

Front cover

Mouse lung undergoing repair after injury. Airway secretory club cells (yellow) are differentiating into alveolar lineage cells, whereas mutant secretory club cells (red) show perturbed differentiation capacity. Nuclei of individual cells are stained blue.

Credit: Catherine Dabrowska, Lee lab



A University of Cambridge Institute funded by Wellcome and the Medical Research Council.



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About Us

The Wellcome - MRC Cambridge Stem Cell Institute is a world-leading research centre with a mission to transform human health through a deep understanding of stem cell biology.

The Institute is core funded by Wellcome and the Medical Research Council to study the fundamentals of stem cell biology in health and disease, and to translate our research findings from bench to bedside to deliver tangible patient benefit.

We currently have 29 research groups with over 300 biological, clinical and physical scientists operating across a wide range of tissues and at multiple scales. This arrangement allows commonalities and differences in stem cell biology to be explored in a cohesive and interdisciplinary manner.

As the hub of a wider stem cell community across the University of Cambridge and neighbouring Institutes, our scientists have developed close collaborations with a wide range of researchers across disciplines.

The Institute currently has 36 affiliated researchers across 13 University departments, as well as the Babraham Institute, Microsoft Research, Wellcome Sanger Institute and EMBL-European Bioinformatics Institute.

Institute research aims to have direct and tangible impacts on society. Our dedicated public engagement team engage groups on a local, national and international level through dedicated events and resources, co-created with charity and research partners. This ensures our scientists are involved in wider conversations about stem cells in Cambridge and beyond.

As well as delivering outstanding research, the Institute is committed to providing a diverse and inclusive working environment for all staff and students. In line with central University activities, the Institute promotes and delivers a range of social and wellbeing initiatives.

Our New Home

In 2019, Institute members will move from our current different locations around Cambridge into the Jeffrey Cheah Biomedical Centre, a new purpose-built home on the Cambridge Biomedical Campus.

The move will bring all of the Institute's research groups under one roof, resulting in a fully integrated, vibrant and cohesive stem cell community, ideally placed to capitalise on its unique intellectual and clinical environment.

Being based at the Cambridge Biomedical Campus will allow for greater collaboration between scientists and clinicians and further advance the application of stem cell discoveries into the patient setting.

Proximity to industrial partners and academic colleagues at other leading research centres on campus will also be fundamentally important to realising the full potential of stem cells.



Cambridge
Biomedical Campus



Institute Research

Research at the Institute falls under three key themes: Stem Cell States, Stem Cells in Disease, and Stem Cells and Therapeutics. Many of our scientists contribute to more than one theme, and within these themes we have particular strengths in pluripotency, haematopoiesis, neural and epithelial stem cells.

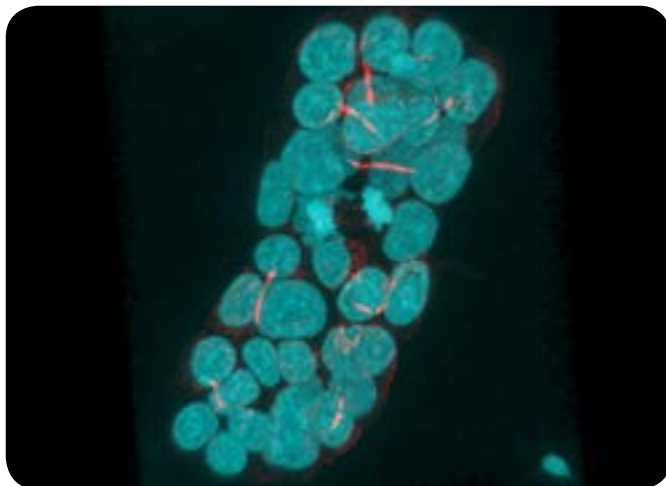
Stem Cell States

Stem cells have the extraordinary ability to develop into any type of cell in the body. We study the fundamentals of stem cell biology to understand the mechanisms by which they self-renew, maintain their states and commit to differentiate into all the cell types of the body.

Establishing new understanding of stem cell biology and behaviour complements and informs our studies of stem cell dysfunction in disease and provides the foundations of our translational aspirations for stem cells and therapeutics.

Group Leaders working on this theme:

M. Alcolea, S. Basu, K. Chalut, A. Cvejic, R. Franklin, B. Göttgens, T. Green, B. Hendrich, T. Káradóttir, D. Kent, E. Laurenti, J.-H. Lee, S. Méndez-Ferrer, J. Nichols, A. Philpott, D. Rowitch, J. Silva, B. Simons, S. Sinha, A. Smith & L. Vallier.



Nichols Lab

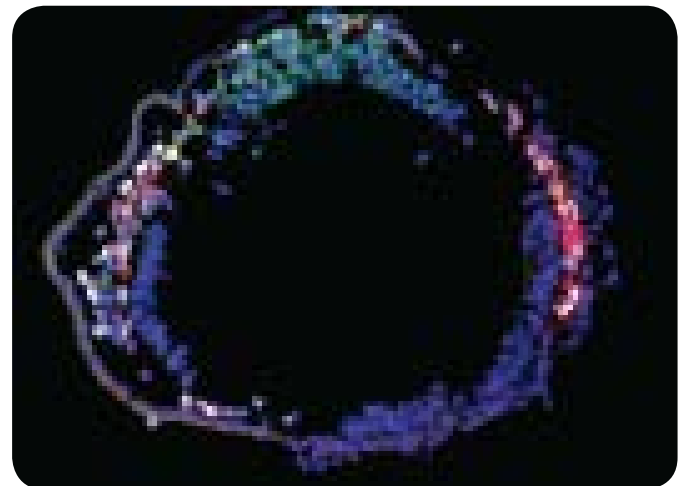
Stem Cells in Disease

Stem cell dysfunction underlies a range of diseases and health challenges that face the global population today. From neurodegenerative and cardiovascular diseases to cancer and ageing, stem cell dysregulation is implicated across the disease spectrum.

Underpinned by our exploration of normal stem cell states, we are investigating the mechanisms responsible for pathological behaviours of stem and progenitor cells. Our researchers focus particularly on different cancer pathophysiology and regenerative failure.

Group Leaders working on this theme:

M. Alcolea, S. Buczacki, K. Chalut, R. Franklin, B. Göttgens, T. Green, D. Hodson, B. Huntly, T. Káradóttir, D. Kent, E. Laurenti, J.-H. Lee, S. Méndez-Ferrer, A. Philpott, I. Ringshausen, D. Rowitch, B. Simons & G. Vassiliou.



Göttgens Lab

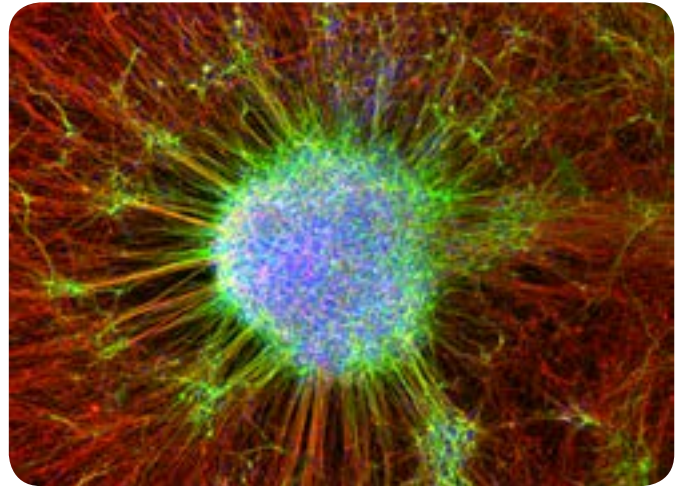
Stem Cells & Therapeutics

Building on the research undertaken into stem cell states and stem cells in disease, Institute researchers are using stem cells to model diseases *in vitro* and to generate new diagnostic and therapeutic approaches to deliver patient benefit.

Several investigators are developing first-in-human clinical trials of cellular therapies using stem cell derivatives, while others work on new diagnostic and prognostic approaches to improve patient outcomes.

Group Leaders working on this theme:

R. Barker, R. Franklin, C. Ghevaert, T. Green, B. Huntly, A. McCaskie, S. Méndez-Ferrer, D. Rowitch, S. Sinha & L. Vallier, G. Vassiliou.



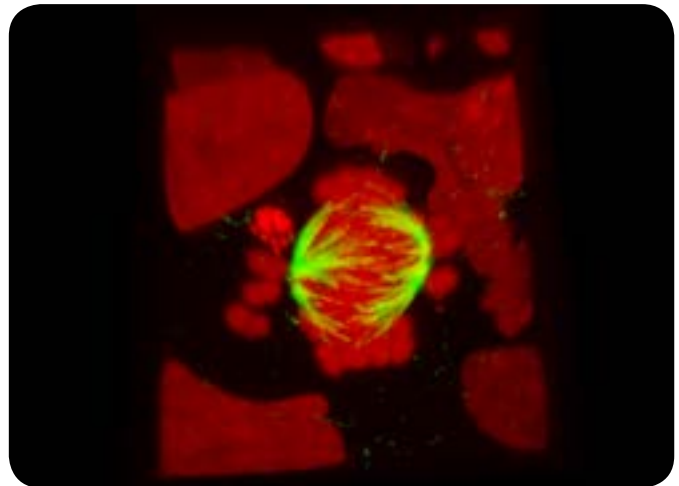
Barker Lab

Core Facilities

Alongside state-of-the-art laboratories, Institute researchers also benefit from a range of core facilities located within the Jeffrey Cheah Biomedical Centre. These facilities include Bioinformatics, Flow Cytometry, Next Generation Sequencing, Imaging, Histology, Biofacilities and Tissue Culture.

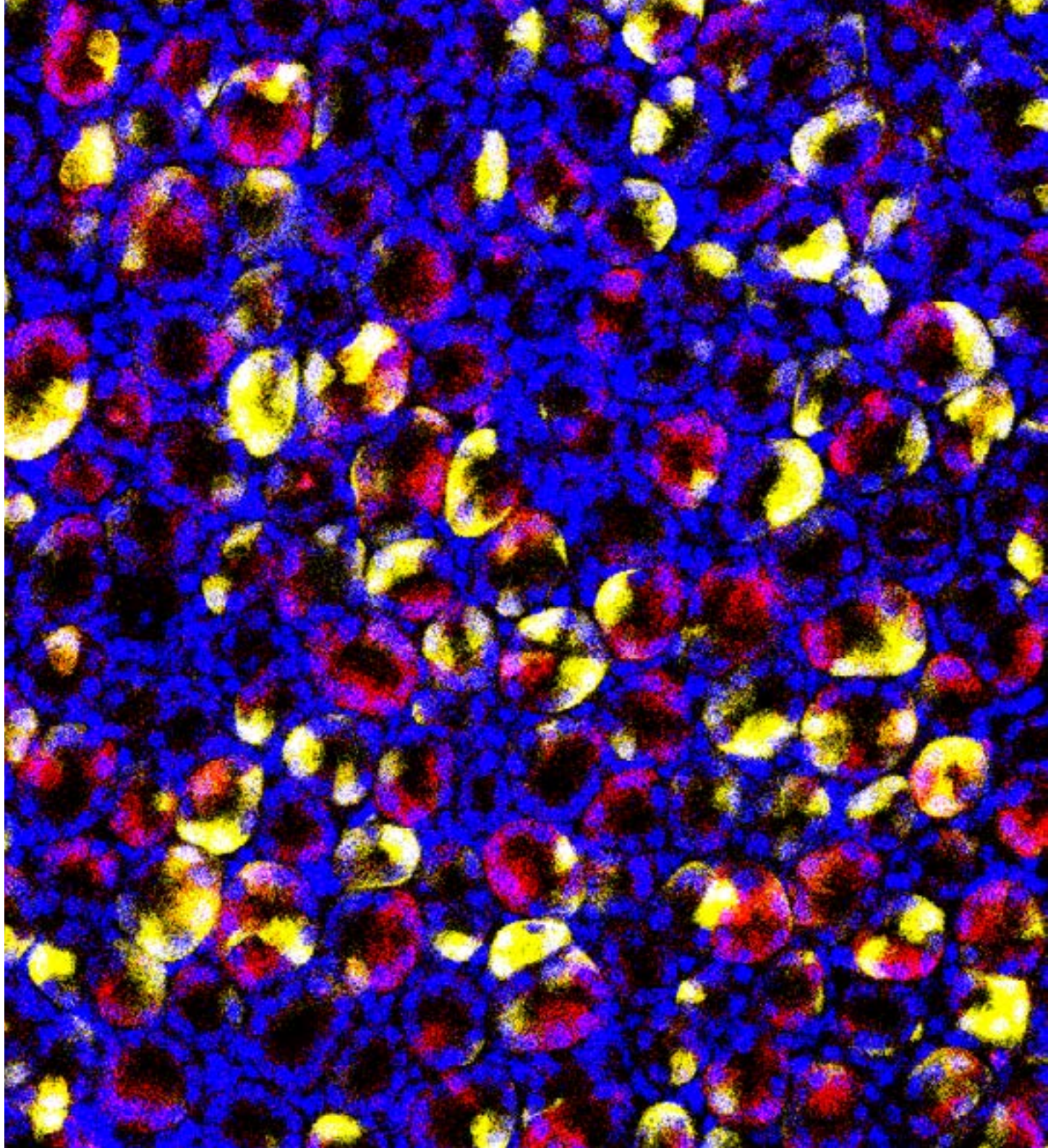
Highly-skilled facility staff provide key services and training to researchers throughout the Cambridge Stem Cell Institute, as well as to affiliated researchers and the wider University when there is excess capacity.

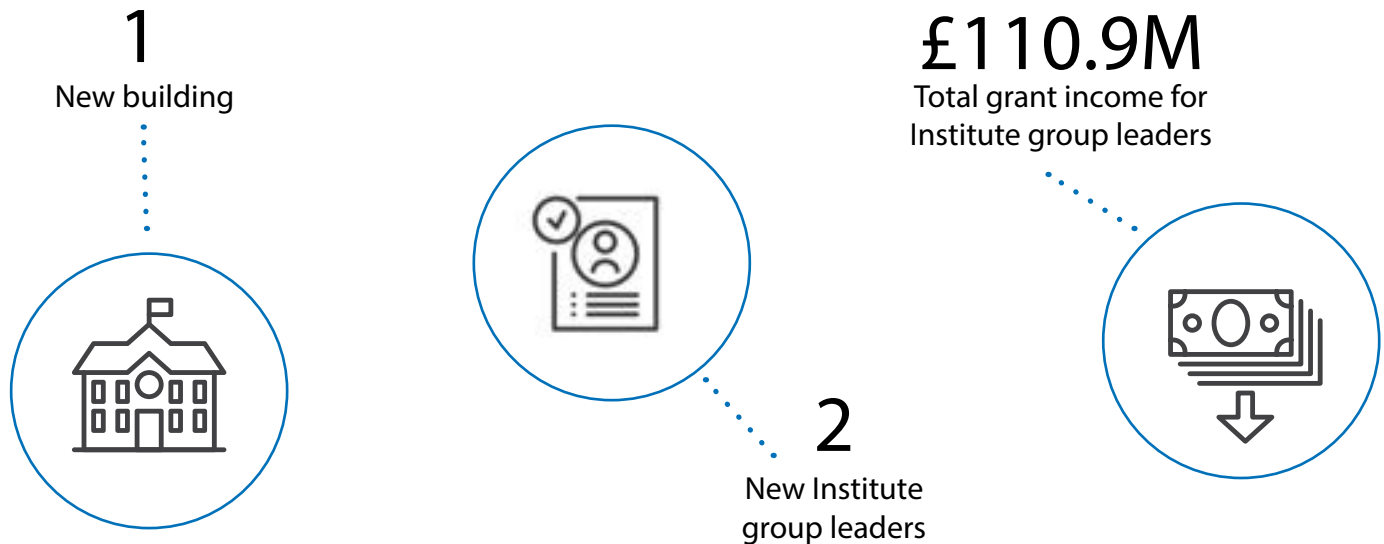
Institute members also have access to the NIHR Cambridge BRC Phenotyping Hub which is equipped with state-of-the-art equipment including high speed cell sorters, bench top analysers, microscopes and high content/high throughput equipment.



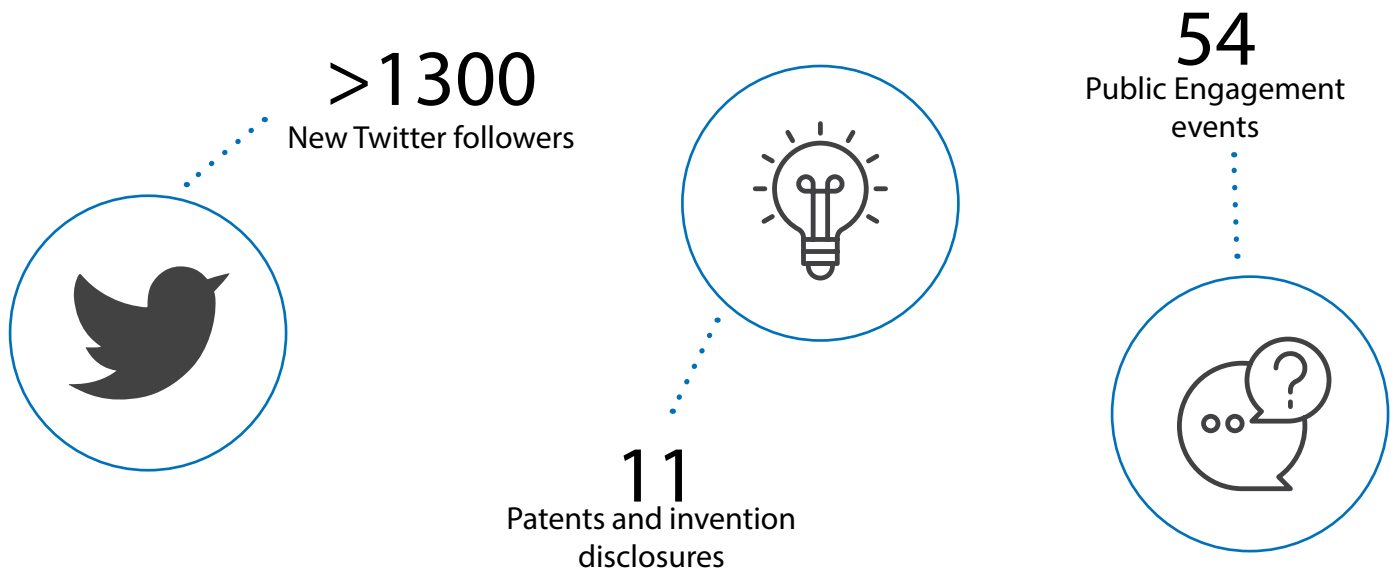
Nichols Lab

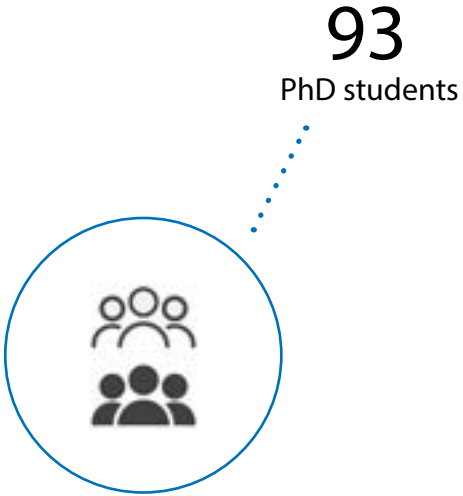
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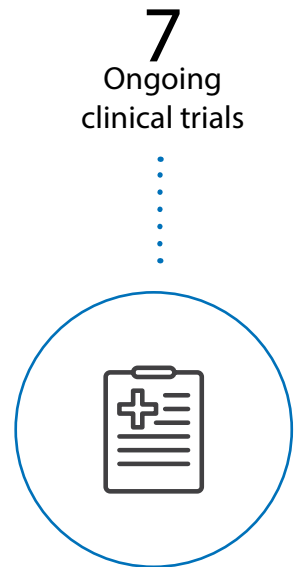
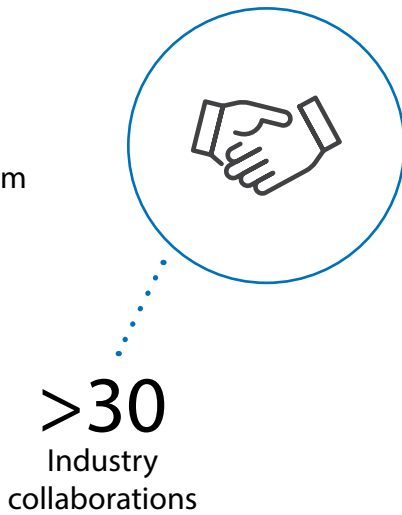
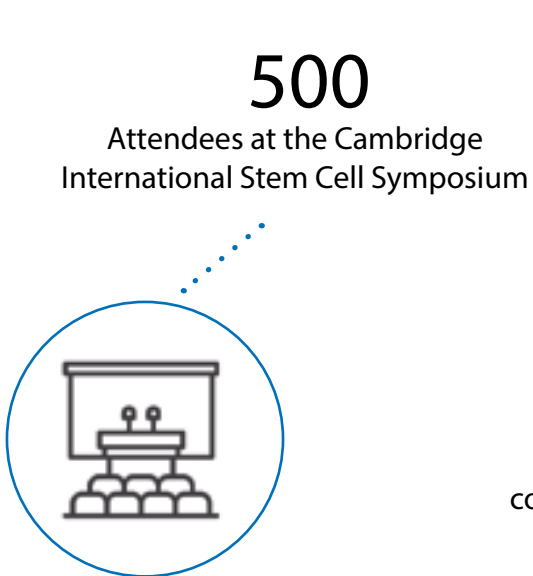


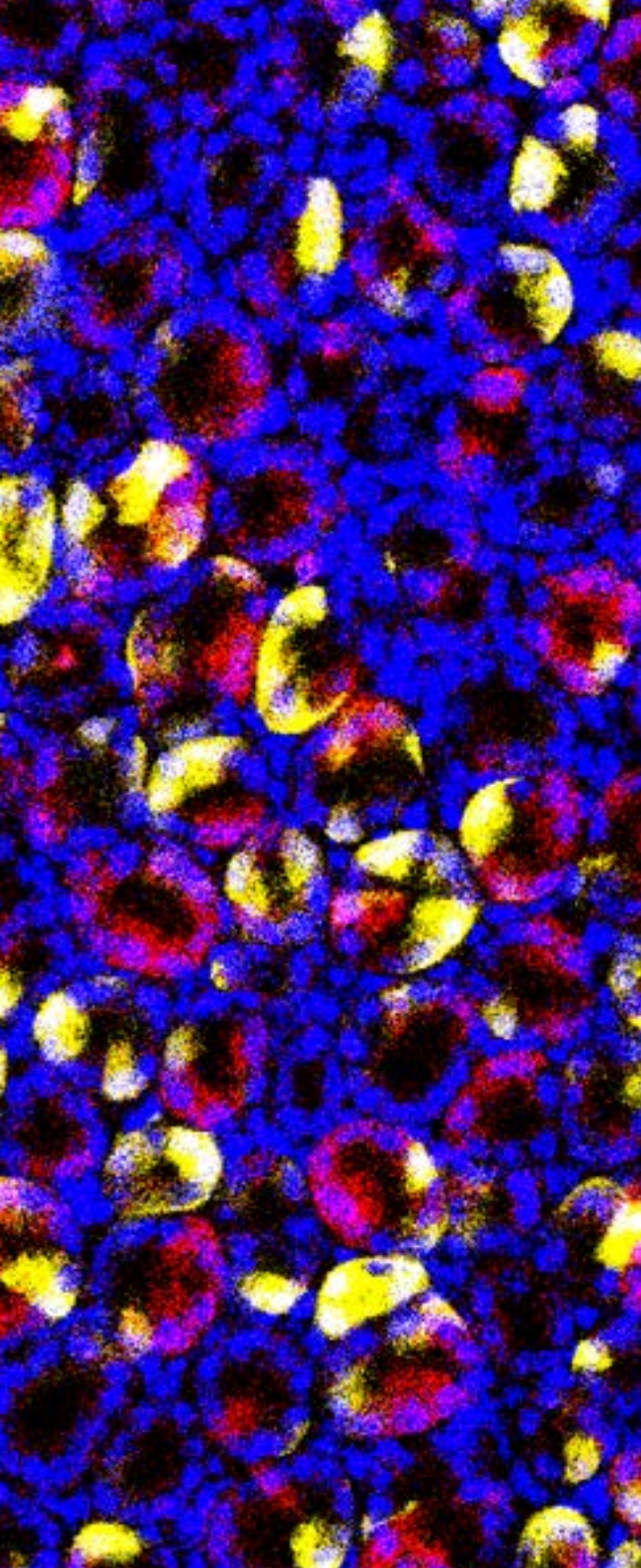
CAMBRIDGE STEM CELL INSTITUTE:





A YEAR IN NUMBERS





The Cambridge Stem Cell Institute continues to make excellent progress towards our 6 key goals:

Relocation to the Cambridge Biomedical Campus

Publication of transformative discoveries

Delivery of early phase clinical trials & diagnostics

Increased engagement with industry

Production of highly skilled stem cell scientists

Provision of an accessible voice on stem cell issues

Image credit: Lemonia Chatzeli

Relocation to the Cambridge Biomedical Campus

The Jeffrey Cheah Biomedical Centre will bring together biological, clinical and physical scientists, working on multiple tissues and at different scales, to advance the understanding of stem cell biology in health and disease.

