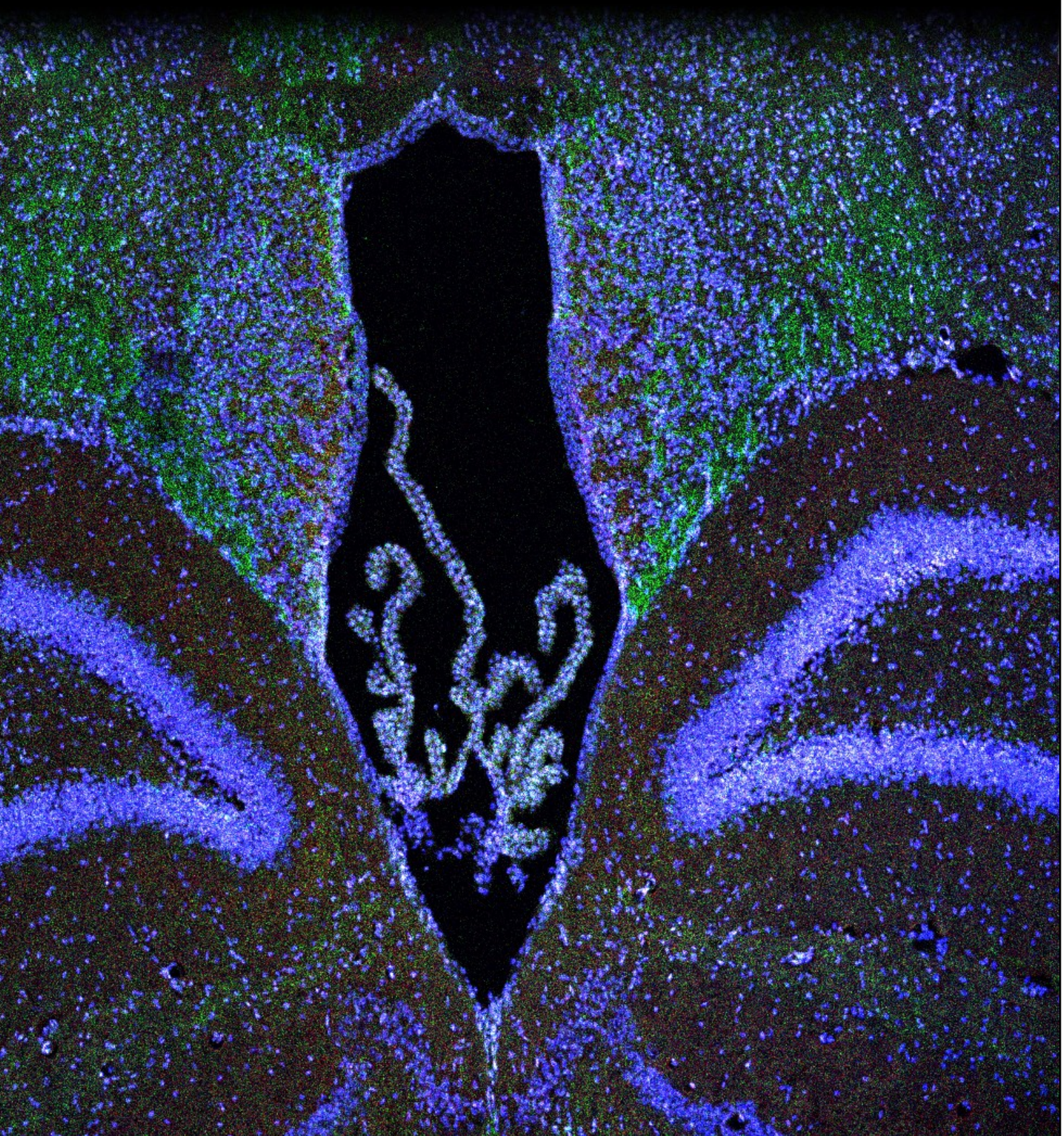
Wellcome Trust - Medical Research Council

Cambridge Stem Cell Institute

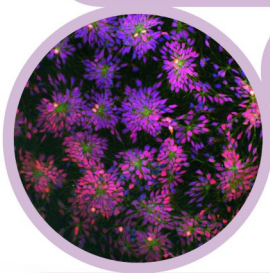
2016



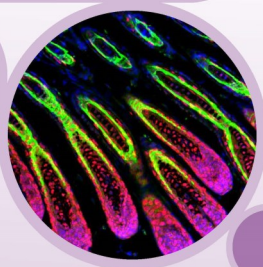
Wellcome Trust - Medical Research Council

Cambridge Stem Cell Institute

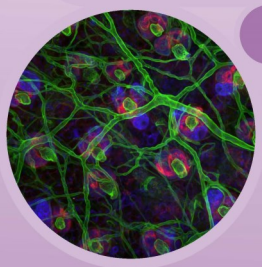
Exploring and defining the properties of stem cells to establish their true medical potential



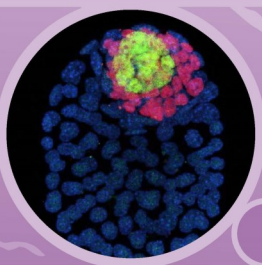
World-leading Institute for stem cell biology and medicine



Outstanding researchers from 29 stem cell laboratories in Cambridge



Cross-disciplinary collaboration



www.stemcells.cam.ac.uk

wellcome

MRC Medical Research Council

UNIVERSITY OF CAMBRIDGE

Contents

Capella building

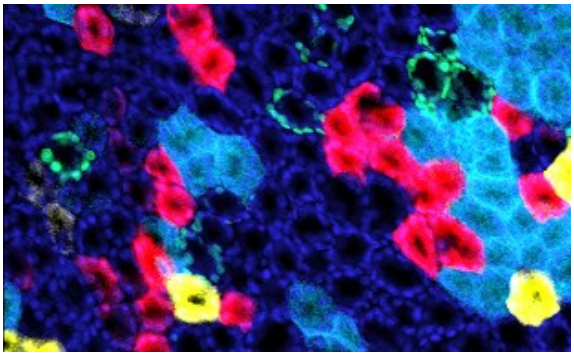
Research

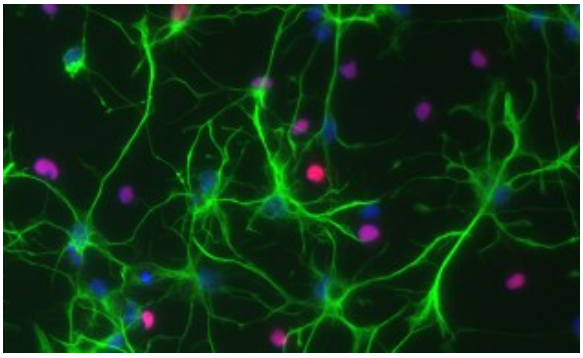
Our research falls into three broad themes: (i) Stem cell states; (ii) Stem cells in disease – malignancy and regenerative failure; (iii) Stem cells & therapeutics. Many PIs contribute to more than one theme. Within these themes we have particular strengths in pluripotency, haematopoiesis, neural and epithelial stem cells.

A key strategy is to embed biological, clinical and physical scientists operating across disparate tissues and at multiple scales, thus allowing commonalities and differences to be explored in a cohesive and inter-disciplinary manner. A network of affiliated PIs provides bridges to basic and disease-focused institutes throughout Cambridge and ensures that CSCI represents the heart of a vibrant stem cell community. Importantly a critical mass of clinician scientists creates synergistic interactions between basic scientists and those driven by disease-focused questions, thus ensuring that CSCI is fully integrated with its clinical environment and empowered to pursue its translational goals.

Theme 1: Stem Cell States

We study the fundamentals of pluripotent and adult stem cells to understand the mechanisms by which they self-renew, maintain their states and commit to differentiate. We aim to achieve new insight into these long-standing issues through a programme of innovative and cross-disciplinary investigation that integrates knowledge at multiple scales across different tissues and organisms.



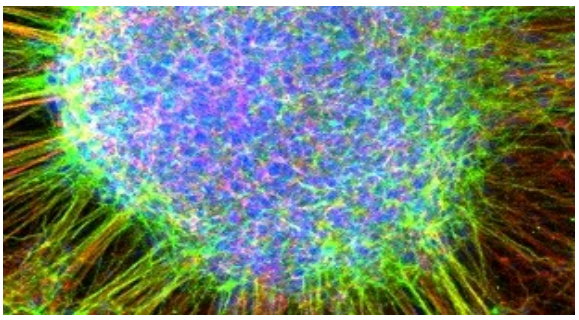


Theme 2: Stem Cell in Disease

Many disease states arise (malignancies) or persist (regeneration failure) as a result of stem and progenitor cell dysfunction. Underpinned by our exploration of normal stem cell states, we are investigating the mechanisms responsible for pathological behaviours of stem and progenitor cells. We focus particularly on malignancy and regenerative failure, in studies which are laying the foundation for new approaches to diagnosis and treatment.

Theme 3: Stem Cells & Therapeutics

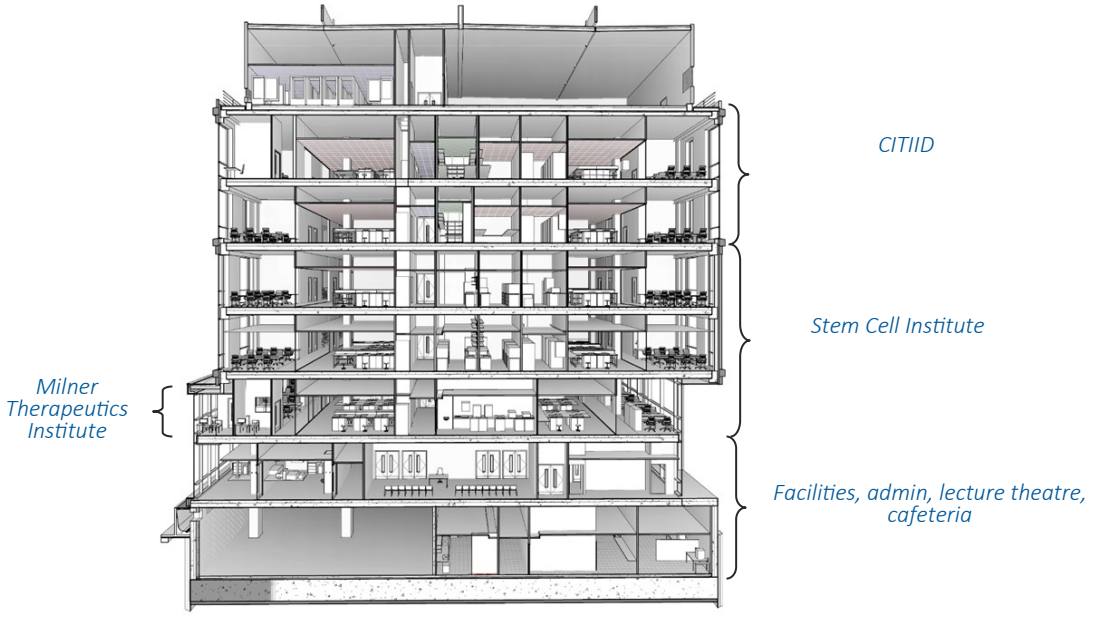
We exploit the potential of stem cells to model diseases *in vitro* and to generate new diagnostic and therapeutic approaches. Patient-derived induced pluripotent stem cells and organoids, combined with advanced genome engineering technology, provide excellent platforms for studying human diseases *in vitro*. In addition several investigators are developing first-in-human clinical trials of cellular therapies using stem cell derivatives.



Project Capella is a new building containing state-of-the-art laboratories currently under construction for the University of Cambridge.

The new building, sited at the Cambridge Biomedical Campus adjacent to Addenbrooke's Hospital and due for completion in 2018, will allow all CSCI groups to work together in one place. This will result in a fully integrated, vibrant and cohesive stem cell community, within a purpose-built new building, which is ideally placed to capitalise on its unique intellectual and clinical environment. Our location at the Addenbrooke's Hospital site will allow for greater collaboration between scientists and clinicians and further advance the application of stem cell discoveries into the patient setting. The Cambridge Biomedical Campus combines medical research, patient care and education on a single site. It is now undergoing major expansion, including the co-location of companies, to become one of the leading biomedical centres in the world by 2020.

Along with CSCI, Capella will also house the **Cambridge Institute for Immunotherapeutics and Infectious Disease** (CITIID), and the **Milner Therapeutics Institute**, both with explicitly translational goals. The building will contain state-of-the-art research facilities along with a cafeteria, seminar room and exhibition space for events. Built by Kier Construction and designed by architects from The Fairhurst Design Group, the six-storey centre will be located directly next to the Cancer Research UK Cambridge Institute.



2016 Progress Report

It has certainly been an eventful 12 months. We came through the year-long renewal process with flying colours, an outcome that reflects not only the highest quality research, but also a tremendous team effort on the part of all involved. 2016 contained numerous other highlights for the Stem Cell Institute, outlined below, and 2017 promises to be equally stimulating, with the Capella building firmly on the horizon and on target to open in the summer of 2018. Our move to Capella will bring together stem cell scientists, both fundamental and translational, working across diverse tissues and at multiple scales. In this way we will create within a single building a world-leading Stem Cell Institute that will also be at the heart of Cambridge's vibrant wider stem cell community. Exciting times!

Tony Green
Institute Director

Developments during 2016

Our major achievement during 2016 was our successful quinquennial renewal as a major research centre by both Wellcome and the Medical Research Council. Tony Green became the new Director of the Institute in April 2016 and led the WT-MRC renewal application which included a review of all PIs and Affiliate PIs and a reshaping of our faculty.

Relocation

A major opportunity and challenge for us going forward will be our relocation from six separate sites to the Capella building, currently planned for summer 2018. The main building structure should be finished in April 2017 and then the work will move on to internal fitting of rooms and labs. We are currently actively planning for this significant relocation which will bring us all together and look forward to the collaborative opportunities this will present. In preparation for this move, a new governance structure is being put in place to bring the Institute together, supported by a senior administrative team led by the Institute Administrator. A number of posts will be filled in early 2017 including the Research Strategy and Communication Manager, Principal Technician, Computer Manager and Public Engagement Manager.

Interdisciplinary Research Centre

We are pleased to announce that in 2016 the CSCI became one of the University's four Interdisciplinary Research Centres (IRC). The University's IRCs are established cross-School initiatives that have demonstrated a critical mass of academic support in at least three Schools and have the explicit endorsement of the University's Research Policy Committee. They extend the research priorities and strategies of the individual Schools by tackling cross-disciplinary challenges and creating a shared cross-School vision in key thematic areas. This builds on the aims and achievements developed by the Stem Cell Strategic Research Initiative over recent years. The Stem Cell IRC involves five of the six University Schools - Biological Sciences, Clinical Medicine, Physical Sciences, Humanities and Social Sciences, and Technology. The Institute aims to extend the research priorities and strategies of these individual Schools by tackling cross-disciplinary challenges to create a shared cross-School vision in stem cell biology and medicine.

Recruitment

Two new junior Group Leaders, Maria Alcolea and Joo-Hyeon Lee, joined us at the end of 2015. Following on from this, we expanded our membership to include:
Professors - David Rowitch who joined us from Harvard, Andrew McCaskie (Surgery) and Anna Philpott (Oncology);
Senior PIs - Sanjay Sinha (Surgery) and George Vassiliou (Haematology);
Junior PIs - Ana Cvejic, Ingo Ringshausen and Daniel Hodson, all from Haematology.
Our Institute currently comprises 29 Principal Investigators and 28 Affiliate PIs.

Leavers

In July, Michaela Frye moved to the Department of Genetics, maintaining her connection to the Institute as an Affiliate PI. Several post-doc fellows moved on to similar positions in industry. In addition Philip Greulich moved to a Lectureship at the University of Southampton and Steffen Rulands took up a position as Group Leader at the Max Planck Institute for Complex Systems.

Awards and Prizes

This year saw Austin Smith awarded the McEwen Award from the ISSCR. Robin Franklin was elected to the Fellowship of the Academy of Medical Sciences. Ben Simons was awarded the Gabor Medal by the Royal Society and David Rowitch 'Doctor of Science' by the University of Cambridge. Brian Huntly was promoted to Professor of Leukaemia Stem Cell Biology. Ana Cvejic received an EMBO Young Investigator Award and Bertie Göttgens was elected President of the International Society for Experimental Hematology.

PhD Programme

In 2016 24 PhD awards were approved for CSCI students and 22 new PhD students have begun or will begin their studies in 2016/17. Our students have achieved a number of awards including: Victoria Mascetti received the Richard J Bing Young Investigator Award, Brandon Wesley was awarded the Robert D Lynch Award and Cavan Bennett received a highly commended poster prize at the BHF Centre of Research Excellence Annual Symposium. CSCI PhD students are authors on 47 published papers, in 23 cases as first author. The annual PhD Day on 12th July was organised by the students including oral and poster presentations of their research. The PhD students organise a bi-weekly informal seminar and discussion club at which they present to their peers.

Research Funding

As of December 2016, the Institute held active research grants to the value of £96.7 million. In total, 47 new research grants were activated for CSCI PIs. These include:

* David Rowitch received a WT Senior Investigator Award for £2.2 million;
* Austin Smith was awarded a £2 million MRC Grant;
* A team led by Robin Franklin secured further funding from the MS Society for the Cambridge Centre for Myelin Repair (£1.6 million);
* David Kent was awarded a £1.2 million ERC grant, starting in 2017;
* Joo-Hyeon Lee and Maria Alcolea were both awarded Sir Henry Wellcome Fellowships by Wellcome and Royal Society to the value of £1.2 and £1.1 respectively;
* Joo-Hyeon Lee and Ana Cvejic also received a ERC grants for £1.1 million each.

Public Engagement

Our researchers have interacted with approximately 3000 members of the public thanks to a dynamic and varied programme of public engagement activities, including innovative new events such as a science comedy evening and a pop-up information exhibit. We have taken measures to ensure public engagement is embedded in our working culture such as: including public engagement in new member inductions, training at internal events and embedding public engagement in research grant applications. Our ambitious 5-year-plan for the Public Engagement Programme has been approved by Wellcome and the MRC as part of our major research centre funding.

Communication

The Institute continued to publish a weekly bulletin and quarterly newsletter. Our proactive social media policy has increased our Twitter followers from 100 in 2014 to 570 in 2015 and now to 1170 in 2016. Our website is constantly updated and improved and we recently moved to a new website format in January 2017.

Seminars and Events

The Institute hosted an excellent annual retreat at Tattersalls in February 2016 and the monthly Stem Cell Club, a hub meeting for the entire Cambridge stem cell community, was well attended throughout the year. For 2017 we are also introducing a flagship monthly External Seminar series. One of the unique and exciting features of the CSCI is the innovation and cross fertilisation that comes from housing stem cell scientists working on different cell systems and such seminars further enhance these opportunities.

In addition, our PIs hosted a number of workshops during this year, including:

* Planning for the Future of Gene Editing – in collaboration with the Public Policy SRI a one-day workshop was convened in January 2016 as an opportunity to catalyse Cambridge's response to the opportunities offered by stem cell research, and to engage with the relevant stakeholders to consider hopes and fears surrounding gene editing. A number of our PIs took part and the workshop brought together a select group of scientists, bioethicists, social scientists and policy makers to discuss the opportunities that may emerge from gene editing technology, the ethical and legal implications of developments, and to discuss what appropriate policy measures need to be in place in order to support the appropriate evolution of gene editing technology.
* Cambridge Intestinal Epithelial Research Symposium – in April 2016 this one-day symposium hosted by Matthias Zilbauer (Affiliate PI) and Bon-Kyoung Koo (PI) brought together Cambridge based researchers and

scientists with an interest in the intestinal epithelium. In addition to presenting current work, sharing experiences and highlighting future perspectives, there was plenty of opportunity for participants to network and connect. It provided a platform to generate ideas and build new collaborations.

* Single Cell Biology 2016 – organised by Bertie Göttgens (PI) and the Wellcome Genome Campus in March. This new Single Cell Biology conference aimed to provide a forum for biologists, methods developers and computational modellers interested in understanding biological variation at the single cell level.

In July 2016 the 5th Cambridge Stem Cell International Symposium was organised on the theme "Quantitative Stem Cell Biology: From Molecules to Models" by Paul Bertone, Elisa Laurenti and Azim Surani. The meeting resulted in an interactive forum for stem cell biologists, clinicians and bioinformaticians to discuss quantitative methods to study the unique biology of stem cells and topics were centred on how genomic, epigenetic, imaging and modelling approaches have provided insights into the regulation of embryonic and adult stem cells.

Research highlights

During the calendar year 2016, CSCI researchers generated 157 publications: these included 102 research reports of which 80 appeared in journals with an impact factor over 5.

Cedric Ghevaert developed an innovative method of producing the precursors of platelets (megakaryocytes) and platelets themselves from human stem cells.

* Moreau T, Evans AL, Vasquez L, Tijssen MR, Yan Y, Trotter MW, Howard D, Colzani M, Arumugam M, Wu WH, Dalby A, Lampela R, Bouet G, Hobbs CM, Pask DC, Payne H, Ponomaryov T, Brill A, Soranzo N, Ouwehand WH, Pedersen RA, Ghevaert C. **Large scale production of megakaryocytes from human pluripotent stem cells by chemically defined forward programming**. *Nature Communications 2016 Apr 7;7:11208* PMCID: PMC4829662

The Nichols lab, in collaboration with Austin Smith, Paul Bertone and Wolf Reik, showed for the first time that it is possible to derive from a human embryo so-called 'naïve' pluripotent stem cells – one of the most flexible types of stem cell, which can develop into all human tissue other than the placenta.

* Guo G, von Meyenn F, Santos F, Chen Y, Reik W, Bertone P, Smith A, Nichols J. **Naïve pluripotent stem cells derived directly from isolated cells of the human inner cell mass**. *Stem Cell Reports. 2016 Apr 12;6 (4):437-46* PMCID: PMC4834040

The Göttgens lab combined extensive biochemical experiments with computational modelling to study some of the transcription factors that define blood stem / progenitor cells in mice.

* Schütte J, Wang H, Antoniou S, Jarratt A, Wilson NK, Riepsaame J, Calero-Nieto FJ, Moignard V, Basilico S, Kinston SJ, Hannah RL, Chan MC, Nürnberg ST, Ouwehand WH, Bonzanni N, de Bruijn MF, Göttgens B. **An experimentally validated network of nine haematopoietic transcription factors reveals mechanisms of cell state stability**. *Elife. 2016 Feb 22;5:e11469* PMCID: PMC4798972

Ben Simons, in collaboration with Cedric Blanpain in Brussels, identified for the first time the 'cell of origin' – the first cell from which the cancer grows – in basal cell carcinoma, the most common form of skin cancer, and followed the chain of events that lead to the growth of these invasive tumours.

* Sánchez-Danés A, Hannezo E, Larsimont J-C, Liagre M, Youssef KK, Simons BD, Blanpain C. **Defining the clonal dynamics leading to mouse skin tumour initiation**. *Nature. 2016 Aug 18;536(7616):298-303* PMCID: PMC5068560

The Franklin lab demonstrated for the first time that the developmental origin of a progenitor population determines its regenerative properties in adults.

* Crawford AH, Tripathi RB, Richardson WD, Franklin RJM. **The developmental origin of oligodendrocyte lineage cells determines their response to demyelination and susceptibility to age-associated functional decline**. *Cell Reports 15: 761-773* PMCID: PMC4850420

The Hendrich Lab identified the function of Sall4, a protein important in early development and a hallmark of many cancers. In this study, they show that Sall4 functions to control gene expression in early embryonic cells, controlling their entry into the neural lineage. It is proposed that Sall4 acts to ensure only the right genes are expressed at the right times during development of pluripotent cells.

* Miller A, Ralser M, Kloet SL, Loos R, Nishinakamura R, Bertone P, Vermeulen M, Hendrich B. **Sall4 controls differentiation of pluripotent cells independently of the Nucleosome Remodelling and Deacetylation (NuRD) complex**. *Development. 2016 Sep 1;143(17):3074-84* PMCID: PMC5047675

The Sinha lab created, for the first time, blood vessel tissues in a petri dish which mimic Marfan syndrome in human arteries.

* Granata A, Serrano F, Bernard WG, McNamara M, Low L, Sastry P, Sinha S. **An iPSC-derived vascular model of Marfan syndrome identifies key 3 mediators of smooth muscle cell death**. Nature Genetics. 2017 Jan;49(1):97-109 PMID: 27893734

The Vallier Lab developed sOPTiKO, a more efficient and enhanced inducible CRISPR genome editing platform. This new approach will aid researchers in developmental biology, tissue regeneration and cancer.

* Bertero A, Pawlowski M, Ortmann D, Snijders K, Yiangou L, Cardoso de Brito M, Brown S, Bernard WG, Cooper JD, Giacomelli E, Gambardella L, Hannan NR, Iyer D, Sampaziotis F, Serrano F, Zonneveld MC, Sinha S, Kotter M, Vallier L. **Optimized inducible shRNA and CRISPR/Cas9 platforms for in vitro studies of human development using hPSCs**. *Development. 2016 Dec 1;143(23):4405-4418*. PMID: 27899508

The Frye lab study reveals that skin stem cells in both normal tissues and tumours synthesize less protein than their differentiating daughter cells, independent of cell division rate.

* Blanco S, Bandiera R, Popis M, Hussain S, Lombard P, Aleksic J, Sajini A, Tanna H, Cortes-Garrido R, Gkatza N, Dietmann S, Frye M. **Stem cell function and stress response are controlled by protein synthesis**. Nature. 2016 Jun 16;534(7607):335-40 PMCID: PMC5040503

Public Engagement

Our Strategy

We believe that it is important for everybody to be able to access, question and influence the latest stem cell research. To achieve this we aim to:

1. Provide regular opportunities for dialogue and collaboration between researchers and the public
2. Professionalise researcher participation through skills training, reward and recognition
3. Increase our understanding of public views and interests
4. Become a trusted advisor and leading voice, enabling the public to make informed judgements

Get Out There!

Throughout 2016 we have focused on finding effective ways to bring research out of the lab. To do so, we have created new activities, games and informational materials and have experimented with original event formats.

We developed an interactive 'pop-up' exhibit, which allows us to discuss our research in new and unexpected locations. All materials have been designed to appeal to a broad and non-scientific audience and to encourage people to share their own views about stem cell research.

We launched our stem cell robots - a completely original hands-on activity developed by researchers to teach the basic principles of differentiation. They have proven hugely popular at science festivals and other drop-in events and have helped us to think creatively about how to represent the intricacies of cell biology.

We brought science comedy to Cambridge by hosting the city's first 'Science Showoff' comedy evening. Our researchers took to the stage to reveal the lighter side of life in the lab. They performed to a sell-out public crowd and raised over £700 for Parkinson's UK.

The 'MRC Game Lab' event invited computer game developers to learn more about stem cells and to compete to create a game inspired by our work in under 48 hours. The fusion of creative minds led to a whole host of new ideas.

In total, we estimate that our researchers have interacted with more than 3,000 members of the public this year. Our growing resources have allowed us to meet and understand the views of a wide range of different people and we are continually inspired by the curiosity, openness and support that our work receives.

Collaborate

A key aim this year has been to improve how we engage with individuals affected by medical conditions. As stem cell research begins to have a greater impact on medicine, it is essential that we provide ways for these groups to access reliable information and to express their views. To start this process we created a series of short films about our work that were made by patients for the wider public (www.stemcells.cam.ac.uk).

With support from patient charities, we used social media to promote the films and to encourage further engagement with research and were delighted by the response. We plan to continue working collaboratively with patients in the future and aim to build long-term links with these communities.

Support Researchers

We aim to ensure that public engagement is embedded in our working culture and is considered an integral part of any research career. In 2016 we introduced several initiatives to help achieve this aim:

- An internal seed fund to support innovative engagement projects led by researchers
- Introductory public engagement training included in all new student inductions
- Skills development activities at the Annual Retreat
- 'Advanced Communication Skills' workshop
- Additional support to include plans for public engagement in all research grants
- Increased travel grants and expenses
- Regular recognition of achievements in weekly bulletin
- Internal prize for commitment to public engagement: *Stanley Strawbridge*
- Institute nomination for the University 'Public Engagement with Research' awards: *The Laurenti group*

Public Engagement 2017 - 2022

We are pleased to confirm that our ambitious 5-year-plan for the Public Engagement Programme has been approved by Wellcome and the MRC as part of our major research centre funding.
The plan includes growth in our public engagement team, increased support for core activities and creative use of public spaces in our new building. We are looking forward to maximising engagement opportunities and building new relationships in our target communities.

Principal Investigators

Maria Alcolea
Epithelial cell fate and plasticity

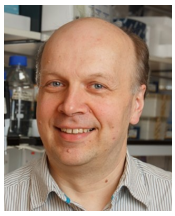
Roger Barker
Parkinson's and Huntington's disease

Kevin Chalut
Physical biology of pluripotency and differentiation

Ana Cvejic
Haematopoietic stem cells

Robin Franklin
Adult neural stem cells and CNS regeneration

Cédric Ghevaert
In vitro production of platelets for transfusion



Bertie Göttgens
Network control of normal & leukaemic blood stem cells

Tony Green
Haematopoiesis

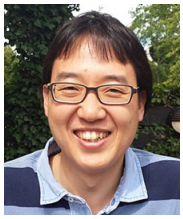
Brian Hendrich
Transcriptional control of stem cell fate

Daniel Hodson
Mutation timing in lymphomagenesis

Brian Huntly
Leukaemia stem cell biology and leukaemogenesis

Ragnhildur Thóra Káradóttir
Neurotransmitter signalling to CNS progenitor cells

David Kent
Single cell fate choice in normal & malignant stem cells



Bon-Kyoung Koo
Homeostatic regulation of adult stem cells

Elisa Laurenti
Human hematopoietic stem cells in health and disease

Joo-Hyeon Lee
Stem cells and niches

Andrew McCaskie
Regenerative therapies for bone and cartilage repair

Simón Méndez-Ferrer
Blood stem cell niches

Jennifer Nichols
Embryonic pluripotency

Anna Philpott
Proneural transcription factors

Stefano Pluchino
Stem cell signalling and brain repair

Ingo Ringshausen
Haematopoietic stem cells and malignancies

David Rowitch
Glial cells and response to injury

José Silva
Biology of induced pluripotency

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

Sanjay Sinha
Vascular diseases

Austin Smith
Pluripotent stem cells

Ludovic Vallier
Mechanisms controlling differentiation of pluripotent stem cells into definitive endoderm

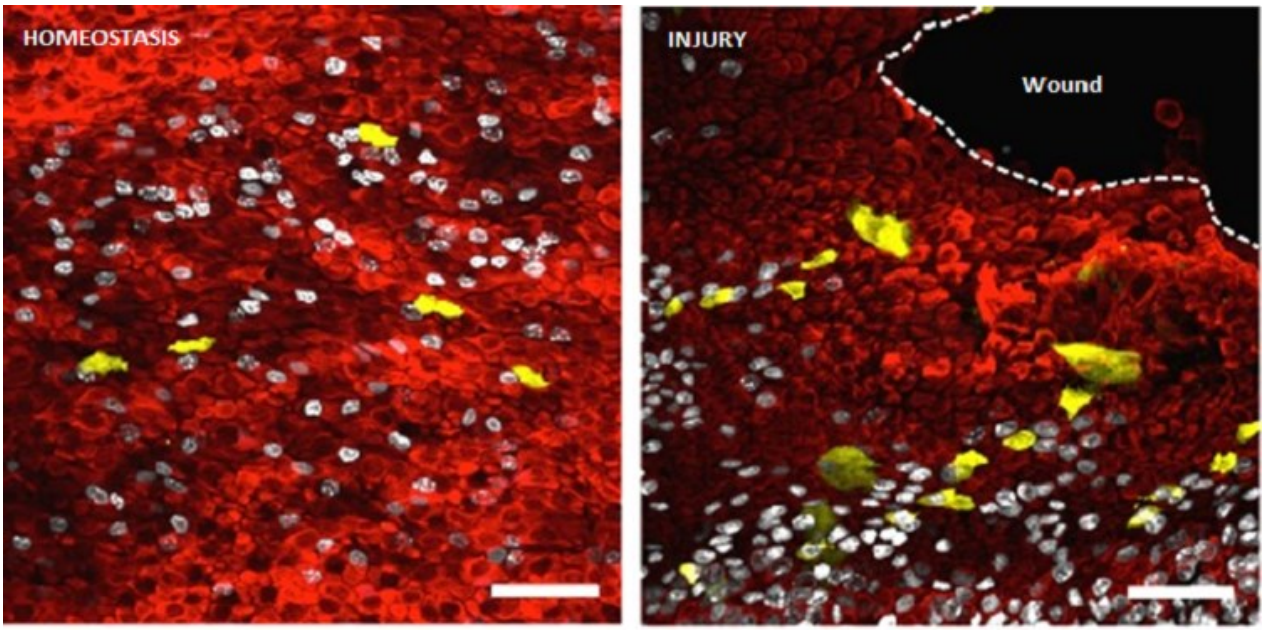
George Vassiliou
Leukaemic haemopoietic stem cells

Maria Alcolea

Epithelial cell fate and plasticity

My research interests have been focused on studying the behaviour of progenitor cells in the mouse oesophagus as a model to unveil the basic rules underlying squamous epithelial cell fate. My work in the field has revealed how this tissue is maintained under homeostatic conditions, and how these rules switch upon injury. More recently I have been able to identify how progenitor cells alter and adapt their behaviour in response to preneoplastic mutations, reflecting their remarkable cellular plasticity. Investigating the cellular and molecular mechanisms governing this dynamic behaviour and the potential implications for early cancer development will constitute the basis of my research programme.

