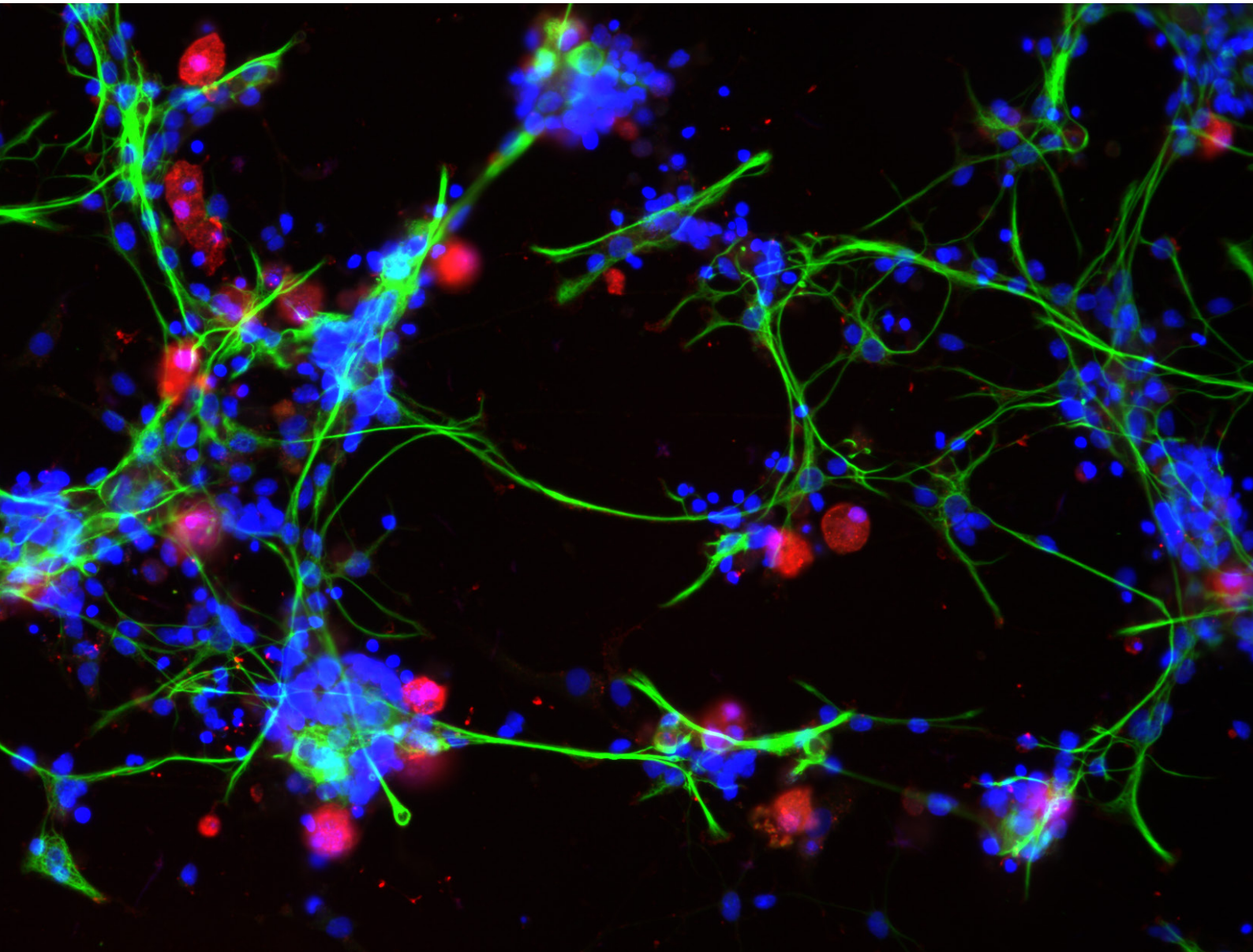
wellcome-MRC
cambridge
stem cell institute

# Annual Report 2019



**Front cover**
In vitro image of astrocytes (green) and microglia (red).
Cell nuclei are shown in blue.

Credit: Khalil Rawji (Franklin lab)

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

UNIVERSITY OF CAMBRIDGE

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# Contents

# 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 28 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.

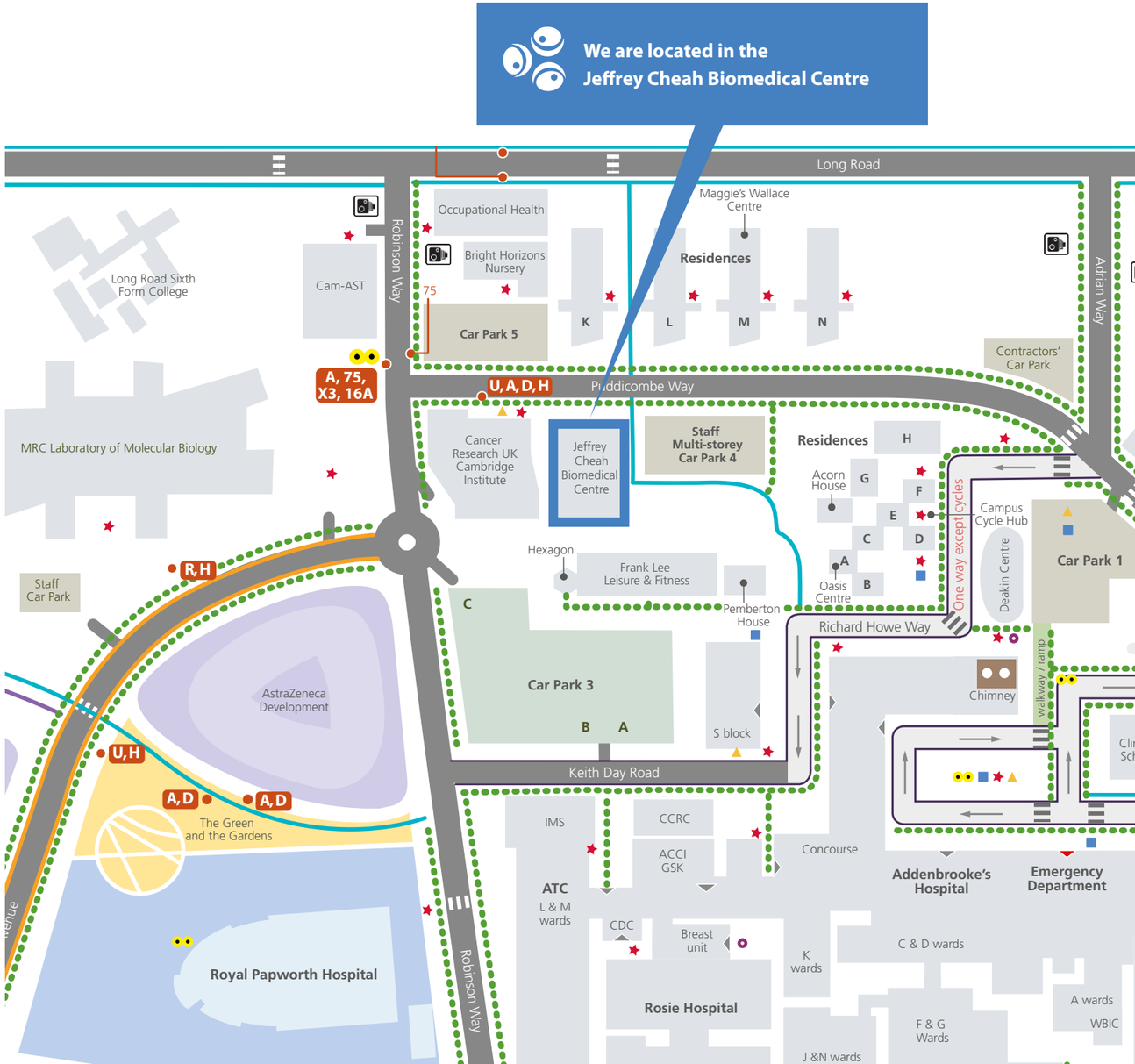
The Institute currently has 35 affiliated researchers across 15 University departments, as well as the Babraham Institute, Microsoft Research, Wellcome Sanger Institute, MRC Laboratory of Molecular Biology and EMBL- European Bioinformatics Institute.

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.

In September 2019, the Institute moved to its new home on the Cambridge Biomedical Campus, following extensive work on all levels to prepare for the relocation.

The move represents a major milestone for the Institute and groups from seven different buildings are now co-located in one building.



# Institute Research

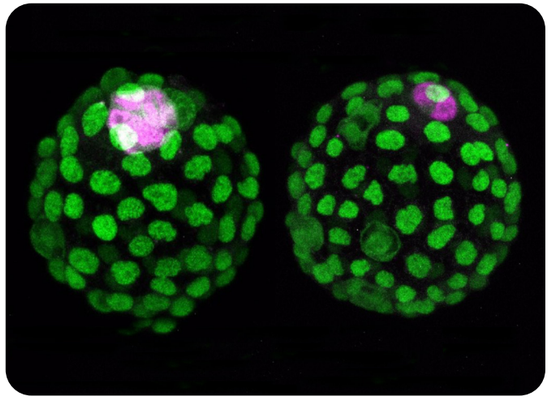
Research at the Institute falls under three key themes: Stem Cell States, Stem Cells in Disease, and Stem Cells and Therapeutics. Many of our scientists contribute to more than one theme, and within these themes we have particular strengths in pluripotency, haematopoiesis, neural and epithelial stem 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, E. Laurenti, J.-H. Lee, S. Méndez-Ferrer, J. Nichols, A. Philpott, D. Rowitch, J. Silva, B. Simons, S. Sinha, A. Smith & L. Vallier.*



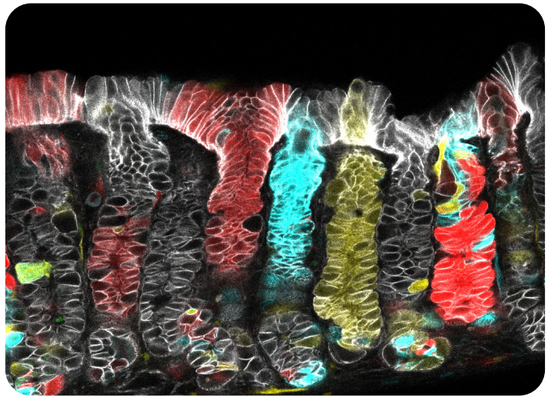
*Hendrich Lab*

### 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, E. Laurenti, J.-H. Lee, S. Méndez-Ferrer, A. Philpott, I. Ringshausen, D. Rowitch, B. Simons & G. Vassiliou.*



*Simons Lab*



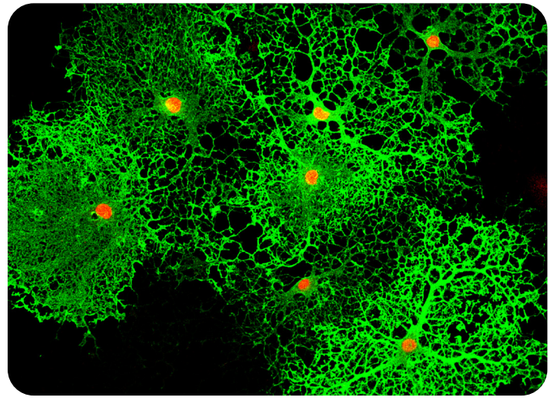


### Stem Cells & Therapeutics

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.*



*Franklin 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.

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.

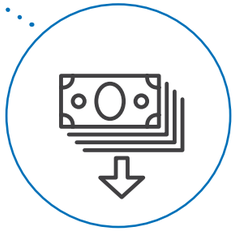
*Credit: Chris Loades*

# Cambridge Stem Cell Institute 2019 in numbers

>2300
Items of equipment moved to JCBC

28
Research groups under one roof

£117.7M
Total grant income for Institute group leaders



93
PhD students

166
Publications

>1200
New Twitter followers

7
Patents and invention disclosures

20
Public Engagement projects and activities organised

15
International and Guest Seminars organised

>40
Industry collaborations

12
Ongoing clinical trials

# Relocation to the Cambridge Biomedical Campus

Following an extension of the building completion, the Institute moved to its new home on the Cambridge Biomedical Campus in September 2019.

Over the last three years, work was carried out at all levels of the Institute to prepare for the relocation. Working groups were established to facilitate the smooth transition and a full HR consultation process with staff took place, resulting in a new administrative infrastructure to support the Institute.

Over 3 months, a complex moving plan was implemented, with 29 research groups, 7 core facilities, and over 2300 items of equipment, from 7 different buildings spread across Cambridge moving to the Jeffrey Cheah Biomedical Centre.

The relocation has already facilitated cross institute interactions and a programme of weekly internal seminars has been launched for PhD students and postdocs to present their work to the Institute community.

There are also several activities, social and research-related, jointly organised with our neighbours at CRUK Cambridge Institute. Further collaborative events and initiatives are also planned for the future.

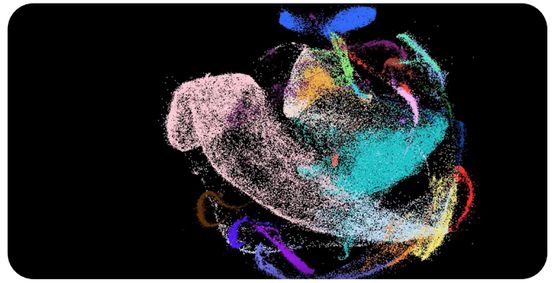
In addition to the Cambridge Stem Cell Institute, the Jeffrey Cheah Biomedical Centre is also home to the Cambridge Institute of Therapeutic Immunology & Infectious Disease and the Milner Therapeutics Institute.

Stem Cell Institute Research groups are located on three floors of the building, with core facilities supporting the building's researchers located on the ground floor and in the basement.

# Publication of Transformative Discoveries

**Elisa Laurenti** co-authored a study where scientists created the first human developmental liver cell atlas, providing crucial insights into how the blood and immune systems develop in the foetus. It is a comprehensive, high-resolution resource that improves our understanding of normal development and assists medical efforts to tackle diseases, such as leukaemia and immune disorders. *Image credit: Newcastle University*

Popescu D-M, Botting RA, Stephenson E, ..., **Laurenti E**, Teichmann SA, Haniffa M. Decoding human fetal liver haematopoiesis. **Nature**, 574, 365–371(2019).



**David Rowitch** co-led two new studies reporting progress in using stem cells to develop new therapies for Pelizaeus-Merzbacher disease (PMD), a rare genetic condition affecting boys that can be fatal before 10 years of age.

Nobuta H, Yang N, Ng YH, ..., **Franklin RJM**, **Rowitch DH**, Wernig M. Oligodendrocyte Death in Pelizaeus-Merzbacher Disease Is Rescued by Iron Chelation. **Cell Stem Cell**, 25(4):531-541.e6. & Gupta N, Henry RG, Kang SM, ..., Huhn SL, Barkovich AJ, **Rowitch DH**. Long-Term Safety, Immunologic Response, and Imaging Outcomes following Neural Stem Cell Transplantation for Pelizaeus-Merzbacher Disease. **Stem Cell Reports**. 13;13(2):254-261.

**Robin Franklin** led new research suggesting that metformin (a common diabetes drug used worldwide to treat diabetes) could hold the key to stopping multiple sclerosis, through its ability to restore cells to a younger, healthier state.

Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells. Neumann B, Baror, Zhao C, ..., **Chalut K**, van Wijngaarden P, **Franklin RJM**. Cell Stem Cell, 25, (4), 473-485.e8.


**Jose Silva** revealed for the first time that cells can actually follow a range of distinct molecular routes in order to reach the same final cell type, demonstrating a surprising flexibility in cell decision making during cell fate change.

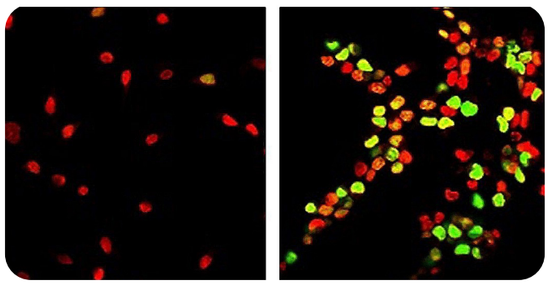
Stuart HT, Stirparo GG, Lohoff T, ..., **Nichols J**, **Göttgens B**, **Silva JCR**. Distinct Molecular Trajectories Converge to Induce Naive Pluripotency. **Cell Stem Cell**, 25(3):388-406.e8.



Institute researchers produced 166 publications in 2019, including 112 peer-reviewed primary research reports. Particular highlights are listed below, with a full list of 2019 Institute publications included on page 78.

**Kevin Chalut** and **Robin Franklin** led a multi-disciplinary team that showed how increasing brain stiffness as we age causes brain stem cell dysfunction, and demonstrates new ways to reverse older stem cells to a younger, healthier state. The results could help develop much-needed treatments for age-related brain diseases.

