neuropharmacology*.

Funding

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.



Human IPSC derived neurons (green) and glia (red) cells.
Image: Sylvia Agathou

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

2014 Publications

Walhovd KB, Johansen-Berg H, Káradóttir RT. Unraveling the secrets of white matter--bridging the gap between cellular, animal and human imaging studies. Neuroscience. PMID: 25003711

Blanco S, Dietmann S, Flores JV1, Hussain S, Kutter C, Humphreys P, Lukk M, Lombard P, Treps L, Popis M, Kellner S, Hölter SM, Garrett L, Wurst W, Becker L, Klopstock T, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Káradóttir RT, Helm M, Ule J, Gleeson JG, Odom DT, Frye M. Aberrant methylation of tRNAs links cellular stress to neuro-developmental disorders. EMBO Journal. PMID: 25063673

Tyzack GE, Sitnikov S, Barson D, Adams-Carr KL, Lau NK, Kwok JC, Zhao C, Franklin RJ, Karadottir RT, Fawcett JW, Lakatos A. Astrocyte response to motor neuron injury promotes structural synaptic plasticity via STAT3-regulated TSP-1 expression. Nature Communications. PMID: 25014177

Karadottir RT, Walhovd KB. The CNS white matter. Neuroscience. PMID: 24650921

Collaborations

Maria-Grazia Spillantini	University of Cambridge - Contribution of OPCs to frontal dementia; paper submitted
David Cavalla	Numedicus - Testing licenced drugs for advancing repair in MS
Klaus Nave/ Sandra Goebels	Max Planck Institute for Experimental Medicine - Regulation of myelination; paper under revision
Colin Watts	University of Cambridge - Regulation of glioma cell proliferation; joint PhD supervision
Heidi Johansen-Berg	University of Oxford - Structural changes in white matter with learning; Neuroscience 2014
Kristine Walhovd	University of Oslo - Changes in white matter with age; Neuroscience 2014
Kristian Franze	University of Cambridge - Mechanosensing receptors in neuronal development
Andras Lakatos	University of Cambridge - Reactivity of astrocytes, regulation of synaptic inputs; paper in Nature Communications
Edward Ruthazer	McGill University - Synaptic communication between axons and OPCs
With SCI Members	
Austin Smith	Functional insertion of implanted neuronal stem cells to neuronal network
Robin Franklin	Understanding the role of neuronal activity in remyelination; joint paper under revision
Michaela Frye	Joint paper

Public Engagement

Event	Format	Date	Participation	Name
Radio interview for Icelandic National Radio	Radio interview	02/2014	Interviewee	Karadottir
Cambridge MS Research Day	Open day	09/2014	Speaker	Volbracht
Big Biology Day	Science Festival	10/2014	Volunteer	Volbracht

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 awarded the Sir Henry Dale Fellowship in 2013. This Fellowship brings together the Royal Society and the Wellcome Trust to support the future leaders of biomedical research.

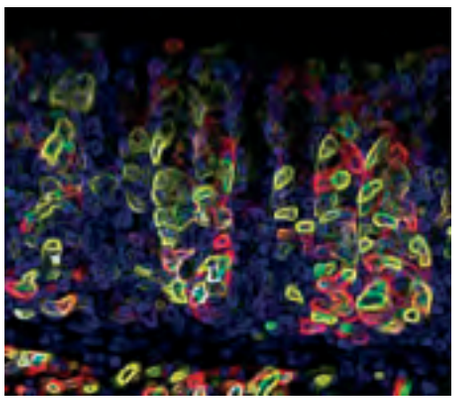
Funding

Wellcome Trust
Royal Society
Marie Curie

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.

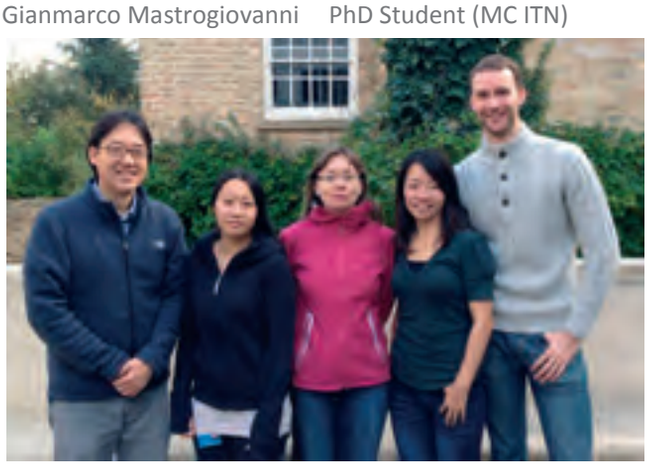
We have identified a novel quiescent Troy+ epithelial stem cell population in the stomach. Upon tissue damage, Troy+ stem cells actively divide to regenerate lost cell types. The discovery of Troy+ stomach stem cells enables us to investigate how an adult tissue can retain its homeostasis after various 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.



Stomach epithelial cells labelled in four colours.
Image: Juergen Fink

Group Members

Roxana Micsik	Postdoc Researcher
Ya-Lin Huang	Postdoc Researcher
Amanda Andersson-Rolf	PhD Student (MRC)
Juergen Fink	PhD Student (WT) (Koo/Simons)
Alessandra Merenda	PhD Student (MC ITN)
Gianmarco Mastrogiovanni	PhD Student (MC ITN)



2014 Publications

Andersson-Rolf A, Fink J, Mustata RC, Koo BK. A video protocol of retroviral infection in primary intestinal organoid culture. JOVE - Journal of Visualized experiments. PMID: 25146755

Koo BK, Clevers H. Stem cells marked by the R-spondin receptor LGR5. Gastroenterology. PMID: 24859206

Key publications prior to 2014

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

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

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

Collaborations

WntsApp Members	Marie Curie Initial Training Network - MCT ITN
Graham Burton/ Ashley Moffett	Centre for Trophoblast Research
Daniel Stange	Universitätsklinikum Carl Gustav Carus
With SCI Members	
Ben Simons	Joint PhD supervision
Meritxell Huch	Adult stem cell organoid culture
Bill Skarnes	CRISPR/Cas genome editing

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Andersson-Rolf

Neural Stem Cells, Cellular Reprogramming and Regenerative Medicine

Mark Kotter

Mark Kotter is an academic neurosurgeon who undertook postgraduate medical training in Austria (Vienna), Germany (Göttingen), and the UK (Cambridge). During his PhD at the University of Cambridge he established the importance of macrophages for the regeneration of CNS white matter. He continues to work on extrinsic and extrinsic regulators of CNS remyelination and has developed an interest in mechanisms of direct cellular reprogramming.

He is particularly interested in clinical translation with a view to promoting regeneration in a clinical setting.

Funding

Qatar Foundation
UK MS Society

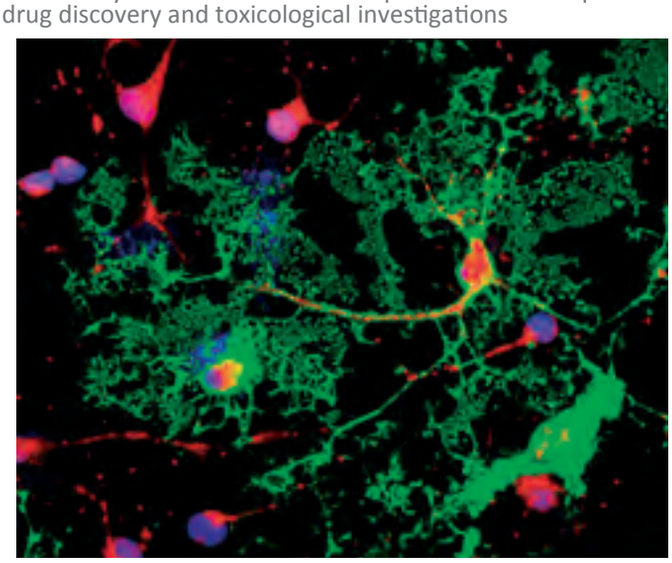
Fellowships

Matthias Pawlowski	German Research Foundation Fellowship

The Kotter group is interested in the biology of adult CNS stem and precursor cells. 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.
Our current focus lies on transcriptional events and metabolic processes that underly OPC differentiation.
We study post mortem changes occurring in human disease and aim to translate these into laboratory questions. Furthermore, we aim at translating our basic findings into clinical studies.

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,
3. Which may be used for the development of cellular platforms for drug discovery and toxicological investigations



Expansion of mitochondria during OPC differentiation

Group Members

Yasir Ahmed Syed	Postdoc Researcher
Ana Amaral	Postdoc Researcher
Matthias Pawlowski	Postdoc Researcher
Ginez Gonzalez	Graduate student
Sarah Ali Abdulla	Graduate student
Simon Rodier	Graduate student
Rana Dhillon	Graduate student

Key Publications prior to 2014

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. (2013) EMBO Molecular Medicine. PMID: 24293318

Amaral AI, Meisingset TW, Kotter MR, Sonnewald U. Metabolic aspects of neuron-oligodendrocyte-astrocyte interactions. (2013) Frontiers in Endocrinology (Lausanne). PMID:23717302

Collaborations

Ursula Sonnewald	Norwegian University of Science and Technology
Klaus-Amin Nave	Max Planck Institute for Experimental Medicine
Amparo Acker-Palmer	Goethe University
Bente Finsen	University of Southern Denmark
Anne Brunet	Stanford University
With SCI Members	
Robin Franklin	Investigating the biology of CNS remyelination; development of clinical applications, including the development of regenerative cell based therapies
Ludovic Vallier	Development of inducible gene expression systems in human pluripotent stem cells and their derivatives; investigating the impact of the cell cycle on transdifferentiation processes and cellular reprogramming

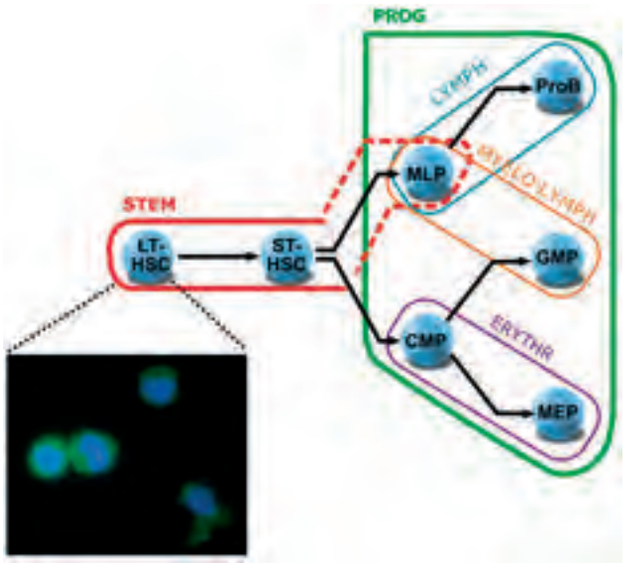
Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Amaral
Interview about Science and medical research surrounding spinal cord injury for possible documentary about Martyn Ashton	Interview	05/2014	Interviewee	Kotter

Human Haematopoietic Stem Cells Biology in Health and Disease

Daily blood cell production is guaranteed throughout life by a hierarchy with haematopoietic stem cells (HSC) at its root. HSC are very different from other haematopoietic cell types and have unique functional properties, such as their infrequent division (quiescence) and their capacity to give rise to all blood cell types.

By using genome-wide profiling and functional assays, the Laurenti laboratory aims to identify the molecular networks at play in human HSC. Our team are particularly interested in defining how the quiescent status of HSC is maintained. We also aim to identify the functional and molecular changes triggered by the stresses that these cells are exposed to, both physiologically and in pathological conditions. As perturbation of HSC regulatory networks drives the first steps of leukaemia, knowledge of HSC specific molecular responses will prove important to design novel therapies against haematopoietic disease.



Transcriptional programs in the human haematopoietic hierarchy. Insert: human haematopoietic stem cells dividing (right panel). Images: Elisa Laurenti/Catherine Frelin

Elisa Laurenti

Elisa Laurenti completed her PhD under the supervision of Prof. Andreas Trumpp in Lausanne, Switzerland.

In 2010 she joined Dr John Dick's laboratory in the University of Toronto where she became interested in the study of human hematopoietic stem cells.

She established her own research group at the Cambridge Stem Cell Institute in 2014.

Funding

Wellcome Trust

Group Members

Emily Calderbank Research assistant
Loretta Dean Other (Research nurse)

2014 Publications prior to joining the SCI

Qiao W, Wang W, Laurenti E, Turinsky AL, Wodak SJ, Bader GD, Dick JE, Zandstra PW. Intercellular network structure and regulatory motifs in the human hematopoietic system. Molecular Systems Biology. PMID: 25028490

van Galen P, Kreso A, Mbong N, Kent DG, Fitzmaurice T, Chambers JE, Xie S, Laurenti E, Hermans K, Eppert K, Marciniak SJ, Goodall JC, Green AR, Wouters BG, Wienholds E, Dick JE. The unfolded protein response governs integrity of the haematopoietic stem-cell pool during stress. Nature. PMID: 24776803

Theocharides AP, Dobson SM, Laurenti E, Notta F, Voisin V, Cheng PY, Yuan JS, Guidos CJ, Minden MD, Mullighan CG, Torlakovic E, Dick JE. Dominant-negative Ikaros cooperates with BCR-ABL1 to induce human acute myeloid leukemia in xenografts. Leukemia. PMID: 24791856

Carnevalli LS, Scognamiglio R, Cabezas-Wallscheid N, Rahmig S, Laurenti E, Masuda K, Jöckel L, Kuck A, Sujer S, Polykratis A, Erlacher M, Pasparakis M, Essers MA, Trumpp A. Improved HSC reconstitution and protection from inflammatory stress and chemotherapy in mice lacking granzyme B. Journal of Experimental Medicine. PMID: 24752302

van Galen P, Kreso A, Wienholds E, Laurenti E, Eppert K, Lechman ER, Mbong N, Hermans K, Dobson S, April C, Fan JB, Dick JE. Reduced lymphoid lineage priming promotes human hematopoietic stem cell expansion. Cell Stem Cell. PMID: 24388174

Collaborations

Didier Trono	EPFL, Switzerland - Joint papers
John Dick	UHN, Canada - Joint papers
Willem Ouwehand/ Mattia Frontini	University of Cambridge - Effects of inflammation on HSC

Rick Livesey

Rick Livesey did his 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. He is currently a Wellcome Trust Senior Investigator.

Funding

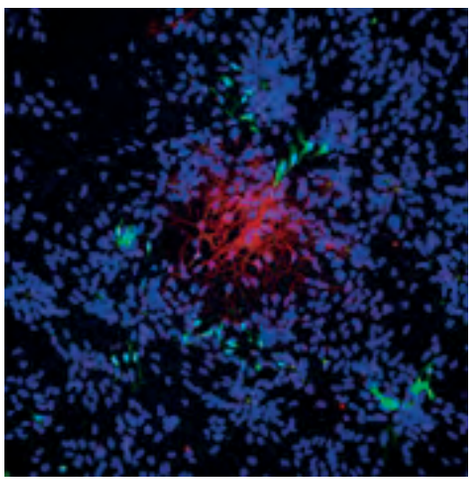
Wellcome Trust
Alzheimer's Research UK
Alborada Trust
EU Innovative Medicines Initiative (IMI)
Medical Research Council
Tau Consortium
AstraZeneca Neuroscience

Human stem cell models of dementia

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

Laura Brightman	Research Assistant
Phil Brownjohn	Postdoc Researcher
Tatyana Dias	Postdoc Researcher
Lewis Evans	Postdoc Researcher
Kirsty Ferguson	Undergraduate Student
Alberto Frangini	Postdoc Researcher
Peter Kirwan	Postdoc Researcher
Teresa Krieger	Graduate Student (Simons/Livesey)
Ayiba Momoh	Research Assistant
Steven Moore	Postdoc Researcher
Tomoki Otani	Graduate Student
Francesco Paonessa	Postdoc Researcher
Manuel Peter	Postdoc Researcher
Nathalie Saurat	Graduate Student
Vickie Stubbs	Research Assistant
James Smith	Research Assistant
Philipp Berg	Graduate Student (Barker/Livesey)

2014 Publications

Ali FR, Cheng K, Kirwan P, Metcalfe S, Livesey FJ, Barker RA, Philpott A. The phosphorylation status of Ascl1 is a key determinant of neuronal differentiation and maturation in vivo and in vitro. Development. PMID: 24821983

Livesey FJ. Human stem cell models of dementia. Human Molecular Genetics. PMID: 24939911

Key Publications prior to 2014

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

Collaborations

John Hardy	Institute of Neurology, UCL - Creation of Alzheimer's Research UK Stem Cell Centre
Henrik Zetterberg	Gothenburg - Proteomic analysis of human neuronal secretome in health and disease
Hugh Robinson	PDN, Cambridge - Analysis and modelling of human neural networks
Tony Holland	Psychiatry, Cambridge - Mechanistic studies of neuropsychiatric phenotypes in models of Down syndrome and Prader-Willi syndrome
Krish Chatterjee	IMS, Cambridge - Mechanistic studies of putative dominant negative thyroid hormone receptor
Barker, Spillantini & Rowe	Neurology, Cambridge - Stem cell models of tauopathies and synucleinopathies
With SCI Members	
Ben Simons	Joint PhD Student supervision

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Berg
Big Biology Day	Science Festival	10/2014	Volunteer	Berg
Bang goes the theory	Interview	03/2014	Interviewee	Livesey
Interview for Radio 4 Today Programme, following the donation from Alzheimer's Research UK	Interview	06/2014	Interviewee	Livesey
BBC Look East coverage of Alzheimer's Research UK donation	Interview	06/2014	Interviewee	Livesey
ITV Anglia coverage of Alzheimer's Research UK donation	Interview	06/2014	Interviewee	Livesey

Jennifer Nichols

Jenny Nichols began her research career with Professor Richard Gardner at the University of Oxford, where she developed a fascination with early mammalian development. She subsequently moved to Edinburgh to join Professor Austin Smith in his newly formed group at the Centre for Genome Research to investigate 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 to become a group leader under at the SCI.