To answer these questions, I will make use of a combination of in vivo lineage tracing techniques, transcriptional network analysis, as well as 3D organoid and explant culture systems.



Oesophageal progenitors (yellow cells) redefine their behaviour in response to injury. White label indicates cells recruited to proliferation (Science 2012, 31;337(6098):1091-3).

In 2007 Maria received her PhD in Biochemistry at the University of the Balearic Islands, Spain. She then moved to Barts Cancer Institute - Queen Mary University of London to start her Postdoctoral training with Dr. P.R. Cutillas, where she used phosphoproteomic approaches to study cancer drug resistance. In 2009 she joined Prof Phil Jones laboratory at the Hutchison/MRC cancer unit where she was awarded a Marie Curie Intra-European Fellowship (FP7). There she spent a total of 6 years studying epithelial stem cell behaviour using genetic lineage tracing approaches and methods from statistical physics.

In 2015, Maria was awarded a Wellcome/The Royal Society Sir Henry Dale Fellowship to establish her own laboratory to study epithelial stem cell plasticity in response to injury and tumour development.

Maria is currently a Principal Investigator at the Wellcome Trust/MRC Cambridge Stem Cell Institute and affiliate to the Oncology Department, University of Cambridge.

Key Publications

Alcolea MP, Greulich P, Wabik A, Frede J, Simons BD, Jones PH. (2014) **Differentiation imbalance in single Oesophageal progenitor cells causes clonal immortalization and field change**. *Nature Cell Biology* Jun;16(6):615-22. PMCID:PMC4085550

Casado P, Alcolea MP, Iorio F, Rodríguez-Prados JC, Vanhaesebroeck B, Saez-Rodriguez J, Joel S, Cutillas PR. (2013) **Phosphoproteomics data classify hematological cancer cell lines according to tumor type and sensitivity to kinase inhibitors**. *Genome Biology*. Apr 29;14(4):R37. PMCID:PMC4054101

Alcolea MP, Jones PH. (2013) **Tracking cells in their native habitat: lineage tracing in epithelial neoplasia**. *Nature Reviews Cancer*. Mar;13(3):161-71. PMID:23388619

Doupé DP*, Alcolea MP*, Roshan A, Zhang G, Klein AM, Simons BD, Jones PH. (2012) **A Single Progenitor Population Switches Behavior to Maintain and Repair Esophageal Epithelium**. *Science*. Aug 31;337(6098):1091-3.*Equal contribution. PMCID:PMC3527005

Alcolea MP, Casado P, Rodríguez-Prados JC, Vanhaesebroeck B, Cutillas PR. (2012) **Phosphoproteomic Analysis of Leukemia Cells under Basal and Drug-treated Conditions Identifies Markers of Kinase Pathway Activation and Mechanisms of Resistance**. *Molecular Cell Proteomics*. 11(8), 453-66. PMCID:PMC3412974

Group Members

* Anne-Lore Bex (Masters Student)
* Paula Jimenez Gomez (Research Assistant)
* Jamie McGinn (PhD Student)

Alcolea Group

Funded by

The Isaac Newton Trust

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THE ROYAL SOCIETY

CANCER RESEARCH UK | CAMBRIDGE CENTRE

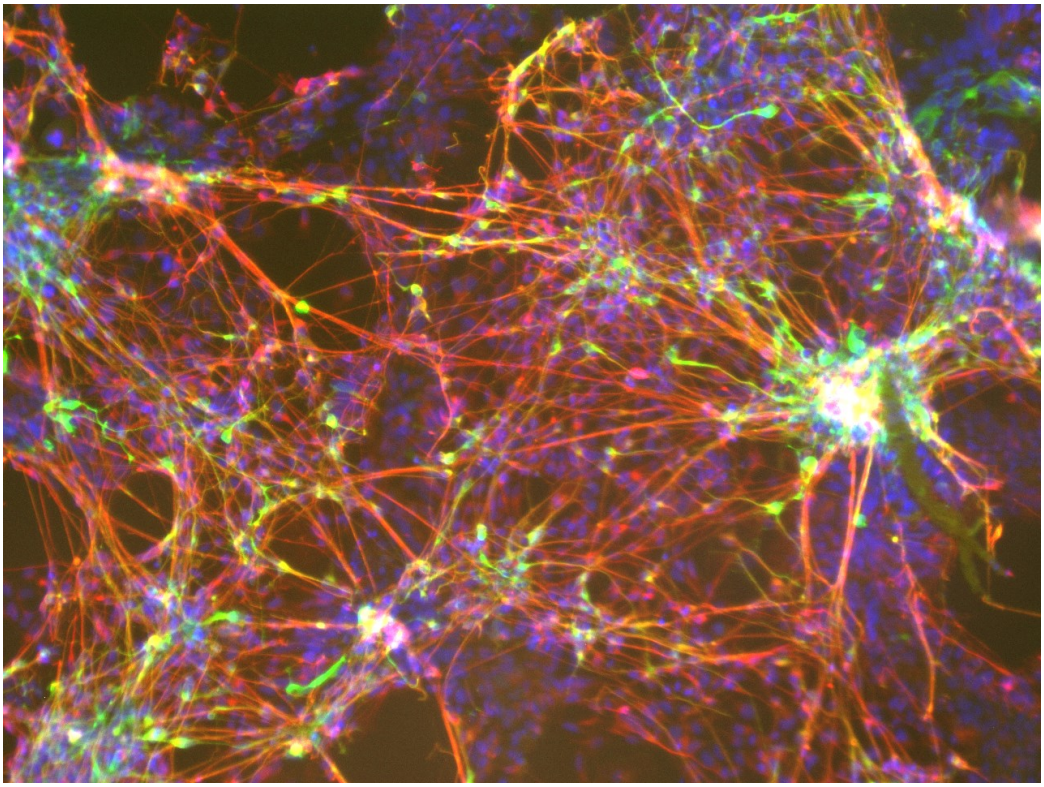
Roger Barker

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 treatment whilst others may not: e.g. dopamine cell therapies from stem cells treatment may be better suited to younger PD patients with a more benign clinical course.

In addition this ability to stratify patients also enables us to undertake studies looking at how these disease subtypes may arise using cells grown from the patients themselves. Typically we harvest these cells from the skin and then turn them into nerve cells in the lab, and by so doing we hope that we can recapitulate what goes wrong in the brain nerve cells in such patients.



Dopaminergic neurons differentiated from embryonic stem cells using a clinical grade protocol and reagents—TH (green), Btub (red)

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 an 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 foetal cell grafting in patients with early Parkinson's Disease.

Key Publications

La Manno G, Gyllborg D, Codeluppi S, Nishimura K, Salto C, Zeisel A, Borm LE, Stott SR, Toledo EM, Villaescusa JC, Lönnerberg P, Ryge J, Barker RA, Arenas E, Linnarsson S. **Molecular Diversity of Midbrain Development in Mouse, Human, and Stem Cells**. *Cell. 2016 Oct 6;167(2):566-580* PMCID: PMC5055122

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Group Members

* Nina Antouli (Graduate Student)
* Nick Blair (Clinical Fellow)
* Marta Camacho Goncalves (Research Assistant)
* Lucy Collins (Post-doc Researcher)
* Danielle Daft (Research Manager)
* Mercy Danga (Research Assistant)
* Natalie V. Guzman (Graduate Student)
* Xiaoling He (Research Assistant)
* Wei-Li Kuan (Post-doc Researcher)
* Sarah Mason (Post-doc Researcher)
* Stine Myklebust (Research Assistant)
* Venkat Pisupati (Post Doctoral Fellow)
* Kirsten Scott (Clinical Research Fellow)
* Tom Stoker (Clinical Research Fellow)
* Simon Stott (Post-doc Researcher)
* Pam Tyers (Research Assistant)
* Romina Vuono (Post-doc Researcher)
* Ruwani Wijeyekoon (Clinical Research Fellow)
* Lindsey Wilkin (Clinical Coordinator)
* Caroline Williams Gray (Clinical Lecturer)

Barker Group

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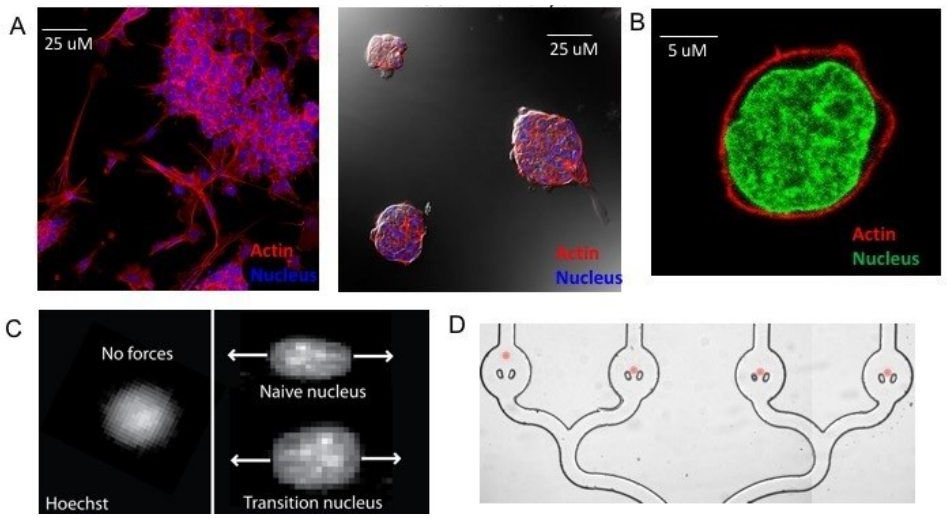
Kevin Chalut

The physical biology of pluripotency and differentiation

The transformation of a stem cell into a mature tissue cell consists of a progression of highly regulated steps. However, the process of differentiation, and how it is regulated, is not well understood, despite the importance both for comprehending embryonic development and for targeted stem cell therapies. Furthermore, differentiation has primarily been studied from a biochemical perspective, while mechanical aspects, despite their importance, have been largely overlooked. We are focused on illuminating biophysical aspects of transitions between states in ES cell differentiation and in embryonic development by utilising quantitative microscopy, microfabrication and microfluidic techniques. Biophysical aspects we focus on include cell mechanics and matrix signalling, where our work has demonstrated that the matrix environment is a potent regulator of transitions by controlling cell spreading and shape. Another biophysical aspect we study is how nuclear mechanics, as driven by chromatin and nuclear envelope structure, influence gene expression and transport of signalling molecules through nuclear pore complexes. We are also developing single cell microfluidic techniques to study transitions between states in ES cell differentiation. These techniques allow us to completely control the microenvironment and signalling environment of single ES cells, and retrieve samples at specific time points for downstream analysis or further experimentation. Our work will shed light on state transitions and differentiation in development, in particular how these transitions are mechanically regulated.



(A) ES cells cultured on soft substrates (right) more effectively form pluripotent colonies than on stiff hydrogels or plastic, demonstrating the importance of controlling the mechanical microenvironment for ES cells.(B) Our lab investigates cell and nuclear shape, as mediated by forces in the nucleus and cytoskeleton. (C) We use biophysical techniques to apply mechanical stresses to ES cells in order to demonstrate the importance of mechanical forces in cell transitions, and the mechanisms by which mechanical forces lead to changes in gene expression. (D) We develop microfluidic techniques for single cell monitoring in order to better understand transitions through phases of pluripotency. Image Credits: Chibeza Agley (A), George Wylde (B) and Andrew Hodgson (D).

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 Cambridge 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.

Key Publications

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Chalut KJ, Ostrander J, Giacomelli M, Wax A. **Light scattering measurements of subcellular structure provide noninvasive early detection of chemotherapy-induced apoptosis**. *Cancer Research* 2009, 69(3). PMCID:PMC2667891

Group Members

* Chibeza Agley (Post-doc Researcher)
* Celine Labouesse (Post-doc Researcher)
* Christophe Verstreken (PhD Student)
* George Wylde (PhD Student)
* Ayaka Yanagida (Post-doc Researcher)

Chalut Group

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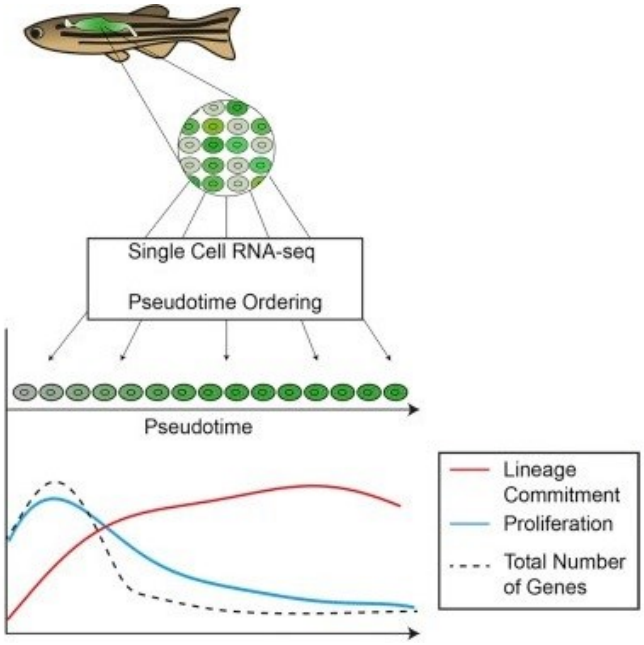
Ana Cvejic

Haematopoietic stem cells

Blood stem cells need to both perpetuate (self-renew) themselves and differentiate into all mature blood cells to maintain blood formation throughout life. Clarifying how HSCs differentiate into diverse cell types is important for understanding how this process is subverted in the generation of blood pathologies. The aim of my group is to bridge this knowledge gap by providing a method in a relevant model organism (zebrafish, Danio rerio) that will allow us to dissect the role of novel blood genes. We combine genetic perturbation with computational sequence and network analysis, to reconstruct and validate gene regulatory networks in zebrafish blood development.
The results from our studies will advance our understanding of how normal fate decisions are instigated and provide clues for the design of novel therapies for blood pathologies.



Single-cell RNA-sequencing reveals the continuous nature of zebrafish thrombocyte development. The progression of cells along this continuum is characterized by a highly coordinated transcriptional program, displaying simultaneous suppression of genes involved in cell proliferation and ribosomal biogenesis as the expression of lineage specific genes increases. Number of genes expressed and mRNA content per cell decrease during differentiation.

In 2008 Ana received her PhD in Biochemistry at the University of Bristol. She then moved to University of Cambridge/Wellcome Trust Sanger Institute to start a Postdoctoral Fellowship with Professor Willem Ouwehand. Over the next three and a half years, Ana independently established haematopoiesis research using the zebrafish model at the Sanger Institute. In 2012 Ana was awarded the CRUK Career Development Fellowship to perform functional characterisation of genes implicated in blood formation using zebrafish as an in vivo model. In 2015 Ana was awarded ERC Starting Grant and in 2016 EMBO Young Investigator Award.

Ana is currently Principal Investigator at the Department of Haematology, University of Cambridge and an Honorary Faculty member at the Sanger Institute.

Key Publications

Carmona SJ, Teichmann SA*, Ferreira L, Macaulay IC, Stubbington MJT, Cvejic A*, Gfeller D* (2017). **Single-cell transcriptome analysis of fish immune cells provides insight into the evolution of vertebrate immune cell types**. *Genome Research* (*joint senior author) PMID: 28087841

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Group Members

* Emmanouil Athanasiadis (Post-doc Researcher)
* Jan Botthof (PhD Student)
* Debbie Goode (Post-doc Researcher)
* Shwethaa Raghunathan (Research Assistant)
* Paulina Strzelecka

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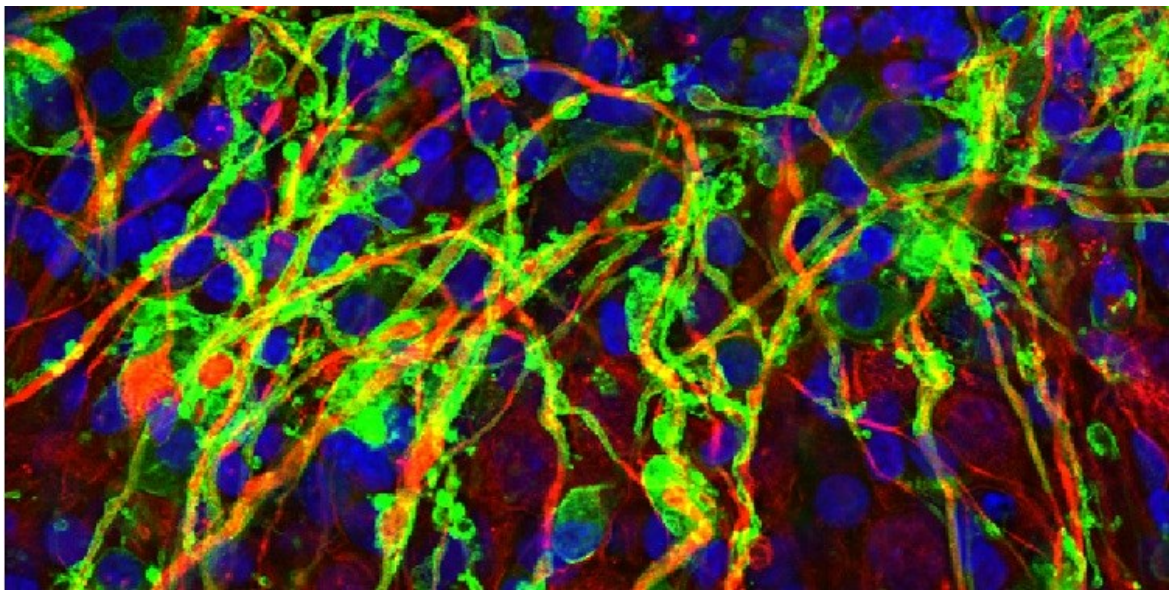
Robin Franklin

Adult neural stem cells and CNS regeneration

The Franklin lab studies the mechanisms of Central Nervous System (CNS) regeneration with a particular focus on remyelination, a regenerative process mediated by adult stem cells in which new myelin sheaths are restored to demyelinated axons. Using a wide range of experimental approaches we are examining extrinsic (environmental) and intrinsic (transcriptional/epigenetic) factors that govern the responses of adult neural stem/precursor cells to injury and their differentiation into oligodendrocytes and other glia following CNS injury.

The potential medical benefits of this research are to stop nerve cell degeneration and therefore provide a treatment for the currently untreatable secondary progressive phase of multiple sclerosis.



Progenitors and oligodendrocytes (green) associating with and myelinating axons (red) in the rodent cerebellum (Credit Dr Dan Ma)

Robin Franklin is Professor of Stem Cell Medicine. He obtained his undergraduate degrees in Physiology and Veterinary Medicine and his PhD in Neuroscience. He has worked predominantly on the biology of myelin regeneration (remyelination) and investigating strategies by which this important regenerative process may be enhanced therapeutically. He is at the forefront of studying the cellular mechanisms of remyelination, providing insights into how adult stem cells are recruited to areas of demyelination and the extrinsic and intrinsic factors that regulate their differentiation into remyelinating oligodendrocytes and other glial cel types.

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 regeneration. He is a Fellow of the Academy of Medical Sciences.

Key Publications

Guzman de la Fuente A, Errea A, van Wijngaarden P, Gonzalez GA, Kerninon C, Jarjour AA, Lewis HJ, Jones CA, Nait-Oumesmar B, Zhao C, Huang JK, ffrench-Constant C, Franklin RJM (2015) **Vitamin D receptor - retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation**. *Journal of Cell Biology 211: 975-985*. PMCID:PMC4674280

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Zawadzka M, Rivers LE, Fancy SPJ, Zhao C, Tripathi R, Jamen F, Young K, Goncharevich A, Pohl H, Rizzi M, Rowitch DH, Kessaris N, Suter U, Richardosn WD, Franklin RJM (2010) **CNS-resident glial progenitor/stem cells prodcude Schwann cells as well as oligodendrocytes during repair of CNS demyelination**. *Cell Stem Cell 6: 578-590*. PMCID:PMC3856868

Group Members

* Roey Baror (PhD Student)
* Natalia Deja (PhD Student)
* Ludovica Di Canio (PhD Student)
* Oihana Errea (Post-doc Researcher)
* Sarah Foerster (PhD Student)
* Tanay Ghosh (Post-doc Researcher)
* Ginez Gonzalez (Post-doc Researcher)
* Joseph Guy (PhD Student)
* Alerie Guzman de la Fuente (Post-doc Researcher)
* Ilias Kazanis (Senior Post-doc Researcher)
* Dan Ma (Post-doc Researcher)
* Freya McClenahan (Post-doc Researcher)
* Chris McMurran (PhD Student)
* Alisa Molotova (PhD Student)
* Daniel Morrison (Senior Technician)
* Bjoern Neumann (Post-doc Researcher)
* Michal Presz (Technician)
* Michael Segel (PhD Student)
* Chao Zhao (Assistant Director of Research)

Franklin Group

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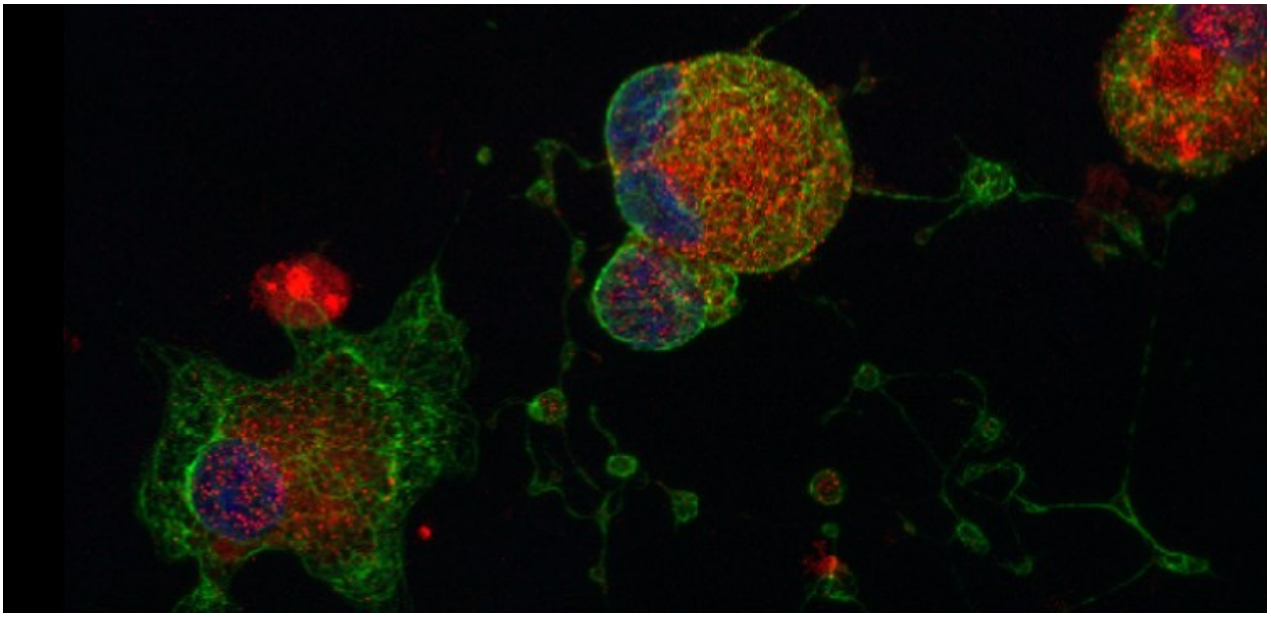
Cédric Ghevaert

In vitro production of platelets for transfusion

The main focus of my group's research is the production of blood cells for human use, namely red cells and platelets. We have developed a particular expertise in the production of these cell types from human pluripotent stem cells using methodologies that are compatible with the production of clinical grade products within the constraints of affordable manufacturing processes. To this end we are combining cellular programming through knowledge and manipulation of transcription factor networks and the creation of 3D biocompatible niches and bioreactors.

As a consultant haematologist for the NHS Blood and Transplant (a partner organisation of the University of Cambridge) I have an expertise recognised world-wide in carrying out first-in-man studies of blood cell survival and recovery in human volunteers. I am the clinical lead for 3 such trials due to take place in the next 5 years on the Cambridge Biomedical Campus.



Megakaryocytes were produced from human pluripotent stem cells through over expression of 3 key transcription factors TAL1, GATA1 and FLI1. These cells are capable of producing platelets that contain the granules (in red) necessary to perform their clotting function after transfusion. Green= alpha-tubulin, Red=P-selectin, Blue=nuclei.

Cédric Ghevaert graduated from the medical school of the University Libre de Bruxelles in 1997 and subsequently became a fellow of the Royal College of Physicians, London (2000). He specialised in Haematology and became a fellow of the Royal College of Pathologists in 2005. He obtained his PhD in 2008 studying novel antibodies for the treatment of bleeding in neonates in Cambridge. He obtained a personal Intermediate Clinical Fellowship from the British Heart Foundation whilst working in Prof Steve Watson's group at the university of Birmingham in 2009.

He took up the post of Senior Lecturer in Transfusion Medicine at the University of Cambridge in 2010, a post funded by the NHS Blood and Transplant. In addition to his academic post, Dr Ghevaert also works as a Consultant Haematologist for the NHSBT.

Key Publications

Moreau T, Evans AL, Vasquez L, Tijssen MR, Yan Y, Trotter MW, Howard D, Colzani M, Arumugam M, Wu WH, Dalby A, Lampela R, Bouet G, Hobbs CM, Pask DC, Payne H, Ponomaryov T, Brill A, Soranzo N, Ouwehand WH, Pedersen RA, Ghevaert C. **Large scale production of platelet forming megakaryocytes from human pluripotent stem cells by a chemically defined forward programming approach**. *Nature Communications 2016 Apr 7;7:11208* PMID:27052461

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Ghevaert C, Herbert N, Hawkins L, Grehan N, Cookson P, Garner SF, Crisp-Hihn A, Lloyd-Evans P, Evans A, Balan K, et al. (2013) **Recombinant HPA-1a antibody therapy for treatment of fetomaternal alloimmune thrombocytopenia: proof of principle in human volunteers**. *Blood 122:313-320*. PMCID:PMC3716198

Albers CA, Paul DS, Schulze H, Freson K, Stephens JC, Smethurst PA, Jolley JD, Cvejic A, Kostadima M, Bertone P,…,Ghevaert C. (2012) **Compound inheritance of a low-frequency regulatory SNP and a rare null mutation in exon-junction complex subunit RBM8A causes TAR syndrome**. Nature *Genetics 44:435-439, S431-432*. PMCID:PMC3428915

Group Members

* Cavan Bennett (PhD Student)
* Amanda Dalby (PhD Student)
* Amanda Evans (Post-doc Researcher)
* Holly Foster (Research Assistant)
* Nina Herbert (Senior Clinical Research Sister)
* Daniel Howard (Post-doc Researcher)
* Thomas Moreau (Post-doc Researcher)
* Annett Müller (Research Assistant)
* Momal Taimoor (Research Assistant)
* Amie Waller (Research Assistant)

Ghevaert Group

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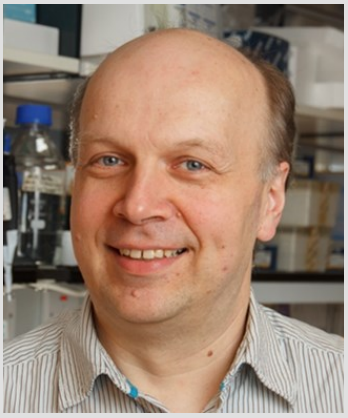
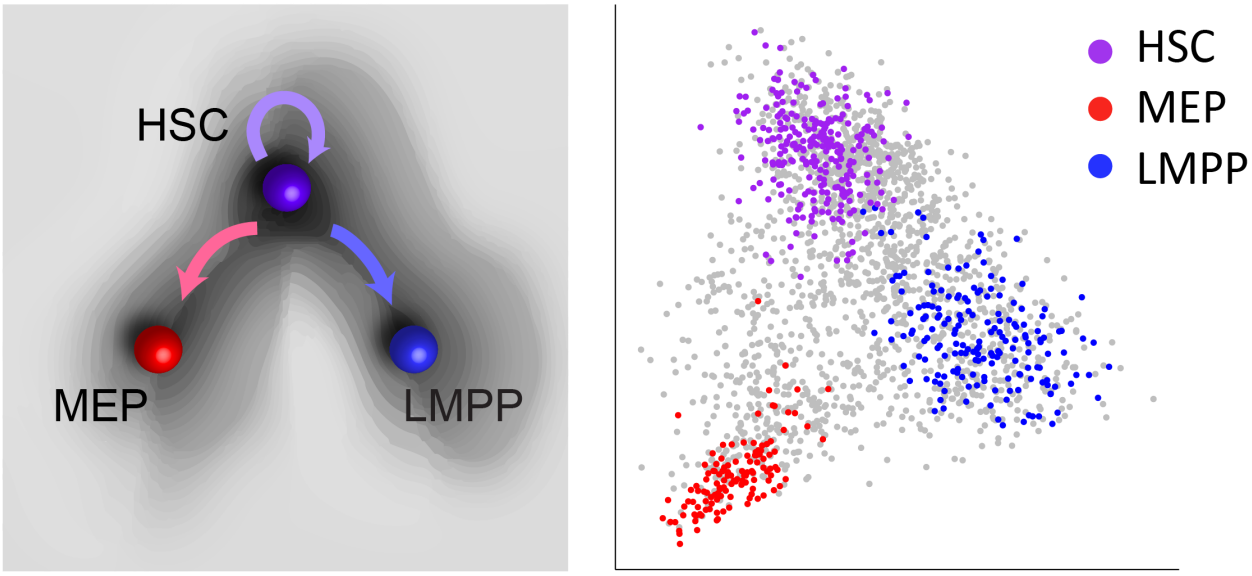


Bertie Göttgens

Network control of normal and leukaemic blood stem cells

The Göttgens group uses a combination of experimental and computational approaches to study how transcription factor networks control the function of blood stem cells and how mutations that perturb such networks cause leukaemia. This integrated approach has resulted in the discovery of new combinatorial interactions between key blood stem cell regulators, as well as experimentally validated computational models for blood stem cells.