Segel M, Neumann B, Hill MFE, ..., Franze K, **Franklin RJM**, **Chalut KJ**. Niche stiffness underlies the ageing of central nervous system progenitor cells. **Nature**, 573(7772):130-134.



**Bertie Göttgens** co-authored multi-disciplinary research studying the genetic activity of over 100,000 embryonic cells to establish the molecular blueprint of early embryo development. This new insight provides fundamentally important information on how mammalian embryos develop during gastrulation, a key stage of development, and paves the way for new understanding of the earliest stages of life.

Pijuan-Sala B, Griffiths JA, Guibentif C, ..., **Nichols J**, Marioni JC, **Göttgens B**. A single-cell molecular map of mouse gastrulation and early organogenesis. **Nature**, 566(7745):490-495.

**Sanjay Sinha** and his team found that, by transplanting an area of damaged tissue with a combination of both heart muscle cells and supportive cells taken from the outer layer of the heart wall, they may be able to help the organs recover from the damage caused by a heart attack.

Bargehr J, Ong LP, Colzani M, ..., Bennett MR, Murry CE, **Sinha S**. Epicardial cells derived from human embryonic stem cells augment cardiomyocyte-driven heart regeneration. **Nature Biotechnology**, 37(8):895-906.

**David Rowitch** co-led a new study pinpointing the cell types affected in brains of multiple sclerosis patients. The research showed that projection neurons are damaged by the body's own immune cells, and that this damage could underpin the brain shrinkage and cognitive changes associated with MS. These new findings provide a platform to develop new specific MS therapies that target damaged brain cells.

Schirmer L, Velmeshev D, Holmqvist S, ..., Shiow LR, Kriegstein AR, **Rowitch DH**. Neuronal vulnerability and multilineage diversity in multiple sclerosis. **Nature**, 573(7772):75-82.

# 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.

**Roger Barker** is involved in several clinical trials investigating new treatments for patients with Parkinson's disease and Huntington's disease, including the TRANSEURO study, an open label transplant study in Parkinson's Disease trial which treated its last patient in May 2018, with results on the primary end point expected in April 2021 (NCT01898390).

Work is ongoing on to develop a trial using human embryonic stem cell-derived midbrain dopaminergic (STEM-PD) progenitor cells. This study is pending regulatory approval, with a planned start April 2021.

**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 (EudraCT 2015-005497-38).

**Simón** was also invoved in the trial studying the Effects of Sympathicomimetic Agonists on the Disease Course and Mutant Allele Burden in Patients with JAK2-mutated Myeloproliferative Neoplasms. The results for this trial were published in 2019 (NCT02311569).

**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 published in 2019, in Stem Cell Reports, 13;13(2):254-261 (NCT01005004 / NCT01391637).

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

**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. All 50 people with MS on the trial have completed the treatment phase and many have come to the end of the trial. Results are expected in 2020 (EudraCT 2014-003145-99).

**Cédric Ghevaert** designed the recovery and survival of stem cell originated red cells (RESTORE) trial, which is due to commence patient recruitment in 2020.

**Dan Hodson** designed the DLBCL Interim Response Evaluation for Customised Therapy (DIRECT) trial which is currently pending regulatory approval and is expected to open in 2020.



# 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 40 active commercial and industrial collaborations. In 2019, 4 patents and 3 invention disclosures were filed.

**Ludovic Vallier** started a new project facilitated by the Milner Institute focusing on the identification of new therapeutics for liver disease. Working with GlaxoSmithKline and Ferring Pharmaceuticals, this project will bring together a novel in vitro human model for non-alcohol fatty liver disease/non-alcoholic steatohepatitis developed in the Vallier group and NASH/NAFLD expertise from the two companies.

Ludovic also established a spinout company, Hepatotarget Therapeutics, that will use stem cell differentiation technology to manufacture mature hepatocytes as a cell therapy for liver disease.

**Ingo Ringshausen** submitted a patent for Therapeutic Treatment using Protein Kinase C (PKC) Inhibitors and Cytotoxic Agents (pending).

**Cedric Ghevaert** has established two spinout companies based on his research. Tropofour Therapeutics is developing a compound to control platelet formation and CellAdvice Ltd is a consultancy for companies involved in tranfusion products or cell therapies.

# 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 174 applications in 2019. We also recruited 1 student to join 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 77 students as of October 2019 and a further 16 students completing their studies last year. In 2019, the PhD students co-authored 43 publications, 24 as first author.

Each year the Institute runs a productive and enjoyable PhD Symposium and Away Day. In 2019, 13 PhD students presented their research projects and Sir John Gurdon gave the keynote lecture 'Half a century at the bench, and still there'. Over 40 posters were on display from students based in Institute and affiliated research groups.

The Institute has been awarded funding to extend the 4-year Wellcome PhD Programme in Stem Cell Biology and Medicine for a further 5 years.

### Clinician Scientists

Approximately 40% of group leader positions at the Institute are clinically based and facilitate collaborations between basic scientists and those driven by disease-focused questions.

The Institute currently hosts 12 clinically trained PhD students and 5 clinical lecturers and clinically trained postdocs/fellows.




# 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 an increase of over 1200 followers in 2019, with over 650K tweet impressions.

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 2019, face-to-face public events allowed researchers to actively engage with thousands of individuals, highlights of which can be found on page 18.


### Representation & Impact

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

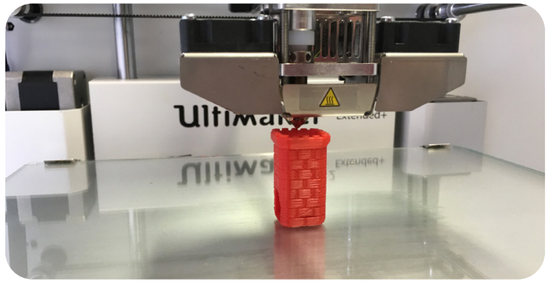
In 2019, the Institute collaborated with EuroStemCell, a public-facing organisation, through contribution to the initiative #openupstemcells, a digital engagement campaign where four of our researchers produced quick and easily accessible films explaining their research in stem cells. The films are now freely available on eurostemcell.org, a hub for people looking for reliable information on stem cell therapies and current research.

# 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.

### 3D Printing Workshop for Stem Cell Scientists

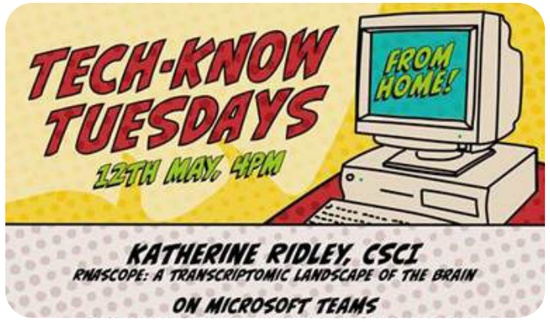
With the support of the University's interdisciplinary small grants schemes, a group of biologists and engineers from the Cambridge Stem Cell Institute ran an interactive three-day workshop to teach the stem cell community about the practical uses of 3D printing technology. The workshop was led by three members of the Kent lab and used worked examples to explore how 3D printing can be used to build practical tools to enhance research in a fast and inexpensive way. The attendees joined from 11 different University Departments in a truly cross-disciplinary event.



### Techknow Tuesdays

This event, set up by institute post-docs Dan Prins (Green lab) and Craig McDonald (Kent lab), brings together researchers from across Cambridge to discuss the latest technologies and their application to stem cell research.

Talks are held monthly and are followed by a chance to network with researchers from across the Institute and other departments from the Biomedical Campus and central Cambridge.




### Stem Cells & Society Seminar Series

The Institute also partnered with the Department of Sociology at the University of Cambridge to run a series of five consecutive seminars on the subject "Stem Cells and Society". The series was led by sociologists Prof Sarah Franklin, Dr Noémie Merleau-Ponty and Dr Karen Jent and was designed to offer a comprehensive introduction to the social issues raised by stem cell research.

Topics up for discussion included how the legislation covering embryo research emerged in the UK, the importance of open dialogue in the development of UK science policy and the role of media coverage and public engagement in shaping percceptions of stem cell research.



### StemCells UK

Working together with The Francis Crick Institute and the Centre for Regenerative Medicine, Edinburgh, we were very pleased to organise the first Stem Cells UK meeting, on 1st October 2019. The meeting brought together stem cell researchers from across the UK sharing research ideas, forging collaborations and meeting friends old and new.

The one day event had over 100 attendees from across the UK stem cell community, with a programme of talks from leading researchers, and networking sessions.


### 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. Since the move to our new building, these Seminars have had a large increase in attendance. They are open to everyone and advertised widely across the Cambridge stem cell community. Seminar topic highlights in 2019 include: cortical interneuron diversity (Oscar Marin, King's College London), reproducibilty in research (Glenn Begley, Biocurate, Australia), developmental lineages (Alexander Schier, Basel's Biozentrum/Harvard University), angiogenesis and vascular metabolistm (Peter Carmeliet, KU Leuven).


### Institute Annual Retreat

This 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.

# Public Engagement

Our public engagement strategy mandates our commitment to engagement at an Institute level in support of the Centre's strategic mission.

## Aim 1: Reach beyond Cambridge to raise awareness about stem cells on a national and international level

**4L Rally, February**
Two PhD students took to the road to engage local communities and deliver educational resources as part of a two-week adventure across the Moroccan dessert.


**#openupstemcells, October**
Researchers answered public questions about stem cells as part of a digital engagement campaign led by EuroStemCell for Stem Cell Awareness Day.


**@Seuninscience**
Oluwaseun Ogundele's YouTube vlog and Instagram made a big impact in 2019, sharing personal stories to inspire young BAME students into lab science.

## Aim 2: Connect to local under-served communities and empower them to access stem cell research

**LifeLab, September**
Institute researchers took stem cells to Ely as part of European Researchers Night, engaging 300 local families and residents on a busy Saturday at the Cathedral.

**Flying in the Air, October**
The Ghevaert group combined research and music for a charity concert for local churchgoers in Newmarket. Raising £1,348 for East Anglian Air Ambulance.


**Stem Cell Beer**
We continued our collaboration with local brewery Moonshine to create a second brew, supporting researchers to reach new faces at beer festivals and pubs.



In 2019 the Institute put its new strategy into action, delivering over 20 projects and activities for thousands of people online and in person.

## Aim 3: Give patients a voice in our research and engagement activities which is valued and utilised

**Art + Science at Jeffrey Cheah Biomedical Centre, December**
We opened our ground floor public space with a big celebration in December in collaboration with Kettle's Yard gallery. A series of new collaborative artworks were unveiled by artists Victoria Morton, Harold Offeh and Dalziel and Scullion, including a piece created with a local branch of the MS Society. A free-standing pinball machine will join the artworks in 2020, encouraging hands-on game play with stem cell differentiation.
Looking ahead, our café and public space will be a place where public and patient groups on the campus can learn about our science and mix with our researchers, supported by a tailored programme of public events and exhibitions.

## Aim 4: Create and open and engaged research culture

Following the move to Jeffrey Cheah Biomedical Centre we set up a Lab Champion network to support 'grass-roots' interest and uptake of public engagement. The group meets informally once a month over coffee to discuss new ideas and share opportunities and training.

Dr Cedric Ghevaert has taken over as academic champion for public engagement, providing leadership through our Steering Committee.

Finally, the Institute awarded £4,750 in public engagement seed funding in 2019, to five researcher-led projects aligned to our strategy. Watch this space for what they deliver in 2020!

# 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

**Elisa Laurenti**
Human haematopoietic stem cells biology in health & disease

**Ingo Ringshausen**
Haematopoietic stem cells & malignancies

**David Rowitch**
Glial cells & response to injury

**José Silva**
Reprogramming and programming cell identity

**Ben Simons**
Stem cell fate in development, maintenance & disease

**Sanjay Sinha**
Vascular diseases

**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

**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

**Anna Philpott**
Proneural transcription factors

**Austin Smith**
Stem cell potency

**Ludovic Vallier**
Differentiation of pluripotent stem cells into definitive endoderm

**George Vassiliou**
Leukaemic haemopoietic stem cells

# MARIA ALCOLEA

## 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.

### LAB MEMBERS

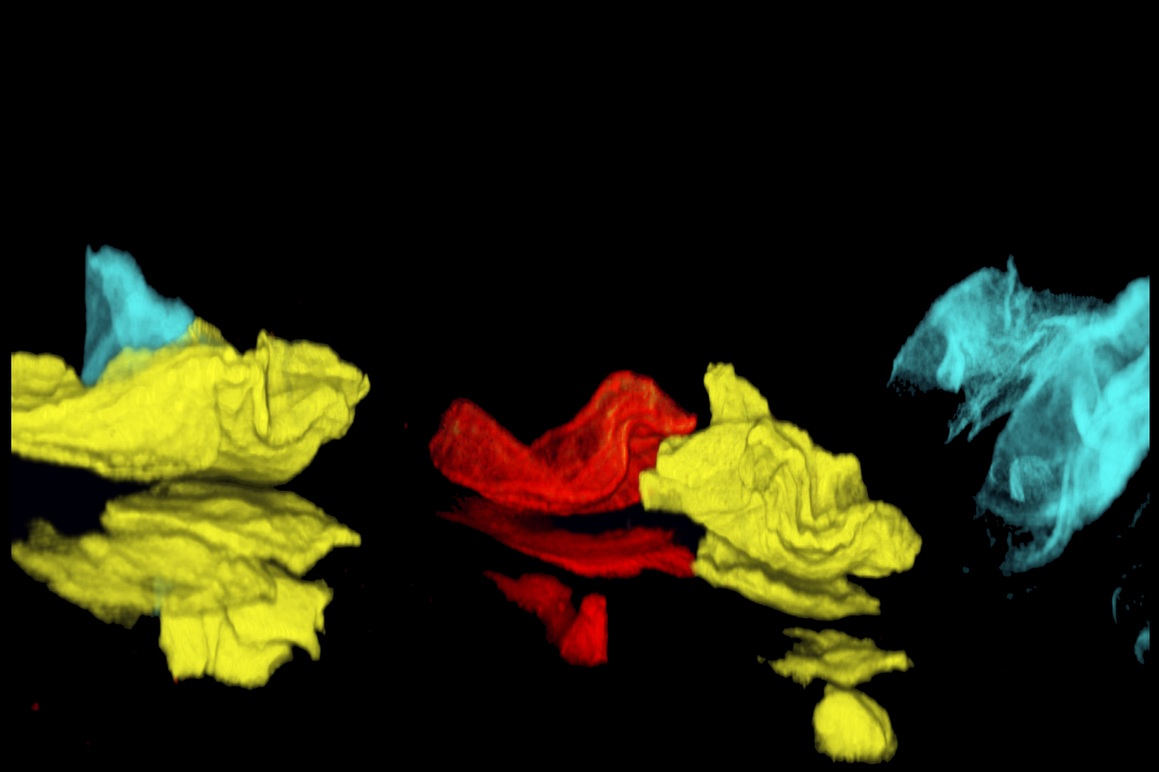
Maria Bejar Serrano
Sara Bisetto
Adrien Hallou
Paula Jimenez-Gomez
Jamie McGinn
Jesus Eduardo Rojo
Greta Skrupskelyte

### 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.

Doupé 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

## 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.

### LAB MEMBERS

Katie Andresen
Emma Cutting
Danielle Daft
Shaline Fazal
Kate Harris
Xiaoling He
Sam Hewitt
Wei-Li Kuan
Sarah Mason
Venkat Pisupati
Shama Qarin
Priya Rogers
Sophie Skidmore
Kelli Tornsey
Pam Tyers
Benjamin Vallin
Zanna Voysey
Alice White

