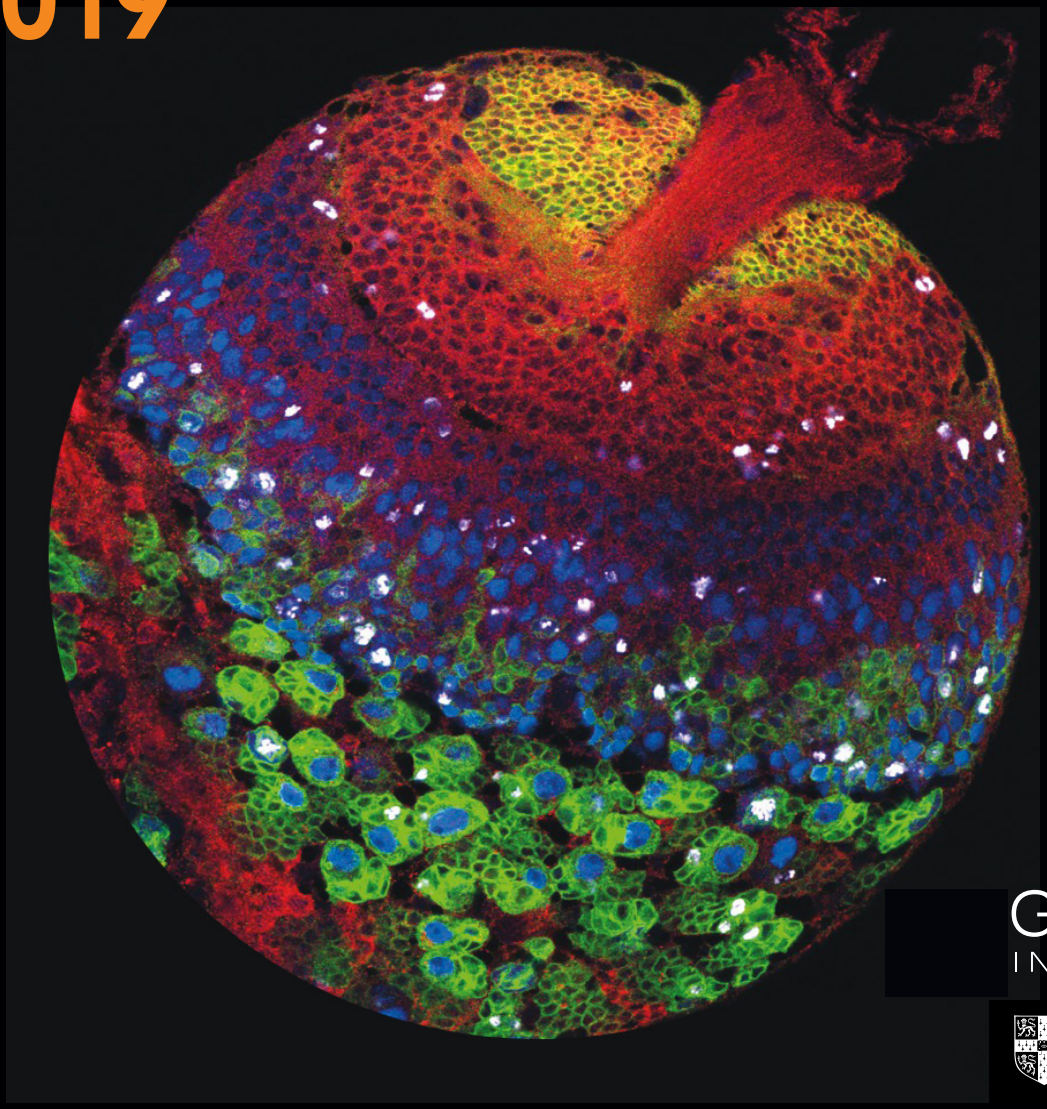
The Wellcome Trust/Cancer Research UK

Gurdon Institute

Prospectus 2019



Gurdon INSTITUTE

UNIVERSITY OF CAMBRIDGE

Studying development to understand disease

The Wellcome Trust/ Cancer Research UK Gurdon Institute
Prospectus 2019

Contents

Welcome

I am delighted to present our new *Prospectus 2019* in my first year as Director of the Gurdon Institute. As you will discover in these pages, 2018 was an exciting and productive year filled with great science, awards and public engagement.

We congratulate Azim Surani for being joint winner of the Canada Gairdner International Award, and Meri Huch for being recognised by four coveted awards (see pp. 8–9). Further, Tony Kouzarides was elected a member of the American Academy of Arts and Sciences, and Ben Simons was awarded the Royal Society's EP Abraham Research Professorship. In March 2018 we also heard the good news that our Athena SWAN Bronze Award, for promoting equality and diversity in the Institute, was renewed for four years.

"Delivering top class discovery science with medical relevance"

We are grateful for the wisdom and advice of our International Scientific Advisory Board, who visited in September and commended us on "delivering top class discovery science with medical relevance".

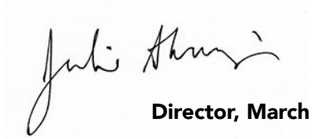
We also had a strong year of public engagement activities (pp. 12–13), with a quarter of our researchers participating. A highlight was our 'Experiments in Art & Science' project, a collaboration with Kettle's Yard (local art gallery and house), which resulted in films and performances to inspire excitement and interest in our science.

Looking ahead, we'll sadly say goodbye to Rick Livesey and his lab in August when they move to University College London's Great Ormond Street Institute of Child Health, where Rick is now Professor of Stem Cell Biology. We will also greatly miss Meri Huch, who is moving her lab to the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden. We congratulate and wish successful futures to them both.

Meanwhile the Milner Therapeutics Institute team, who have been incubating here since 2016, will move to new premises on the Cambridge Biomedical Campus. We look forward to seeing the fruits of their enterprise of bringing pharma companies and academic researchers together.

Finally, we are excited to welcome two new group leaders who are pursuing quantitative aspects of biology, both of whom are also physicists. Fengzhu Xiong arrives in June to study cellular and physical mechanisms of developmental symmetry in the chick embryo. Ben Simons will also join us as a group leader, having been an associate member for several years, applying statistical physics methods to stem cell biology.

I hope that you enjoy reading about our thriving Institute.

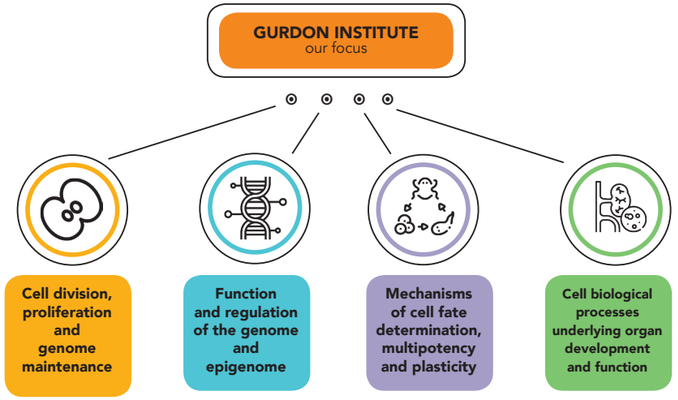


Director, March 2019

About the Institute

The Gurdon Institute is a world-leading centre for research at the interface between developmental biology and cancer biology.

Our research is focussed in **four** overlapping areas:



We investigate these areas in both normal development and cancer using multiple model systems, from yeast to human organoids (see pp. 16–49). Since our formation in 1991, our research has led to **major insights** into the molecular and cellular defects that give rise to cancer and other diseases of ageing, and findings have been successfully translated to drug discovery through spinout companies.