Current research focuses on (i) single cell genomics of early blood development, (ii) computer models to chart the transcriptional landscape of blood stem and progenitor cell differentiation, (iii) transcriptional consequences of leukaemogenic mutations in leukaemia stem/progenitor cells, and (iv) molecular characterisation of human blood stem/progenitor cell populations used in cell and gene therapy protocols.



Reconstruction of differentiation trajectories from single cell gene expression profiles provides unprecedented insights into the dynamic processes that drive blood stem cell differentiation. The diagram on the left shows putative differentiation trajectories of a haematopoietic stem cell (HSC) into Megakaryocyte-Erythroid Progenitors (MEP) or Lymphoid-primed Multi Potential Progenitors (LMPP). The diagram on the right shows a diffusion map representation of single cell expression profiles generated from primary blood stem and progenitor cells, with HSCs, MEPs and LMPPs highlighted using the same colour scheme as the left hand panel .

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.

Key Publications

Scialdone A, Tanaka Y, Jawaid W, Moignard V, Wilson NK, Macaulay IC, Marioni JC, Göttgens B. (2016). **Resolving Early Mesoderm Diversification through Single Cell Expression Profiling.** *Nature 535 (7611): 289-293* PMCID: PMC4947525

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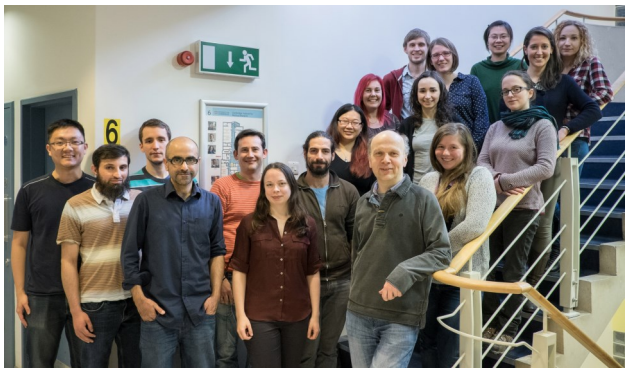
Moignard V, Macaulay IC, Swiers G, Buettner F, Schütte J, Calero-Nieto FJ, Kinston S, Joshi A, Hannah R, Theis FJ, Jacobsen SE, de Bruijn MFT, Göttgens B. (2013) **Characterisation of transcriptional networks in blood stem and progenitor cells using high-throughput single cell gene expression analysis.** Nature *Cell Biology 15: 363-372*. PMCID:PMC3796878

Wilson NK, Foster SD, Wang X, Knezevic K, Schütte J, Kaimakis P, Chilarska P, Kinston S, Ouwehand WH, Dzierzak E, Pimanda JE, de Bruijn MF, Göttgens B. (2010). **Combinatorial transcriptional control in blood stem/progenitor cells: genome-wide analysis of ten major transcriptional regulators**. *Cell Stem Cell 7(4):532-544*. PMID: 20887958

Group Members

* Silvia Basilico (PhD Student)
* Fernando Calero (Senior Researcher)
* Joakim Dahlin (Post-doc Researcher)
* Carolina Guibentif (Post-doc Researcher)
* Fiona Hamey (PhD Student)
* Rebecca Hannah (Research Assistant)
* Wajid Jawaid (PhD Student)
* Sarah Kinston (Research Asisstant)
* Iwo Kucinski (Post-doc Researcher)
* Vasileios Ladopoulos (Post-doc Researcher)
* Winnie Lau (Post-doc Researcher)
* Chee Lim (PhD Student)
* Sonia Nestorowa (PhD Student)
* Blanca Pijuan Sala (PhD Student)
* Moosa Qureshi (PhD Student)
* Xiaonan Wang (Post-doc Researcher)
* Nicola Wilson (Senior Researcher)



Göttgens Group

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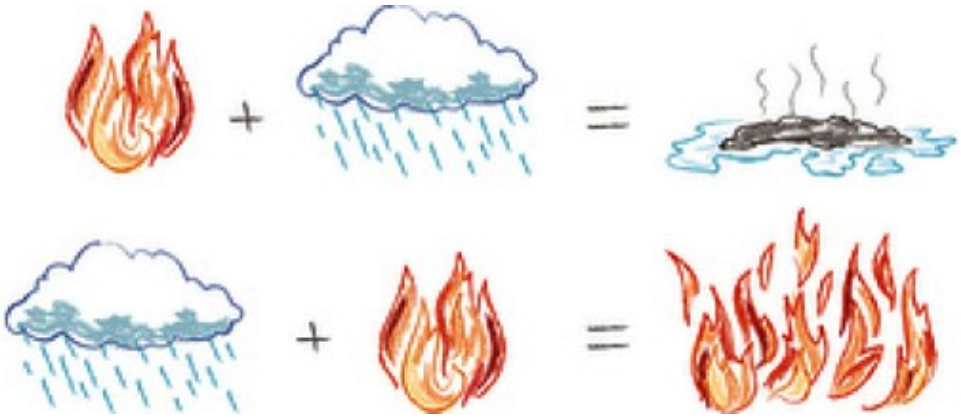
Tony Green

Haematopoiesis

The Green Lab focuses on the mechanisms whereby blood stem cells are subverted during the genesis of haematological malignancies. Over the past decade we have increasingly concentrated on JAK/STAT signalling which is dysregulated in many cancers and plays a key role in multiple stem cell systems. In particular we have explored the molecular and cellular pathogenesis of a group of pre-leukaemic disorders, the myeloproliferative neoplasms (MPNs), in studies which have spanned basic, translational and clinical research. The myeloproliferative neoplasms 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. We described the MPN "mutational landscape" and identified causal mutations which revolutionised their diagnosis and catalysed development of therapeutically valuable JAK-family tyrosine kinase inhibitors.

Our 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; the first demonstration in any cancer that mutation order affects stem and progenitor behaviour, thus influencing clinical presentation, disease outcome and response to therapy; and the description of paradigm-shifting non-canonical mechanisms of JAK/STAT signalling.



Order Matters: By studying patients with somatic mutations of both JAK2 and TET2 we have demonstrated, for the first time in any tumour, that the order in which somatic mutations are acquired influences stem/progenitor cell function and therefore tumour behaviour (Ortmann, C. A., Kent, D. G. et al. N. Engl. J. Med. 372, (2015); image adapted from Nature Reviews Genetics 16, 193, 2015).

Tony Green studied medicine (Cambridge and University College Hospital London) and trained in haematology (Royal Free Hospital and Cardiff). He gained his PhD studying oncogenic retroviruses (London) and spent a post-doctoral period at the Walter and Eliza Hall Institute (Melbourne), moving to Cambridge in 1991 as a Wellcome Clinical Senior Fellow. He was subsequently appointed Professor of Haemato-oncology (1999), Head of the University Department of Haematology (2000), and Director of the Wellcome Trust-MRC Cambridge Stem Cell Institute (2016).

Professor Green's research has focused on human myeloproliferative neoplasms (MPNs) in studies which have spanned basic, translational and clinical research. He was elected Fellow of the Academy of Medical Sciences (2001), Newton Abraham Visiting Professor, University of Oxford (2011), Distinguished Visiting Professor Cancer Science Institute, Singapore (2009-10), Grinberg/Wisch Visiting Professor, Mount Sinai Medical Center, New York (2013), and Clement A Finch Visiting Professor, University of Washington (2015) and President of the European Haematology Association (2015-2017).

Key Publications

Park HJ, Li J, Hnnah R, Biddie S, Leal-Cervantes A, Kirschner K, Flores Santa Cruz D, Sexl V, Göttgens B, Green AR. **Cytokine-induced megakaryocytic differentiation is regulated by genome-wide loss of a uSTAT transcriptional program**. EMBO *Journal 2016 Mar 15;35(6):580-94*. PMCID: PMC4801948

*Ortmann CA, *Kent DG, Nangalia J, Silber Y, Wedge DC, Grinfeld J,....Harrison CN, Vassiliou G, Vannucchi A, Campbell PJ, Green AR. **Effect of mutation order on myeloproliferative neopl asms**. *Co-first author. *New England Journal of Medicine, 372(7):601-12, 2015* PMCID:PMC4660033

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Group Members

* Federico Comoglio (Post-doc Researcher)
* David Flores-Santa-Cruz (Research Assistant)
* Jacob Grinfeld (PhD Student)
* Carlos Gonzalez-Arias (PhD Student)
* Tina Hamilton (Technician)
* Thorston Klampfl (Post-doc Researcher)
* Juan Li (Senior Scientist/Researcher)
* Stephen Loughran (Post-doc Researcher)
* Francesca Nice (Research Assistant)
* Thomas Oellerich (Post-doc Researcher)
* Francesca Pagano (Post-doc Researcher)
* Hyun Jung Park (Post-doc Researcher)
* Dean Pask (Technician)
* Daniel Prins (Post-doc Researcher)
* Rachel Sneade (Reseach Assistant)

Green Group

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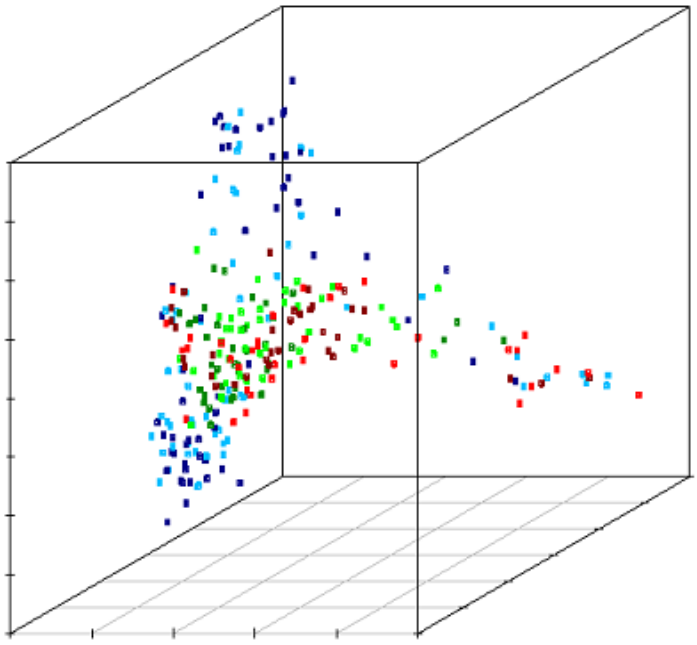
Brian Hendrich

Transcriptional control of stem cell fate

Embryonic stem (ES) cells hold enormous promise for personalised medicine and drug discovery since they can be maintained indefinitely and are pluripotent. 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 very hard to control in culture. 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 repress. Therefore in order to understand how to direct cellular identity, seek to understand how subtle differences in gene expression patterns in seemingly identical cells influence any subsequent differentiation decisions. By understanding how ES cells make different developmental decisions this work will bring the medical promise of stem cells closer to realisation.



Single cell gene expression data from 8-cell (red), 16-cell (green) and 32-cell (blue) embryos visualised in a Diffusion plot. (O'Shaughnessy-Kirwan et al. 2015) (Image Credit Patrick Lombard)

Brian Hendrich grew up near Seattle, Washington, and is consequently a consummate coffee snob. 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 Senior Research Fellow in the Basic Biomedical Sciences, and Director of the PhD Programme in Stem Cell Biology and Medicine for the Wellcome Trust - MRC Cambridge Stem Cell Institute.
He can often be found cycling the quieter roads of East Anglia, in search of a hill.

Key Publications

Miller A, Ralser M, Kloet S L, Loos R, Nishinakamura R, Bertone P, Vermeulen M, Hendrich B. (2016). **Sall4 controls differentiation of pluripotent cells independently of the Nucleosome Remodelling and Deacetylation (NuRD) complex**. *Development, 143 (17):3074-84*. PMCID: PMC5047675

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PMCID: PMC4432814

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Reynolds N, Salmon-Divon M, Dvinge H, Hynes-Allen A, Balasooriya G, Leaford D, Behrens A, Bertone P, Hendrich B. (2012) **NuRD-mediated deacetylation of H3K27 facilitates recruitment of Polycomb Repressive Complex 2 to direct gene repression.** *EMBO Journal. 31(3), 593–605.*
PMCID:PMC3273378

Group Members

* Thomas Burgold (Post-doc Researcher)
* Robin Floyd (Technician)
* Sarah Gharbi (Research Assistant)
* Bertille Montibus (Post-doc Researcher)
* Nicola Reynolds (Senior Scientist)
* Maria Xenophontos (PhD Student)

Hendrich Group

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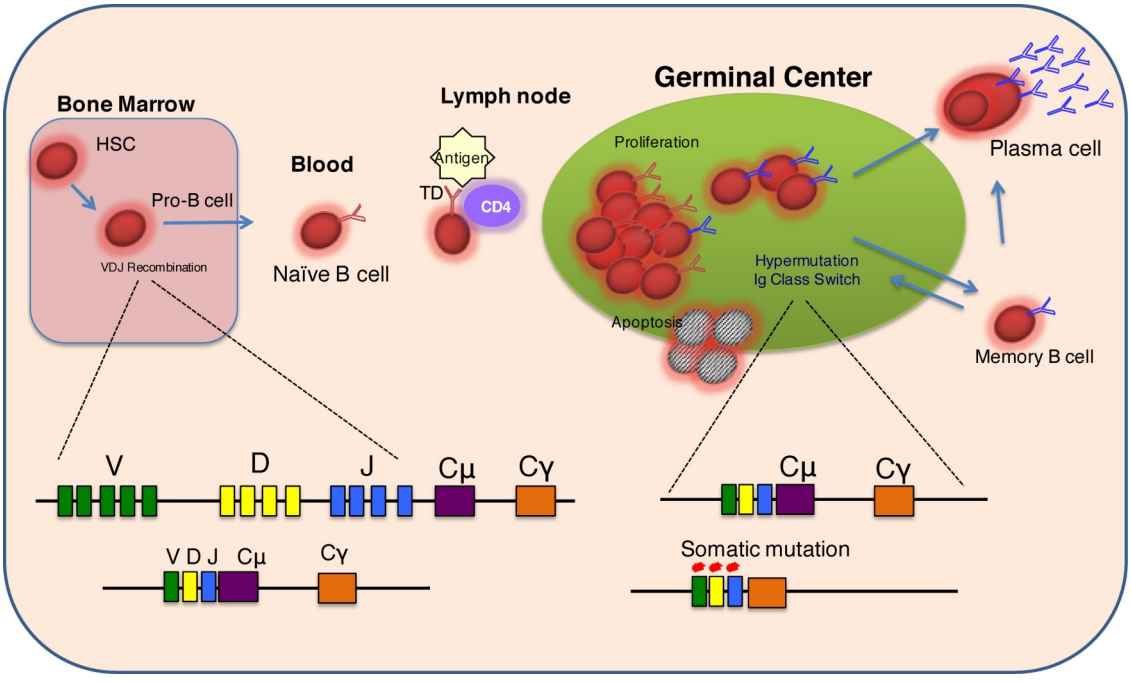
Daniel Hodson

Mutation timing in lymphomagenesis

Normal B lymphocytes progress through a series of developmental stages that begin with the haematopoietic stem cell. Progression through each of these stages is tightly controlled at both the transcriptional and post-transcriptional levels. Genetic alterations and mutations, which can occur at any stage from the haematopoietic stem cell to the post-germinal centre B cell, can lead to loss of this normal regulation and subsequently to the development of lymphoid malignancies such as non-Hodgkin Lymphoma (NHL), which is the 6th commonest form of human cancer. Understanding how these genetic alterations corrupt cell fate choices at each stage of lymphocyte development will be the key to identifying cellular pathways that can be therapeutically targeted.

My group is developing novel cell culture models to study the effects of these genetic alterations in human lymphocytes. In particular, we are interested to study how these genetic alterations lead to changes at the level of mRNA translation and how these post-transcriptional changes then contribute to lymphomagenesis. We use a variety of techniques including exome and RNA sequencing, ribosome profiling, iCLIP and xenografts to identify the developmental timing of these genetic alterations, their mechanistic contribution to lymphomagenesis and the implications this has for the treatment and monitoring of patients.



The Unique and Dangerous Life of the B Cell

Dr Hodson studied Medicine at Cambridge University and then clinical medicine at Oxford University. He subsequently trained as a clinical haematologist with a special interest in lymphoid malignancies. During his haematology training he undertook a PhD in molecular immunology at the Babraham Institute in Cambridge under the supervision of Dr Martin Turner, where he studied the contribution of post-transcriptional regulation to the normal lymphocyte development. In 2010 he moved to the National Cancer Institute, USA as a post-doctoral fellow in the lab of Dr Lou Staudt where he developed expertise in the application of functional genomics to the study of B cell lymphomas.

In 2015 he returned to Cambridge as a Medical Research Council Clinician Scientist and group leader in the CSCI and the Department of Haematology.
His group researches the molecular mechanisms that underlie lymphomagenesis. Dr Hodson also holds an honorary consultant contract in the Haematology Department at Addenbrooke's Hospital.

Key Publications

Galloway A, Saveliev A, Łukasiak S, Hodson DJ, Bolland D, Balmanno K, Ahlfors H, Monzón-Casanova E, Mannurita SC, Bell LS, Andrews S, Díaz-Muñoz MD, Cook SJ, Corcoran A, Turner M. **RNA-binding proteins ZFP36L1 and ZFP36L2 promote cell quiescence**. *Science 2016; 352 (6284):453-9* PMID: 27102483

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Schmitz R, Young RM, Ceribelli1 M, Jhavar S, Xiao W, Zhang M, Wright G, Shaffer A, Hodson DJ,... Wilson W, Waldmann TA, Rowe M, Mbulaiteye SM, Rickinson AB, Staudt LM. **Burkitt Lymphoma Pathogenesis and Therapeutic Targets from Structural and Functional Genomics**. *Nature 2012: 490: 116-120*. PMCID:PMC3609867

Turner M, Hodson DJ. **An emerging role of RNA-binding proteins as multifunctional regulators of lymphocyte development and function**. *Advances in Immunology 2012 May; (115): 161-185*. PMID:22608259

Turner M, Hodson D. **Regulation of lymphocyte development and function by RNA binding proteins**. *Current Opinion in Immunology. 2012 Apr;24(2):160 -5*. PMID:22326859

Group Members

* Rebecca Caeser (PhD Student)
* Miriam Di Re (Research Assistant)
* Jane Gao (Post-doc Researcher)
* Jade Gong (Post-doc Researcher)

Hodson Group

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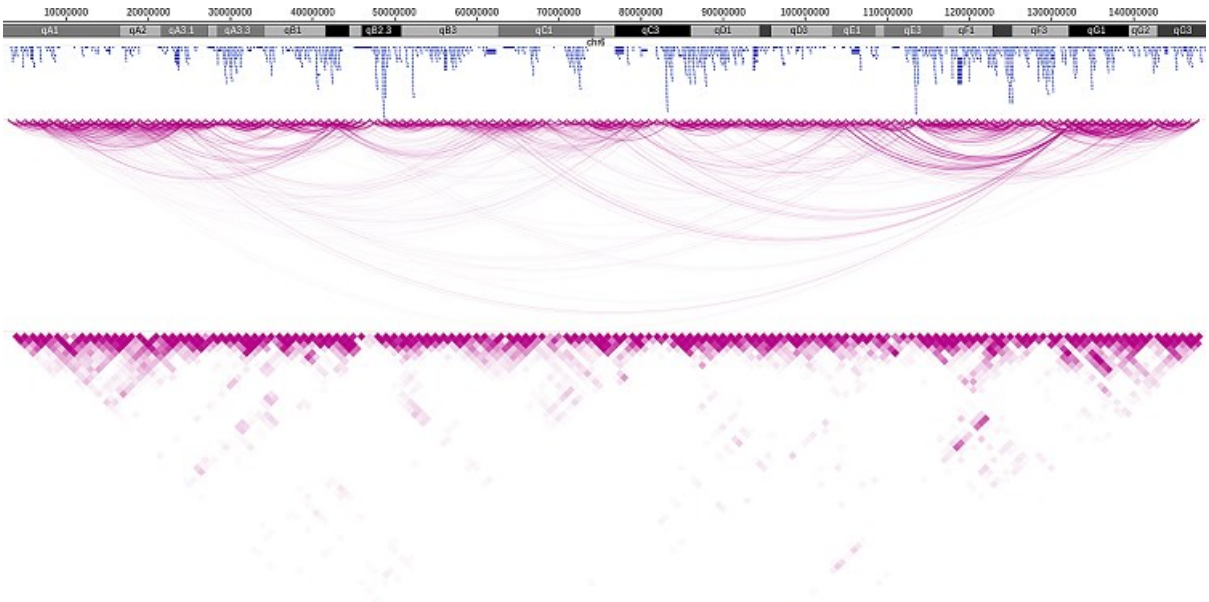
Brian Huntly

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 malignancies. 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 lymphomas (pre-leukaemic stem cells). Many of these mutations alter epigenetic regulation, enhancer function and transcriptional programmes and these are all ongoing areas of investigation within the lab.

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 has already entered early phase clinical trials in relapsed blood cancers.



DNA-DNA interaction mapping by a modified chromosome conformation capture method, capture Hi-C (Chi-C) are demonstrated on Ch6 in HPC7 haematopoeitic progenitor cells. We are currently using this method to interrogate abnormal leukaemia stem cell transcription. (Credit Shabana Vohra)

Prof Brian Huntly is a clinical academic who combines running a laboratory group with his practice as a Consultant Haematologist in Addenbrooke's Hospital. He studied Medicine at Edinburgh, trained in Haematology in Dundee and Cambridge and is a member of the Royal College of Physicians and a Fellow of the Royal College of Pathologists.

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

Key Publications

Giotopoulos G, Van der Weyden L, Osaki H, Rust A, Meduri E, Chan WI, Paul D, Horton SJ, Gallipoli P, Pimanda JE, Prinjha R, Tenen DG, Vassiliou GS, Koschmieder S, Adams DJ, Huntly BJP. **A novel murine model identifies cooperating mutations and therapeutic targets critical for the progression of chronic myeloid leukemia (CML).** *Journal Experimental Medicine 2015 Sep 21;212(10):1551-69*. PMCID:PMC4577832

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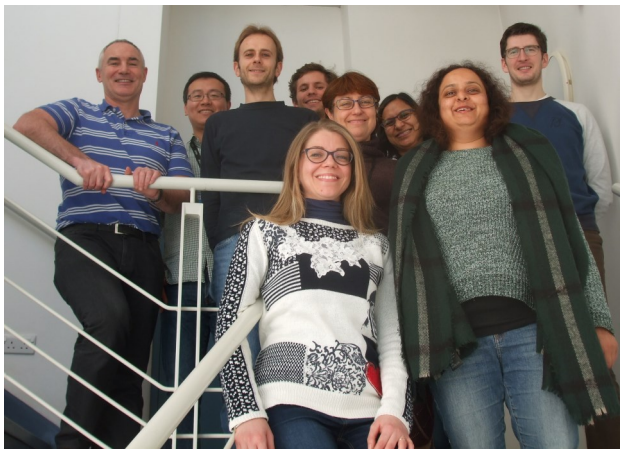
Group Members

* Shuchi Agrawal Singh (Post-doc Researcher)
* Paola Arimondo (Visiting Researcher)
* Faisal Basheer (PhD Student)
* Paolo Gallipoli (Post-doc Researcher)
* George Giotopoulos (Post-doc Researcher)
* Sarah Horton (Post-doc Researcher)
* Ludovica Marando (PhD Student)
* Eshwar Meduri (Post-doc Researcher)
* Daniel Sasca (Post-doc Researcher)
* Olivia Sheppard (Research Assistant)
* Shabana Vohra (Post-doc Researcher)
* Haiyang Yun (Post-doc Researcher)



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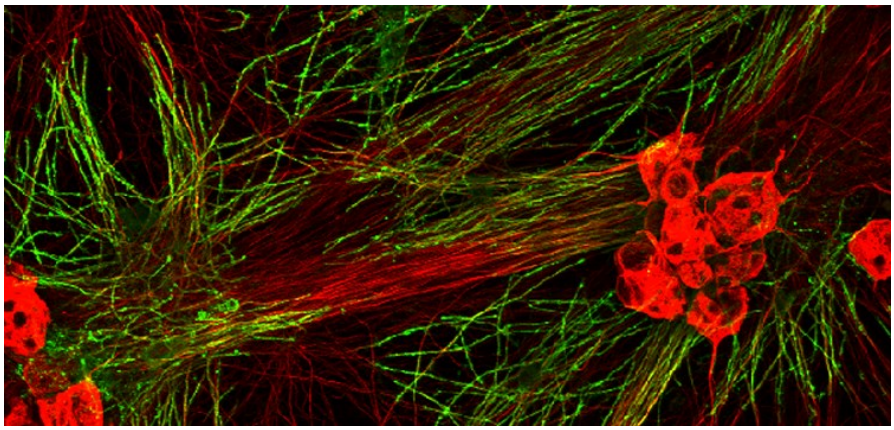
Ragnhildur Thóra Káradóttir

Neurotransmitter signalling to CNS progenitor cells

The CNS white matter links billions of neurons in the grey matter. Its function depends on oligodendrocytes enwrapping neuronal axons with myelin to synchronize and increase information flow between neurons: essential for our cognitive abilities, our perception of the world and our motor skills. The importance of myelin becomes evident in diseases, such as multiple sclerosis, where myelin damage leads to cognitive and motor disability. Moreover, recent magnetic resonance imaging and genome-wide association studies have highlighted the contribution of myelin to many diseases that were previously considered 'neuronal' like dementia, schizophrenia, autism and bipolar disorder. However, unique to the CNS, myelin regeneration can occur spontaneously in demyelinating disease, as adult oligodendrocyte precursor cells (OPCs; a CNS stem cell that comprises 5% of all cells in the brain) respond to the demyelinating injury and differentiate into new myelinating oligodendrocytes. However, this process often fails, making OPCs differentiation an important therapeutic target.

We have previously shown that OPCs express neurotransmitter receptors and receive synaptic inputs from neuronal axons in the white matter, hence are capable of sensing changes in neuronal activity. The lab's interest is to understand how signals from neurons induce OPCs to differentiate and myelinate axons during development and with normal ageing; this also could be an underlying mechanism for white matter plasticity.

The devastating consequences of dys/demyelination, in diseases like cerebral palsy, spinal cord injury and multiple sclerosis makes it important to study how OPCs differentiation is regulated. We are actively investigating how OPCs respond to myelin injury and whether neuronal activity and neurotransmitter signalling may regulate the myelin repair process. Our ultimate aim is to find new treatments for white matter disease.



White matter in a dish! Myelinating co-culture where oligodendrocyte precursor cells (that are plated on top of DRG axons) differentiate into myelinating oligodendrocytes (green; MBP) that myelinate the DRG axons (red; neurofilament). (Credit Kimberley Evans)

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.

Key Publications

Gautier HO, Evans K, Lundgaard I, James F, Lao-Peregrin C, Franklin RJM, Káradóttir R (2015). **Neuronal activity regulates remyelination via glutamate signaling to oligodendrocyte progenitors**. *Nature Communications 6: 8518*. PMCID:PMC4600759

Lundgaard I, Luzhynskaya A, Stockley JH, Wang Z, Evans KA, Swire M, Volbracht K, Gautier HO, Franklin RJM, ffrench-Constant C, Attwell D, Káradóttir R (2013). **Neuregulin and BDNF induce a switch to NMDA receptor dependent myelination by oligodendrocytes**. *PLoS Biology 11(12): e1001743*. PMCID:PMC3876980

Káradóttir R, Hamilton N, Bakiri Y & Attwell D (2008). **Spiking and nonspiking classes of oligodendrocyte precursor glia in CNS white matter**. *Nature Neuroscience 11(4): 450-456.* PMCID:PMC2615224

Káradóttir R, Attwell D (2006). **Combining patch-clamping of cells in brain slices with immunocytochemical labelling to define cell type and developmental stage**. Nature *Protocols 1(4): 1977-1985*. PMCID:PMC2682777

Káradóttir R, Cavalier P, Bergersen LH, Attwell D (2005). **NMDA receptors are expressed in oligodendrocytes and activated in ischaemia**. *Nature 438: 1162-1166*. PMCID:PMC1416283

Group Members

* Sylvia Agathou (PhD Student)
* Kimberly Evans (Research Assistant)
* Mariann Kovacks (Visiting Student)
* Deborah Kronenberg-Versteeg (Post-doc Researcher)
* Moritz Matthey (PhD Student)
* Claudia Pama (PhD Student)
* Balazs Varga (Post-doc Researcher)
* Katrin Volbracht (PhD Student)

Káradóttir Group

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David Kent

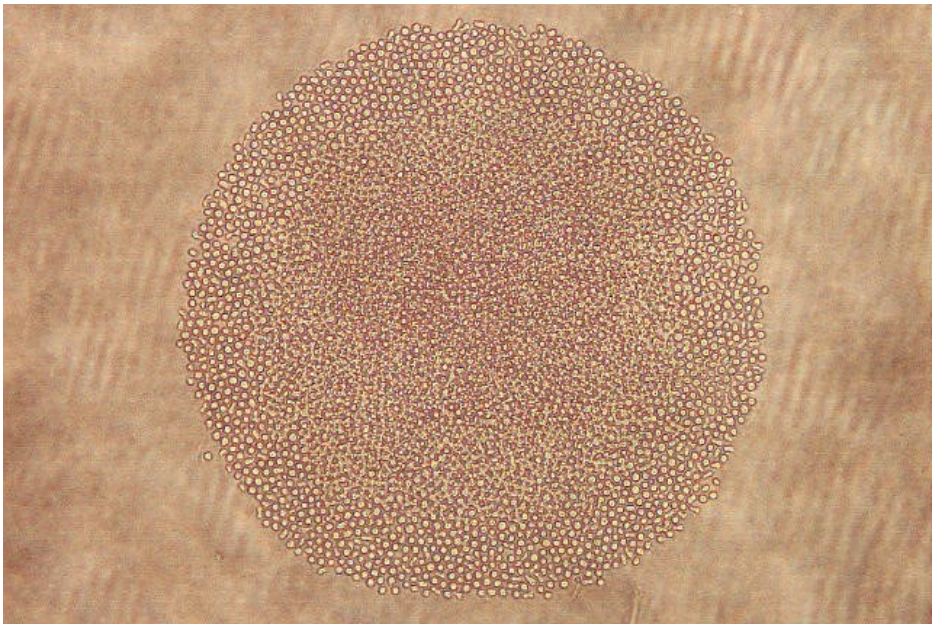
Single cell fate choice in normal & malignant stem cells

One of the simplest and most provocative concepts in all of stem cell biology is how a single stem cell can give rise to any of the highly specialised cell types of a given tissue while also having the capacity to make a new stem cell. At a population level, this decision making process must exist in a tightly regulated balance in order to avoid tissue degeneration (too few stem cells) or progression to cancer (too many stem cells).