In 2018 the Institute entered the final stages of preparation for the relocation to the Jeffrey Cheah Biomedical Centre on the Cambridge Biomedical Campus.

Following a short extension of the building completion date, the move is scheduled for Spring 2019. Working groups, chaired by group leaders and covering Biofacilities, Computing & Bioinformatics, Flow Cytometry, Imaging & Histology and Cell Culture, are finalising plans for the move.

On the Cambridge Biomedical Campus, we join a thriving community where the worlds of academia, industry and medicine come together to tackle some of the most significant healthcare challenges that face us today.

As part of the fastest-growing biomedical campus in Europe, we can ensure patients benefit from our pioneering research into health and disease: from neurodegenerative and cardiovascular, to cancer and ageing.



Publication of Transformative Discoveries

Institute researchers produced 171 publications in 2018, including 112 peer-reviewed primary research reports. Particular highlights are listed below, with a full list of 2018 Institute publications included on page 82.

Grinfeld J, Nangalia J, Baxter J ... Gerstung M, **Green A**, Campbell P. Classification and Personalized Prognosis in Myeloproliferative Neoplasms. **New England Journal of Medicine** 379, 1416-1430 (2018)

Bertero A, Brown S, Madrigal P ... Stunnerberg H, Mendjan A, **Vallier L**. The SMAD2/3 interactome reveals that TGF β controls m6A mRNA methylation in pluripotency. **Nature** 555, 255-259 (2018)

Abelson A, Collord G, Ng S ... Brennan P, **Vassiliou G**, Shlush L. Prediction of acute myeloid leukaemia risk in healthy individuals. **Nature** 559, 400-404 (2018)

Lee-Six H, Øbro N, Shepherd M ... **Green A**, **Kent D**, Campbell P. Population dynamics of normal human blood inferred from spontaneous somatic mutations. **Nature** 561, 472-478 (2018)

Lescroart F, Wang X, Lin X ... Kinston S, **Göttgens B**, Blanpain C. Defining the earliest step of cardiovascular lineage segregation by single cell RNA-seq. **Science** 358, 1177-1181 (2018)

Pilz G, Bottes S, Betizeau M ... **Simons B**, Helmchen F, Jessberger S. Live imaging of neurogenesis in the adult mouse hippocampus. **Science** 359, 658-662 (2018)

Gozdecka M, Meduri E, Mazan M ... Adams D, **Vassiliou G**, **Huntly B**. UTX-mediated enhancer and chromatin remodeling suppresses myeloid leukemogenesis through non-catalytic inverse regulation of ETS and GATA programs. **Nature Genetics** 50, 883-894 (2018)

Sousa E, Stuart H, Bates L ... **Nichols J**, Dietmann S, **Silva J**. Exit from Naive Pluripotency Induces a Transient X Chromosome Inactivation-like State in Males. **Cell Stem Cell** 22, 919-928 (2018)

Tomic G, Morrissey E, Kozar S ... Itzkovitz S, **Philpott A**, Winton DJ. Phospho-regulation of ATOH1 Is Required for Plasticity of Secretory Progenitors and Tissue Regeneration. **Cell Stem Cell** 23, 436-443 (2018)

Kitadate Y, Jorg D, Tokue M, ..., Takahashi S, **Simons B**, Yoshida S. Competition for mitogens regulates spermatogenic stem cell homeostasis in an open niche. **Cell Stem Cell** 24, 79-92 (2018)

Booth C, Barkas N, Neo W ... **Huntly B**, Jacobsen S, Mead A. Ezh2 and Runx1 Mutations Collaborate to Initiate Lympho-Myeloid Leukemia in Early Thymic Progenitors. **Cancer Cell** 33, 274-291 (2018)

Griveau A, Seano G, Shelton S ... Mehta S, Jain R, **Rowitch D**. A Glial Signature and Wnt7 Signaling Regulate Glioma-Vascular Interactions and Tumor Microenvironment. **Cancer Cell** 33, 874-889 (2018)

Rulands S, Lescroart F, Chabab S ... **Philpott A**, Blanpain C, **Simons B**. Universality of clone dynamics during tissue development. **Nature Physics** 14, 469-474 (2018)

Delivery of early phase clinical trials

Institute researchers are involved in a number of active clinical trials which show promise for the translation of stem cell research from bench to bedside.

Brian Huntly's dose escalation study to investigate the clinical activity of BET inhibitors in subjects with relapsed, refractory hematologic malignancies is ongoing, with primary completion date scheduled for 2020 (NCT01943851).

Simón Méndez-Ferrer's trial investigating the redeployment of tamoxifen to modulate the bone marrow niche and treat myeloproliferative neoplasms was extended in 2018 to follow up on response and durability (2015-005497-38).

Roger Barker's TRANSEURO open label transplant study in Parkinson's Disease trial treated its last patient in May 2018, with results on the primary end point expected in 2021 (NCT01898390).

David Rowitch concluded a five-year long term follow-up study of a neural stem cell therapy trial for Connatal Pelizaeus-Merzbacher Disease, with results currently submitted for publication (NCT01005004 / NCT01391637).

Andrew McCaskie is leading a trial to evaluate the efficacy of adipose derived mesenchymal stromal cells in patients with knee osteoarthritis (NCT02838069).

Roger Barker began a trial to study the effects of OXB-102 in patients with bilateral, idiopathic Parkinson's Disease, with primary completion date estimated for June 2022 (NCT03720418).

Robin Franklin continued the trial of Retinoid X receptor gamma agonists in multiple sclerosis patients to regulate the differentiation of central nervous system progenitors into remyelinating oligodendrocytes. The trial is due to report in 2019 (2014-003145-99).

Cédric Ghevaert designed the recovery and survival of stem cell originated red cells (RESTORE) trial, which is currently pending approval from the Health Research Authority.





During the last year, research at the Institute has demonstrated a number of potential new avenues for the development of future diagnostic, prognostic and therapeutic interventions.

David Rowitch continues to research sonic hedgehog (Shh) agonists for the development of oligodendrocytes to aid neuroprotection. New findings indicate that the Shh agonist is also highly effective in neuroprotection against neonatal stroke in a murine model, with data publication due in 2019.

Cédric Ghevaert and his team developed a clinical grade cell line that can produce megakaryocytes and platelets with high efficiency. The cell line and forward programming technology have been licensed to Platelet Biogenesis, with major funding now secured for a future clinical trial.

Tony Green and collaborators combined extensive genetic and clinical information from over 2000 patients with myeloproliferative neoplasms (MPNs) to generate a new method to make personally tailored disease predictions for individual patients suffering from MPNs.

The researchers showed this new method outperforms all current schemes available to make disease predictions, and will allow individualised treatment strategies for MPN patients to be developed.

Sanjay Sinha has shown that grafting stem cell-derived epicardial cells along with cardiomyocytes leads to much larger and more functional grafts when attempting to regenerate the damaged rat heart. This work will have major implications for optimising the composition of cell therapies that will be trialled in larger animal models and in patients with heart failure.

George Vassiliou and colleagues demonstrated the use of blood tests to predict acute myeloid leukaemia (AML) risk in healthy individuals. The research could allow earlier detection and monitoring of people at risk of AML, and gives new avenues for reducing the risk of developing this form of cancer.

Robin Franklin showed that a new combination of drugs could rejuvenate ageing brain stem cells, rendering them more efficient at regenerating myelin-forming oligodendrocytes. This approach is likely to have important therapeutic effects in the regenerative medicine of chronic demyelinating disease such as multiple sclerosis.

Increased engagement with industry

Institute members are actively engaged with industry and enterprise partners as reflected by licensing agreements, collaborative projects and start-up companies. The Institute currently has over 30 active commercial and industrial collaborations. In 2018, 4 patents and 7 invention disclosures were filed, across the fields of biophysics, cardiology, neurobiology, organoid development and haematopoiesis.

Kevin Chalut developed a new hydrogel protocol that allows the study of mechanical signalling in stem cells. The work shows that stem cells grown on soft substrates have increased self-renewal capacity compared to those grown on a stiff substrate.

A patent has been filed and commercial directions are being explored with Cambridge Enterprise and Stem Cell Technologies.

Ludovic Vallier and Fotis Sampaziotis, in collaboration with Kourosh Saeb-Parsy, have established a method for fabricating artificial common bile ducts using densified collagen tubes. This approach relies on biliary organoids being engineered into functioning bile ducts which could reduce the need for liver transplantation in diseases such as biliary atresia.

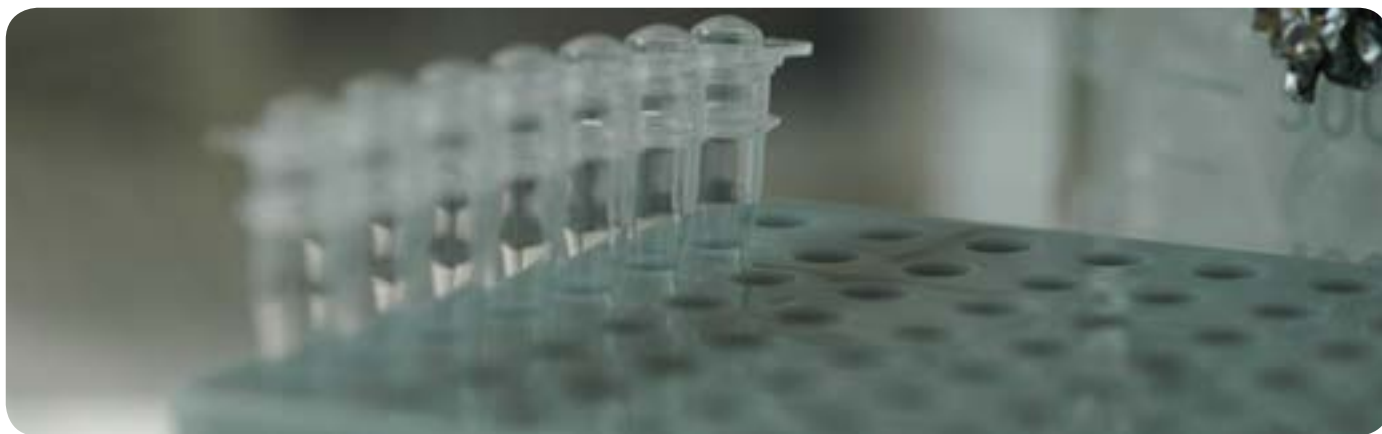
A patent has been filed and licensing options are currently explored with the newly created start-up company **Bilitech**.

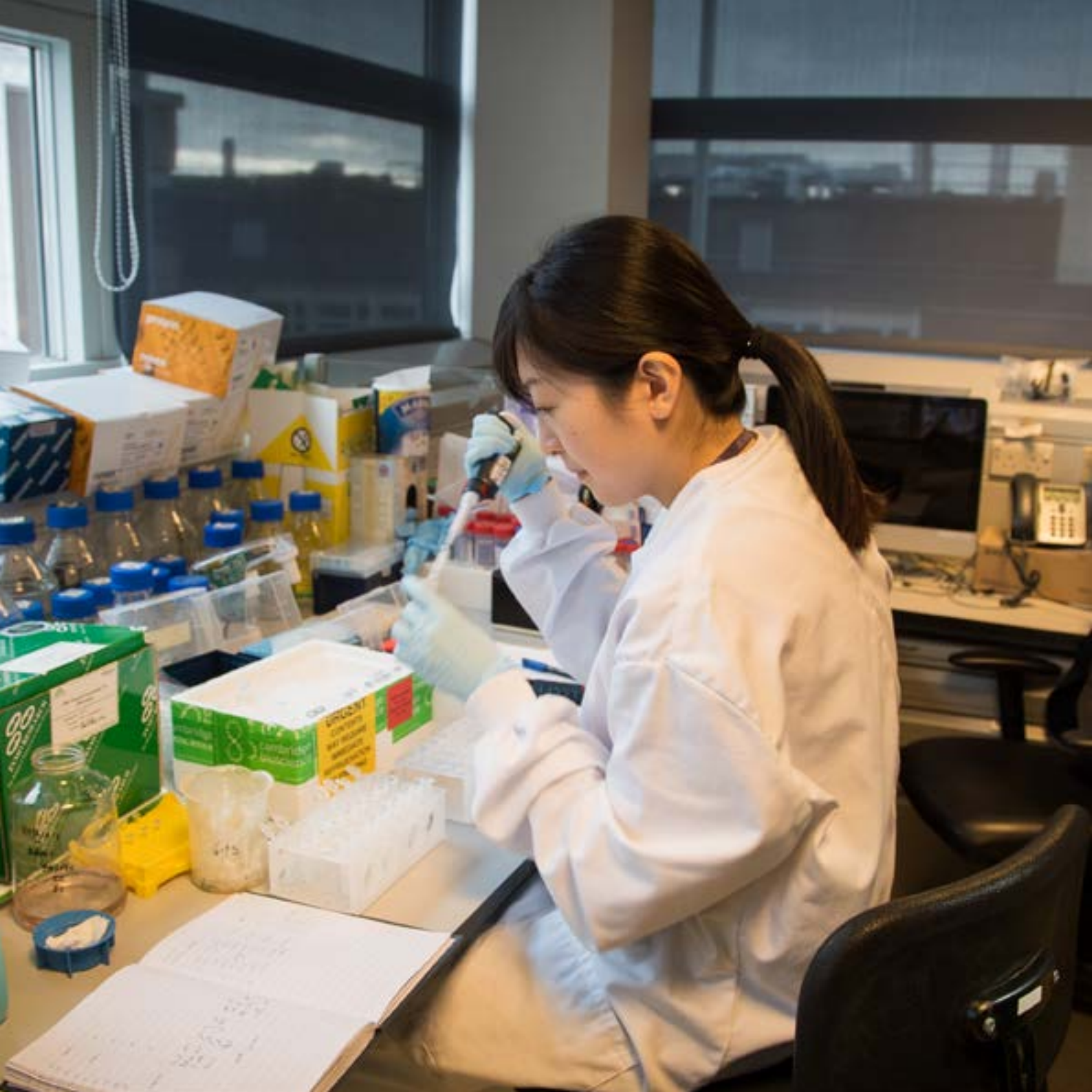
Robin Franklin established two new industrial projects with Biogen. The first explores the biology and therapeutic potential of aberrant splice variants of key oligodendrocyte differentiation transcription factors in ageing adult central nervous system progenitors.

The second project is developing magnetic resonance based imaging technologies to monitor adult central nervous system progenitor cell differentiation *in vivo*.

Bertie Göttgens has a new collaboration with AstraZeneca to characterise new models of acute myeloid leukaemia that provide access to the earliest stages of disease development. This work will have important implications for the identification of drug targets specifically targeted at leukaemia initiating cells.

Prof Göttgens also continues his collaboration with **Elisa Laurenti** and group leaders at GSK as part of the Cambridge–GSK alliance.





Production of skilled stem cell scientists

The Institute is committed to training the next generation of skilled and sought-after clinical and non-clinical stem cell scientists to strengthen the global academic and industrial community.

PhD Programmes

The 4-year Wellcome PhD Programme in 'Stem Cell Biology & Medicine' competitively recruited 4 new students from 181 applications in 2018. We also ran the 4-year MRC PhD Programme in 'The Physical Biology of Stem Cells'. These two programmes represent the heart of a vibrant PhD student community at the Institute, with a total of 67 students as of October 2018 and a further 26 students completing their studies last year. In 2018, the PhD students co-authored 42 publications, 18 as first author.

Each year the Institute runs a productive and enjoyable PhD Symposium and Away Day. In 2018, 13 PhD students presented their research projects and over 40 posters were on display from students based in Institute and affiliated research groups.

Clinician Scientists

The Institute currently hosts 13 clinically trained PhD students, 6 clinical lecturers and 7 clinically trained postdocs/fellows. 37% of group leader positions at the Institute are clinically based and facilitate collaborations between basic scientists and those driven by disease-focused questions.

Group Leader Recruitment in 2018

With the recruitment of Dr Simon Buczacki and Dr Srinjan Basu, we now have a hub of 29 research groups within the Institute, spanning a broad range of research areas. All group leaders are eligible to host PhD students, providing a vibrant and diverse training ground for the next generation of stem cell and clinician scientists. More details of all our group leaders and their research interests can be found on pages 22 – 81.



Accessible and authoritative voice

As a world-leading Institute, we are committed to providing an accessible and authoritative voice on a range of stem cell topics and issues.

Communications & Engagement

Researchers and the Institute communications team work together with Wellcome, the MRC and University press offices to ensure the best research from the Institute is successfully showcased via the press and on social media. The Institute Twitter account (@SCICambridge) saw a 60% increase in followers in 2018, with over 700K tweet impressions and 23K profile visits.

The Public Engagement team continue to deliver a diverse range of events and activities to ensure our scientists engage with a broad spectrum of public voices. These encounters serve to enhance the quality of the scientific questions we ask and help the public to build trust in stem cell research. In 2018, face-to-face public events allowed researchers to actively engage with over 4000 individuals, highlights of which can be found on page 20.



Representation & Impact

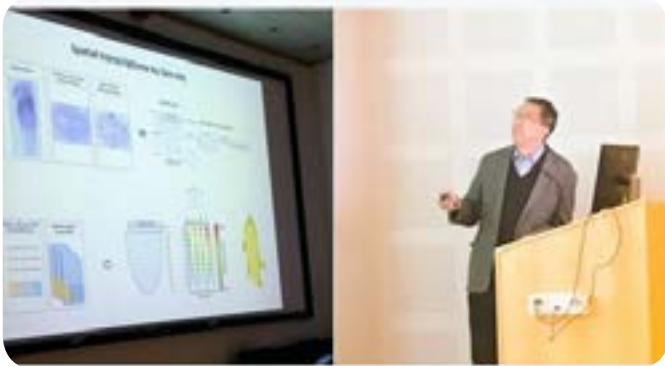
Institute members hold senior positions on a number of research society boards, research funding committees (including Bloodwise, Biotechnology and Biological Sciences Research Council & National Institute of Health Research) and journal editorial boards (including Blood, Development & Journal of Experimental Medicine).

The Institute engages with the University's Policy and Impact teams and is developing activities in these areas. For example, in 2018 Institute Group Leader Prof Ludovic Vallier presented oral evidence to the Royal College of Surgeons Commission into the Future of Surgery.



Seminars and Events

The Institute runs a range of interdisciplinary research events throughout the year to bring together the vibrant and wide-reaching stem cell community across Cambridge and beyond.



International Seminar Series

The Institute's International Seminar Series features world-leading scientists who are invited to present their work to all Institute researchers and affiliates. Seminar topic highlights in 2018 include: stem cell bioengineering (Peter Zandstra, University of Toronto); stem cells in cardiovascular disease (Christine Mummery, Leiden University); and modelling neural diseases with human pluripotent stem cells (Lorenz Studer, Memorial Sloan Kettering Cancer Center, New York), among many others.



Stem Cell Club

Increased effort was made in 2018 to promote this interdisciplinary seminar series to the wider stem cell community across Cambridge, with recorded attendees from Departments within the Schools of Humanities & Social Sciences, Biological Sciences, Physical Sciences, Clinical Medicine and Technology. With this widened participation, Stem Cell Club is delivering on its aim to spark new conversations on stem cell research between individuals from a range of backgrounds and disciplines.



Institute Annual Retreat

This popular event focusses on fostering an integrated, collaborative culture between all levels of the Cambridge Stem Cell Institute and affiliated researchers. The Retreat features talks from Institute and affiliate group leaders as well as flash talks and poster presentations from postdocs and PhD students. The evening social event allows all attendees to relax and interact over a glass of wine or 'Regenerator', the Institute beer developed as part of a public engagement project with Moonshine Brewery.

Cambridge International Stem Cell Symposium

The Institute organised the Cambridge International Stem Cell Symposium in 2018, which brought together members of the global stem cell community for three days of talks, poster sessions and industry presentations. The event attracted over 500 attendees, including members of the publishing and biotech industries, alongside academic delegates.

The programme included a range of research presentations across a broad spectrum of topics, including: the fundamental biology of stem cell development; the physical role of the stem cell environment in brain ageing; the use of stem cells in the production of platelets for human transfusion; and a number of presentations examining the future applications of stem cell research for therapeutic intervention in disease.

Delegates also had time to socialise during the Symposium dinner held at Trinity College. Students, Post-docs and Group Leaders shared research stories as well as email addresses as new collaborations and research partnerships formed.



Public Engagement

In 2018, the Institute coordinated 54 face-to-face public engagement events, reaching over 4,000 individuals. Through a range of digital content, including films, podcasts and social media posts, a further 14,000 have been engaged online.



Ely Beer Festival, January

Scientists shared their research stories over a pint of Regenerator – the Institute ale designed to engage ‘harder to reach’ adults with stem cell science.



Science at the Women’s Institute, February

PhD student Jennifer Jia collaborated with ‘Neural Knitworks’ to actively engage members of the Women’s Institute through a scientific talk and knitting neurons!

Engaging patients and the public with



Infinite Potentials, June

In collaboration with the SciArt Center (New York) and artists from around the world, the Institute delivered ‘Infinite Potentials’, an art exhibition exploring the future potential of stem cells.



Corpus Public Art, July

Scottish team Matthew Dalziel and Louise Scullion were commissioned to produce ‘Corpus’, a large structural artwork to be displayed outside the Jeffrey Cheah Biomedical Centre.

The Public Engagement team have developed a new engagement strategy that focusses on the next 3 years and covers the start of life in the Jeffrey Cheah Biomedical Centre. The new strategy builds on opportunities to engage with new local audiences, including patient and carer groups, while also developing reach to national and international audiences.



Story Collider, March

In partnership with Cambridge Junction, the Institute organised The Story Collider, a hit international storytelling show, combining personal anecdotes and research stories.