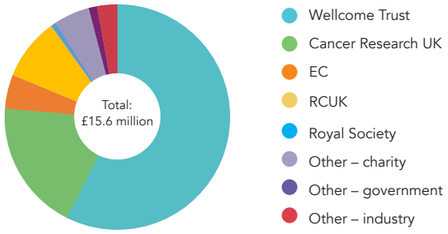
The Gurdon Institute's **principal sponsors** are Wellcome and Cancer Research UK, who support our excellent infrastructure through core grants, and our research through direct grants to group leaders. Our research is also funded by other sources including national and international governmental and charitable grants. Scientific progress and future plans are assessed at regular intervals by our International Scientific Advisory Board (p.65).

The Institute is embedded within the University of Cambridge, providing unparalleled opportunities for collaborations and interactions across Cambridge's vibrant research environment, including through department affiliations and teaching.

We benefit from:

- Core facilities with state-of-the-art equipment and support including super-resolution microscopy, next-generation sequencing and bioinformatics (pp. 50–51)
- Central support services providing administration, computing and IT, stores, media preparation and glass washing (pp. 50–51).
- A wealth of stimulating seminars and masterclasses, an annual Institute Retreat, and Institute postdoc and PhD student groups (pp. 56–59).
- Active and creative public engagement between our scientists and the wider public (pp. 12–13).
- An on-site canteen, social events and sports groups, which enhance our welcoming and inclusive environment.
- An Athena SWAN Bronze Award for promoting equality and diversity across our workforce.

Gurdon Institute funding 2017–18



The Gurdon Institute in numbers

100 papers published by our academics each year, in the leading journals in our fields

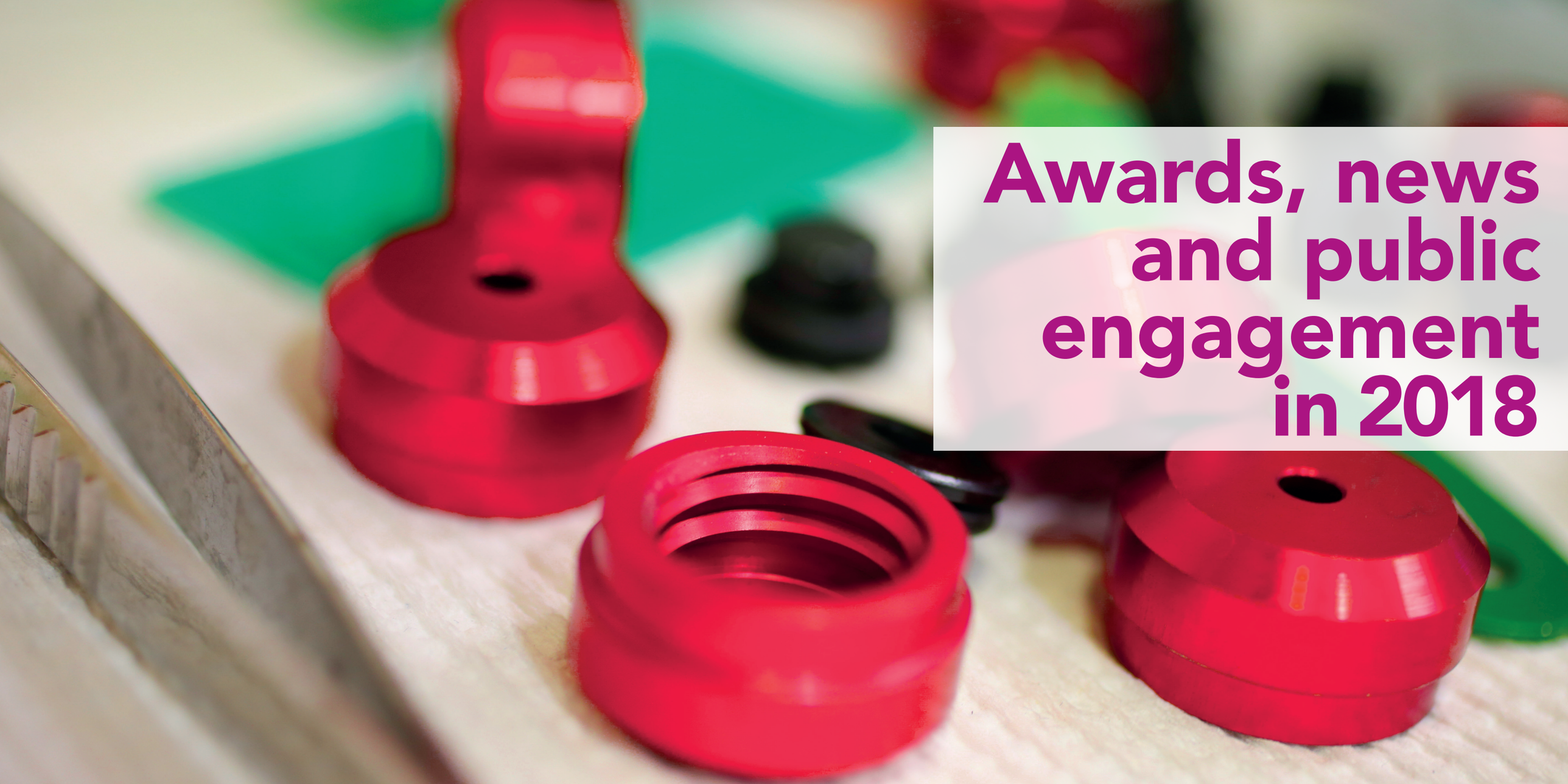
16 group leaders

300 scientists and support staff

40 nationalities represented among research staff

Join us

We have a thriving community of graduate students and postdocs who contribute to and benefit from our exciting research environment. We welcome enquiries from those interested in joining us, which can be done by writing to the relevant group leader.



Awards, news and public engagement in 2018

Awards in 2018

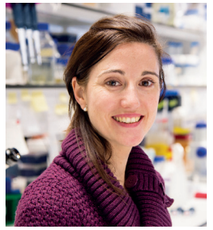
Azim Surani is joint winner of top research award in Canada

The Gurdon Institute's Director of Germline and Epigenetics Research, Azim Surani (pictured opposite), was joint winner of Canada's top research award, announced in March 2018. With Davor Solter of the Max Planck Institute of Immunobiology and Epigenetics, he received the 2018 **Canada Gairdner International Award** at a gala ceremony in Toronto in October "for their discovery of mammalian genomic imprinting that causes parent-of-origin specific gene expression and its consequences for development and disease".

In 1984, Solter and Surani released parallel studies demonstrating the concept that chromosomes retained a 'memory' of their parental origin, and Surani coined the term 'imprinting' to describe this. Their work is one of the key discoveries that started the field of epigenetics, the study of heritable changes in gene function without changes in the DNA sequence.

The award laurates received a $100,000 honorarium and later participated in an outreach program of presentations to share their research with Canadian researchers and school students. On the Gurdon Institute YouTube channel you can find a video in which Azim explains the concept of genomic imprinting and his subsequent findings.

Meri Huch scoops awards recognising excellent young researchers



Group leader Meri Huch collected several awards in 2018, beginning with the **Women in Cell Biology Early Career Medal** from the British Society for Cell Biology (BSCB). This medal is awarded annually to "an outstanding female cell biologist" who has recently started their independent research career, to inspire the next generation of female scientists. Meri's medal lecture, delivered at a science conference in Manchester in March, can be watched on the BSCB YouTube channel.

Meri was also awarded the **Dame Sheila Sherlock Prize** from the British Association for the Study of Liver (BASL), and gave a prize lecture at BASL's Annual Meeting in York in September. This annual award recognises the research contributions of young investigators in the field of Hepatology.

In November Meri was announced to be one of 26 new **EMBO Young Investigators**, to receive a competitive four-year award designed to help young investigators establish their research groups. Finally, at the Cambridge Independent's Science & Technology Awards, Meri Huch scooped the Highly Commended award in the **Researcher of the Year** category, for her organoid research.