Our lab focuses on how cell fate decisions are made on a single cell level in an effort to understand how to expand stem cell populations outside the body (for cell replacement or as a cell source for gene therapy) and how subversion of this process leads to cancer.

The lab is currently focused on understanding:
1) The molecular drivers of stem cell heterogeneity (self-renewal durability, lineage commitment);
2) The physical and quantitative biology of stem cells (mechanical signalling, mathematical modelling);
3) How myeloid cancers develop from single stem and progenitor cells in mouse models and primary human patient samples;
4) The role of the immune cell microenvironment in disease evolution.

Areas of particular interest include normal stem cell fate choice, clonal evolution of myeloid malignancies, physical biology of stem cells, and tools/approaches for expanding blood stem cells outside the body.



A small colony of cells derived from a single blood stem cell. Hundreds of such colonies can be assessed for their proliferation kinetics and blood cell types produced.

David Kent earned a B.Sc. in Genetics and English Literature at the University of Western Ontario, Canada (1999-2003) and obtained his Ph.D. in normal adult blood stem cell biology at the University of British Columbia, Canada (2003-2009). His postdoctoral research was at the University of Cambridge where he primarily studied malignant blood stem cell biology. His research group studies fate choice in single blood stem cells and how changes in their regulation lead to cancers.

David is currently the Stem Cell Institute's Public Engagement Champion and has a long history of public engagement and outreach including the creation of The Black Hole, a website and blog that provides information on and analysis of issues related to the education and training of scientists.

Key Publications

Nestorowa S, Hamey FK, Pijuan Sala B, Diamanti E, Shepherd M, Laurenti E, Wilson NK, Kent DG, Göttgens B. **A Single Cell Resolution Map of Mouse Haematopoietic Stem and Progenitor Cell Differentiation**. *Blood. 2016 Jun 30. pii: blood-2016-05-716480* PMID: 27365425

Schulte R, Wilson NK, Prick JC, Cossetti C, Maj MK, Göttgens B, Kent DG. **Index sorting resolves heterogeneous murine hematopoietic stem cell populations**. *Experimental Hematology. 2015 Sep;43 (9):803-11*. PMCID: PMC4571925

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*Ortmann CA, *Kent DG, Nangalia J, Silber Y, Wedge DC, Grinfeld J, Baxter EJ, Massie CE, Papaemmanuil E, Menon S, Godfrey AL, Dimitropoulou D, Guglielmelli P, Bellosillo B, Besses C, Döhner K, Harrison CN, Vassiliou GS, Vannucchi A, Campbell PJ Green AR. *co-first authors. **Effect of mutation order on myeloproliferative neoplasms**. *New England Journal Medicine. 2015 Feb 12;372(7):601-12*. PMCID:PMC4660033

Kent DG, Li J, Tanna H, Fink J, Kirschner K, Pask DC, Silber Y, Hamilton TL, Sneade R, Simons BD, Green AR. **Self-renewal of single mouse hematopoietic stem cells is reduced by JAK2V617F without compromising progenitor cell expansion**. *PLoS Biology. 2013;11(6):e1001576* PMCID:PMC3672217

Group Members

* Miriam Belmonte (Research Assistant)
* James Che (PhD Student)
* Nina Friesgaard Oebro (Post-doc Researcher)
* Caroline Oedekoven (PhD Student)
* Mairi Shepherd (PhD Student)

Kent Group

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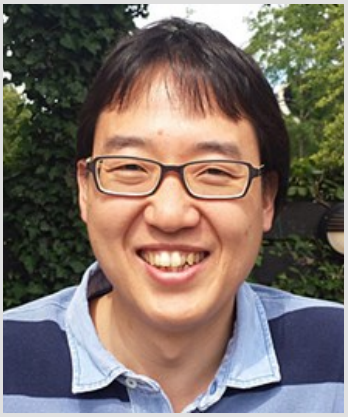
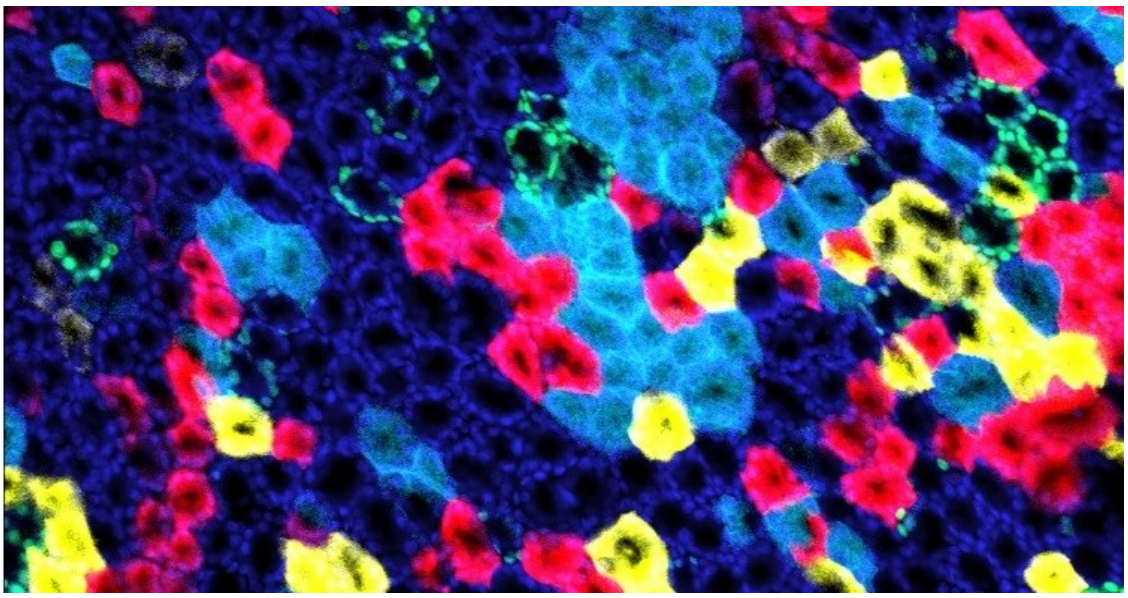


Bon-Kyoung Koo

Homeostatic regulation of adult stem cells

Homeostatic turnover in adult tissues is governed by the interplay of a multitude of signalling pathways. 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.

Dr Koo investigates the role of an important class of modulators – E3 ubiquitin ligases – in tissue homeostasis. He has found two important regulators – Mib1 and RNF43. Mib1 has a crucial role in Notch ligand activation in niche cells and RNF43 attenuates Wnt activation in intestinal stem cells. His research focuses on additional E3 ubiquitin ligases that have an important role in stem cell – niche interactions in adult tissues.



Clone competition in stomach glands (Credit Juergen Fink)

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 participates in the Marie Curie Initial Training Network "WntsApp" and was recently awarded with the Sir Henry Dale Fellowship (2013) and ERC starting grant (2015).

Key Publications

Koo BK*†, van Es JH*, van den Born M, Clevers H†. **Porcupine inhibitor suppresses paracrine Wnt-driven growth of Rnf43;Znrf3-mutant tumors.** *PNAS Jun 16;112(24):7548-50.* *equal contribution PMCID:PMC4475934

Schwank G*, Koo BK*, 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. 2013 Dec 5;13(6):653-8.* *equal contribution PMID:24315439

Stange DE*, Koo BK*, 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, Clevers H. **Differentiated Troy+ Chief Cells Act as Reserve Stem Cells to Generate All Lineages of the Stomach Epithelium**. *Cell. 2013 Oct 10; 155(2):357-368.*equal contribution PMCID:PMC4094146

Koo BK, Spit M, Jordens I, Low TY, Stange DE, van de Wetering M, van Es JH, Mohammed S, Heck AJR, Maurice MM, Clevers H. **Tumour suppressor RNF43 is a stem cell E3 ligase that induces endocytosis of Wnt receptors**. Nature *2012 Aug 30;488(7413):665-9*. PMID:22895187

Koo BK*, Lim HS*, Song R, Yoon MJ, Yoon KJ, Moon JS, Kim YW, Kwon MC, Yoo KW, Kong MP, Lee J, Chitnis AB, Kim CH, Kong YY. **Mind bomb 1 is essential for generating functional Notch ligands to activate Notch**. *Development. 2005 Aug;132 (15):3459-70*. PMID:16000382

Group Members

- Amanda Andersson-Rolf (PhD Student)
- Catherine Dabrowska (Research Assistant)
- Seungmin Han (Post-doc Researcher)
- Jihoon Kim (Post-doc Researcher)
- Hyunki Kim (Visiting Scholar)
- Gianmarco Mastrogiovanni (PhD Student)
- Alessandra Merenda (PhD Student)

Koo Group

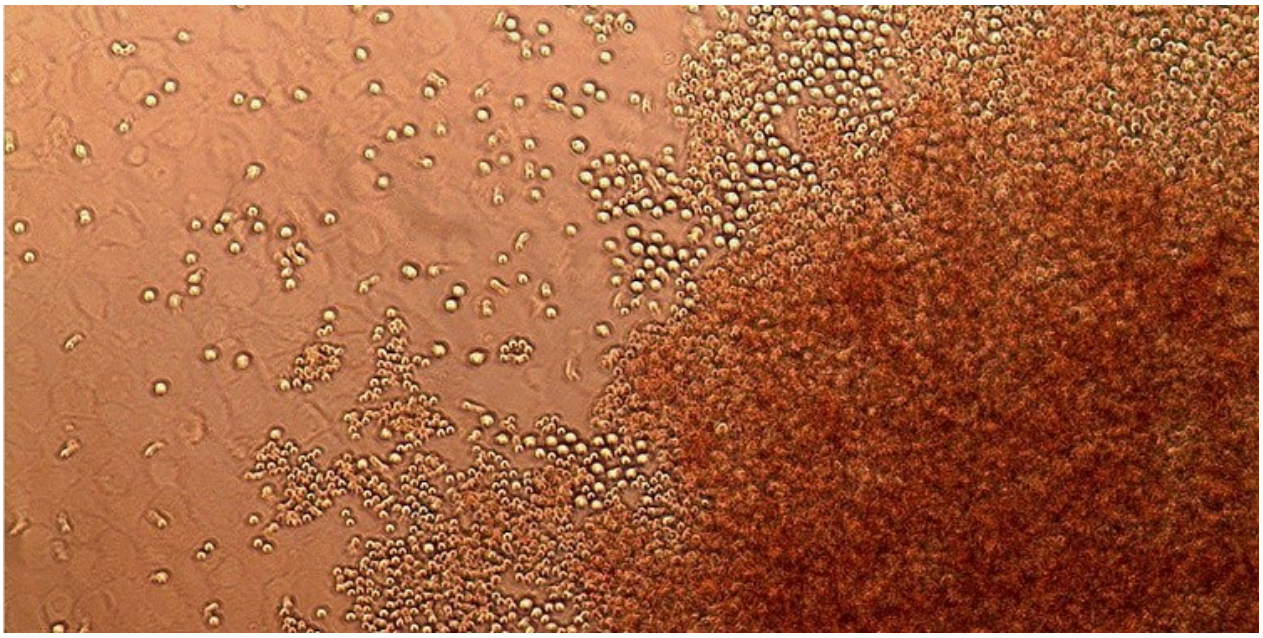
Funded by

Elisa Laurenti

Human haematopoietic stem cells biology in health and disease

Haematopoietic stem cells (HSC) are responsible for life-long blood production. They are the best-studied stem cell type owing to decades of research with animal models. Despite the high incidence of blood-related diseases, and accumulating evidence that certain aspects of HSC biology are species-specific, very little is known on human HSC. My laboratory develops integrated approaches combining in vitro and in vivo single cell assays, transcriptomics and bioinformatics to study human HSC and progenitor cells.

We are currently investigating how cell cycle regulation, inflammation and ageing, processes intimately linked to disease initiation, affect human HSC unique molecular and functional properties. Understanding how the cellular and molecular composition of the HSC/progenitor compartment changes in stress conditions and throughout a human lifetime has important implications for regenerative medicine and treatment of blood cancers.



A colony of different blood cells arising from a single adult human haematopoietic stem cell (Credit: Antonella Santoro)

Elisa Laurenti received her Master in Biological Sciences from the University of Bologna in 2003. She then undertook her PhD under the supervision of Prof. Andreas Trumpp at the Swiss Institute for Cancer Research in Lausanne, Switzerland. In 2010 she joined Dr John Dick's laboratory at University Health Network (Toronto, Canada) where she became interested in the study of human hematopoietic stem cells.

In 2014, she established her own research group at the Cambridge Stem Cell Institute and Department of Haematology of the University of Cambridge. She is currently a Wellcome Trust and Royal Society Sir Henry Dale Research Fellow.

Key Publications

Laurenti E*, Frelin C*, Xie S*, Ferrari R, Dunant CF, Zandi S, Neumann A, Plumb I, Doulatov S, Chen J, April C, Fan J-B, Iscove N, Dick JE. **CDK6 Levels Regulate Quiescence Exit in Human Hematopoietic Stem Cells**. Cell *Stem Cell, 2015 Feb 19; 16 (3):302-313*. PMCID:PMC4359055 * equal contribution

Laurenti E, Doulatov S, Zandi S, Plumb I, Chen J, April C, Fan J-B, Dick JE. **The transcriptional architecture of human hematopoiesis identies multilevel control of lymphoid commitment**. *Nature Immunology, 2013 Jul; 14(7): 756-63*. PMID:23708252

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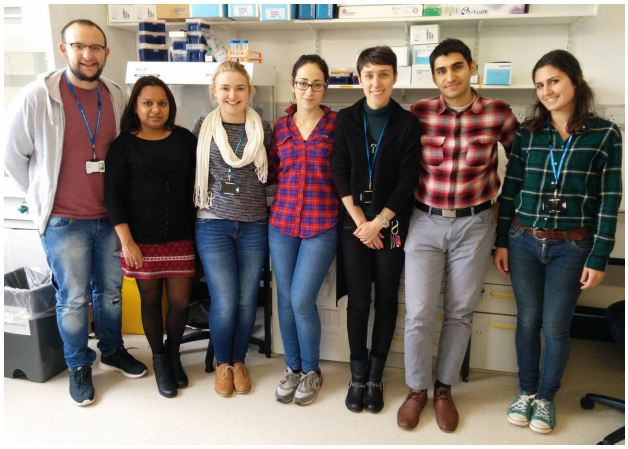
Group Members

* Serena Belluschi (PhD Student)
* Emily Calderbank (Research Assistant/ PhD Student)
* Valerio Ciaurro (Erasmus Student)
* Alexander Kaden Kheirallah (Post-doc Researcher)
* Myrna Maquinana (Research Nurse)
* Priyanka Tibarewal (Post-doc Researcher)



Laurenti Group

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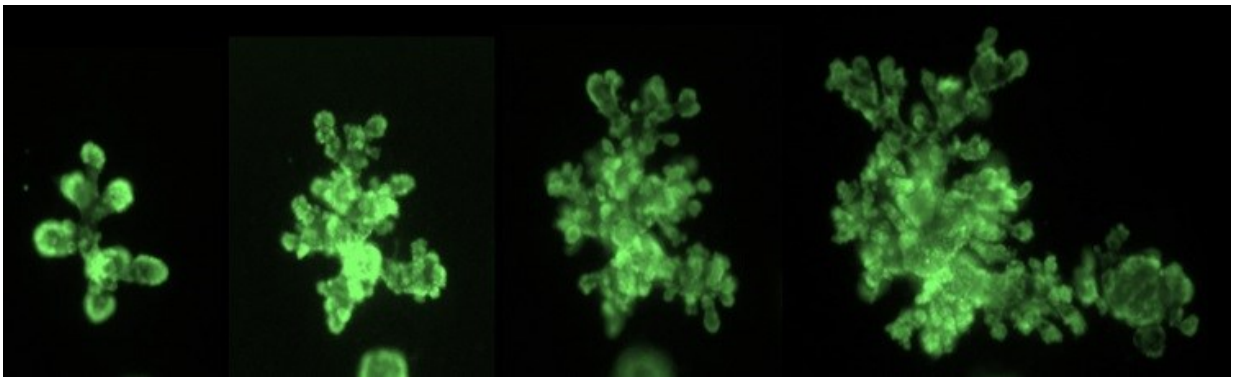
Joo-Hyeon Lee

Stem cells and niches

In the lung, multiple stem/progenitor cells that reside in a distinct niche regenerate the lost epithelium upon tissue injury, yet it is unknown how stem cells are instructed to selectively replace the injured epithelial cells. Our lab focuses on identifying the key stem-stromal cell interactions and regulatory networks that allow proper lineage specification and tissue regeneration. Dissecting the precise mechanisms how niches develop and remodel in homeostasis, regeneration and injury repair will help us to find better ways to derive lineage differentiation of stem cells, establish stem cell transplantation methods, and eventually lead us to novel insights on the pathogenesis of lung diseases.

Our goals include:
1) Identifying the functional role of diverse pulmonary stromal cells in regulating stem cell lineage differentiation during lung homeostasis, regeneration and injury repair.
2) Defining the regulatory networks of stem cell and stroma interactions in lung regeneration and tumourigenesis.
3) Exploring the contribution of stem cell niche dysregulation in pulmonary pathogenesis. We will use systemic approaches combining in vivo genetic mouse models and ex vivo human and mouse lung organoid co-culture systems.



Branching of Lung Organoid co-cultured with Endothelial cells

Joo-Hyeon Lee was fascinated by stem cell research through PhD studies under the supervision of Prof. Daesik Lim in KAIST, Korea. She then joined Prof. Carla Kim's laboratory in Harvard Medical School where she became interested in the study of adult lung stem cells. She established her own research group at the Cambridge Stem Cell Institute in 2016 and focuses on understanding cellular behaviour and regulatory networks of adult stem and niche cells.

Joo-Hyeon is currently Faculty member at the Department of Physiology, Development, and Neuroscience, University of Cambridge and was recently awarded with the Sir Henry Dale Fellowship and ERC starting grant.

Key Publications

Choi J, Iich E, Lee JH (2016) **Organogenesis of adult lung in a dish: Differentiation, disease and therapy**. *Developmental Biology. 420(2):278-86*
PMID: 27713058

Lee JH, Kim CF (2014) **Mesenchymal progenitor panoply**. *Science 346 (6211):810-1* (perspectives).
PMID:25395521

Lee JH, Bhang DH, Beede A, Huang TL, Stripp B, Bloch KD, Wagers AJ, Tseng YH, Ryeom S, Kim CF (2014) **Lung stem cell differentiation in mice directed by endothelial cells via a BMP4-NFATc1-Thrombospondin-1 axis**. Cell *156(3):440-55*.
PMCID:PMC3951122

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PMCID:PMC3604082

Lee KP*, Lee JH*, Kim TS, Park HD, Byun JS, Kim MC, Jeong WI, Calvisi DF, Kim JM, Lim DS (2010) **The Hippo–Salvador pathway restrains hepatic oval cell proliferation, liver size, and liver tumorigenesis**. *PNAS. 107:8248-53.*
PMCID:PMC2889558 *Equal contribution

Group Members

* Jinwook Choi (Post-doc Researcher)
* Catherine Dabrowska (Research Assistant)
* Julie Watson (Post-doc Researcher)

Lee Group

Funded by

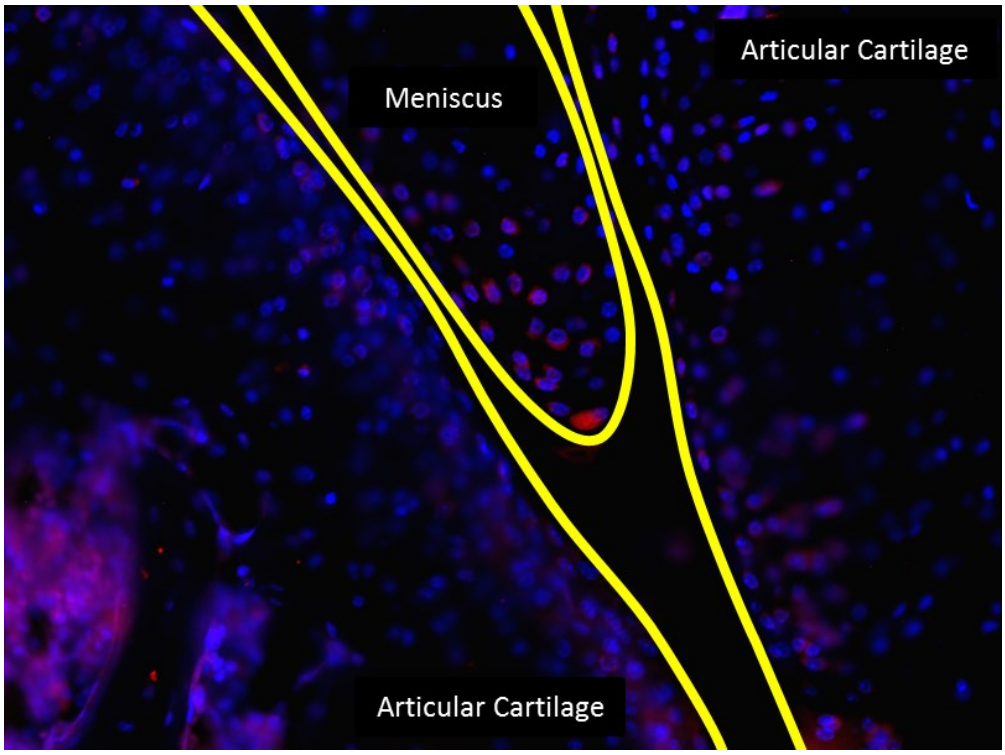
Andrew McCaskie

Regenerative therapies for bone and cartilage repair

Professor McCaskie's aim is to develop innovative therapies for musculoskeletal disease, particularly in Osteoarthritis (OA) which affects around 8 million people in the UK alone. He is currently developing translational pathways for regenerative therapy in this area, linking laboratory research with clinical treatment, including clinical trials.

Laboratory research programmes focus on the opportunity to use adult stem/stromal populations, along with other relevant cell types (haematopoietic and chondrocyte) either alone or with tissue engineering approaches to target early disease. Research also considers the mechanisms of joint destruction relevant to repair.

Translational and clinical programmes seek to use stratified and experimental medicine approaches, particularly focused on imaging and tissue analysis during cartilage repair surgery. The latter will include cell characterisation by phenotype and single cell analysis to understand the role played by cell therapies in the repair of joint tissues.



Immunofluorescence image of a section through a joint illustrating the cellularity (nuclei stained blue) of the articular cartilage and meniscus. The boundaries of the two apposing articular cartilage surfaces and the meniscal tissue are marked with yellow lines.

Professor McCaskie is the Professor of Orthopaedic Surgery and Head of the Department of Surgery at the University of Cambridge. He is the Director of the Arthritis Research UK Tissue Engineering Centre, which brings together many centres; University of Cambridge, Newcastle University, the University of Aberdeen, Keele University/the Robert Jones and Agnes Hunt Hospital NHS Foundation Trust in Oswestry and the University of York. Funded by a core grant of £2.4 million over the first five years from Arthritis Research UK, the Centre grant was recently renewed (£1.9M) until 2021. The centre brings together leading clinicians, engineers and biologists from research and clinical groups and to develop regenerative therapies for people with Osteoarthritis.

Professor McCaskie leads the Smart Step programme (£1.1M) as part of Stage II UK Regenerative Medicine Platform. The programme aims to develop cell-free approaches to Osteoarthritis and establish a translational pipeline for their development. He also facilitates clinical engagement as part of the Centre for Innovative Manufacturing in Medical Devices (MeDe) lead by Leeds University.

Key Publications

Haddad FS, McCaskie AW. **From needle to knife**. Bone Joint Journal 2015 97-B(1):1-2. PMID:25568405

Evangelou E, Kerkhof HJ,...McCaskie A,...Valdes AM. **A meta-analysis of genome-wide association studies identifies novel variants associated with osteoarthritis of the hip**. *Annals Rheumatic Diseases. 2014;73:2130-2136* PMCID:PMC4251181

Rodriguez-Fontenla C, Calaza M, Evangelou E, Valdes AM,...McCaskie A,...Zeggini E, Spector TD, Gonzalez A. **Assessment of osteoarthritis candidate genes in a meta-analysis of 9 genome-wide association studies**. Arthritis Rheumatology. 2014 Apr;66(4):940-9 PMCID:PMC4660891

Elliott KS, Chapman K, Day-Williams A,...McCaskie A, ...The arcOGEN consortium,...Zeggini E. **Evaluation of the genetic overlap between osteoarthritis with body mass index and height using genome-wide association scan data**. Annals *Rheumatic Diseases. 2013, 72(6), 935-941*. PMCID:PMC3664369

Zeggini E, Panoutsopoulou K,....McCaskie A, Wilkinson JM, Ralston SH, Valdes AM, Spector TD, Loughlin J. **Identification of new susceptibility loci for osteoarthritis -the arcOGEN study**. Lancet 2012, 380, 815-23. PMID: 22763110.

Group Members

* Anna Albiero (PhD Student)
* Francesca Emily Beaton (PhD Student)
* Mark Birch (Deputy Research Director)
* Karim Fekir (Post-doc Researcher)
* Sophie Frankham-Wells (PhD Student)
* Frances Henson (Research Fellow)
* Wasim Khan (University Lecturer)
* Helen Lydon (Post-doc Researcher)
* Stephen McDonnell (University Lecturer)
* Karin Newell (Research Assistant)
* Virginia Piombo (Post-doc Researcher)

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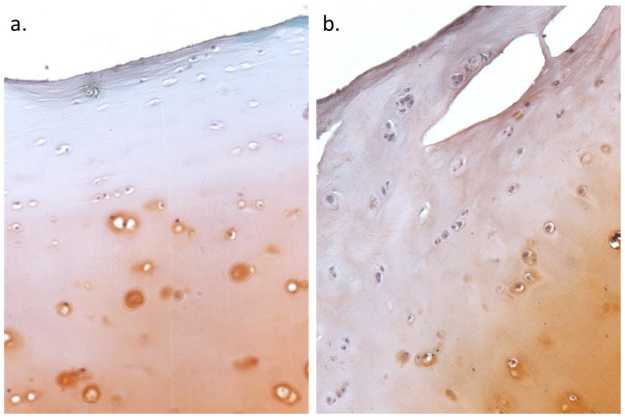
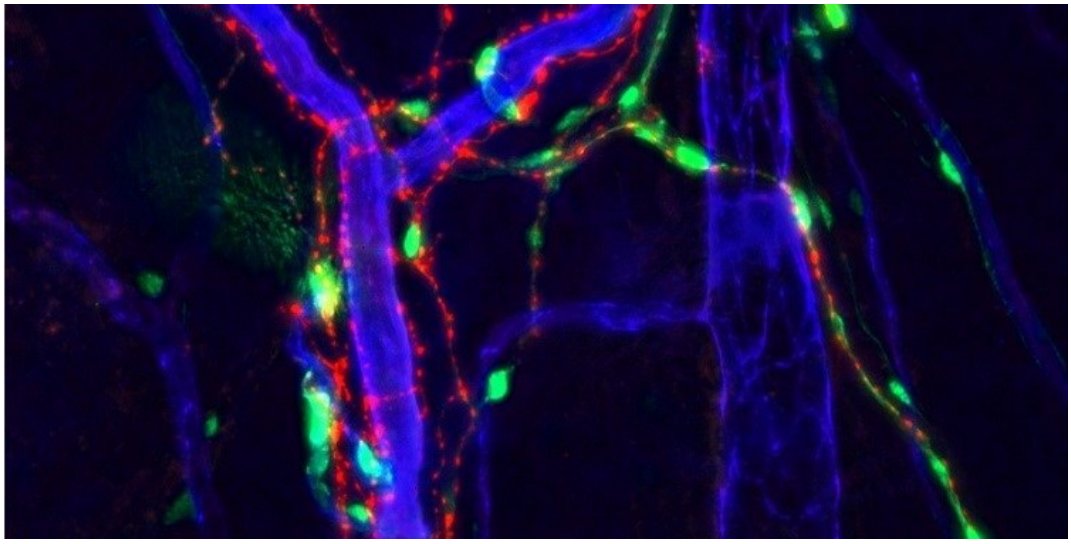


Sections of human articular cartilage showing a) the abundant matrix and distribution of individual cells (chondrocytes) in an undamaged specimen whilst b) illustrates the fibrillation and loss of structural integrity associated with osteoarthritis.

Simón Méndez-Ferrer

Blood stem cell niches

The Méndez-Ferrer laboratory research focuses on the regulation of the haematopoietic stem-cell niche in health and disease. Blood stem cells reside in specialised niches which allows them to self-renew, proliferate, differentiate and migrate according to the organism's requirements. The group studies multisystem regulatory mechanisms by which the haematopoietic stem cell niche fulfils these complex functions and how the deregulation of these mechanisms contributes to haematological disorders. The group has demonstrated that the brain regulates a peripheral stem cell niche in the bone marrow partly through sympathetic innervation of nestin+ niche cells. Protection of this regulatory network, whose constituents might share a related ancestry, can block the manifestation of myeloproliferative neoplasms. Our research indicates that neuroendocrine regulation of bone marrow stem cells by adrenergic signals or by sex hormones could potentially offer novel therapeutic approaches. We study the interaction of mesenchymal and haematopoietic stem cells and its implications for bone marrow transplantation procedures and the development of myeloproliferative neoplasias.



Peri-vascular nestin+ niche stem cells are innervated by sympathetic fibers in the bone marrow. Projection stack (~100 µm) of fluorescent images showing the distribution of Nestin-GFP+ cells (green), CD31/PECAM+ vascular endothelial cells (blue) and tyrosine hydroxylase+ sympathetic nerve fibers (red) after whole mount staining of the skull bone marrow. (Credit Isern and Méndez-Ferrer, Curr Osteoporos Rep. 2011 Dec;9(4):210-8.)

Méndez-Ferrer has discovered a connection with bone marrow, the brain and other systemic signals which controls the behaviour of blood stem cells. His research has contributed to the dissection of the "niches" in which stem cells reside and to the understanding of the role of these niches in the development of myeloproliferative diseases.

