CAMBRIDGE STEM CELL NEWS

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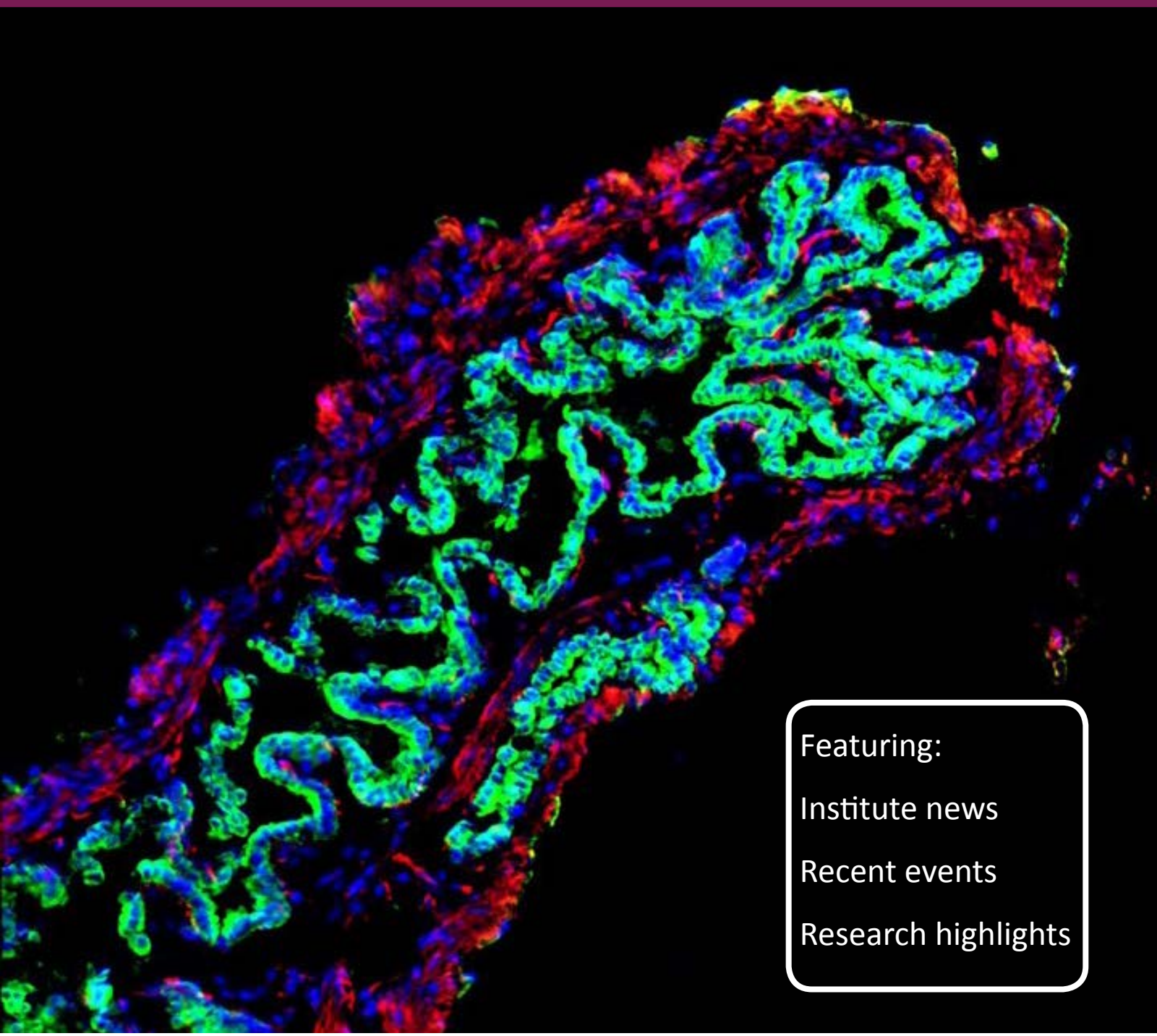
Issue 13 - Autumn 2017

Transforming Lives through Stem Cell Research



Featuring:

Institute news

Recent events

Research highlights

Wellcome Trust - Medical Research Council
Cambridge Stem Cell Institute

In this issue:

Prof Tony Green Institute Director

The Cambridge Stem Cell Institute has been a hive of activity over the spring and summer months, both in terms of our research and the preparations for our relocation next year. The end of April saw the topping out of the Capella building, our new purpose-built home on the Cambridge Biomedical Campus, and it is now only just over a year until we move in. Having all of our researchers under the same roof will help enormously to foster innovation and create the scientific synergies that come from physical proximity and canteen conversations.

The Institute has continued its commitment to collaborative, cross-disciplinary research with a workshop held in May to address the current position and future directions of myelin and stem cell research in Cambridge. Interdisciplinary work is also a feature of a number of ongoing research projects within the Institute. As one example, the Vallier lab has been working closely with clinicians and engineers to develop cellular scaffolding on which to grow functioning liver tissue for potential use in transplantation. More details on this and other ongoing research, along with a list of recent Institute publications, can be found in the following pages.