### KEY PUBLICATIONS

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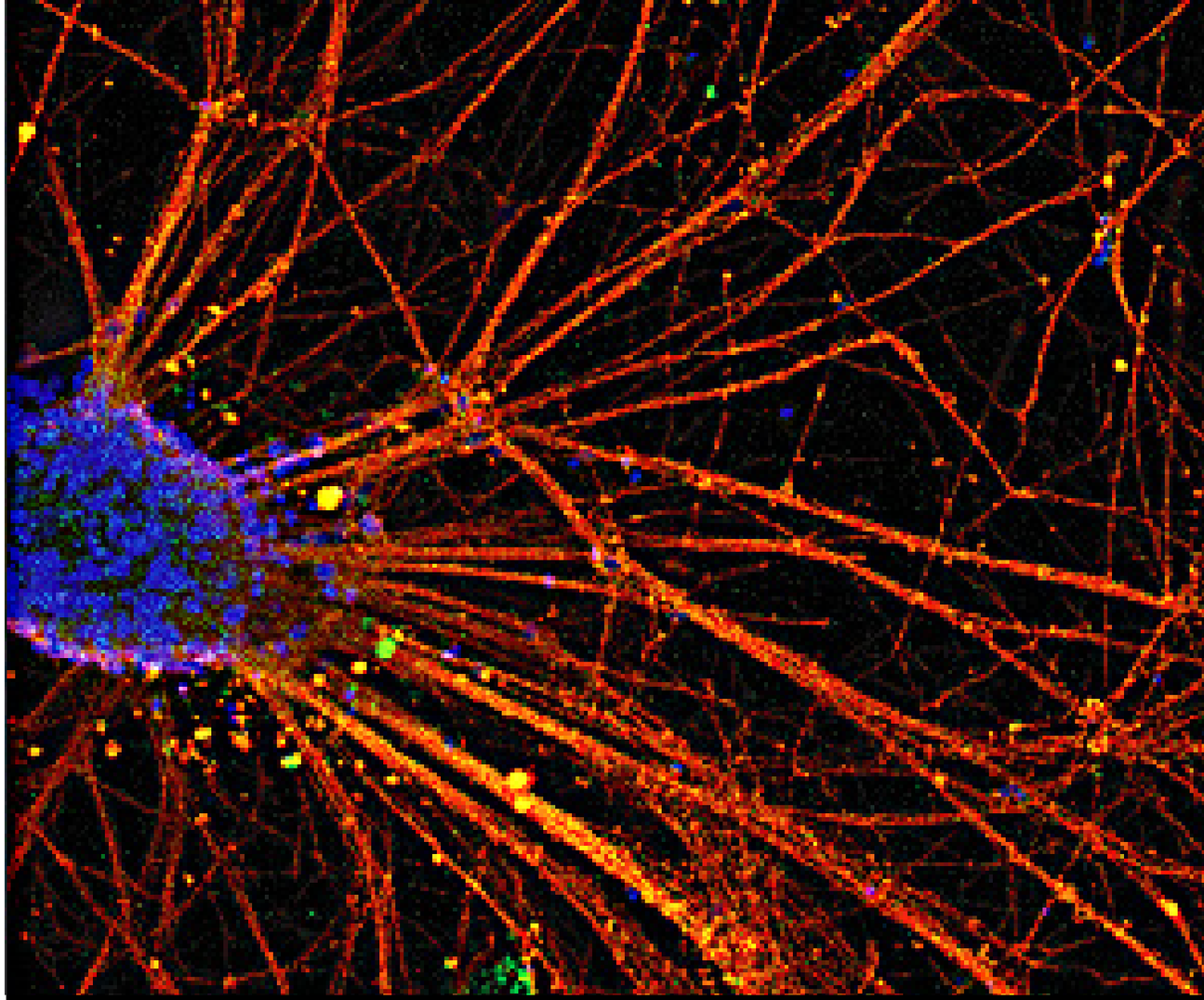

*Dopaminergic neurons differentiated from human pluripotent stem cells using GMP compliant differentiation protocol—TH (green), btub (red)*

*Credit: Civia Chen*

# SRINJAN BASU

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

## LAB MEMBERS

Igor de Almeida
Stanley Strawbridge
Maike Steindel
Oliver Davis
Jorg Morf

The generation of diverse cell types from stem cells is a hallmark of metazoan biology, yet the mechanisms that initiate and subsequently stabilise cell type-specific gene expression programmes remain ill-defined.

Our research focuses on developing single-cell and single-molecule imaging approaches to improve understanding of the dynamics of stem cell renewal and differentiation. Specifically, we are interested in how the dynamics of signalling molecules and chromatin binding proteins regulate gene expression during stem cell fate transitions and why these pathways are often mis-regulated during early cancer progression.

Single-cell and single-molecule approaches are key to understanding how these proteins work due to the considerable cellular and molecular 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 mouse 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 and tracking them as they perform their function in live cells.

## KEY PUBLICATIONS

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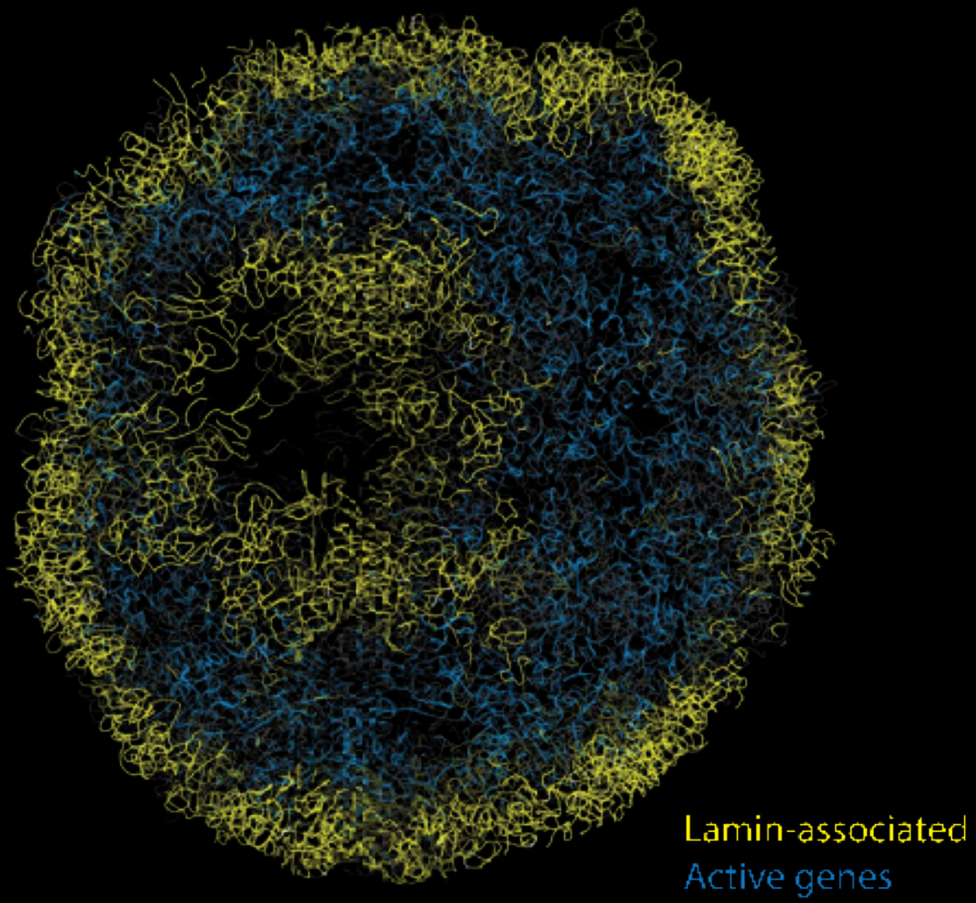


*Genome architecture of a single mouse embryonic stem cell with gene-poor lamin regions in yellow separating away from active genes in blue*

*Credit: Tim Stevens, MRC-LMB*

# SIMON BUCZACKI

# Colorectal cancer cell identity and tumour evolution

## LAB MEMBERS

Mahnaz Darvish Damavandi
Christopher Ward

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

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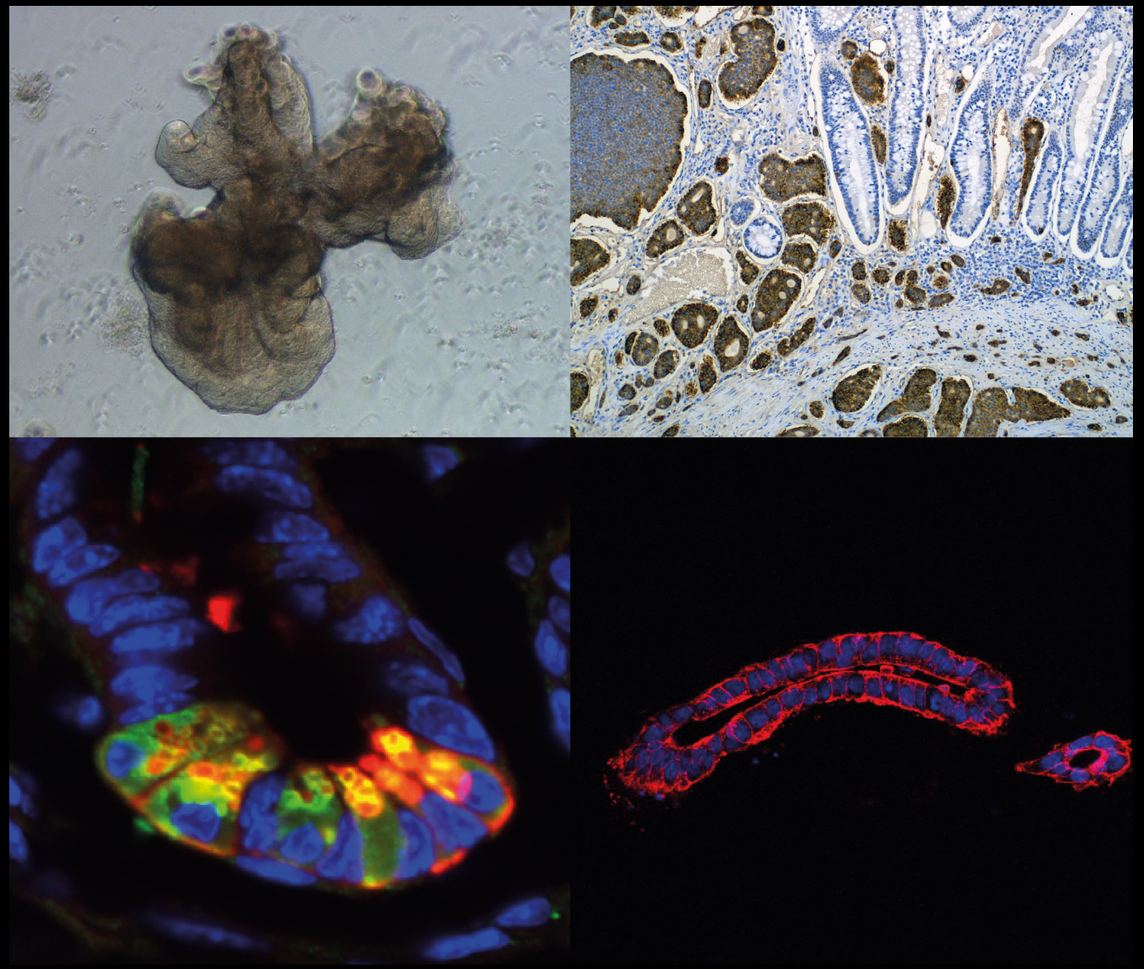

*A human small bowel organoid (upper left), a human intestinal neuroendocrine tumour (upper right), a mouse intestinal crypt highlighting Paneth cells (lower left) and a human colorectal cancer organoid (lower right).*

*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
Carla Mulas
Sarah Pallett
Bao Xiu Tan

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 during stem cell differentiation and 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

Segel M, Neumann B, Hill MFE, Weber IP, Viscomi C, Zhao C, Young A, Agley CC, Thompson AJ, Gonzalez GA, Sharma A, Holmqvist S, Rowitch DH, Franze K, Franklin RJM, **Chalut KJ**. Niche stiffness underlies the ageing of central nervous system progenitor cells. **Nature** 573, 130–134.

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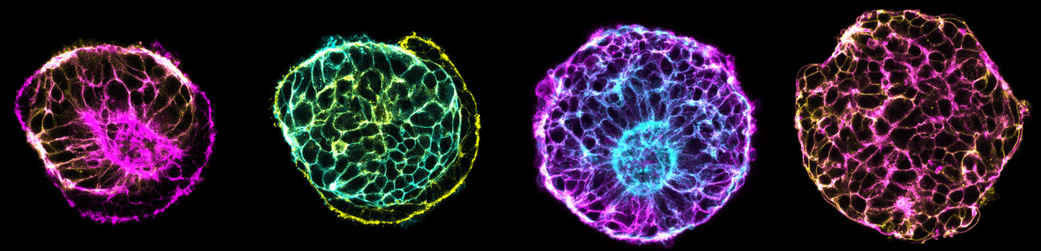

*Two confocal slices of two human Embryonic Stem Cell colonies showing overlay of actin and EPCAM (a cell adhesion molecule) in changing colors. hES cells were grown on soft hydrogels and appear to self-organise in 3d structures. Images were taken with a 40x, oil objective on Leica SP5. Colonies are approximately 40µm in diameter.*

*Credit: Celine Labouesse/Patrick Rericha*

# ANA CVEJIC

# Haematopoietic stem cells

## LAB MEMBERS

Brynelle Myers
Elisa Panada
Anna Maria Ranzoni
Simone Riva
Andrea Tangherloni
Henry Xu

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 haemopoietic 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 particularly, 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

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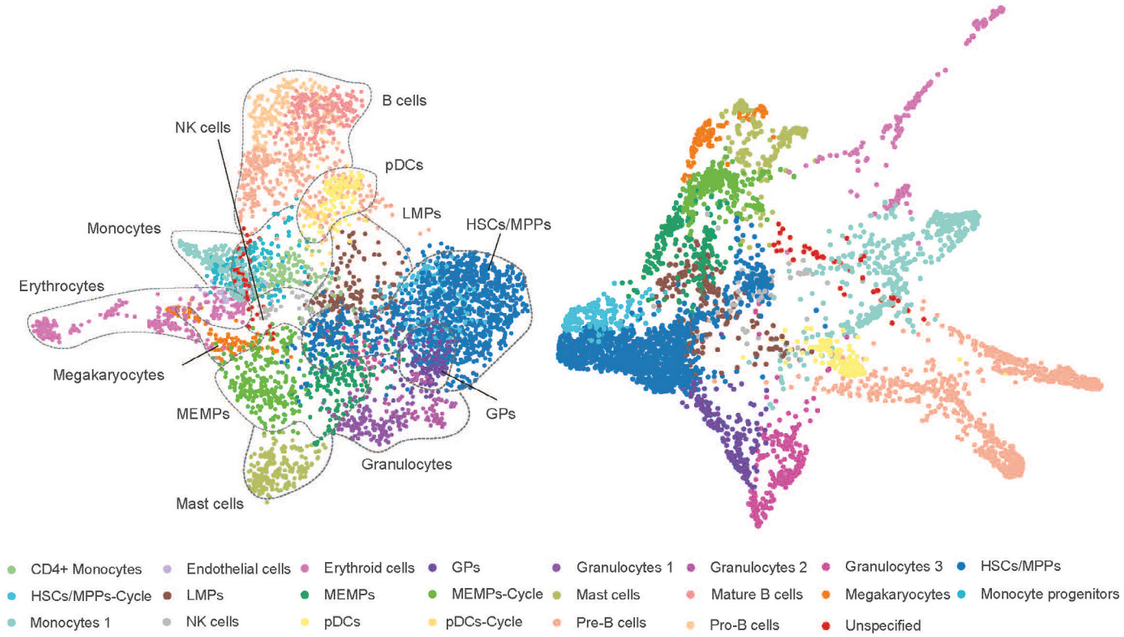


*Uniform Manifold Approximation and Projection (UMAP) visualisation (left) and Force-Directed Graph (FDG) representation (right) of human foetal haematopoietic cells from liver and bone marrow.*

*Credit: Andrea Tangherloni & Anna Maria Ranzoni*

# 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 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
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Tanay Ghosh
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Myfanwy Hill
Daniel Morrison
Bjoern Neumann
Feride Oeztuerk-Winder
Khalil Rawji
Amar Sharma
Zhaozong Wu
Adam Young
Chao Zhao