Key Publications

Sánchez-Aguilera A, Arranz L, Martín-Pérez D, García-García A, Stavropoulou V, Kubovcakova L, Isern J, Martín-Salamanca S, Langa X, Skoda RC, Schwaller J, Méndez-Ferrer S. **Estrogen signaling selectively induces apoptosis of hematopoietic progenitors and myeloid neoplasms without harming steady-state hematopoiesis**. *Cell Stem Cell 15: 791-780, 2014*. PMID:25479752

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Arranz L, Sánchez-Aguilera A, Martín-Pérez D, Isern J, Langa X, Tzankov A, Lundberg P, Muntión S, Tzeng Y-S, Lai D-M, Schwaller J, Skoda RC, Méndez-Ferrer S. **Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms**. *Nature 512: 78-81, 2014*. PMID:25043017

Isern J, Martín-Antonio B, Ghazanfari R, Martín AM, del Toro R, Sánchez-Aguilera A, Arranz L, Martín-Pérez D, López JA, Suárez-Lledó M, Marín P, Van Pel M, Vázquez J, Fibbe WE, Scheding S, Urbano-Ispizúa A, Méndez-Ferrer S (2013). **Self-renewing human mesenspheres promote hematopoietic stem cell expansion**. *Cell Reports 3(5):1714-24* PMID:23623496

Méndez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, MacArthur BD, Lira SA, Scadden DT, Ma'ayan A, Enikolopov GN, Frenette PS (2010). **Mesenchymal and haematopoietic stem cells form a unique bone marrow niche**. *Nature 466:829-834* PMCID:PMC3146551

Group Members

* Claire Fielding (Research Assistant)
* Dorian Forte (Visiting PhD Student)
* María García-Fernández (Post-doc Researcher)
* Andrés García-García (Visiting PhD Student)
* Antony Ho (PhD Student)
* Chrysa Kapeni (Post-doc Researcher)
* Claudia Körn (Post-doc Researcher)
* Tom McKerrell (Clinical Lecturer)
* Flavia Peci (PhD Student)
* Justyna Rak (Research Associate)

Méndez-Ferrer Group

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Jennifer Nichols

Embryonic pluripotency

Murine embryos develop a pluripotent epiblast by the late blastocyst stage. This tissue is the source of the foetus; it can also be propagated in vitro as embryonic stem (ES) cells. Understanding how the pluripotent lineage is specified, maintained and relinquished during development is critical to establish protocols for efficient capture and controlled differentiation of ES cells in culture. Pluripotent cell lines have been generated from other mammals, but they differ significantly from murine ES cells. To begin to understand the underlying distinctions, we have characterised the 'naïve' pluripotent epiblast in mouse embryos in detail. Combining these studies with a recently developed culture regime based upon inhibition of differentiation and polarisation, we have captured and propagated the equivalent naïve state from human embryos. To further our understanding of cell fate decisions in early mouse embryos, we use a combination of genetic modification, ex vivo culture and molecular profiling to investigate the roles of relevant pluripotency factors and signalling pathways. Mouse ES cells can be transplanted into embryos to produce chimaeras. Using labelled ES cells, we can monitor the dynamics of integration and subsequent differentiation. We have shown that ES cells beginning the process of exit from pluripotency are actively eliminated from early host embryos when injected alongside naïve pluripotent ES cells, but can occasionally incorporate into the epiblast in the absence of such competition. Currently, we are using chimaeras to investigate early lineage segregation in the host embryo in response to administration of normal or mutant ES cells.

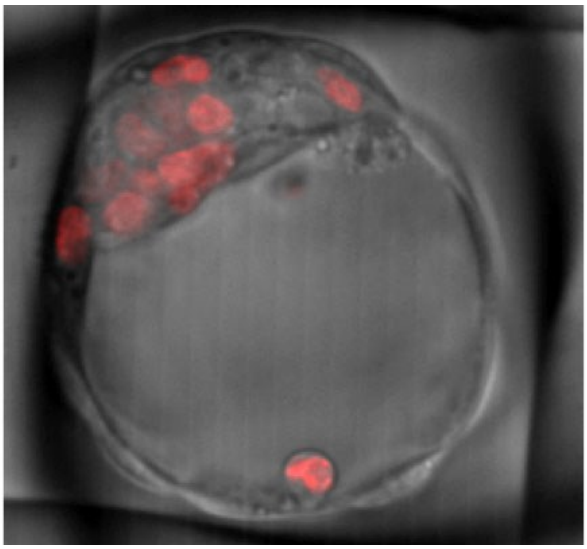

Image of a mouse embryonic chimaera during live imaging, showing embryonic stem cells (red nuclei) integrating in the inner cell mass and a dying ES cell that remains in contact with the mural trophectoderm

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 as a group leader at the CSCI. In October 2014 she became reader of embryonic pluripotency in the Department of Physiology, Development and Neuroscience.

Key Publications

Guo G, von Meyenn F, Santo F, Chen Y, Reik W, Bertone P, Smith A, Nichols J. **Naïve pluripotent stem cells derived directly from isolated cells of the human inner cell mass** . *Stem Cell Reports. 2016 Apr 12;6(4):437-46* PMCID: PMC4834040

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Chia G, Muñoz Descalzo S, Kurowski A, Leitch H, Lou X, Mansfield W, Etienne-Dumeau C, Grabole N, Mulas C, Niwa H, Hadjantonakis A. K, Nichols J (2014). **Oct4 is required for lineage priming in the developing inner cell mass of the mouse blastocyst**. *Development 141, 1001-10* PMCID:PMC3929414

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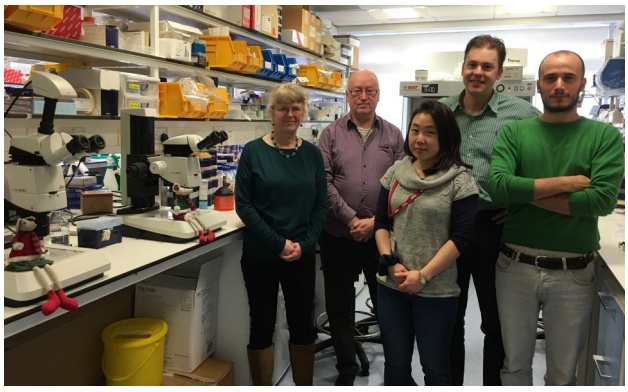
Roode M, Blair K, Snell P, Elder K, Marchant S, Smith A, Nichols J (2012). **Human hypoblast formation is not dependent on FGF signalling**. *Developmental Biology 361, 358-63* PMCID:PMC3368271

Group Members

* Thorsten Boroviak (Post-doc Researcher)
* Kenneth Jones (Research Assistant)
* Carla Mulas (Post-doc Researcher)
* Ayaka Yanagida (Post-doc Researcher)



Nichols Group

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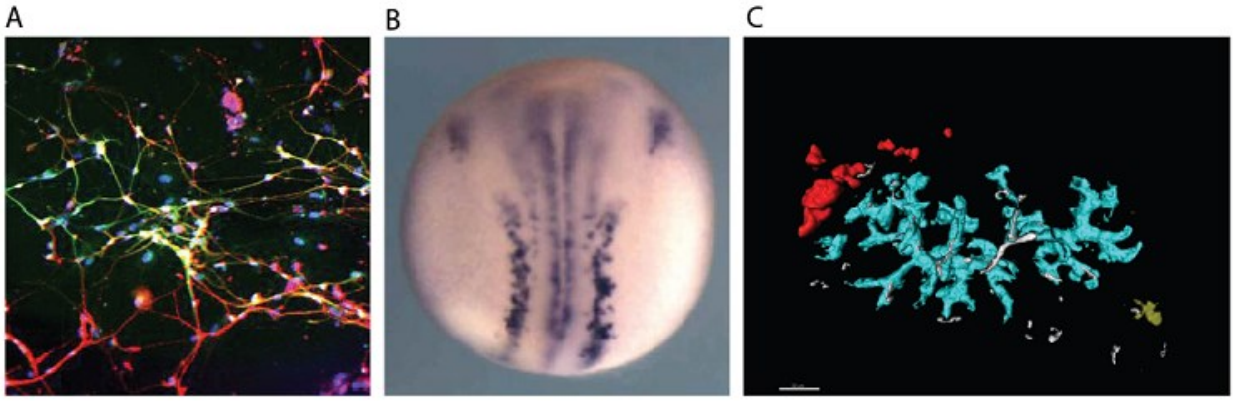
Anna Philpott

Proneural transcription factors

We aim to characterise mechanisms that co-ordinate cell cycling with stem cell maintenance and differentiation during development, homeostasis and disease. In particular, we have uncovered a conserved regulatory mechanism where cdk-dependent phosphorylation of multiple proneural proteins promotes maintenance of progenitor/stem status, while dephosphorylation drives differentiation.

Our future aims are three-fold: we will further characterise the molecular mechanisms that link cell cycling and differentiation: We will use this understanding to develop methods potentiating the directed differentiation of proneural protein-regulated tissues, including neurons and pancreatic islets: We will also investigate perturbation of the balance between stem-ness/progenitor maintenance and differentiation that is a frequent hallmark of multiple cancers, focussing on molecular regulation of proliferation and differentiation in neuroblastoma, glioblastoma and insulinoma, with the aim of developing new therapeutic strategies.



(A) Neurons generated by transcription factor-mediated forward programming. (B) Neurons stained purple in a developing Xenopus frog embryo. (C) Confetti coloured labelling of pancreatic ducts.

Anna Philpott graduated from the University of Cambridge with a BA degree in Natural Sciences in 1988 and a PhD in Molecular Cell Biology in 1991. She held post-doctoral fellowships at Massachusetts General Hospital Cancer Centre in 1992, moving to the Department of Cell Biology at Harvard Medical School in 1993.

She returned to the University of Cambridge in 1998 to a Lectureship in the Department of Oncology, where she is currently Professor of Cancer and Developmental Biology and Deputy Head of Department.

Key Publications

Wylie LA, Hardwick LJ, Papkovskaia TD, Thiele CJ, Philpott A. (2015) **Ascl1 phospho-status regulates neuronal differentiation in a Xenopus developmental model of neuroblastoma**. Disease *Models & Mechanisms. 8, 429-41*. PMCID:PMC4415893

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Ali F, Hindley C, McDowell G, Deibler GR, Jones A, Kirschner M, Guillemot F, Philpott A (2011) **Cell cycle-regulated multi-site phosphorylation of Neurogenin 2 coordinates cell cycling with differentiation during neurogenesis**. *Development 138, 4267-77*. PMCID:PMC3171226

Vosper JM, McDowell GS, Hindley CJ, Fiore-Heriche CS, Kucerova R, Horan I, Philpott A (2009) **Ubiquitination on canonical and non-canonical sites targets the transcription factor neurogenin for ubiquitin-mediated proteolysis**. *Journal of Biological Chemistry, 284, 15458-68*. PMCID:PMC2708843

Group Members

* Fahad Ali (Post-doc Researcher)
* Roberta Azzarelli (Post-doc Researcher)
* Daniel Marcos Corchado (Post-doc Researcher)
* John Davies (Senior Research Lab Technician)
* Sebastien Gillotin (Post-doc Researcher)
* Laura Hardwick (PhD Student)
* Aoibheann McNally (PhD Student)
* Magdalena Sznurkowska (PhD Student)

Philpott Group

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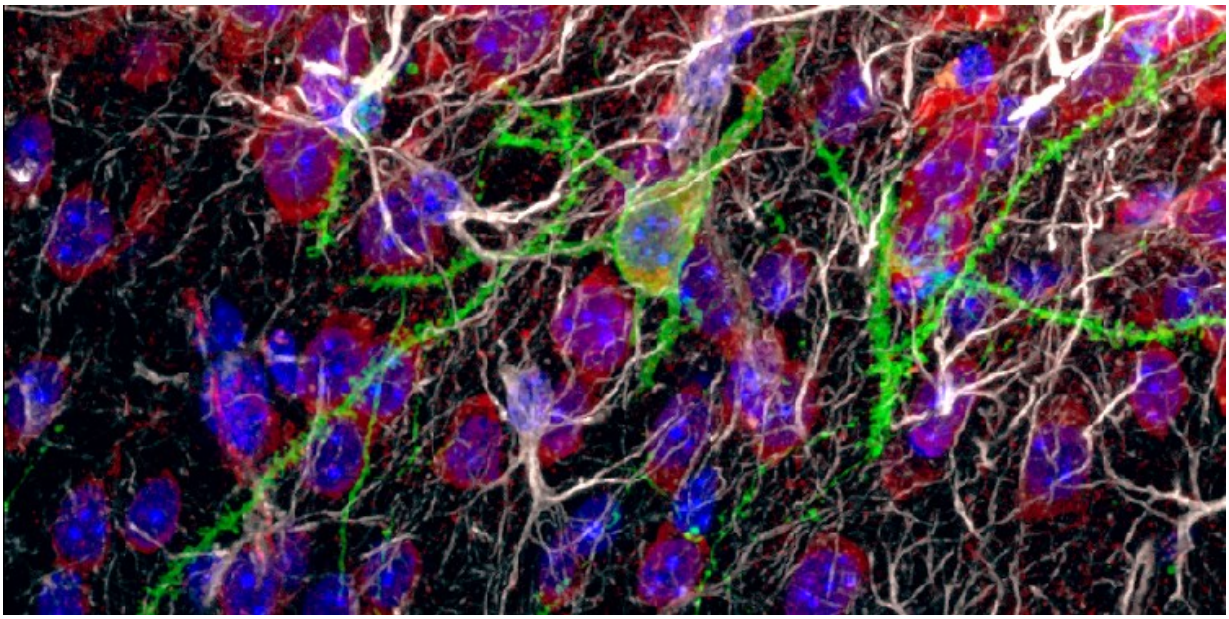
Stefano Pluchino

Stem cell signalling and brain repair

The major contribution of Stefano Pluchino's studies has been the demonstration of the [constitutive vs inducible] immune modulatory functions of neural stem cells (NSCs). Current projects in his lab are exploring the different modalities by which transplanted NSCs engage programs of cell-to-cell communication with cells in the host microenvironment.

His group's main research efforts are now towards some key challenges that include:
1. The development of protocols for safe human stem cells under standardised conditions;
2. The identification of the cell injection, cell dosage and cell type/stage;
3. The identification of mechanisms of stem cell integration and signalling in vivo; and
4. The discovery of new biomakers of stem cell survival, biodistribution and function.

The Pluchino lab is fully committed to delivering next-generation stem cell therapies into clinics for the treatment of highly invalidating neurological disorders that include multiple sclerosis, stroke and traumatic injuries of the brain/spinal cord.



Transplanted iNSCs (green) migrate in the injured CNS accumulating close to reactive GFAP+ astrocytes (white), while differentiate into NeuN+ (red) neurons with fully formed spines. Nuclei are stained with DAPI (blue). (Credit Luca Peruzzotti-Jametti and Giulio Volpe)

Stefano Pluchino received his MD and PhD degrees at the University of Siena, Italy, and additional training at Cambridge University, UK. He is University Reader in Regenerative Neuroimmunology (2016) and Honorary Consultant in Neurology. He's also non-tenured Professor of Regenerative Neuroscience at the University Vita-Salute San Raffaele in Milano (Italy; since 2005) and adjunct Associate Professor in Neurology at the University of Vermont College of Medicine in Burlington (USA; since 2008). Stefano Pluchino has been awarded the Italian Multiple Sclerosis Foundation (FISM) Rita Levi-Montalcini prize for outstanding research in MS (2007) and the International Royan Award for outstanding research in Stem Cell Biology and Technology (2010).

Dr Pluchino is a 2009 Italian Ministry of Health Young Investigator Awardee and 2010 European Research Council (ERC) Starting Independent Researcher and member of the Division of Stem Cell Neurobiology, within the Department of Clinical Neurosciences.

Key Publications

Volpe G, Bernstock JD, Peruzzotti-Jametti L, Pluchino S. **Modulation of host immune responses following non-hematopoietic stem cell transplants: Prospects for therapy in Progressive Multiple Sclerosis**. *Journal of Neuroimmunology 2016 Dec 15. pii: S0165-5728 (16) 30312-5*
PMCID: 28034466

Drago D, Basso V, Gaude E, Volpe G, Peruzzotti-Jametti L, Bachi A, Musco G, Andolfo A, Frezza C, Mondino A, Pluchino S. **Metabolic determinants of the immune modulatory function of neural stem cells**. *Journal of Neuroinflammation 2016 Sep 2;13 (1):232* PMCID: 27590826

Cossetti C, Iraci N, Mercer TR, Leonardi T, Alpi E, Drago D, Alfaro-Cervello C, Saini H, Davis M, Schaeffer J, Muller W, Garcia-Verdugo JM, Mathivanan S, Bachi A, Enright A, Mattick JS, Pluchino S. **Extracellular vesicles from neural stem cells transfer IFN-g via Ifngr1 to activate Stat1 signalling in target cells**. *Molecular Cell 2014 Oct 23;56(2):193-204* PMCID:PMC4578249

Pluchino S, Zanotti L, Rossi B, Brambilla E, Ottoboni L, Salani G, Martinello M, Cattalini A, Bergami A, Furlan R, Comi G, Constantin G, Martino G. **Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism**. *Nature 2005; 436 (7048): 266-71* PMID: 16015332

Pluchino S, Quattrini A, Brambilla E, Gritti A, Salani G, Dina G, Galli R, Del Carro U, Amadio S, Bergami A, Furlan R, Comi G, Vescovi AL, Martino G. **Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis**. *Nature 2003; 422(6933): 688-94* PMID: 12700753

Group Members

* Jayden A. Smith (Post-doc Researcher)
* Beatrice Balzarotti (Technician)
* Sara Bandiera (Undergraduate Student)
* Alice Braga (Visiting PhD Student)
* Joshua Bernstock (PhD Student)
* Florian Gessler (PhD Student)
* Nunzio Iraci (Post-doc Researcher)
* Tommaso Leonardi (PhD Student)
* Giulia Manferrari (Undergraduate Student)
* Dai Matsuse (Post-doc Researcher)
* Emanuele Mauri (PhD Student)
* Luca Peruzzotti-Jametti (PhD Student)
* Rebecca Rogal (Post-doc Researcher)
* Jeroen Verheyen (PhD Student)
* Giulio Volpe (MPhil Candidate)

Pluchino Group

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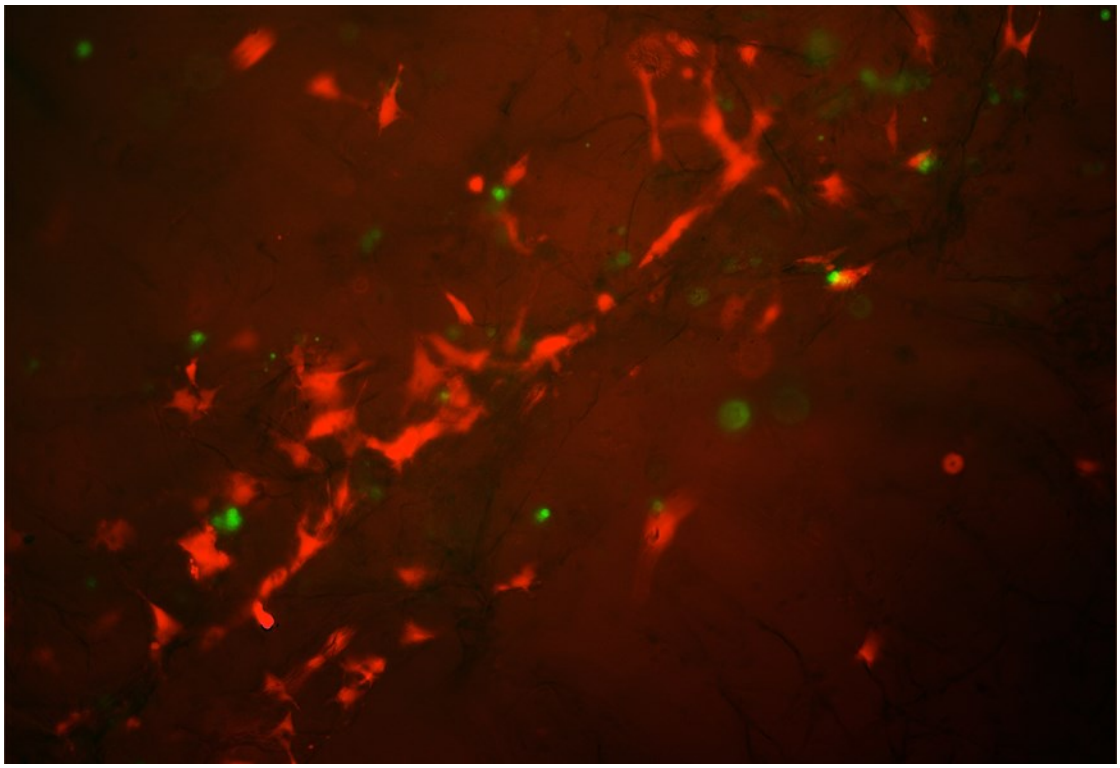
Ingo Ringshausen

Haematopoietic stem cells and malignancies

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in western countries. Although CLL is a putative mature B cell malignancy, it has very recently been shown that the maturation of CD34+CD38- HSPC from CLL patients is skewed towards the lymphoid linage. Importantly, the majority of stem and progenitor cells from CLL patients carry disease specific mutations in NOTCH1, SF3B1, TP53 and XPO. These recent reports suggest that the initial oncogenic events can occur at the earliest stages of B cell specification in the stem cell compartment.

Our group previously demonstrated that malignant cells actively re-program mesenchymal stromal cells, a process that is dependent on the activation of NF-κB and essential for disease propagation. We are now interested in understanding how clonal evolution from a pre-malignant progenitor to a treatment-resistant B cell malignancy affects the activation and reprogramming of niche cells in the bone marrow microenvironment and how this contributes to microenvironment-mediated drug resistance.

Related to this, we are investigating how the lymphoma-remodelled microenvironment impairs normal HSC biology, leading to bone marrow failure.



Malignant B cells (green) actively remodel Bone marrow mesenchymal stromal cells (red)

Ingo Ringshausen studied medicine at the Johannes Gutenberg University in Mainz/ Germany and London/ Canada. After his graduation in 1999 he started his medical training in Internal Medicine and Haematology/ Oncology at the Technical University in Munich. Between 2003 and 2006 he joined the group of Gerard Evan at UCSF on a postdoctoral fellowship. After his board certification in 2010 he became a Consultant in the Department of Haematology/ Oncology in Munich and subsequently an independent group leader.

In 2014 he joined the Department of Haematology in Cambridge and is now appointed as Consultant Haematologist at Addenbrooke's hospital and a Principal Investigator at the CSCI.

Key Publications

Wagner M, Oelsner M, Moore A, Götte F, Kuhn PH, Haferlach T, Fiegl M, Bogner C, Baxter J, Peschel C, Follows GA, Ringshausen I (2015) **Integration of innate- into adaptive- immune responses in ZAP-70 positive chronic lymphocytic leukaemia**. *Blood. 2016 Jan 28;127(4):436-48* PMID:26508782

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Ringshausen I, Schneller F, Bogner C, Hipp S, Duyster J, Peschel C, Decker T. **Constitutively activated phosphatidylinositol-3 kinase (PI-3K) is involved in the defect of apoptosis in B-CLL: association with protein kinase Cdelta**. *Blood 2002. 100(10): p. 3741-8* PMID:12393602

Group Members

* Jingyu Chen (Post-doc Researcher)
* Maurizio Mangolini (Post-doc Researcher)
* Andrew Moore (Post-doc Researcher)
* Eugene Park (PhD Student)
* Antonella Santoro (PhD Student)
* Vijitha Sathiaseelan (PhD Student)

Ringshausen Group

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David Rowitch

Glial cells and response to injury

Professor David Rowitch is a neonatologist and neuroscientist whose laboratory investigates brain development and how this can be affected by injuries. He focuses on cells the “white matter” in brain that are essential for communication between brain centres and to control body movements. He has applied these principles to better understand white matter injury in premature infants and leukodystrophy. Rowitch lead the first human clinical trial of direct neural stem cell transplantation focused on the rare and fatal leukodystrophy, Pelizaeus-Merzbacher Disease (PMD).

His work in the field of neurobiology has earned him numerous awards, including the Basil O’Connor Award, Harry Weaver Award, Kimmel Foundation Scholar Award, James S. McDonnell Foundation Research Award and Harrington Scholar-Innovator award. He was appointed a Howard Hughes Medical Institute Investigator in 2008 and is currently a Wellcome Trust Senior Investigator. In 2016 he became Professor and Head of Paediatrics in the University of Cambridge.

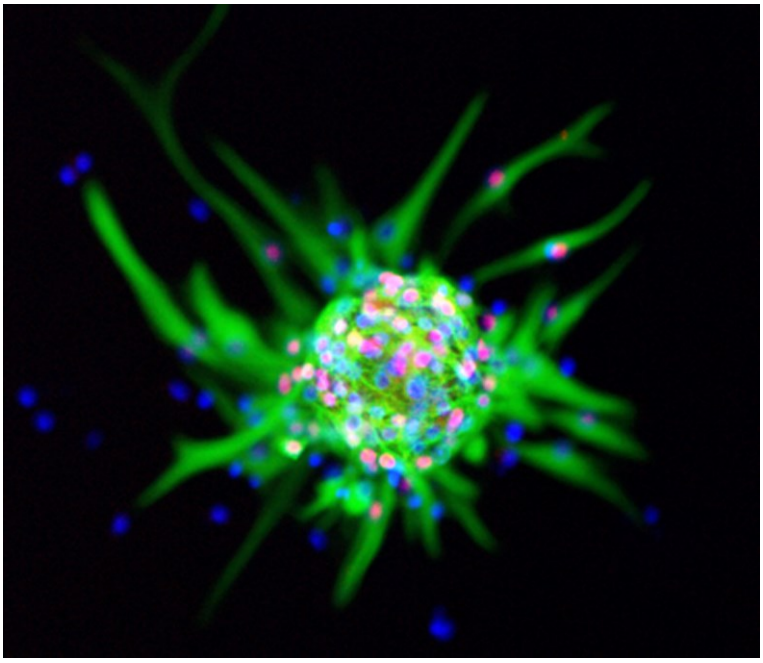

Image from my lab taken by Vivi Heine in 2008 shows a collection neural stem cells stained with nestin (green), and Olig2 (red), a marker of glial progenitors. Such cell collections can "self-organize" to generate specialized cell progeny without external instructions

David Rowitch, MD PhD ScD is Professor and Head of Paediatrics at the University of Cambridge, and he holds a joint appointment at UCSF (Pediatrics and Neurological Surgery). He is a neonatologist and neuroscientist whose laboratory investigates genetic factors that determine development and diversity of glial cells of the brain and the response to injury. He has applied these principles to better understand white matter injury in premature infants, brain cancer and leukodystrophy. Rowitch lead the first human clinical trial of direct neural stem cell transplantation focused on the rare and fatal leukodystrophy, Pelizaeus-Merzbacher Disease (PMD).

His work in the field of neurobiology has earned him numerous awards. He became a Howard Hughes Medical Institute Investigator in 2008 and Professor of Paediatrics at Cambridge University and Wellcome Trust Senior Investigator in 2016. His interest in precision medicine focuses on applications of genomic technologies to diagnose and better understand the biological basis and rational treatment of rare neurological disorders.

Key Publications

Yuen TJ, Silbereis JC, Griveau A, Chang SM, Daneman R, Fancy SP, Zahed H, Maltepe E, Rowitch DH. **Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis**. *Cell 2014 Jul 17;158(2):383-96*. PMCID: PMC4149873

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Muroyama Y, Fujiwara Y, Orkin SH, Rowitch DH. **Specification of astrocytes by bHLH protein SCL in a restricted region of the neural tube**. *Nature 2005 Nov 17;438(7066):360-3*. PMID:16292311

Group Members

* Staffan Holmqvist (Post-doc Researcher)
* Srikirti Kodali (PhD Student)
* John Stockley (Post-doc Researcher)

Rowitch Group

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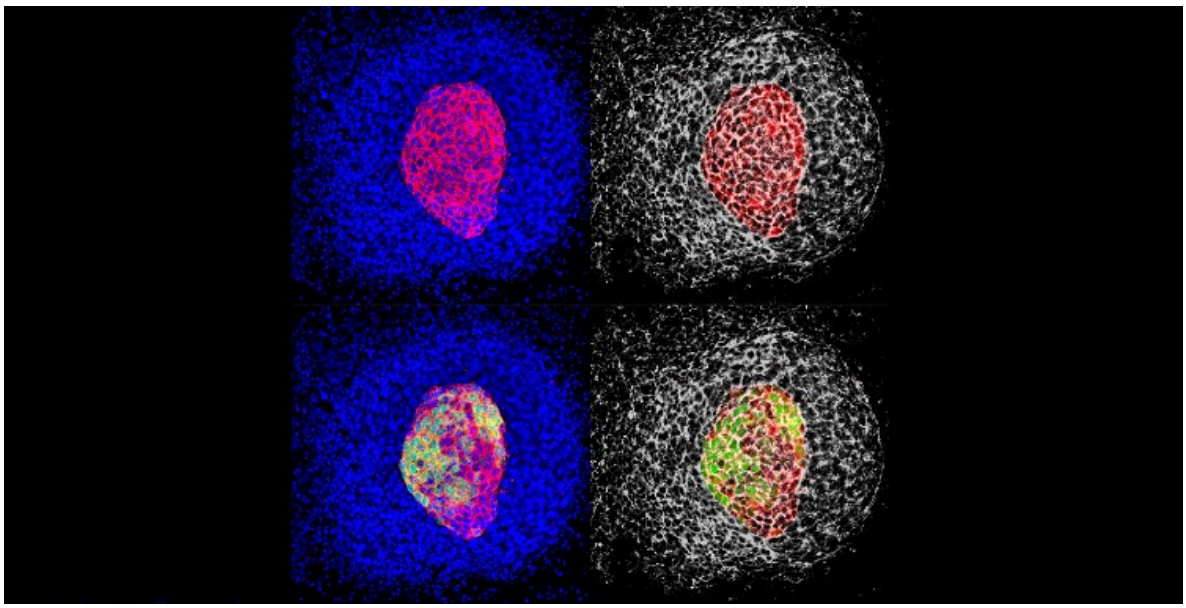
José Silva

Biology of induced pluripotency

My lab investigates the underlying biology of reprogramming a differentiated cell identity back into a naïve pluripotent stem cell identity, a process known as induced pluripotency.

We are interested in determining the molecular mechanisms by which the key reprogramming players establish the naïve pluripotent stem cell identity and in deciphering the transcriptional and epigenetic regulation taking place during this process. This is of fundamental relevance to understanding the biology of naïve pluripotent stem cells, learning how to induce a bonafide cell identity change and generating better naïve pluripotent stem cells to use as a platform for studies in in vitro developmental biology and in applications for regenerative medicine.



Panel depicting the appearance of induced pluripotent stem cells (green) from an identified pre-determined to reprogram cell population (red). Non-red cells (grey and blue only) failed to acquire reprogramming competence. (Credit Chibeza Agley)

José received his first degree in Biology from the University of Porto, in Portugal. He joined the GABBA graduate program from the 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 CSCI investigating the biology of induced pluripotency. His work was initially supported by a Next Generation Award (2008) and subsequently by a Wellcome-Trust Research Fellowship Award (2009). Recently, José was awarded a Wellcome-Trust Senior Research Fellowship. He started this in May 2014.