The public engagement team continues to come up with creative ideas for ways in which we can reach out to the wider community. Recent projects include an art-science collaboration, where 11 of our researchers were paired with local Cambridge artists to create works inspired by stem cell research. And in May, following an inspired collaboration between Institute PhD students and Moonshine brewery, we saw the launch of a real ale called ‘Regenerator’ – Arnold Schwarzenegger eat your heart out!

Lastly we are putting together plans for a special Cambridge International Stem Cell Symposium in September next year. We already have a stellar line up of speakers from all round the world and this promises to be an outstanding way to celebrate the coming together of the Cambridge Stem Cell Institute in its new building.

The Wellcome - MRC Cambridge Stem Cell Institute is a world-leading centre for stem cell research with a mission to transform human health through a deep understanding of stem cell biology. Bringing together biological, clinical and physical scientists, the Institute explores and defines the properties of stem cells to establish their true medical potential.

Institute Updates

NEW BUILDING TOPS OUT

April saw the topping out of our new home on the Cambridge Biomedical Campus, a historic milestone for the Cambridge Stem Cell Institute. The new building will house our 29 research groups, resulting in a fully integrated stem cell research hub at the centre of the Cambridge Biomedical Campus.

The Campus is a single site that will feature world-class biomedical research facilities, two research hospitals and a range of industrial partners. Becoming part of this thriving translational environment will enable the therapeutic potential of stem cells to be more readily realised.

We will be sharing the new building with Cambridge Institute of Therapeutic Immunology and Infectious Diseases (CITIID) and the Milner Therapeutics Institute, both of whom have explicitly translational goals.

Professor Tony Green, Cambridge Stem Cell Institute Director said *"Moving into our new home on the Cambridge Biomedical Campus, and having all of our scientists located under one roof, will help enormously with the cross fertilisation of ideas that comes from ad hoc corridor and canteen conversations."*

Image from left: **Prof Patrick Maxwell** (Clinical School), **Prof Sir Leszek Borysiewicz** (Vice Chancellor), **Mark Pengelly** (National Director Kier), **Prof Abigail Fowden** (Biological School), **Prof Tony Green** (Cambridge Stem Cell Institute), **Prof Ken Smith** (CITIID), **Prof Tony Kouzarides** (Milner Therapeutics Institute)

PUBLIC ENGAGEMENT WITH RESEARCH AWARD

Cambridge Stem Cell Institute group leader **Dr Elisa Laurenti** has won one of six University of Cambridge Public Engagement with Research Awards. She received a £1,000 prize presented by Vice-Chancellor Professor Sir Leszek Borysiewicz in an award ceremony in July.

Elisa has been a leading force in public engagement at the Cambridge Stem Cell Institute, particularly as coordinator for the Stem Cell Robots – an activity that has become central to many different events.

Dr Laurenti said *"This is a great honour and the prize was awarded to me as the coordinator of the Stem Cell Robots activity, but really I would like to extend it to all of my collaborators and colleagues that have been fundamental in making this activity a success: Dr Stéphane Magnenat, from École Polytechnique Fédérale de Lausanne, Laboratoire de Systèmes Robotiques lab, co-awardee and co-inventor of the Thymio robots; Shiling Wang and Dr Cyrille Dunant who contributed excellent coding skills; and Christophe Barraud of Mobsya, who provided the robots."*

INTERNATIONAL SEMINAR SERIES

This monthly seminar series features world-leading scientists who are invited to present their work to the Institute. In May, **Michael Rendl** from Mount Sinai, New York, joined us to speak about hair follicle formation, and in June, **Maria Elena Torres-Padilla**, Director of the Institute of Epigenetics and Stem Cells, Munich, presented on cellular plasticity in mouse embryos.

Mark Ungrin from the University of Calgary presented research on microscale tissue engineering, and in July, **Peggy Goodell** from the Baylor College of Medicine, Texas, spoke on immortal stem cells.

August saw two talks, one from **Toshio Suda** of the Cancer Science Institute of Singapore who spoke about the metabolism of haematopoietic stem cells, and another from **Benoit Bruneau**, University of California, on transcription in heart development. The final seminar of the 16/17 academic year was from **Sebastian Jessberger**, University of Zurich, on neurogenesis in the adult hippocampus.

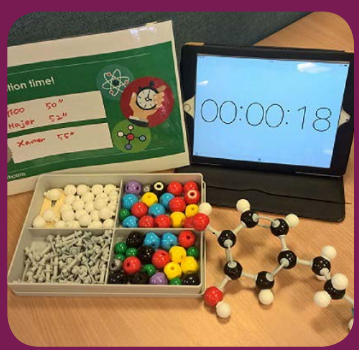
Recent Events

ANNUAL PHD DAY SYMPOSIUM

This years' annual PhD Day Symposium was held in July at the Clinical School on the Cambridge Biomedical Campus. Over 80 Cambridge Stem Cell Institute members were in attendance, including the PhD students, PIs, Affiliate PIs and PostDocs. The current Cambridge Stem Cell Institute PhD student representative, **Alisa Molotova** (Franklin lab) was the key organiser this year, with assistance from our Graduate Administrator, Jo Jack.