## KEY PUBLICATIONS

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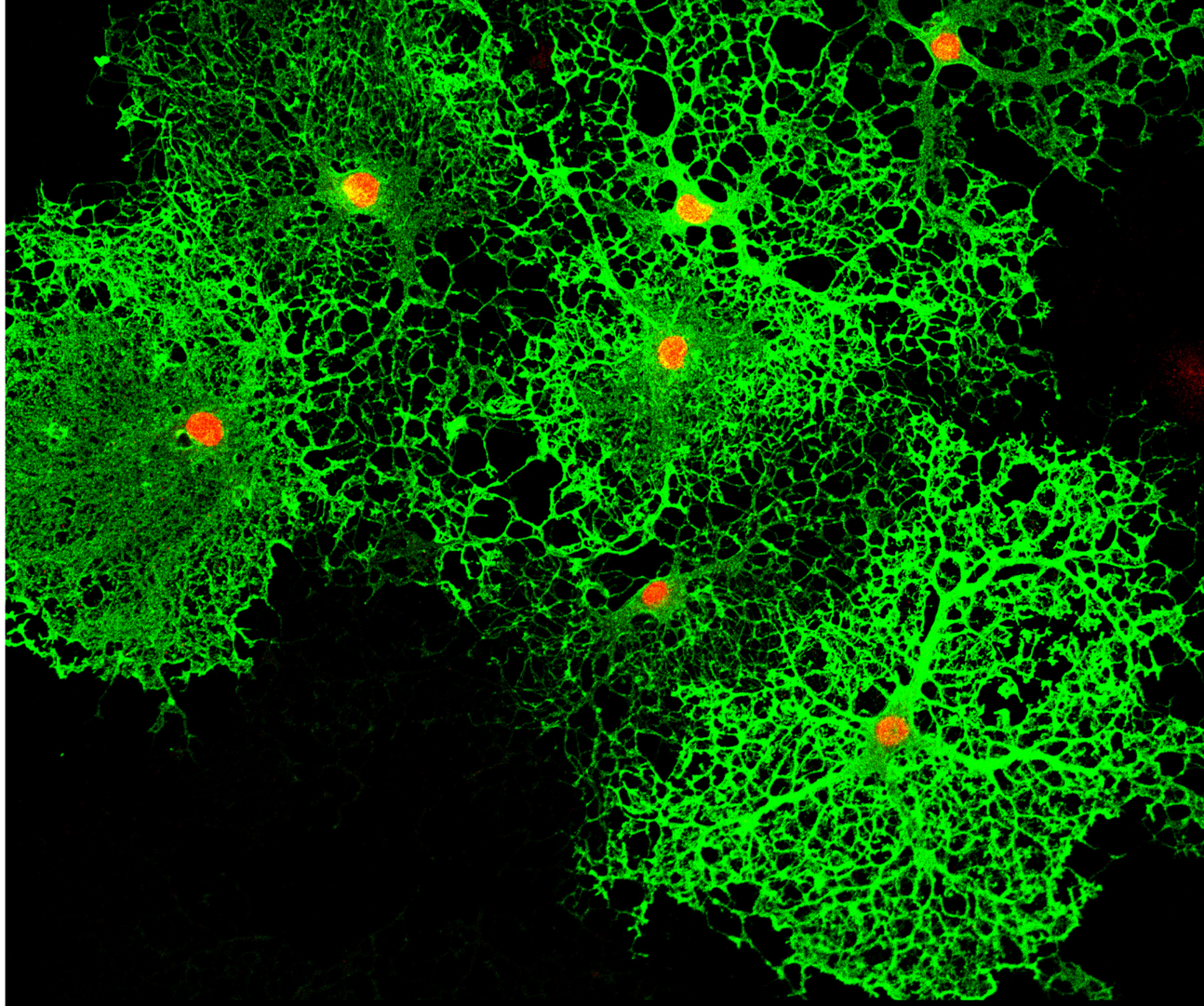

*Oligodendrocytes differentiated from adult CNS progenitors*

*Credit: Bjoern Neumann*

# CÉDRIC GHEVAERT

# *In vitro* production of platelets for transfusion

## LAB MEMBERS

Amanda Evans
Holly Foster
Nina Herbert
Daniel Howard
Winnie Lau
Moyra Lawrence
Amanda Niven
Adam Pullen
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

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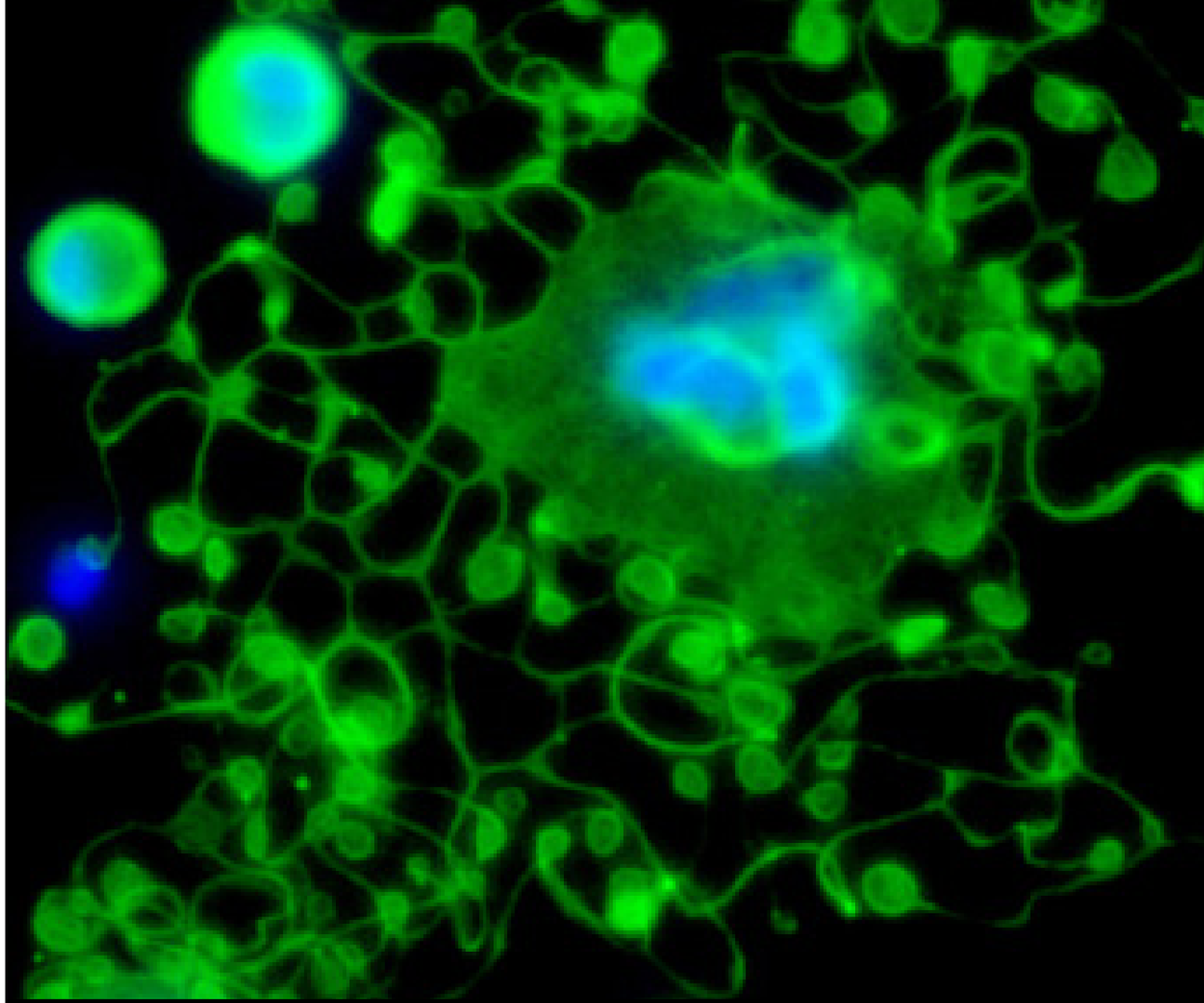

*Fluorescent image of a megakaryocyte produced in the laboratory from stem cells isolated from cord blood. The megakaryocyte is in the process of releasing platelets, the little blood corpuscle that is responsible for blood clotting. The nucleus of the cell is stained in blue with DAPI. In green is one 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
Myriam Haltalli
Rebecca Hannah
Ivan Imaz-Rosshandler
Alison Kennedy
Sarah Kinston
Iwo Kucinski
Mariana Quiroga Londono
Kat Sturgess
Mai-Linh Ton
Sam Watcham
Xiaonan Wang
Nicola Wilson

### KEY PUBLICATIONS

Pijuan-Sala B, Wilson NK, Xia J, Hou X, Hannah RL, Kinston S, Calero-Nieto FJ, Poirion O, Preissl S, Liu F, **Göttgens B**. Single-cell chromatin accessibility maps reveal regulatory programs driving early mouse organogenesis. **Nature Cell Biology**, 22; 487–497.

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*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

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.

### LAB MEMBERS

Marina Akasaka
Juliet Aungier
Hugo Bastos
Miriam Belmonte
Tina Hamilton
Thorsten Klampfl
Joe Lee
Juan Li
Stephen Loughran
Hyun Jung Park
Dean Pask
Daniel Prins
Rachel Sneade
Michelle Wantoch
Matthew Williams

### KEY PUBLICATIONS

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

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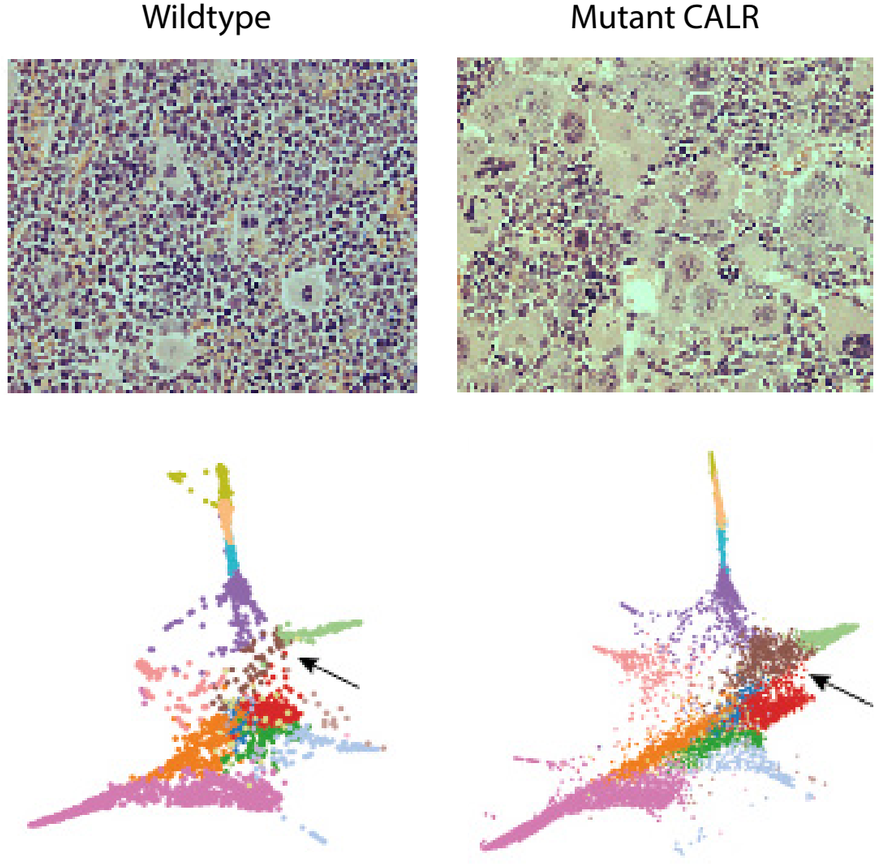


*Knock-in mice expressing mutant calreticulin develop markedly increased megakaryopoiesis (upper panels). Single cell RNAseq analysis of haematopoietic stem and progenitor cells reveals a novel megakaryocytic progenitor population (lower panels, brown dots indicated by arrows).*

*Credit: Juan Li, Daniel Prins & Sam Watcham*

# BRIAN HENDRICH

# Transcriptional control of stem cell fate

## LAB MEMBERS

Robin Floyd
Dominic Hall
Andria Koulle
Oluwaseun Ogundele
Ramy Ragheb
Nicola Reynolds

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

Ragheb R, Gharbi S, Cramard J, Ogundele O, Kloet S, Burgold T, Vermeulen M, Reynolds N, **Hendrich B**. Differential regulation of lineage commitment in human and mouse primed pluripotent stem cells by NuRD. **bioRxiv** doi: https://dx.doi.org/10.1101/2020.02.05.935544.

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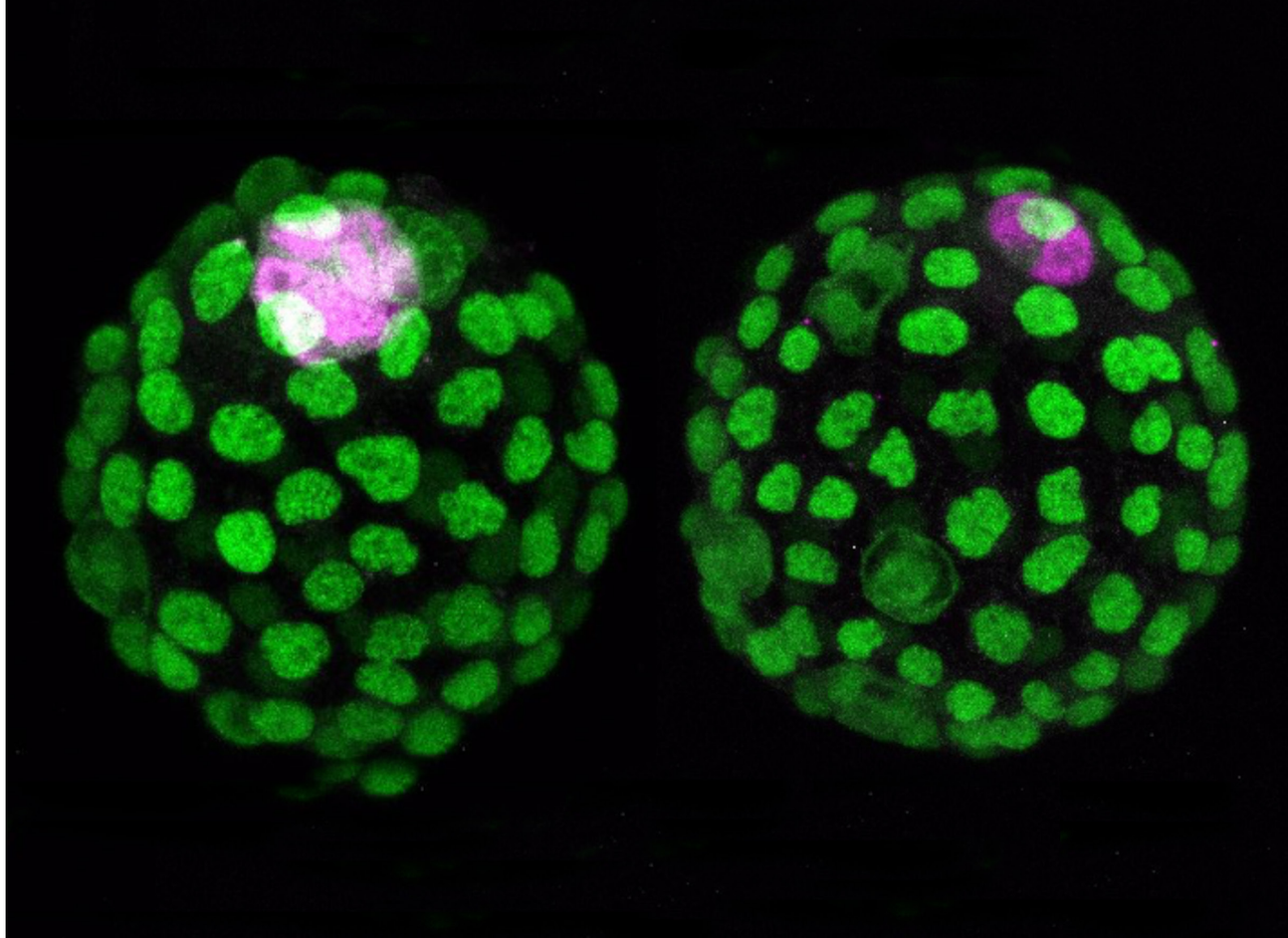

*Chimaeric blastocysts were created using wild type mouse embryos and either wild-type embryonic stem (ES) cells (left) or ES cells in which the important chromatin remodelling complex, NuRD, was missing (right). ES cells were labelled with a protein, here shown in white. The embryos are also stained for nuclear markers of trophectoderm (Cdx2 - Green) or inner cell mass (Sox2 - Magenta). Wild type ES cells contribute significantly to the inner cell mass lineage but never to the trophectoderm lineage. In contrast, cells lacking the NuRD complex contribute poorly to chimaeric blastocysts because they are unable to properly respond to the developmental cues and contribute significantly to the inner cell mass, though they also fail to adopt the inappropriate identity of trophectoderm cells. These and other experiments in the lab have shown how chormatin remodelling is important for stem cells to properly execute lineage decisions and form the normal range of differentiated cell types. Burgold et al. 2019 doi: http://doi.org/10.15252/embj.2018100788*

*Photo credit: Nicola Reynolds and Brian Hendrich*

# DANIEL HODSON

# Mutation timing in lymphomagenesis

## LAB MEMBERS

Miriam Di Re
Laura Everton
Rachel Fenner
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