Online Blood Films, April

Cédric Ghevaert and colleagues worked with patient groups to develop a series of Q&A videos addressing questions on lab grown blood cells. The videos have had over 6000 views online.

stem cell research throughout 2018

European Researchers Night, September

Institute members travelled to Peterborough to take part in European Researchers Night as part of a range of events across 27 countries to engage the public with scientific research projects.



Stem Cell Film Screening, November

Coordinated by renowned artist Harold Offeh, researchers worked with film makers to produce a series of short films to give an artistic interpretation of the science being undertaken at the Jeffrey Cheah Biomedical Centre.



Principal Investigators



Maria Alcolea
Epithelial cell fate & plasticity



Roger Barker
Parkinson's & Huntington's disease



Srinjan Basu
Single-cell and single-molecule imaging



Simon Buczacki
Colorectal cancer cell identity & tumour evolution



Kevin Chalut
Physical biology of pluripotency & differentiation



Brian Hendrich
Transcriptional control of stem cell fate



Daniel Hodson
Mutation timing in lymphomagenesis



Brian Huntly
Leukaemia stem cell biology & leukaemogenesis



Thóra Káradóttir
Neurotransmitter signalling to CNS progenitor cells



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



Anna Philpott
Proneural transcription factors



Ingo Ringshausen
Haematopoietic stem cells & malignancies



David Rowitch
Glial cells & response to injury



José Silva
Biology of induced pluripotency



Ben Simons
Stem cell fate in development, maintenance & disease



Ana Cvejic
Haematopoietic
stem cells



Robin Franklin
Adult neural
stem cells & CNS
regeneration



Cédric Ghevaert
In vitro production of
platelets for
transfusion



Bertie Göttgens
Decision making in
haematopoietic
stem cells



Tony Green
Haematopoiesis



Elisa Laurenti
Human haematopoietic
stem cells biology in
health & disease



Joo-Hyeon Lee
Stem cells
& niches



Andrew McCaskie
Regenerative
therapies for bone
& cartilage repair



Simón Méndez-Ferrer
Blood stem cell
niches



Jennifer Nichols
Embryonic
pluripotency



Sanjay Sinha
Vascular diseases



Austin Smith
Stem cell potency



Ludovic Vallier
Differentiation of
pluripotent stem cells
into definitive endoderm



George Vassiliou
Leukaemic
haemopoietic
stem cells

MARIA ALCOLEA



LAB MEMBERS

Maria Bejar Serrano
Adrien Hallou
Paula Jimenez-Gomez
Jamie McGinn
Greta Skrupskelyte

Epithelial cell fate and plasticity

Our research focusses on studying the behaviour of progenitor cells in the mouse oesophagus as a model to unveil the basic rules underlying squamous epithelial cell fate. Our work in the field has revealed how this tissue is maintained under homeostatic conditions, and how these rules switch upon injury.

More recently we 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, constitutes the basis of our ongoing research programme.

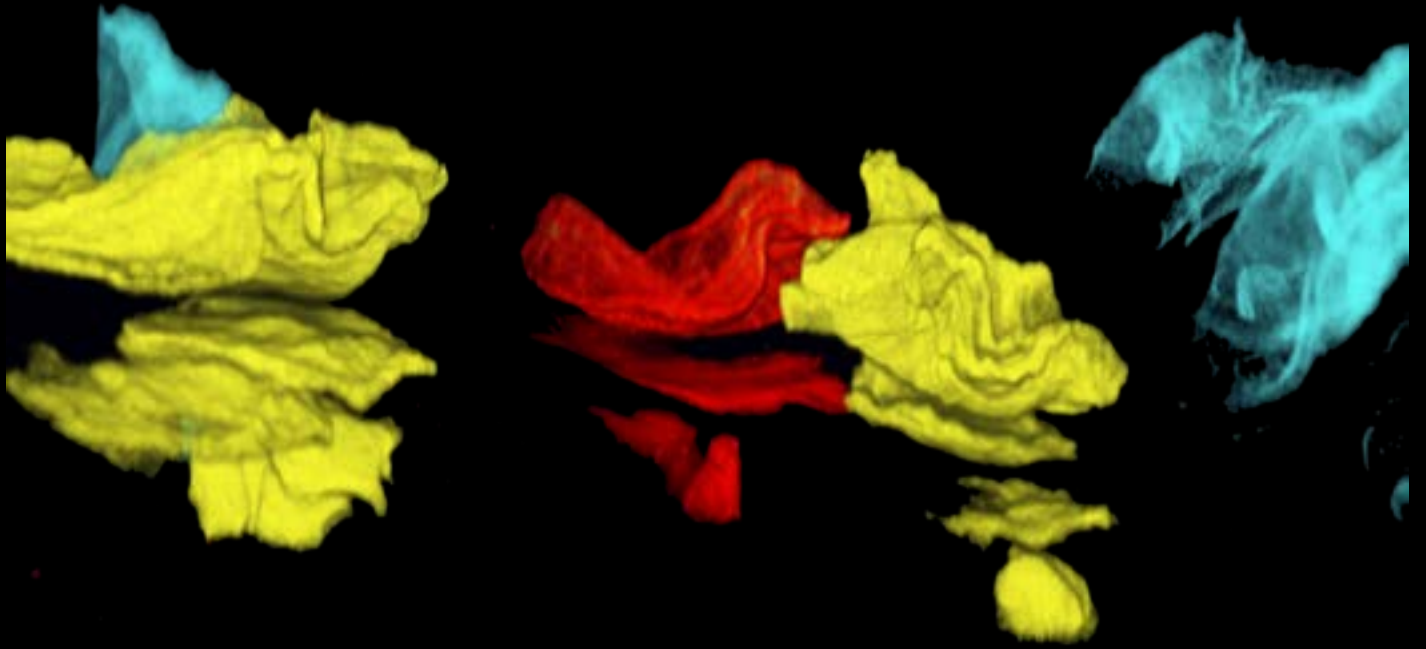
To answer these questions, we will make use of a combination of *in vivo* lineage tracing techniques, transcriptional network analysis, as well as 3D organoid and explant culture systems.

KEY PUBLICATIONS

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

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

Doupe DP1, **Alcolea MP**, Roshan A, Zhang G, Klein AM, Simons BD, Jones PH. A single progenitor population switches behavior to maintain and repair esophageal epithelium. **Science**. 2012 Aug 31;337(6098):1091-3.



Multicolour genetic marking of oesophageal stem cells allows to track behavior at single cell resolution.

Credit: Jamie McGinn

ROGER BARKER



LAB MEMBERS

Nina Antouli
 Marta Camacho Goncalves
 Danielle Daft
 Mercy Danga
 Xiaoling He
 Wei-Li Kuan
 Sarah Mason
 Tom Stoker
 Pam Tyers
 Lindsey Wilkin
 Caroline Williams-Gray
 Shamma Qarin
 Katie Andresen
 Laura Sherlock
 Alice White
 Kate Harris
 Molly O'Reilly
 Venkat Pisupati
 Shaline Fazal

Parkinson's and Huntington's disease

Our main interests revolve around two relatively common, chronic neurodegenerative disorders of the nervous system - 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.

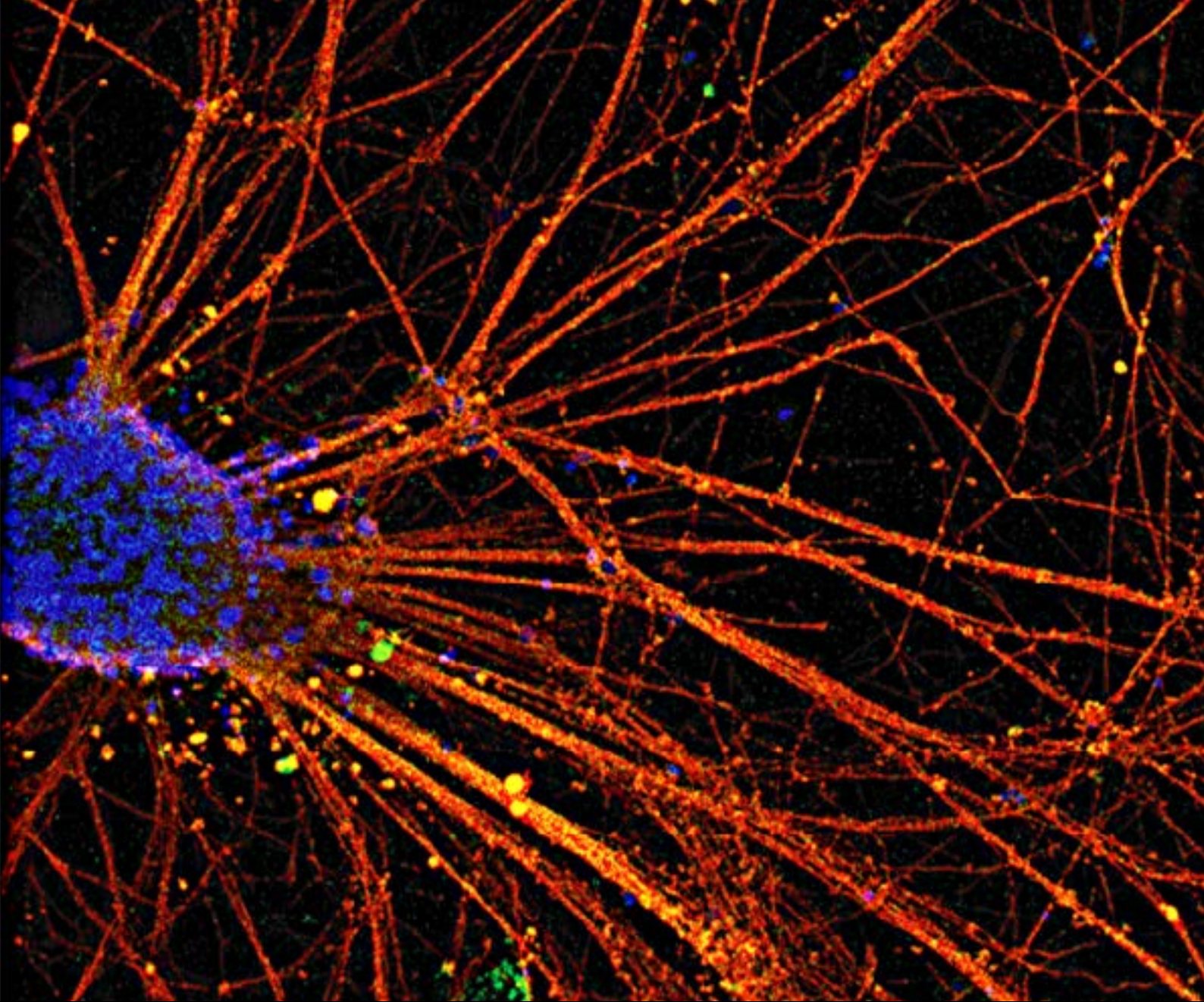
In addition, this ability to stratify patients also enables us to undertake studies looking at how these disease subtypes may arise using cells grown from the patients themselves. Typically we harvest these cells from the skin and then turn them into nerve cells in the lab, and by so doing we hope that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

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.

Barker RA, Götz M, Parmar M. New approaches for brain repair-from rescue to reprogramming. **Nature**. 2018 May;557(7705):329-334.

Barker RA, Mason SL, Harrower TP, ..., Pickard JD, Rosser AE, Dunnett SB; the NEST-UK collaboration (2013). The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. **Journal of Neurology, Neurosurgery & Psychiatry**. 2013 Jun;84(6):657-65.



Dopaminergic neurons differentiated from human pluripotent stem cells using GMP compliant differentiation protocol—TH (green), btub (red)

Credit: Civia Chen

SRINJAN
BASU

Single-cell and single-molecule imaging approaches in stem cell biology



LAB MEMBERS

Igor de Almeida

Our research focuses on developing single-cell and single-molecule imaging approaches to improve understanding of stem cell renewal and differentiation.

In particular, we are interested in how chromatin binding proteins regulate genome architecture and gene expression during stem cell fate transitions and why they are often misregulated during early cancer progression. Single-cell approaches are key to understand how these proteins work due to the considerable cell heterogeneity that occurs during stem cell fate transitions.

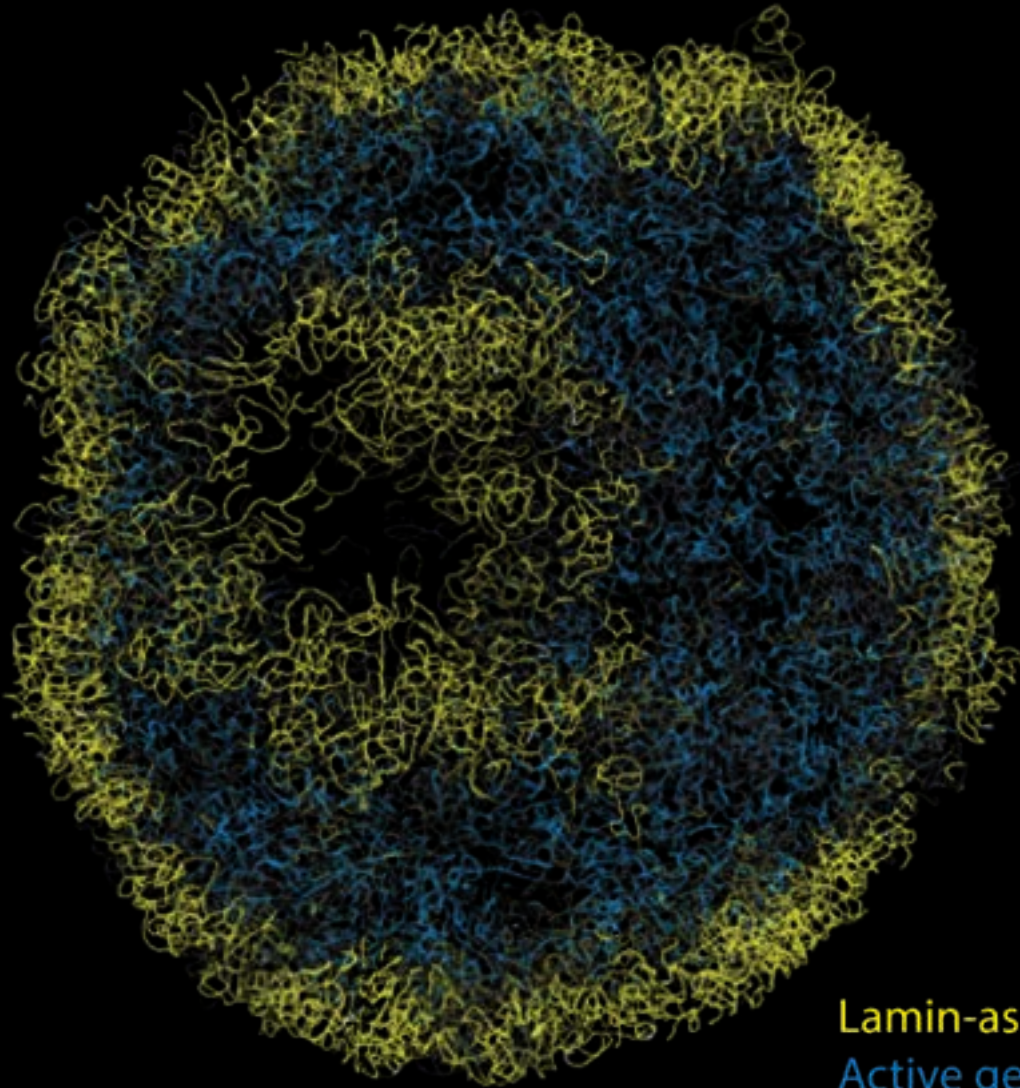
In recent years, we have developed several biophysical and computational approaches to answer these questions. For example, we have established a method combining imaging and single-cell Hi-C to study genome architecture inside individual embryonic stem cells. To understand how proteins interact with each other and with chromatin, we have set up several *in vitro* and live-cell single-molecule imaging approaches capable of localising single proteins at <15 nm resolution.

KEY PUBLICATIONS

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Lando D, **Basu S**, Stevens TJ, Riddell A... Lee SF, Hendrich B, Klenerman D, Laue ED (2017). Combining fluorescence imaging with Hi-C to study 3D genome architecture of the same single cell. **Nature Protocols**. 2018 May;13(5):1034-1061.



Lamin-associated
Active genes

Genome architecture of a single mouse embryonic stem cell with gene-poor lamin regions in yellow separating away from active genes in blue

Credit: Tim Stevens, MRC-LMB

SIMON BUCZACKI



LAB MEMBERS
Chrysa Koukorava

Colorectal cancer cell identity and tumour evolution

We are interested primarily in the role sub-clonal interactions play in colorectal cancer cell identity and behaviour. We believe that the behaviour of normal intestinal cells is often analogous to that seen in oncogenically transformed cells. We therefore also study the behaviour of progenitor and differentiated cells from normal intestinal tissues to provide insights into cancer cell behaviour.

We are particularly interested in understanding the mechanisms and links behind cancer cell plasticity and identity switching. We use genetic manipulation of patient derived organoids to understand the role of competitive and co-operative interactions in tumour evolution and cellular identity.

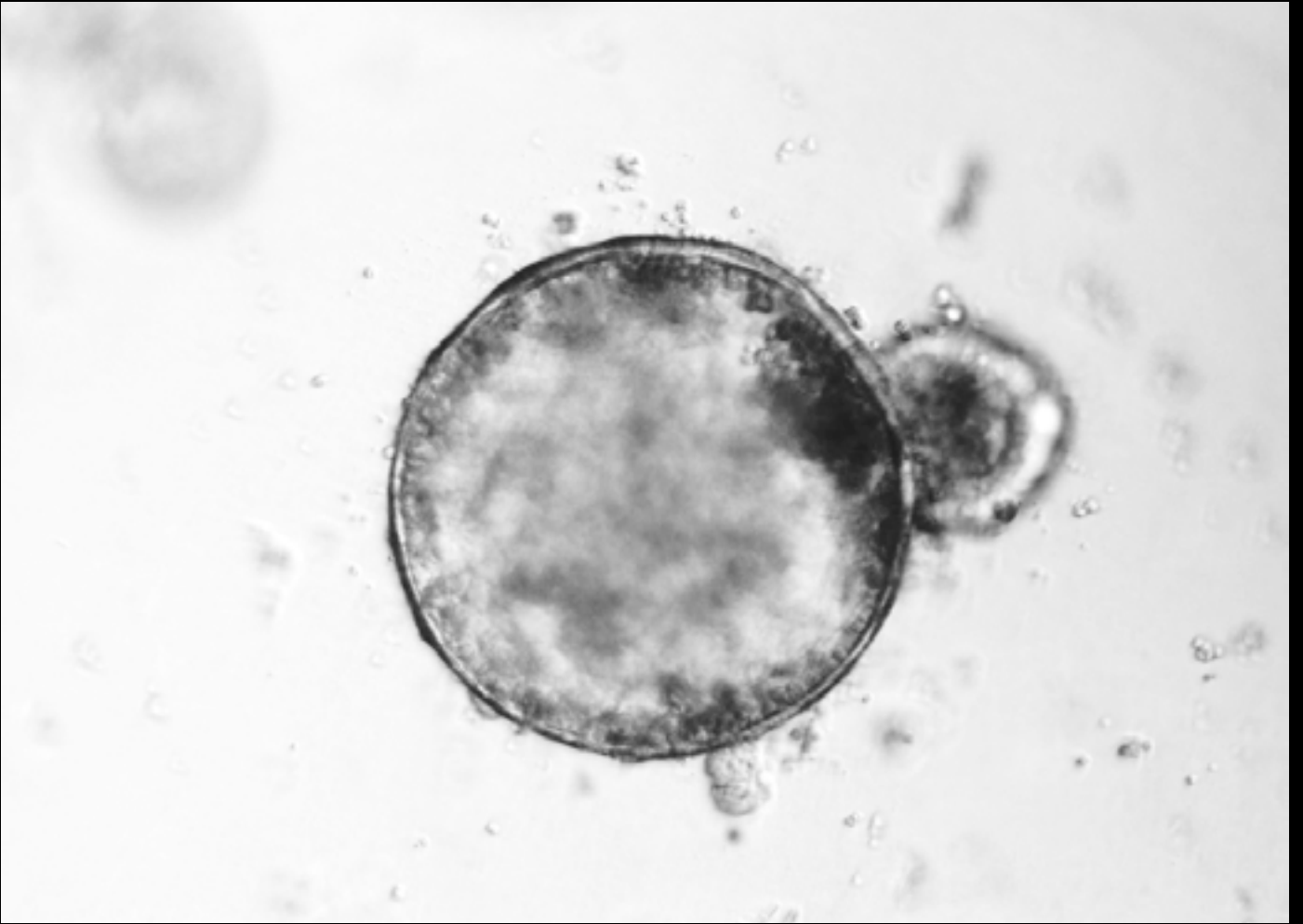
The lab is also committed to understanding the fundamental biology of small intestinal neuro-endocrine tumours through organoid biology and mouse modelling.

KEY PUBLICATIONS

Buczacki SJA, Popova S, Biggs E, Koukorava C, Buzzelli J, Vermeulen L, Hazelwood L, Francies H, Garnett MJ and Winton DJ. Itraconazole targets cell-cycle heterogeneity in colorectal cancer. **The Journal of Experimental Medicine**. 2018. Jul 2;215(7): 1891-1912.

Vermeulen L, Morrissey E, van der Heijden M, Nicholson AM, Sottoriva A, **Buczacki S**, Kemp R, Tavare S, Winton DJ. Defining stem cell dynamics in models of intestinal tumor initiation. **Science**. 2013; 342(6161): 995-998 .

Buczacki SJA, Ireland Zecchini H, Nicholson AM, Russell R, Vermeulen L, Kemp R, Winton DJ. Intestinal label-retaining cells are secretory precursors expressing Lgr5. **Nature**. 2013. Mar 7;495(7439):65-9.



Intestinal tumour organoid growing in three dimensions.

Credit: Simon Buczacki

KEVIN CHALUT

The physical biology of pluripotency and differentiation



LAB MEMBERS

James Baye
Elena Corujo-Simon
Mehdi Hamouda
Andrew Hodgson
Celine Labouesse
Sarah Pallett
Carla Mulas
Bao Xiu Tan
Ayaka Yanagida

The transformation of a stem cell into a mature tissue cell consists of a progression of highly regulated steps, which 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 embryonic stem cell differentiation and in embryonic development by utilising tools and concepts of physics and bioengineering alongside molecular biology.