The event took place over a full day, with talks and poster presentations from the students. The talks were judged by Group Leaders, with the first prize going to **Lucia Cordero Espinoza** (Huch lab) and second prize to **Fiona Hamey** (Göttgens lab) - they each won a £500 travel grant donated by Microsoft Research. The prize for best poster was awarded to **Mairi Shepherd** (Kent lab), who won a £50 Amazon voucher.

The event was generously sponsored by **Abcam**, **Biology Open**, **Microsoft Research**, **Peprotech** and **StemCell Technologies**.

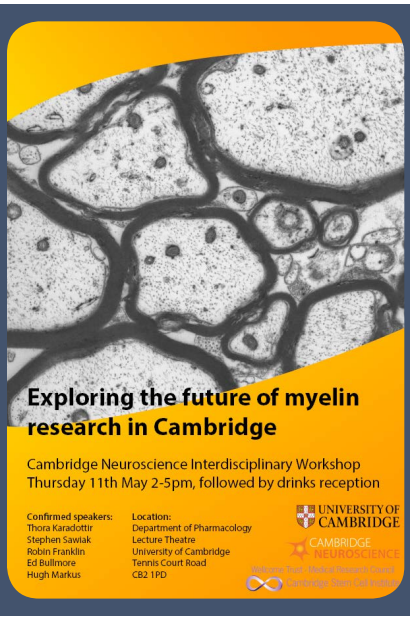


STEM CELLS AT CAMBRIDGE BRAINFEST

The Cambridge Stem Cell Institute took part in the first 'BRAINFest' in a vibrant take-over of the Cambridge Corn Exchange in June.

Researchers from the **Káradóttir** and **Franklin** labs developed interactive activities to initiate conversations with the public on a range of topics including: why insulating the neurons in your brain is so important, how brain stem cells play their part in this process, and what impact stem cell research is having on new therapies for diseases such as Multiple Sclerosis.

Professor Roger Barker also spoke about his pioneering Parkinson's disease research in the opening night showcase.



EXPLORING THE FUTURE OF MYELIN RESEARCH

In early May, scientists from a range of research backgrounds came together for a cross-disciplinary workshop with the aim of identifying common goals in myelin research and to plan collaborative projects to increase understanding in this field.

Advances in myelin research are keenly anticipated, with diseases including Multiple Sclerosis, Cerebral Palsy and Schizophrenia all linked to myelin dysfunction.

The workshop facilitated an open and creative conversation on how myelin research could best be developed in Cambridge, with students, post-doctoral researchers and professors all sharing ideas on the best 'next steps' for this important field.

This highly successful event was jointly organised by Cambridge Stem Cell and Cambridge Neuroscience, two of the University's Interdisciplinary Research Centres, established to tackle cross-disciplinary challenges and create a shared cross-School vision in key thematic areas.

CREATIVE COLLISIONS

The Cambridge Stem Cell Institute is always looking for innovative ways to prompt debate about stem cell research and gather perspectives from the wider community.

This spring, we tackled this head-on as 11 of our principal investigators were paired with local Cambridge artists to create works that both challenge and celebrate the potential of stem cells. The resulting artworks were exhibited for a two week run at Michaelhouse café in the centre of Cambridge, as part of the **MRC Festival of Medical Research**.

The Exchanges project was the brainchild of two graduate students **Katie Tremble** and **Mariana Alves (Silva Lab)** and was delivered in partnership with Pint of Science. Alongside the exhibition, the pair also produced a series of podcast interviews with participating artists and scientists, allowing the public to dig deeper into the motivations behind the research and the impact of these 'creative collisions'.

The project was funded by a Public Engagement Seed Fund grant from the Cambridge Stem Cell Institute.

Listen to the podcasts at:

www.stemcells.cam.ac.uk/public/podcasts

REGENERATOR AT CAMBRIDGE BEER FESTIVAL

May saw the unveiling of our first stem cell beer, Regenerator, born out of a collaboration with Cambridge based Moonshine Brewery. Students **Tim Lohoff (Nichols Lab)** and **Daniel Bode (Kent Lab)** launched their 4.2% session ale at Cambridge Beer Festival, 22 – 27 May, to sell-out success.

The driver behind the project was to stimulate conversations between scientists and 'hard to reach adult' groups that may not usually attend science-themed events or festivals. As part of this, a team of 5 PhD students attended the Beer Festival for an afternoon. Equipped with 'conversation starters' including pipette samples of the beer, they were able to engage over 100 people in face to face discussions about stem cells and their future therapeutic potential. Festival goers remarked on how 'reassuring it was to hear from dedicated young scientists' with researchers benefiting from the challenge of framing their stem cell research in the context of 'real world' questions and personal anecdotes of disease.

Looking ahead, Regenerator will be rolled out across a range of local pubs in a series of stem-cell themed evenings, quizzes and talks. Once again we hope to challenge our researchers to engage hard to reach adults and build a broader 'taste' for stem cell science.

Dates and locations of 'Regenerator On Tour' can be found at

www.stemcells.cam.ac.uk/events/publicevents

Research highlights

3D CELL SCAFFOLDING SUPPORTS FUTURE TRANSPLANT THERAPIES

Prof Ludovic Vallier and **Dr Fotis Sampaziotis** recently published pioneering research in which they have grown and transplanted artificial bile ducts in the lab that have the potential to treat liver disease in children.