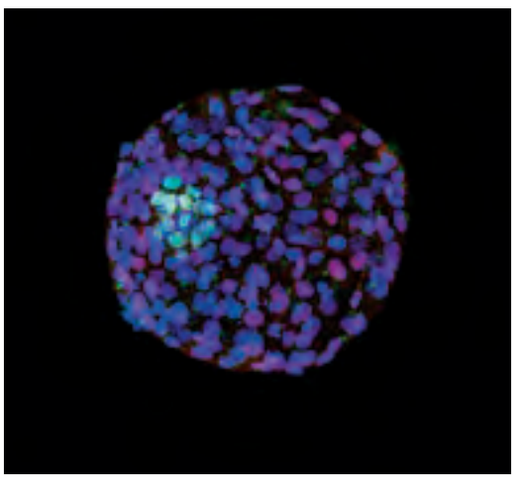
Funding

Wellcome Trust
BBSRC

Embryonic Pluripotency

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 purpose of our research is to discover how the pluripotent cells are assigned, maintained and primed in the embryo. ES cells can be very efficiently derived from murine embryos cultured in the presence of Erk and GSK3 inhibitors, which both prevent differentiation and promote expansion of the epiblast. Although pluripotent cell lines have been derived from other mammals, these differ from murine ES cells, and are more similar to so called 'epiblast stem cells' (EpiSCs) derived from post-implantation mouse embryos.

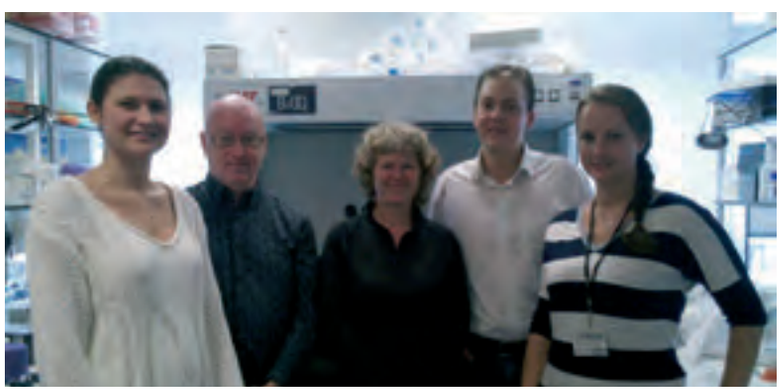
We are interested in how differences in early embryonic development of various mammalian species influence their subsequent behaviour in culture. We combine functional, molecular and genetic approaches to investigate epiblast development and potential in murine and primate embryos.



Human blastocyst donated for research with informed consent, stained for markers of naïve pluripotency: Klf4 is in green, Tfcp2l1 in red and nuclei in blue. Its diameter is around 0.4mm.
Image: Jennifer Nichols

Group Members

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



2014 Publications

Le Bin GC, Muñoz-Descalzo S, Kurowski A, Leitch H, Lou X, Mansfield W, Etienne-Dumeau C, Grabole N, Mulas C, Niwa H, Hadjantonakis AK, Nichols J. Oct4 is required for lineage priming in the developing inner cell mass of the mouse blastocyst. Development. PMID: 24504341

Boroviak T, Loos R, Bertone P, Smith A, Nichols J. The ability of inner-cell-mass cells to self-renew as embryonic stem cells is acquired following epiblast specification. Nature Cell Biology. PMID: 24859004

Boroviak T, Nichols J. The birth of embryonic pluripotency. Philosophical Transactions of the Royal Society B. PMID: 25349450

Stuart HT, van Oosten AL, Radzisheuskaya A, Martello G, Miller A, Dietmann S, Nichols J, Silva JC. NANOG amplifies STAT3 activation and they synergistically induce the naive pluripotent program. Current Biolog. PMID: 24462001

Takashima Y, Guo G, Loos R, Nichols J, Ficz G, Krueger F, Oxley , Santos F, Clarke J, Mansfield W, Reik W, Bertone P, Smith A. Resetting transcription factor control circuitry toward ground-state pluripotency in human. Cell. PMID: 25215486

Frankenberg SR, Frank D, Harland R, Johnson AD, Nichols J, Niwa H, Schöler HR, Tanaka E, Wylie C, Brickman JM. The POU-er of gene nomenclature. Development. PMID: 25053425

Collaborations

Anna Katerina Hadjantonakis	Memorial Sloane Kettering Cancer Centre - Joint paper
Silvia Munoz-Descalzo	University of Bath - Joint paper
Harry Moore	University of Sheffield
Fabienne Devrecker	Universite Libre de Bruxelles (ULB)
Joshua Brickman	University of Copenhagen, Danstem - Joint paper
Berenika Plusa	University of Manchester - Joint paper
Erika Sasaki	Keio University
With SCI Members	
Austin Smith	Multiple papers
Azim Surani	Joint paper
Jose Silva	Multiple papers
Kevin Chalut	Joint Leverhulme Trust grant
Christine Watson	Joint paper
Alfonso Martinez-Arias	Joint paper
Paul Bertone	Joint paper

Awards & Prizes

Awardee	Award
Stoyana Alexandrova	Seed Funding “Exploring the physical properties of exit form pluripotency in vivo”
Agata Kurowski	British Society for Developmental Biology registration grant

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	CSCR lab tour	03/2014	Demonstrator	Nichols
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Kurowski
Cambridge Alumni Festival	Alumni Festival	09/2014	Demonstrator	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.

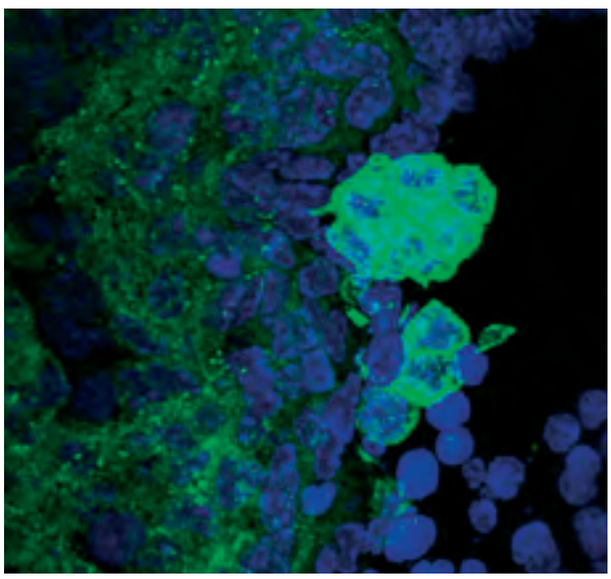
Funding

Kay Kendall Leukaemia Fund
Leukaemia & Lymphoma Research
Gabrielle's Angel Foundation

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.



c-kit+ intra-aortic cluster of emerging haematopoietic cells in the dorsal aorta
Image: Simon Fitch

Group Members

Chrysa Kapeni	Research Assistant/ Graduate Student
Neil Barrett	Graduate Student
Wendi Bacon	Graduate Student
Simon Fitch	Postdoc Researcher
Camille Malouf	Postdoc Researcher
Nada Zaidan	Graduate Student

2014 Publications

Mirshekar-Syahkal B, Fitch SR, Ottersbach K. From greenhouse to garden: the changing soil of the hematopoietic stem cell microenvironment during development. Stem Cells. PMID: 24578221

Key Publications prior to 2014

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. (2013) PMID:23327922

Malouf C, Ottersbach K. The Unconventional Embryo: Immune-Restricted Potential Precedes Multipotentiality. Cell Stem Cell. (2013) PMID:24209755

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

Collaborations

Sten Eirik Jacobsen	Weatherall Institute of Molecular Medicine, Oxford - Sharing of unpublished protocols
Thomas Milne	Weatherall Institute of Molecular Medicine, Oxford - Exchange of data and advise on leukaemia project
John Pimanda	University of New South Wales - Joint papers
Pablo Menendez	University of Barcelona - Exchange of reagents and protocols for leukaemia mouse model
Amy Wagers	Harvard Stem Cell Institute - Joint paper
With SCI Members	
Bertie Gottgens	Joint papers
Tony Green	Joint papers
Brian Huntly	Joint papers

Public Engagement

Event	Format	Date	Participation	Name
London International Youth Science Forum	Public Talk	07/2014	Speaker	Ottersbach

Mechanics of Mesoderm Differentiation in Mammalian Pluripotent Stem cells

Roger Pedersen

Roger Pedersen received his PhD in Biology from Yale in 1970. From 1971, he headed a research programme at UCSF exploring developmental potency and cell fate in early mouse development. In 2001 he relocated to Cambridge, where he led a team devoted to delivering human pluripotent stem cells to clinical use.

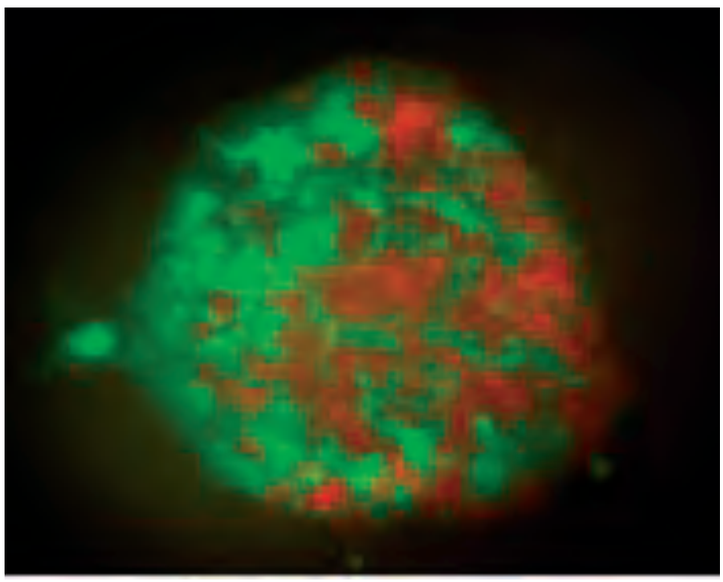
Roger became an Emeritus Professor in October 2014.

Funding

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

The Pedersen Lab focuses 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.

Their focus on mesoderm has now led 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. They also study the potential opportunities for guiding differentiation of pluripotent human stem cells into other cell types with potential clinical applications.



Migratory behaviour in human embryonic stem cells

Group Members

Sasha Mendjan	Postdoc Researcher
Mariaestela Ortiz	Postdoc Researcher
Daniel Ortmann	Postdoc Researcher
Filipa Soares	Graduate student (Pedersen/Vallier)
Victoria Mascetti	Graduate student
Stan Wang	Graduate student

2014 Publications

Mendjan S, Mascetti VL, Ortmann D, Ortiz M, Karjosukarso DW, Ng Y, Moreau T, Pedersen RA. NANOG and CDX2 pattern distinct subtypes of human mesoderm during exit from pluripotency. Cell Stem Cell. PMID: 25042702

Roberts RM, Loh KM, Amita M, Bernardo AS, Adachi K, Alexenko AP, Schust DJ, Schulz LC, Telugu BP, Ezashi T, Pedersen RA. Differentiation of trophoblast cells from human embryonic stem cells: to be or not to be? Reproduction. PMID: 24518070

Cheung C, Bernardo AS, Pedersen RA, Sinha S. Directed differentiation of embryonic origin-specific vascular smooth muscle subtypes from human pluripotent stem cells. Nature Protocols. PMID: 24675733

Soares FA, Chandra A, Thomas RJ, Pedersen RA, Vallier L, Williams DJ. Investigating the feasibility of scale up and automation of human induced pluripotent stem cells cultured in aggregates in feeder free conditions. Journal of Biotechnology. PMID: 24440272

Mascetti VL, Pedersen RA. Naiveté of the human pluripotent stem cell. Nature Biotechnology. PMID: 24406934

Veillard AC, Marks H, Bernardo AS, Jouneau L, Laloë D, Boulanger L, Kaan A, Brochard V, Tosolini M, Pedersen R, Stunnenberg H, Jouneau A. Stable methylation at promoters distinguishes epiblast stem cells from embryonic stem cells and the in vivo epiblasts. Stem Cells and Development. PMID: 24738887

Collaborations

With SCI Members

Ludovic Vallier	Joint papers
Kim Jensen	Joint papers

Stefano Pluchino

Stefano Pluchino received his MD and PhD from the University of Siena, Italy, where he qualified in Neurology. He then went on to hold two post doc positions with Gianvito Martino at the San Raffaele Institute.

Currently, Stefano is a University Lecturer - Honorary Consultant in Neurology within the Department of Clinical Neurosciences, University of Cambridge, and is a ERC Starting Independent Researcher.

Funding

Italian Ministry of Health
European Research Council
EU 7FP
The Evelyn Trust
The Bascule Charitable Trust
The Great Britain Sakakawa Foundation

Fellowships

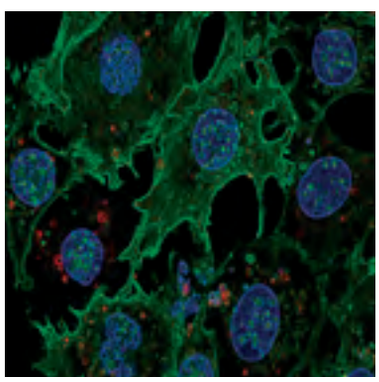
Giulio Volpe	EU Lifelong Learning Programme Fellowship
Luca Peruzzotti-Jametti	WT Research Training Fellowsip

Stem cell Signalling and Brain Repair

We have shown in animal disease models that neural stem cell (NSC) grafts protect the nervous system from slowly progressing secondary damage (neurodegeneration). However, before envisaging any human applications of such innovative therapies we need to confront with some key challenges:

1. The development of scale up protocols for safe stem cells under standardized conditions;
2. Route of cell injection, cell dosage and cell type/stage – learning from pre clinical models and providing feasibility concepts in humans;
3. Mechanisms of tissue repair/protection – investigating the modalities of stem cell integration and/or signalling;
4. Biomarkers of stem cell survival, biodistribution and functional effects.

Current projects are dealing with both pre clinical validation of the therapeutic potential of next generation directly induced NSCs, as well as exploitation of the different modalities by which grafted NSCs signal to the host immune system.



Fast two-hour uptake of CD63-RFP neural stem cell-derived extracellular membrane vesicles (EVs; red) packed via target cell fEGFP (green) membranes in vitro
Image: CongJian Zhao

Group Members

Dai Matsuse	Postdoc Researcher
Elena Giusto	Postdoc Researcher
Nunzio Iraci	Postdoc Researcher
Jayden A. Smith	Postdoc Researcher
Joshua Bernstock	Graduate Student
Matteo Donega'	Graduate Student
Irene Falk	Graduate Student
Florian Gessler	Graduate Student
Tommaso Leonardi	Graduate Student
Luca Peruzzotti-Jametti	Graduate Student
Jeroen Verheyen	Graduate Student
Giulio Volpe	Visiting Researcher
Iacopo Bicci	Undergraduate Student
Beatrice Balzarotti	Technician
Beatriz Vega-Blanco	Technician

2014 Publications

Cossetti C, Iraci N, Mercer TR, Leonardi T, Alpi E, Drago D, Alfaro-Cervello C, Saini HK, Davis MP, Schaeffer J, Vega B, Stefanini M, Zhao C, Muller W, Garcia-Verdugo JM, Mathivanan S, Bachi A, Enright AJ, Mattick JS, Pluchino S. Extracellular Vesicles from Neural Stem Cells Transfer IFN-γ via Ifngr1 to Activate Stat1 Signaling in Target Cells. Molecular Cell. PMID: 25242146

L'Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Serapide MF, Pluchino S, Marchetti B. Wnt/β-catenin signaling is required to rescue midbrain dopaminergic progenitors and promote neurorepair in ageing mouse model of Parkinson's disease. Stem Cells. PMID: 24648001

Cerri F, Salvatore L, Memon D, Martinelli Boneschi F, Madaghiele M, Brambilla P, Del Carro U, Taveggia C, Riva N, Trimarco A, Lopez ID, Comi G, Pluchino S, Martino G, Sannino A, Quattrini A. Peripheral nerve morphogenesis induced by scaffold micropatterning. Biomaterials. PMID: 24559639

L'Episcopo F, Tirolo C, Caniglia S, Testa N, Morale MC, Serapide MF, Pluchino S, Marchetti B. Targeting Wnt signaling at the neuroimmune interface for dopaminergic neuroprotection/repair in Parkinson's disease. Journal of Molecular Cell Biology. PMID: 24431301

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Donegà M, Giusto E, Cossetti C, Schaeffer J, Pluchino S. Systemic injection of neural stem/progenitor cells in mice with chronic EAE. Journal of Visualized Experiments. PMID: 24798882

Hermann DM, Peruzzotti-Jametti L, Schlechter J, Bernstock JD, Doeppner TR, Pluchino S. Neural precursor cells in the ischemic brain - integration, cellular crosstalk, and consequences for stroke recovery. Frontiers in Cellular Neuroscience. PMID: 25278840

Collaborations

Regina Armstrong	Uniformed Services University of the Health Sciences - Joint grants
Fabio Biscarini	University of Modena-Reggio Emilia - Joint grants
Mari Dezawa	Tohoku University - Joint grants and student supervision
Frank Edenhofer	University of Wurzburg - Joint grants and student supervision
Anton Enright	EBI-EMBL - Joint papers, grants and students supervision
Peixuan Guo	University of Kentucky - Joint projects and grants
John Hallenbeck	NIH/NINDS - Joint PhD students supervision
Phil Holliger	MRC-LMB - Joint projects and grants
Steve Jacobson	NIH/NINDS - Joint PhD students supervision
Steffen Jung	The Weizmann Institute of Science - Joint grants
Alon Monsonegro	Ben-Gurion University - Joint grants
With SCI Members	
Robin Franklin	Joint grants and student supervision

Awards & Prizes

Awardee	Award	Organisation
Irene Falk	Gates Cambridge Scholarship	The Gates Cambridge Trust
Florian Gessler	Gates Cambridge Scholarship	The Gates Cambridge Trust
Luca Peruzzotti-Jametti	Scholarship	Van Geest Foundation

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Donega
Big Biology Day	Science Festival	10/2014	Volunteer	Donega

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.