Surani (pictured) and Solter's finding was one of the key discoveries that started the field of epigenetics

- Senior group leader **Tony Kouzarides** was elected an **International Honorary Member of the American Academy of Arts and Sciences**, in the Biological Sciences class. Academy members are world leaders in the arts and sciences, business, philanthropy and public affairs, and belong to one of the oldest learned societies in the USA, founded in 1780.

- **Ben Simons** received the **EP Abraham Research Professorship** from the Royal Society in March 2018. The research professorships are the Society's premier research awards, providing long-term support to release the best leading researchers from teaching and administration duties.

- For his talk on 'The structural plasticity of the Zika virus genome in living human cells', Miska lab postdoc **Omer Ziv** won an **RNA Society award** at the EMBO Workshop 'RNA structure meets function' in Stockholm in July. The award included a cash sum to cover travel costs.

News highlights in 2018

New institute that converts science into therapies emerges from the Gurdon

The Milner Therapeutics Institute has been incubating within the Gurdon Institute since it began with one employee in 2016. Founded by Tony Kouzarides (centre), the Milner's aim is to bring pharma companies and academic researchers together, faster, to speed up new drug development.

During 2018 the team expanded to six with expertise in bioinformatics, research translation and commercial relationships, in anticipation of moving to their new premises in the Jeffrey Cheah Biomedical Centre on the Cambridge Biomedical Campus in 2019. Tony will remain at his Gurdon Institute lab.

How do you thank the man who saved your life?

Grandmother Sandy Tansley, aged 73, was prescribed olaparib in a clinical trial for her ovarian cancer, and has now been cancer-free for five years. Worldwide Cancer Research, who were funding Steve Jackson when he made his research discovery underlying the development of olaparib, brought patient and scientist together for the first time and released a short video of their meeting. (Find 'The Meeting' video on their YouTube channel.)

Olaparib has also been licensed for use in breast cancers and is in clinical trials for further cancer sites.

18 members of Hubrecht Institute visit from Utrecht

In September we hosted a one-day visit from the Hubrecht Institute, Utrecht, The Netherlands. Eighteen of their group leaders and senior staff, including director Alexander van Oudenaarden (second row, second from left), joined our group leaders and senior team for research talks, one-to-one meetings, tours of the Institute and finally a dinner at King's College. All agreed that the day had been an enjoyable way to explore potential new research collaborations.

Co-inventor of CRISPR-Cas9 gene editing delivers hugely popular McLaren lecture

Our Anne McLaren Lecture in March, part of the Gurdon Institute Seminar Series, was the most popular ever, no doubt due to the fame of the speaker: Jennifer Doudna, Professor and HHMI Investigator at UC Berkeley, California.

The audience came from across Cambridge to hear the co-inventor of CRISPR technology describe her discovery and her latest research on the Cas family of enzymes. Steve Jackson (left) and Eric Miska hosted Jennifer's visit.

Public engagement

Our Public Engagement with Research goals are to inspire the young generation with low science capital regionally and nationally, enable communities to value and have confidence in fundamental research and make Public Engagement (PE) part of our research culture.

In 2018 we recruited a dedicated PE Assistant, Naomi Clements-Brod, to support our half-time PE Manager and Research Associate, Hélène Doerflinger. This enabled us to devise and run additional new initiatives, which also resulted in a big increase in the number of hours dedicated by researchers to participating, especially by more senior lab members.

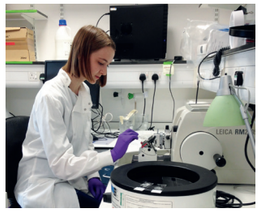
'Experiments in Art & Science'

This year-long collaboration with local art gallery and house, Kettle's Yard, brought three young artists to the Institute to meet and collaborate with researchers in three different labs, with the only instruction being to produce an output that could be shared with the public at a variety of events. Artists Laura Wilson, David Blandy and Rachel Pimm chose to work with the Zegerman, Livesey and Miska labs, respectively.

The outputs were one film (with 2D and 3D versions), one 90-minute dance performance, and one narrative text work (presented as video). The works were shown at different stages: at an Open Day at Kettle's Yard, at the Cambridge Live BIG Weekend, in an internal Happy Hour for Institute staff and then at a public event on site for the University's Festival of Ideas. Both artists and researchers came away with new insights into their own and others' work. Several noted the significant overlap in how artists and scientists experiment with the world around them. We shared the project's progress and results in blogs on the Kettle's Yard website, on our website and Twitter account, and with a short video made of the on-site event (available on our YouTube channel).

Formal work experience programme for A-level Biology students

While different labs have regularly hosted sixth-formers for summer work experience, these visits were not coordinated across the Institute and the students were not part of a cohort. Our new formal programme was piloted in July 2018, whereby 11 students from state schools stayed for one week in one of ten labs. In addition to spending hands-on time observing or running simple experiments, the students jointly took part in several skills-based workshops and delivered presentations. All the students said they would recommend the programme to a friend or fellow student. It will be repeated in 2019 with funding from the University's Widening Participation scheme.



"I got the feeling of accomplishment and scientific duty in being able to represent the Institute's research to the public"

Cambridge Science Festival

- An afternoon of seven different microscopy activities on site in the tea room brought in 242 visitors and involved 28 participants from the Institute, one of whom commented: "I got the feeling of accomplishment and scientific duty in being able to represent the Institute's research to the public".

- 'Food for thought', an evening lecture at the Old Divinity School by Andrea Brand, about stem cells in the brain, had an audience of 119, many of whom stayed for the reception afterwards to continue questions and discussion with Andrea and her lab members over drinks. One visitor said: "lovely to get an insight in to where scientists are looking and how the discoveries are progressing".

Other activities

- The Mobile Lab visited six classes of Year 5 students at four different local schools, taking 20 microscopes and specific activities for the students to get 'hands on' with preparing and observing samples.
- Two sixth-form workshops were held at the Institute in which a school group attended a short presentation about microscopy and cancer research and then worked on an activity of analysing samples.
- Our microscopy experts Alex Sossick and Nicola Lawrence led an Institute visit and a microscope-building project in a 9-week collaboration with the Cambridge Academy for Science and Technology. The project was highly rated by the 22 students, and one of them commented: "building a microscope = new skills learned".
- 24 University alumni enjoyed a talk and lab tour.

Focus on research

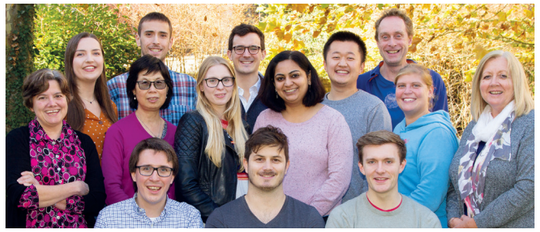
Julie Ahringer

Developmental regulation of chromatin structure and function

How is chromatin structure regulated to direct correct gene expression programmes?
Animal development is an extraordinary process during which a single-celled totipotent zygote produces a myriad of different tissues and cell types. Differential control of chromatin structure establishes the gene expression programmes that drive cellular identity. Deciphering this control is necessary for understanding how the genome directs development and the diseases that result from chromatin dysregulation.

We study how cell-type specific gene expression and chromatin organisation are achieved using the simple *C. elegans* model, focussing on controls and interactions at regulatory elements, how euchromatin and heterochromatin are formed, and the regulation of 3D nuclear organisation. Taking advantage of the experimental amenability and defined lineage of *C. elegans*, we apply high-throughput genomics, super-resolution microscopy, single-cell analyses, and computational approaches to understand core mechanisms of gene expression regulation in development.

Modification patterns >
C. elegans embryonic nuclei showing nuclear lamina (red), histone H3K9me2 (green) and DNA (blue); the heterochromatin histone modification H3K9me2 is found in discrete foci in the nucleus.