Working with colleagues in the Department of Engineering, the group extracted primary cells (cholangiocytes) from bile ducts and grew these on a biodegradable collagen scaffold. After 4 weeks, the cells had fully covered the miniature scaffold, resulting in artificial tubes which exhibited key features of normal, functioning bile ducts. These artificial ducts were then successfully used to replace damaged bile ducts in mice, with the animals recovering without further complications.

"Our work has the potential to transform the treatment of bile duct disorders," explains **Professor Vallier.** *"At the moment, our only option is liver transplantation, so we are limited by the availability of healthy organs. In future, we believe it will be possible to generate large quantities of bioengineered tissue that could replace diseased bile ducts and provide a powerful new therapeutic option without this reliance on organ transplants."*

"This research demonstrates the power of tissue engineering and regenerative medicine," adds **Dr Sampaziotis**. *"These artificial bile ducts will not only be useful for transplantation, but could also be used to model other diseases of the bile duct and potentially develop new drug treatments."*

This work was supported by the Medical Research Council, Sparks children's medical research charity and the European Research Council.

Read more: www.stemcells.cam.ac.uk/news

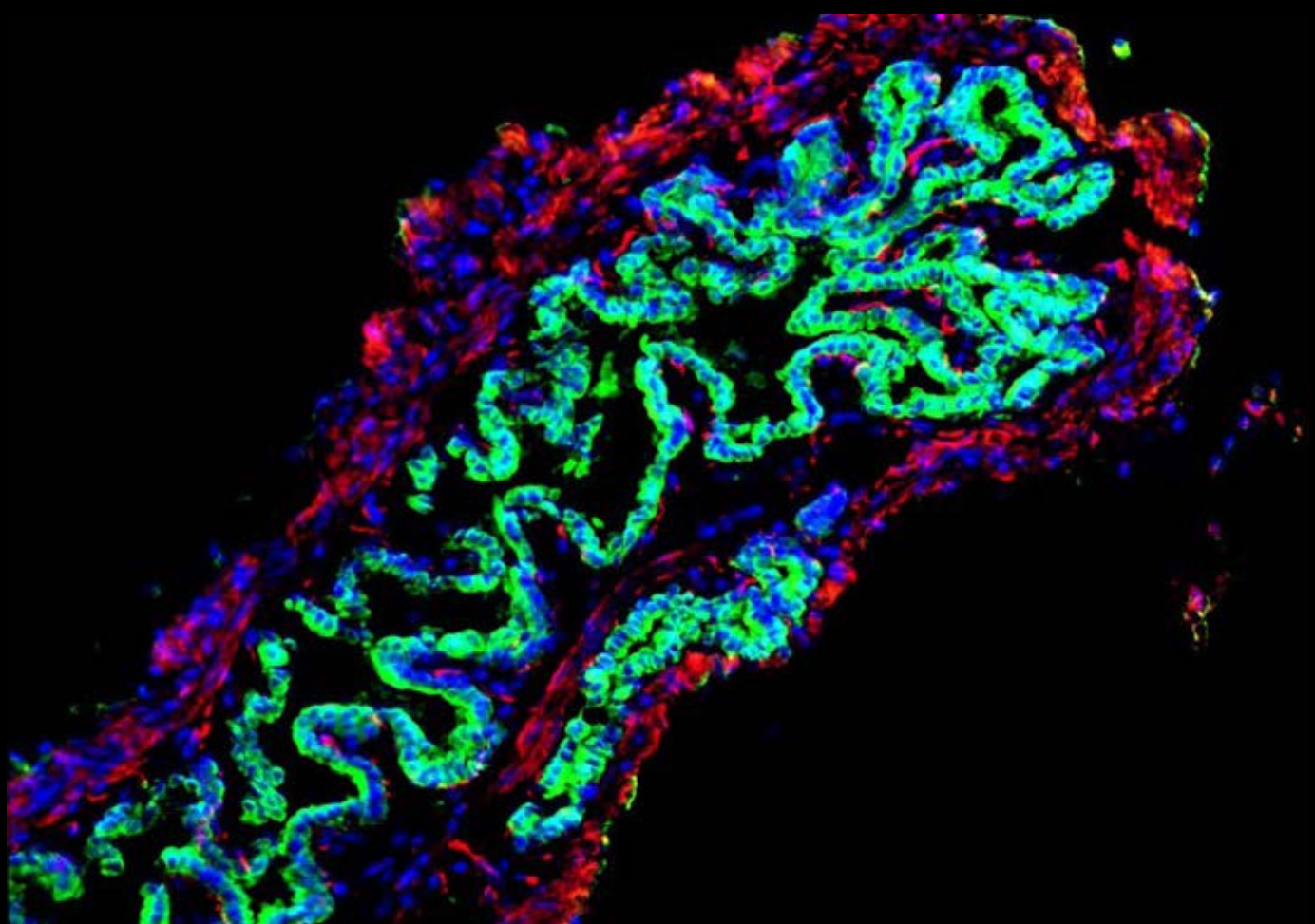


Image: Mouse gallbladder following repair with bioengineered stem cells (green) Credit: Vallier Lab

FISH RESEARCH ADVANCES OUR UNDERSTANDING OF CHILDHOOD DISEASE

Dr Ana Cvejic has developed a new zebrafish model to study the origins of Fanconi anemia, a paediatric disease that causes fatal bone marrow failure and predisposes children to cancer.