She joined the SCI in 2011.

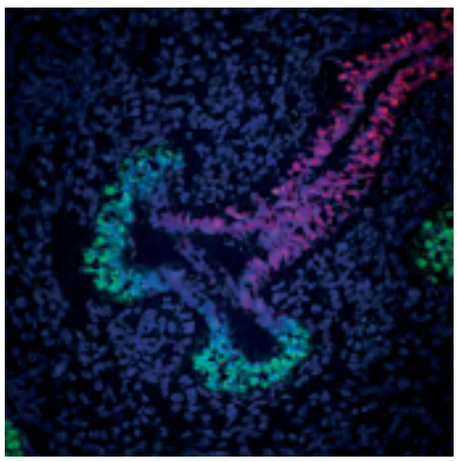
Funding

Wellcome Trust
MRC

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.



Epithelial stem cells (green) in a developing human lung
Image: Marko Nikolić

Group Members

Gayan Balasooriya	Graduate student
Christoph Budjan	Graduate student
Jo-Anne Johnson	Graduate student
Usua L. Garay	Postdoc Researcher
Marko Nikolic	Graduate student

2014 Publications

Rawlins EL, Giangreco A. The best laid schemes of airway repair. European Respiratory Journal. PMID: 25082909

Key Publications prior to 2014

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

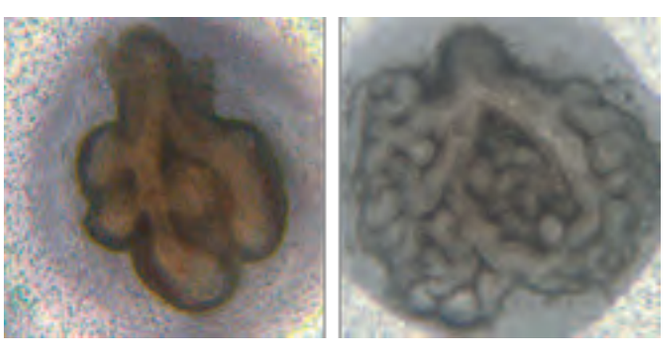
Rawlins EL, Ostrowski LE, Randell SH, Hogan BLM. Lung development and repair: contribution of the ciliated lineage. (2007) Proceedings of the National Academy of Sciences USA. PMID: 17194755

Collaborations

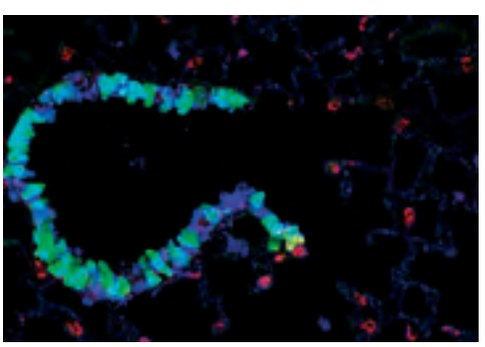
Albert Basson	King's College London - Sharing animal resources, paper in preparation
Cedric Blanpain	Universite Libre de Bruxelles - Lineage studies in mouse trachea
With SCI Members	
Bertie Gottgens	Assistance with single cell experiments, paper in preparation
Ben Simons	Collaboration on stem cell hierarchy in the mouse trachea, paper in preparation
Alfonso Martinez-Arias	Joint PhD Student supervision

Awards & Prizes

Awardee	Award	Organisation
Gayan Balasooriya	Best Poster Presenter	Gordon Research Conferences



Lung development: differentiated cell identity



Adult lung stem cells: cell lineage and control

José Silva

José Silva 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 PI at the SCI investigating the biology of induced pluripotency. His work was initially supported by a Next Generation Award (2008) and subsequently by a Wellcome-Trust Fellowship Award (2009). Recently, José was awarded a Wellcome-Trust Senior Research Fellowship. He started this in March 2014.

Funding

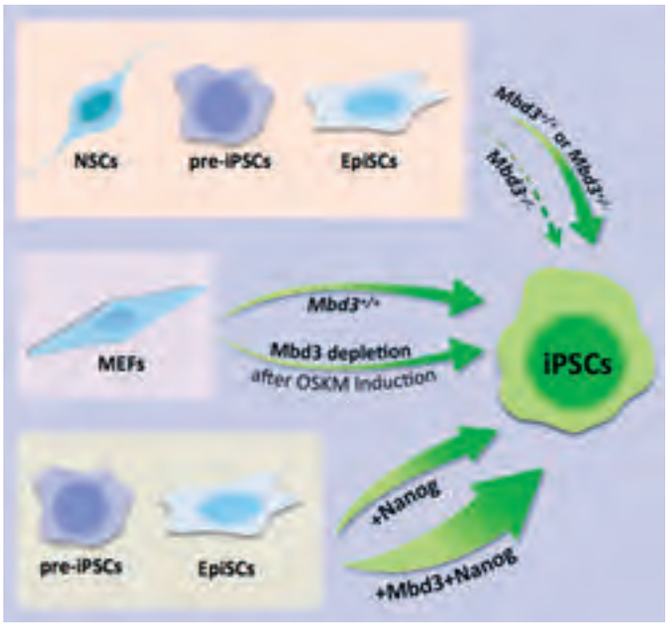
Wellcome Trust

MRC

Isaac Newton Trust

Biology of Induced Pluripotency

The aim of our lab is to understand the underlying biology of the conversion of a differianted cell back into a pluripotent cell, 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 indispensable before these can be used in biomedical applications.



Mbd3 facilitates cell reprogramming into pluripotent stem cells. These new cells have the potential to become any cell of the adult animal making them highly relevant for regenerative medicine.
Image: Yael Costa and Rodrigo Santos

Group Members

Yael Costa	Postdoc Researcher
Kathryn Tremble	Graduate Student
TY So	Research Assistant
Elsa Sousa	Graduate Student
Hannah Stuart	Graduate Student
Lawrence Bates	Graduate Student
Chibeza Agley	Postdoc Researcher (Silva/Chalut)
Charlotte Handford	Research assistant
Rodrigo dos Santos	Graduate Student
Moyra Lawrence	Graduate Student

2014 Publications

dos Santos RL, Tosti L, Radzisheuskaya A, Caballero IM, Kaji K, Hendrich B, Silva JC. MBD3/NuRD facilitates induction of pluripotency in a context-dependent manner. Cell Stem Cell. PMID: 24835571

Stuart HT, van Oosten AL, Radzisheuskaya A, Martello G, Miller A, Dietmann S, Nichols J, Silva JC. NANOG amplifies STAT3 activation and they synergistically induce the naive pluripotent program. Current Biology. PMID: 24462001

Christophorou MA, Castelo-Branco G, Halley-Stott RP, Oliveira CS, Loos R, Radzisheuskaya A, Mowen KA, Bertone P, Silva JC, Zernicka-Goetz M, Nielsen ML, Gurdon JB, Kouzarides T. Citrullination regulates pluripotency and histone H1 binding to chromatin. Nature. PMID: 24463520

Schwarz BA, Bar-Nur O, Silva JC, Hochedlinger K. Nanog is dispensable for the generation of induced pluripotent stem cells. Current Biology. PMID: 24461999

Silva JC, Pera RA. Editorial overview: cell reprogramming, regeneration and repair. Current Opinion in Genetics & Development. PMID: 25468515

Collaborations

Konrad Hochedling	HHMI and MGM Cancer Center, Boston, USA - Joint paper
Tony Kouzarides	Gurdon Institute - Joint paper
With SCI Members	
Jenny Nichols	Multiple papers
Kevin Chalut	Joint grant application and supervision
Brian Hendrich	Joint paper

Awards & Prizes

Awardee	Award	Organisation
José Silva	Promoted to Principal Research Associate (Reader)	University of Cambridge
José Silva	Wellcome Trust Senior Research Fellow	Wellcome Trust

Public Engagement

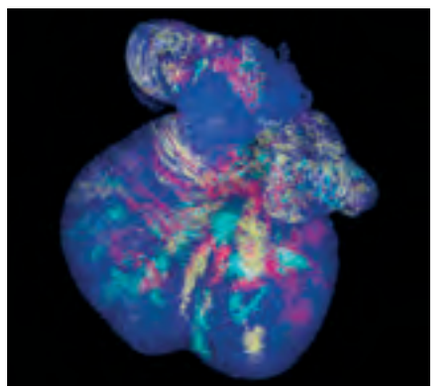
Event	Format	Date	Participation	Name
Science Festival Talk: “Reprogramming Adult Stem Cells Back into Embryonic Stem Cells”	Public Talk	03/2014	Speaker	Silva
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Lawrence, Stuart, Santos
Interview for Portuguese Science Radio Show “Conselho Cientifico” at University of Coimbra	Interview	09/2014	Interviewee	Silva

Tracing stem cell fate in development, maintenance, and disease

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.



Mouse heart marked with fluorescently labelled cells clonally marked by a genetic labelling system.
Image: Fabienne Lescroart

Group Members

Juergen Fink	Graduate Student (Koo/Simons)
Philip Greulich	Postdoc Researcher
Edouard Hannezo	Postdoc Researcher
Chris Hindley	Postdoc Researcher
Teresa Krieger	Graduate Student (Simons/Livesey)
Crystal McClain	Postdoc Researcher
Steffen Rulands	Postdoc Researcher
Hinal Tanna	Graduate Student
Magdalena Sznurkowska	Graduate Student (Simons/Philpott)

Ben Simons

Ben Simons 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 quantum 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 Physics.

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

Funding

Wellcome Trust
Human Frontiers Science Programme

Fellowships

Philip Greulich	German Academic Exchange Service

2014 Publications

Ritsma L, Ellenbroek SI, Zomer A, Snippert HJ, de Sauvage FJ, Simons BD, Clevers H, van Rheenen J. Intestinal crypt homeostasis revealed at single-stem-cell level by in vivo live imaging. Nature. PMID: 24531760

Hara K, Nakagawa T, Enomoto H, Suzuki M, Yamamoto M, Simons BD, Yoshida S. Mouse spermatogenic stem cells continually interconvert between equipotent singly isolated and syncytial states. Cell Stem Cell. PMID: 24792118

Gao P , Postiglione MP, Krieger TG, Hernandez L, Wang C, Han Z, Streicher C, Papusheva E, Insolera R, Chugh K, Kodish O, Huang K, Simons BD, Luo L, Hippenmeyer S, Shi S-H. Deterministic progenitor behavior and unitary neuron production in the neocortex. Cell. PMID: 25417155

Lescroart F, Chabab S, Lin X, Rulands S, Paulissen C, Rodolosse A, Auer H, Achouri Y, Dubois C, Bondue A, Simons BD, Blanpain C7 Early lineage restriction in temporally distinct populations of Mesp1 progenitors during mammalian heart development. Nature Cell Biology. PMID: 25150979

Barbera M, di Pietro M, Walker E, Brierley C, Macrae S, Simons BD, Jones PH, Stingl J, Fitzgerald RC. The human squamous oesophagus has widespread capacity for clonal expansion from cells at diverse stages of differentiation. Gut. PMID: 24572143

Alcolea MP, Greulich P, Wabik A, Frede J, Simons BD, Jones PH. Differentiation imbalance in single oesophageal progenitor cells causes clonal immortalization and field change. Nature Cell Biology. PMID: 24814514

Amoyel M, Simons BD, Bach EA. Neutral competition of stem cells is skewed by proliferative changes downstream of Hh and Hpo. EMBO Journal. PMID: 25092766

Baker AM, Cereser B, Melton S, Fletcher AG, Rodriguez-Justo M, Tadrous PJ, Humphries A, Elia G, McDonald SA, Wright NA, Simons BD, Jansen M, Graham TA. Quantification of crypt and stem cell evolution in the normal and neoplastic human colon. Cell Reports. PMID: 25127143

Centanin L, Ander JJ, Hoeckendorf B, Lust K, Kellner T, Kraemer I, Urbany C, Hasel E, Harris WA, Simons BD, Wittbrodt J. Exclusive multipotency and preferential asymmetric divisions in post-embryonic neural stem cells of the fish retina. Development. PMID: 25142461

Collaborations

Erika Bach	New York University School of Medicine
Cedric Blanpain	Universite Libre de Bruxelles
Hans Clevers	Hubrecht Institute
Songhai Shi	Memorial Sloane Kettering Cancer Centre
Hongjun Song	John Hopkins Medical School
William Harris	University of Cambridge
Jacco van Rheenen	Hubrecht Institute
Shosei Yoshida	National Institute for Basic Biology
Jochen Wittbrodt	University of Heidelberg
Samuel Janes	University College London
Peter Dirks	Hospital for Sick Children, Toronto
With SCI Members	
Tony Green	
Anne Ferguson-Smith	

Awards & Prizes

Awardee	Award	Organisation
Ben Simons	Franklin Medal and Prize	Institute of Physics

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

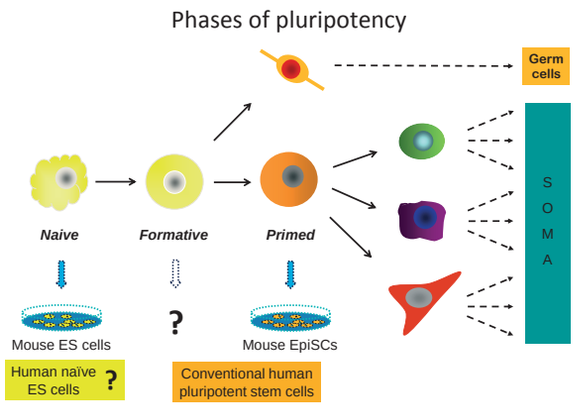
BBSRC
MRC
Wellcome Trust
EC
JST
JPA

Fellowships

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

Stem Cell Potency

Our group studies pluripotent stem cells that can be expanded in vitro while retaining the ability to generate all types of cell. Our goal is to understand how pluripotency is generated and to reveal the molecular programme that proceeds into multilineage commitment (see Figure). We seek to find common principles that underpin pluripotency in different mammalian species. In mouse, stem cells corresponding to the beginning and end states of pluripotency can be captured and propagated. We are currently focussing on determining conditions for obtaining and propagating human stem cells in the initial naïve state analogous to mouse embryonic stem cells. We are also investigating the isolation and stable propagation of cells in the intermediate formative stage of pluripotency. Our long-term goal is to control the growth and differentiation of human pluripotent stem cells to obtain insights into early human embryo development and for applications in drug discovery and regenerative medicine.



Pluripotency can be divided into three phases; naïve, formative, and primed. Mouse embryonic stem cells correspond to naïve pluripotency while post-implantation epiblast stem cells (EpiSCs) represent primed pluripotency. Conventional human pluripotent stem cells are similar to EpiSCs.