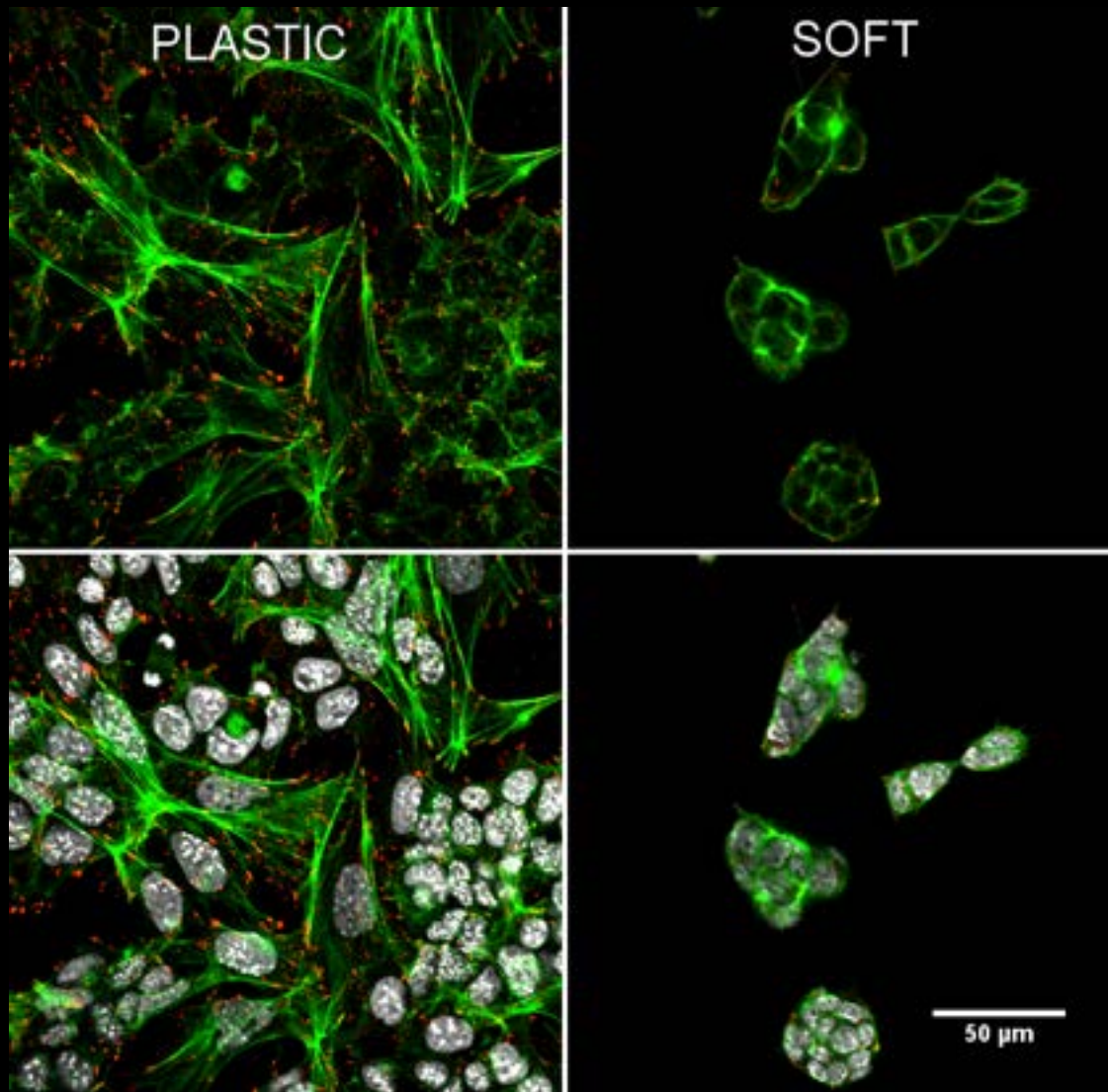
The biophysical aspects we focus on include cell mechanics and matrix signalling, as well as how nuclear mechanics influence gene expression and transport of signalling molecules through nuclear pore complexes. We are also developing single cell microfluidic techniques to study transitions between states in embryonic stem cell differentiation.

KEY PUBLICATIONS

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Revell C, Blumenfeld R. & **Chalut KJ**. Force-based three-dimensional model predicts mechanical drivers of cell sorting. **Proceedings of the Royal Society B: Biological Sciences**. 2019, 286. <http://doi.org/10.1098/rspb.2018.2495>.

Pagliara S, Franze K, McClain C, Wylde G, Fisher C, Franklin R, Kabla A, Keyser U, **Chalut KJ**. Auxetic nuclei in embryonic stem cells exiting pluripotency. **Nature Materials**. 2014, 13, 638-644.



Soft StemBond hydrogels allow recapitulating the morphology of naive pluripotency state in which cells grow as round colonies instead of spreading out as on plastic. White: nucleus, green: actin, red: focal adhesions.

Credit: Chibeza Agley



LAB MEMBERS

Brynelle Myers
Paulina Strzelecka
Anna Maria Ranzoni
Andrea Tangherloni

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 haematopoietic stem and progenitor cells (HSPCs) differentiate into diverse cell types is important to understand how this process is subverted in the generation of blood pathologies.

The aim of our group is to decipher how differentiation pathways of HSPCs are influenced by different microenvironments. To achieve that we use state-of-the-art single-cell RNA-seq data generation combined with computational analysis to establish principles of blood lineage differentiation. In particular, we are focusing on the dissection of the heterogeneity of cellular states in the blood system. Our research involves the use of both human samples and model organism (zebrafish, *Danio rerio*). Currently we focus our research on human foetal haematopoietic cells to reveal the dynamics and cellular programmes active during human blood development. We have also performed extensive analysis of lung cancer patient samples to investigate the influence of tumour microenvironment in the context of pathological differentiation of myeloid progenitors.

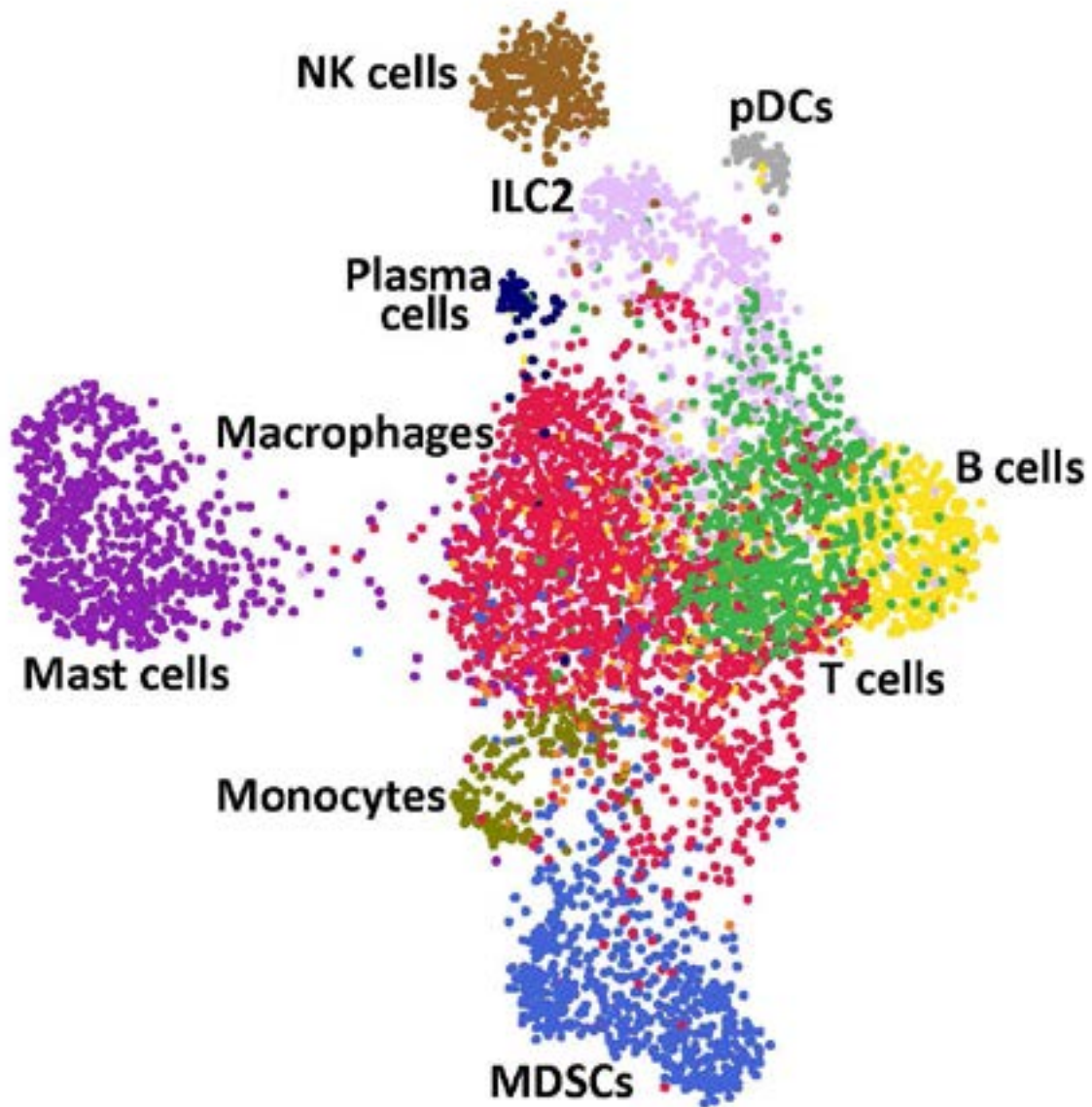
The results from our studies will advance our understanding of how normal fate decisions are instigated and provide clues for the design of novel therapies for blood pathologies.

KEY PUBLICATIONS

Hernández PP, Strzelecka PM, Athanasiadis EI, Hall D, Robalo AF, Collins CM, Boudinot P, Levraud JP, **Cvejic A**. Single-cell transcriptional analysis reveals ILC-like cells in zebrafish. **Science Immunology**. 2018 Nov 16;3(29).

Athanasiadis EI, Botthof JG, Andres H, Ferreira L, Lio P, **Cvejic A**. Single-cell RNA-sequencing uncovers transcriptional states and fate decisions in haematopoiesis. **Nature Communications**. 2017 Dec 11;8(1):2045.

Macaulay IC, Svensson V, Labalette C, Ferreira L, Hamey F, Voet T, Teichmann SA, **Cvejic A**. Single-Cell RNA-Sequencing Reveals a Continuous Spectrum of Differentiation in Hematopoietic Cells. **Cell Reports**. 2016 Feb 2;14(4):966-977.



Uniform Manifold Approximation and Projection (UMAP) plot of CD45+Lin- and Lin-CD33+HLA-DR-/low cells from lung adenocarcinoma.

Credit: Andrea Tangherloni & Paulina Strzelecka

ROBIN FRANKLIN

Adult neural stem cells and CNS regeneration



Our research investigates 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.

LAB MEMBERS

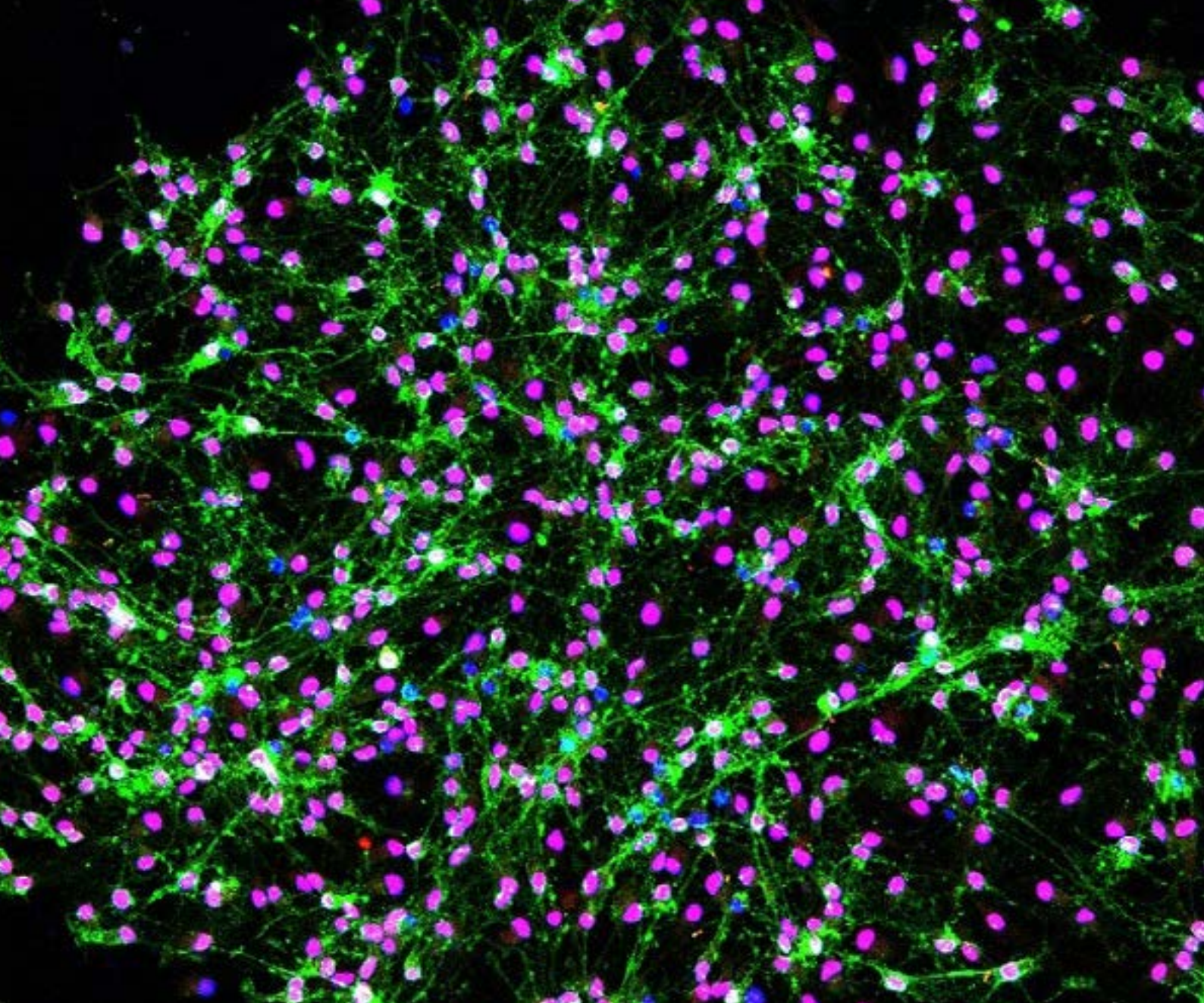
Nejma Belaadi
 Juan Cubillos
 Sarah Foerster
 Tanay Ghosh
 Ginez Gonzalez
 Myfanwy Hill
 Alisa Molotova
 Bjoern Neumann
 Feride Oeztuerk-Winder
 Khalil Rawji
 Michael Segel
 Amar Sharma
 Adam Young
 Chao Zhao

KEY PUBLICATIONS

Ulanska-Poutanen J, Mieczkowski J, Zhao C, Konarzewska K, Kaza B, Pohl HBF, Bugajski L, Kaminska B, **Franklin RJM**, Zawadzka M. Injury-induced perivascular niche supports alternative differentiation of adult CNS progenitor cells. **eLife**. 2018;7:e30325.

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de la Fuente AG, Errea O, van Wijngaarden P, ..., Huang JK, ffrench-Constant C, **Franklin RJ**. Vitamin D receptor - retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation. **Journal of Cell Biology**. 2015 Dec 7;211(5):975-85.



Central nervous system progenitor cells isolated from the aged adult rodent brain.

Credit: Bjoern Neumann

CÉDRIC GHEVAERT

In vitro production of platelets for transfusion



LAB MEMBERS

Jose Ballestran
Amanda Evans
Holly Foster
Nina Herbert
Daniel Howard
Amanda Niven
Amie Waller
James Warland
Souradip Mookerjee

The main focus of our research is the production of blood cells for human use, namely red cells and platelets. We have developed 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.

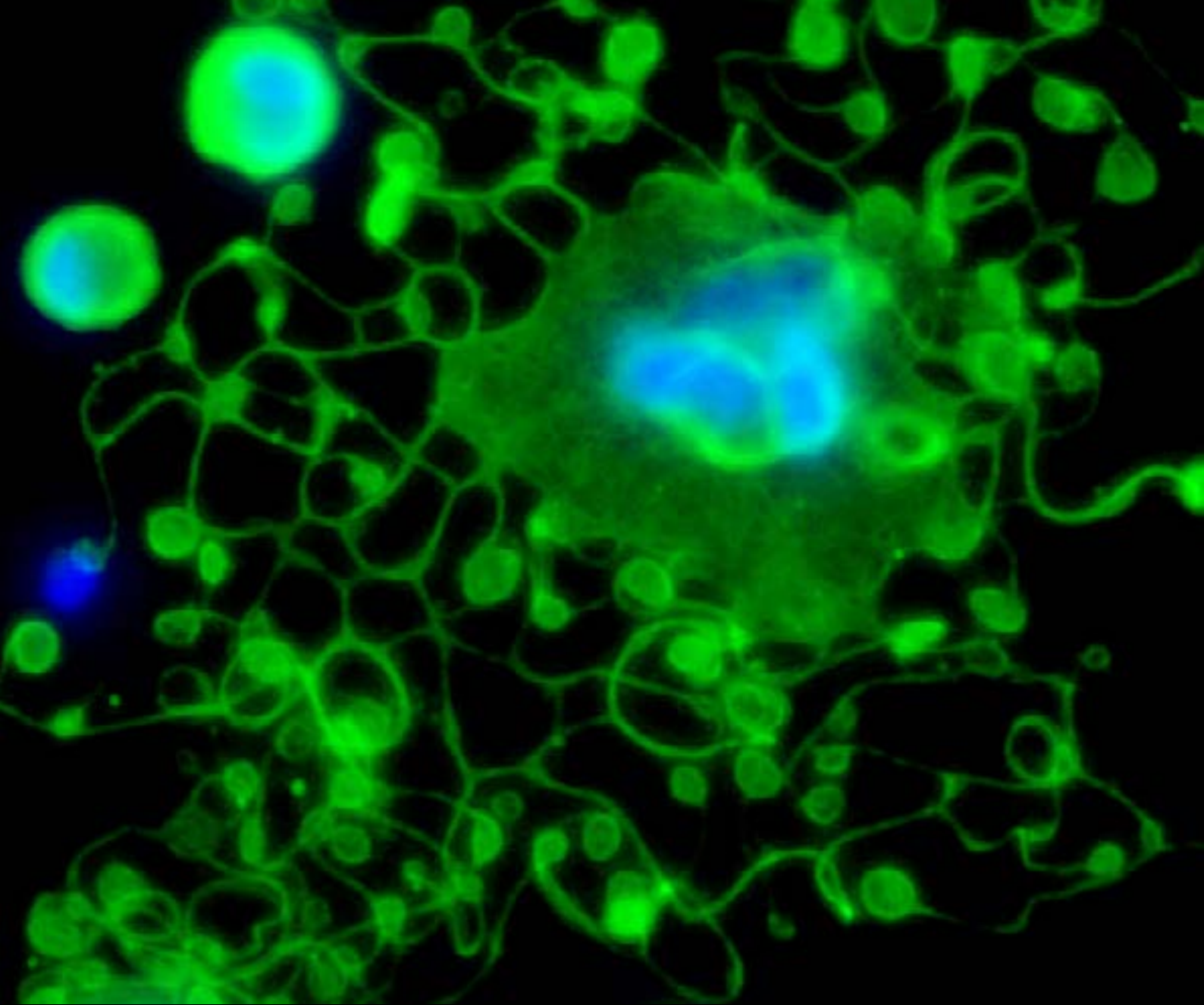
Our expertise is recognised world-wide in carrying out first-in-man studies of blood cell survival and recovery in human volunteers. The RESTORE trial, which is looking at recovery and survival of manufactured red cells in healthy volunteers, is due to start in 2019.

KEY PUBLICATIONS

Dalby A, Ballester-Beltrán J, Lincetto C, Mueller A, Foad N, Evans A, Baye J, Turro E, Moreau T, Tijssen MR, **Ghevaert C**. Transcription Factor Levels after Forward Programming of Human Pluripotent Stem Cells with GATA1, FLI1, and TAL1 Determine Megakaryocyte versus Erythroid Cell Fate Decision. **Stem Cell Reports**. 2018; 11(6):1462-1478.

Shepherd JH, Howard D, Waller AK, Foster HR, Mueller A, Moreau T, ... **Ghevaert C**, Best S, Cameron R. Structurally graduated collagen scaffolds applied to the ex vivo generation of platelets from human pluripotent stem cell-derived megakaryocytes: Enhancing production and purity. **Biomaterials**. 2018;182:135-44.

Moreau T, Evans AL, Vasquez L, Tijssen MR, Yan Y, Trotter MW, ... **Ghevaert C**. Large-scale production of megakaryocytes from human pluripotent stem cells by chemically defined forward programming. **Nature Communications**. 2016;7:11208.



Fluorescent image of a megakaryocyte produced in the laboratory from stem cells isolated from cord blood. The megakaryocyte is in the process of releasing platelets, the little blood corpuscle that is responsible for blood clotting. The nucleus of the cell is stained in blue with DAPI. In green is one of the main components of the skeleton of the cell (tubulin) that drives the production of platelets.

Credit: Maria Colzani

BERTIE GÖTTGENS

Cellular decision making in normal and leukaemic blood stem cells



We use 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.

Our current research focuses on (i) single cell genomics of early blood development, (ii) modelling 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.

LAB MEMBERS

Melania Barile
Fernando Calero Nieto
Carolina Guibentif
Fiona Hamey
Rebecca Hannah
Ivan Imaz-Rosshandler
Alison Kennedy
Sarah Kinston
Iwo Kucinski
Sonia Shaw
Blanca Pijuan Sala
Sam Watcham
Xiaonan Wang
Nicola Wilson

KEY PUBLICATIONS

Pijuan-Sala P, Griffiths JA, Guibentif C, Hiscock TW, Jawaid W, Calero-Nieto FJ, Mulas C, Ibarra-Soria X, Tyser RCV, Ho DLL, Reik W, Srinivas S, Simons BD, Nichols J, Marioni JC, **Göttgens B**. A single-cell molecular map of mouse gastrulation and early organogenesis. **Nature**. 2019 Feb;566(7745):490-495.

Lescroart F, Wang X, Lin X, Swedlund B, Gargouri S, Sánchez-Dànes A, Moignard V, Dubois C, Paulissen C, Kinston S, **Göttgens B**, Blanpain C. Defining the earliest step of cardiovascular lineage segregation by single-cell RNA-seq. **Science**. 2018 Mar 9;359(6380):1177-118.

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.



Molecular Map: each dot represents a single cell in the developing embryo. The dots are coloured based on which major cell type they represent.

Credit: Blanca Pijuan-Sala

TONY
GREEN

Haematopoiesis and myeloid malignancies



LAB MEMBERS

Juliet Aungier
Hugo Bastos
Jeremy Deuel
Tina Hamilton
Thorsten Klampfl
Juan Li
Stephen Loughran
Hyun Jung Park
Dean Pask
Daniel Prins
Rachel Sneade
Michelle Wantoch
Matthew Williams

Our lab focuses on the mechanisms whereby blood stem cells are subverted during the development of haematological malignancies, with particular focus on JAK/STAT signalling, which is dysregulated in many cancers and plays a key role in multiple stem cell systems.

In particular, we explore the molecular and cellular pathogenesis of a group of pre-leukaemic disorders, the myeloproliferative neoplasms (MPNs), in studies which span basic, translational and clinical research. The MPNs harbour mutations that activate the JAK/STAT pathway, are experimentally tractable and provide a paradigm for the earliest stages of tumorigenesis.

In work which transformed MPN diagnosis and catalysed development of therapeutic JAK-family kinase inhibitors, we and others identified phenotypic driver mutations in JAK2 or CALR which activate the JAK/STAT pathway and are present in most MPN patients. We are employing a variety of genomic approaches to explore MPN biology and improve patient management. In parallel, we are investigating the functional consequences of JAK2 and CALR mutations in work which has led to unexpected insights into cancer biology, human haematopoiesis and cytokine signalling.

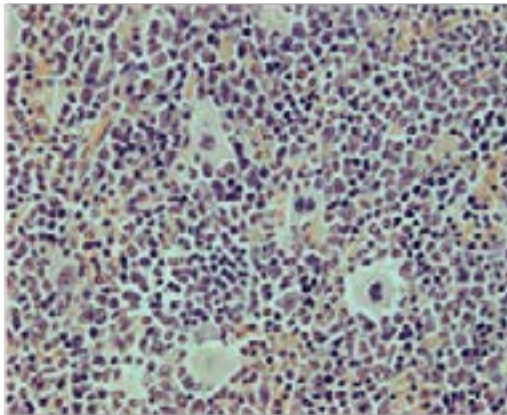
KEY PUBLICATIONS

Grinfeld J, Nanglia J, Baxter EJ, ..., Gerstung M, **Green AR**, Campbell PJ. (2018). Disease heterogeneity and personalized prognosis in myeloproliferative neoplasms. **New England Journal of Medicine**. 2018;379:1416-30.