The research team used genetically altered zebrafish to investigate RAD51, a gene recently discovered to be involved with Fanconi anemia and DNA repair. Their studies showed that fish without the RAD51 gene were hypersensitive to DNA damage, one of the key features of Fanconi anemia.

Through observation of the developing fish eggs, the scientists learned that disease symptoms, normally diagnosed in childhood, are actually linked to changes in blood stem cells during embryonic development.

"Using fish from the Sanger Institute Zebrafish Mutation Project, we have developed an important new model to advance research into Fanconi anemia" explains Dr Cvejic. *"We have investigated the gene RAD51, which was known to be involved in the development of this disease, however the specifics of the biology were unclear."*

"Our results show that changes in RAD51 drive dysfunction of blood stem cells during embryonic development which leads on to the typical bone marrow failure seen in children with the disease. We are confident that further research using our model will increase understanding of Fanconi anemia, and will have significant impacts on the development of new therapeutics for people living with this disease."

This research is supported by the Medical Research Council, Wellcome and Cancer Research UK, as well as the European Hematology Association and the Isaac Newton Trust.

Read more: www.stemcells.cam.ac.uk/news

Image: Swimming Zebrafish

IMPROVING THE BALANCING ACT IN CANCER THERAPY

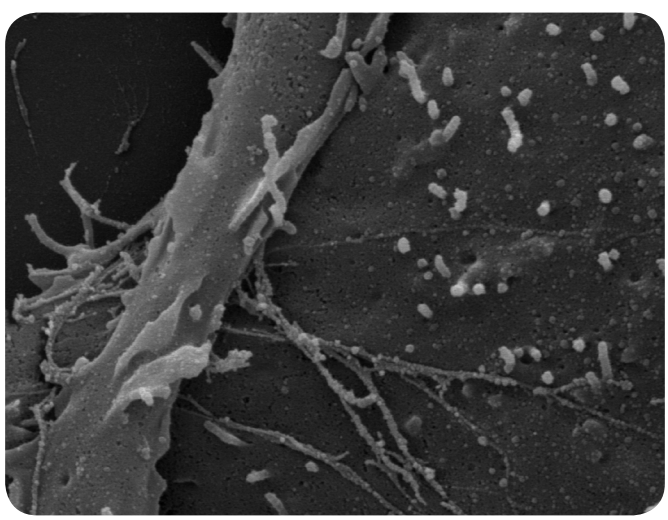


Image: Details of numerous extracellular membrane vesicles associated with a long cellular process on a neural stem cell.

Dr Stefano Pluchino and his team have revealed new insights into cellular signaling processes that could improve chemotherapy treatments.

The scientists showed that small signalling packages (known as extracellular vesicles) have the specific enzyme activity required to kill some cancer cells, without depleting essential nutrients required for healthy cell function.

The findings significantly extend our understanding of cell signalling biology whilst also having important clinical applications for cancer treatments.

"Current drug treatments of acute lymphoblastic leukaemia present a difficult balancing act: removing enough asparagine so that cancer cells cannot survive, but leaving enough glutamine to ensure normal cells in the body can thrive", explained **Dr Pluchino.** *"The discovery that the Asparaginase-like 1 in vesicles depletes asparagine but does not affect the glutamine could provide an alternative anti-cancer therapy that could limit side effects such as liver toxicity that occur when glutamine is depleted".*

The discovery of this 'clean-acting' Asparaginase-like 1 enzyme and the development of technologies around this research forms the basis of a patent owned by Cambridge Innovation Technologies Consulting Ltd, of which **Dr Pluchino** is a Co-founder and Director. This research demonstrates the potential for the understanding of fundamental cell biology to be scaled up to improve human health.

This research is supported by the European Research Council, Medical Research Council, the Italian Multiple Sclerosis Association, the UK Regenerative Medicine Platform Hub "Acellular Approaches to Therapeutic Delivery", the Evelyn Trust and the Bascule Charitable Trust.

Read more: www.stemcells.cam.ac.uk/news

Interview

15 MINS WITH...DR THOR THEUNISSEN

Dr Thor Theunissen was one of the first PhD students to study at the Cambridge Stem Cell Institute. Now he is about to open his own lab in the Department of Developmental Biology and Center of Regenerative Medicine at Washington University in St. Louis. We asked him about his time at the Institute and how it prepared him for his future career.

Q1: What made you want to do your PhD at the Cambridge Stem Cell Institute?
I became interested in stem cell research as an undergraduate at Harvard. During my senior year I looked into opportunities to pursue postgraduate studies in Europe. My advisers at the time, Doug Melton and Stuart Orkin, recommended that I apply to Cambridge given the quality of its stem cell community. The Wellcome Trust PhD Programme in Stem Cell Biology had just been launched, and I was fortunate to be among four PhD students admitted in the Programme's first year.