Co-workers
Alex Appert, Lindsey Bartram, Francesco Carelli, Chiara Cerrato, Yan Dong, Andrea Frapporti, Csenge Gal, Yuanhang Jiang, Rhys McDonough, Karolina Oniszczuk, Jacques Serizay, Przemyslaw Stempor, Isaac Walton

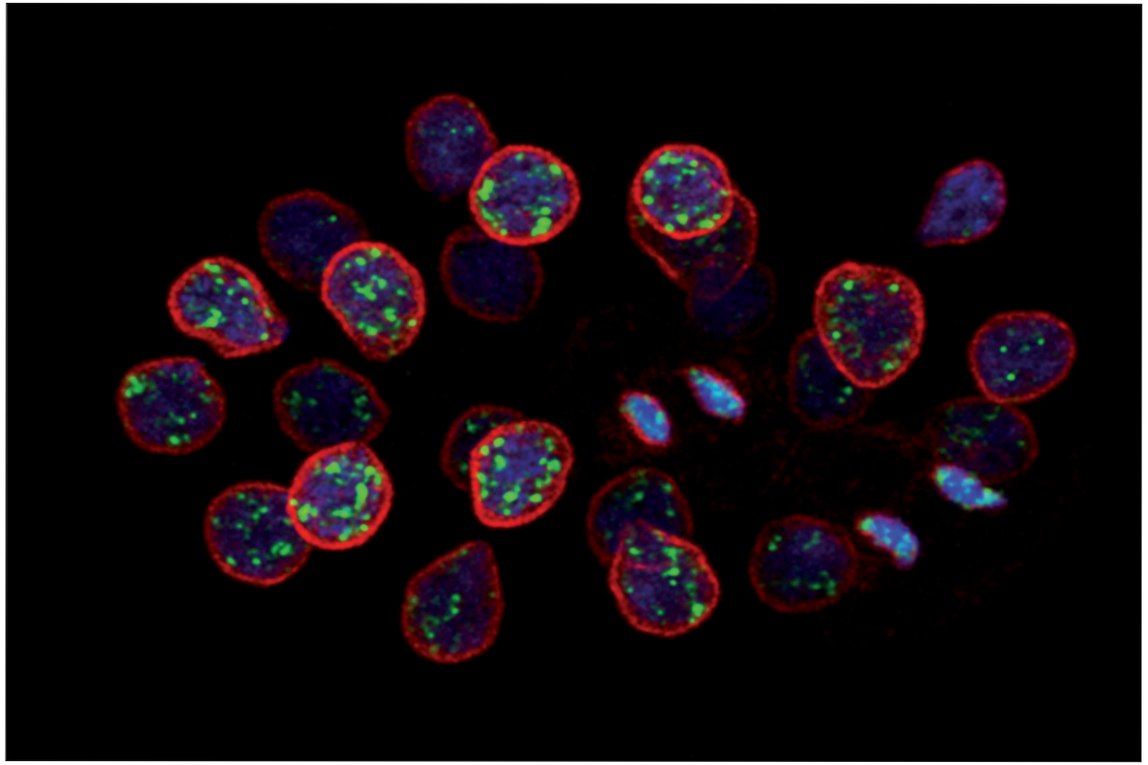


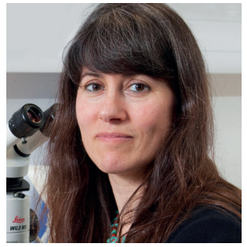
IMAGE BY ANDREA FRAPPORTI.

"We study how cell-type specific gene expression and chromatin organisation are achieved"

Selected publications

> Jänes J *et al.* (2018) Chromatin accessibility dynamics across C. elegans development and ageing. ***eLife 7***: e37344.
> McMurchy AN *et al.* (2017) A team of heterochromatin factors collaborates with small RNA pathways to combat repetitive elements and germline stress. ***eLife 6***: e21666.
> Evans KJ *et al.* (2016) Stable C. elegans chromatin domains separate broadly expressed and developmentally regulated genes. ***Proc Natl Acad Sci*** 113 (45): E7020-E7029.

Andrea Brand



Time to wake up: regulation of stem cell quiescence and proliferation

Stem cell populations in tissues as varied as blood, gut and brain spend much of their time in a mitotically dormant, quiescent, state. A key point of regulation is the decision between quiescence and proliferation. The ability to reactivate neural stem cells *in situ* raises the prospect of potential future therapies for brain repair after damage or neurodegenerative disease. Understanding the molecular basis for stem cell reactivation is an essential first step in this quest.

In *Drosophila*, quiescent neural stem cells are easily identifiable and amenable to genetic manipulation, making them a powerful model with which to study the transition between quiescence and proliferation. These stem cells exit quiescence in response to a nutrition-dependent signal from the fat body, a tissue that plays a key role in the regulation of metabolism and growth. My lab combines cutting-edge genetic and molecular approaches with advanced imaging techniques to study the reactivation of *Drosophila* neural stem cells *in vivo*. This enables us to deduce the sequence of events from the level of the organism, to the tissue, the cell, and finally the genome.

New brain cells >
We discovered a new population of neural stem cells (which we named EONs) that are generated by the embryonic neuroepithelium. Neuroepithelial cells are labelled in magenta and neural stem cells in cyan [Hakes, Otsuki & Brand (2018) Development 145: dev166207].

Co-workers
Neha Agrawal, Diana Arman, Benjamin Badger, Catherine Davidson, Anna Hakes, Leia Judge, Robert Krautz, Stephanie Norwood, Takumi Suzuki, Jocelyn Tang, Christine Turner, Jelle van den Ameele, Rebecca Yakob, Mo Zhao

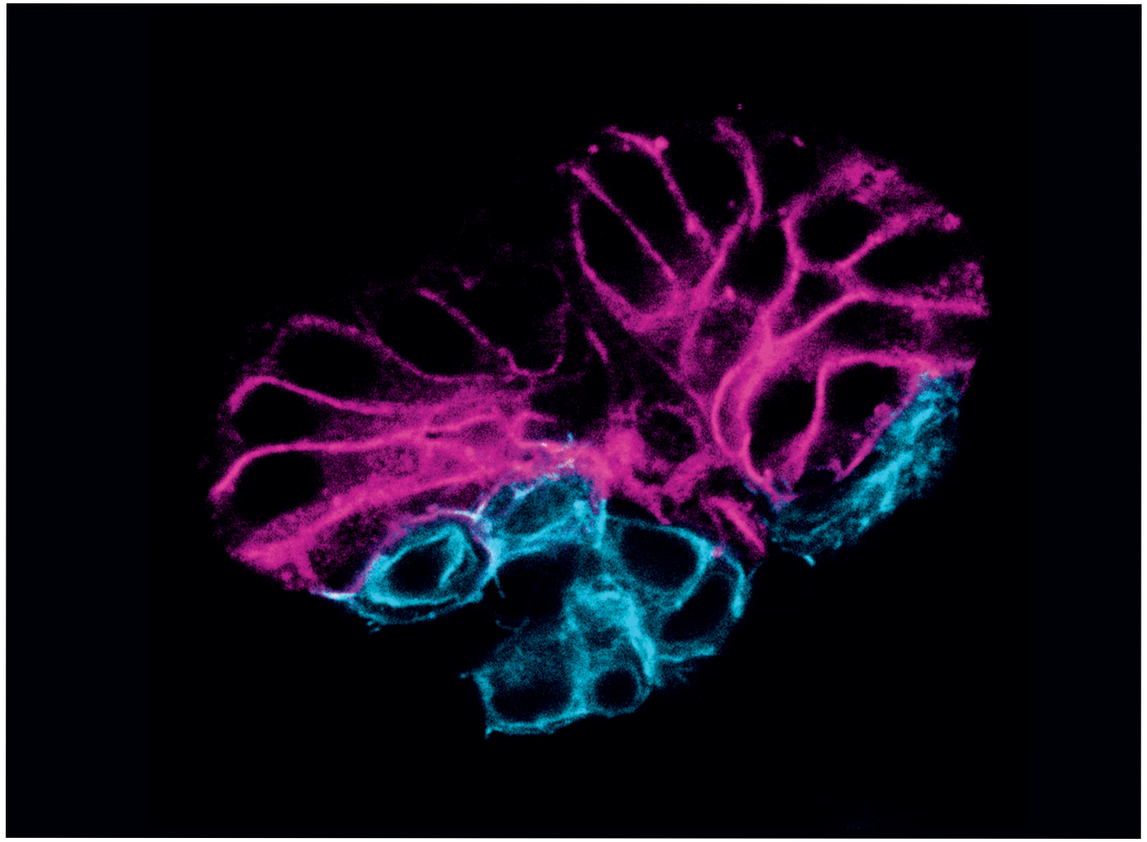


IMAGE BY ANNA HAKES.