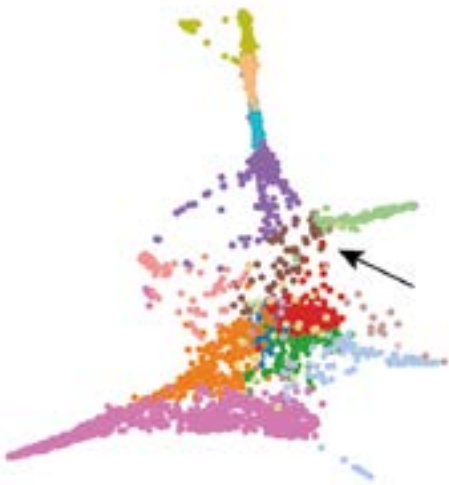
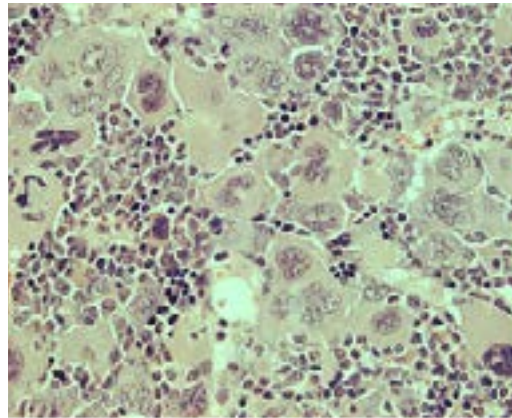
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Wildtype



Mutant CALR



Knock-in mice expressing mutant calreticulin develop markedly increased megakaryopoiesis (upper panels). Single cell RNAseq analysis of haematopoietic stem and progenitor cells reveals a novel megakaryocytic progenitor population (lower panels, brown dots indicated by arrows).

Credit: Juan Li, Daniel Prins & Sam Watcham

BRIAN HENDRICH



LAB MEMBERS

Laura Ablasser
Robin Floyd
Andria Koulle
Oluwaseun Ogundele
Ramy Ragheb
Nicola Reynolds

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, our lab seeks to understand how subtle differences in gene expression patterns in seemingly identical cells influence any subsequent differentiation decisions.

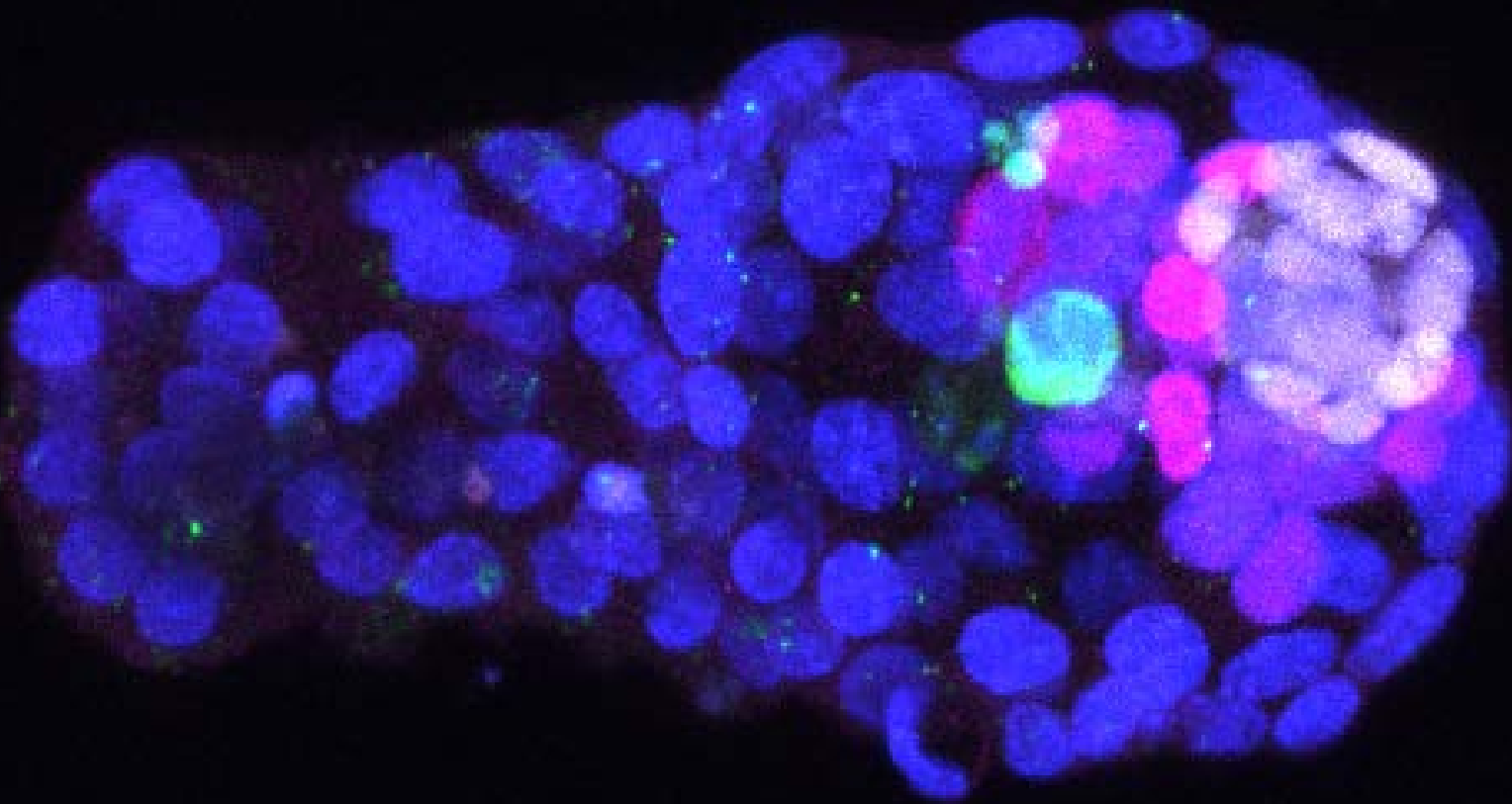
By understanding how ES cells make different developmental decisions, we hope to bring the medical promise of stem cells closer to realisation.

KEY PUBLICATIONS

Burgold T, Barber M, Kloet S, Cramard J, Gharbi S, Floyd R, Kinoshita M, Ralser M, Vermeulen M, Reynolds N, Dietmann S, and **Hendrich B.** (2019). The Nucleosome Remodelling and Deacetylation complex suppresses transcriptional noise during lineage commitment. **The EMBO Journal.** *In press.*

Bornelöv S, Reynolds N, Xenophontos M, Gharbi S, Johnstone E, Floyd R, Ralser M, Signolet J, Loos R, Dietmann S, Bertone P, **Hendrich B.** The Nucleosome Remodeling and Deacetylation Complex Modulates Chromatin Structure at Sites of Active Transcription to Fine-Tune Gene Expression. **Molecular Cell.** 2018 Jul 5;71(1):56-72.e4.

Miller A, Ralser M, Kloet SL, 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.



Mouse embryo at 4.5 days post fertilisation. Cells in white have formed epiblast, those in magenta have formed primitive endoderm and those in blue are trophoblast. The green cells are undergoing programmed cell death. The embryo is homozygous mutant for Sall4 and has not specified a proper primitive endoderm layer.

Credit: Brian Hendrich

DANIEL HODSON

Mutation timing in lymphomagenesis



LAB MEMBERS

Rebecca Caeser
Miriam Di Re
Jane Gao
Jade Gong
Joanna Krupka
Hendrik Runge

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. Our group is developing novel cell culture models to study the effects of these genetic alterations in human lymphocytes. In particular, we are interested in studying 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.

KEY PUBLICATIONS

Caeser R, Collord G, Yao WQ, Chen Z, Vassiliou GS, Beer PA, Du MQ, Scott MA, Follows GA & **Hodson DJ**. Targeting MEK in vemurafenib-resistant hairy cell leukemia. **Leukemia**. 2019 Feb;33(2):541-545.

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Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, Wang JQ, Roulland S, ..., **Hodson DJ**, ..., Pittaluga S, Wilson WH, Staudt LM. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. **New England Journal of Medicine**. 2018 Apr 12;378(15):1396-1407.

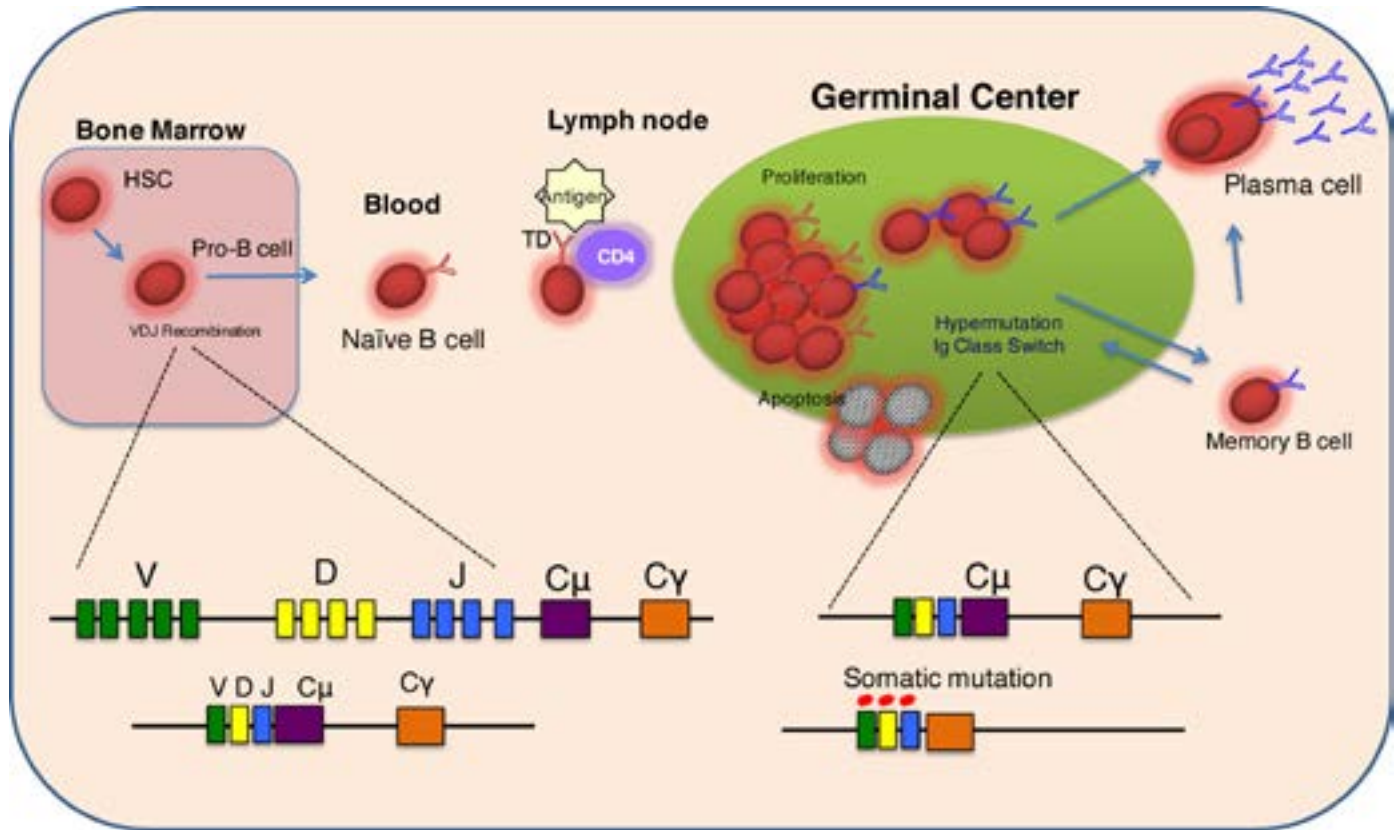


Diagram showing the unique and dangerous life of the B lymphocyte with recurrent episodes of deliberately induced DNA damage contributing to the risk of transformation to B cell lymphoma.

Credit: Hodson Lab

BRIAN
HUNTLY

Leukaemia stem cell biology and leukaemogenesis



LAB MEMBERS

Shuchi Agrawal Singh
George Giotopoulos
Sarah Horton
David Lara
Pedro Madrigal
Ludovica Marando
Eshwar Meduri
Niche Narayan
Nathalie Sakakini

Associate member:
Paolo Gallipoli

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 our research 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, all of which are ongoing areas of investigation within the lab.

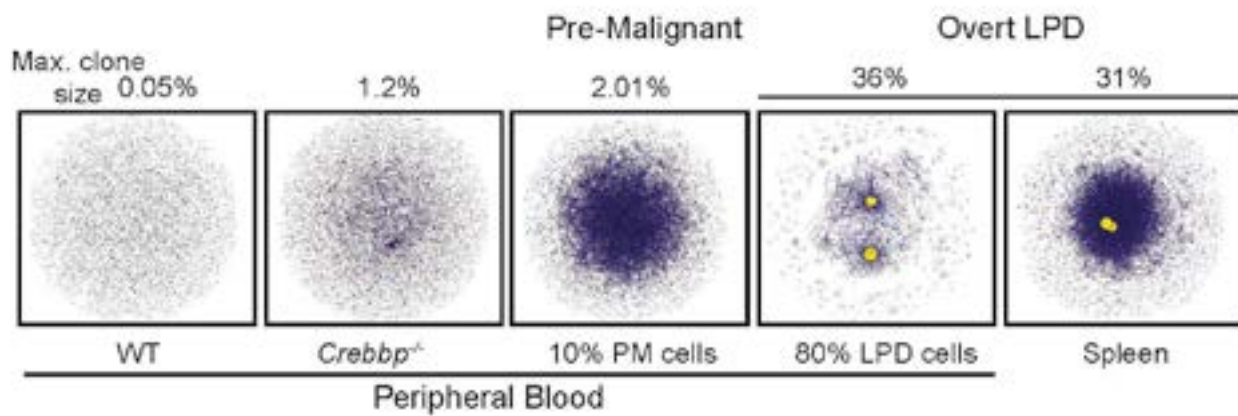
Therapeutically, a recent example of our work is the identification of the Bromodomain and extra terminal (BET) proteins as critical mediators of leukaemia stem cells in Acute Myeloid Leukaemia. An inhibitor of these proteins has already entered early phase clinical trials in relapsed blood cancers.

KEY PUBLICATIONS

Gozdecka M, Meduri E, Mazan M, ..., Adams D, Vassiliou GS, **Huntly BJP**. UTX-mediated enhancer and chromatin remodelling suppresses myeloid leukaemogenesis through non-catalytic inverse regulation of ETS and GATA expression programmes. **Nature Genetics**. 2018 Jun;50(6):883-894.

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Basheer F, Giotopoulos G, Meduri E, ... Campbell P, Vassiliou G, **Huntly BJP**. Contrasting requirements during disease evolution identify EZH2 as a therapeutic target in AML. **Journal of Experimental Medicine**. 2019 Apr 1;216(4):966-98.



Charting the clonal evolution of lymphoma (from left to right), using specific immunoglobulin rearrangements as specific clonal cellular barcodes (taken from Horton et al, Nature Cell Biology 2017).

Credit: Sarah Horton

RAGNHILDUR THÓRA KÁRADÓTTIR

Neurotransmitter signalling to central nervous system progenitor cells



LAB MEMBERS

Paul Charlesworth
Sarah Crisp
Omar De Faria Junior
Kimberley Evans
Jennifer Jia
Yasmine Kamen
Claudia Pama
Balazs Varga

Our lab investigates how the process of myelination in the central nervous system (CNS) is regulated, and how myelin regeneration could be manipulated to tackle diseases such as cerebral palsy, spinal cord injury and multiple sclerosis.

Unique to the CNS, myelin regeneration can occur spontaneously due to the presence of brain stem cells called oligodendrocyte precursor cells (OPCs) which differentiate into new myelinating oligodendrocytes. However, this process often fails, making OPCs differentiation an important therapeutic target and the focus of investigation in our lab.

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 aims 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.

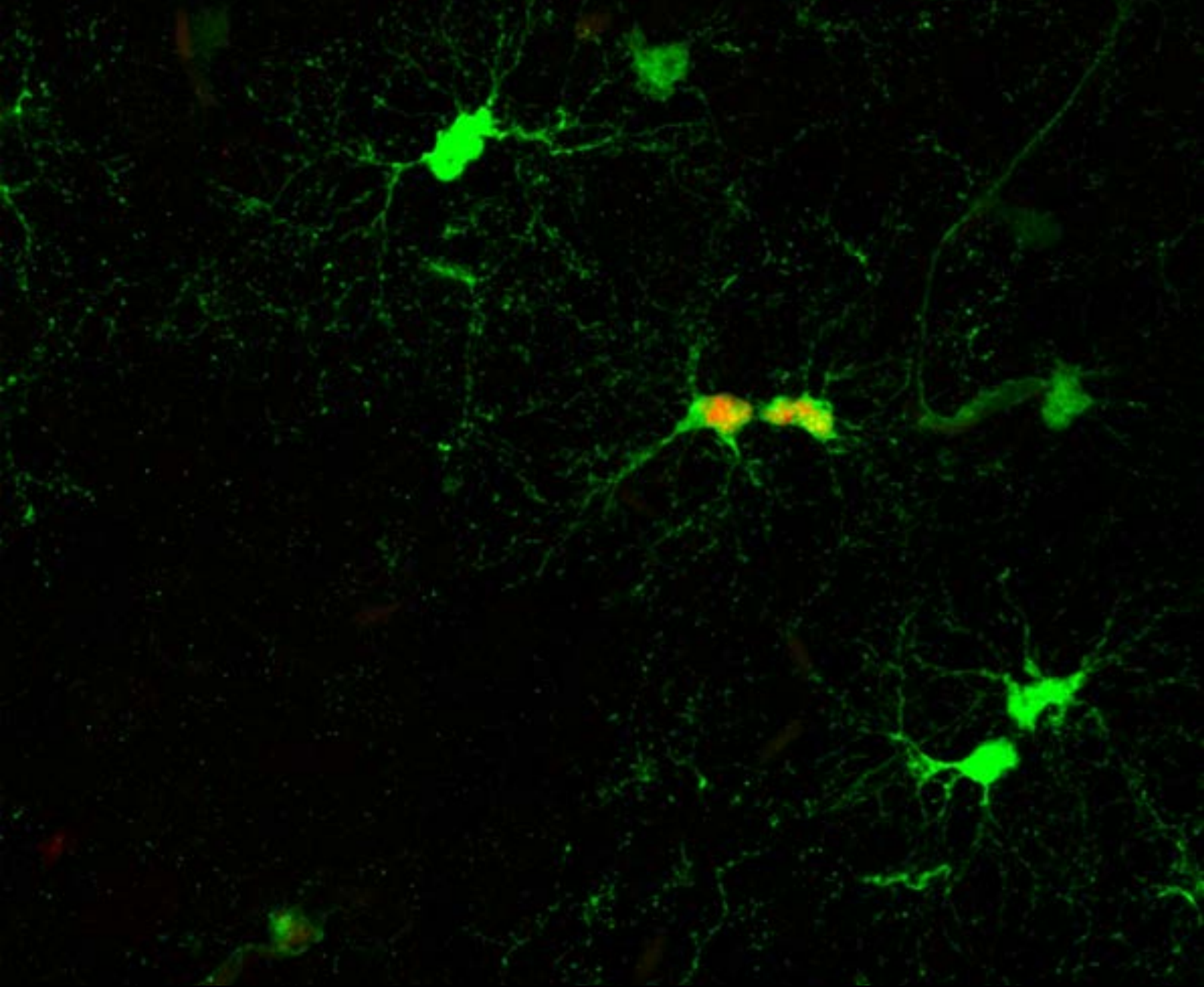
We are actively investigating how OPCs respond to myelin injury and whether neuronal activity and neurotransmitter signalling may regulate the myelin repair process. Our ultimate aim is to find new treatments for white matter disease.

KEY PUBLICATIONS

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

Lundgaard I, Luzhynskaya A, Stockley JH, ..., ffrench-Constant C, Attwell D, **Káradóttir R**. Neuregulin and BDNF induce a switch to NMDA receptor dependent myelination by oligodendrocytes. **PLoS Biology**. 2013 Dec;11(12):e1001743.



Proliferating oligodendrocyte progenitor cells in a mouse brain slice.

Credit: Kimberley Evans

DAVID
KENT

Single cell fate choice in normal and malignant stem cells



LAB MEMBERS

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Craig McDonald
Juan Rubio-Lara
Mairi Shepherd

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.

Key research themes under investigation in the lab are:

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. The early stages of cancer evolution from single cells (myeloproliferative neoplasms and myelodysplastic syndromes)
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.

KEY PUBLICATIONS

Shepherd MS, Li J, Wilson NK, Oedekoven CA, Li J, Belmonte M, Fink J, Prick JCM, Pask DC, Hamilton TL, Loeffler D, Rao A, Schröder T, Göttgens B, Green AR, **Kent DG**. Single-cell approaches identify the molecular network driving malignant hematopoietic stem cell self-renewal. **Blood**. 2018 Aug 23;132(8):791-803.

Lee-Six H, Øbro NF, Shepherd MS, Grossmann S, Dawson K, Belmonte M, Osborne RJ, Huntly BJP, Martincorena I, Anderson E, O'Neill L, Stratton MR, Laurenti E, Green AR, **Kent DG**, Campbell PJ. Population dynamics of normal human blood inferred from somatic mutations. **Nature**. 2018 Sep;561(7724):473-478.

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 hematopoietic stem and progenitor cell differentiation. **Blood**. 2016 Aug 25;128(8):e20-31.



Whole genome sequencing of colonies grown from single stem cells from a normal individual allows reconstruction of the family tree of blood cell production (Lee-Six et al., Nature 2018).

Credit: Mairi Shepherd

ELISA LAURENTI



LAB MEMBERS

Serena Belluschi
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Kendig Sham
Aditi Vedi

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. Our 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.