Q2: What is your favourite memory from your time at the Institute?
After completing my rotations I joined José Silva's lab for my PhD project. This was an exciting time as José had just started as an independent investigator and had many ideas that he wanted to explore. We were a small group of PhD students and one postdoc working on a highly topical question: what is the sequence of events during somatic cell reprogramming, and what is the role of endogenous transcription factors during this process? I have great memories of the camaraderie in the group and the experience of being part of a new lab. I also enjoyed living in the historic city of Cambridge and meeting other graduate students at King's College.

Q3: How did your time at the Institute prepare you for your future career?
My current research is strongly influenced by concepts and approaches to stem cell biology that were developed at the Cambridge Stem Cell Institute. The main objective of my work has been to derive human pluripotent stem cells in a "naive" state that resemble the pre-implantation blastocyst. Conventional human embryonic stem cells and induced pluripotent stem cells are more similar to the post-implantation epiblast and frequently display lineage bias during differentiation.

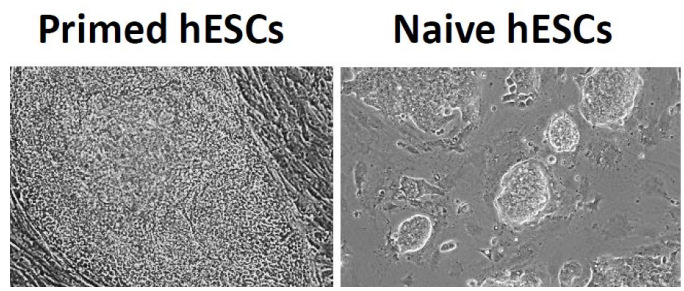
The concept of naive pluripotency was first proposed by Jenny Nichols and Austin Smith, and they have identified many essential regulators of naive pluripotency in rodent models. Extending these concepts to the human system has been more difficult however, and the question of whether a human "ground state" exists has generated significant interest.

As a postdoc in Rudolf Jaenisch's lab at the Whitehead Institute/MIT, I identified a combination of five small molecules that induces key features of naive pluripotency in human embryonic stem cells and induced pluripotent stem cells. These cells are globally similar to naive human pluripotent cells recently isolated by Austin's lab, though the two protocols rely on different combinations of chemical inhibitors.

Q4: What advice would you offer to current PhD students at the Institute?
Identify a question that truly fascinates you and pursue it with determination. Stem cell research requires a great personal commitment and long, unpredictable hours. Progress is usually slow and may seem incremental to non-specialists. To stay motivated when experiments don't go well, you have to be naturally curious about the underlying biology.

Q5: What most excites you about stem cell research?

Our field is undergoing a major transformation due to a confluence of new technologies. The advent of single cell biology, in particular single cell RNA-seq, has made it possible to uncover stem cell heterogeneity at an unprecedented scale. In addition, we can now define the expression signatures of discrete subpopulations of cells in human embryos, which provides a critical benchmark to examine the identity of distinct stem cell states isolated in vitro.



Microscope images of conventional (primed) human embryonic stem cells and naive human embryonic stem cells generated in the presence of 5 small molecule inhibitors. Credit Thor Theunissen.

Single cell epigenomics will be an important area to keep an eye on, as it may give insights into asynchronous and heterogeneous cell fate transitions such as differentiation and reprogramming. Finally, the CRISPR revolution has made it possible to edit genes at will in human pluripotent cells. This is a rather amazing development given that only a handful of genes were successfully targeted in human ES cells as recently as 10 years ago!

Q6: What will be the research focus of your new lab?

The focus of my lab will be to investigate the molecular mechanisms regulating distinct states of pluripotency and their applications in regenerative medicine. An important objective will be to determine whether certain states of pluripotency are favorable for modeling human development and disease. I also retain a keen interest in developing improved strategies to derive human pluripotent stem cells and to understand what drives the onset of genetic and epigenetic instability during stem cell culture.

We would like to extend our thanks to Thor for talking to us about his time at the Cambridge Stem Cell Institute and we wish him the very best of luck for the exciting next stage of his career at Washington University.

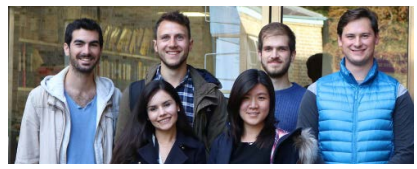
If you are part of the alumni community from the Cambridge Stem Cell Institute, and would like to share your experiences, please contact Abi Herrmann sci-coordinator@stemcells.cam.ac.uk.

FOUR YEAR PHD PROGRAMME IN STEM CELL BIOLOGY & MEDICINE

Stem cell research is one of the most exciting and rapidly developing areas in current biomedical science. The challenges involved in this area are complex and range across many different disciplines from basic science through disease modelling to clinical medicine. Consequently, students on this Programme come from a variety of different backgrounds with little or no specialist education in this field. This course provides students with a thorough introduction to the concepts and practices of stem cell research through a structured PhD Programme with a broad-ranging first year.