Group Members

Yaoyao Chen	Postdoc Researcher
James Clarke	Laboratory manager
Rosalind Drumond	Research assistant
Ge Guo	Postdoc Researcher
Tuzer Kalkan	Postdoc Researcher
Masaki Kinoshita	Postdoc Researcher
Martin Leeb	Postdoc Researcher
Meng Amy Li	Postdoc Researcher
Rika Takashima	Assistant
Yasuhiro Takashima	Postdoc Researcher
Mariya Rostovskaya	Postdoc Researcher
Meryem Ralser	Bioinformatician
Harry Leitch	Visiting Researcher
Nicholas Bredenkamp	Postdoc Researcher
Sam Myers	Graduate Student
Ella Jones	Research assistant
Stanley Strawbridge	Graduate Student
Isabelle Nett	Postdoc Researcher
Yasmin Paterson	Research assistant

2014 Publications

Dunn SJ, Martello G, Yordanov B, Emmott S, Smith AG. Defining an essential transcription factor program for naïve pluripotency. Science. PMID: 24904165

Leeb M, Dietmann S, Paramor M, Niwa H, Smith A. Genetic exploration of the exit from self-renewal using haploid embryonic stem cells. Cell Stem Cell. PMID: 24412312

Takashima Y, Guo G, Loos R, Nichols J, Ficz G, Krueger F, Oxley D, Santos F, Clarke J, Mansfield W, Reik W, Bertone P, Smith A. Resetting transcription factor control circuitry toward ground-state pluripotency in human. Cell. PMID: 25215486

Herberg M, Kalkan T, Glauche I, Smith A, Roeder I. A model-based analysis of culture-dependent phenotypes of mESCs. PLoS One. PMID:24643025

Yang SH, Kalkan T, Morissroe C, Marks H, Stunnenberg H, Smith A, Sharrocks AD. Otx2 and Oct4 drive early enhancer activation during embryonic stem cell transition from naive pluripotency. Cell Reports. PMID: 24931607

Boroviak T, Loos R, Bertone P, Smith A, Nichols J. The ability of inner-cell-mass cells to self-renew as embryonic stem cells is acquired following epiblast specification. Nature Cell Biology. PMID: 24859004

Martello G, Smith A. The nature of embryonic stem cells. Annual Review of Cell and Developmental Biology. PMID: 25288119

See page 61 for additional publications from the Smith group

Collaborations

Hitoshi Niwa	RIKEN Centre for Developmental Biology
Yves Barde	Swiss National Science Foundation Biozentrum - 'Sinergia' Consortium
Clare Blackburn	University of Ediburgh - 'EuroStemCell' Consortium
Francis Stewart	Technische Universitaet, Dresden - 'SyBoSS' Consortium
Daniel Pipeleers	Centre for Beta Cell Therapy in Diabetes, Brussels - 'BetaCell Therapy' Consortium
Tom Burdon	The Roslin Institute, Edinburgh
Norbert Hubner	Max-Dulbruck-Centre for Molecular Medicine - 'Eura Trans' Consortium
Stephen Emmott/ Sarah-Jane Dunn	Microsoft Research Cambridge
Henk Stunnenberg/ Hendrik Marks	Nijmegen Centre for Molecular Life Sciences
Christian Dani	University of Nice
Peter Andrews	University of Sheffield
David Williams	Loughborough University
Stem Cell Technologies	PluriMes Consortium
With SCI Members	
Jenny Nichols	Joint papers
Azim Surani	
Roger Barker	
Thora Karadottir	
Paul Bertone	Joint papers
Wolf Reik	

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Rostovskaya
Cambridge Literary Festival, "Thinking aloud 1—Stem Cells"	Public Talk	04/2014	Speaker	Smith
Interview for The Guardian	Interview	01/2014	Interviewee	Smith
Interview on BBC World Service	Interview	01/2014	Interviewee	Smith
Interview on National Public Radio	Radio Interview	01/2014	Interviewee	Smith
Interview for Time Magazine	Interview	01/2014	Interviewee	Smith
Interview with Anna Azvolinsky, Science	Interview	06/2014	Interviewee	Smith
Interview for The Stem Cell Podcast	Interview	08/2014	Interviewee	Smith
Interview for Portuguese Science Radio show "Conselho Cientifico" at University of Coimbra	Interview	09/2014	Interviewee	Smith

Specification and Programming of the Germline for Totipotency and Development

Azim Surani

Azim Surani was 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 and in 2014 McEwan Award for Innovation, The International Society for Stem Cell Research.

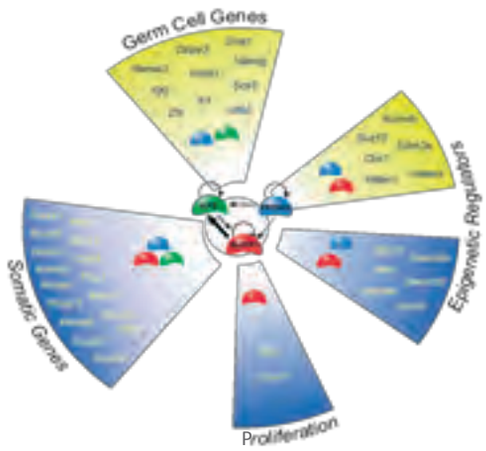
Funding

Wellcome Trust
Human Frontier Science Programme
British Council, Israel (BIRAX)
BBSRC

Fellowships

Ufuk Gunesdogan	EC Marie Curie Postdoctoral Fellowship
Toshihiro Kobayashi	JSPS Postdoctoral Fellowship for Research Abroad
Julia Tischler	Austrian Academy of Science Fellowship
Wolfram Gruhn	EMBO Fellowship

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.



The transcriptional network for mouse primordial germ cell specification . Image: Erna Magnusdottir

Group Members

Delphine Cougot	Postdoc Researcher
Vinh Dang Do	Postdoc Researcher
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

2014 Publications

Singer ZS, Yong J, Tischler J, Hackett JA, Altinok A, Surani MA, Cai L, Elowitz MB. Dynamic heterogeneity and DNA methylation in embryonic stem cells. Molecular Cell. PMID: 25038413

Magnúsdóttir E, Surani MA. How to make a primordial germ cell. Development. PMID: 24381195

Kim S, Günesdogan U, Zylicz JJ, Hacket JA, Cougot D, Bao, S, Lee C, Dietmann S, Allen GE, Sengupta R, Surani MA . PRMT5 protects genomic integrity during global DNA demethylation in primordial germ cells and preimplantation embryos. Molecular Cell. PMID: 25457166

Hackett JA, Surani MA. Regulatory Principles of Pluripotency: From the Ground State Up. Cell Stem Cell. PMID: 25280218

Günesdogan U, Magnúsdóttir E, Surani MA. Primoridal germ cell specification: a context-dependent cellular differentiation event. Philosophical Transactions of the Royal Society B. PMID: 25349452

Irie N, Weinberger L, Tang WW, Kobayashi T, Viukov S, Manor YS, Dietmann S, Hanna JH, Surani MA. SOX17 Is a Critical Specifier of Human Primordial Germ Cell Fate. Cell. PMID: 25543152

Irie N, Tang WW, Azim Surani M. Germ cell specification and pluripotency in mammals: a perspective from early embryogenesis. Reproductive Medicine and Biology. PMID: 25298745

Collaborations

Michael Elowitz/Uri Alon	California Institute of Technology
Jacob Hanna	The Weizmann Institute of Science
Patrick Chinnery	Wellcome Centre for Mitochondrial Research
Ramiro Alberio	University of Nottigham
With SCI Members	
Austin Smith	
Jenny Nichols	

Awards & Prizes

Awardee	Award	Organisation
Azim Surani	2014 McEwen Award for Innovation	ISSCR
Wolfram Gruhn	EMBO Long term fellowship	EMBO

Ludovic Vallier

Ludovic Vallier 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
EU FP7
MRC/UKRMP II

Mechanisms Controlling Differentiation of Pluripotent Stem Cells into Definitive Endoderm

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.

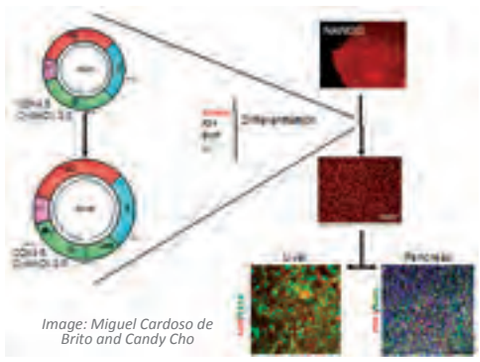
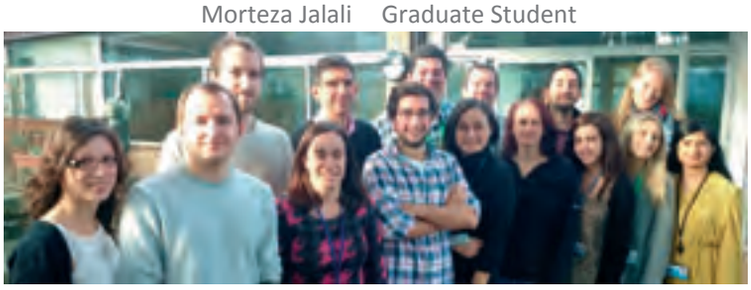


Image: Miguel Cardoso de Brito and Candy Cho

Cell cycle regulation of human pluripotent stem cells differentiation.

Group Members

Stephanie Brown	Research Assistant
Sapna Vyas	Research Assistant
Imbisaat Geti	Research Assistant /PhD student
Nicholas Hannan	Postdoc Researcher
Siim Pauklin	Postdoc Researcher
Mariya Chhatriwala	Postdoc Researcher
Pedro Madrigal	Postdoc Researcher
Kasia Tilgner	Postdoc Researcher
Sasha Medjan	Postdoc Researcher
Filipa Soares	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
Ranna El Khairi	Graduate student
Casey Rimland	Graduate student
Ana Osnato	Graduate student
Loukia Yiangou	Graduate student (Vallier/Sinha)
Kathleen Elliott	Graduate Student
Morteza Jalali	Graduate Student



2014 Publications

Gieseck RL 3rd, Hannan NR, Bort R, Hanley NA, Drake RA, Cameron GW, Wynn TA, Vallier L. Maturation of induced pluripotent stem cell derived hepatocytes by 3D-culture. PLoS One. PMID: 24466060

Soares FA, Chandra A, Thomas RJ, Pedersen RA, Vallier L, Williams DJ. Investigating the feasibility of scale up and automation of human induced pluripotent stem cells cultured in aggregates in feeder free conditions. Journal of Biotechnology. PMID: 24440272

Rouhani F, Kumasaka N, de Brito MC, Bradley A, Vallier L, Gaffney D. Genetic background drives transcriptional variation in human induced pluripotent stem cells. PLoS Genetics. PMID: 24901476

Jalali M, Kirkpatrick WN, Cameron MG, Pauklin S, Vallier L. Human stem cells for craniomaxillofacial reconstruction. Stem Cells and Development. PMID: 24564584

Vallier L. Heps with pep: direct reprogramming into human hepatocytes. Cell Stem Cell. PMID: 24607399

Gieseck RL 3rd, Colquhoun J, Hannan NR. Disease modeling using human induced pluripotent stem cells: Lessons from the liver. Biochimica et Biophysica Acta (BBA). PMID: 24943800

Baxter M, Withey S, Harrison S, Segeritz C, Zhang F, Atkinson-Dell R, Rowe C, Gerrard DT, Sison-Young R, Jenkins R, Henry J, Berry AA, Mohamet L, Best M, Fenwick SW, Malik H, Kitteringham NR, Goldring CE, Piper Hanley K, Vallier L, Hanley NA. Phenotypic and functional analyses show stem cell-derived hepatocyte-like cells better mimic fetal rather than adult hepatocytes. Journal of Hepatology. PMID: 25457200

See page 61 for additional publications from the Vallier group

Collaborations

Neil Hanley	University of Manchester - Multiple joint papers
Jorge Ferrer	Imperial College London - Multiple joint papers
Stephen Dalton	University of Georgia - Joint paper
Andrew Hatersley	University of Exeter - Joint paper
Daniel Gaffney	Wellcome Trust Sanger Institute - Joint paper
David Lomas	University College London - Multiple joint papers
Oliver Bilker	Wellcome Trust Sanger Institute - Scientific collaboration
Gordon Dougan	Wellcome Trust Sanger Institute - Scientific collaboration
Paolo di Coppi	University College London - Multiple joint papers
Darrell Kotton	Boston University - Joint paper
Siddharthan Chandran	University of Edinburgh - Joint paper and grant application
With SCI Members	
Kim Jensen	Joint paper and grant application
Roger Pedersen	Multiple joint papers

Awards & Prizes

Awardee	Award	Organisation
Casey Rimland	Gates Scholar	Gates Cambridge Trust
Trey Gieseck	Selected for the Global Young Scientists Summit 2015	National Research Foundation (NRF) Singapore
Alessandro Bertero	Keystone Conference selected talk	Keystone Conference
Siim Pauklin	Keystone Meeting Scholarship	Keystone Conference
Filipa Soares	Travel Grant	ISSCR Annual Meeting

Public Engagement

Event	Format	Date	Participation	Name
Cambridge Science Festival	Science Festival	03/2014	Volunteer	Osnato, El Khairi
SET for Britain	Poster Presentation - Parliament House	06/2014	Presenter	Hannan
Big Biology Day	Science Festival	10/2014	Volunteer	Osnato
Neonatal Diabetes Family Days - Exeter University	Open Day	03/2014	Speaker & Volunteer	El Khairi

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.

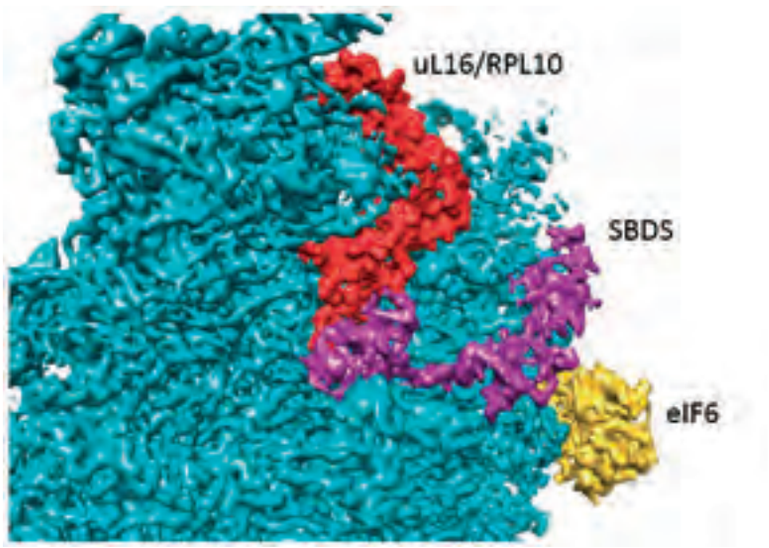
Funding

Leukaemia & Lymphoma Research
Medical Research Council

Mechanisms of ribosome assembly and stem cell subversion

Ribosomes are essential for the generation of all the cellular proteins required for growth. How these macromolecular machines are assembled with high fidelity and the surveillance mechanisms that monitor this process still remain poorly understood.

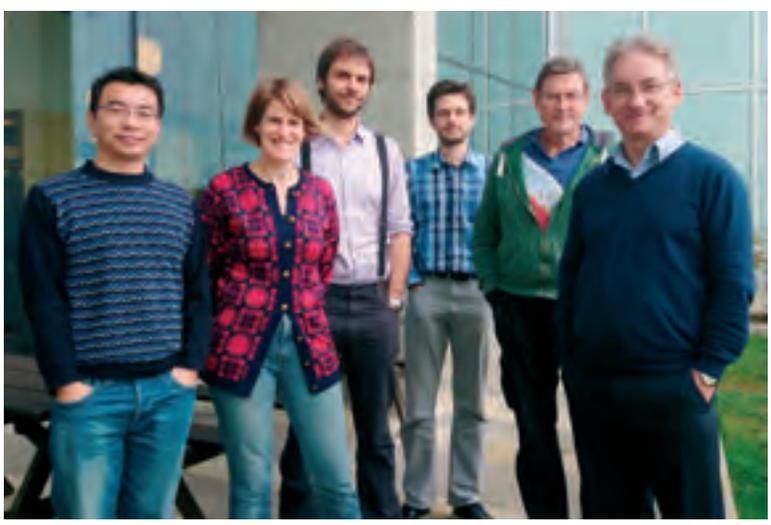
We apply genetic, biochemical and structural (including X-ray crystallography, NMR and cryo-electron microscopy) approaches to probe the mechanisms of ribosome biogenesis and understand how defects in this process cause stem cell subversion and cancer predisposition.