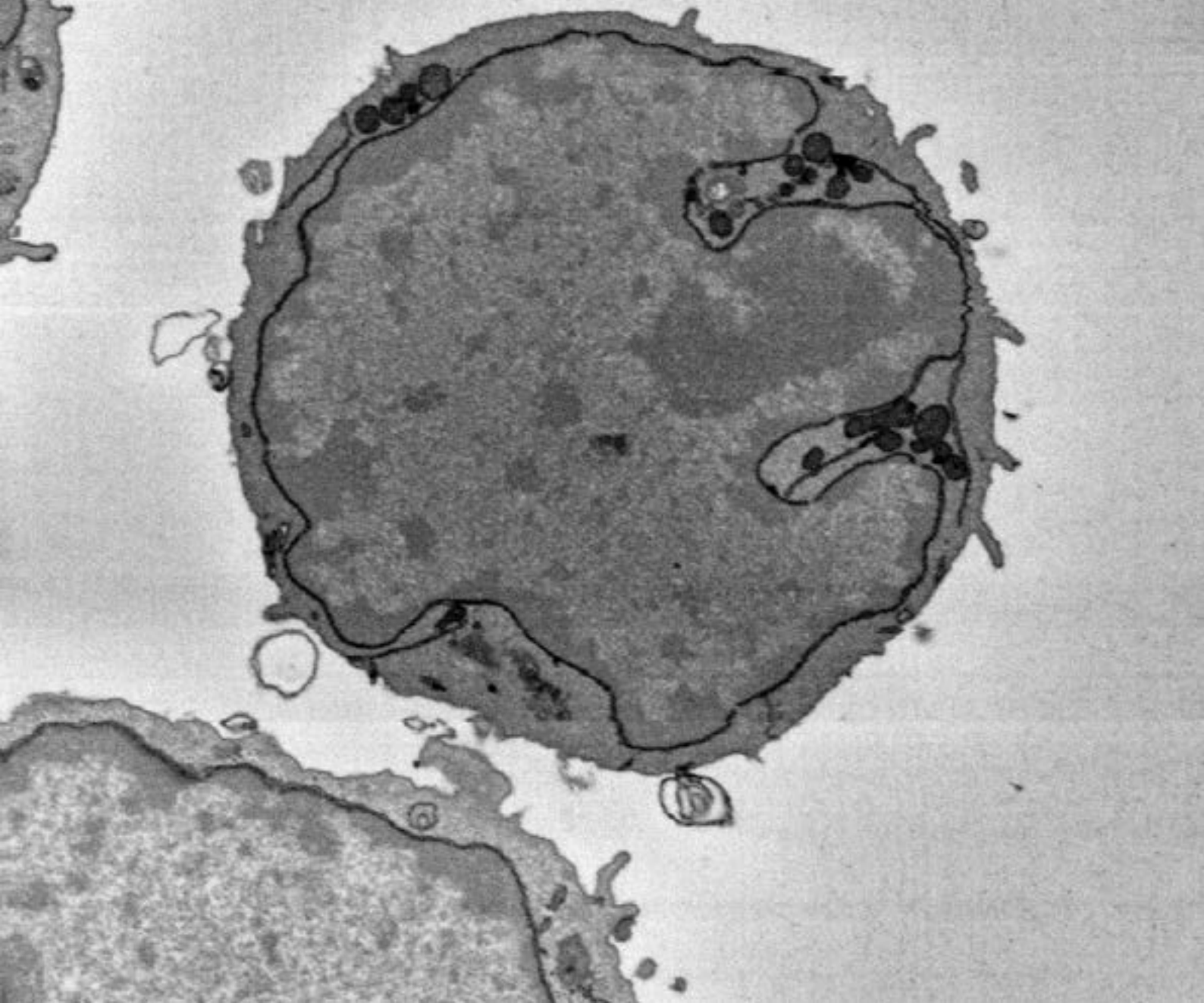
We also study HSC clonal dynamics in humans, in particular how these are affected by specific preleukaemic mutations. Understanding how the cellular and molecular composition of the HSC/progenitor compartment changes in stress conditions and throughout a human lifetime has important implications for regenerative medicine and treatment of blood cancers.

KEY PUBLICATIONS

Belluschi S, Calderbank EF, Ciaurro V, Pijuan-Sala B, Santoro A, Mende N, Diamanti E, Sham KYC, Wang X, Lau WWY, Jawaid W, Göttgens B, **Laurenti E**. Myelo-lymphoid lineage restriction occurs in the human haematopoietic stem cell compartment before lymphoid-primed multipotent progenitors. **Nature Communications**. 2018 Oct 5;9(1):4100.

Laurenti E & Göttgens B. From haematopoietic stem cells to complex differentiation landscapes. **Nature**. 2018 Jan 24;553(7689):418-426.

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**. 2015Feb 19; 16 (3):302-313.



Scanning electron microscopy image of a quiescent human haematopoietic stem cell.

Credit: Serena Belluschi & Ross Coates

JOO-HYEON LEE

Stem cells and niches



LAB MEMBERS

Jinwook Choi
Catherine Dabrowska
Kelly Evans
Antranik Mavousian
Vishal Menon
June Young Park

The lung is a very slow cycling organ that is composed of diverse epithelial and stromal cell types, but has capacity to rapidly regenerate new cells after injury. Our group is trying to understand how stem cells respond to different signals from their local environment and orchestrate the changes in chromatin, transcription, translation, and cellular dynamics in homeostasis and injury repair.

We investigate the regulatory networks that need to be turned on and off at the right time and place for stem cells to become activated and generate specialised cell types during regeneration. We are also interested in defining cellular heterogeneity and plasticity during this process. Elucidating the normal process of lung dynamics will provide us a foundation to understand lung diseases and cancer.

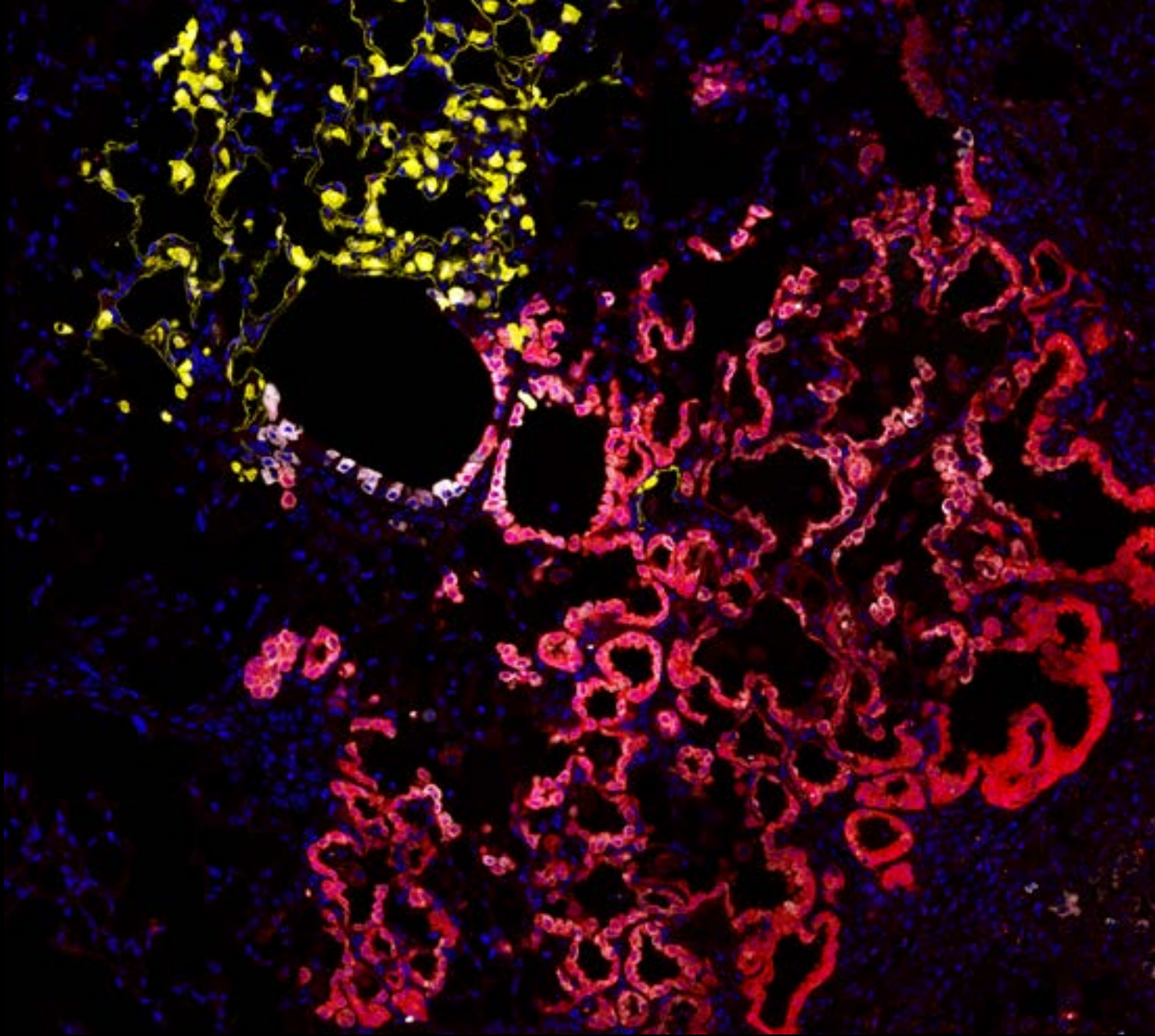
We couple *ex vivo* 3D organoid cultures of human and mouse lungs with genetic tools, *in vivo* transgenic mouse models with lineage tracing techniques, quantitative mathematic modelling of clonal dynamics, and bioinformatics at the single cell level.

KEY PUBLICATIONS

Lee JH and Rawlins ER. Developmental mechanisms and adult stem cells for therapeutic lung regeneration. **Developmental Biology**. 2018 Jan 15;433(2):166-176.

Lee JH, Tammela T, Hofree M, Choi J, Marjanovic ND, Han S, Canner DA, Wu K, Paschini M, Bhang DH, Jacks T, Regev A, Kim CF. Anatomically and functionally distinct lung mesenchymal populations marked by Lgr5 and Lgr6. **Cell**. 2017 Sep 7;170(6):1149-1163.e12.

Lee JH, Bhang DH, Beede A, Huang TL, Stripp B, Bloch KD, Wagers AJ, Tseng YH, Ryeom S, Kim CF. Lung stem cell differentiation in mice directed by endothelial cells via a BMP4-NFATc1-Thrombospondin-1 axis. **Cell**. 2014 Jan 30;156(3):440-455.



Fluorescent image of a mouse lung undergoing repair after injury. Airway secretory club cells labelled with yellow are differentiating into alveolar lineage cells, whereas mutant secretory club cells labelled with red show perturbed differentiation capacity. Nuclei of individual cells are stained with DAPI (blue).

Credit: Catherine Dabrowska

ANDREW MCCASKIE



LAB MEMBERS

Anna Albiero
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 Mark Birch
 Roger Brooks
 Karim Fekir
 Frances Henson
 William Hotham
 Andrew Hotchen
 Wasim Khan
 Stephen McDonnell
 Karin Newell
 Matt Seah

Regenerative therapies for bone and cartilage repair

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

Our 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.

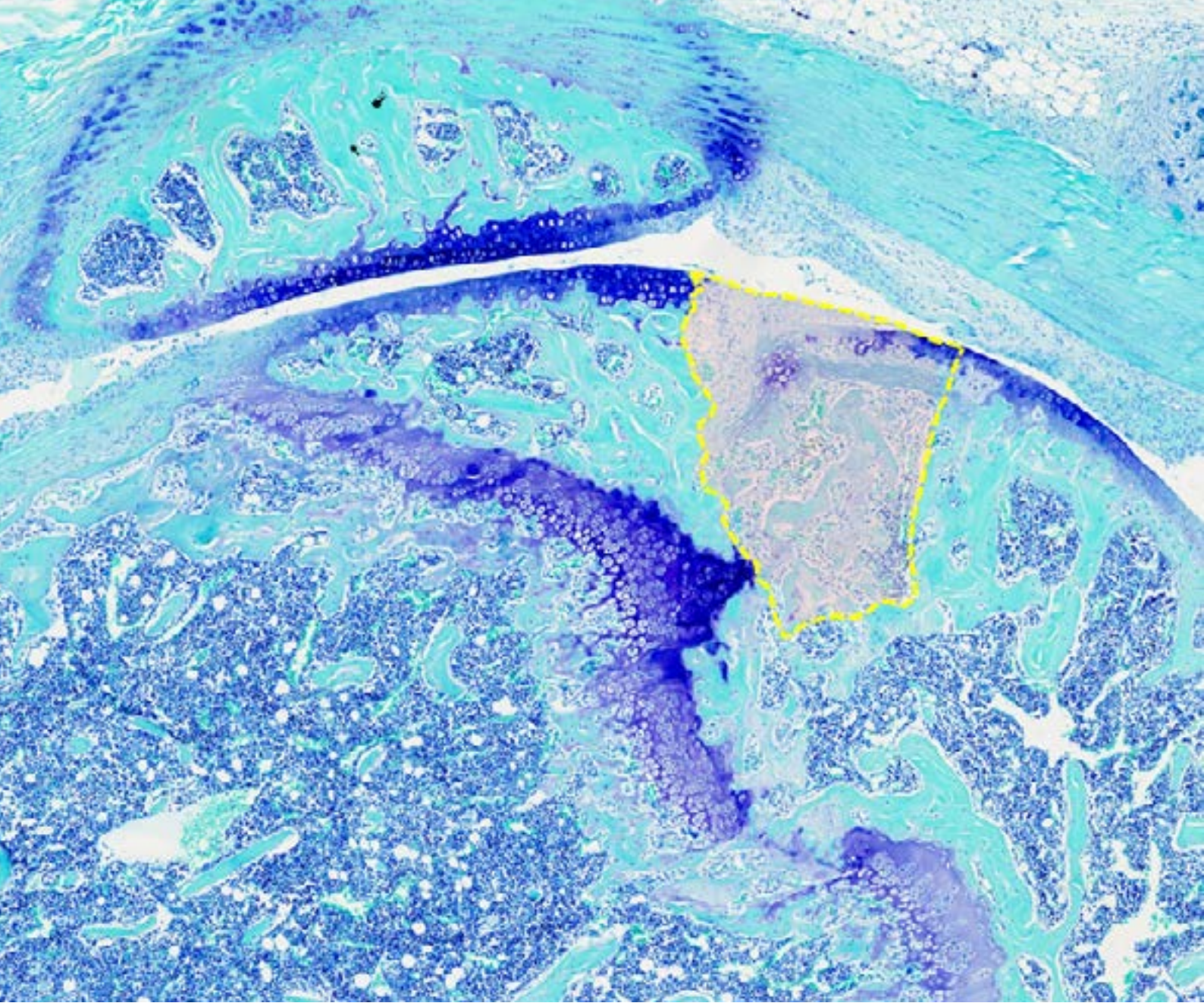
The translational and clinical programmes seek to use stratified and experimental medicine approaches, particularly focused on imaging and tissue analysis during cartilage repair surgery. The latter will include cell characterisation by phenotype and single cell analysis to understand the role played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

KEY PUBLICATIONS

Zengini E, Hatzikotoulas K, Tachmazidou I, ... **McCaskie A**, ... Zeggini E. Genome-wide analyses using UK Biobank data provide insights into the genetic architecture of osteoarthritis. **Nature Genetics**. 2018 Apr;50(4):549-558.

Steinberg J, Brooks R, Southam L, ... **McCaskie AW**, Zeggini E. Widespread Epigenomic, Transcriptomic and Proteomic Differences Between Hip Osteophytic and Articular Chondrocytes in Osteoarthritis. **Rheumatology** (Oxford). 2018 Aug 1;57(8):1481-1489.

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 of the Rheumatic Diseases**. 2014 Dec;73(12):2130-6.



Osteochondral repair of a synovial joint injury.

Credit: Francesca Beaton

SIMÓN MÉNDEZ-FERRER

Blood stem cell niches



LAB MEMBERS

Claire Fielding
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Chrysoula Kapeni
Thomas McKerrell

Our 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.

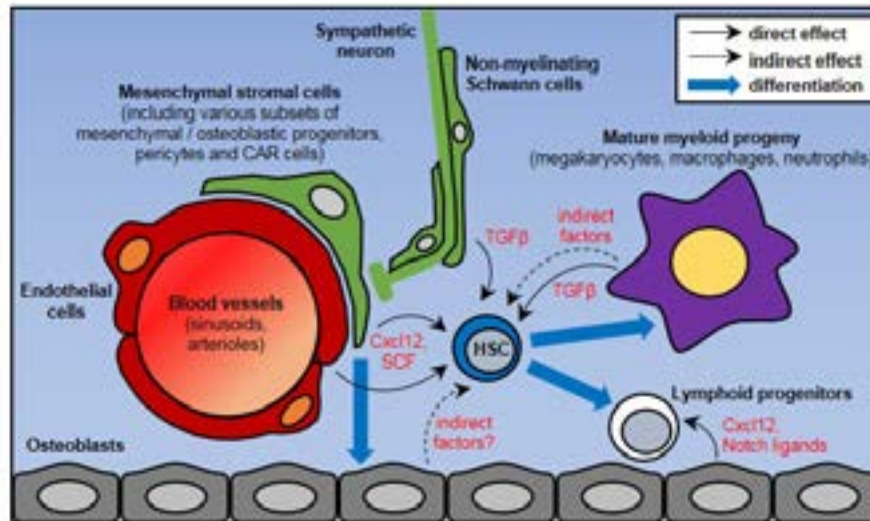
KEY PUBLICATIONS

García-García A, Korn C, García-Fernández M, Domingues O, Villadiego J, Martín-Pérez D, Isern J, Bejarano-García JA, Zimmer J, Pérez-Simón JA, Toledo-Aral JJ, Michel T, Airaksinen MS, **Méndez-Ferrer S**. Dual cholinergic signals regulate daily migration of hematopoietic stem cells and leukocytes. **Blood**. 2019 Jan 17;133(3):224-236.

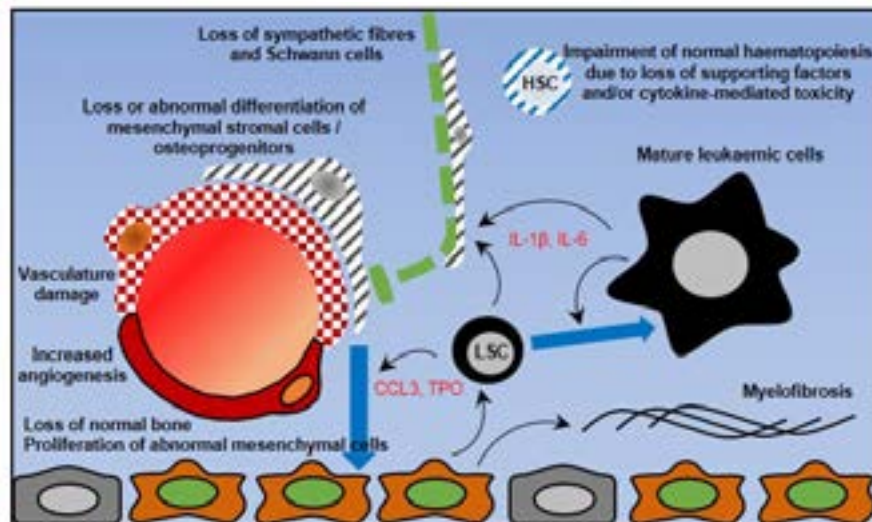
Del Toro R, Chèvre R, Rodríguez C, Ordóñez A, Martínez-González J, Andrés V, **Méndez-Ferrer S**. Nestin(+) cells direct inflammatory cell migration in atherosclerosis. **Nature Communications**. 2016 Sep 2;7:12706.

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**. 2014 Dec 4;15(6):791-804.

NORMAL HSC NICHE



LEUKAEMIC NICHE



Overview of the main components of the haematopoietic stem cell (HSC) niche and their alterations in leukaemia. Simplified schematic of the normal HSC niche (upper panel) and its alterations in the context of malignancy. The diagram illustrates some of the best characterized candidate niche cells and factors, particularly those that have been found altered in leukaemias. The lower panel summarizes niche abnormalities observed in various experimental models representing different leukaemia types. Therefore, it does not intend to propose a general model nor to describe the pathophysiology of any particular malignancy. HSC hematopoietic stem cell, LSC leukaemia stem/initiating cell.

Credit: Abel Sánchez-Aguilera & Simón Méndez-Ferrer. *Cell Mol Life Sci.* 2017 Feb;74(4).

JENNIFER NICHOLS



LAB MEMBERS

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 Peter Baillie-Johnson
 Elena Corujo-Simon
 Kenneth Jones
 Tim Lohoff
 Sophie Morgani
 Giuliano Stirparo
 Stanley Strawbridge
 Ayaka Yanagida

Embryonic pluripotency

Murine embryos develop a pluripotent epiblast by the late blastocyst stage which is the source of the foetus. Understanding how the pluripotent lineage is specified, maintained and relinquished during development is critical to establish protocols for efficient capture and controlled differentiation of embryonic stem cells in culture.

To begin to understand the process of lineage specification, our group 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.

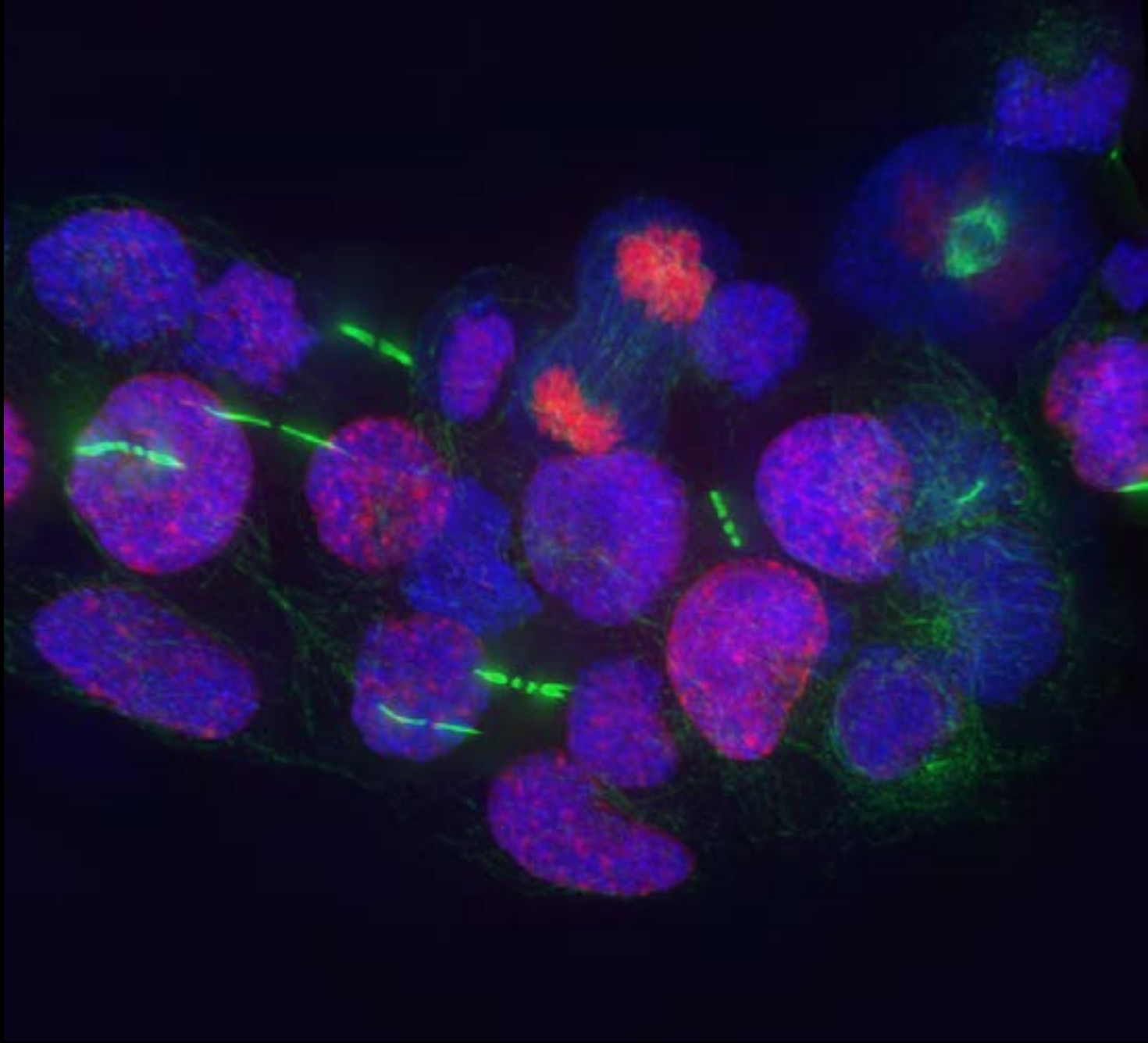
To further our understanding of cell fate decisions in early mouse embryos, we use a combination of genetic modification, *ex vivo* culture and molecular profiling to investigate the roles of relevant pluripotency factors and signalling pathways. Currently, we are using chimaeras to investigate early lineage segregation in the host embryo in response to administration of normal or mutant embryonic stem cells.