"The ability to reactivate neural stem cells *in situ* raises the prospect of potential future therapies"

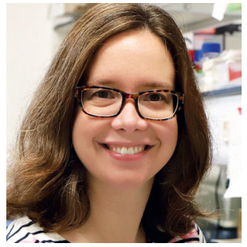
Selected publications

> Otsuki L & Brand AH (2018) Cell cycle heterogeneity directs the timing of neural stem cell activation from quiescence. ***Science*** 360: 99–102.

> Cheetham SW & Brand AH (2018) RNA-DamID reveals cell-type-specific binding of roX RNAs at chromatin-entry sites. ***Nat Struct Mol Biol*** 25:109–114.

> Spéder P & Brand AH (2018) Systemic and local cues drive neural stem cell niche remodelling during neurogenesis in Drosophila. ***Elife*** 7: e30413.

Jenny Gallop



Membranes, actin and morphogenesis

How do cells move their membranes?
The cell membrane, as the boundary of the cell, is moulded into shape by dynamic remodelling of its links to the actin cytoskeleton during cell division, polarisation, movement, differentiation and for everyday housekeeping. In disease, the actin machinery is hijacked by invading pathogens. Some actin regulators are overexpressed and redeployed during cancer metastasis, and control of the actin cytoskeleton can be disrupted in genetic diseases, causing intellectual disability, kidney dysfunction and other problems.

We are studying how actin filaments polymerise at two types of specialised structures at the cell membrane: filopodia, which are fingerlike protrusions, and endocytic vesicles, which bud inwards to bring in components from the membrane or environment. We have developed model systems using phospholipid bilayers and frog egg extracts that allow us to follow the molecular events of actin assembly in different contexts. By focusing on unusual predictions from these in vitro assays, we work out how the actin cytoskeleton is regulated by imaging cells in accessible, native developmental contexts in fruit fly and frog embryos.

Watching filopodia grow >
Three-dimensional reconstruction of filopodia-like structures growing from a supported lipid bilayer. The structures were segmented based on fluorescent actin intensity in a stack of microscopy images of size 76.13 x 76.13 x 30 microns. Colours were randomly assigned as a guide for the eye. The segmentation was performed using a custom image-analysis pipeline.

Co-workers
Ulrich Dobramysl, Jonathan Gadsby, Julia Mason, Kathy Oswald, Pantelis Savvas Ioannou

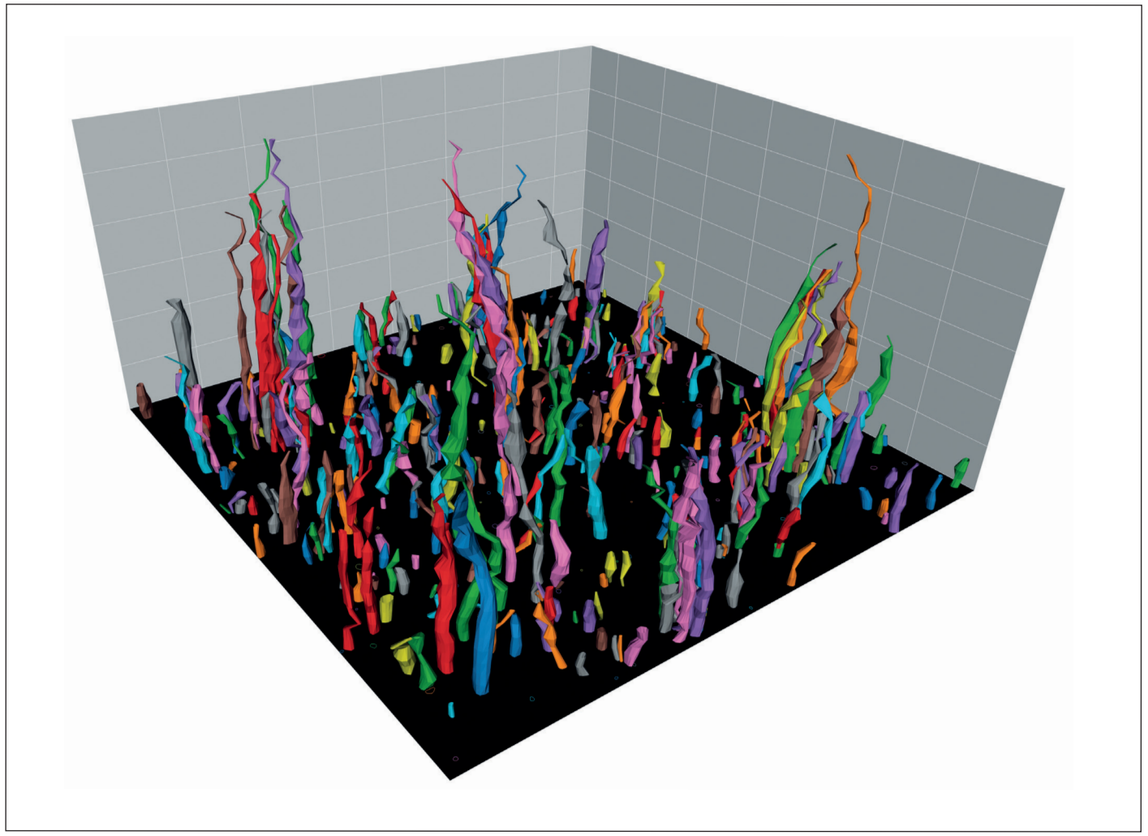


IMAGE GENERATED BY ULRICH DOBRAMYSL FROM MICROSCOPY IMAGES BY IRIS JARSCH AND AN ANALYSIS PIPELINE DESIGNED BY RICHARD BUTLER.

"Using phospholipid bilayers and frog egg extracts allows us to follow the molecular events of actin assembly"

Selected publications

> Richier B *et al.* (2018) Integrin signaling downregulates filopodia during muscle-tendon attachment. ***J Cell Sci*** 131: jcs21733.
> Daste F *et al.* (2017) Control of actin polymerization via the coincidence of phosphoinositides and high membrane curvature. ***J Cell Biol*** 216: 3745–3765.
> Urbančič V *et al.* (2017) Filopodyan: An open-source pipeline for the analysis of filopodia. ***J Cell Biol*** 216: 3405–3422.

John Gurdon

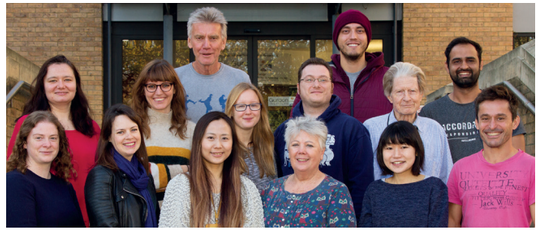
Nuclear reprogramming by oocytes and eggs

Can we make cell reprogramming more efficient?
Our group focuses on somatic cell nuclear transfer to amphibian eggs and oocytes from two complementary points of view. One aims to identify the molecules and mechanisms by which the cytoplasm of an egg or oocyte can reprogramme the nucleus of a differentiated somatic cell to behave like that of an embryo. From this state, many different kinds of cells for replacement can be generated.