60S ribosomal subunit maturation visualised by cryo-electron microscopy
Image: Alan Warren

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 2014

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

Collaborations

Sjors Scheres	MRC LMB - Co-investigator on MRC Programme Grant
Mark Bycroft	MRC LMB - Co-Investigator on MRC Programme Grant
Minmin Yu	MRC LMB - Solved structures of ligand-protein complexes with Christine Hilcenko in the group
Rob Kay	MRC LMB - Collaborator on recent Cryo-EM paper
Cornelis Carlkhoven	ERIBA, Netherlands - Collaborator on Blood paper submission
Marieke von Lindern	Sanquin Research , Netherlands - Collaborator on Blood paper submission

Awards & Prizes

Awardee	Award	Organisation
Alan Warren	MRC Programme Fund	Medical Research Council

Public Engagement

Event	Format	Date	Name
Charity Fundraising - communicating research to the public about Schwachman-Diamond syndrome	Public Talk	11/2014	Warren
LMB Open Day - Interactive activities for children and adults	Open Day	06/2014	Churcher, Hilcenko
Cambridge Science Festival - Interactive activities	Science Festival	03/2014	Churcher

Additional Group Publications

Barker Group

Onorati M, Castiglioni V, Biasci D, Cesana E, Menon R, Vuono R, Talpo F, Goya RL, Lyons PA, Bulfamante GP, Muzio L, Martino G, Toselli M, Farina C, Barker RA, Biella G, Cattaneo E. **Molecular and functional definition of the developing human striatum.** *Nature Neuroscience*. PMID: 25383901

Drouin-Ouellet J, Barker RA. **Stem cell therapies for Parkinson's disease: are trials just around the corner?** *Regenerative Medicine*. PMID: 25372072

Franklin Group

Montani L, Buerki-Thurnherr T, de Faria JP, Pereira JA, Dias NG, Fernandes R, Gonçalves AF, Braun A, Benninger Y, Böttcher RT, Costell M, Nave KA, Franklin RJ, Meijer D, Suter U, Relvas JB. **Profilin 1 is required for peripheral nervous system myelination.** *Development.* PMID: 24598164

Franklin RJ, Snyder EY. **Special issue on stem cells: "the end of the beginning**. *Experimental Neurology.* PMID: 24950181

Gottgens Group

Joshi A, Gottgens B. **Concerted bioinformatic analysis of the genome-scale blood transcription factor compendium reveals new control mechanisms**. *Molecular Biosystems.* PMID: 25133983

Tanaka Y, Sanchez V, Takata N, Yokomizo T, Yamanaka Y, Kataoka H, Hoppe PS, Schroeder T, Nishikawa S. **Circulation-independent differentiation pathway from extraembryonic mesoderm toward hematopoietic stem cells via hemogenic angioblasts**. *Cell Reports.* PMID: 24981862

Sive JI, Göttgens B. **Transcriptional network control of normal and leukaemic haematopoiesis**. *Experimental Cell Research.* PMID: 25014893

Ng FS, Calero-Nieto FJ, Göttgens B. **Shared transcription factors contribute to distinct cell fates**. *Transcription.* PMID: 25425188

Ng FS, Schütte J, Ruau D, Diamanti E, Hannah R, Kinston SJ, Göttgens B. **Constrained transcription factor spacing is prevalent and important for transcriptional control of mouse blood cells**. *Nucleic Acids Research.* PMID: 25428352

Shaham L, Vendramini E, Ge Y, Goren Y, Birger Y, Tijssen MR, McNulty M, Geron I, Schwartzman O, Goldberg L, Chou ST, Pitman H, Weiss MJ, Michaeli S, Sredni B, Göttgens B, Crispino JD, Taub JW, Izraeli S. **MicroRNA-486-5p is an erythroid oncomiR of the myeloid leukemias of Down syndrome**. *Blood.* PMID: 25533034

Smith Group

Kinoshita M. **How are pluripotent cells captured in culture?** *Reproductive Medicine and Biology, dx.doi.org/10.1007/s12522-014-0199-8*

Kalkan T, Smith A. **Mapping the route from naive pluripotency to lineage specification**. *Philosophical Transactions of the Royal Society B*. PMID: 25349449

Vallier Group

Soares FA, Sheldon M, Rao M, Mummery C, Vallier L. **International coordination of large-scale human induced pluripotent stem cell initiatives: Wellcome Trust and ISSCR workshops white paper.** *Stem Cell Reports*. PMID: 25496616

Sampaziotis F, Segeritz CP, Vallier L. **Potential of human Induced Pluripotent Stem Cells in studies of liver disease**. *Hepatology*. PMID: 25502113

Pluripotent Stem Cell Platform

The UKRMP's Cell Behaviour, Differentiation and Manufacturing Hub, the Pluripotent Stem Cell Platform (PSCP), builds upon emerging pluripotent stem cell (PSC) technologies to establish optimised processes for consistent and scalable cell manufacturing to meet the requirements of clinicians, regulatory authorities and industry for cell therapy applications. The PSCP commenced in February 2014.

The PSCP is developing protocols for transgene-free, EUCTD-compliant, production, expansion and safety qualification of PSCs; methods to understand and minimise functionally significant genetic or epigenetic variants during PSC manufacturing; standardised PSC differentiation protocols to underpin the derivation, manufacture and banking of therapeutically relevant, lineage-specific, intermediate stem cells.

The PSCP will also provide qualified processes for manufacturing regulatory compliant PSC products suitable for clinical use. As disease exemplars the PSCP will focus initially on the degenerative conditions of Parkinson's disease and neuropathic deafness.

http://www.ukrmp.org.uk/hubs/pscp/

UK Regenerative Medicine Platform

Project Manager

Dr Philip Driver
pmd46@cam.ac.uk

Staff

Dr Ruchi Sharma, Research Associate
Dr Loriana Vitillo, Research Associate
Catherine Durance, Research Assistant
Vasiliki Symeonidou, Research Assistant

Principal Investigators

Hub Director
Professor Peter Andrews, University of Sheffield

Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute
Professor Austin Smith
Professor Robin Franklin
Professor Roger Barker
Dr Ludovic Vallier

University of Sheffield, Centre for Stem Cell Biology
Professor Harry Moore
Dr Marcelo Rivolta

Loughborough University, EPSRC Centre for Innovative Manufacturing in Regenerative Medicine
Professor David Williams,
Professor Nicholas Medcalf
Dr Rob Thomas

NIBSC
Professor Glyn Stacey

Wellcome Trust Sanger Institute
Professor Mike Stratton
Dr Kosuke Yusa

Babraham Institute
Professor Wolf Reik

Bioinformatics

Sabine Dietmann, Meryem Ralser, Patrick Lombard, Jelena Aleksic, Lila Diamanti

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 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. At a more integrative level, it helps analyze and catalogue the biological pathways and networks that are an important part ofsystems 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.

Training

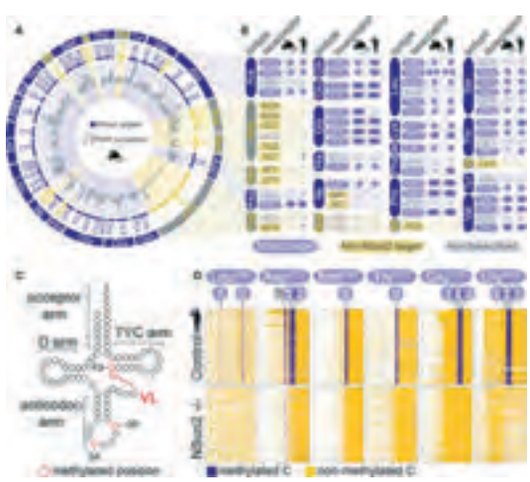
Training for experimentalists is provided in PERL scripting, R/Bioconductor statistical computing and applications of open-source software platforms, such as Galaxy or SeqMonk.

Examples of publications in 2014

Leeb M, Dietmann S, Paramor M, Niwa H, Smith A. Genetic exploration of the exit from self-renewal using haploid embryonic stem cells. Cell Stem Cell. PMID: 24412312

Blanco S, Dietmann S, Flores JV, Hussain S, Kutter C, Humphreys P, Lukk M, Lombard P, Treps L, Popis M, Kellner S, Hölter SM, Garrett L, Wurst W, Becker L, Klopstock T, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Káradóttir RT, Helm M, Ule J, Gleeson JG, Odom DT, Frye M. Aberrant methylation of tRNAs links cellular stress to neuro-developmental disorders. EMBO Journal. PMID: 25063673

Sánchez-Castillo M, Ruau D, Wilkinson AC, Ng FS, Hannah R, Diamanti E, Lombard P, Wilson NK, Gottgens B. CODEX: a next-generation sequencing experiment database for the haematopoietic and embryonic stem cell communities. Nucleic Acids Research. PMID: 25270877



Core Bioinformatics Staff

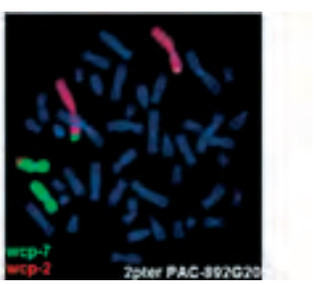
Sabine Dietmann (Manager)
Lila Diamanti
Patrick Lombard

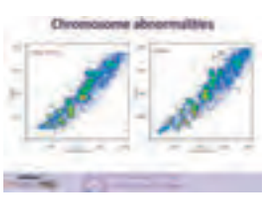
Other SCI Bioinformaticians

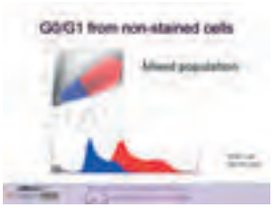
Meryem Ralser (Smith & Hendrich Labs)
Jelena Aleksic (Frye Lab)
Tommaso Leonardi (Pluchino Lab)
Felicia Ng, Rebecca Hannah, Manuel Sanchez-Castillo, David Ruau (Gottgens Lab)
Eshwar Meduri (Huntly Lab)

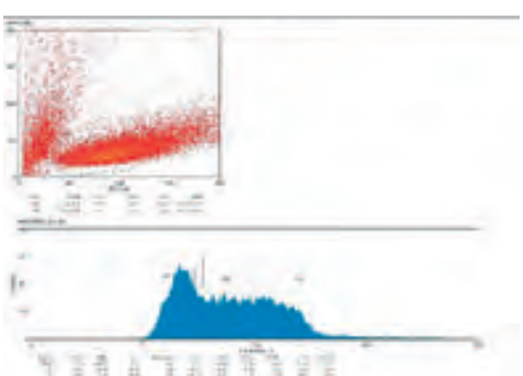
Flow Cytometry

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 opto-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:

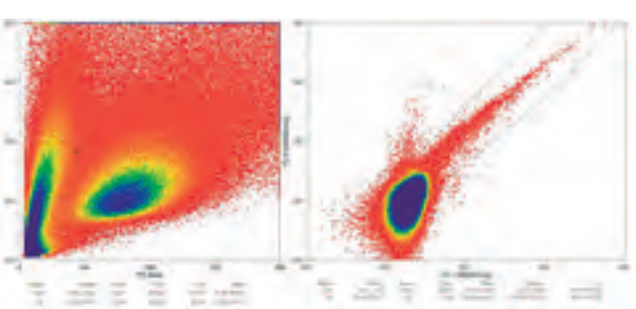
Beckman Coulter MoFlo 3 laser system with up to 12 parameters.
BioRad S3 Bench to sorter with 2 lasers and 7 parameters.
A BD Aria IIu sorter with 3 lasers and up to 12 parameters.

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 (Manager)

Histopathology

Kate Bird, John Brown and Helen Skelton

Histopathology is the study of the microscopic anatomy of tissue. It enables the morphological examination of DNA, proteins, bacteria and other tissue components in both normal and diseased specimens.

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. Slides can be stained with haematoxylin and eosin or a variety of tinctorial stains.

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. 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.

RNAScope

We now offer a bespoke RNA-in situ service for formalin fixed paraffin embedded tissues, using the ACD Ltd RNAScope systems. We can offer RNA-In situ probes from over a thousand sequences or have probe made for you. We offer either single or dual staining with this system.

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 immunohistochemical stainer is also available.

Training

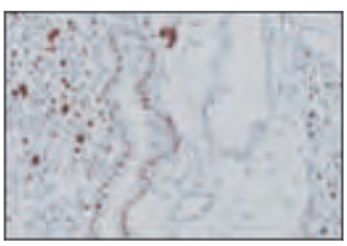
Training is available for all SCI members in cryosectioning and microtomy, immunohistochemical techniques and TMA manufacture.

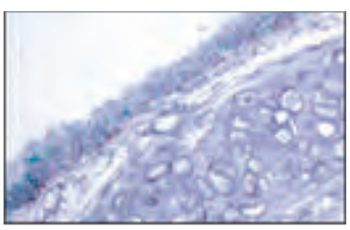
External Requests

The SCI histology facility is happy to discuss training and provision of services for all Cambridge University researchers.

Staff
John Brown (Manager), Helen Skelton, Kate Bird, Andrea Starling

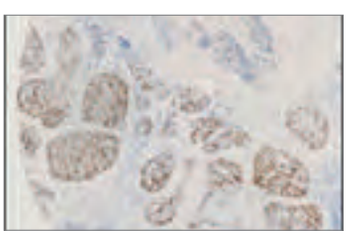
RNAScope with DAB chromogen for MYC

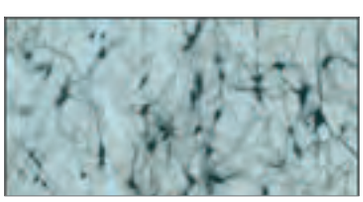




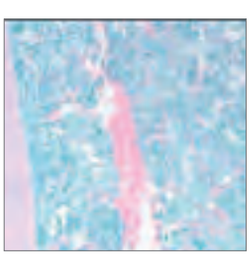
RNAScope Duplex staining (red & blue)

Immunohisto-chemistry on tissue microar-ray – ki67 (brown)





Golgi Cox silver stain for dendritic processes in the brain



Giemsa stain for Haemopoetic cells in bone marrow

Advanced Light Microscopy

Peter Humphreys

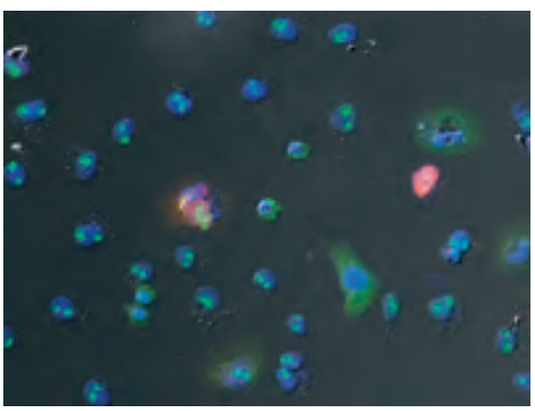
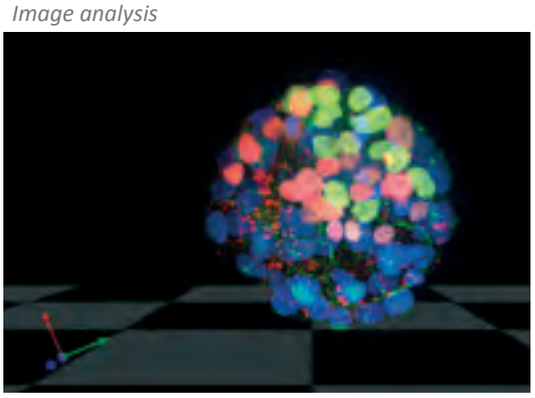


Image analysis



Labelled blastocyst

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

- 2x Leica SP5 Confocal Microscopes
- Andor Revolution XD Spinning Disk Confocal microscope
- High Content screening/live cell imaging Leica Matrix HCS/ GE InCell
- Nikon Biostation IM
- Essen Incucyte HD
- Zeiss Imager structured illumination & transmitted light (H&E)
- Tissue Culture Microscopes & research grade fluorescence microscopes.
- Zeiss LSM 710 Fluorescence Correlation Spectroscopy/ lifetime imaging

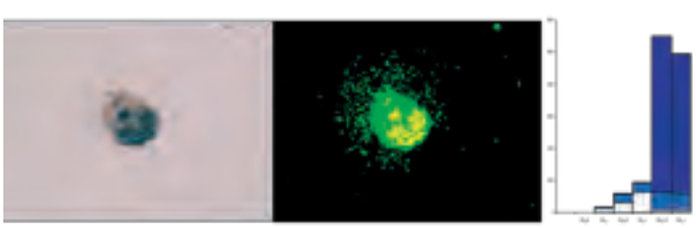
Training

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

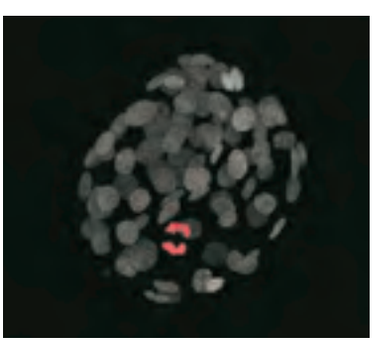
Data Analysis

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



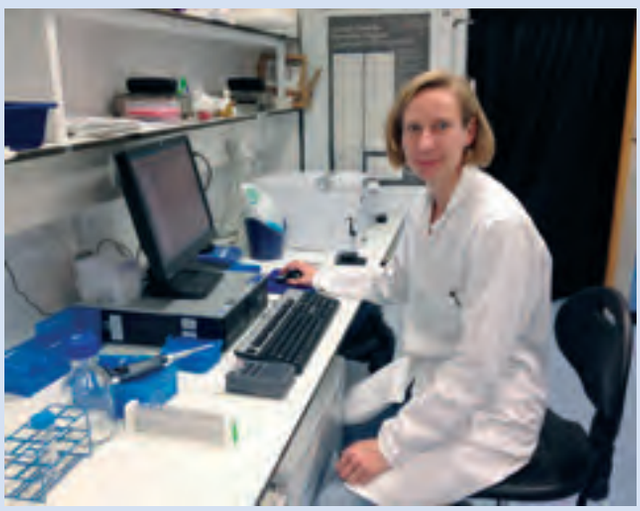
Colony analysis

Staff
Peter Humphreys (Manager)



Blastocyst with dividing cell labelled

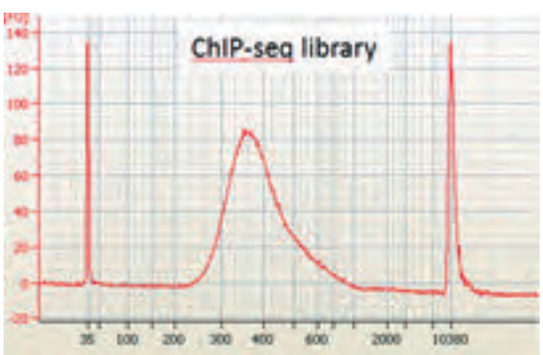
Next Generation Sequencing Libraries



Maike Paramor

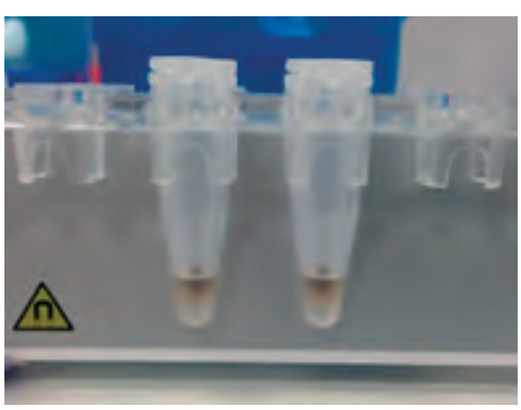
This facility provides the preparation of DNA/RNA libraries for Next Generation Sequencing (NGS) projects to support all SCI scientists.