Key Publications

Santos R, 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 (2014). 15(1):102-10* PMCID:PMC4082719

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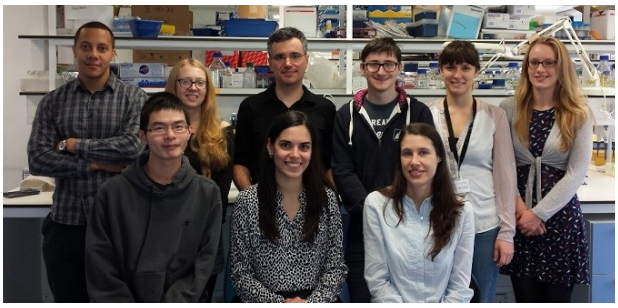
Silva J, Barrandon O, Nichols J, Theunissen T, Kawaguchi J, Smith A. **Promotion of Reprogramming to Ground State Pluripotency by Signal Inhibition**. *PLoS Biology (2008) Oct 21;6(10):e253* PMCID:PMC2570424

Group Members

* Chibeza Agley (Post-doc Researcher)
* Mariana Alves (MSc Student)
* Lawrence Bates (PhD Student)
* Yael Costa (Post-doc Researcher)
* Charlotte Handford (Research Assistant)
* Sergey Hladkov (PhD Student)
* Elsa Sousa (PhD Student)
* Hannah Stuart (PhD Student)
* Kathryn Tremble (PhD Student)



Silva Group

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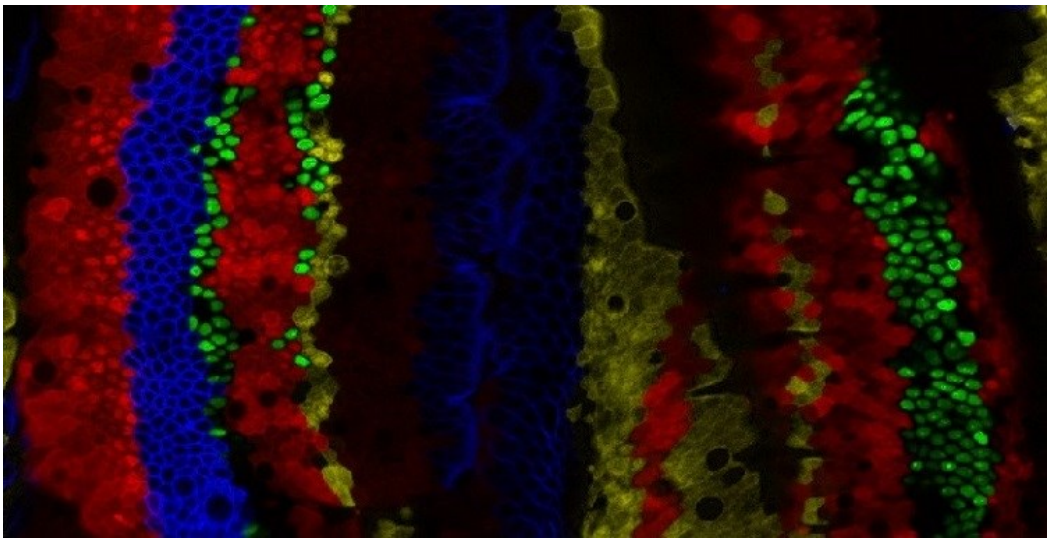
Ben Simons

Tracing stem cell fate in development, maintenance, and disease

With a background in theoretical condensed matter physics, my group is using concepts from non-equilibrium statistical physics and mathematics to address the fate behaviour of stem and progenitor cells in the development, maintenance and regeneration of tissues and factors leading to their dysregulation in diseased states. In particular, we have combined long-term lineage tracing studies using transgenic animal models with static marker-based assays to resolve strategies of stem cell self-renewal in the maintenance of epithelial tissues, including mammalian brain, epidermis, intestine, lung and testis. Our studies have emphasized the role of stochastic fate decisions in the regulation of stem cell fate, questioning the nature of stem cell identity, and offering new perspectives on stem cell regulation. Lately, we have extended these approaches to study the development of adult tissues, from the specification of pseudo-stratified neuroepithelia (retina and cortex) to the patterning of the heart.

To develop this program, we are extending this approach to study the development of ductal tissues, including the liver, lung, mammary epithelium, pancreas and prostate. At the same, we are collaborating with partner labs to address the cellular basis of tumour initiation using the clonal activation of oncogenic mutations or the action of carcinogens. We are also making use of genetic lineage tracing approaches to study the process of remyelination in spinal cord.

Finally, we are working with colleagues at the Sanger and Babraham to develop statistical approaches to address single cell transcriptional and epigenetic profiling data, with the aim of resolving the factors controlling symmetry breaking and cell fate specification in the developing mouse embryo.



Lineage labelled intestinal crypts and villi in mice

Ben has a background in theoretical condensed matter physics. Having obtained his PhD at the Cavendish Laboratory in Cambridge researching high temperature superconductivity, he undertook post-doctoral research in 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 EPSRC, MRC, and the Wellcome Trust with whom he holds a Senior Investigator Award.

Key Publications

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 (2014). 159, 775-788* PMCID:PMC4225456

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 (2014). 14, 658-672* PMCID:PMC4010676

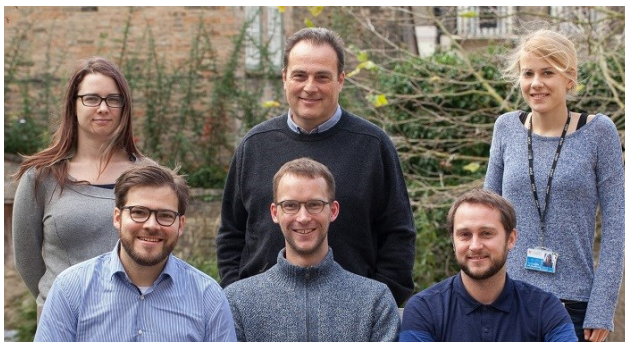
Ritsma L, Ellenbroek SIJ, Zomer A, Snippert HJ, de Sauvage FJ, Simons BD, Clevers H, van Rheenen J. **Intestinal crypt homeostasis revealed at single-stem-cell level by in vivo live imaging**. *Nature (2014) 507, 362-365* PMCID:PMC3964820

Driessens G, Beck B, Caauwe A, Simons BD, Blanpain C. **Defining the mode of tumour growth by clonal analysis.** *Nature (2012). 488, 527-530* PMID:22854777

Simons BD, Clevers H. **Strategies for homeostatic stem cell self-renewal in adult tissues**. *Cell (2011). 145, 851-862* PMID:21663791

Group Members

* Roberta Azarelli (Post-doc Researcher)
* Silvia Benito (PhD Student)
* Juergen Fink (Post-doc Researcher)
* Seungmin Han (Post-doc Researcher)
* Edouard Hannezo (Post-doc Researcher)
* David Jorg (Post-doc Researcher)
* Jamie McGinn (PhD Student)
* Magdalena Sznurkowska (PhD Student)
* Julia Tischler (Post-doc Researcher)



Simons Group

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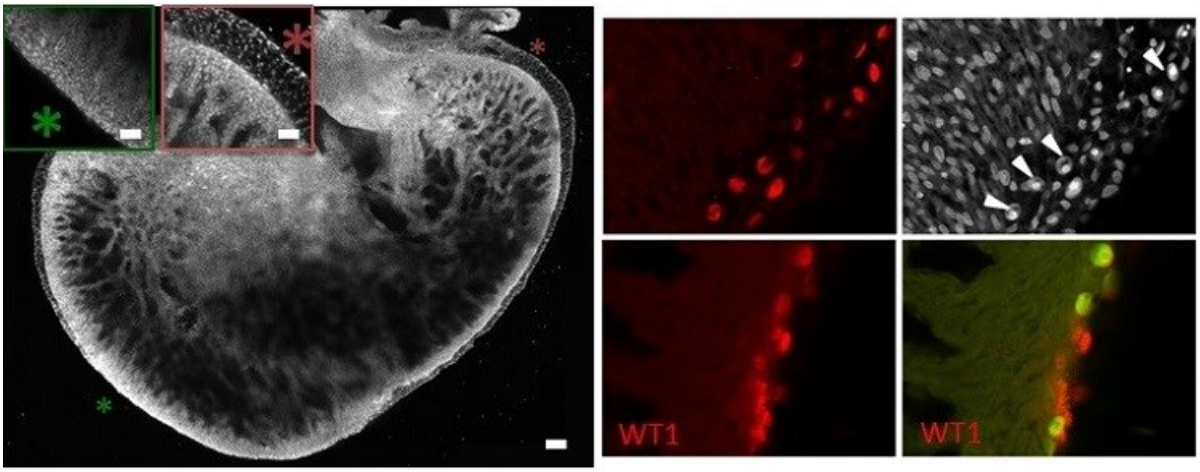
Sanjay Sinha

Vascular diseases

My lab's overall aim is to develop new treatments for vascular diseases, in particular those involving vascular smooth muscle cells (SMC), using a stem cell based approach.

We have pioneered the generation of embryonic lineage-specific vascular SMC, through the lateral mesoderm, paraxial mesoderm, neural crest and epicardium, from human embryonic stem cells (hESC) and induced pluripotent stem cells, using chemically defined conditions. We have utilised this system to model genetically triggered aortopathies, such as Marfan and Loeys-Dietz syndromes. These "disease-in-a-dish" models are being used to understand the pathobiology of these conditions and to screen for new treatments.

Additionally we are testing the regenerative potential of hESC-derived epicardium and other cardiovascular cell types for heart repair after myocardial infarction, either through direct injection or in the form of an in vitro generated myocardial "patch".



Whole mount confocal image of embryonic chick heart showing epicardium and the localisation of injected hESC-derived epicardial cells (red and green) to their developmental niche
Image credit: Gambardella and Iyer

Dr Sanjay Sinha is a British Heart Foundation (BHF) Senior Research Fellow at the University of Cambridge. He completed medical training in Cambridge, followed by cardiology clinical training and a PhD in Manchester. Dr Sinha then carried out post-doctoral studies in the USA with Prof Gary Owens on smooth muscle biology before establishing an independent group at Cambridge.

He is also a Consultant in Cardiology and he combines his research work with clinical duties at Addenbrooke's Hospital, Cambridge, where he treats patients with a wide variety of cardiovascular diseases.

Key Publications

Granata A, Serrano F, Bernard WG, McNamara M, Low L, Sastry P, Sinha S. **An iPSC-derived vascular model of Marfan syndrome identifies key mediators of smooth muscle cell death**. *Nature Genetics 2017; 49:97-109* PMID: 27893734

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Cheung C, Bernardo AS, Trotter MW, Pedersen RA, Sinha S. **Generation of human vascular SMC subtypes provides insights into embryological origin-dependent disease susceptibility**. *Nature Biotechnology 2012;30:165-73* PMCID:PMC3272383

Sinha S, Hoofnagle MH, Kingston PA and Owens GK. **TGF-b1 signaling contributes to the development of SMC from embryonic stem cells**. *American Journal Physiology – Cell Physiology 2004; 287:C1560-C1568*. PMID:15306544

Group Members

* Johannes Bargehr (PhD Student)
* Will Bernard (Research Assistant)
* Maria Colzani (Post-doc Researcher)
* Laure Gambardella (Post-doc Researcher)
* Sophie McManus (PhD Student)
* Madeline McNamara (PhD Student)
* Lay Ping Ong (PhD student)
* Felipe Serrano (Post-doc Researcher)
* Priya Sastry (PhD Student)
* Esther Tan (Masters Student)
* Loukia Yiangou (PhD Student)

Sinha Group

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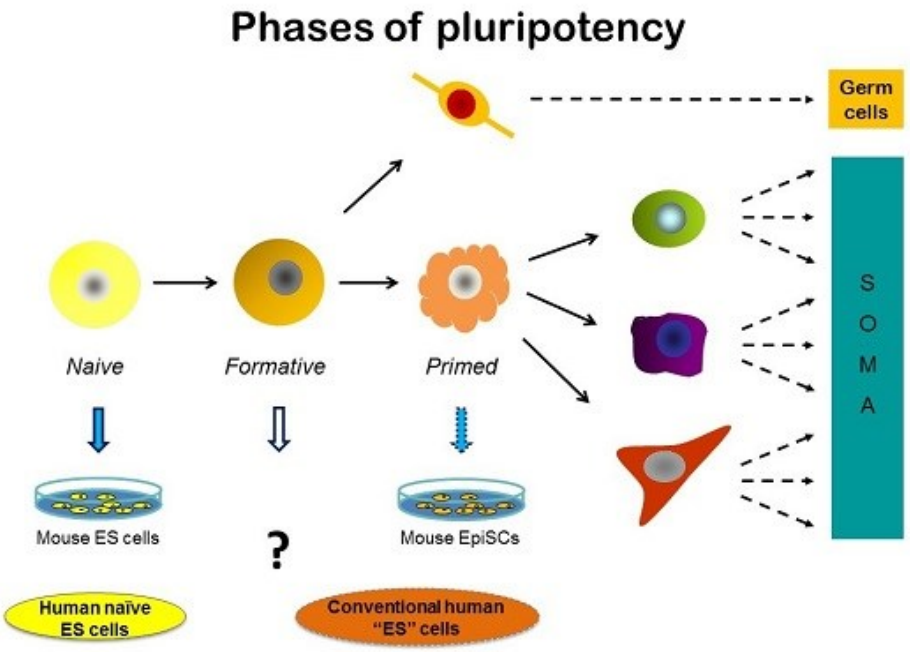
Austin Smith

Pluripotent stem cells

We study pluripotent stem cells derived from early embryos or generated by somatic cell reprogramming. These cell lines retain the potential to generate all somatic cell types. Our goal is to understand how pluripotent stem cells maintain broad developmental potency and how they prepare for and make cell fate decisions. Ultimately we aim to control the lineage decision process. We compare pluripotent cells from rodents and primates to elucidate common principles and species-specific adaptations.



We propose that pluripotency may be partitioned into three phases; naïve, formative, and primed. Mouse embryonic stem cells correspond to the naïve stage while post-implantation epiblast stem cells (EpiSCs) represent primed pluripotency. Conventional human pluripotent stem cells are more similar to EpiSCs. Our current research indicates that these human cells can be "reset" to a naïve state and furthermore that naive cells may be captured directly from the human embryo. (Credit – adapted from Smith A. Development 2017 144: 365-373)

As an undergraduate in Oxford Austin Smith became captivated by pluripotency. He pursued this interest 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 was the founding 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 and in 2016 he received the ISSCR McEwen award for Innovation.

Key Publications

Kalkan T, Olova N, Roode M, Mulas C, Lee HJ, Nett I, Marks H, Walker R, Stunnenberg HG, Lilley KS, Nichols J, Reik W, Bertone P, Smith A. **Tracking the embryonic stem cell transition from ground state pluripotency**. Development 2017 doi:10.1242/dev.142711 PMID: 28174249

Smith A. (2017) **Formative pluripotency: the executive phase in a developmental continuum**. *Development 2017 144: 365-373*; PMID: 28143843

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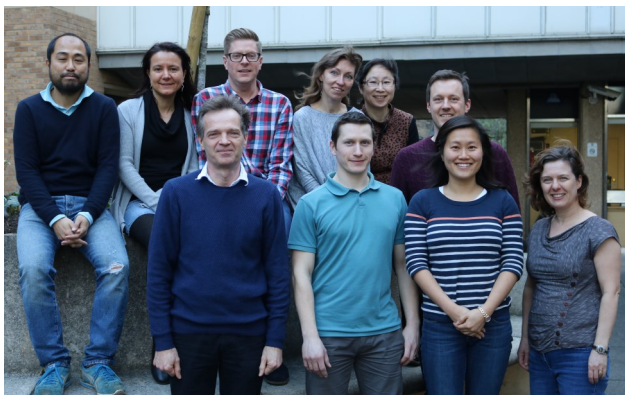
Group Members

* Nicholas Bredenkamp (Post-doc Researcher)
* James Clarke (Laboratory Manager)
* Rosalind Drumond (Research Assistant)
* Ge Guo (Post-doc Researcher)
* Tuzer Kalkan (Post-doc Researcher)
* Masaki Kinoshita (Post-doc Researcher)
* Meng Amy Li (Henry Wellcome Fellow)
* Sam Myers (PhD Student)
* Mariya Rostovskaya (Post-doc Researcher)



Smith Group

Funded by

Microsoft Research · The Isaac Newton Trust · wellcome · MRC Medical Research Council · BBSRC bioscience for the future

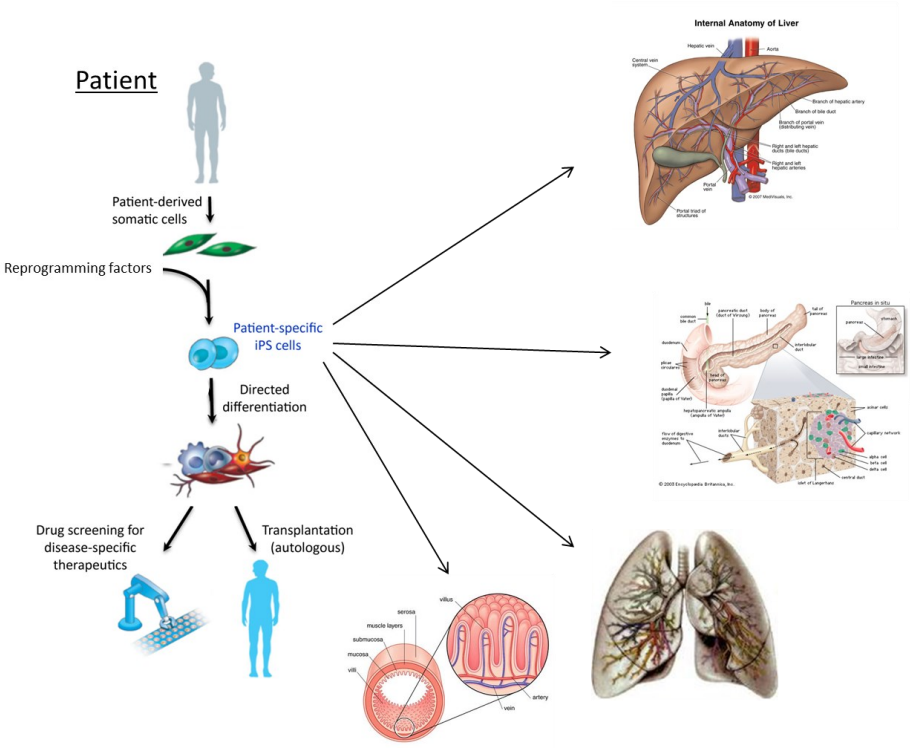
Ludovic Vallier

Mechanisms controlling differentiation of pluripotent stem cells into definitive endoderm

Understanding the mechanisms controlling early cell fate decisions in human development has major importance for regenerative medicine. Indeed the generation of fully functional cell types from stem cells is only achievable by recapitulating a normal succession of cell fate choice. 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 transition between pluripotency and the endoderm lineage. For that, we use human pluripotent stem cells (hESCs and hIPSCs) as in vitro model of development to study the interplays between transcriptional networks, epigenetic modifications and cell cycle which ultimately orchestrate the earliest step of differentiation. The resulting knowledge allows the development of new culture system to drive differentiation of pluripotent stem cells into pancreatic, hepatic, lung and gut 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 to uncover the common mechanisms controlling self-renewal and differentiation in both pluripotent and somatic stem cells.



LV group studies the basic molecular mechanisms controlling cell fate decisions during ealry embryonic development and in adult organs. For that, we use human pluripotent stem cells as in vitro model of development for the pancreas, liver, gut and lung. The resulting cells are also used to generate cell types relevant clinical application including basic studies of diseases and cell based therapy. (Credit Ludovic Vallier)

Ludovic graduated in Molecular biology and Immunology from the University Claude Bernard Lyon I in 1997. In 2001, he earned his PhD at École Normale Supérieure 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 Professor of 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.

Key Publications

Bertero A, Pawlowski M, Ortmann D, Snijders K, Yiangou L, Cardoso de Brito M, Brown S, Bernard WG, Cooper JD, Giacomelli E, Gambardella L, Hannan NR, Iyer D, Sampaziotis F, Serrano F, Zonneveld MC, Sinha S, Kotter M, Vallier L. (2016) **Optimized inducible shRNA and CRISPR/Cas9 platforms for in vitro studies of human development using hPSCs**. *Development. 2016 Dec 1;143 (23):4405-4418*. PMID: 27899508

Sampaziotis F, Cardoso de Brito M, Madrigal P, Bertero A, Saeb-Parsy K, Soares FAC, Schrumpf E, Melum E, Karlsen TH, Bradley JA, Gelson WTH, Davies S, Baker A, Kaser A, Alexander GJ, Hannan NRF* and Vallier L* (2015). **Cholangiocytes derived from human induced pluripotent stem cells for disease modeling and drug validation**. *Nature Biotechnology. Aug;33(8):845-52* *joint authorship PMCID:PMC4768345

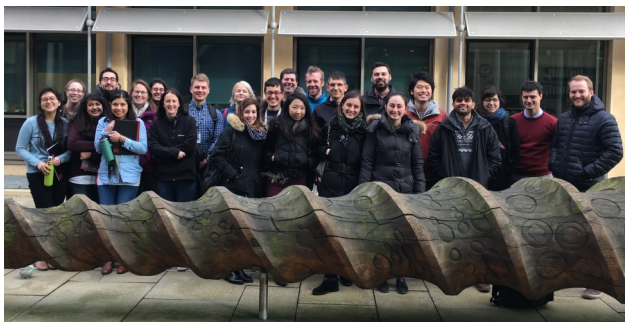
Pauklin S, Vallier L. (2013) **The cell-cycle state of stem cells determines cell fate propensity**. *Cell 155 (1):135-147.* PMCID:PMC3898746

Yusa K*, Rashid ST*, Strick-Marchand H, Varela I, Liu PQ, Paschon DE, Miranda E, Ordóñez A, Hannan N, Rouhani FJ, Darche S, Alexander G, Marciniak SJ, Fusaki N, Hasegawa M, Holmes MC, Di Santo JP, Lomas DA*, Bradley A*, Vallier L* (2011). Targeted **gene correction of α1-antitrypsin deficiency in induced pluripotent stem cells**. Nature. *Oct 12;478 (7369):391-4* *joint authorship PMCID:PMC3198846

Brons IGM, Smithers LE, Trotter M, Rugg-Gunn P, Chuva de Sousa Lopes SM, Howlett SK, Clarkson A, Ahrlund-Richter L, Pedersen RA, Vallier L (2007) **Derivation of pluripotent Epiblast Stem Cells from pluripotent embryos**. *Nature. 12;448 (7150):191-5*. PMID: 17597762

Group Members

* Stephanie Brown (Research Assistant)
* Giovanni Canu (PhD Student)
* Imbisaat Geti (Research Assistant/PhD Student)
* Kim Jee Goh (Post-doc Researcher)
* Rodrigo Grandy (Post-doc Researcher)
* Ranna El Khairi (PhD Student)
* Pedro Madrigal (Post-doc Researcher)
* Carola Morell (Post-doc Researcher)
* Shota Nakanoh (Post-doc Researcher)
* Daniel Ortmann (Post-doc Researcher)
* Ana Osnato (PhD Student)
* Casey Rimland (PhD Student)
* Alexander Ross (PhD student)
* Fotis Sampaziotis (PhD Student)
* Samantha Tilson (PhD student)
* Rute Tomaz (Post-doc Researcher)
* Brandon Wesley (PhD student)
* Loukia Yiangou (PhD Student)



Vallier Group

Funded by

MRC Medical Research Council

NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

erc European Research Council

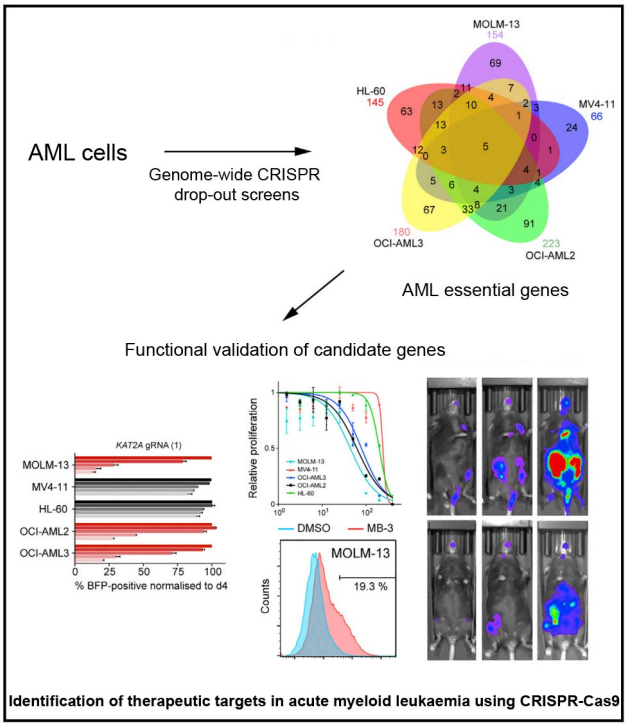
George Vassiliou

Leukaemic haemopoietic stem cells

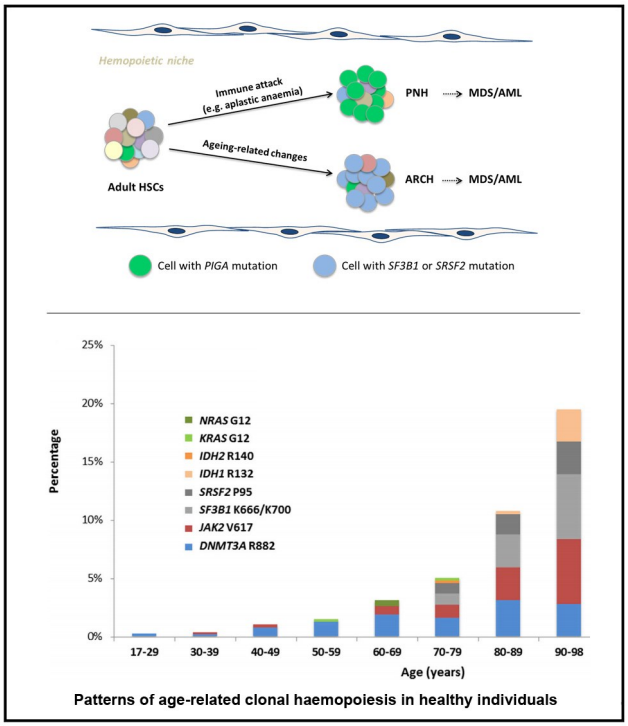
The Vassiliou Group seeks to understand the molecular mechanisms involved in transformation of normal to leukaemic haemopoietic stem cells and to identify their differential genetic vulnerabilities in order to develop novel anti-leukaemic therapies.

To achieve these aims the group uses three main approaches:

* Generation and study of bespoke mouse models of somatic mutation drivers of myeloid malignancies, in order to define their molecular, genomic and phenotypic effects on haemopoietic stem and progenitor cells
* Application of genetic screens to identify the molecular pathways involved in the transformation of HSCs (transposon mutagenesis) and the survival of leukaemic stem cells (genome-wide CRISP Cas9 screens)
* Sequencing-based approaches to detect and track the evolution of pre-clinical haemopoietic clones in haematologically normal individuals, in order to understand the factors involved in leukaemic progression.



Identification of therapeutic targets in acute myeloid leukaemia using CRISPR-Cas9



Patterns of age-related clonal haemopoiesis in healthy individuals

George Vassiliou graduated from the Royal London Hospital Medical College in 1994, having obtained an intercalated BSc in Pharmacology with Basic Medical Sciences in 1991. He carried out his basic medical training in London and Cambridge and became a member of the Royal College of Physicians in 1997. He went on to train in Haematology at the Hammersmith and Great Ormond Street Hospitals, and received his PhD from the University of Cambridge in 2005. After completing his Haematology training in Cambridge he became a Member of the Royal College of Pathologists in 2005 and from 2006-11 carried out a postdoctoral period in Allan Bradley's Laboratory at the Wellcome Trust Sanger Institute, funded by a Cancer Research UK Clinician Scientist Fellowship.

In 2011 he won a Wellcome Trust Senior Fellowship in Clinical Science and became a member of Faculty and Group Leader at the Sanger Institute. He joined the Faculty of the Cambridge Stem Cell Institute in 2015. Additionally, he has been an honorary Consultant Haematologist at Cambridge University Hospitals since 2006.