The first year of the programme is designed to give training in the conceptual foundations, experimental systems, practical techniques, and current state of knowledge in stem cell biology and medicine. In parallel with workshops and discussion sessions, three laboratory rotations give the students practical research training and the experience of working with different stem cell types and in different laboratories. This empowers the students to make an informed decision when choosing their research question and host laboratory for the PhD project (in years 2-4).

Application for 2018 entry onto our Four Year PhD Programme in Stem Cell Biology & Medicine opens in October 2017. Please visit our website www.stemcells.cam.ac.uk/study for more details of the Programme, including instructions on how to apply.



Recent Publications

A unifying theory of branching morphogenesis. Hannezo E, Scheele C, Moad M, Drogo N, Heer R, Sampogna R, van Rheenen J and Simons BD. **Cell.** 2017 Sep 21: 171 (1):242-255

Genome editing reveals a role for OCT4 in human embryogenesis. Fogarty N, McCarthy A, Snijders K, Powell B, Kubikova N, Blakeley P, Lea R, Elder K, Wamaitha S, Kim D, Maciulyte V, Kleinjung J, Kim J, Wells D, Vallier L, Bertero A, Turner J and Niakan K. **Nature.** 2017 Sep 20; DOI:10.1038/nature24033

Fate mapping of human glioblastoma reveals an invariant stem cell hierarchy. Lan X, Jörg D, Cavalli F, Richards L, Nguyen L, Vanner R, Guilhamon P, Lee L, Kushida M, Pellacani D, Park N, Coutinho F, Whetstone H, Selvadurai H, Che C, Luu B, Carles A, Moksa M, Rastegar N, Head R, Dolma S, Prinos P, Cusimano M, Das S, Bernstein M, Arrowsmith C, Mungall A, Moore R, Ma Y, Gallo M, Lupien M, Pugh T, Taylor M, Hirst M, Eaves C, Simons BD and Dirks P. **Nature.** 2017 Sep 14;549(7671):227-232

Mbd3/NuRD controls lymphoid cell fate and inhibits tumorigenesis by repressing a B cell transcriptional program. Loughran S, Comoglio F, Hamey F, Giustacchini A, Errami Y, Earp E, Göttgens B, Jacobsen S, Mead A, Hendrich B and Green A. **Journal of Experimental Medicine.** 2017 Sep 12; DOI: 10.1084/jem.20161827

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

Early loss of Crebbp confers malignant stem cell properties on lymphoid progenitors. Horton S, Giotopoulos G, Yun H, Vohra S, Sheppard O, Bashford-Rogers R, Rashid M, Clipson A, Chan W, Sasca D, Yiangou L, Osaki H, Basheer F, Gallipoli P, Burrows N, Erdem A, Sybirna A, Foerster S, Zhao W, Sustic T, Petrunkina Harrison A, Laurenti E, Okosun J, Hodson D, Wright P, Smith K, Maxwell P, Fitzgibbon J, Du M, Adams D and Huntly B. **Nature Cell Biology.** 2017 Sep;19(9):1093-1104

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Chronic activation of JNK JAK/STAT and oxidative stress signalling causes the loser cell status. Kucinski I, Dinan M, Kolahgar G and Piddini E. **Nature Communications.** 2017 Jul 26;8(1):136

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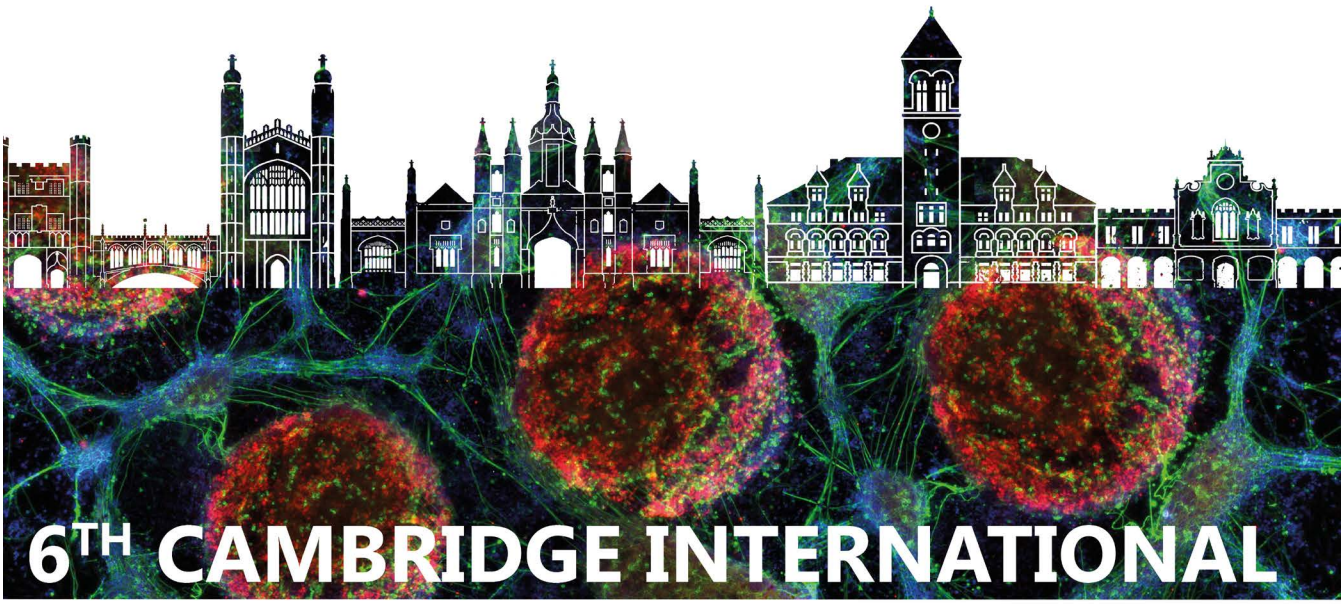