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.



Services

- Help and advice with project planning
- Transcriptome/RNA-seq libraries
- Small RNA libraries
- ChIP-seq libraries
- DNA/amplicon libraries
- Nextera libraries
- Single cell or low input amount of RNA libraries
- Access to a Fluidigm C1 for single cell projects
- 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.

Currently available preparations/kits:

- Illumina small RNA library kit
- Nextflex directional RNA seq kit V2 (Illumina)
- Nextflex adapters for multiplexing up to 24 samples (Illumina)
- Nextflex rapid DNA libraries and ChIP libraries
- NEBNext reagents for standard Illumina
- Nextera XT reagents for tagmentation libraries
- Covaris S2 instrument for DNA/RNA shearing and chromatin shearing
- Bioanalyzer for QA of libraries and input material

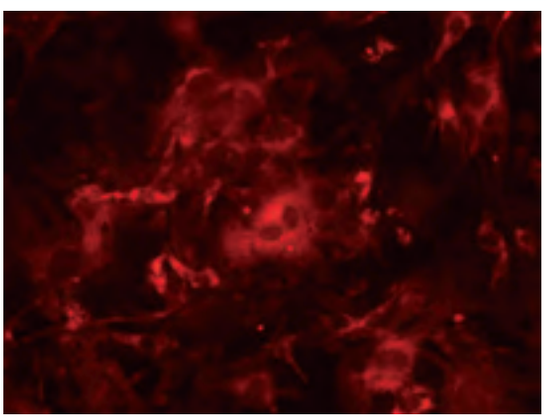
Sequencing

The SCI has purchased a 10% share in two HiSeq2500 sequencing machines 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. Even if you choose to prepare your NGS libraries in your own labs, this access is available to all SCI members.

Staff
Maike Paramor (Manager)

Tissue Culture

Jean Thompson, Miranda King, Sally Lees, Kamila Bulczak



DSred Mef cells

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 (Manager) Kamila Bulczak Diana Breitmaier Jean Thompson Roy Ramon-Pelegrin

IT

Paul Barrow and Paul Sumption

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 Infomation 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 9.30am - 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

Resources & Other Support Services

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 6 years, this platform has derived and characterised more then 700 hIPSC lines from 200 patients suffering from neurodegenerative diseases, cardiovascular syndromes, metabolic and blood disorders. More recently, the core facility has started to generate disease models using genome editing technology to introduce genetic anomalies in hIPSCs. 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 Wellcome Trust- MRC Stem Cell Institute Anne McLaren Laboratory, 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 Addenbrooke's Biomedical Campus. http://www.cambridge-brc.org.uk/.

For more information about the BRC hIPSC core facility please visit: http://www.cambridge-brc.org.uk/hipsc-core-facility or contact: lv225@cam.ac.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.

General Administration

Institute Administrator: Lynn Kennedy (until Sept. 2014)
Principal Assistant: Jeanne Estabel
SCI Coordinator: Vacant post
Senior Clerical Assistant: Jo Jack
Principal Sec./Austin Smith's PA: Bethan Rees
Administrative Assistant (Data): Susana Camacho
Administrative Assistant (HR): Edita Paralova
Receptionist: Klara Cichovska
LRM Lab Manager: Morgan Alexander
Public Engagement Officer: Vacant post
Plurimes Office: Jenny Nelder & Charlotte Taylor
Regenerative Medicine Secretary: Helen Anderson
Senior Grants/Accounts Clerk: Louise Carter
Accounts Clerks: Liz Irvine & David Hughes

Building Maintenance Team

Snr. Chief Building Services Tech.: Alistair Finlayson
Chief Building Services Technician: Paul Vaes
Custodian: Christian Zwierzanski
Assistant: Andrew Ayling
Cleaners: Roy Pelegrin & Agne Jukneviciene
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 2014 the Institute welcomed two new Affiliate members:

- Professor Andrew McCaskie— Department of Surgery, University of Cambridge
- Dr Meritxell Huch - Wellcome Trust/ Cancer Research UK Gurdon Institute

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 Genetics

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 Meritxell Huch
Stem Cells and Tissue regeneration. Implications in disease and cancer

UNIVERSITY OF CAMBRIDGE
Gurdon 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

Professor Andrew McCaskie
Translational research into regenerative treatments for musculoskeletal disease

UNIVERSITY OF CAMBRIDGE
Dept of Surgery

Dr Jenny Pell
Regulation of adult muscle stem cell behaviour

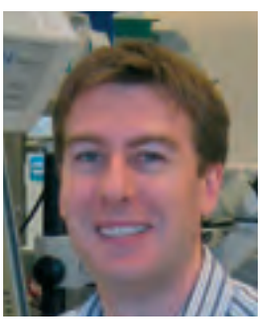
UNIVERSITY OF CAMBRIDGE
Dept of Pharmacology

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

The Steering Committee functions as the executive group for all Institute-wide policies and is responsible for strategic management of the Institute, allocation of Institute grant resources as well as Group Leader recruitment and retention decisions. The committee is chaired by the Institute Director and its members include the Head of Translational Science, theme leaders, Training Director, and a representative of junior group leaders.

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
Committee
Secretary

Clinical Translation Committee

The Clinical Translation Committee formulates and oversees the mission and strategy of the translational activities of the SCI in translating biological research into applications beneficial to human health. The Committee is chaired by the Head of Translational Science and its members include the Institute Director, a representative from the Office of Translational Research and the Pluripotent Stem Cell Platform (PSCP), SCI Investigators and Affiliates.

Robin Franklin
Head of
Translational
Science, **Chair**

Roger Barker
SCI PI

Martin Bennett
BHF Professor of
Cardiovascular
Sciences

Philip Driver
PSCP Project
Manager

Tony Green
SCI PI

Brian Huntly
SCI PI

Andrew McCaskie
SCI Affiliate PI

Austin Smith
Institute Director

Ludovic Vallier
SCI PI

Jana Voigt
Office of Translational
Research

Rick Livesey
SCI PI

International Scientific Advisory Board

The International Scientific Advisory Board of highly distinguished stem cell researchers provides expert evaluation of the individual research programmes through annual visits and reports to the Steering Committee, University and Funders. The ISAB also make recommendations to the Steering Committee on Group Leader recruitment and retention and provides advice on the Institute strategy.

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

Prof Cédric Blanpain Université Libre de Bruxelles

Dr Meinrad Busslinger Vienna Biocenter

Prof Maarten van Lohuizen Netherlands Cancer Institute

Prof David Rowitch UCSF Children's Hospital

Prof David Scadden Harvard Stem Cell Institute

Governance Committee

The Governance Committee ensures University oversight of and support for the joint Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute. This includes communication with sponsors regarding recruitment, funding arrangements, commitments and other strategic issues. The Committee is jointly chaired by the Head of the School of Clinical Medicine and the Head of the School of Biological Sciences and its members include the Institute Director, Head of Translational Science, the Pro-Vice-Chancellor for Research and representatives from the Schools of Biological Science, Clinical Science and Physical Science.

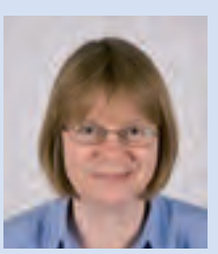
The committee normally meets once per year with sponsor representatives invited as observers.

Patrick Maxwell Head of the School of Clinical Medicine

Duncan Maskell Head of the School of Biological Sciences

Austin Smith Institute Director

Robin Franklin Professor of Stem Cell Medicine



Lynn Gladden Pro-Vice Chancellor for Research

Anne Fergusson-Smith Biological Sciences

Brian Hendrich Biological Sciences and SCI

Tony Green Clinical Medicine and SCI

Gillian Griffiths Clinical Medicine

Ben Simons Physical Sciences and SCI

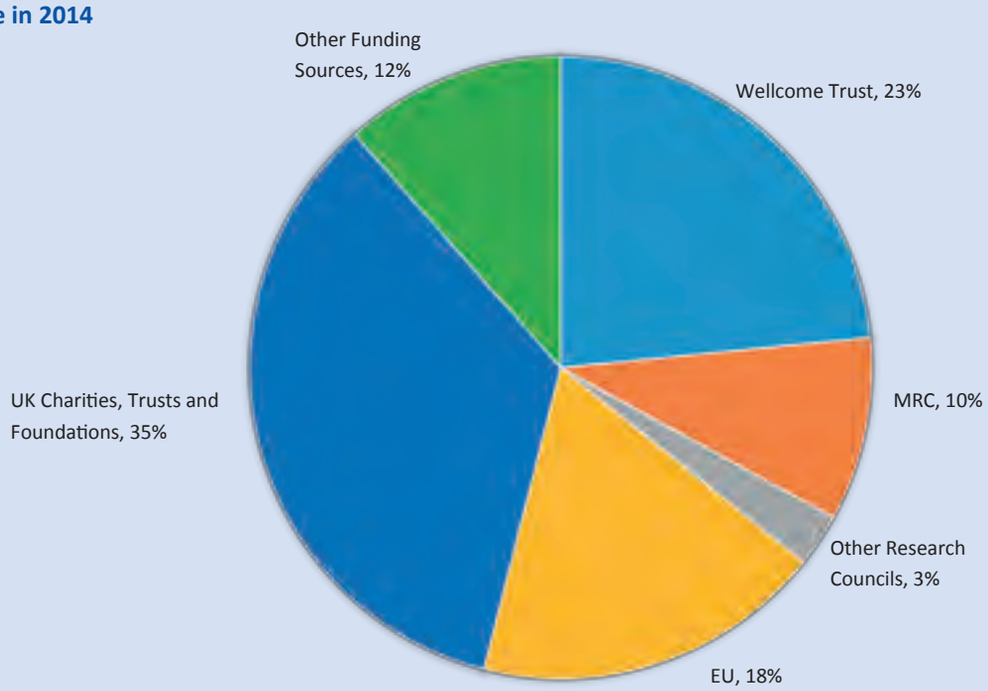
Funding

2014 SCI Budget

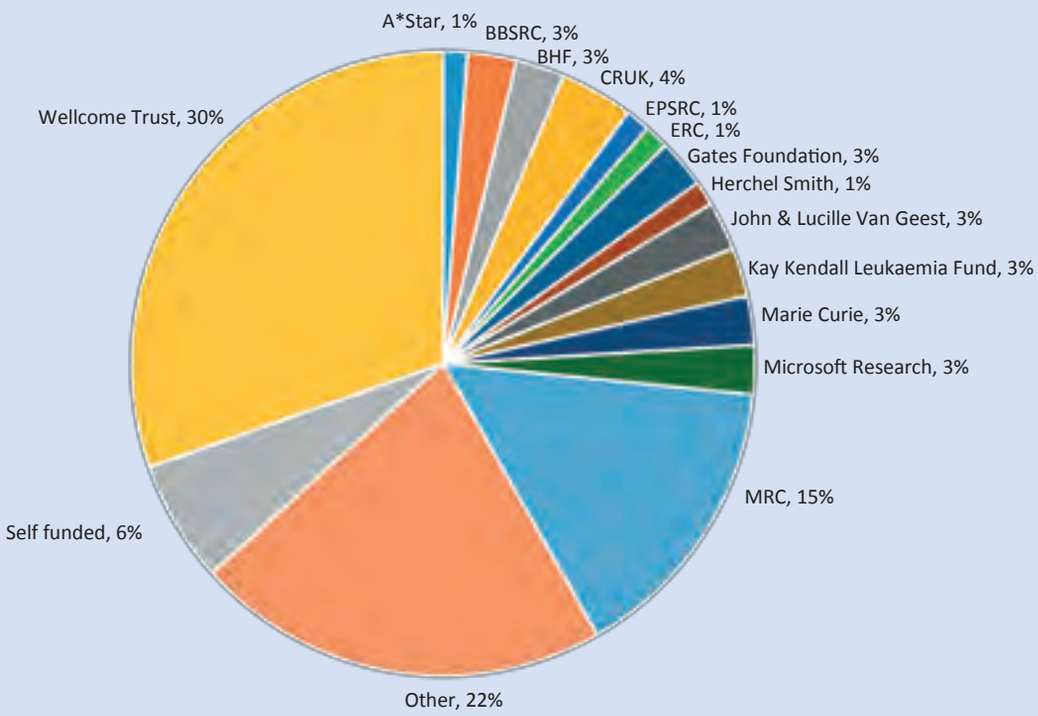
The Institute is funded by the University of Cambridge and also a core grant from the Wellcome Trust and Medical Research Council. In addition to this funding researchers secure individual research grants from a variety of funding sources. In 2014:

- SCI held active research grants to a value of £72 million (excluding Wellcome Trust/MRC Core Funding)
- 22 new grants were awarded to SCI investigators.
- Research grant expenditure from January to December 2014 was £13,822,228 (excluding Wellcome Trust/MRC Core Funding)

Research Grant Expenditure in 2014



Student Funding in 2014



Funding Bodies and Sponsors

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

Highlights of 2014

New Stem Cell Institute Building Project Capella

The new building to house all of the SCI groups is on track to open at the beginning of 2018. The architects and construction company have been appointed and Stage 2 of the construction design began in October 2014.

The building will be on the Addenbrooke's Hospital biomedical research campus which will facilitate translational interactions.

Wellcome Trust Senior Investigator Award

Tony Green

Fellow of the Academy of Medical Sciences

Bertie Göttgens

4th Annual Cambridge Stem Cell International Symposium "Stem Cells in Medicine"

The Symposium was organised into three sessions: stem cells and regeneration, stem cells and disease modelling and stem cells and malignancy.
The meeting attracted 80 delegates from 9 countries.

Feedback from the Symposium was very positive. Participants commented on the intimate format which facilitated good interactions.

See pg. 79 for more details

Professor of Stem Cell Medicine and Head of Translational Science

Robin Franklin took up the University Professorship of Stem Cell Medicine and the post of the Head of Translational Science in the SCI from 1st January.

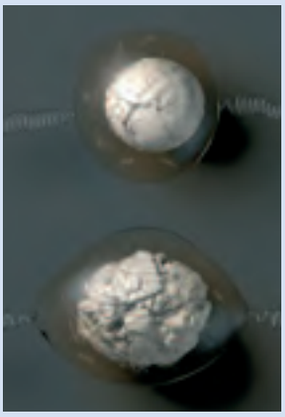
Robin has established a Clinical Translation Committee that convenes regularly to oversee and promote translational research within the SCI.

Public Engagement

The SCI participated in the Cambridge Science Festival and Cambridge Alumni Festival, including public talks, stands with engaging activities for all ages and tours of the Gleeson Building labs.

See pg. 83 for more details

Stem cells exhibit unusual absorption property

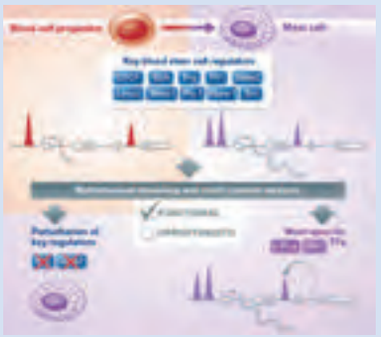


Dr Kevin Chalut led a study that reports having observed auxeticity in the nuclei of embryonic stem cells.

Dr Chalut and colleagues treated the transitioning cell's cytoplasm with a coloured dye and found that when they stretched the nucleus, it absorbed the dye, suggesting that it had expanded to become porous. It is possible that it does so to absorb molecules which would help the cell differentiate.

Pagliara S, Franze K, McClain CR, Wylde GWS, Fisher CL, Franklin RJM, Kabla AJ, Keyser UF, Chalut KJ. "Auxetic nuclei in embryonic stem cells exiting pluripotency". Nature Materials. PMID: 24747782

The uncommon roles of common gene regulatory factors in the genomes of differentiating cells



Bertie Göttgens' team reported genome-wide binding profiles for 10 transcription factors (TFs) in blood progenitors and mast cells, and showed through a combination of experimental and computational modelling approaches that (i) differential binding of shared TFs is predictive of differential gene expression, (ii) cell-type specific TFs may reorganise global binding profiles of shared TFs, and (iii) cell-type specific binding of shared TFs is not predominantly opportunistic.

Calero-Nieto FJ, Ng FS, Wilson NK, Hannah R, Moignard V, Leal-Cervantes AI, Jimenez-Madrid I, Diamanti E, Wernisch L, Göttgens B. "Key regulators control distinct transcriptional programmes in blood progenitor and mast cells". The EMBO Journal. PMID: 24760698.

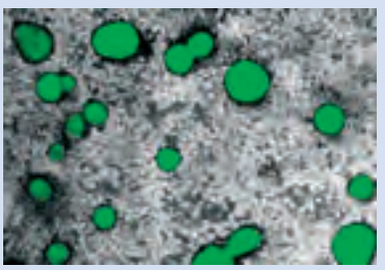
McEwen Award for Innovation

Azim Surani

Franklin Medal and Prize

Ben Simons

MBD3/NuRD Facilitates Induction of Pluripotency

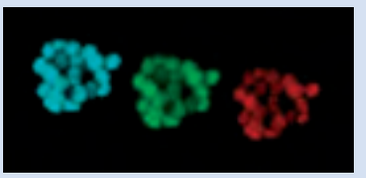


The Silva lab in collaboration with Brian Hendrich demonstrated that the transcriptional regulator NuRD is required for the efficient generation of iPSCs.