The other aim is to identify the molecules and mechanisms that stabilise the differentiated state of somatic cells, as a result of which they resist reprogramming procedures. For these purposes we use single nuclear transfer to unfertilised eggs or multiple nuclear transfer to ovarian oocytes.

We make use of the special properties of an amphibian oocyte to inject messenger RNA that codes for a transcription factor protein. When this has been synthesised, it concentrates in the oocyte nucleus. The next day we inject plasmid DNA directly into the oocyte nucleus, where the factor causes transcription, and later expression, of a reporter gene in the plasmid.

Molecules and mechanisms >
Top: *Two types of nuclear transfer experiments, with eggs or oocytes.*
Bottom: *The Xenopus oocyte can be used to provide a functional test for the binding of a cell-fate-determining transcription factor, such as Ascl1 for nerve. Once expression of the first plasmid DNA is established, a second plasmid is not able to compete because of the stable binding of the factor.*



Co-workers
Can Aztekin, Dilly Bradford, Nigel Garrett, Eva Hörmanseder, Khayam Javed, Jerome Jullien, Mami Oikawa, Christopher Penfold, Ming-Hsuan Wen

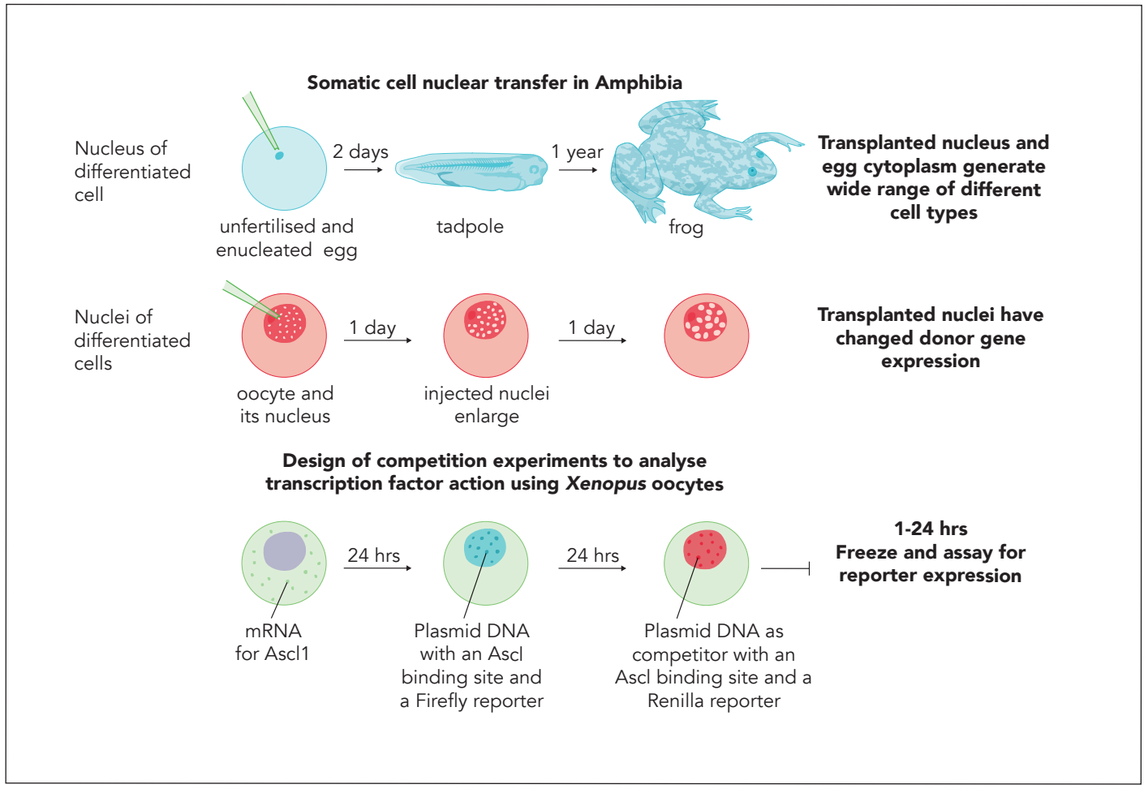


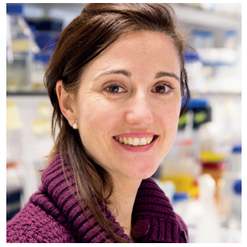
ILLUSTRATION BY CLAUDIA FLANDOLI.

"From this state, many different kinds of cells for replacement can be generated"

Selected publications

> Hörmanseder E *et al.* (2017) H3K4 methylation-dependent memory of somatic cell identify inhibits reprogramming and development of nuclear transfer embryos. ***Cell Stem Cell*** 21: 135-143.e6.
> Jullien J *et al.* (2017) Gene resistance to transcriptional reprogramming following nuclear transfer is directly mediated by multiple chromatin repressive pathways. ***Mol Cell*** 65: 873–884.e8.
> Jullien J *et al.*. (2011) Mechanisms of nuclear reprogramming by eggs and oocytes: a deterministic process? ***Nat Rev Mol Cell Biol*** 12: 453–459.

Meritxell Huch



Stem cells and tissue regeneration in liver and pancreas

How can we repair diseased liver and pancreas?
In adult mammals, many tissues have the capacity to self-renew to maintain healthy function in homeostasis and after damage. But the capacity for cell turnover varies. In the intestine and stomach, adult stem cell populations are constantly replenishing, while in the liver and pancreas cell proliferation is limited. Chronic liver disease and pancreatic cancer are strongly associated with inflammation and tissue damage, which activates stem cells and progenitor cells to repair lost tissue. Our goal is to understand the activation mechanism in order to harness it for therapeutic strategies.

We have established a novel culture system, liver organoids, which allows the massive and infinite expansion of mouse liver cells into three-dimensional structures that resemble functional liver tissue. When transplanted into a mouse model of liver disease ('FAH –/–'), these cells partially rescued the liver phenotype. We also work with pancreas cells and diseased human liver cells in culture, and are testing how well our models can represent human pathology in a dish.

Liver tumours in a dish >
Bright-field microscope image of single hepatocellular carcinonoma-derived organoid.

Co-workers
Luigi Aloia, Robert Arnes, Lucia Cordero Espinoza, Nikitas Georgakopoulos, Patricia Inacio, Mewanthi Flaminia Kaluthantrige Don, Gianmarco Mastrogiovanni, Kathy Oswald, Nicole Prior