6TH CAMBRIDGE INTERNATIONAL STEM CELL SYMPOSIUM

19th-21st September 2018

Confirmed speakers include:

Cédric Blanpain
Université Libre de Bruxelles

Elena Cattaneo
University of Milan

Frederic de Sauvage
Genentech Inc

Stuart Forbes
University of Edinburgh

Allon Klein
Harvard University

Cristina Lo Celso
Imperial College London

Hiro Nakauchi
Stanford University

Malin Parmar
Lund University

Emmanuelle Passegué
Columbia Stem Cell Initiative

Tom Rando
Stanford University

Peter Reddien
Massachusetts Institute of Technology

Bill Richardson
Wolfson Institute

Dirk Schübeler
Friedrich Miescher Institute for Biomedical Research

David Scadden
Harvard University

Masayo Takahashi
RIKEN Center for Developmental Biology

Adrian Thrasher
University College London

Andreas Trumpp
HI-STEM

Fiona Watt
King's College London

Organised by:

Wellcome Trust - Medical Research Council
Cambridge Stem Cell Institute

Registration opens in December 2017

www.stemcells.cam.ac.uk/symposium2018

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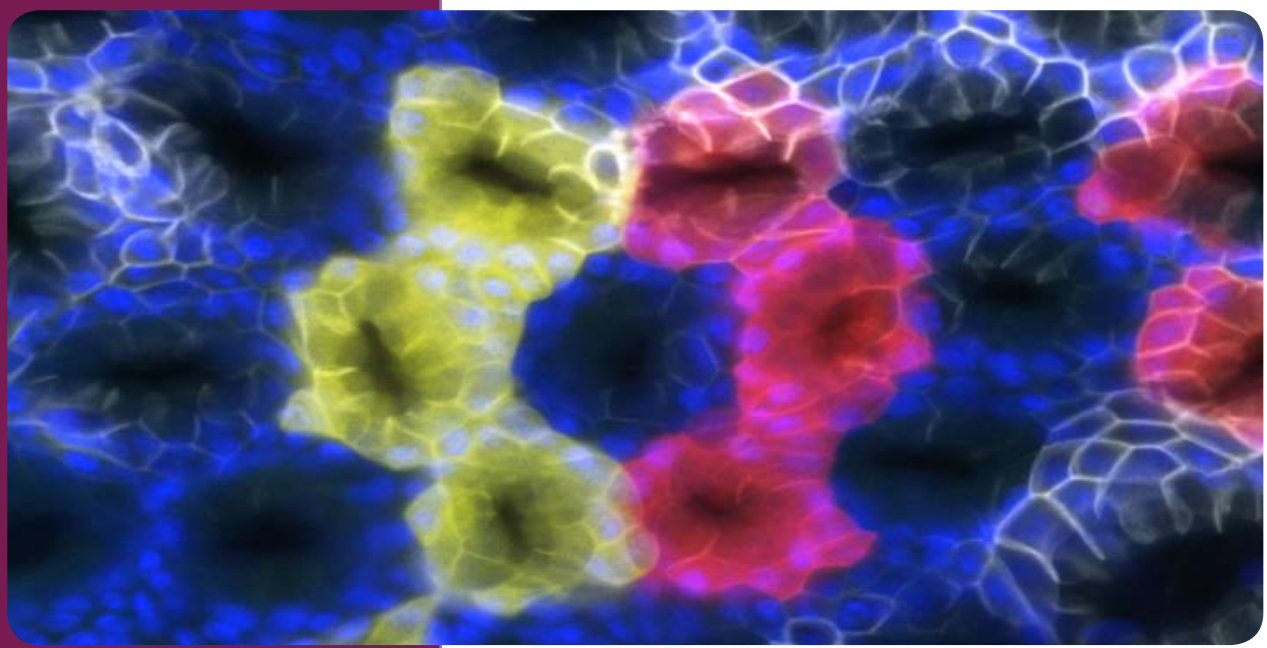
Cambridge Stem Cell News is produced by the Cambridge Stem Cell Institute to provide an accessible summary of recent Institute research, events and interdisciplinary activities.

We are keen to hear feedback on the publication and are also very open to suggestions for features and content for future editions.

To share your thoughts simply email sci-coordinator@stemcells.cam.ac.uk



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Our regular office hours are
Monday to Friday, 9 a.m. to 5 p.m.

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www.stemcells.cam.ac.uk

Front Cover Image: Mouse gallbladder following repair with bioengineered stem cells Credit: Vallier Lab

Back Cover Image: Stomach glands labelled in different colours and organised in a hexagon shape. Credit: Jurgen Fink

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