In addition, its enhanced activity can further boost the generation of iPSCs. This demonstrates that NuRD, an essential DNA regulator for the generation of specialised cells such as skin and brain cells, is also key to the reversion of the specialised cells back into an early embryonic state (iPSCs).

Santos RS, Tosti L, Radzisheuskaya A, Caballero I, Kaji K, Hendrich B, Silva JCR. "Mbd3/NuRD facilitates induced pluripotency in a context dependent manner". Cell Stem Cell. PMID: 24835571

Defining an essential transcription factor program for naïve pluripotency



Austin Smith's group collaborated with Microsoft Research to development a powerful new computational modelling method.

The successful conjunction of computation and experimentation enabled the authors to delineate a potential minimal transcription factor circuitry that determines embryonic stem cell self-renewal.

Dunn SJ, Martello G, Yordanov B, Emmott S, Smith AG. "Defining an essential transcription factor program for naïve pluripotency". Science. PMID: 24904165

New Group Leader

Elisa Laurenti joined the Institute in September 2014, in the newly refurbished SCI laboratories in the Clifford Allbutt Building.

Elisa's research focuses on the functional properties and molecular circuits of human blood stem cells in health and disease.

2014 SCI International Symposium: Stem Cells in Medicine

Session 1: Stem Cells and Regeneration

Malin Parmar
Lund University, SWEDEN
"Generation of authentic dopamine neurons from human embryonic stem cells"

Giulio Cossu
University of Manchester, UK
"Cell therapy for muscular dystrophy: lessons learned and the road to clinical efficacy"

Stephen Fancy
University of California, USA
"Parallel states of pathological Wnt signaling in human white matter brain injury and colon cancer"

Kenneth Chien
Karolinska Institute, SWEDEN
"A map for regenerative cardiovascular medicine"

Molly Stevens
Imperial College London, UK
"Engineering and exploring the cell-material interface"

Rachael Pearson
University College London, UK
"Repairing the diseased retina by photoreceptor transplantation: getting donor cells from A to B"

Shane Grealish
Lund University, SWEDEN
"Studying the synaptic connectivity between host rat and transplanted neurons derived from human embryonic stem cells in rat model of Parkinson's disease"

Session 2: Stem Cells and Disease Modelling

Marius Wernig
Stanford University, USA
'Direct reprogramming towards neural fates'

Ricardo Dolmetsch
Novartis Institutes for Biomedical Research, USA
'Insights into the brain of a child with autism'

Steven Finkbeiner
University of California, San Francisco, USA
'Using Patient-derived iPSCs and Single Cell Analysis to Develop Models of Neurodegenerative Disease'

Priyanka Dutta
UCB Biopharma, BELGIUM
'New insights into the role of mitochondria dysfunction in human iPSC-derived dopaminergic neurons'

Lorenz Studer
Memorial Sloan-Kettering Cancer Center, New York, USA
'Human pluripotent stem cells in modelling and treating neural disease'

Stephen Haggarty
Harvard Medical School, USA
'Enabling Novel Therapeutic Discovery for Neuropsychiatric Disorders Using Human Stem Cell Models '

Deepak Srivastava
King's College London, UK
'Subcellular localization of psychosis susceptibility protein ZNF804A in human neurons'

Francesco Saverio Tedesco
University College London, UK
'Human Artificial Chromosomes and iPS cells: New Therapeutic Strategies for Muscle Disorders'

Our 4th Annual Symposium was organised by Robin Franklin, Rick Livesey and Roger Barker. The Symposium attracted 80 delegates from 9 countries. Talks were presented by 15 invited speakers and 6 short talks selected from abstracts. 18 posters were presented by the delegates.

Our Stem Cell Symposium Series

Session 3: Stem Cells and Malignancy

Emmanuelle Passegué
University of California, San Francisco, USA
'Competitive strategies of transformed HSCs: lessons learned from CML biology '

Ulrich Steidl
Albert Einstein College of Medicine, New York, USA
'Transcriptional regulation of pre-leukemic stem cells in myelodysplastic syndrome and acute myeloid leukaemia '

Lay Teng Ang
Genome Institute of Singapore, SINGAPORE
'Efficient endoderm induction and patterning from human pluripotent stem cells: by logically guiding lineage bifurcations'

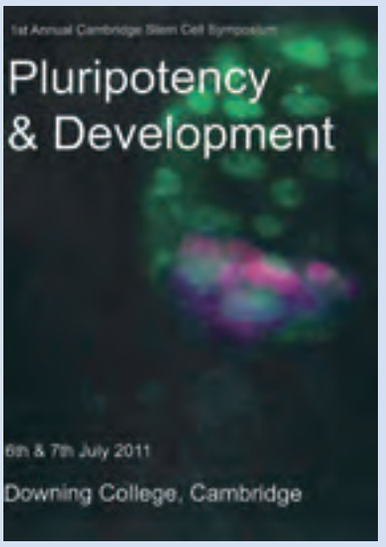
Julia Frede
University of Cambridge, UK
'Cellular Dynamics in Oesophageal Squamous Carcinogenesis'

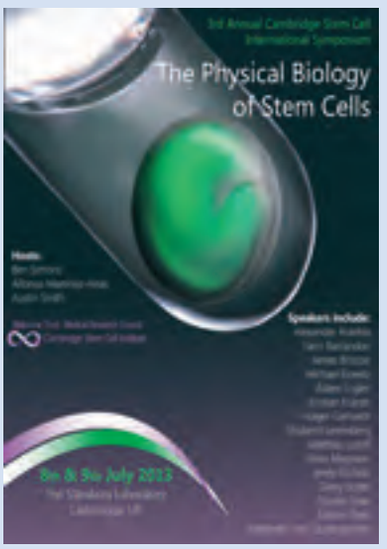
Tessa Holyoake
University of Glasgow, UK
'Targeting survival pathways in CML stem cell persistence and kinase inhibitor resistance'

Paresh Vyas
University of Oxford, UK
'Stem and progenitor cells in normal haemopoeisis and acute myeloid leukaemia'

The next Symposium will be held in the summer of 2016.

Previous:





Seminars

Stem Cell Club Seminar Series

Date	Title	Speaker
19/02/14	Deciphering the functions of the epitranscriptome	Shobbir Hussain
	Quantitative methods applied to the study of murine intestinal stem cells in homeostasis and cancer	Ed Morrissey
	Activin/Nodal signalling controls the H3K4 trimethylation landscape in pluripotent stem cells	Alessandro Bertero
20/03/14	The metabolic regulation of progenitor cell proliferation	Nicola Love
	Network modelling of single cell gene expression profiles reveals regulatory hierarchies controlling blood development from mesoderm	Bertie Gottgens
	Liver and pancreas progenitor/stem cells and organoid cultures	Meritxell Huch
17/04/14	Epigenetic reprogramming and stem cell potency	Wolf Reik
	Non-invasive in vivo imagining of inflammation in the islets of Langerhans	Maja Wallberg
	Primate preimplantation embryos utilise a signalling environment divergent from mouse	Thorsten Boroviak
15/04/14	Understanding Cellular Heterogeneity	Sarah Teichmann
	Visualizing a critical step in ribosomal subunit maturation that is corrupted in leukemia	Alan Warren
	Input and output of pluripotency-associated transcription factor network	Hitoshi Niwa
05/06/14	Defining an essential transcription factor program for naïve pluripotency	Sara-Jane Dunn
	IMBD3/NuRD facilitates induction of pluripotency	Rodrigo Santos
	Probing embryonic stem cell signalling networks using protein engineering	Greg Findlay
24/07/14	Megakaryocytes forward programming from human pluripotent stem cells: new perspectives for biological and clinical application	Thomas Moreau
	Generation and regeneration of the thymus with a single transcription factor	Nicholas Bredenkamp
	Decoding the central role of rcor1 in proliferation versus differentiation in haematopoiesis	Ana Cvejic
29/10/14	Transcriptional regulation of the quiescent human hematopoietic stem cell pool	Elisa Laurenti
	Differences in protein synthesis rate regulate stem cell functions	Sandra Blanco
	The mechanical control of neuronal development	Kristian Franze
19/11/14	Human Induced Pluripotent Stem Cell Derived Cholangiocytes for Disease Modeling and Drug Validation	Fotis Sampaziotis
	Cell Division in the Mammary Epithelium	John Stingl
	Dynamics of the Airway Epithelial Cell Hierarchy	Julie Watson

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

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.

Seminars by External Speakers

Date	Title	Speaker
23/01/14	Programming and Reprogramming the Genome	Konrad Hochedlinger, Harvard Stem Cell Institute
05/02/14	Mechanisms of hepatic differentiation	Frederic Lemaigre, De Duve Institute, Belgium
06/03/14	Chromatin organisation in embryonic stem cells	Peter Rugg-Gunn, Babraham Institute
20/03/14	How Cohesin Regulates Gene Expression	Matthias Merkenschlager, Imperial College London
27/03/14	Chromatin alterations in leukemogenesis: new roles for old players	Saverio Minucci, IFOM-IEO Campus, Milan, Italy
03/04/14	Tartan Pluripotency	Ian Chambers, University of Edinburgh
17/04/14	Genome-wide recessive genetic screening in mammalian cells with a lentiviral CRISPR-guide RNA library	Kosuke Yusa, Sanger Institute
15/04/14	Navigating Nature Cell Biology	Nathalie Lebot, Nature Cell Biology
16/05/14	Microenvironmental Regulation of Lung Stem Cell Differentiation	Joo-Hyeon Lee, Children's Hospital Boston
22/05/14	Establishing pancreatic identity: from fate specification to morphogenesis	Francesca Spagnoli, Max-Delbrück Center for Molecular Medicine
19/06/14	How stems cells protect themselves against genotoxic metabolism	KJ Patel, LMB, Cambridge
30/06/14	Creating mice with human or chimpanzee livers as a tool for human experimental genetics	Ken-ichi Yamamaru, Kumamoto University
16/07/14	Pluripotency: the basis for multilineage potential and efficient pluripotent stem cell differentiation by logically guiding lineage bifurcations	Kyle Loh, Stanford School of Medicine
31/07/14	Bone marrow, the skeleton and stem cells: biology, diseases and controversies	Paolo Bianco, Sapienza University of Rome
04/09/14	Chromatin dynamics during oocyte development and fertilization	Petra Hajkova, MRC - Clinical Sciences Centre, London
25/09/14	Differentiation of human embryonic stem cells in confined two dimensional patterns recapitulates the early embryo	Eric Siggia, Rockefeller University, New York
09/10/14	Cardiovascular Development - Insights into Regeneration	Karl Laugwitz, Technische Universitat Munchen
20/10/14	Niche signaling and metabolic regulation of stem cells	Postdoc seminar: Linheng Li, Stowers Institute for Medical Research, USA
06/11/14	Immune regulation of regeneration	Postdoc seminar: Nadia Rosenthal, EMBL Australia, UCL UK
13/11/14	Oscillating progenitor cells in the embryonic mesoderm	Andy Oates, NIMR Developmental Biology, London, UK
27/11/14	Role of microRNAs in skin and hair follicle development	Mohammed Ahmed , University of Oxford, Sir William Dunn School of Pathology

Public Engagement

Researchers from the Stem Cell Institute regularly share their enthusiasm for science with members of the public. Highlights this year include:

- Austin Smith & Bertie Göttgens gave a presentation at the Cambridge Literary Festival
- Robin Franklin gave a series of radio interviews for the BBC
- Robin Franklin gave the keynote lecture at this years MS Life, the annual meeting of members of the MS Society
- Rick Livesey appeared on the BBC's 'Bang Goes the Theory'
- Austin Smith - interviews with Time magazine, The Guardian, and Science
- The Institute hosted public lab tours as part of the University's Science and Alumni Festivals
- Post-docs and PhD students ran stem cell lessons in secondary schools and at summer schools
- PhD students & post-docs organised activities during the Cambridge Science Festival and the Big Biology Day
- Four public talks with Q&A sessions were hosted by Institute PIs at the Cambridge Science Festival

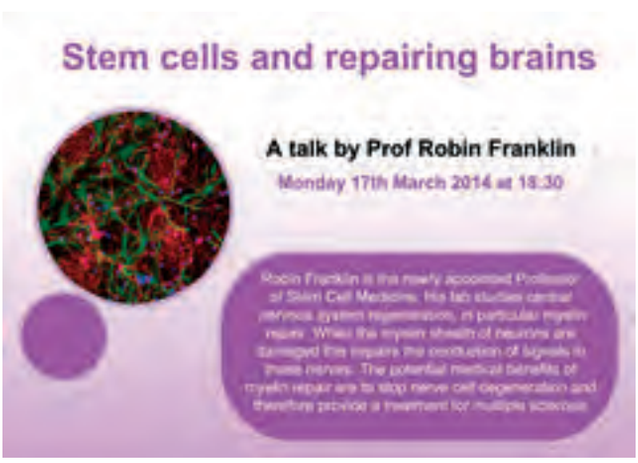
The SCI was also successful in applying to the Wellcome Trust for a full-time Public Engagement Officer. Recruitment for the post is underway. Our commitment to public engagement is further highlighted by the provision of a public engagement training workshop for all SCI members at the 2014 Annual Meeting. This was led by the University's Head of Public Engagement.

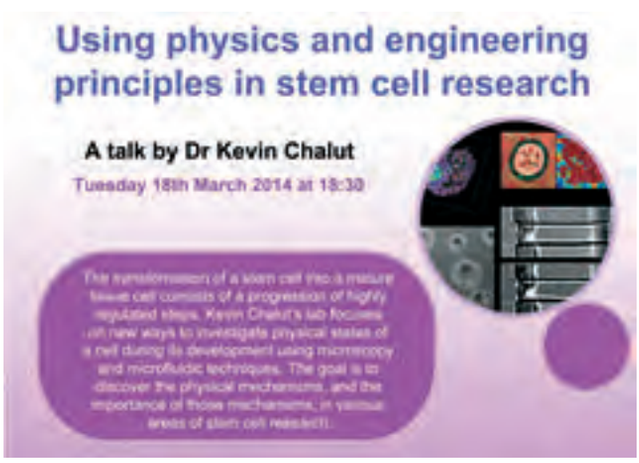
Science Festival Talks

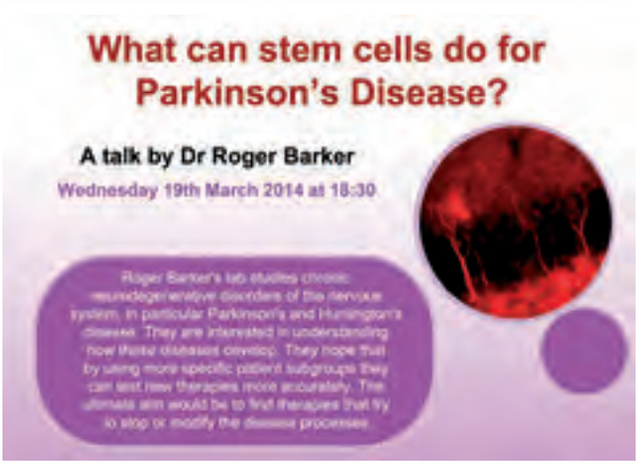
University of Cambridge Science Festival

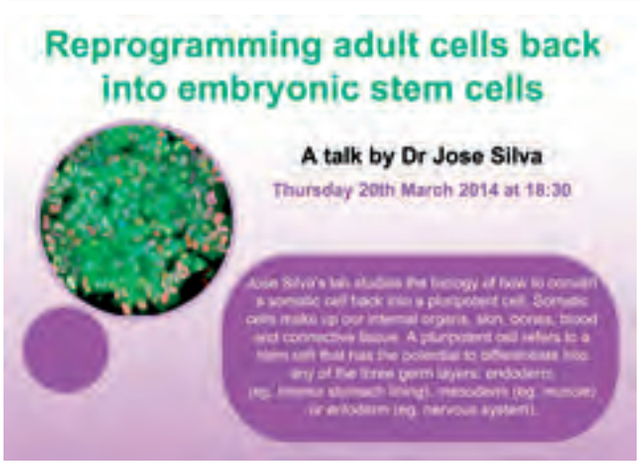
More than 350 members of the public attended our Science Festival stem cell talks. Each presentation was followed by a question and answer session as well as one-to-one sessions with audience members.

> *"I liked the fact that the speaker left lots of time at the end for questions as some of the questions were very interesting and I learnt a lot from his answers."*









> *"As someone without any scientific background, I felt I learnt something basic - and fascinating - about different cells and their functions. Also got a general sense of how stem cell research might lead to better therapeutics. Good slides, material expertly paced and pitched. Wonderfully interesting. Thank you."*

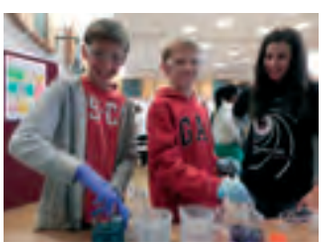
Activity Days

Stem Cell Discoveries

At the Cambridge Science Festival's activity days the SCI hosted a stand with engaging activities for all ages. The drop-in sessions were held on two consecutive weekends in March and our event included posters, games and hands-on practical experiments. We engaged with approximately 200 visitors over 3 days.