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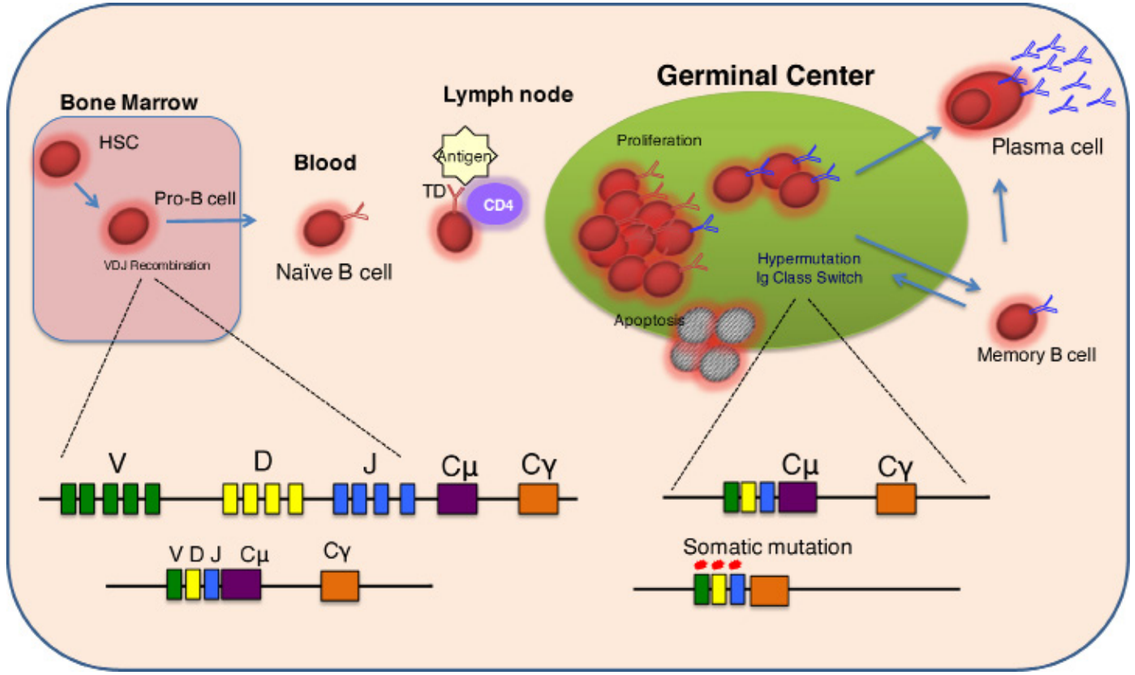


*Diagram showing the unique and dangerous life of the B lymphocyte with recurrent episodes of deliberately induced DNA damage contributing to the risk of transformation to B cell lymphoma.*

*Credit: Hodson Lab*

# BRIAN HUNTLY

# Leukaemia stem cell biology and leukaemogenesis

## LAB MEMBERS

Shuchi Agrawal Singh
Alicia Garcia-Gimenez
George Giotopoulos
Sarah Horton
David Lara
Pedro Madrigal
Ludovica Marando
Eshwar Meduri
Nisha Narayan
Simon Richardson
Nathalie Sakakini

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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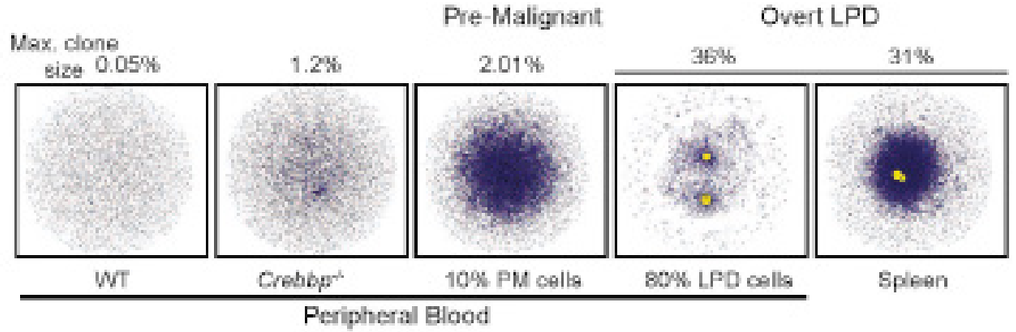


*Charting the clonal evolution of lymphoma (from left to right), using specific immunoglobulin rearrangements as specific clonal cellular barcodes (taken from Horton et al, Nature Cell Biology 2017).*

*Credit: Sarah Horton*

# RAGNHILDUR THÓRA KÁRADÓTTIR

## Neurotransmitter signalling to central nervous system progenitor cells

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 investigtion 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.

### LAB MEMBERS

Giulia Bonetto
Paul Charlesworth
Sarah Crisp
Omar De Faria Junior
Kimberley Evans
Jennifer Jia
Yasmine Kamen
Helena Pivonkova
Sebastian Timmler
Balazs Varga

### KEY PUBLICATIONS

Spitzer S, Sitnikov S, Kamen Y, Evans KA, Kronenberg-Versteeg D, Dietmann S, de Faria O, Agathou S & **Káradóttir R**. Oligodendrocyte progenitor cells become regionally diverse and heterogeneous with age. **Neuron**. 2019 Feb 6;101(3):459-471.

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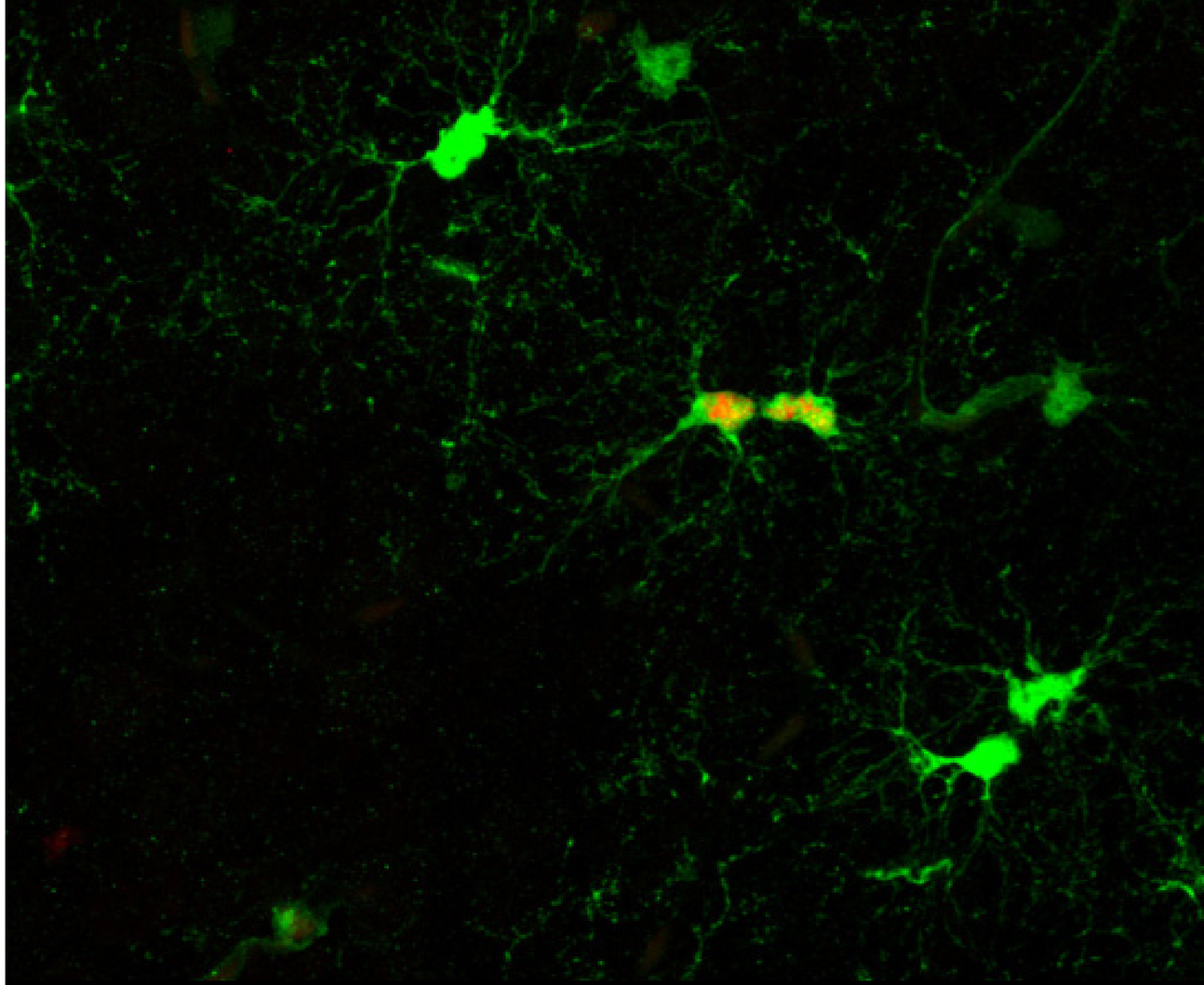

*Proliferating oligodendrocyte progenitor cells in a mouse brain slice.*

*Credit: Kimberley Evans*

# ELISA LAURENTI

# Human haematopoietic stem cells biology in health and disease

## LAB MEMBERS

Emily Calderbank
Anna Clay
Samuel Eyrolle-Cellier
Daniel Hayler
Carys Johnson
Nicole Mende
Kendig Sham
Aditi Vedi

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

Popescu D, Botting RA, Stephenson E, Green K, Webb S, Jardine L, Calderbank EF,… Regev AD, Chedotal A, Roberts I, Gottgens B, Behjati S*, **Laurenti E***, Teichmann SD*, Haniffa M*. Decoding human fetal liver haematopoiesis. **Nature**, 574, 2019, 365-371. *equal contribution

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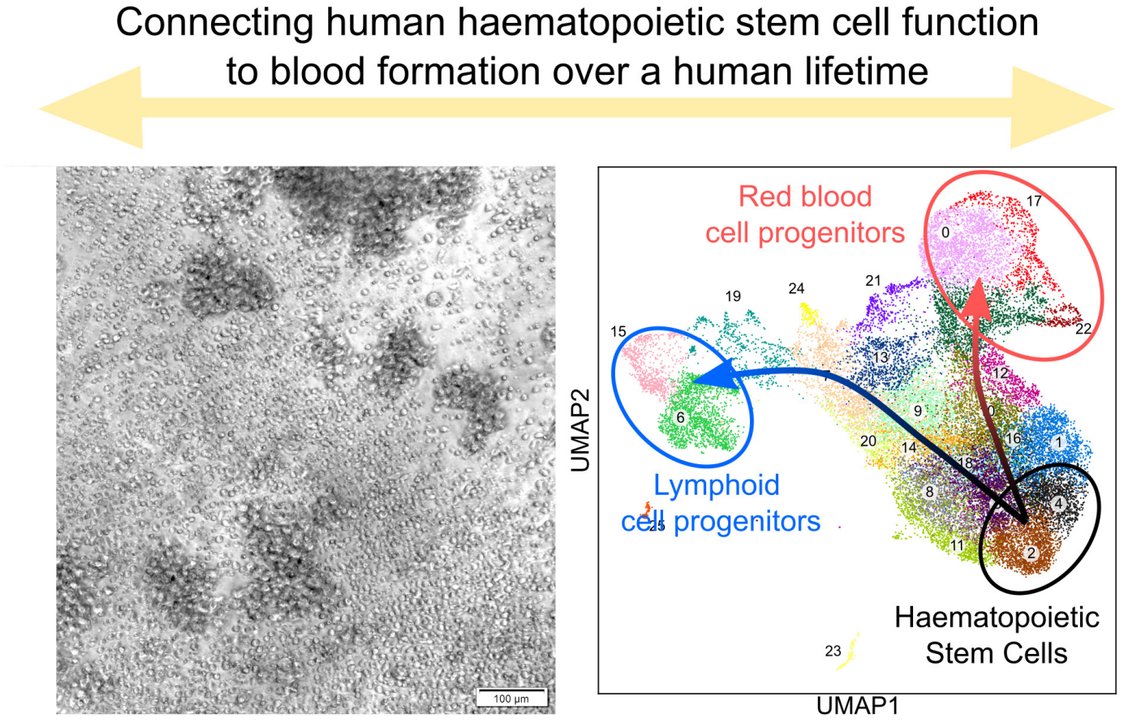


*Left: image of different blood cell types originated from a single human haematopoietic stem cell in vitro (credit: Aditi Vedi);*
*Right: the transcriptional landscape of the human haematopoietic hierarchy, derived from single cell transcriptomics (credit: Hugo Bastos, Nicole Mende).*

# JOO-HYEON LEE

## Stem cells and niches

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.

### LAB MEMBERS

Jinwook Choi
Catherine Dabrowska
Frances England
Kelly Evans
Rhys Fox
Antranik Mavousian
Vishal Menon
Sagar Varankar
June Young Park

### KEY PUBLICATIONS

Ombrato L, Nolan E, Kuerlac I, Mavousian A, Bridgeman V, Heinze I, Chakravarty P, Horswell S, Gonzales-Gualda E, Matacchione G, Weston A, Kirkpatrick J, Husain E, Speirs V, Collinson L, Ori A, **Lee JH**† and Malanchi I†. Metastatic niche labelling reveals tissue parenchyma stem cell features. **Nature**, 572 (7771), 603-608.

**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**,170(6):1149-1163.e12.

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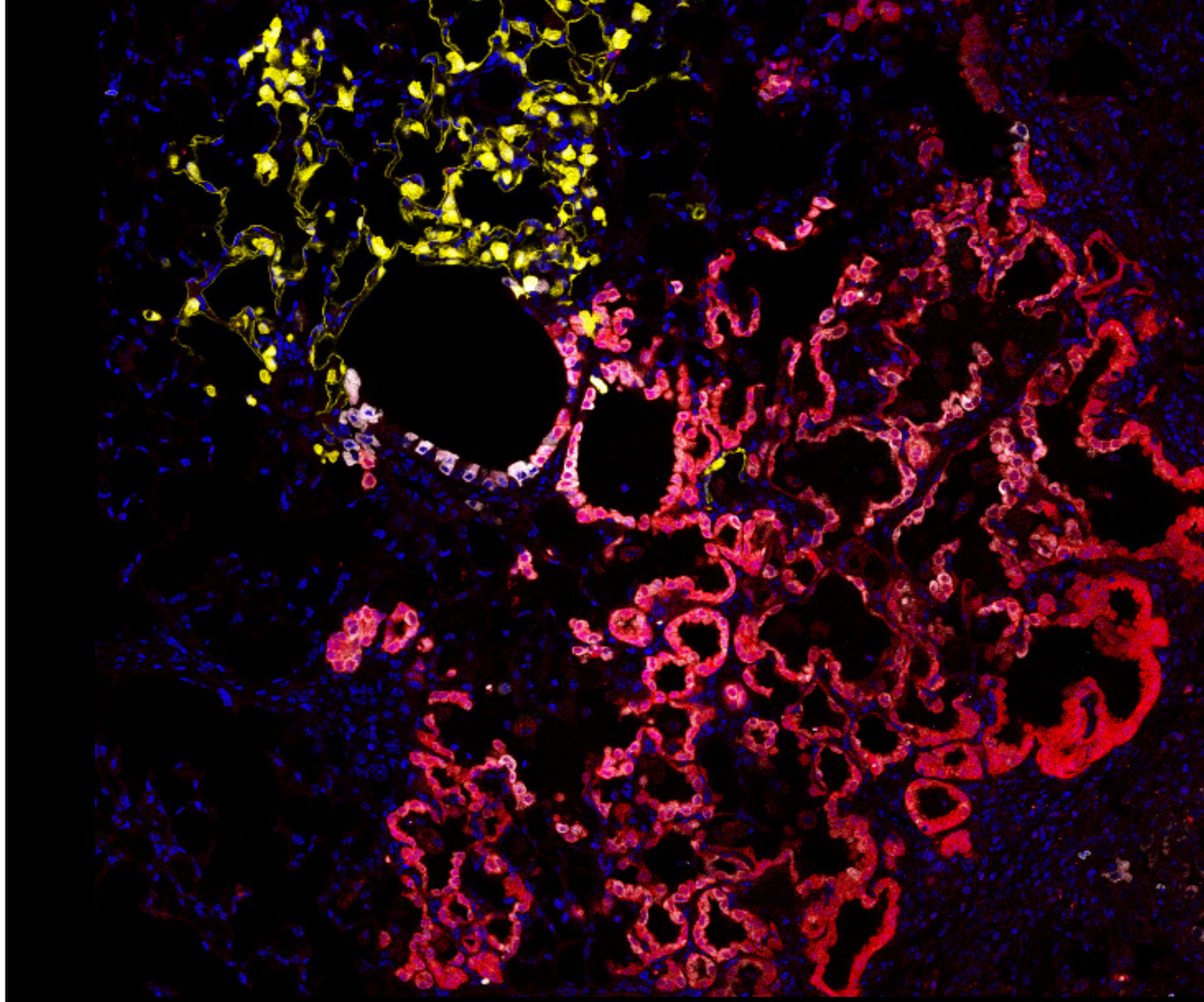

*Fluorescent image of a mouse lung undergoing repair after injury. Airway secretory club cells labelled with yellow are differentiating into alveolar lineage cells, whereas mutant secretory club cells labelled with red show perturbed differentiation capacity. Nuclei of individual cells are stained with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

*Credit: Catherine Dabrowska*

# ANDREW MCCASKIE

## 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.

### LAB MEMBERS

Mohammad Alkhrayef
Francesca Beaton
Mark Birch
Roger Brooks
Stephen Gadomski
Frances Henson
William Hotham
Andrew Hotchen
Wasim Khan
Sarah Lindsay
Stephen McDonnell
Karin Newell
Matthew Seah

### KEY PUBLICATIONS

Palmer AJR, Ayyar Gupta V, Fernquest S, ... **McCaskie AW**, ... Carr AJ, Beard DJ, Glyn-Jones S, FAIT Study Group. Arthroscopic hip surgery compared with physiotherapy and activity modification for the treatment of symptomatic femoroacetabular impingement: multicentre randomised controlled trial. BMJ 364, l185.