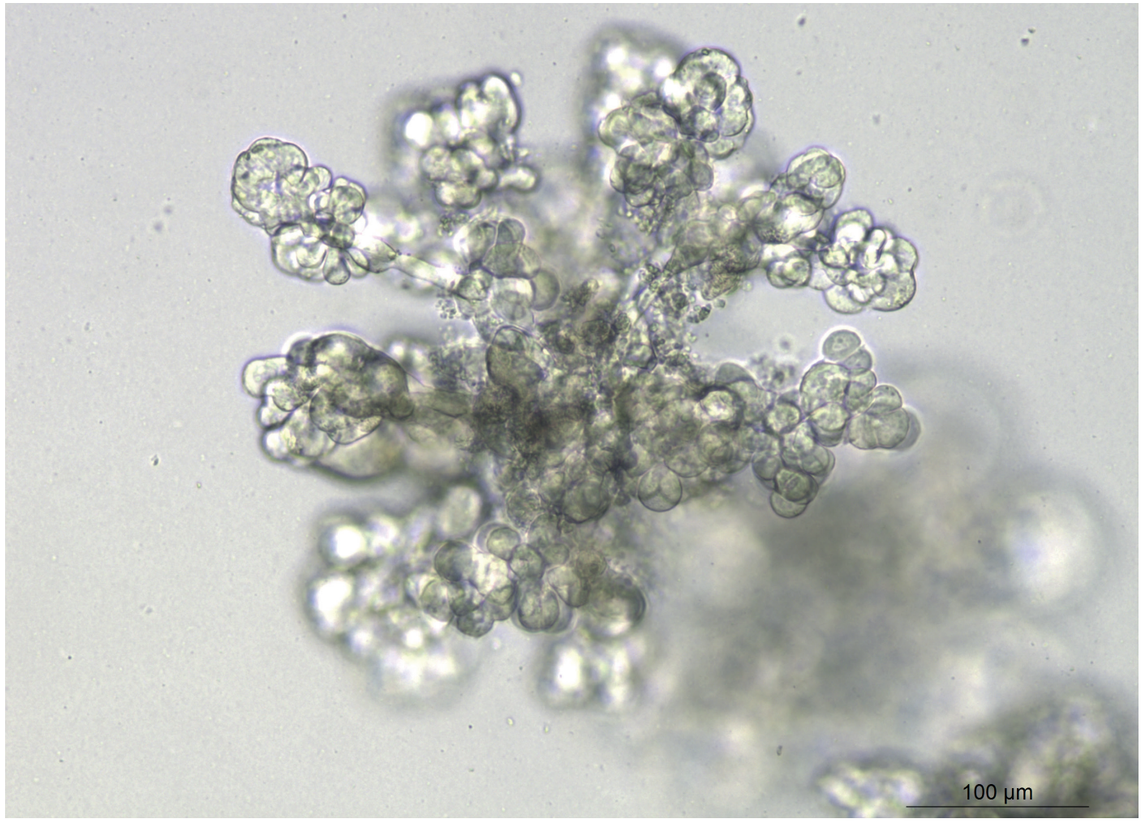


IMAGE BY LAURA BROUTIER.

"We are testing how well our models can represent human pathology in a dish"

Selected publications
> Prior N *et al.* (2018) Lgr5+ stem/progenitor cells reside at the apex of the embryonic hepatoblast pool. ***bioRxiv*** 485870.
> Broutier L *et al.* (2017) Human primary liver cancer-derived organoid cultures for disease modeling and drug screening. ***Nat Med*** 23: 1424 –1435.
> Huch M *et al.* (2015) Long-term culture of genome-stable bipotent stem cells from adult human liver. ***Cell*** 160: 299–312.

Steve Jackson

Maintenance of genome stability

DNA is constantly damaged by environmental and endogenously arising agents. Cell survival and genome integrity are promoted by the DNA-damage response (DDR), which detects, signals the presence of and repairs DNA damage. DDR defects are associated with developmental disorders, immunodeficiencies, infertility, premature ageing and cancer. Our research aims to characterise the cell biology and mechanisms of established and new DDR pathways and components, and to apply this knowledge to better understand and treat human diseases. Recently we have successfully used CRISPR-Cas9 synthetic viability screens to identify novel DDR proteins and define drug-resistance mechanisms. First, the novel protein complex Shieldin, that shields the ends of broken DNA and regulates DNA repair. Second, we have identified mechanisms in cells lacking the apical DDR kinase ATM that cause them to become resistant to certain anti-cancer drugs. These results are important for both understanding cancer drug resistance in the context of sporadic cancers and highlighting potential therapeutic targets for the genetic disease ataxia-telangiectasia. Finally, our studies in a mouse model of Hutchinson-Gilford progeria syndrome (HGPS) showed that chemical or genetic inhibition of the enzyme NAT10 increased both the healthspan and lifespan of these mice. These findings suggest a therapeutic approach to HGPS and, potentially, other premature ageing diseases.

Identifying drug-resistance mechanisms >
Using our platform for screening large numbers of gene knockouts for their ability to confer resistance to cancer drug action, we identified Shieldin. Testing the levels of Shieldin in tumours could help predict whether they will respond to drugs such as the PARP inhibitor, olaparib.

Co-workers
Iñigo Ayestaran Basagoitia, Linda Baskcomb, Rimma Belotserkovskaya, Ramsay Bowden, Julia Coates, Guiseppina D'Alessandro, Mukerrem Demir, Harveer Dev, Kate Dry, Yaron Galanty, Maryam Ghaderi Najafabadi, Soren Hough, Rebecca Lloyd, Donna Lowe, Maria Martin Agudo, David Morales, Francisco Muñoz Martinez, Domenic Pilger, Fabbio Puddu, Elisenda Raga Gil, Helen Reed, Israel Salguero Corbacho, Matylda Sczaniecka-Clift, John Thomas

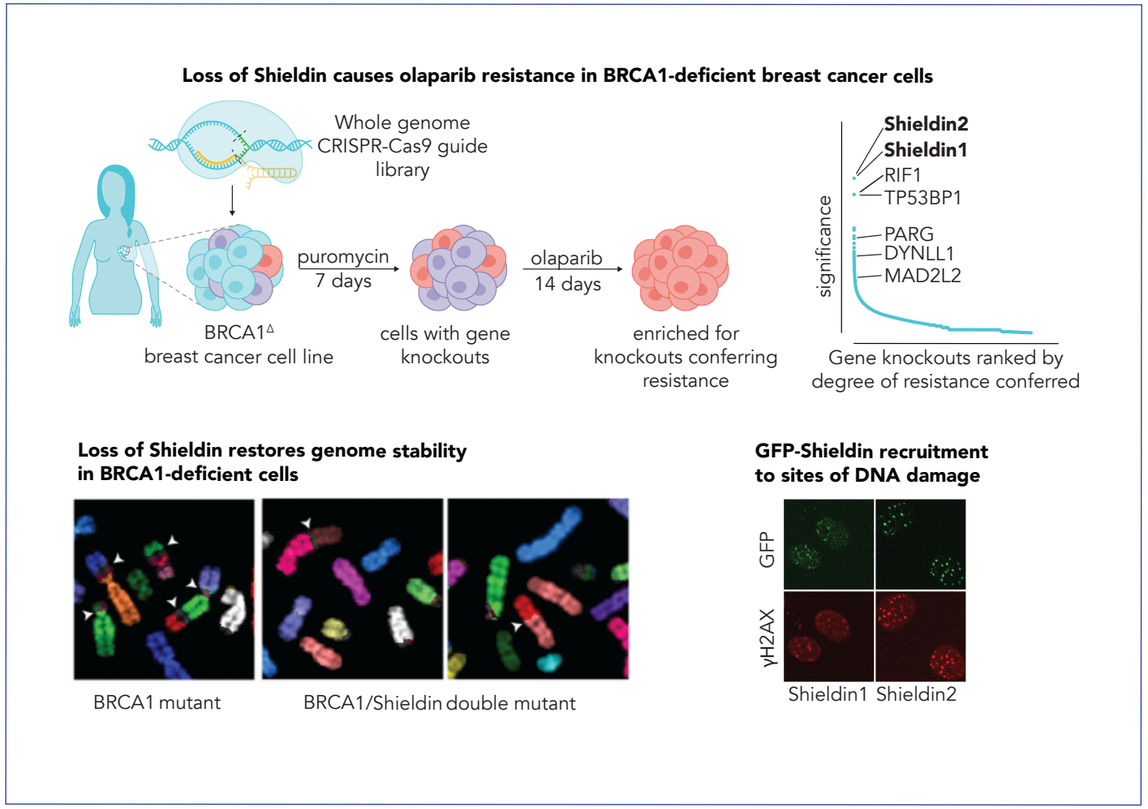


ILLUSTRATION BY CLAUDIA FLANDOLI.