Key Publications

Tzelepis K, Koike-Yusa H, De Braekeleer E, Li Y, Metzakopian E, Dovey OM, Mupo A, Grinkevich V, Li M, Mazan M, Gozdecka M, Ohnishi S, Cooper J, Patel M, McKerrell T, Chen B, Domingues AF, Gallipoli P, Teichmann S, Ponstingl H, McDermott U, Saez-Rodriguez J, Huntly BJ, Iorio F, Pina C, Vassiliou GS, Yusa K (2016) **A CRISPR Dropout Screen Identifies Genetic Vulnerabilities and Therapeutic Targets in Acute Myeloid Leukemia**. *Cell Reports 17, 1193-1205.* PMCID: PMC5081405

Mupo A, Seiler M, Sathiaseelan V, Pance A, Yang Y, Agrawal AA, Iorio F, Bautista R, Pacharne S, Tzelepis K, Manes N, Wright P, Papaemmanuil E, Kent DG, Campbell PC, Buonamici S, Bolli N, Vassiliou GS. (2016) **Hemopoietic-specific Sf3b1-K700E knock-in mice display the splicing defect seen in human MDS but develop anemia without ring sideroblasts**. *Leukemia, doi:10.1038/leu.2016.251*
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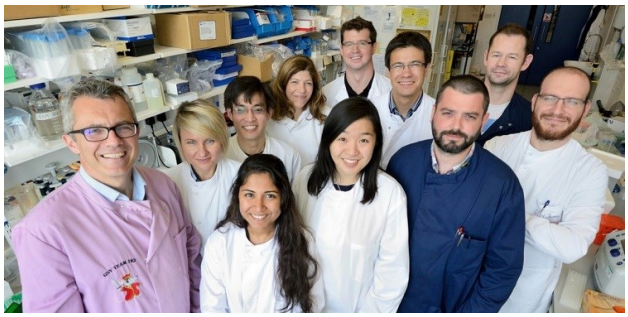
McKerrell T, Vassiliou GS (2015) **Aging as a driver of leukemogenesis**. *Science Translational Medicine 7, 306fs338*. PMID:26400908

McKerrell T, Park N, Moreno T, Grove CS, Ponstingl H, Stephens J, Understanding Society Scientific G, Crawley C, Craig J, Scott MA, Hodkinson C, Baxter J, Rad R, Forsyth DR, Quail MA, Zeggini E, Ouwehand W, Varela I, Vassiliou GS (2015) **Leukemia-associated somatic mutations drive distinct patterns of age-related clonal hemopoiesis**. *Cell Reports 10, 1239-1245* PMCID:PMC4542313

Vassiliou G*, Cooper JL, Li J, Rad R, Rice S, Uren A, Rad L, Ellis P, Andrews R, Grove C, Banerjee R, Wright P, Arends M, Bradley A*. **Mutant nucleophosmin and cooperating pathways drive leukemia initiation and progression in mice**. *Nature Genetics, 2011, May;43(5):470-5* *co-corresponding authors PMCID:PMC3084174

Group Members

* Vijay Baskar (Senior Bioinformatician)
* Grace Collord (PhD Student)
* Jonathan Cooper (Senior Research Assistant)
* Joao Dias (Visiting Bioinformatician)
* Etienne De Brakeleer (Post-doc Researcher)
* Oliver Dovey (Post-doc Researcher)
* Monika Dudek (Research Assistant)
* Dimitris Garyfallos (PhD Student)
* Gonia Gozdecka (Post-doc Researcher)
* Suruchi Pacharne (Post-doc Researcher)
* Konstantinos Tzelepis (PhD Student)



Vassiliou Group

Funded by

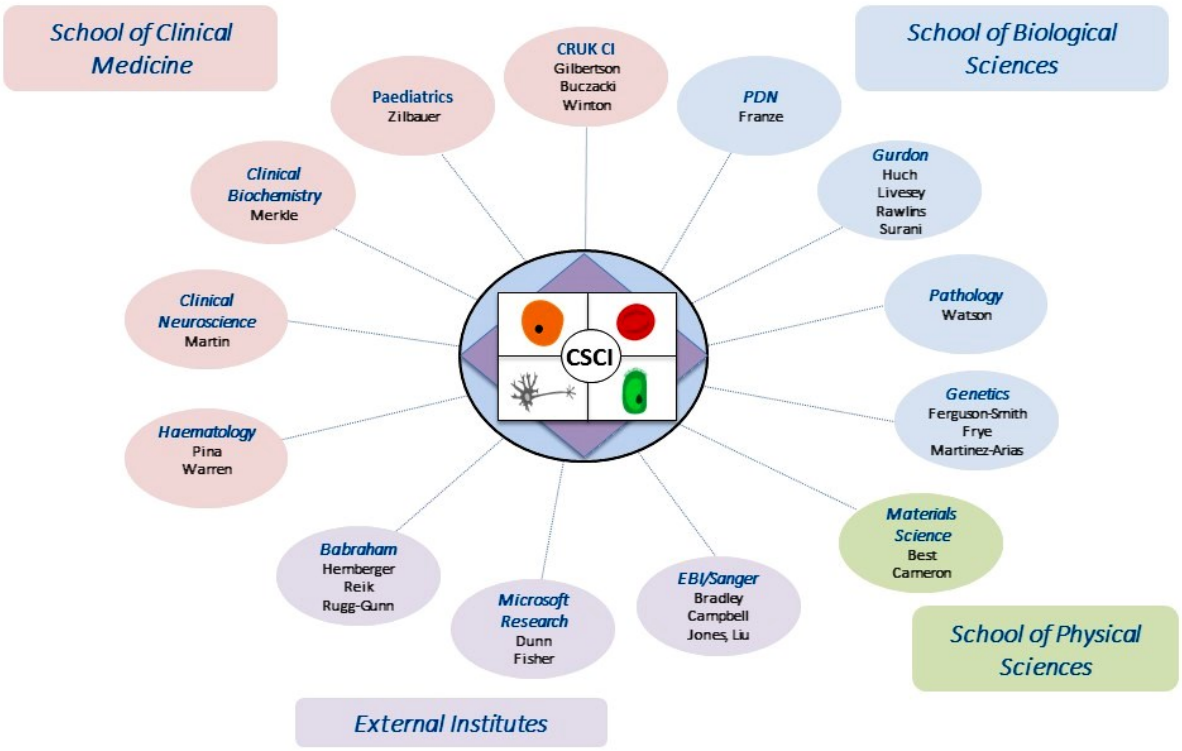
wellcome · act Addenbrooke's Charitable Trust · The Kay Kendall Leukaemia Fund · Bloodwise Formerly Leukaemia & Lymphoma Research · Cancer Research UK

Affiliated Principal Investigators

We are fortunate to have a network of affiliated PIs, across the University and surrounding institutions, who help ensure that CSCI is well integrated with the broader stem cell community in Cambridge. Affiliated PIs 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.

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

- have access, for collaborative studies, to CSCI 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 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 CSCI student events.



In 2016, we welcomed new Affiliate PIs: Prof Serena Best, Dr Simon Buczacki, Prof Ruth Cameron, Dr Peter Campbell, Dr Sara-Jane Dunn, Dr Jasmin Fisher, Prof Richard Gilbertson, Dr Cristina Pina and Dr Matthias Zilbauer.

Professor Serena Best
Medical Materials

Cambridge Centre for Medical Materials

Work at CCMM is focussed on designing, creating and characterising three dimensional environments for cells. We have an intensely interdisciplinary approach and welcome the opportunities for discussion and potential collaboration.

Professor Allan Bradley
Genome Engineering

Wellcome Trust Sanger Institute

The Bradley laboratory is a multi-disciplinary environment with a number of parallel research themes. One of our core disciplines is the development and use of genetic technologies which we primarily apply to the mouse genome, although we also embrace studies in other mammalian genomes.

Dr Simon Buczacki
Cellular quiescence in intestinal homeostasis and tumorigenesis

Cambridge Cancer Centre

My scientific and clinical interests lie within translational surgical oncology. In particular I have specialised interests in the fields of intestinal stem and cancer stem cell biology. My research philosophy centres around the tenet of applying an understanding of normal cellular behaviour to that of oncogenically transformed populations. It therefore follows that my research encompasses the study of normal intestinal stem cell biology using contemporary tools such as GEMMs, lineage tracing and organoid assays in combination with the use of NGS and xenotransplantation to help understand clonogenic cancer cell behaviour. I have a particular interest related to cellular quiescence and have developed robust tools to understand and manipulate their behaviour to clinical advantage.

Professor Ruth Cameron
Medical Materials

Cambridge Centre for Medical Materials

Work at CCMM is focussed on designing, creating and characterising three dimensional environments for cells. We have an intensely interdisciplinary approach and welcome the opportunities for discussion and potential collaboration.

Affiliated Principal Investigators

Dr Peter Campbell

Cancer genomics

Wellcome Trust Sanger Institute

Peter Campbell's research programme focuses on the genetic changes our cells acquire as we go through life, and how these mutations are related to ageing, cancer and other disease processes. Dr Peter Campbell is Head of Cancer Genetics and Genomics at the Institute and is joint head of the Cancer Genome Project. He is also a practising haematologist at Addenbrooke's Hospital in Cambridge.

Dr Sara-Jane Dunn

Decision making in stem cells

Microsoft Research

Sara-Jane's research is focused on the theory of how and why cells perform computation. Current work is seeking to uncover the program that governs naïve pluripotency and differentiation decisions in embryonic stem cells.

Professor Anne Ferguson-Smith

Stem cells and the epigenetic programme

Department of Genetics

We are identifying and characterizing factors required for the targeting and maintenance of epigenetic states at particular genomic regions in stem cells in vitro and in vivo. In addition, we use genomic imprinting as a model system to study the programming of specific genes important for the properties and fate of stem cells. Recently we have been studying developmental contexts in which genomic imprinting can be used as a developmental switch to control gene dosage and the consequences for the stem cell niche when this process goes wrong. We apply genetic, epigenetic and biochemical approaches to mouse germ cells, preimplantation embryos, and stem and progenitor cells in pre and postnatal development, and embryonic stem cells in culture.

Dr Jasmin Fisher

Executable biology

Microsoft Research

Executable Biology is working to understand the orchestration of biological systems through construction, execution, and analysis of computational models describing biological phenomena, in particular cell fate decisions and molecular mechanisms of cancer:

- Signalling networks regulating cell fate decisions during development and cancer.
- Application of formal methods to model and analyse biological systems.
- Design of formal modelling languages and tools tailored for biology.

Dr Kristian Franze
CNS development and disease

Department of Physiology, Development and Neuroscience

Mechanics in nervous system development and pathology. We are taking an interdisciplinary approach to investigate how cellular forces, local cell and tissue compliance and cellular mechanosensitivity contribute to CNS development and disease.
Methods we are exploiting include atomic force microscopy, traction force microscopy, custom-built simple and complex compliant cell culture substrates, optical microscopy including confocal laser scanning microscopy and cell biological techniques.

Dr Michaela Frye
Stem cells homeostasis and disease

Department of Genetics

Our lab focuses on the identification and characterization of post-transcriptional modifications that regulate the maintenance of adult stem cells.
We further explore whether modulation of RNA-methylation pathways can help to protect from human diseases such as cancer.

Professor Richard Gilbertson
Childhood brain tumours

Cancer Research UK Cambridge Institute

Research focuses on tackling childhood brain and CNS cancers using genomics, molecular pathology and bioinformatics.

Dr Myriam Hemberger
Trophoblast stem cells

Babraham Institute

The focus of our work is on the establishment, maintenance and differentiation of trophoblast cells leading to formation of a functional placenta. Trophoblast cells are the major building blocks of the developing placenta. They are the first cell type to arise very early in development when they are set apart from cells giving rise to the embryo itself.
Our two main areas of research are:

- Transcriptional and epigenetic regulation of the trophoblast stem cell compartment
- Establishment of a functional placenta

Dr Meritxell Huch
Stem Cells and Tissue Regeneration

Gurdon Institute

Our aim is to understand the molecular mechanism by which liver or other adult cells sense the damage infringed to the tissue and start the repairing process. Understanding these mechanisms is crucial to improve our knowledge on the basics of cancer initiation, as during tumorigenesis, similar mechanisms have to be put in place to activate the resting cells to start proliferating.

Affiliated Principal Investigators

Dr Phil Jones

Epidermal Stem Cells

Wellcome Trust Sanger Institute

The Jones Group uses transgenic models, advanced imaging, novel sequencing approaches and quantitative methods to define the critical evolutionary steps that lead to non-melanoma skin and oesophageal cancer, and test the ability of targeted therapies to reduce the risk of cancer development.
Current projects include:

- Mapping mutations in normal human tissues
- Modelling clonal evolution in pre-cancer

Phil Jones is Leader of the "Stem cells and Cancer" programme, MRC Cancer Cell Unit and is also a Consultant in Medical Oncology at Addenbrooke's Hospital.

Dr Pentao Liu

Human iPS Cells

Wellcome Trust Sanger Institute

We use various approaches including genetics, genomics and cell biology to study gene functions in normal development and disease such as cancer. We are particularly interested in stem cell self-renewal, differentiation, and lineage choice.

Dr Rick Livesey

Human Stem Cell Models of Dementia

Gurdon Institute

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.

Professor Keith Martin

Neuroprotection and repair of the visual system

Cambridge Centre for Brain Repair

Glaucoma is the commonest cause of irreversible blindness in the world. The condition involves progressive death of retinal ganglion cells in the eye resulting in irreversible visual loss. An important goal of our group is to understand better the mechanisms of retinal ganglion cell (RGC) death in glaucoma, to develop methods to protect RGC thus slowing the progression of glaucomatous visual loss, and ultimately to restore vision in those blind due to the disease. We use stem cell and gene therapy approaches and have achieved potent RGC neuroprotection in animal models of glaucoma. We are also developing new methods to improve RGC axonal regeneration after optic nerve injury.
Some current projects:

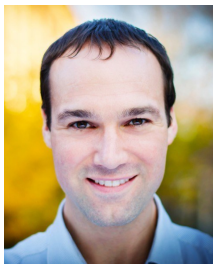
- Stem cells as a potential treatment for glaucoma
- Working towards human clinical trials of a novel gene therapy for glaucoma
- The role of activated retinal glia in survival and regeneration of retinal neurons

Professor Alfonso Martinez-Arias

The structure and function of living matter

Department of Genetics

We are interested in the structure and function of Living Matter with a special interest in developmental processes which create tissues and organs from single cells through defined programme of gene expression. Cells have the capacity to read and interpret those programmes and change accordingly. Our research is focused on how this happens using a combination of classical genetics, quantitative measurements, image analysis and modelling. We use mouse Embryonic Stem (ES) cells and Drosophila Intestinal Stem Cells (ISC) to ask questions about: stochastic and deterministic processes in cell fate decisions; cell and tissue dynamics during morphogenesis; Wnt/Notch signalling in developmental homeostasis.



Dr Florian Merkle

Human stem cell models of obesity and neurological disease

WT-MRC Institute of Metabolic Science

The goal of the Merkle laboratory is to elucidate the molecular and cellular basis of disease in order to improve human health. A main focus of our group is obesity, a disease with few effective treatments that leads to millions of premature deaths each year. Obesity is thought to largely arise from the abnormal function of specific populations of neurons in the hypothalamus that regulate appetite and body weight. We differentiate human pluripotent stem cells into these hypothalamic neurons in vitro, and study their phenotypic responses to the metabolic cues that regulate their activity in vivo using a multidisciplinary array of approaches. We then use pharmacology and CRISPR/Cas9-based gene editing to study how obesity-associated environmental factors and genetic mutations might alter their responsiveness. By carrying out this work, we aim to reveal disease mechanisms and identify new therapeutic targets to help combat the obesity epidemic.

Dr Cristina Pina

Haematopoietic stem cells

Department of Haematology

Haematopoietic stem cells balance molecular programmes of self-renewal and differentiation in order to sustain mature blood cell production and maintain a pool of undifferentiated multipotent cells throughout the lifetime of the individuals. Corruption of some of these programmes in favour of self-renewal and/or blocking differentiation may result in malignant transformation to generate leukaemia. Additionally, stem cells have the capacity to respond to increased demands in production of mature lineages, e.g. upon injury.

Dr Emma Rawlins

Stem Cell Fate in the Mammalian Lung

Gurdon Institute

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.

Affiliated Principal Investigators

Professor Wolf Reik

Epigenetic reprogramming in mammalian development

Babraham Institute

Epigenetic modifications such as DNA methylation and histone marks are often relatively stable in differentiated and in adult tissues in the body, where they help to confer a stable cell identity on tissues. The process of epigenetic reprogramming, by which many of these marks are removed from DNA, is important for the function of embryonic stem cells and in reprogramming stem cells from adult tissue cells. When this erasure goes wrong there may be adverse consequences for healthy development and ageing, which can potentially extend over more than one generation.
Our insights into the mechanisms of epigenetic reprogramming may help with developing better strategies for stem cell therapies and to combat age related decline. We have also recently initiated work on epigenetic regulation of social behaviours in insects, where we are interested in how patterning and regulation of DNA methylation in the brain is linked with the evolution of sociality.

Dr Peter Rugg-Gunn

Epigenetic regulation of pluripotency and development

Babraham Institute

Our research group investigates how epigenetic processes are involved in regulating stem cells and the early stages of mammalian development. Specifically, we study interactions between epigenetic processes and other key molecular components, such as signalling pathways and transcription factors, in order to understand how these multiple events are coordinated. This research will provide crucial insight into how distinct cell types are formed in the embryo and will uncover new and safer ways to use stem cells for regenerative medicine and other biomedical applications. Our findings may also have broad impact on understanding environmental influences on the epigenome, which has major implications for diet and other external factors during pregnancy.

Professor Azim Surani

Specification and programming of the germline for totipotency and development

Gurdon Institute

Specification of primordial germ cell (PGC) occurs from equipotent postimplantation epiblast. BLIMP1, PRDM14 and AP2g are necessary and sufficient for mouse PGC specification, and initiation of the germline epigenetic program which is critical towards establishment of the totipotent state. Recently we found that SOX17 is one of the key regulators of human PGC specification; this amongst other factors indicate major mechanistic differences between mouse and human. We are also exploring mechanism of epigenetic reprogramming of human germline, and investigating loci that are resistant to reprogramming.

Professor Alan Warren

Defective ribosome assembly and stem cell subversion

Cambridge Institute for Medical Research

Eukaryotic ribosome assembly is an essential, highly conserved process involving the concerted action of more than 200 assembly factors. Surprisingly, mutations in ribosomal proteins or the ribosome assembly factors perturb haematopoietic stem cell function, promoting the development of bone marrow failure, leukaemia and cancer. We have discovered that the SBDS protein deficient in the leukaemia predisposition disorder Shwachman-Diamond syndrome (SDS) mediates a key quality control step that licences the entry of nascent cytoplasmic large ribosomal subunits into the actively translating pool of ribosomes. What are the molecular mechanisms of eukaryotic ribosome assembly? How is this process regulated and monitored? How do defects in this process perturb stem cell function and increase the risk of cancer? To address these questions, we combine genetics, biochemistry and structural studies. In particular, we use single-particle cryo-electron microscopy to visualise key ribosome assembly intermediates.

Professor Christine Watson

Stem cell and lineage determining factors in mammary gland

Department of Pathology

We are interested in identifying transcriptional regulators that control lineage commitment of mammary stem cells. We have identified a novel gene, Zfp157, that is a master regulator of the alveolar lineage. Further work is focussed on lineage tracing using fluorescent fusion proteins and H2B-GFP to isolate and characterise long label-retaining cells.

Dr Doug Winton

Intestinal stem cells

Cancer Research UK Cambridge Institute

Renewing tissues and many cancers are maintained by a small number of long-lived stem cells. Most models of stem cell organisation take account of their longevity and assume that they are stable populations carrying unique identifying characteristics. However, this interpretation now seems too simplistic. For example the cell surface signatures of stem cells may not be as stable over time as previously thought. Our approach is pragmatic: to identify novel ways of assaying stem cells in situ with respect to the functional end-points that are integral to their biology.

Dr Matthias Zilbauer

Intestinal stem cell biology

Department of Paediatrics

The Zilbauer group's main research interest lies in the field of mucosal immunology of the GI tract during health and paediatric diseases particularly Inflammatory Bowel Diseases (IBD) and Necrotising Enterocolitis (NEC). More specifically, the group has been investigating the role of epigenetic mechanisms (i.e. DNA methylation) in regulating gene expression and cellular function of the human intestinal epithelium. In close collaboration with the Koo group, human intestinal epithelial organoids are being developed as functional models to investigate intestinal epithelial biology during health and disease. In addition to organoids derived from intestinal mucosal samples, induced pluripotent stem cells (iPSCs) can be differentiated into intestinal epithelium, which is the subject of an ongoing collaboration with the Vallier group. Our overall aim is to further develop and validate these highly promising organoid culture models into powerful and reliable tools, which can then be used to develop novel treatments as well as testing existing drugs and hence allowing a personalized treatment approach.

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 Wellcome, 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 4-Year (1+3) PhD Programme

Wellcome 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 examined for 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

2013 Starters

Sarah Foerster, Loukia Yangou, Anna Osnato

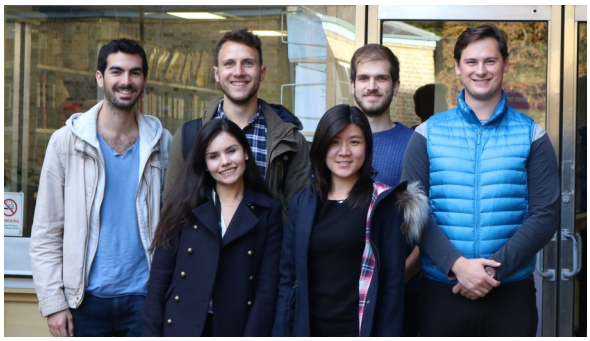
2014 Starters

Fiona Hamey, Caroline Oedekoven, Lucia Cordero Espinosa, Sam Myers, Anastasiya Sybirna, Olivia Harris

2015 Starters

Theresa Bartels, Blanca Pijuan Sala, Alisa Molotova, Cora Olpe, Julia Spindel

2016 Starters



James Baye, Tim Lohoff, Sam Watcham, Daniel Bode Aracely Castillo Venzor, Bao Xiu Tan

Current Students in CSCI labs (as of Oct-2016)

2012 Starters

Miguel Cardoso de Brito, Vallier Lab
Amanda Dalby, Ghevaert Lab
Maria Xenophontos, Bertone Lab

2013 Starters

Faisal Basheer, Huntly Lab
Joshua Bernstock, Pluchino Lab
Lucy Collins, Barker Lab
Natalia Deja, Franklin Lab
Ranna El Khairi, Vallier Lab
Sarah Forster, Franklin Lab
Nikoletta Gkatza, Frye Lab
Joseph Guy, Franklin Lab
Yun Huang, Surani Lab
Anna Osnato, Vallier Lab
Rameen Shakur, Vallier Lab
Crystal Spectre, Vallier Lab
Magdalena Sznurkowska, Simons Lab
Jeroen Verheyen, Pluchino Lab
George Wylde, Chalut Lab
Loukia Yiangou, Sinha Lab
Nada Zaidan, Göttgens Lab

2014 Starters

Silvia Basilico, Göttgens Lab
Lawrence Bates, Silva Lab
Francesca Beaton, McCaskie Lab
Rebecca Caeser, Hodson Lab
Amanda Collier, Rugg-Gunn Lab
Lucia Cordero Espinosa, Huch Lab
Ludovica Di Canio, Franklin Lab
Shlomit Erdi, Martinez-Arias Lab
Florian Gebler, Pluchino Lab
Imbisaat Geti, Vallier Lab
Jacob Grinfeld, Green Lab
Fiona Hamey, Göttgens Lab
Olivia Harris, Watson Lab
Wajid Jawaid, Göttgens Lab
Aleksandra Lewicka, Jones Lab
Chee Lim, Göttgens Lab
Gianmarco Mastrogiovanni, Koo Lab
Alessandra Merenda, Koo Lab
Chris McMurran, Franklin Lab
Samuel Myers, Smith Lab
Caroline Oedekoven, Kent Lab
Luca Peruzzotti-Jametti, Pluchino Lab
Casey Rimland, Vallier Lab
Fotis Sampaziotis, Vallier Lab
Michael Segal, Franklin Lab
Elsa Sousa, Silva Lab
Stanley Strawbridge, Smith Lab
Anastasiya Sybirna, Surani Lab
Katie Tremble, Silva Lab
Christophe Verstreken, Chalut Lab

2015 Starters

Ana Albiero, McCaskie Lab
Theresa Bartels, Rowitch Lab
Serena Belluschi, Laurenti Lab
Giovanni Canu, Vallier Lab
Grace Collord, Vassiliou Lab
Giles Donnelly, Martinez-Arias Lab
Andres Garcia, Mendez-Ferrer Lab
Carlos Gonzalez-Arias, Green Lab
Sergey Hladkov, Silva Lab
Timo Kohler, Chalut Lab
Mikel McKie, Huch Lab
Madeline McNamara, Sinha Lab
Alisa Molotova, Franklin Lab
Sonia Nestorowa, Göttgens Lab
Cora Olpe, Winton Lab
Claudia Pama, Karadottir Lab
Blanca Pijuan Sala, Göttgens Lab
Moosa Qureshi, Göttgens Lab
Vijitha Sathiaseelan, Ringshausen Lab
Julia Spindel, Reik Lab
Alessio Strano, Livesey Lab
Helena Valle, Martinez-Arias Lab

Our Students work alongside world-class scientists in an enriching and stimulating environment. 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 connections which will lead to successful scientific careers.

PhD Programme in Stem Cell Biology and Medicine

Key CSCI PhD student academic calendar events

Stem Cell Biology Discussion Course

All new CSCI PhD students in their first year are strongly encouraged to attend the Institute's core Stem Cell Biology Discussion Course sessions, with those on the Wellcome and MRC Four Year Programmes being expected to attend these as part of their MRes course. In term 1, the '*Introduction to the CSCI*' sessions are led by CSCI PIs as an introduction to their research fields. In terms 2 and 3, the '*Stem Cell Biology Discussion Course*' sessions are group discussions. Each week the lead PI(s) provides papers for students to read, and discussion topics for them to think about prior to the session. This will then form the basis of the discussion.

Wellcome /MRC 4-year Student Presentation Day (Annually, June)

There is an annual event for all students on the Wellcome and MRC 4-Year Stem Cell Programmes, attended by all Wellcome and MRC Physical Biology of Stem Cells 4-Year PhD students. Each student gives a presentation to fellow students and the PhD Programme Committee. A College dinner for all those involved is held in the evening.

PhD Day (Annually, July)

This is an annual event for all CSCI PhD students, where CSCI PhD students in the penultimate year of their PhD present their work orally, followed by questions/ discussion. All other PhD students are expected to present a poster. All CSCI members are invited to attend. It is an excellent opportunity to hear about other labs, work and prepare oral presentations.

Internal & External Seminars

The CSCI, affiliated departments, and students themselves, organise regular seminars for internal and external participation. Students are expected to attend all seminars in whichever department students find themselves.

> "Highly demanding first year but overall very enriching"

There are two platforms housed at the Cambridge Stem Cell Institute which support local and national activity in the biomedical application of pluripotent stem cells.

UK RPM Pluripotent Stem Cell Platform (PSCP)

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/

Staff
Nicholas Blair - Post-doc Researcher
Mercy Danga - Research Assistant
Venkat Pisupati - Research Assistant

NIHR/BRC hIPSC Core Facility

The NIHR Cambridge Biomedical Centre (BRC) hIPSCs core facility was created in 2009 to promote the clinical applications of human Induced Pluripotent Stem Cells (hIPSCs). The main activity 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, genome editing of hIPSCs for gene correction or for gene mutation is a growing activity for the BRC hIPSCs core facility. This platform also provides training to derive, grow and characterise hIPSC lines. Finally, the BRC hIPSC core facility is managing several research and development programs aiming to establish new methods of differentiation, inducible systems for gene targeting and more recently derivation of organoid from a diversity of organs including gut and liver.
During the past seven years, the BRC hIPSCs core facility has derived and characterised hIPSCs lines from 600 patients suffering from neurodegenerative diseases, cardiovascular syndromes, metabolic and blood disorders. These projects have been directed by clinicians and basic scientists associated with different institutions in Europe and also with diverse BRC themes related to Neurosciences, Metabolic Science, Cardiovascular Medicine, Haematology, Surgery and Hepatology/Thoracic Medicine.

Located in the 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 of the Cambridge Stem Cell Institute.

www.cambridge-brc.org.uk/hipsc-core-facility

Staff
Ludovic Vallier - Director
An-Sofie Lenaerts - Manager
Sophie Glen - Research Assistant
June Kadiwala - Research Assistant
Paulina Materek - Research Assistant
Kirsten Snijders - Research Assistant

Paul Bertone

Group Leader and Director of Informatics

Paul Bertone received his PhD in Molecular, Cellular, and Developmental Biology from Yale University where he developed novel technologies for large-scale genome analysis, protein function and computational biology. He produced the first high-resolution transcription map of the entire human genome, the first ChIP-based studies to map genome-wide transcription factor binding sites in human cells, and the first functional proteome microarray system for any organism. Prior to joining the CSCI he founded his research group at the European Bioinformatics Institute, part of the European Molecular Biology Laboratory, holding joint appointments in the Genome Biology and Developmental Biology Units at EMBL Heidelberg.

At CSCI the Bertone Group applies functional genomic approaches to stem cell biology and embryonic development. Recently they have investigated key regulatory pathways essential to the maintenance of naïve pluripotency, characterised the first authentic naïve human pluripotent cells, and identified species-specific pathway usage in early mammalian embryos.

Genomic analysis of pluripotency in embryonic development

We study embryonic and tissue-specific stem cells using a combination of experimental and computational methods, leveraging state-of-the-art genomic technologies to address fundamental aspects of development and disease. We wish to achieve a comprehensive molecular understanding of the naive pluripotent state and to characterise species-specific attributes of pluripotent cell specification. We study the emergence of pluripotent cells in rodent, human and non-human primate embryos to define the transcriptional regulatory networks that induce and support naive pluripotency. A second research area entails the analysis of tumour -initiating neural stem cells that drive glioblastoma. We carry out genome-wide analyses to determine chromosomal, mutational and transcriptional aberrations in patient-derived cell lines. These data provide a unified framework for the characterisation and functional analysis of corrupted stem cell populations that support cancer progression.

Marmoset blastocyst immunostained to show pluripotency factor NANOG localised to the inner cell mass, primitive endoderm specifier GATA6, outer trophectoderm marker CDX2 and nuclei.

Group Members

* Ewan Johnstone (PhD Student)
* Giuliano Stirparo (Research Associate)
* Maria Xenophontos (PhD Student)

Boroviak T, Loos R, Lombard P, Behr R, Sasaki E, Nichols J, Smith A, Bertone P (2015) **Lineage-specific profiling delineates the emergence and progression of naïve pluripotency in mammalian embryogenesis.** *Developmental Cell 2015 Nov 9;35(3):366-82* PMCID:PMC4643313

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 (2014) **Resetting transcription factor control circuitry toward ground state pluripotency in human**. *Cell 11;158(6):1254-69*. PMCID:PMC4162745

Engström PG, Steijger T, Sipos B, Grant GR, Kahles A, Rätsch G, Goldman N, Hubbard TJ, Harrow J, Guigó R, Bertone P (2013) **Systematic evaluation of spliced alignment programs for RNA-seq data**. *Nature Methods 10: 1185–91*. PMCID:PMC4018468

Steijger T, Abril JF, Engström PG, Kokocinski F, Hubbard TJ, Guigó R, Harrow J, Bertone P (2013) **Assessment of transcript reconstruction methods for RNA-seq**. *Nature Methods 10: 1177–84.* PMCID:PMC3851240

Engström PG, Tommei D, Stricker SH, Ender C, Pollard SM, Bertone P (2012) **Digital transcriptome profiling of normal and glioblastoma-derived neural stem cells identifies genes associated with patient survival**. *Genome Medicine 9;4(10):76*. PMCID:PMC3556652

Funded by

BBSRC bioscience for the future

Bioinformatics

Head of Bioinformatics: Sabine Dietmann
Co-workers: Michael Barber, Susanne Bornelov, Lila Diamanti and Lena Morrill

The CSCI Bioinformatics Group employs computational approaches to gain insights into the biology of stem cells. The group performs data analysis for a wide range of genomics experiments in partnership with groups across the institute.
This includes development of computational pipelines for high-throughput sequencing applications, with particular expertise in transcriptomics, epigenetics and single-cell profiling techniques.

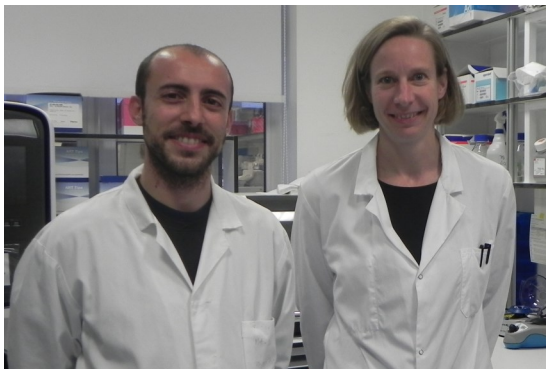
Flow cytometry

Flow cytometry Manager: Andy Riddell
Co-workers: Annie Hoxhalli

This is a multi-site facility comprising of expert-led high speed cell sorters and self-use sorter/analyser equipment in support of research by CSCI member groups.