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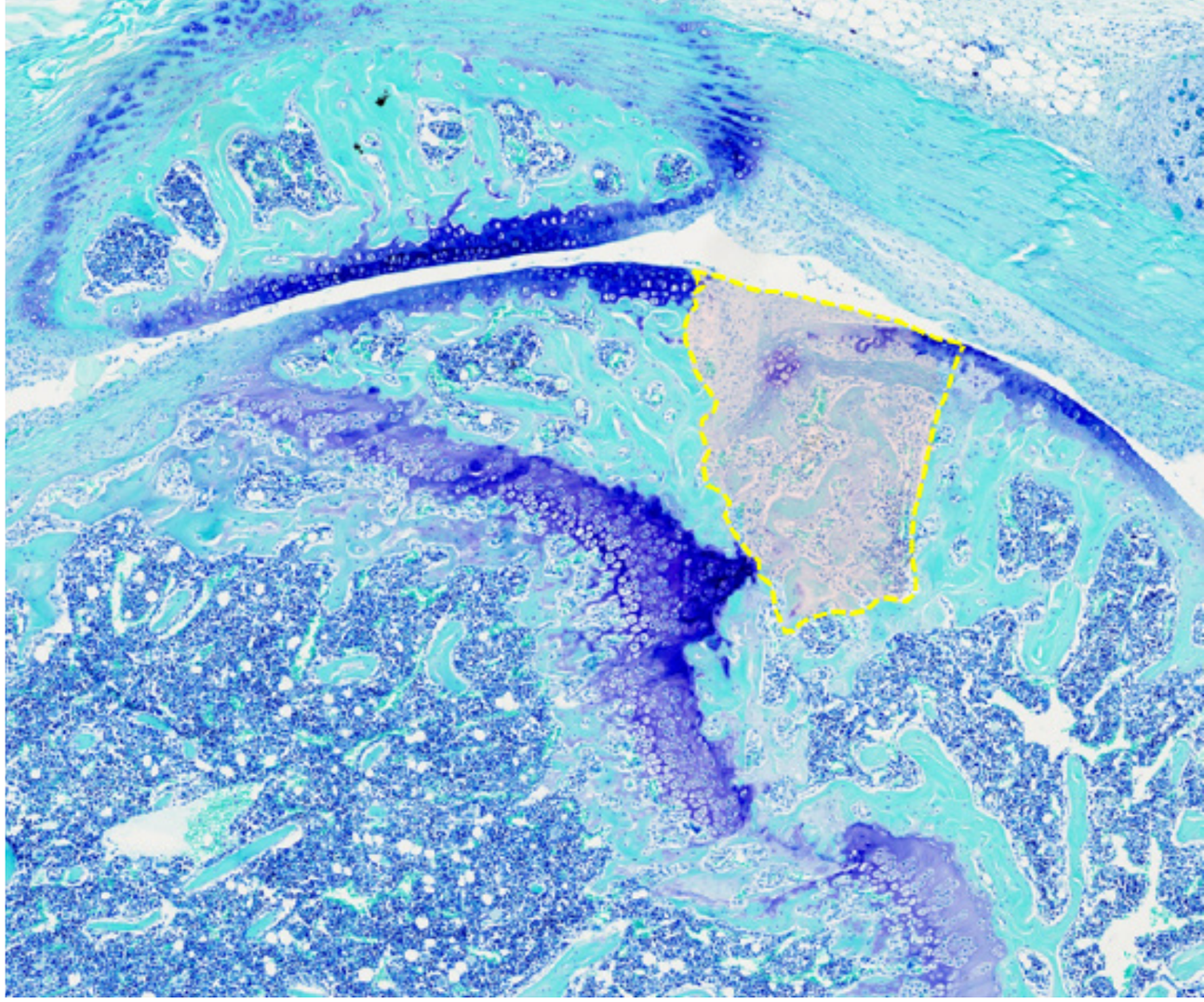

*Osteochondral repair of a synovial joint injury.*

*Credit: Francesca Beaton*

# SIMÓN MÉNDEZ-FERRER

## Blood stem cell niches

### LAB MEMBERS

Claire Fielding
Zijian Fang
Giuditta Corbizi Fattori
Stephen Gadomski
Elodie Grockowiak
Antony (Ya-Hsuan) Ho
Thomas McKerrell
Francesca Panvini
Antonio Rodriguez Romera
Jun Zhang

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

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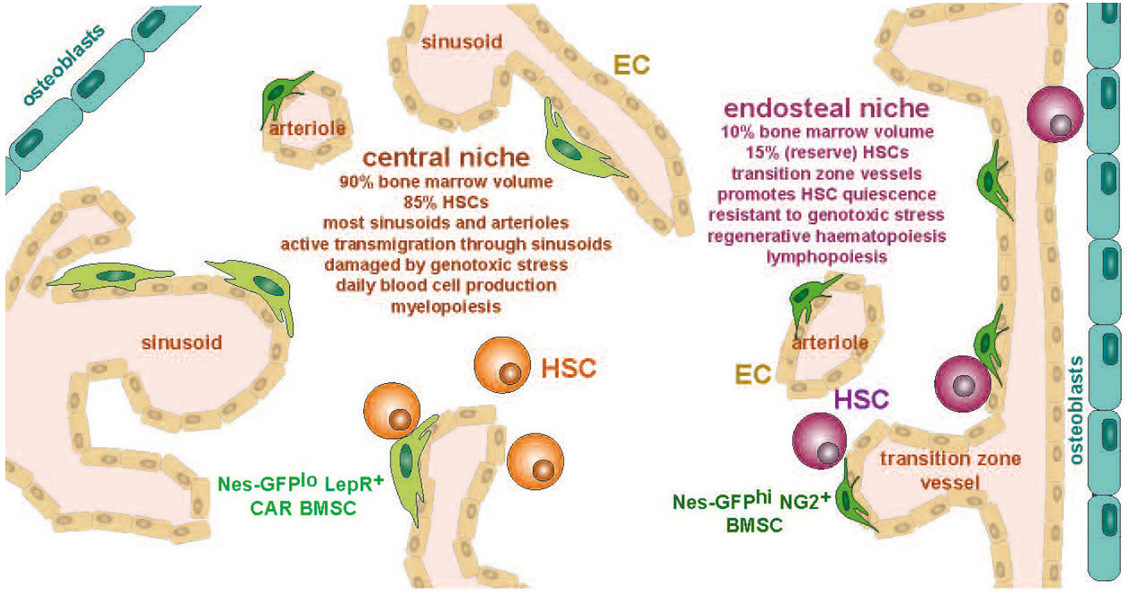


*Schematic summarizing the key cell types and functional features of the central and endosteal bone marrow (BM) niches of haematopoietic stem cells (HSCs).*

*Credit: Méndez-Ferrer, S., Bonnet, D., Steensma, D.P. et al. Bone marrow niches in haematological malignancies. Nat Rev Cancer (2020). https://doi.org/10.1038/s41568-020-0245-2*

# JENNIFER NICHOLS

# Embryonic pluripotency

## LAB MEMBERS

Takuya Azami
Elena Corujo-Simon
Kenneth Jones
Tim Lohoff
Sophie Morgani
Arthur Radley
Connor Ross

The Nichols lab is interested in how the mammalian embryo is formed and regulated. We scrutinise the roles of transcription factors and signalling pathways involved in establishing and maintaining the pluripotent epiblast (founder of the foetus) during embryogenesis. For this, we employ immunocytochemistry and quantitative confocal analysis as well as single cell transcriptional profiling to complement more traditional experimental tools.

We have developed robust protocols for derivation of embryonic stem cells (ESCs) from mouse embryos, which we utilise as an in vitro proxy to investigate the processes of lineage specification using directed differentiation and various types of organoids and micropattern devices. Much of our current work involves the generation of chimaeras using injection of wild type or genetically modified ESCs into host mouse embryos. This allows us to determine the roles of genes in cell potency, morphology and behaviour in the context of a normal embryonic environment as well as the regulative response of the host embryo as it adapts to the influx of supernumerary cells.

We benefit from the kind donation of spare human embryos from assisted conception programmes to our project for derivation of human ESCs. We are expanding and characterising multiple clonal cell lines to further our understanding of early human development.

## KEY PUBLICATIONS

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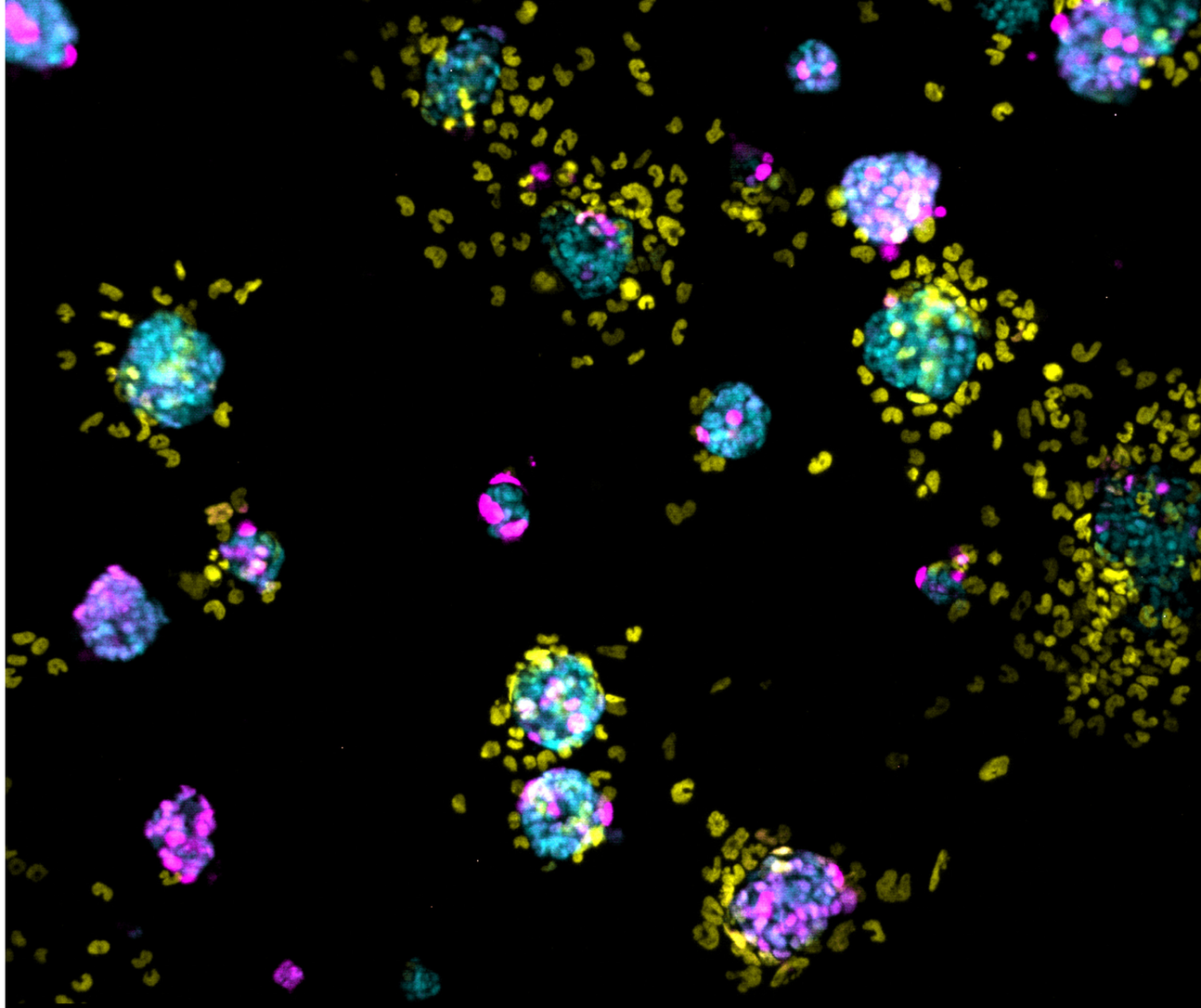

*Confocal image of early differentiating human naive embryonic stem cell colonies showing markers for whole epiblast (cyan), naive epiblast (yellow), hypoblast (magenta).*

*Credit: Nichols lab*

# ANNA PHILPOTT

## 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.

### LAB MEMBERS

Lewis Chaytor
Daniel Marcos Corchado
Frances Connor
Imogen Duncan
Fani Memi
Lidiya Mykhaylechko
Lydia Parkinson
Toshiaki Shigeoka
Laura Woods

### KEY PUBLICATIONS

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.

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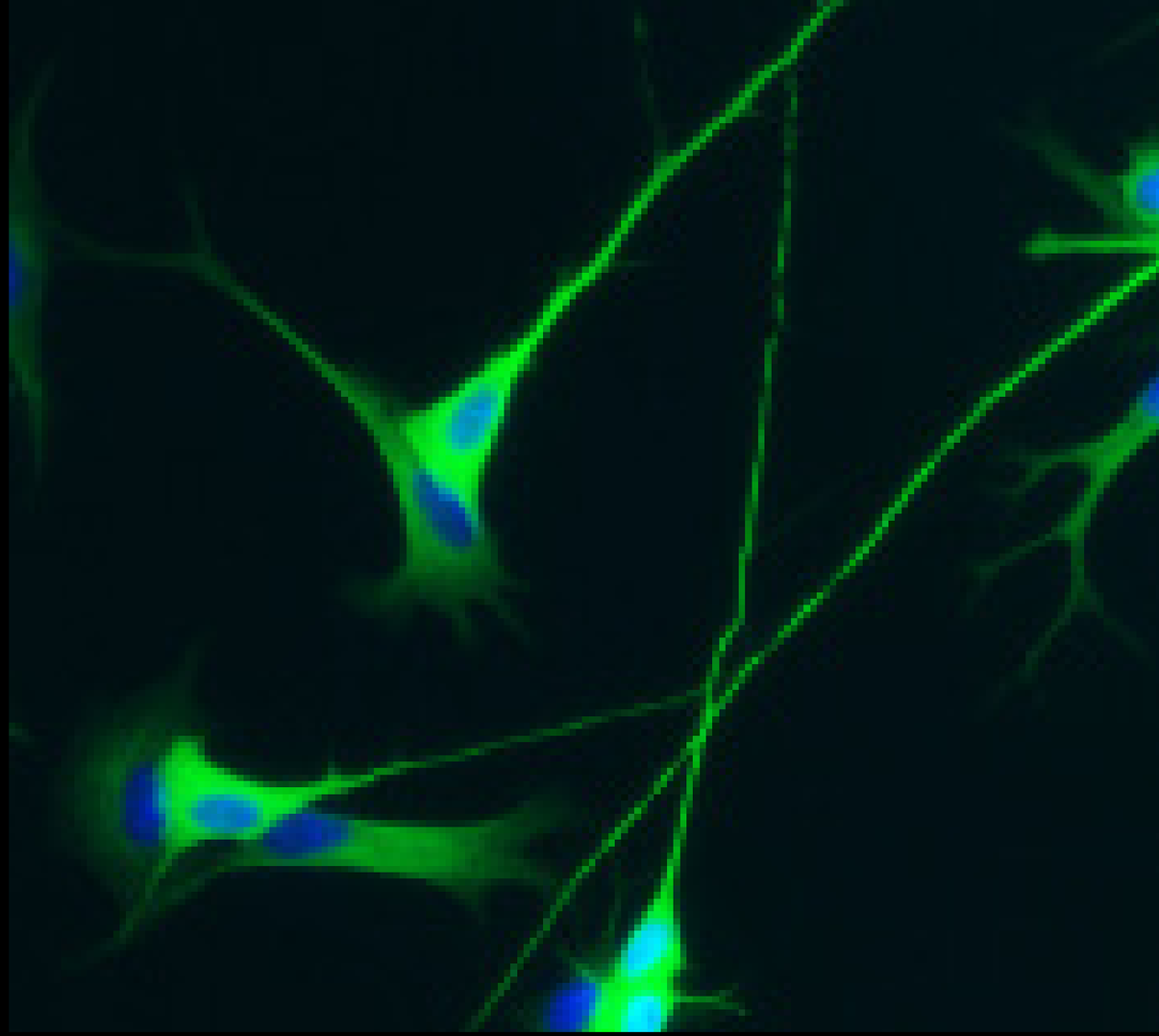

*Neuroblastoma cancer cells stop dividing and differentiate into neurons on treatment with drugs targeting the key transcriptional regulator ASCL1.*

*Credit: Daniel Marcos-Corchado*

# INGO RINGSHAUSEN

# Haematopoietic stem cells and malignancies

## LAB MEMBERS

Jingyu Chen
Maurizio Mangolini
Andrew Moore
Eugene Park
Antonella Santoro

Our research group studies the molecular processes underlying the cross-communication between normal and malignant haematopoiesis and their microenvironment. It has recently been shown that CD34+ CD38- HSPCs can contribute to oncogenic transformation into mature B cell malignancies, such as Chronic Lymphocytic Leukemia. Similar to normal cells, tumour cells require signals from their surrounding environment to survive and proliferate. Our work has identified vulnerabilities of cancer cells in this cross-talk, which can be exploited therapeutically. We have identified kinases activated in bone marrow stroma cells, which are essential for tumour-associated inflammation and tumour progression. We are now (1) focussed on defining how tumour-host interactions are modulated along tumour-evolution, from the Cell-of-Origin (COO) to lymphoma-stem cells to therapy-refractory disease. These studies are important to (2) fully understand lymphomagenesis and how the tumour microenvironment contributes to drug resistance and minimal-residual disease (MRD) following systemic anti-cancer therapies.