30 volunteers from our labs participated and were able to talk directly to the public about stem cell research and answer their questions.

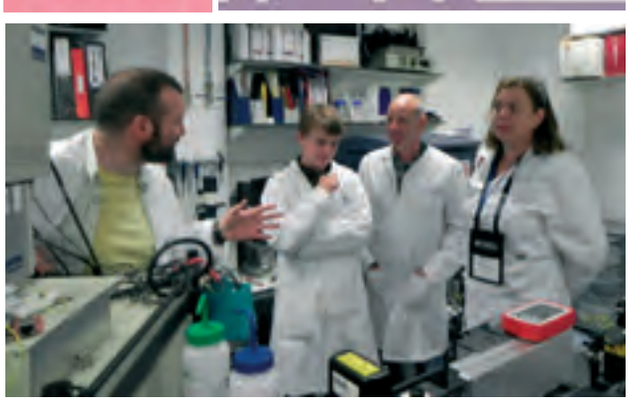
biology week 2014



In October the Institute participated in the 'Big Biology Day' at Hills Road Sixth Form College, Cambridge. The event involved SCI members offering interactive activities for children and their parents to celebrate the life sciences and engage them with an array of biological topics through hands-on activities, crafts and displays.

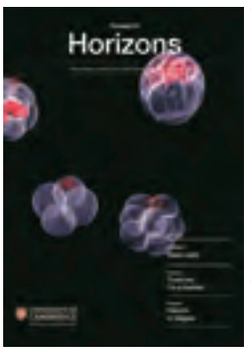
University of Cambridge Science Festival

University of Cambridge Alumni Festival 2014



The Institute organised tours of the Gleeson Building labs for both the Science and Alumni Festivals. Both tours included an introductory talk by the Director/ Head of Translational Science followed by a tour of the facilities and finally a Q&A session with Group Leaders. The SCI Tour was identified by Alumni Festival attendees as being in the Top 10 activities run at the Festival.

Spotlight on Stem Cells



The University supports a number of Strategic Initiatives which build on the existing research base in Cambridge to tackle research challenges that can only be addressed by multi-disciplinary teams of researchers. In 2010 the University established a Stem Cell Strategic Initiative.

This year the University chose to highlight the Stem Cell Strategic Initiative in its magazine "Research Horizons".

The "spotlight on stem cells" included 7 articles about the work done by our SCI members:

- The Ultimate Stem Cell, *Austin Smith & Jenny Nichols*
- Lengthening the journey to Joint Replacement, *Austin Smith & Andrew McCaskie*
- Orchestral Manoeuvres: Multiple sclerosis faces the music, *Robin Franklin, Thora Karadottir, Mark Kotter, Stefano Pluchino*
- The man with a thousand brains, *Rick Livesey*
- Stem Cell Physical, *Kevin Chalut, Ben Simons*
- Testing time for stem cells, *Ludovic Vallier*
- Taking a shot at Parkinson's, *Roger Barker*

Public Engagement Training

SCI highlighted its commitment to public engagement by providing public engagement training for all SCI members at the 2014 Annual Meeting.

Introductory talks were given by the University's Head of Public Engagement. They were followed by four interactive workshops led by experienced Public Engagement professionals:

- Communicating science through the media: Introduction to radio interviews and media releases by Hannah Critchlow, Neuroscience Editor for The Naked Scientists
- Handling public questions about stem cell research by Nicola Buckley, University's Head of Public Engagement
- Creating activities for the 2015 Science Festival and other outreach events by Helene Doerflinger, Gurdon Institute

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, BBSRC 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 (1+3) 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. Upon successful completion 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:

2011 Starters


Anne-Louise Miller


Martyna Popis


Agnieszka Wabik

2012 Starters


Philipp Berg


Juergen Fink


Elena Itskovich


Moritz Matthey

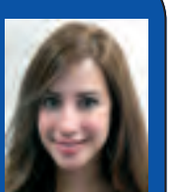
2013 Starters


Amanda Andersson Rolf *


Sarah Förster


Riina Lampela


Anna Osnato


Loukia Yiangou

2014 Starters


Lucia Cordero Espinoza


Fiona Hamey *


Olivia Harris


Caroline Oedekoven


Anastasiya Sybirna

> "There are many highly motivated and inspiring scientists around and that makes the SCI an amazing place for being a scientist"

* Students funded by the MRC

In 2014, SCI students were co-authors on 44 papers, of which 21 of these were first authored by students.

Current SCI Students funded by other sponsors *(as of Oct-2014)*

C = Clinicians
MB = MB PhD students

All SCI 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.

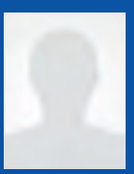

Sarah Ali Abdulla


Sylvia Agathou


Wendi Bacon


Neil Barrett
C


Faisal Basheer


Silvia Basilico


Lawrence Bates


Joshua Bernstock
C


Alessandro Bertero


Lucy Collins


Abbe Crawford


Pedro Da Silva


Natalia Deja
C


Ludovica Di Canio


Matteo Donegà


Ranna El Khairi
C

Kathleen Elliot

Irene Falk


Florian Geßler


Imbisaat Geti


Nikoletta Gkatza


Ginez Gonzalez

Jacob Grinfeld
C


Yun Huang
MB / C


Morteza Jalali
C

Wajid Jawaid
C


Jo-Anne Johnson
C


Fatima Junaid
MB


Chrysa Kapeni


Agata Kurowski


Tommaso Leonardi


Chee Lim


Victoria Mascetti


Gianmarco Mastrogio-vanni

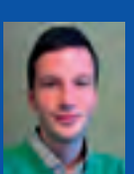
Chris McMurran
C


Alessandra Merenda


Samuel Myers


Jyoti Nangalia
C


Muktha Natrajan


Bjoern Neumann


Felicia Ng


Marco Nikolic
C


Matthias Pawlowski
C


Luca Peruzzotti -Jametti


Abdul Sajini

Fotis Sampaziotis

Michael Segel

Jonathan Sive
C

Filipa Soares

Elsa Sousa

Sonia Spitzer

Stanley Strawbridge

Hannah Stuart

Katie Tremble
MB

Jeroen Verheyen

Christophe Verstreken

Katrin Volbrach

Stan Wang

Stevan Wing

Steven Woodhouse

George Wylde

Crystal Chia Ying

Nada Zaidan

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 subsequent progression of our PhD students indicates the success of our programme:

Name & PhD Start Date	PhD 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. 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, Prof. Melton's Lab, Harvard University, USA
Kathryn Blair (2007)	Gates Foundation	Bench Biologist at Seven Bridges Genomics, Massachusetts
Maria Mascarenhas (2008)	MRC	Applying for positions
Alexander Goncharevich (2008)	WT	Postdoctoral researcher in Robin Franklin's lab at the University of Cambridge
Gloryn Chia (2008)	WT	Postdoctoral Fellow, Dr Egli's lab, Columbia University
Jamie Trott (2008)	WT	Postdoctoral Fellow, Institute of Molecular Biology, Singapore
Nils Grabole (2008)	WT	Postdoctoral Fellow, Roche, Basel, Switzerland
Claire Cox (2008)	MRC	Marketing Assistant/Scientific Writer at Axol Bioscience Ltd, Cambridge, UK
Aoife O'Shaughnessy-Kirwan	BBSRC/Pfizer	Currently re-training as a Genetic Councillor at Cardiff University
Hayley Frend (2009)	WT	Science Communication Manager, Cancer Research UK
Nicola Love (2009)	WT	Applying for post-doc positions
Paulina Chilarska (2009)	WT	Founder and Chief Executive Officer of Media and PR company 'Golden Line Limited', Shanghai, China
Robert Fordham (2009)	MRC	Postdoctoral Research Fellow, Prof. Sansom's lab, Beatson Institute for Cancer Research, Glasgow
Jason Signolet (2009)	MRC	Research Assistant, Dr Hendrich's lab , SCI, Cambridge
Jignesh Tailor (2009)	BRC	Specialty Registrar in Neurosurgery in London
Marta Lesko (2009)	MRC	Research Associate, Prof Watts' lab, King's College London
Anouk Van Oosten (2009)	BBSRC	Clinical Research Associate, The Netherlands
Anna Godfrey (2010)	Kay Kendall Leukaemia Fund	Specialist Registrar in Haematology, UK
Jan Zylicz (2010)	WT	Post-doctoral researcher, Institute Curie, Paris, France
Sarah Putwain (2010)	WT	Veterinary Clinical Pathologist, PTDS Ltd., UK
Mahalia Page (2010)	MRC	Research Associate, University College London
Aliaksandra Radzisheuskaya (2010)	Darwin Trust	Postdoctoral Associate, Prof Helin, The Biotech Research & Innovation Centre, University of Copenhagen, Denmark
Sarah Putwain (2010)	WT	Veterinary Clinical Pathologist at PTDS Ltd., UK
Joana Flores (2010)	WT	Chief Operating Officer at Healx
Anna Guinot (2010)	Herchel Smith	PostDoc, Institute of Physiology, University of Zurich
Harry Leitch (2011)	Merck, Sharp & Dohme	Doctor on the Academic Foundation program and research fellow at Wolfson College, and visiting Research Fellow in Prof Smith's Group at the SCI, Cambridge
Stoyana Alexandrova (2011)	MRC	Postdoc, Dr Nichols' lab, Stem Cell Institute, Cambridge
Moyra Lawrence (2011)	WT	Post-doc, Schneider lab , Institut Génétique Biologie Moléculaire Cellulaire (IGBMC), Illkirch, France
Victoria Moignard (2011)	MRC	Continuing research work in Dr. Göttgens lab
Carla Mulas (2011)	BBSRC	Research Associate, Dr Nichols lab, SCI, Cambridge
Rodrigo Luiz dos Santos (2011)	Foundation for Science & Technology	Scientist in Cell Engineering Team at Horizon Discovery Cambridge, UK

2014 Alumni

Name	Position	Next destination
Terri-Anne Badcock	Technician	Technician, Department of Physiology, Development and Neuroscience
Charley Beresford	Technician	Senior Technician, CRUK CI
Kathryn Cook	Technician	Principal Technician, BioFocus
Charlotte Coppen	Technician	Pathology Assistant, Huntingdon Life Sciences
Mark Dawson	Post-doc Researcher, Huntly Lab	Peter Macallum Centre, Melbourne, Australia
Iwona Driskell	Post-doc Researcher, Frye Lab	Axol Bioscience, Cambridge
Cynthia Fisher	Research Associate, Chalut Lab	STEMCELL Technologies
Shobbir Hussain	Post-doc Researcher, Frye Lab	Lecturer in Molecular Genetics of Disease, University of Bath
Antony Hynes-Allen	Research Assistant, Hendrich Lab	Research Assistant, University College London
Kim Jensen	Principal Investigator	Associate Professor, BRIC, University of Copenhagen, Denmark
Graziano Martello	Post-doc Researcher, Smith Lab	Assistant Professor, University of Padua, Italy
Emma Martinez-Sanchez	Research Associate, Koo Lab	Press Release and Communications Manager, EARA, London
Aoife O'Shaugnessy-Kirwan	Research Associate, Hendrich Lab	Re-training as genetic counsellor, Cardiff University
Atul Pandey	Technician	Service Technician, Department of Physiology, Development and Neuroscience
Chandrika Rao	Technician, Rawlins Lab	Regenerative Medicine PhD, Edinburgh
David Ruau	Post-doc Researcher, Gottgens Lab	Team Leader, Astra Zeneca
Jason Signolet	Research Associate, Hendrich Lab	Adelaide, Australia
John Stockley	Post-doc Researcher, Franklin Lab	Senior Research Scientist, MedImmune
Gillian Tannahill	Post-doc Researcher, Pluchino Lab	GSK Immunology at Stevenage, Principal Scientist
Juan-Jose Ventura	Principal Investigator	Associate Professor, University of Leuven, Netherlands

2014 Publications

Research Reports

Leeb M, Dietmann S, Paramor M, Niwa H, Smith A. **Genetic Exploration of the Exit from Self-Renewal using Haploid Embryonic Stem Cells**. *Cell Stem Cell.* PMID: 24412312

Soares F, Chandra A, Thomas R, Pedersen R, Vallier L, Williams D. **Investigating the Feasibility of Scale up and Automation of Human Induced Pluripotent Stem Cells Cultured in Aggregates in Feeder Free Conditions**. *Journal of Biotechnology.* PMID:24440272

Stuart HT, van Oosten AL, Radzisheuskaya A, Martello G, Miller A, Dietmann S, Nichols J, Silva JC. **NANOG amplifies STAT3 activation and they synergistically induce the naïve pluripotent program**. *Current Biology.* PMID:24462001

Le Bin GC, Muñoz-Descalzo S, Kurowski A, Leitch H, Lou X, Mansfield W, Etienne-Dumeau C, Grabole N, Mulas C, Niwa H, Hadjantonakis AK, Nichols J. **Oct4 is required for lineage priming in the developing inner cell mass of the mouse blastocyst**. *Development.* PMID: 24504341

Lescroart F, Chabab S, Lin X, Rulands S, Paulissen C, Rodolosse A, Auer H, Achouri Y, Dubois C, Bondue A, Simons BD, Blanpain C. **Early lineage restriction in temporally distinct populations of Mesp1 progenitors during mammalian heart development**. *Nature Cell Biology.* PMID: 25150979

Ruiz EJ, Oeztuerk-Winder F, Ventura JJ. **A paracrine network regulates the cross-talk between human lung stem cells and the stroma**. *Nature Communications.* PMID:24430801.

Hara K, Nakagawa T, Enomoto H, Suzuki M, Yamamoto M, Simons BD, Yoshida S. **Mouse spermatogenic stem cells continually interconvert between equipotent singly isolated and syncytial states**. *Cell Stem Cell.* PMID: 24792118

Dickel DE, Zhu Y, Nord AS, Wylie JN, Akiyama JA, Afzal V, Plajzer-Frick I, Kirkpatrick A, Gottgens B, Bruneau BG, Visel A, Pennacchio LA. **Function-based Identification of Mammalian Enhancers Using Site-Specific Integration**. *Nature Methods.* PMID: 24658141

Ritsma L, Ellenbroek SI, Zomer A, Snippert HJ, de Sauvage FJ, Simons BD, Clevers H, van Rheenen J. **Intestinal crypt homeostasis revealed at single-stem-cell level by in vivo live imaging**. *Nature.* PMID:24531760

Sun D, Luo M, Jeong M, Rodriguez B, Xia Z, Hannah R, Wang H, Le T, Faull KF, Chen R, Gu H, Bock C, Meissner A, Gottgens B, Darlington GJ, Li W, Goodell MA. **Epigenomic profiling of young and aged HSCs reveals concerted changes during aging that reinforce self-renewal**. *Cell Stem Cell.* PMID: 24792119

Herberg M, Kalkan T, Glauche I, Smith A, Roeder I. **A Model-Based Analysis of Culture-Dependent Phenotypes of mESCs**. *PLoS One.* PMID:24643025

Calero-Nieto FJ, Ng FS, Wilson NK, Hannah R, Moignard V, Leal-Cervantes AI, Jimenez-Madrid I, Diamanti E, Wernisch L, Gottgens B. **Key regulators control distinct transcriptional programs in blood progenitor and mast cells**. *EMBO Journal.* PMID: 24760698

Pagliara S, Franze K, McClain CR, Wylde GW, Fisher CL, Franklin RJ, Kabla AJ, Keyser UF, Chalut KJ. **Auxetic nuclei in embryonic stem cells exiting pluripotency**. *Nature Materials.* PMID: 24747782

Hyatt AJ, Wang D, van Oterendorp C, Fawcett JW, Martin KR. **Mesenchymal stromal cells integrate and form longitudinally aligned layers when delivered to injured spinal cord via a novel fibrin scaffold**. *Neuroscience Letters.* PMID: 24680849

Buettner F, Moignard V, Gottgens B, Theis FJ. **Probabilistic PCA of censored data: accounting for uncertainties in the visualisation of high-throughput single-cell qPCR data**. *Bioinformatics.* PMID: 24618470

Barbera M, di Pietro M, Walker E, Brierley C, Macrae S, Simons BD, Jones PH, Stingl J, Fitzgerald RC. **The human squamous oesophagus has widespread capacity for clonal expansion from cells at diverse stages of differentiation**. *Gut.* PMID: 24572143

Dos Santos RL, Tosti L, Radzisheuskaya A, Caballero IM, Kaji K, Hendrich B, Silva JC. **Mbd3/NuRD facilitates induction of pluripotency in a context dependent manner.**. *Cell Stem Cell. PMID: 24835571.*

Cerri F, Salvatore L, Memon D, Martinelli Boneschi F, Madaghiele M, Brambilla P, Del Carro U, Taveggia C, Riva N, Trimarco A, Lopez ID, Comi G, Pluchino S, Martino G, Sannino A, Quattrini A. **Peripheral nerve morphogenesis induced by scaffold micropatterning**. *Biomaterials.* PMID: 24559639

L'episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Serapide MF, Pluchino S, Marchetti B.. **Wnt/β-catenin signaling is required to rescue midbrain dopaminergic progenitors and promote neurorepair in ageing mouse model of Parkinson's disease**. *Stem Cells.* PMID: 24648001

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Fast two-hour uptake of CD63-RFP neural stem cell-derived extracellular membrane vesicles (EVs; red) packed via target cell fEGFP (green) membranes in vitro
Image: CongJian Zhao

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