Flow Cytometry is a powerful technique that streams particles past a laser allowing users to analyse large numbers of particles very quickly. It collects multiple different measurements of each particle simultaneously.
A sorter can be used to separate out populations of particles according to those measurements. The particles can be cells such as stem cells, bacteria, plant cells etc., or even small biological particles for example nuclei or chromosomes. The application of flow cytometry is in the Institute is evolving with the advancement of laser technologies and detection techniques.

Genomics



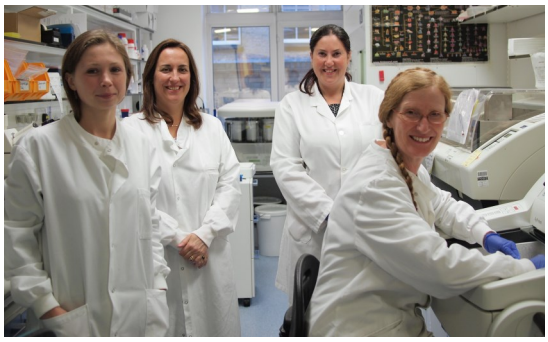
Genomics Manager: Maike Paramor
Co-workers: Joaquin Martinez

In recent years, the demand for Next Generation Sequencing (NGS) methods in stem cell research has increased rapidly. However, the technical challenge of library production is often daunting and time-consuming, and forms the major bottleneck of many projects.

The Cambridge Stem Cell Institute benefits greatly from its well established Genomics Facility, which produces NGS libraries on demand. This facility provides project planning advice, and a fast and professional turnaround for many different types of NGS library preparation. Its main goal is maximum support for CSCI researchers, but is also open to provide a local service to external groups. The Genomics Facility has built a collaboration with the sequencing core at CRUK to enable the best possible data acquisition through cutting-edge sequencing technology.

Core Facilities

Histology



Histology Manager: Irina Pshenichnaya
Co-workers: Helen Skelton, Kate Bird and Andrea Starling

The Histology team at the Cambridge Stem Cell Institute specialise in cutting and staining of frozen sections and paraffin wax embedded tissues for all Cambridge University researchers. They can provide advice and services on a wide range of molecular techniques as well as traditional tinctorial staining. They can give guidance on the fixation, processing, sectioning and downstream applications on a wide range of biological samples.
The facility is a well-equipped histopathology laboratory with tissue processing, embedding, microtomy and cryotomy machines available for use by both histology staff and trained researchers.

Imaging

Imaging Manager: Peter Humphreys

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

Expert advice, assistance and training are available for: all aspects of imaging for researchers, image analysis and custom analysis tools, processing of image volumes (deconvolution, 3D reconstruction).

IT

IT Manager: Paul Sumption was in post until December 2016. He will be replaced by Mark Sharpley from March 2017.
Co-workers: Paul Barrow and Marcelo Zappone

The IT support team provides advice and support to all members of the CSCI. They also run a bioinformatic facility infrastructure.

Tissue Culture

Tissue Culture Manager: Sally Lees
Co-workers: Diana Breitmaier, Jean Thompson and Kamila Bulczak

The Tissue Culture Facility provides services such as conditioned media production, growth factors, mycoplasma screening, MEF isolation and quality controlled reagents.

Administration

Louise Balshaw, Institute Administrator
sci-administrator@stemcells.cam.ac.uk

Jeanne Estabel, Principal Technician

Research Strategy and Communication Manager
sci-coordinator@stemcells.cam.ac.uk

Philippa Russell, Public Engagement Officer
scipeo@stemcells.cam.ac.uk

Susana Camacho, Administrative Assistant (Data)
sci-records@stemcells.cam.ac.uk

Gillian Currie, Administrative Assistant
Translational Medicine
regmedpa@stemcells.cam.ac.uk

Institute Secretary
scisecretary@stemcells.cam.ac.uk

Finance

Louise Carter, Senior Grants/Accounts Clerk (Maternity Leave)/ **Alexandra Charter** (Maternity Cover)
sci-grants@stemcells.cam.ac.uk

David Hughes & **Hervé Vaultrin**, Grants/Accounts Clerks
sci-finance@stemcells.cam.ac.uk

HR and Graduate Administration

Edita Paralova, HR Administrator
HR: hr@stemcells.cam.ac.uk
Recruitment: jobs@stemcells.cam.ac.uk

Jo Jack, PhD Administrator (Maternity Leave)/ **Lindsay Abbott** (Maternity Cover)
sci-phd@stemcells.cam.ac.uk

Gleeson Building

Andrew Ayling, Custodian
asa42@cam.ac.uk

James Bagstaff, Chief Building Services Technician
jwpb3@cam.ac.uk

Agne Jukneviciene, Cleaner
aj464@cam.ac.uk

Jane Leech, Glass Washer and Media Technician
jl569@cam.ac.uk

David Schwarz, Senior Chief Building Services Technician

Roy Pelegrin, Cleaner
rr379@cam.ac.uk

Jennifer Ring, Glass Washer and Media Technician
jbr39@cam.ac.uk

Wendy Russell, Receptionist/Secretary
reception@stemcells.cam.ac.uk

Christian Zwierzanski, Custodian
cz304@cam.ac.uk

PluriMes Project

Jenny Nelder, PluriMes Project Manager
plurimes-office@stemcells.cam.ac.uk

Charlotte Butler
PluriMes Administrative Assistant

Lorraine McAlister, Temporary PluriMes Administrative Assistant

Laboratory for Regenerative Medicine

Helen Gossage, Principal Research Laboratory Technician
hjg30@cam.ac.uk

Funding

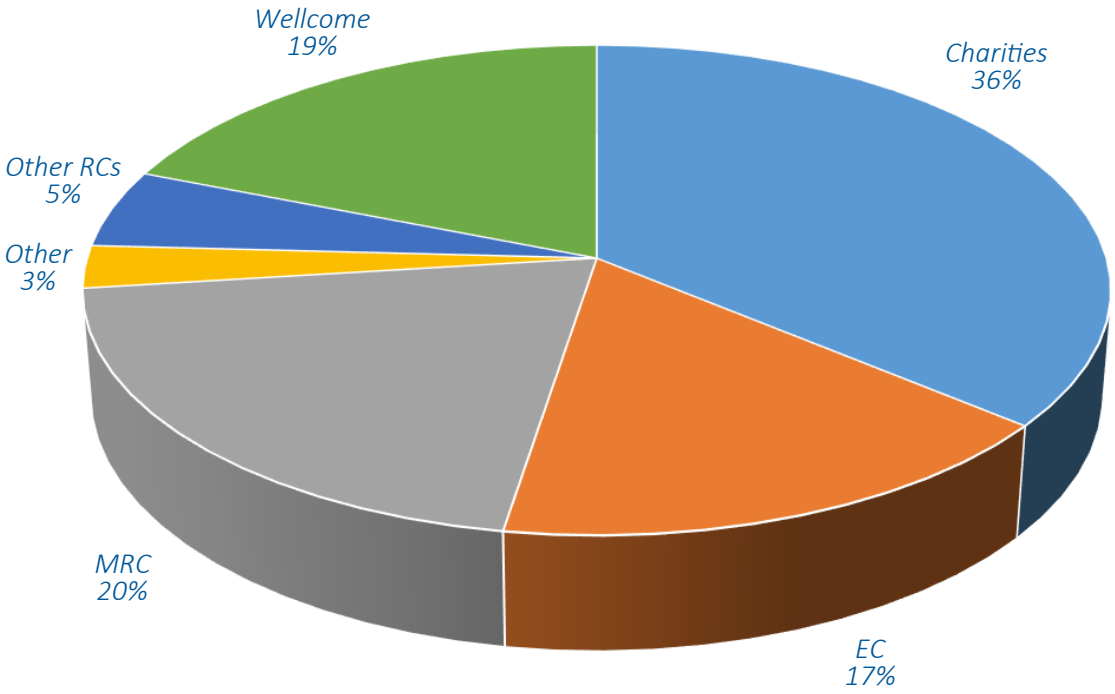
2016 CSCI Budget

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

In 2016:

* CSCI PIs held active research grants to a value of £96.7 million (excluding Wellcome /MRC Core Funding).
* 47 new grants were awarded to CSCI investigators.
* Research grant expenditure for 2016 was £17.6 million (excluding Wellcome /MRC Core Funding)

CSCI Expenditure



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 Senior Advisory Committee. The ISAB also makes recommendations on Group Leader recruitment and retention and provides advice on the Institute's 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 Scadden

Harvard Stem Cell Institute

Dr Ben Ebert

Harvard Medical School

Prof Magdalena Götz

Ludwig-Maximilians-University Munich

Senior Advisory Committee

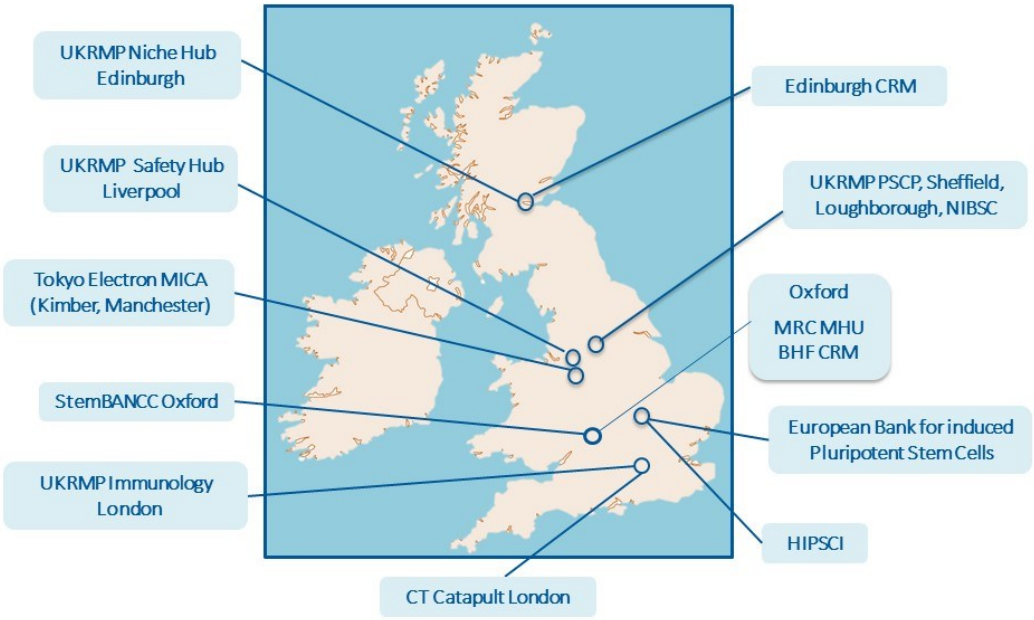
The Senior Advisory Committee is responsible for strategy, space and allocation of resources.

Professor Tony Green, Institute Director	Professor Brian Huntly	Professor David Rowitch
Professor Roger Barker	Professor Andrew McCaskie	Professor Ben Simons
Professor Robin Franklin	Dr Jenny Nichols	Professor Austin Smith
Professor Bertie Göttgens	Professor Anna Philpott	Professor Ludovic Vallier

There are a number of Institute wide committees, including the Senior Advisory Committee, Public Engagement Committee and PhD Programme Advisory Committee. As we approach the move to the Capella building, a number of working groups are actively looking at the most effective ways that the Institute can operate within the building. A unified governance structure will be put in place upon relocation.

Collaborations

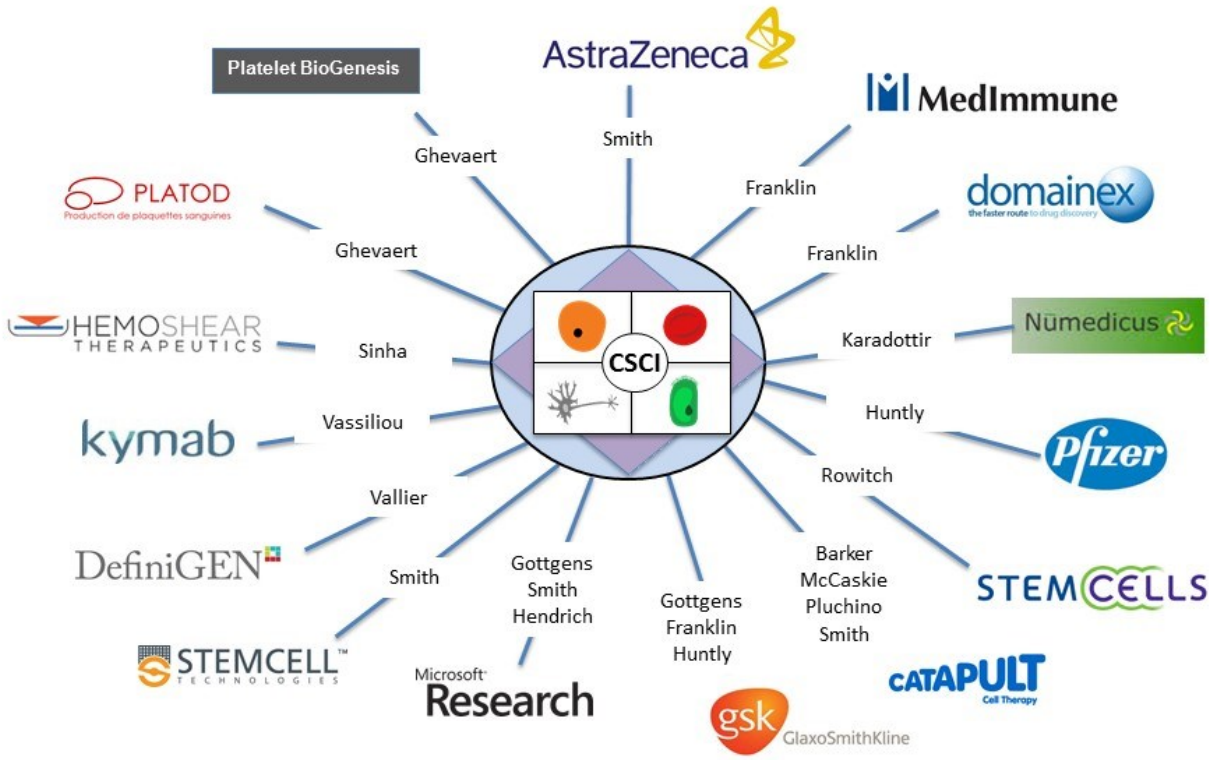
Integrated within national stem cell community



International collaborations - European liaisons - 44 connections spanning 13 countries

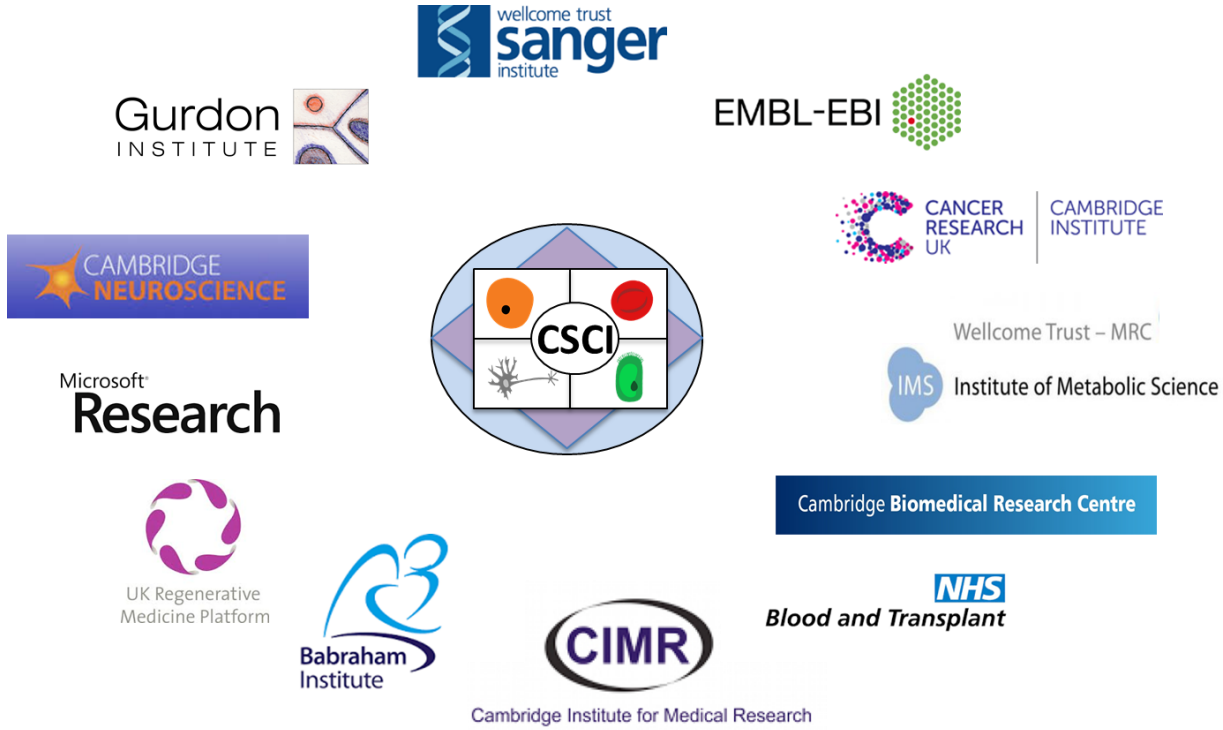
International collaborations—Long distance relationships

Industrial collaborations



Collaborations

Network of local strategic partnerships



Examples of local strategic partnerships

wellcome trust sanger institute · EMBL-EBI

Adams
Bradley
Campbell
Jones
Liu
Marioni
Stratton
Teichman

HIPSCI

Single cell genomics

Babraham Institute

Fraser
Hemberger
Reik
Rugg-Gunn
Turner

Nuclear dynamics

Epigenetics

Signaling

Gurdon INSTITUTE

Gurdon
Huch
Kouzarides
Livesey
Rawlins
Surani

Reprogramming

Organoids

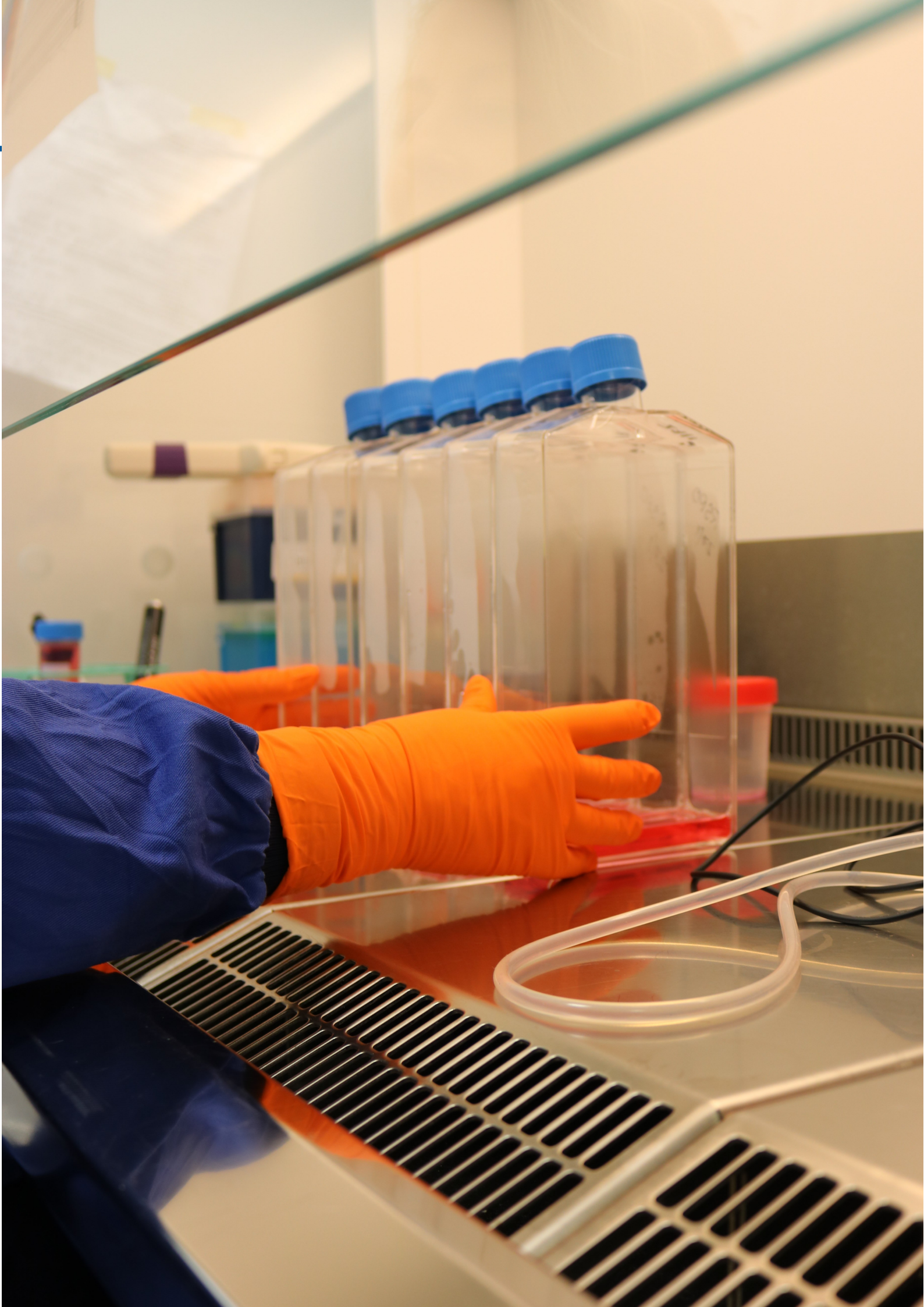
Chromatin

CANCER RESEARCH UK · CAMBRIDGE INSTITUTE

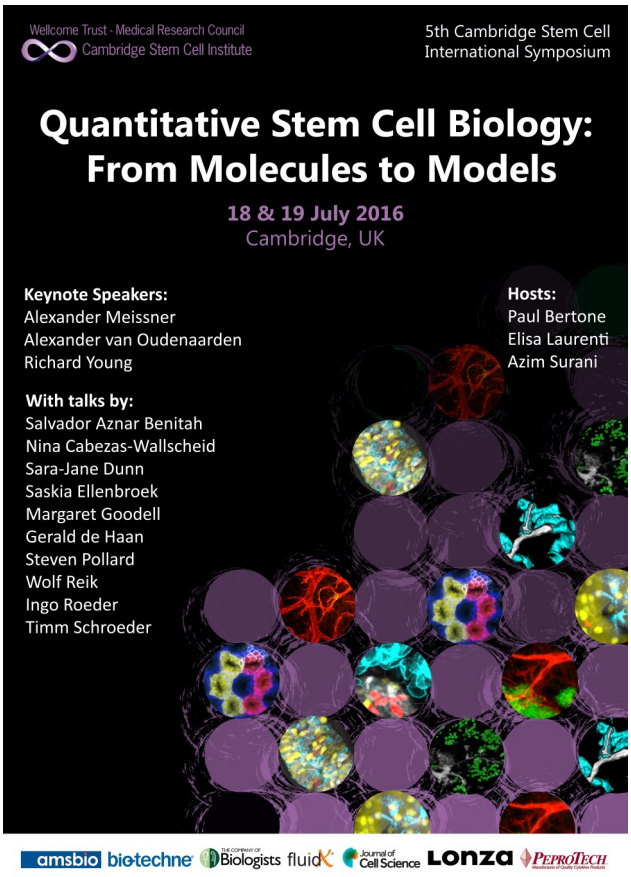
Buczaki
Caldas
Carroll
Gilbertson
Miller
Odom
Winton

Epithelial malignancies

Early biology of cancer



2016 International Symposium: Quantitative Stem Cell Biology: From Molecules to Models



The 5th Cambridge Stem Cell International Symposium

Organised by Paul Bertone, Elisa Laurenti and Azim Surani, the Symposium attracted 90 delegates from 8 countries.

Thirteen invited speakers and 5 short talks lined up an outstanding array of unpublished data, presenting new experimental and analytical techniques aimed at understanding stem cell regulation at all scales. 28 posters were presented by the delegates.

A stimulating modelling session provided a theoretical framework for interpretation of quantitative stem cell biology data and discussions around gene editing technologies such as CRISPR shed a light on the way these techniques are already changing the extent to which stem cells can be manipulated.

This opens up exciting avenues for understanding stem cell biology, but importantly also for the design of new regenerative medicine strategies.

Session 1: Epigenetic Control of Stem Cell Properties

Steven Pollard, MRC Centre for Regenerative Medicine, University of Edinburgh, UK
Programming and Reprogramming Brain Tumour Stem Cells

Wolf Reik, Babraham Institute, Cambridge, UK
Epigenetic reprogramming in mammalian development

Margaret Goodell, Baylor College of Medicine, Texas, USA
DNMT3A in Normal and Malignant Hematopoiesis

Noa Novershtern, Weizmann Institute of Science
High Resolution Mapping of Deterministic iPSC Reprogramming to Murine Ground State Pluripotency

Development commissioned a review from Steven Pollard:

Development 2016 143: 4097-4100; doi: 10.1242/dev.140541

Session 2: Imaging Stem Cell Activity

Timm Schroeder, Department of Biosystems Science and Engineering, ETH Zurich, Switzerland
Long-term single cell quantification: New tools for old questions

Saskia Ellenbroek, Cancer Biophysics, Hubrecht Institute, The Netherlands
Intravital imaging of epithelial stem cells and cancer

David Suter, EPFL, Switzerland
Mitotic bookmarking activity of SOX2 and its role in pluripotency and differentiation

Session 3: Genomic Regulation of Stem Cells

Nina Cabezas-Wallscheid, German Cancer Research Center (DKFZ), Germany
Molecular and Functional Heterogeneity of Dormant HSCs

Salvador Aznar Benitah, Institute for Research in Biomedicine, Barcelona, Spain
Diet-dependent reprogramming of transcriptional oscillations in adult stem cells during ageing

Richard Young, Whitehead Institute & Massachusetts Institute of Technology, USA
3D Regulatory landscape of human pluripotency

"The talks were of an extremely high standard"

Session 4: Modelling of Stem Cell Systems

Ingo Roeder, Technische Universität Dresden, Institute for Medical Informatics and Biometry, Germany
Computational Stem Cell Biology – A modelling perspective

Sara-Jane Dunn, Computational Science Laboratory, Microsoft Research Cambridge, UK
Uncovering Biological Computation in Embryonic Stem Cells

Naomi Moris, Department of Genetics, University of Cambridge
Probing transcriptional heterogeneity in cell fate decisions through modulation of the epigenetic regulator Kat2a

Session 5: The Physiology of Stem Cells

Gerald de Haan, European Research Institute for the Biology of Ageing, University Medical Center Groningen, The Netherlands
Ageing of haematopoietic stem cells

Sergei Doulatov, Boston Children's Hospital
Drug Discovery Using Induced Pluripotent Stem Cells Identifies Autophagy as a Therapeutic Pathway for Anemia

Joaquina Delas, CRUK-CI, UK
Role of Long Noncoding Rnas In Normal Murine Hematopoiesis And Malignant Transformation

Alexander van Oudenaarden, Hubrecht Institute, KNAW & University Medical Center Utrecht, The Netherlands
Single-cell mRNA sequencing reveals rare intestinal cell types

Seminars

CSCI Seminar Series

Date	Title	Speaker
15/01/16	Genetically modified marmoset models in biomedical science	Erika Sasaki, Keio University
18/01/16	Keeping up with the Joneses : how social interactions control stem cell self-renewal and differentiation	Marc Amoyel, NYU School of Medicine
03/02/16	Skeletal Stem Cells: History, Origins and Functions	Pamela Robey, National Institute of Dental and Craniofacial Research, National Institutes of Health, USA
12/05/16	High throughput engineering of pre-vascularised micro-tissues for rapid host vascularisation and stem cell delivery	Ninna Rossen, University of Copenhagen
02/06/16	Engineering stem cell self-organization	Matthias Lütolf, Laboratory of Stem Cell Bioengineering, EPFL, Lausanne
30/06/16	Age-selective segregation of organelles by stem cells	Pekka Katajisto, University of Helsinki
08/07/16	Transcriptional control of early lineages in the mouse embryo	Miguel Manzanarres, Centro Nacional de Investigaciones Cardiovasculares-CNIC, Madrid
14/07/16	IPSC-derived macrophages as a tool to study tissue-resident macrophages	Florent Ginhoux, Singapore Immunology Network (SIgN)
27/07/16	Transcription factor interactions in pluripotent cells	Ian Chambers, Centre for Regenerative Medicine, University of Edinburgh

Stem Cell Club Seminar Series

Date	Title	Speaker
24/02/16	Spatiotemporal regulation of haematopoietic stem cell niches by dual cholinergic signalling	Andres Garcia-Garcia
	The role of EZH2 in human pluripotency and differentiation	Peter Rugg-Gunn
	Human stem cell-based models of obesity and neurodegeneration	Florian Merkle
30/03/16	Molecular mechanisms driving activation of adult liver progenitors	Luigi Aloia
	Trophoblast Stem Cells: A finely tuned balance between interacting transcription factors governs self-renewal and differentiation	Myriam Hemberger
	Demethylation mechanisms underlying epigenetic memory erasure and cell identity in iPSCs	Inês Milagre
20/04/16	Linking H3K4 methylation to metabolic switching in the epiblast	Francis Stewart
	Cell cycle regulation of differentiation in development and disease	Fahad Ali
	Stomach stem cells in homeostatic turnover of mouse adult stomach epithelium	Bon-Kyoung Koo
11/05/16	Human embryonic lungs: progenitor cells and organoids	Emma Rawlins
	Resolving early mesoderm diversification through single cell profiling	Bertie Göttgens
	Stem Cells for glaucoma	Keith Martin
15/06/16	Defining the clonal dynamics leading to tumor initiation in the epidermis	Edouard Hannezo
	Ephemeron promotes the transition from ground state pluripotency via Lin28a	Meng Amy Li
	Impairment of DNA methylation maintenance is the main cause of global demethylation in naive embryonic stem cells	Ferdinand von Meyenn
27/07/16	Glial development and applications to patients with leukodystrophy	David Rowitch
	Vascular disease modelling using iPS: new insights into Marfan Syndrome	Alessandra Granata
	Translating the Science of Stem Cells	Tim Allsopp
07/09/16	Lung stem cell niche in health and disease	Joo-Hyeon Lee
	Resolving potential white matter dysfunction in Alzheimer's disease with a novel method development	Ragnhildur Thora Karadottir
	WhY not? Redundant roles for the lysine demethylase UTX and its Y-chromosome paralogue UTY in leukaemia	George Vassiliou
19/10/16	Mechanical signalling in self-renewal and ageing	Kevin Chalut
	Epigenetic resetting of human naive pluripotency	Ge Guo
	Choosing ATAC-seq for chromatin biology: advantages and disadvantages	Ewan Johnstone
30/11/16	Genome wide CRISPR-Cas9 pooled and arrayed library screens	Emmanouil Metzakopian
	Genome editing: making blood cells with added values	Cedric Ghaevert
	Role of Cell Cycle during early lineage commitment	Rodrigo Grandy

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On the Cover

Brain meninges
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My lab so colourful
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SCI Review created by:
SCI Coordinator: sci-coordinator@stemcells.cam.ac.uk
SCI Records: sci-records@stemcells.cam.ac.uk