KEY PUBLICATIONS

Mulas C, Chia G, Jones KA, Hodgson AC, Stirparo GG, **Nichols J**. Oct4 regulates the embryonic axis and coordinates exit from pluripotency and germ layer specification in the mouse embryo. **Development**. 2018 Jun 18;145(12).

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):437-446.

Alexandrova S, Kalkan T, Humphreys P, Riddell A, Scognamiglio R, Trumpp A, **Nichols J**. Selection and dynamics of embryonic stem cell integration into early mouse embryos. **Development**. 2016 Jan 1;143(1):24-34.



Confocal snapshot of a chimaeric mouse embryo showing embryonic stem cells (red nuclei) integrating into the host inner cell mass.

Credit: Nichols Lab

ANNA PHILPOTT



LAB MEMBERS

Lewis Chaytor
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John Davies
Fani Memi
Lydia Parkinson

Proneural transcription factors

We aim to understand how cells adopt a specific fate and to uncover 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 in tissues as diverse as nerve, muscle, pancreas and gut.

Our future aims are three-fold, we will:

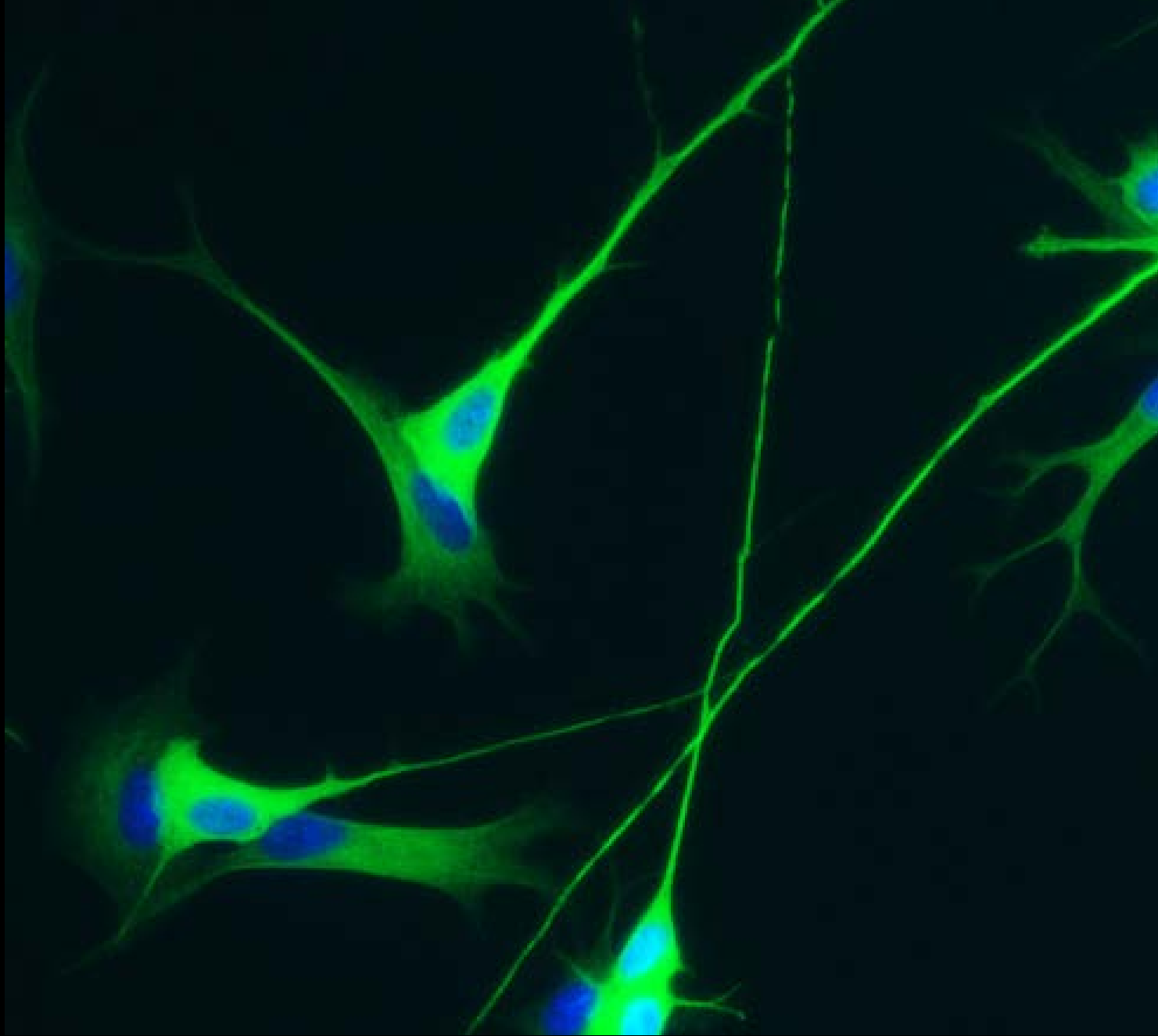
1. Further characterise the molecular mechanisms that link cell cycling and differentiation
2. Investigate perturbation of the balance between stem-ness/progenitor maintenance and differentiation that is a frequent hallmark of multiple cancers, focussing on molecular regulation of proliferation and differentiation in neuroblastoma, glioblastoma and insulinoma, with the aim of developing new therapeutic strategies
3. Probe fundamental mechanisms that determine the fate trajectory and differentiation of different cell types during development focussing on the epigenome and co-factors that control this process at the level of individual cells.

KEY PUBLICATIONS

Azzarelli R, Simons B and **Philpott A**. The developmental ontogeny of neurological cancers: a cellular and molecular framework. **Development**. 2018 May 14;145(10).

Tomic G, Morrissey E, Kozar S, Ben-Moshe S, Hoyle A, Azzarelli R, Kemp R, Chilamakuri CSR, Itzkovitz S, **Philpott A**, Winton DJ. Phospho-regulation of ATOH1 Is Required for Plasticity of Secretory Progenitors and Tissue Regeneration. **Cell Stem Cell**. 2018 Sep 6;23(3):436-443.

Azzarelli R, Hurley C, Sznurkowska MK, ..., Simons BD, Winton D, **Philpott A**. Multi-site Neurogenin3 Phosphorylation Controls Pancreatic Endocrine Differentiation. **Developmental Cell**. 2017 May 8;41(3):274-286.



Neuroblastoma cancer cells stop dividing and differentiate into neurons on treatment with drugs targeting the key transcriptional regulator ASCL1.

Credit: Daniel Marcos-Corchado



LAB MEMBERS

Jingyu Chen
Maurizio Mangolini
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Eugene Park
Antonella Santoro
Vijitha Sathiaselan

Our research group studies the processes underpinning chronic lymphocytic leukaemia, the most common leukaemia in western countries. Similar to normal blood stem cells, malignant cells from patients with B cell lymphomas require signals from their surrounding environment for cell survival and proliferation. Benign bystander cells provide crucial support for malignant cells, mediated by direct cell-cell contact and soluble factors.

Understanding these cell-cell communications from a molecular viewpoint opens new directions to treat blood-born malignancies. Through our research we want to understand:

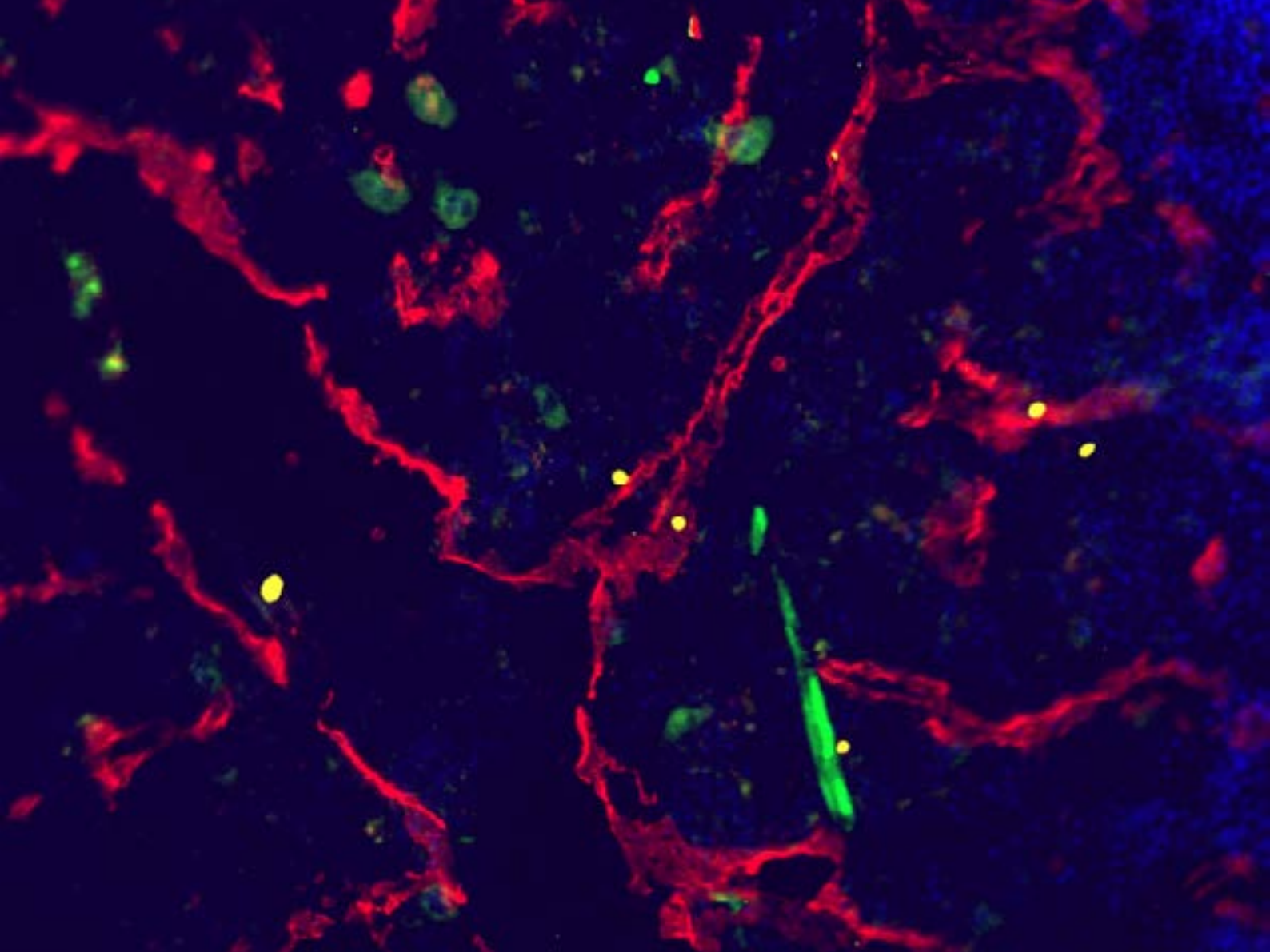
1. How this cell-cell communication changes over time?
2. Are malignant cells from patients with relapsed disease equally dependent on these cell-cell signals?
3. How does this communication between malignant cells and their micro-environment affect the function of normal haematopoietic stem cells and the production of normal blood cells?

KEY PUBLICATIONS

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Lutzny G, Kocher T, Rudelius M, ..., Peschel C, Egle A, **Ringshausen I**. Proteinkinase C- β dependent activation of NF- κ B in stromal cells is indispensable for the survival of chronic lymphocytic leukemia B-cells in vivo. **Cancer Cell**. 2013 Jan 14;23(1):77-92.

Ringshausen I, O'Shea CC, Finch AJ, Swigart LB, Evan GI. Mdm2 is critically and continuously required to suppress lethal p53 activity in vivo. **Cancer Cell**. 2006. 10(6): p. 501-14.



Malignant B cells (yellow) actively remodel Bone marrow mesenchymal stromal cells (Nestin+ cells in green, endothelial cells are in red).

Credit: Ringshausen Lab

DAVID ROWITCH



LAB MEMBERS

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John Finlay
Courtney French
Gemma Girdler
Clement Hallou
Staffan Holmqvist
Ajay Kumar
Kirti Prakash
Katherine Ridley
John Stockley

Glial cells and response to injury

My lab investigates genetic factors that determine development and diversity of glial cells of the brain and the response to injury. Our research to establish functional diversity of astrocytes is funded by Wellcome Trust, and new ERC-funded studies will investigate precise synthetic mechanisms of oligodendrocytes during myelination. We have applied these principles to better understand white matter injury in premature infants, brain cancer, multiple sclerosis and leukodystrophy.

Building on this fundamental research, I led the first human clinical trial of direct neural stem cell transplantation focused on the rare and fatal leukodystrophy, Pelizaeus-Merzbacher Disease (PMD); we are using stem cell biology to decipher the basis for failed myelination in these patients.

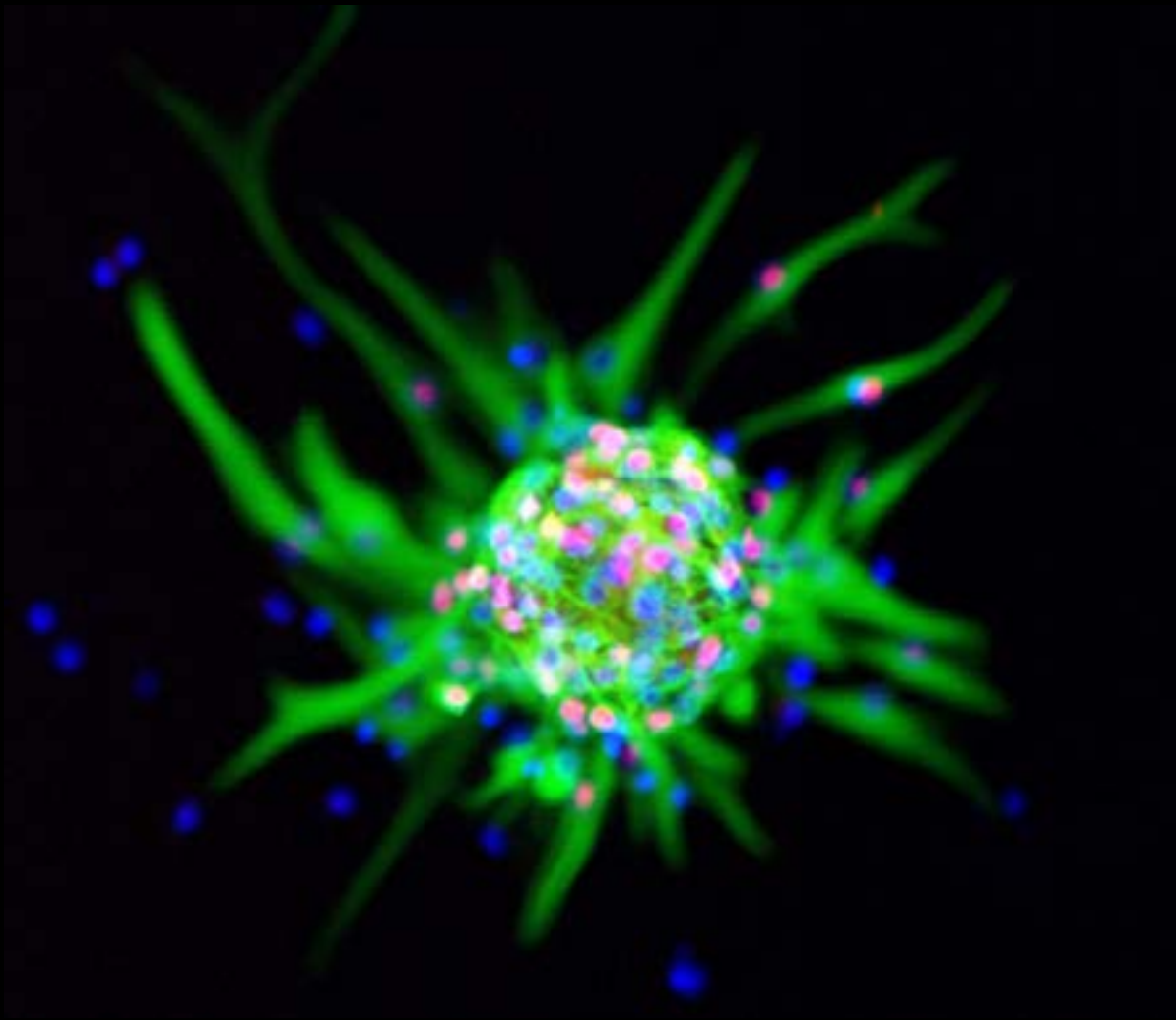
Our interest in precision medicine focuses on applications of genomic technologies to diagnose and better understand the biological basis and rational treatment of rare neurological disorders.

KEY PUBLICATIONS

French CE, Delon I, Dolling H, ..., NIHR BioResource—Rare Disease; Next Generation Children Project, **Rowitch DH**, Raymond FL. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. **Intensive Care Medicine**. 2019 Mar 7. doi: 10.1007/s00134-019-05552-x.

Griveau A, Seano G, Shelton SJ, ..., Mehta S, Jain RK, **Rowitch DH**. A Glial Signature and Wnt7 Signaling Regulate Glioma-Vascular Interactions and Tumor Microenvironment. **Cancer Cell**. 2018 May 14;33(5):874-889.

Kelley KW, Ben Haim L, Schirmer L, Tyzack GE, Tolman M, Miller JG, Tsai HH, Chang SM, Molofsky AV, Yang Y, Patani R, Lakatos A, Ullian EM, **Rowitch DH**. Kir4.1-Dependent Astrocyte-Fast Motor Neuron Interactions Are Required for Peak Strength. **Neuron**. 2018 Apr 18;98(2):306-319.



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.

Credit: Vivi Heine



LAB MEMBERS

Lawrence Bates
Yael Costa
Sergey Hladkov
Katsiaryna Maskalenka
Elsa Sousa

The research in our lab is focussed on understanding the biology of reprogramming a differentiated cell identity back into a naïve pluripotent stem cell identity, a process known as induced pluripotency. We build on this acquired knowledge to also study the principles governing cell identity change, cell potency, epigenetic regulation and the mechanisms regulating developmental processes taking place in naïve pluripotent stem cells. Our central lines of research are:

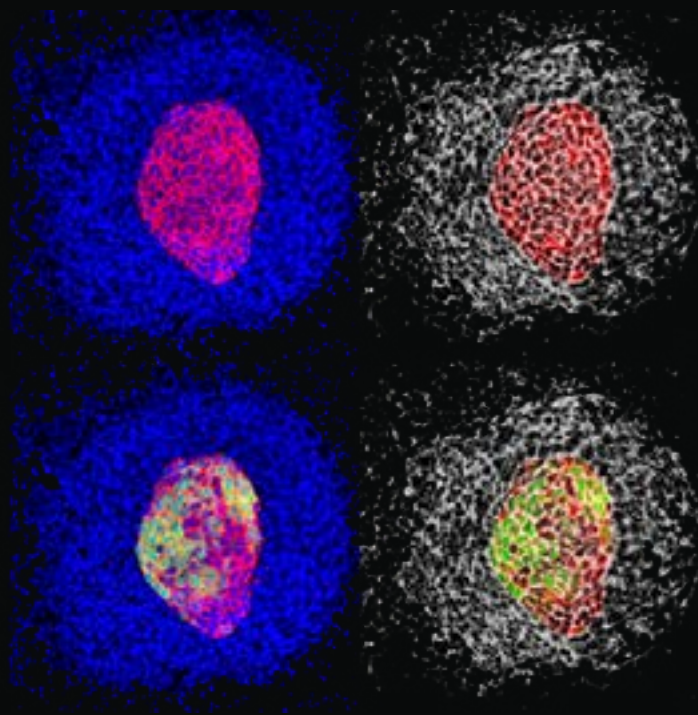
1. Understanding the fundamental biology of nuclear reprogramming. Nuclear reprogramming is a fundamental process in biology and also a great model system to study cell identity change.
2. Determining the potential of programming pluripotent stem cells to defined stem cell types of interest. The creation of bonafide pluripotent stem cells from somatic cells by the use of defined factors has opened up the possibility for the generation of any cell type in the petri dish.
3. Studying the relationship between drivers of reprogramming and epigenetic processes taking place in naïve pluripotent stem cells. Normal development is somewhat a mirror of reprogramming and we are now asking if the drivers of reprogramming also regulate other cellular processes such as the initiation of X-chromosome inactivation.

KEY PUBLICATIONS

Sousa EJ, Stuart HT, Bates LE, Ghorbani M, Nichols J, Dietmann S, **Silva JCR**. Exit from Naïve Pluripotency Induces a Transient X Chromosome Inactivation-like State in Males. **Cell Stem Cell**. 2018 Jun 1;22(6):919-928.e6.

Santos R, Tosti L, Radzsheuskaya A, Caballero I, Kaji K, Hendrich B, **Silva JCR**. Mbd3/NuRD facilitates induced pluripotency in a context dependent manner. **Cell Stem Cell**. 2014 Jul 3;15(1):102-10.

Stuart HT, van Oosten AL, Radzsheuskaya A, Martello G, Miller A, Dietmann S, Nichols J, **Silva JCR**. NANOG amplifies STAT3 activation and they synergistically induce the naïve pluripotent program. **Current Biology**. 2014 Feb 3;24(3):340-6.



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

BEN
SIMONS

Tracing stem cell fate in development, maintenance and disease



LAB MEMBERS

Roberta Azzarelli
Lemonia Chatzeli
Clara Dure
Adrian Hallou
Seungmin Han
Tom Hiscock
Min-Kyu Yum

Research in our group uses 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 resolved 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. We have extended these approaches to study the development of adult tissues, including the eye, heart, liver, lung, mammary epithelium, pancreas and prostate.