In parallel (3), we study how the tumour-remodelled bone marrow microenvironment affects normal HSC function and contributes to secondary bone marrow failure. Therapeutic interventions with these cross-talks could be exploited to maintain HSC function and thereby eliminate tumour cells, while maintaining and improving immune functions in patients with B cell malignancies.

## KEY PUBLICATIONS

Park E, Chen J, Moore A, Mangolini M, Santoro A, Boyd JR, Schjerven, Ecker V, Buchner M, Williamson JC, Lehner PJ, Gasparoli L, Williams O, Bloehdorn J, Stilgenbauer S, Leitges M, Egle A, Schmidt-Supprian M, Frietze S, **Ringshausen I**. Stromal cell protein kinase C-β inhibition enhances chemosensitivity in B cell malignancies and overcomes drug resistance. **Science Translational Medicine**, 2020 Jan 15;12 (526), eaax9340.

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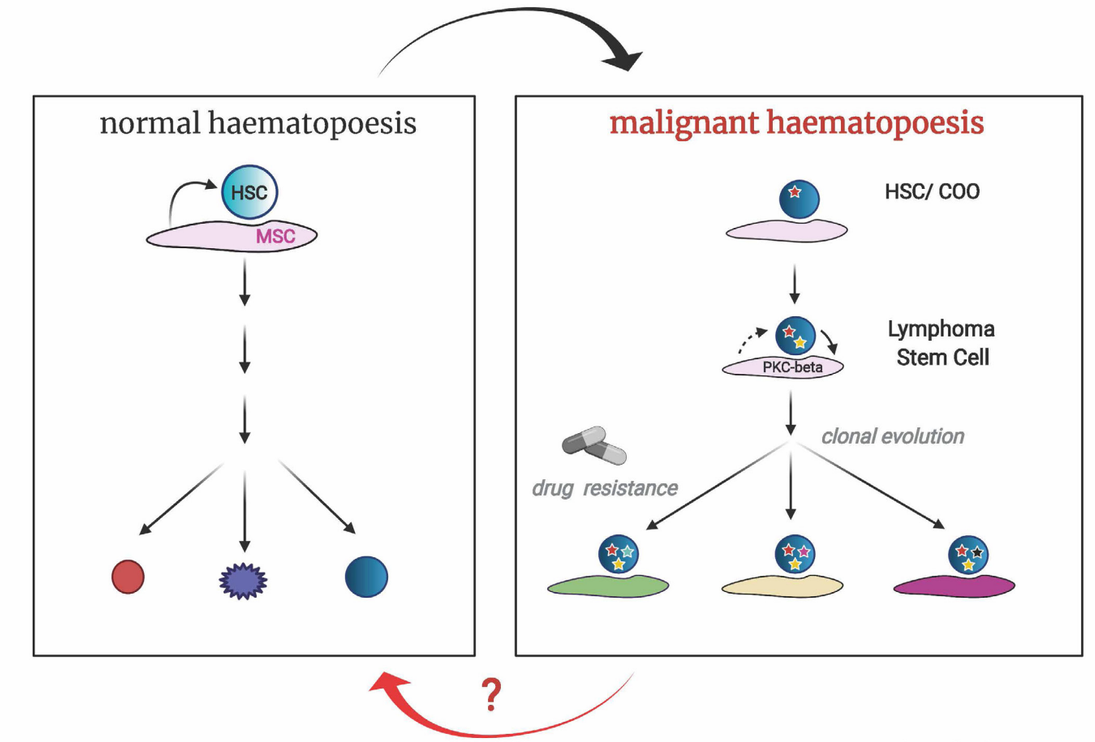
Lutzny G, Kocher T, Rudelius M, ..., Peschel C, Egle A, **Ringshausen I**. Proteinkinase C-β dependent activation of NF-κB in stromal cells is indispensable for the survival of chronic lymphocytic leukemia B-cells in vivo. **Cancer Cell**. 2013 Jan 14;23(1):77-92.




*designed with Biorender.com*

# DAVID ROWITCH

# 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.

## LAB MEMBERS

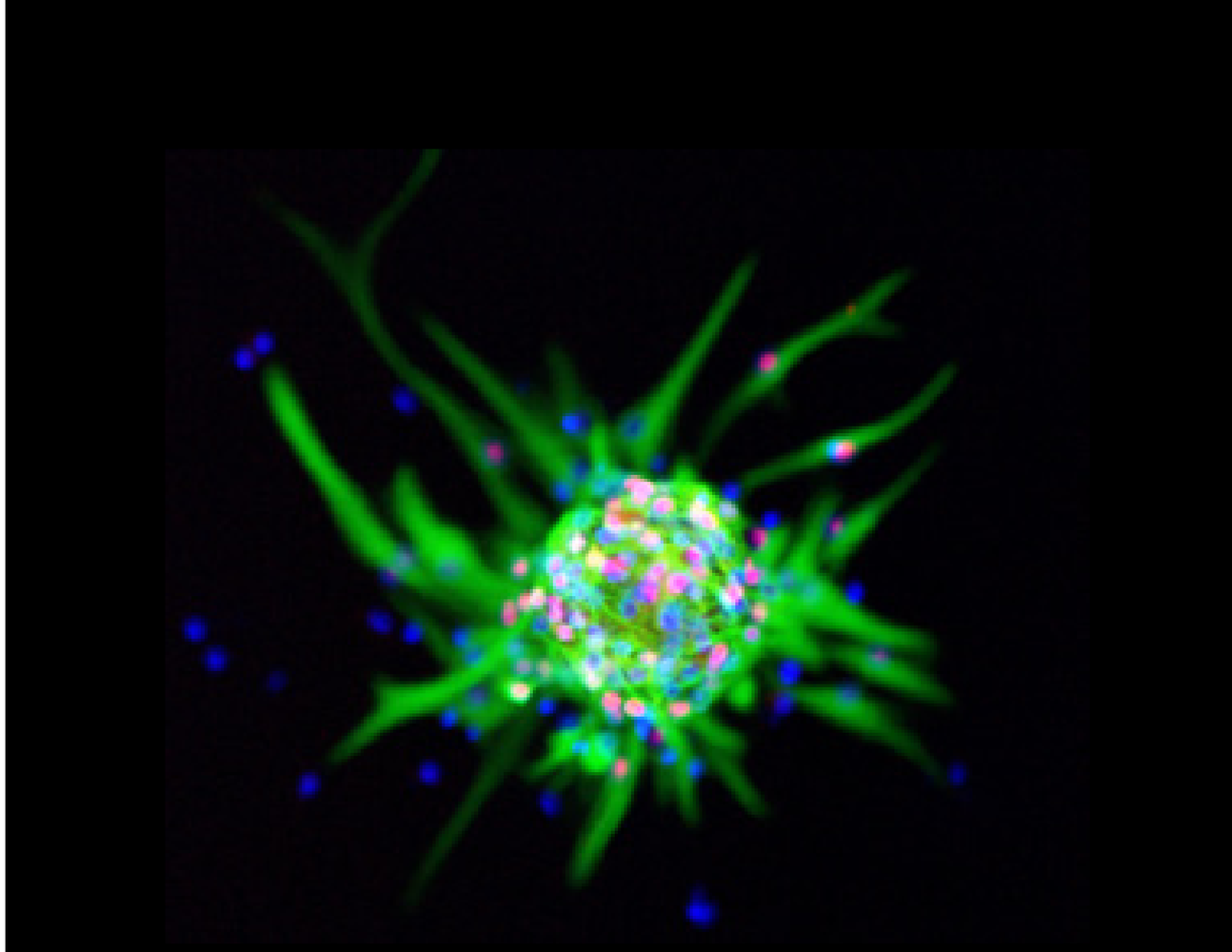
Theresa Bartels
Harry Bullstrode
Mark Charlton-Perkins
Courtney French
Gemma Girdler
Staffan Holmqvist
Ajay Kumar
Guy Lam
Katherine Ridley
John Stockley
Adrien Vaquie
Zhaoyang Xu

## KEY PUBLICATIONS

Bayraktar OA, Bartels T, Holmqvist S, ..., Holt MG, Geschwind DH, **Rowitch DH**. Astrocyte layers in the mammalian cerebral cortex revealed by a single-cell in situ transcriptomic map. **Nature Neuroscience**, 8(7641):427–10.

Schirmer L, Velmeshev D, Holmqvist S, ..., Shiow LR, Kriegstein AR, **Rowitch DH**. Neuronal vulnerability and multilineage diversity in multiple sclerosis. **Nature**. 573 (7772), 75-82.

Nobuta H, Yang N, Ng YH, Marro SG, Sabeur K, Chavali M, Stockley JH, Killilea DW, Walter PB, Zhao C, Huie P, Goldman SA, Kriegstein AR, Franklin RJM, **Rowitch DH**, Wernig M. Oligodendrocyte Death in Pelizaeus-Merzbacher Disease Is Rescued by Iron Chelation. **Cell Stem Cell** 25(4):531-541.e6



*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*

# JOSÉ SILVA | Reprogramming and programming cell identity

## LAB MEMBERS

Lawrence Bates
Yael Costa
Imogen Stockwell
Daniel Yamamoto

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 programing 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

Stuart HT, Stirparo GG, Lohoff T, Bates LE, Kinoshita M, Lim CY, Sousa EJ, Maskalenka K, Radzisheuskaya A, Malcolm AA, Alves MRP, Lloyd RL, Nestorowa S, Humphreys P, Mansfield W, Reik W, Bertone P, Nichols J, Göttgens B, **Silva JCR**. Distinct molecular trajectories converge to induce naive pluripotency. **Cell Stem Cell**, 25(3):388-406.e8

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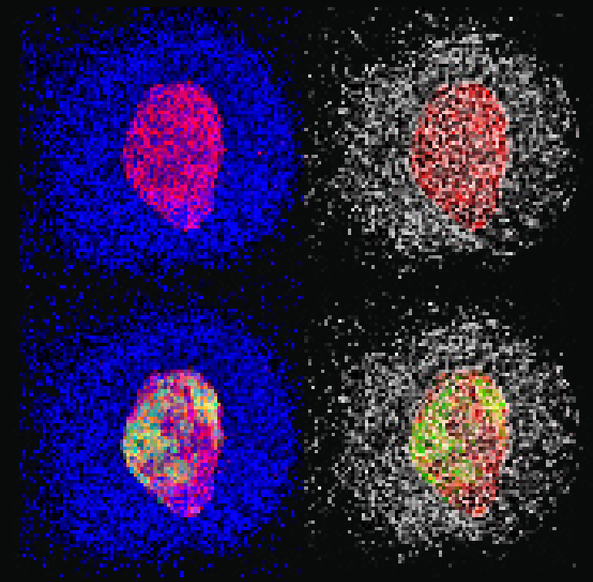

*Panel depicting the appearance of induced pluripotent stem cells (green) from an identified pre-determined to reprogram cell population (red). Non-red cells (grey and blue only) failed to acquire reprogramming competence.*

*Credit: Chibeza Agley*

# BEN SIMONS

## Tracing stem cell fate in development, maintenance and disease

### LAB MEMBERS

Ignacio Bordeu
Lemonia Chatzeli
Adrien Hallou
Seungmin Han
Tom Hiscock
Daniel Kunz
Min-Kyu Yum

Research in our group combines experimental lineage tracing strategies and single-cell methods with 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 renewal programmes in the regulation of stem cell fate, questioning the nature of stem cell identity and function. We have extended these approaches to study the development and patterning of adult tissues, including the eye, heart, mammary epithelium, pancreas and skin epidermis. At the same, we are collaborating with partner labs to address the cellular basis of tumour initiation.

We also work with colleagues at the Babraham Institute 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.

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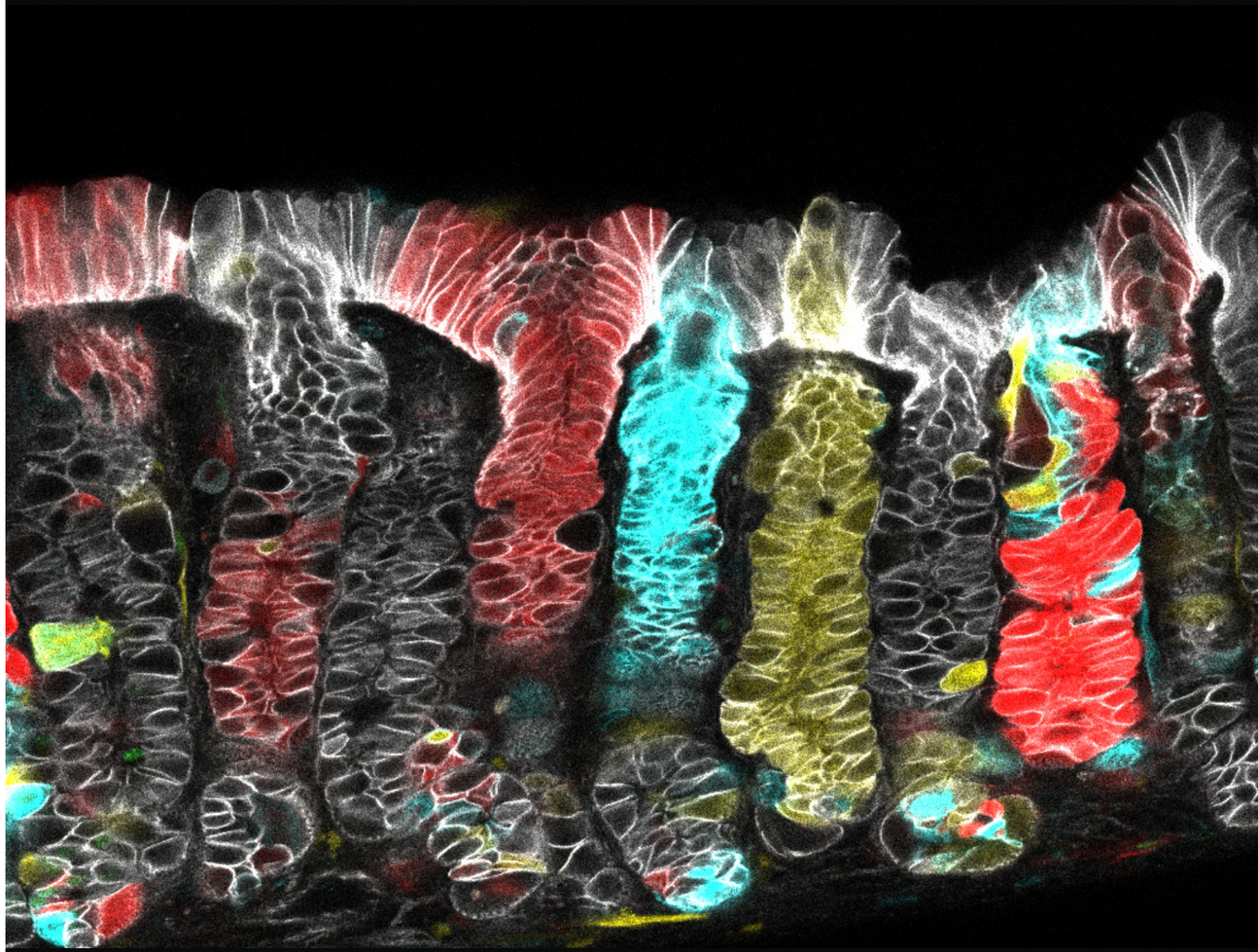

*Mouse stomach corpus glands labelled with a multicolour confetti reporter system.*

*Credit: Simons Lab*

# SANJAY SINHA

## Cardiovascular disease

### LAB MEMBERS

Semih Bayraktar
Maria Colzani
Hongorzul Davaapil
Laure Gambardella
Peter Holt
Aishwarya Jacob
Vincent Knight-Schrijver
Robyn Macrae
Ping Ong
Deborah Passey
Alex Petchey
Deeti Shetty

Our lab's overall aim is to develop new treatments for cardiovascular diseases, in particular those involving vascular smooth muscle cells and epicardium, 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".