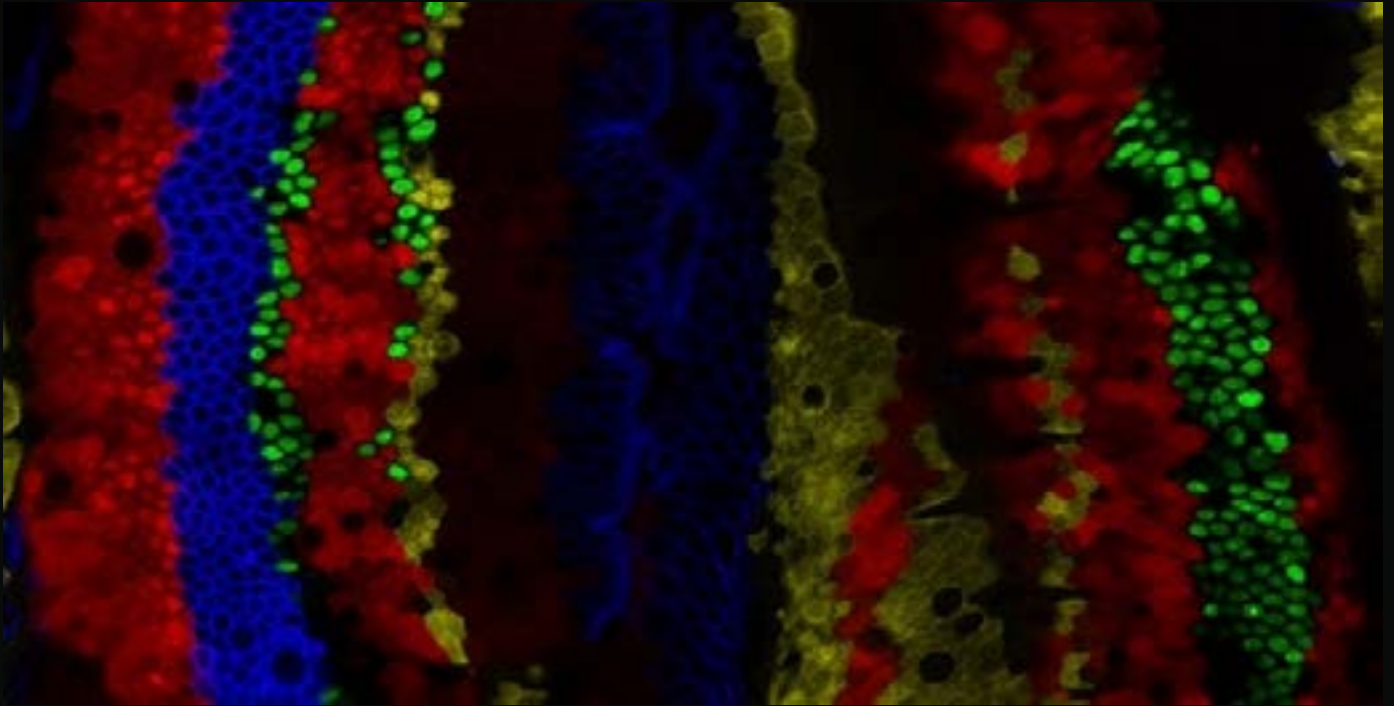
At the same, we are collaborating with partner labs to address the cellular basis of tumour initiation, and are also making use of genetic lineage tracing approaches to study the process of remyelination in spinal cord. We also work with colleagues at the Sanger and Babraham Institutes to develop statistical 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.

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 Nov 6;159(4):775-88.

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 May 1;14(5):658-72.

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 Mar 20;507(7492):362-365.



Lineage labelled intestinal crypts and villi in mice.

Credit: Simons Lab

SANJAY SINHA

Vascular disease



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

We have pioneered the generation of embryonic lineage-specific vascular smooth muscle cells, 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".

LAB MEMBERS

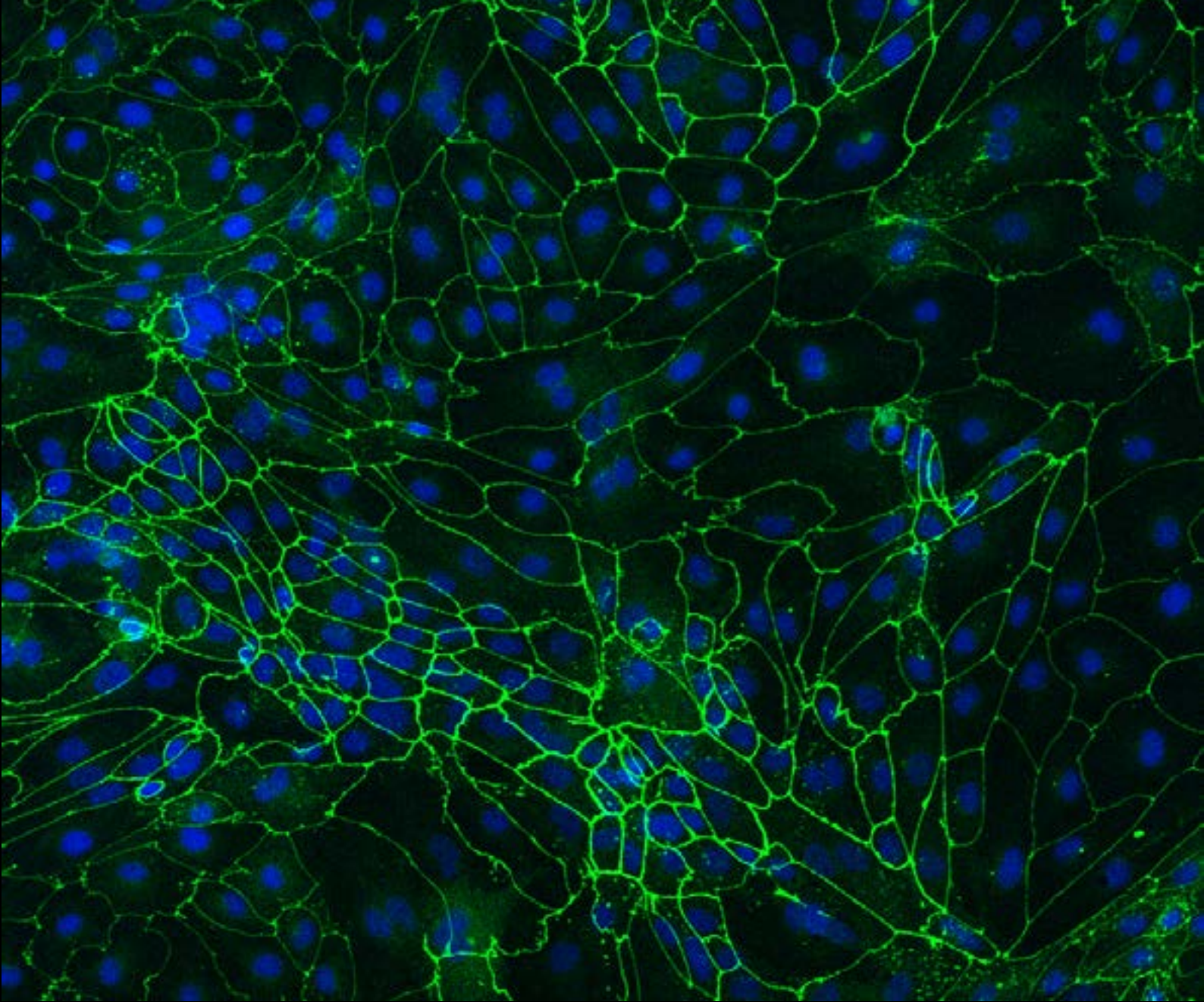
Will Bernard
 Maria Colzani
 Hongorzul Davaapil
 Laure Gambardella
 Debbie Ho
 Peter Holt
 Aishwarya Jacob
 Vincent Knight-Schrijver
 Robyn Macrae
 Sophie McManus
 Ping Ong
 Alex Petchey
 Felipe Serrano-Tejero

KEY PUBLICATIONS

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Epicardial cells generated from human embryonic stem cells form a sheet, also known as mesothelium. The tight junction protein1 (ZO1) is seen at cell peripheries (green) and contributes to the cell-cell junctions.

Credit: Laure Gambardella

AUSTIN SMITH

Pluripotent stem cell biology



We study pluripotent stem cells derived from early embryos or generated by somatic cell reprogramming. These cell lines harbour 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. We compare pluripotent cells from different mammals to elucidate common principles and species-specific adaptations.

Our research focusses on the developmental origins and plasticity of the pluripotency gene regulatory network. We seek to expose the molecular logic governing early development, pluripotency transitions, stem cell self-renewal, and lineage potential.

LAB MEMBERS

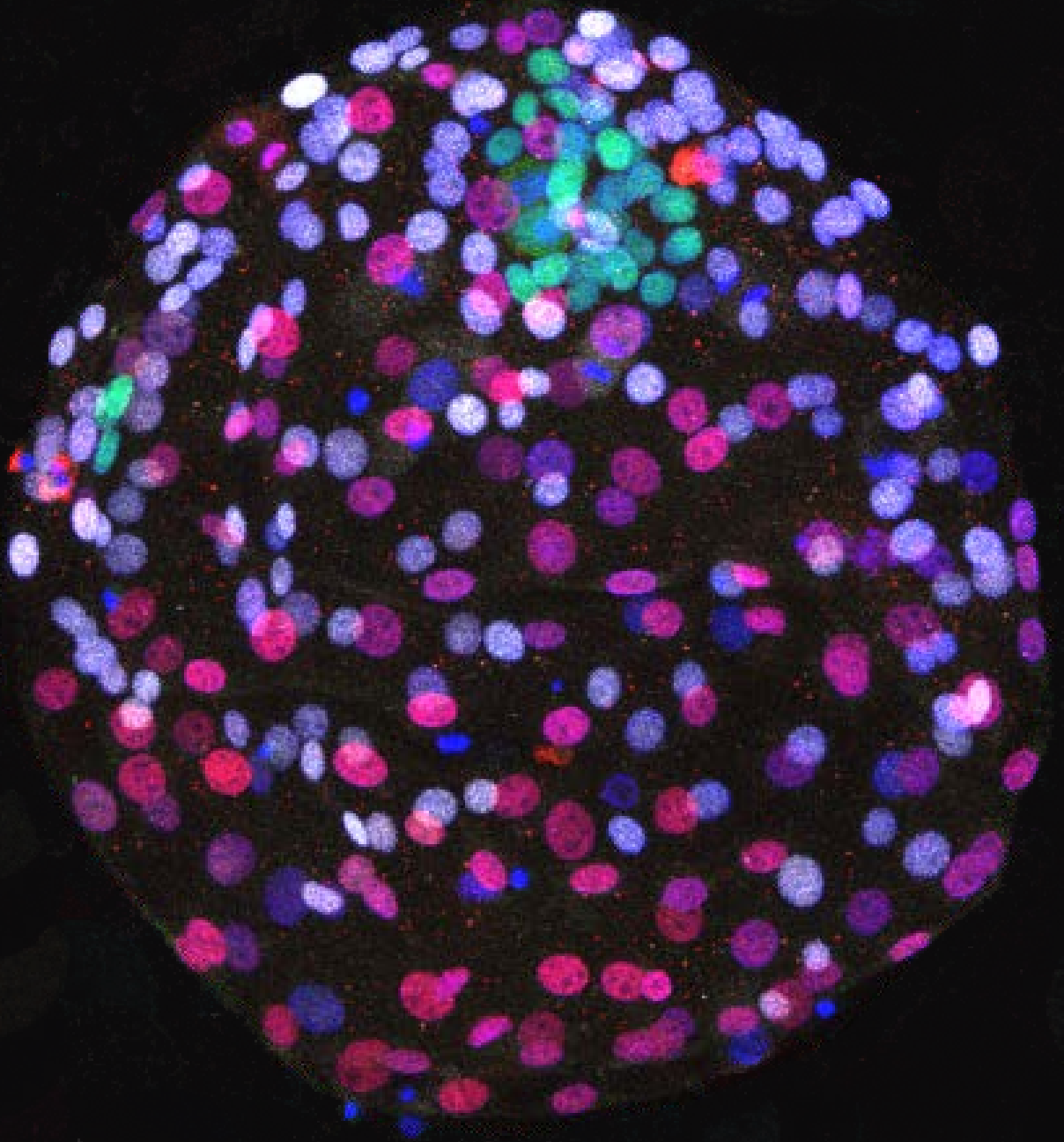
Nicholas Bredenkamp
James Clarke
Rosalind Drumond
Ge Guo
Masaki Kinoshita
Arthur Radley

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Sheep blastocyst regenerated from an isolated inner cell mass. Immunostaining shows lineage-specific transcription factors: SOX2 (epiblast, green); GATA3 (trophoblast, red); SOX17 (hypoblast, white). Nuclei are visualised with Dapi (blue).

Credit: Ge Guo

LUDOVIC VALLIER



LAB MEMBERS

Teresa Brevini
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Mechanisms controlling differentiation of pluripotent stem cells into definitive endoderm

Understanding the mechanisms controlling early cell fate decisions in human development has major implications for regenerative medicine. Indeed the generation of fully functional cell types from stem cells is only achievable by recapitulating a natural 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 interplay 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 systems to drive differentiation of pluripotent stem cells into pancreatic, hepatic, lung and gut cells. These cells are then used to model disease *in vitro*, especially metabolic disorders affecting the liver.

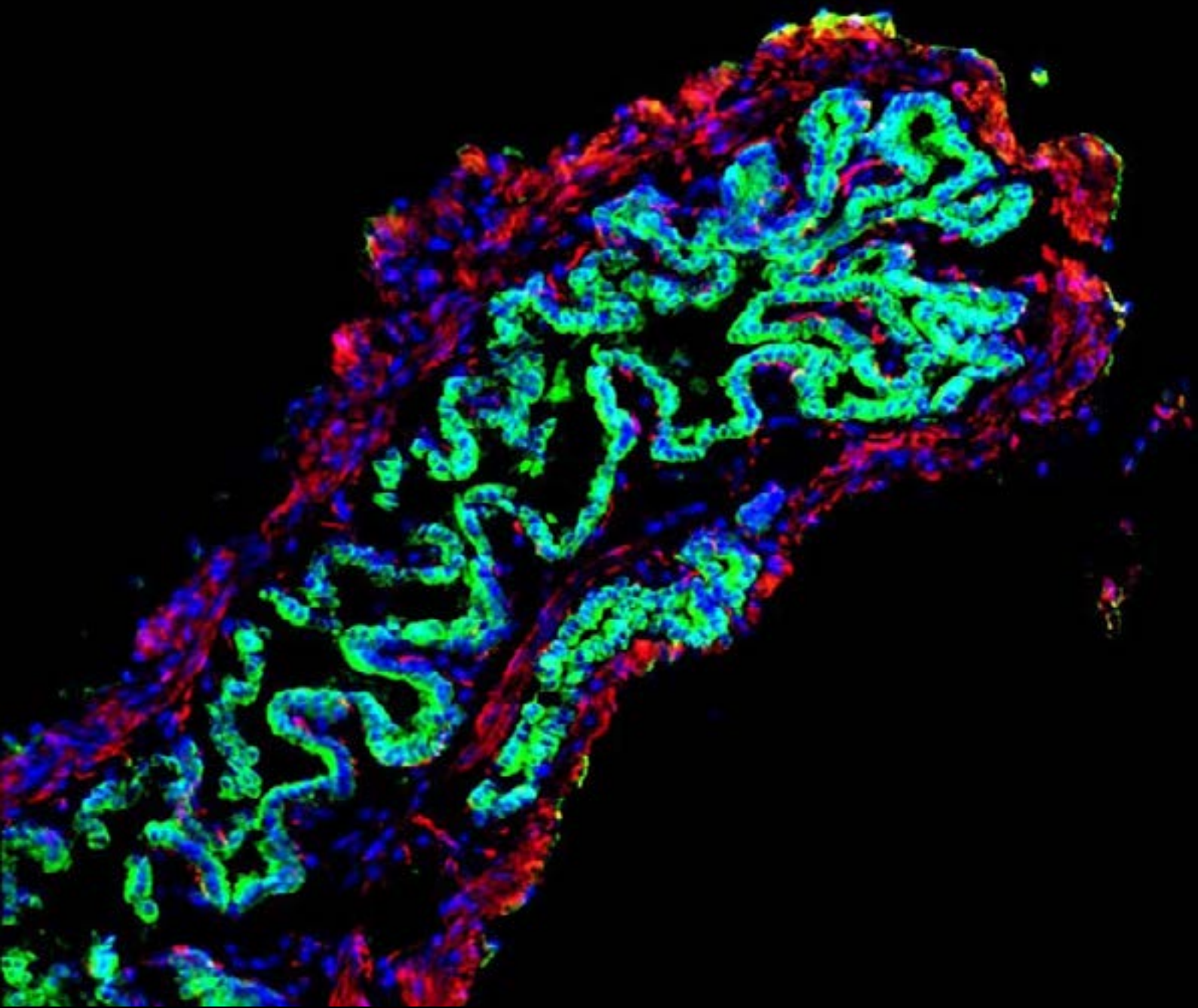
Furthermore, we are currently investigating how similar mechanisms could regulate adult stem cells self-renewal /differentiation during organ regeneration. Overall, our objective is to understand basic mechanisms of differentiation to generate cells for a diversity of clinical applications including disease modelling and cell based therapy.

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Mouse gallbladder following repair with human cholangiocytes organoids (green).

Credit: Fotis Sampaziotis

GEORGE VASSILIOU



LAB MEMBERS

Clea Barcena
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Dimitris Garyfallos
Gonia Gozdecka
Muxin Gu
Andreas Hadjimitsis
Josep Nomdedeu
Suruchi Pacharne
Pedro Quiros
Justyna Rak

Leukaemic haemopoietic stem cells

Our group seeks to understand the cell-autonomous and cell-non-autonomous processes involved in transformation of normal to leukaemic haemopoietic stem cells and to identify genetic vulnerabilities of myeloid malignancies that can be exploited as targets of novel anti-leukaemic therapies.

To achieve these aims the group uses three main approaches:

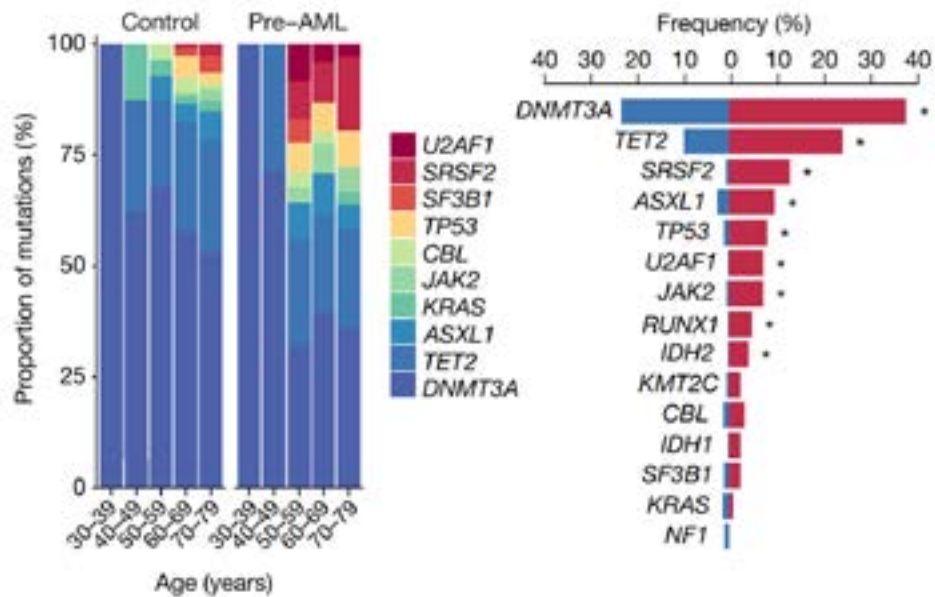
1. Application of genetic screens to identify and investigate genetic vulnerabilities of acute myeloid leukaemia and related cancers in order to develop new therapeutic approaches;
2. Generation and study of bespoke mouse models of somatic mutations driving human myeloid malignancies, in order to define their molecular, genomic and phenotypic effects on haemopoietic stem and progenitor cells and to develop leukaemic models for study in translational studies;
3. Detection and tracking of the evolution of clonal haematopoiesis in healthy individuals, in order to understand the factors involved in leukaemic progression and develop new approaches for early detection.

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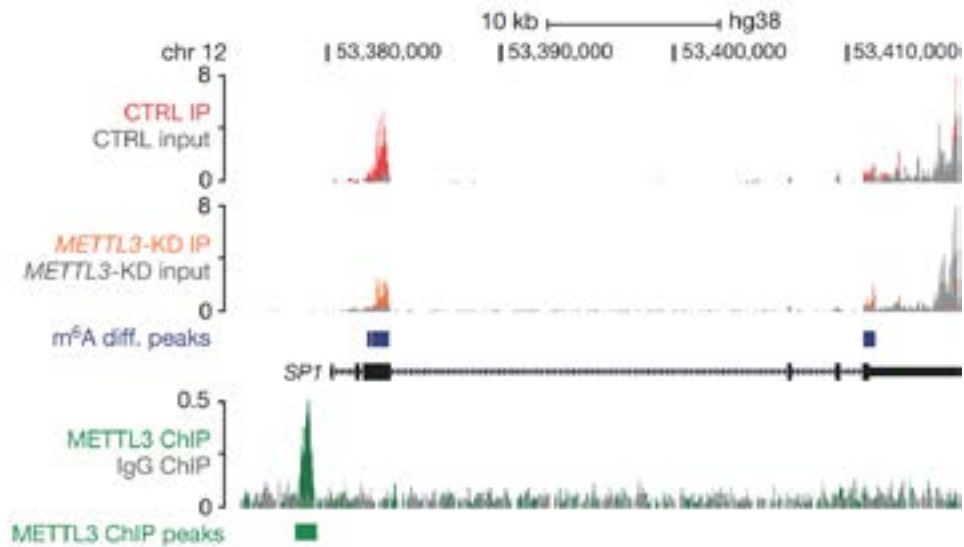
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Characteristics of clonal haematopoiesis mutations years before AML development



METTL3 binding at transcription start sites is associated with m⁶A modifications of cognate RNA

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Institute researchers produced 171 publications in 2018 across a range of topics and research themes.

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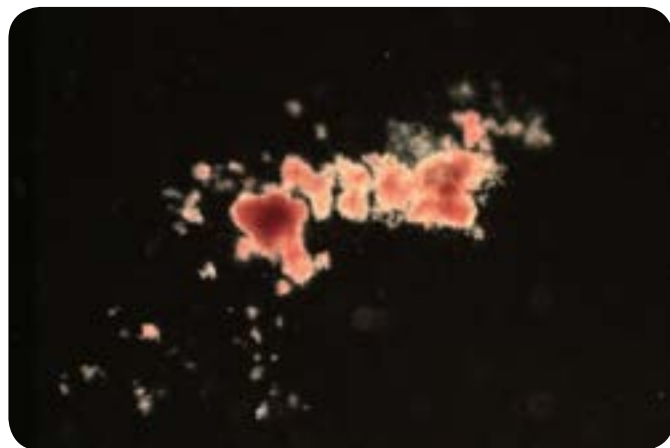
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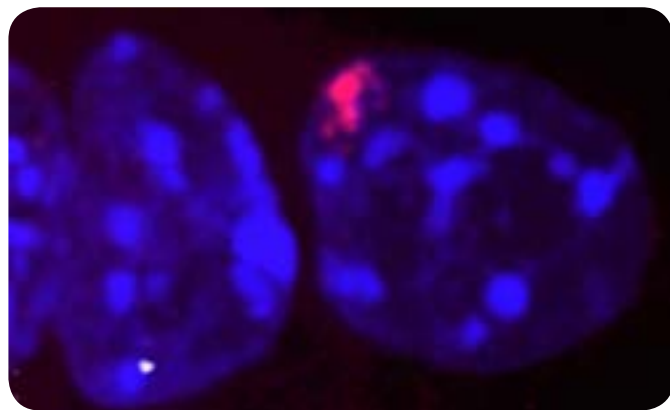
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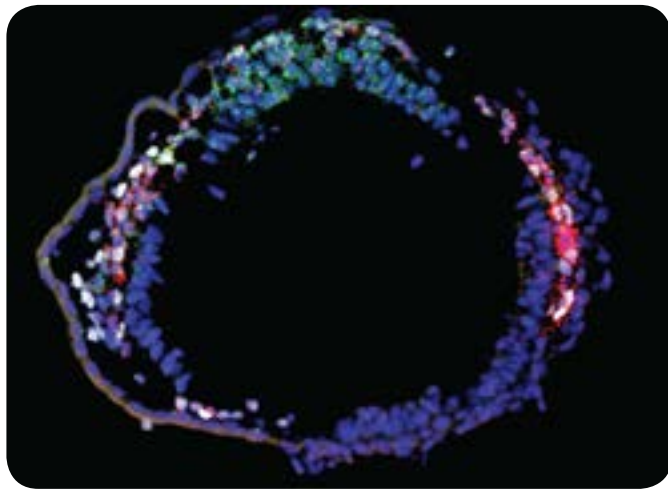
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