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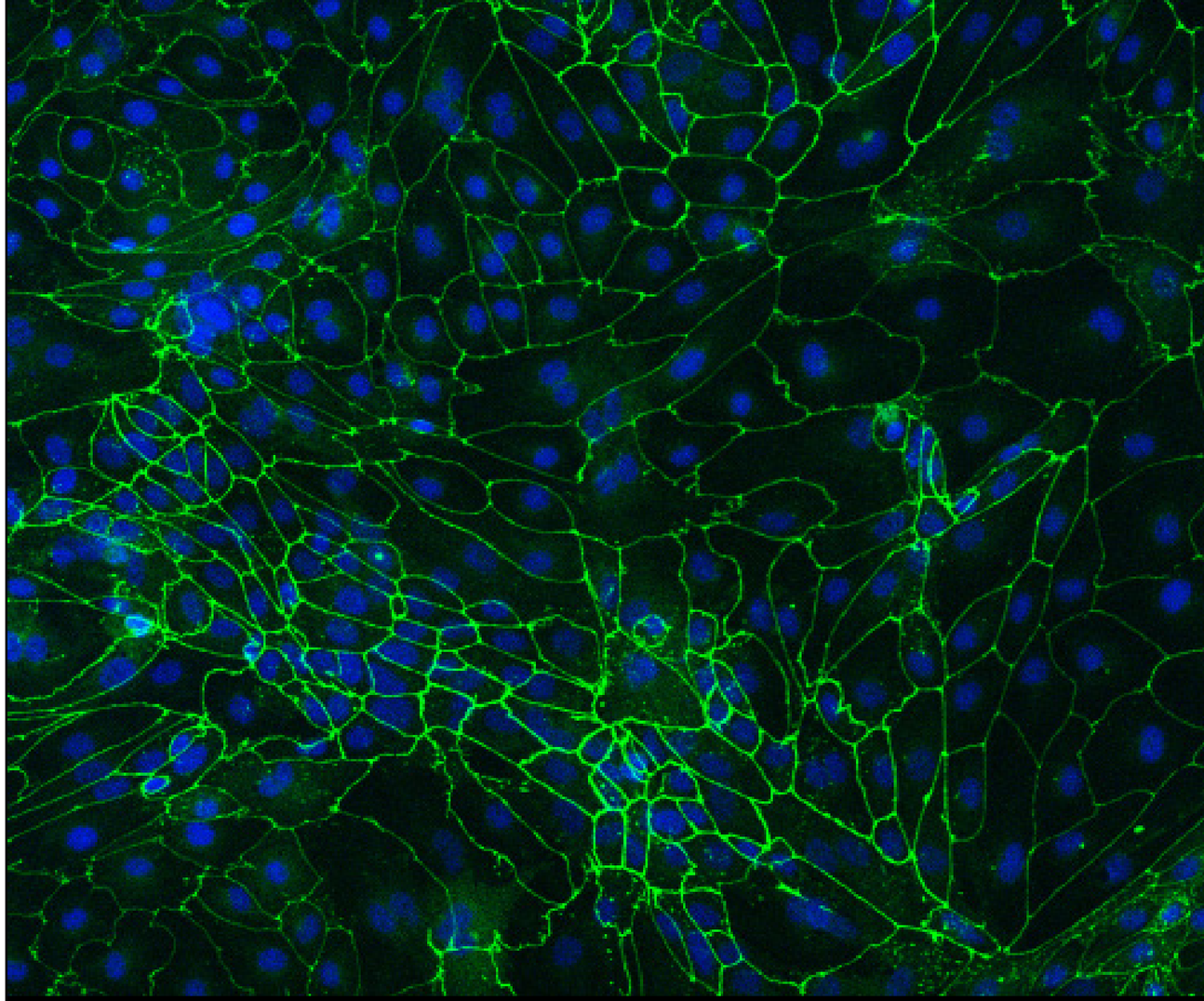

*Epicardial cells generated from human embryonic stem cells form a sheet, also known as mesothelium. The tight junction protein1 (ZO1) is seen at cell peripheries (green) and contributes to the cell-cell junctions.*

*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

James Clarke
Anish Dattani
Rosalind Drumond
Ge Guo
Tao Huang
Masaki Kinoshita
Arthur Radley
Giuliano Stirparo
Ayaka Yanagida

## KEY PUBLICATIONS

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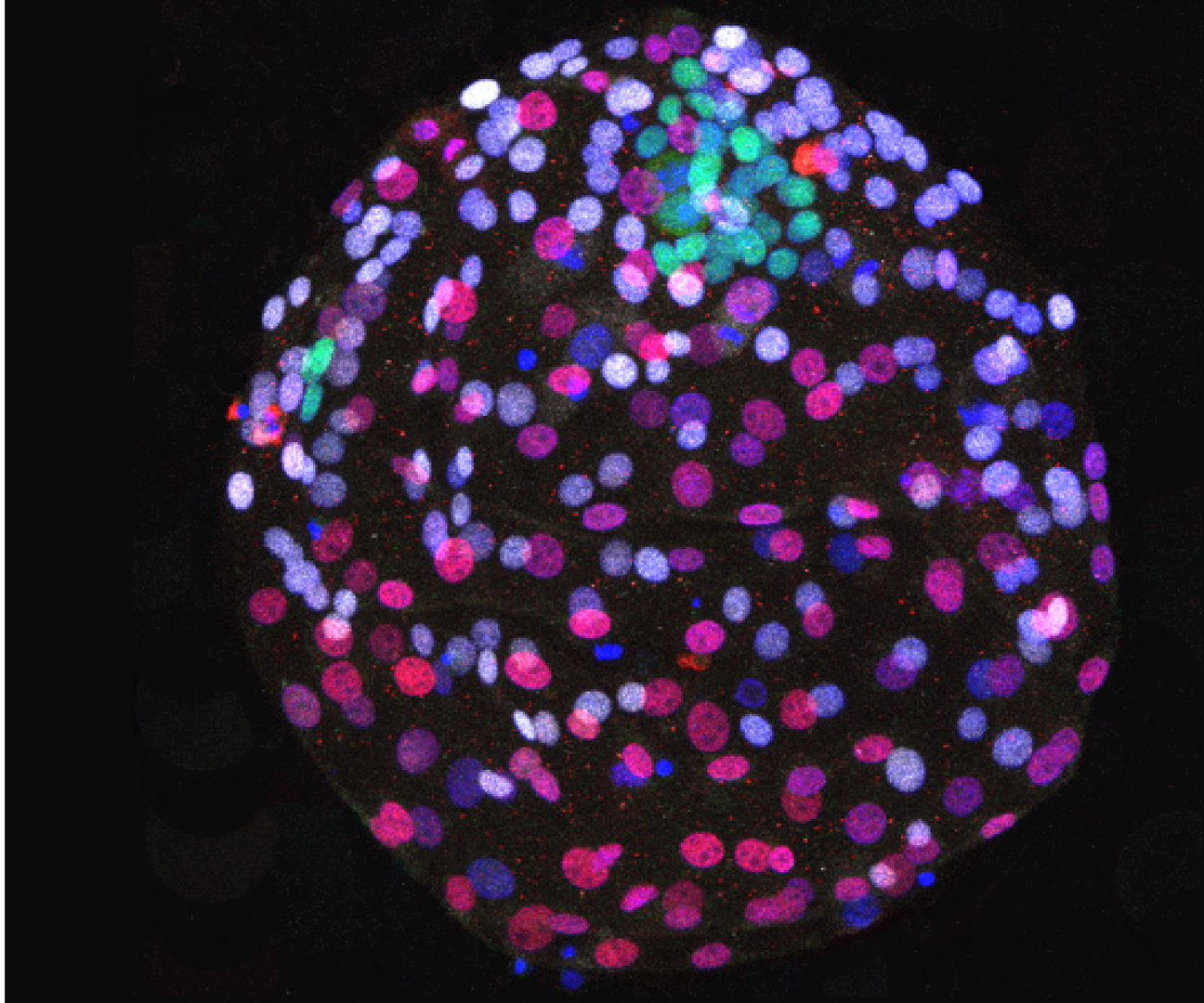

*Sheep blastocyst regenerated from an isolated inner cell mass. Immunostaining shows lineage-specific transcription factors: SOX2 (epiblast, green); GATA3 (trophoblast, red); SOX17 (hypoblast, white). Nuclei are visualised with Dapi (blue).*

*Credit: Ge Guo*

# LUDOVIC VALLIER

## Mechanisms controlling differentiation of pluripotent stem cells into definitive endoderm

### LAB MEMBERS

Teresa Brevini
Stephanie Brown
Dominika Dziedzicka
Vasileios Galanakis
Chris Gribben
Fatima Lugtu
Carola Morell
Shota Nakanoh
Anna Osnato
Marion Perrin
Laetitia Pinte
Alexander Ross
Fotios Sampaziotis
Rute Tomaz
Marta Vila-Gonzalez
Brandon Wesley
Katherina Zacharis

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.

### KEY PUBLICATIONS

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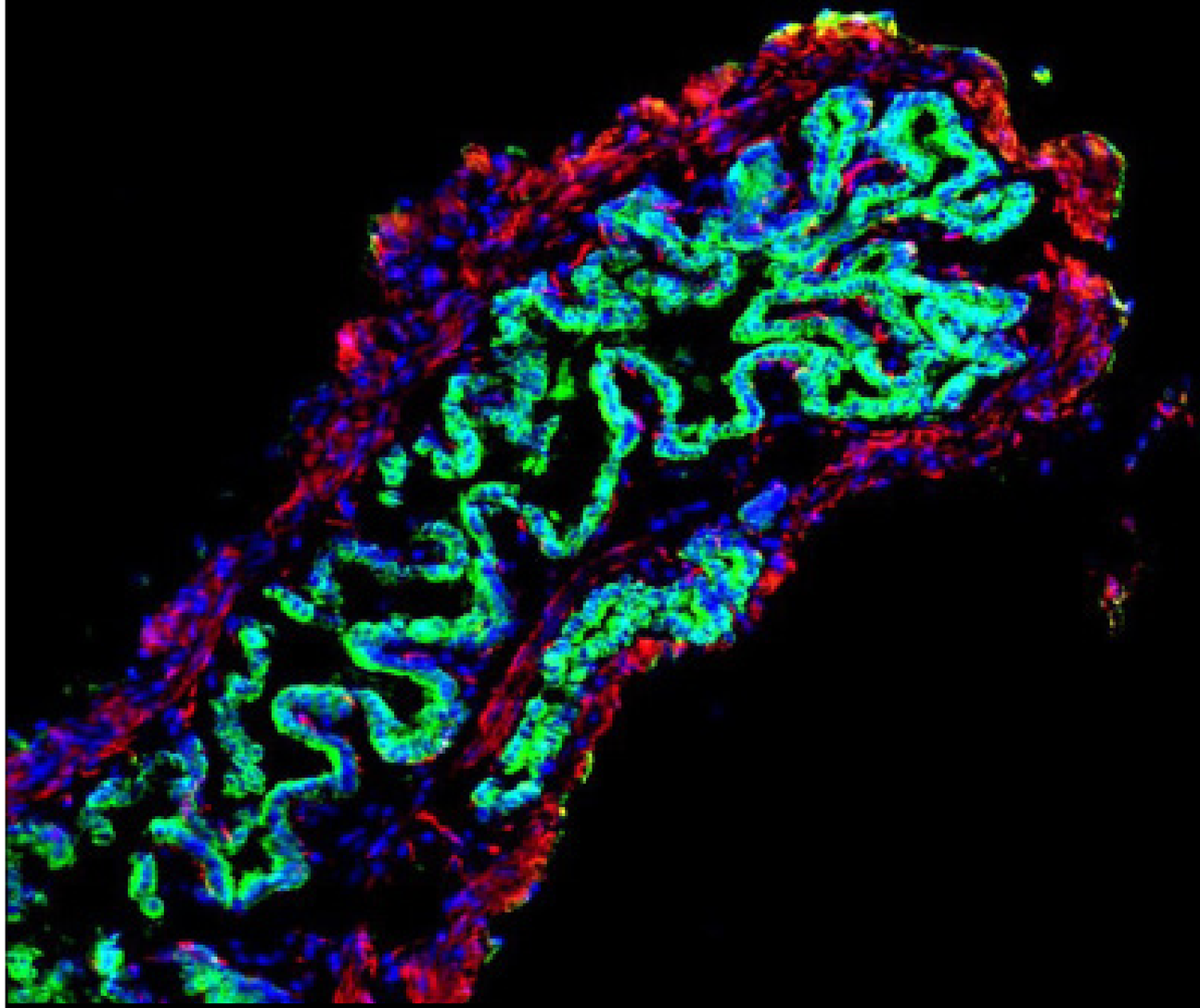

*Mouse gallbladder following repair with human cholangiocytes organoids (green).*

*Credit: Fotis Sampaziotis*

# GEORGE VASSILIOU

# Leukaemic haemopoietic stem cells

## LAB MEMBERS

Clea Barcena
Jonathan Cooper
Aristi Damaskou
Filipa Domingues
Monika Dudek
Margarete Fabre
Dimitris Garyfallos
Gonia Gozdecka
Muxin Gu
Suruchi Pacharne
Pedro Quiros
Justyna Rak
Thomas Sheahan

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.

## KEY PUBLICATIONS

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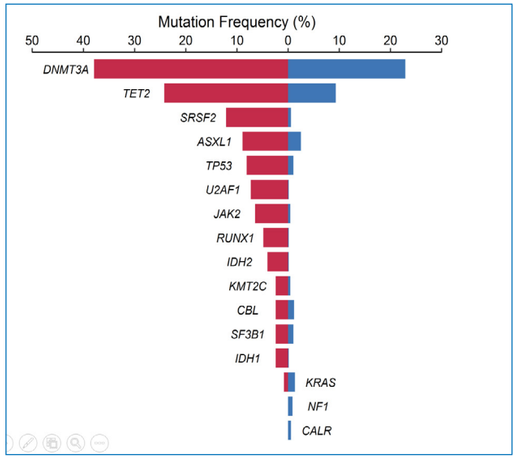
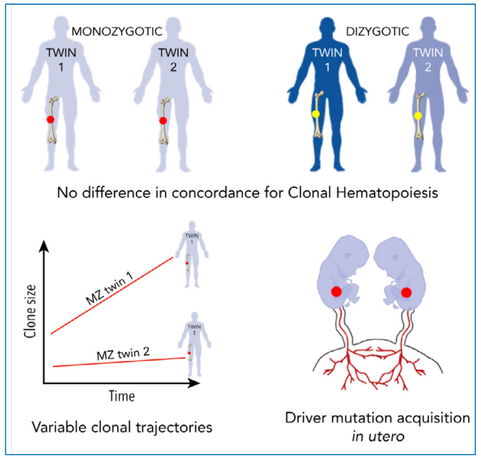
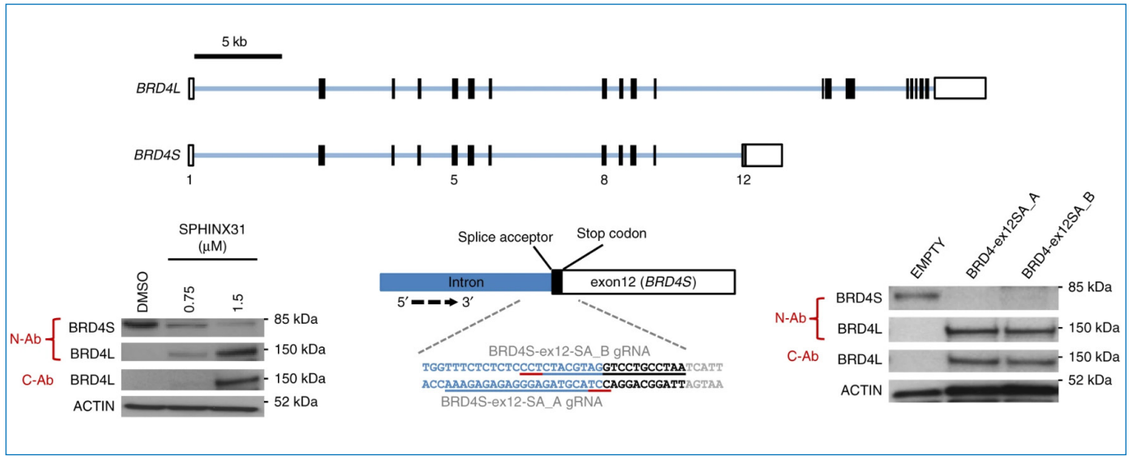



Prediction of AML development on healthy individuals
(*Abelson, Collord et al, Nature 2018*)




Characteristics of clonal haematopoiesis in identical twins
(*Fabre et al, Blood 2020*)




New therapeutic targets in AML: SRPK1 inhibition alters splicing of BRD4
(*Tzelepis et al, Nature Comms 2018*)

*Credit: Vassiliou Lab*

# Alumni

## DAVID KENT

## Single cell fate choice in normal and malignant stem cells

In 2019, David Kent moved his lab to the University of York and the York Biomedical Research Institute to take up a position as Reader in Haematology and continue his research in the field.

The Kent 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.



# Research Publications

Institute researchers produced 166 publications in 2019 across a range of topics and research themes.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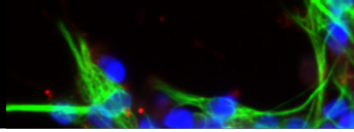

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