"We have successfully used CRISPR-Cas9 synthetic viability screens to identify novel DDR proteins and define drug-resistance mechanisms"

Selected publications

> Balmus G*et al*. (2019) ATM orchestrates the DNA-damage response to counter toxic non-homologous end-joining at broken replication forks. ***Nat Commun*** 10: 87.
> Dev H *et al*. (2018) Shieldin complex promotes DNA end-joining and counters homologous recombination in BRCA1-null cells. ***Nat Cell Biol*** 20: 954–965.
> Balmus G *et al*. (2018) Targeting of NAT10 enhances healthspan in a mouse model of human accelerated aging syndrome. ***Nat Commun*** 9: 1700.

Tony Kouzarides

Epigenetic modifications and cancer

Do enzymes that modify chromatin and RNA offer therapeutic targets?

DNA exists in the cell nucleus wrapped around histone proteins to form chromatin. The DNA and histones are decorated with many types of covalent chemical modifications, which can affect transcription and other cellular processes. In addition, non-coding RNAs that regulate chromatin function can be similarly chemically modified. Our lab is involved in characterising the pathways that mediate and control DNA, RNA and histone modifications. We try to understand the cellular processes they regulate, their mechanism of action and their involvement in cancer.

Our focus at the moment is modifications of messenger RNA (mRNA) and non-coding RNA. There are very few modifications identified on these low-abundance RNAs, unlike on transfer RNA and ribosomal RNA, where there are many. We have been developing sensitive technologies to detect modifications, such as specific antibodies, chemical reactivity assays and mass spectrometry. Using these, we have been able to detect a number of novel modifications on mRNA and microRNA (short length non-coding RNAs) and have shown that these function to regulate mRNA translation and microRNA processing. Furthermore, we have shown that the enzymes that mediate these modifications are implicated in acute myeloid leukaemia.

The crucial role of modifications >
Gene expression can be regulated by chemical modifications before and during transcription, including of non-coding RNA.

Co-workers
Minaam Abbas, Andrej Alendar, Carlos Almeida Guedes de Melo, Andrew Bannister, Alistair Cook, Namshik Han, Marie Klimontova, Sri Lestari, Nikki Mann, Valentina Migliori, Luca Pandolfini, Helena Santos Rosa, Konstantinos Tzelepis, Daniel Wing

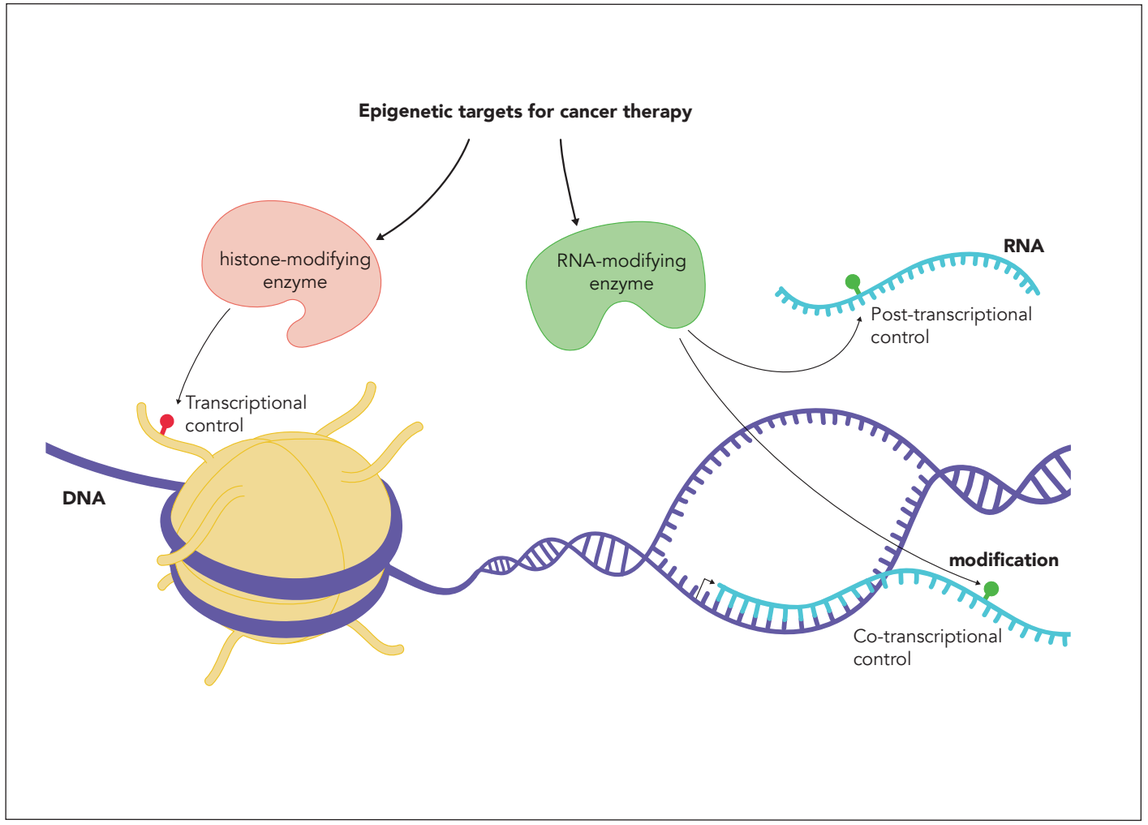


ILLUSTRATION BY CLAUDIA FLANDOLI.

"We have been developing sensitive technologies to detect modifications, such as specific antibodies, chemical reactivity assays and mass spectrometry"

Selected publications

> Barbieri I *et al.* (2017) Promoter-bound METTL3 maintains myeloid leukaemia by m6A-dependent translation control. ***Nature*** 552: 126–131.
> Christophorou MA *et al.* (2014) Citrullination regulates pluripotency and histone H1 binding to chromatin. ***Nature*** 507: 104–108.
> Dawson MA *et al.* (2011) Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. ***Nature*** 478: 529–533.

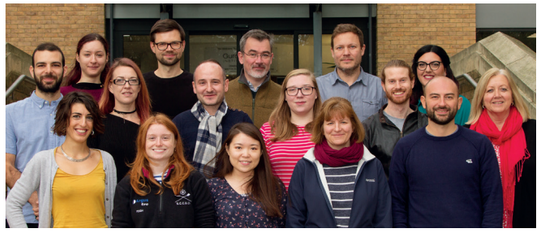
Rick Livesey

Development, evolution and degeneration of the brain

Studying human brain development and disease in the lab.
The human cerebral cortex, the thinking, decision-making, largest part of our brain, sets us apart from other animals – and poses a challenge for biomedical researchers. Animal models cannot capture the spectrum of characteristics of the human cerebral cortex in development or disease, and so our research uses human cells in tissue culture. Our methods for differentiating human pluripotent stem cells into different types of cells allow us to study neurons and the neural circuits they make, starting from living patients' cells. We are studying how the human cerebral cortex develops and how that differs from other animals, and how variations in development lead to disease.

We also apply these approaches to study neurodegeneration in dementia, particularly Alzheimer's disease. Using stem cells from patients with genetic forms of Alzheimer's disease, we have modelled disease pathogenesis in neurons in culture. We use these systems to understand how Alzheimer's disease starts and progresses in the brain, and to test the efficacy of potential therapeutic strategies.

Looking inside Alzheimer's neurons >
Live-cell imaging of iPS cell-derived neurons generated from non-dementia control (left), and from donors with inherited Alzheimer's disease (right). Mitochondrial networks are seen to be disrupted in the Alzheimer's neurons, which carry a mutation in Presenilin-1. Neuronal cultures are stained with nuclear marker (blue) and mitochondria tracker (red).



Co-workers
Philip Brownjohn, Ashley Campbell, Lewis Evans, Jayne Fisher, Elsa Ghirardini, Moritz Haneklaus, Silvia Hnatova, Oi Ying (Christy) Hung, Federica Marinaro, Steven Moore, Francesco Paonessa, James Smith, Frances St George-Hyslop, Alessio Strano, Victoria Stubbs, Ellie Tuck

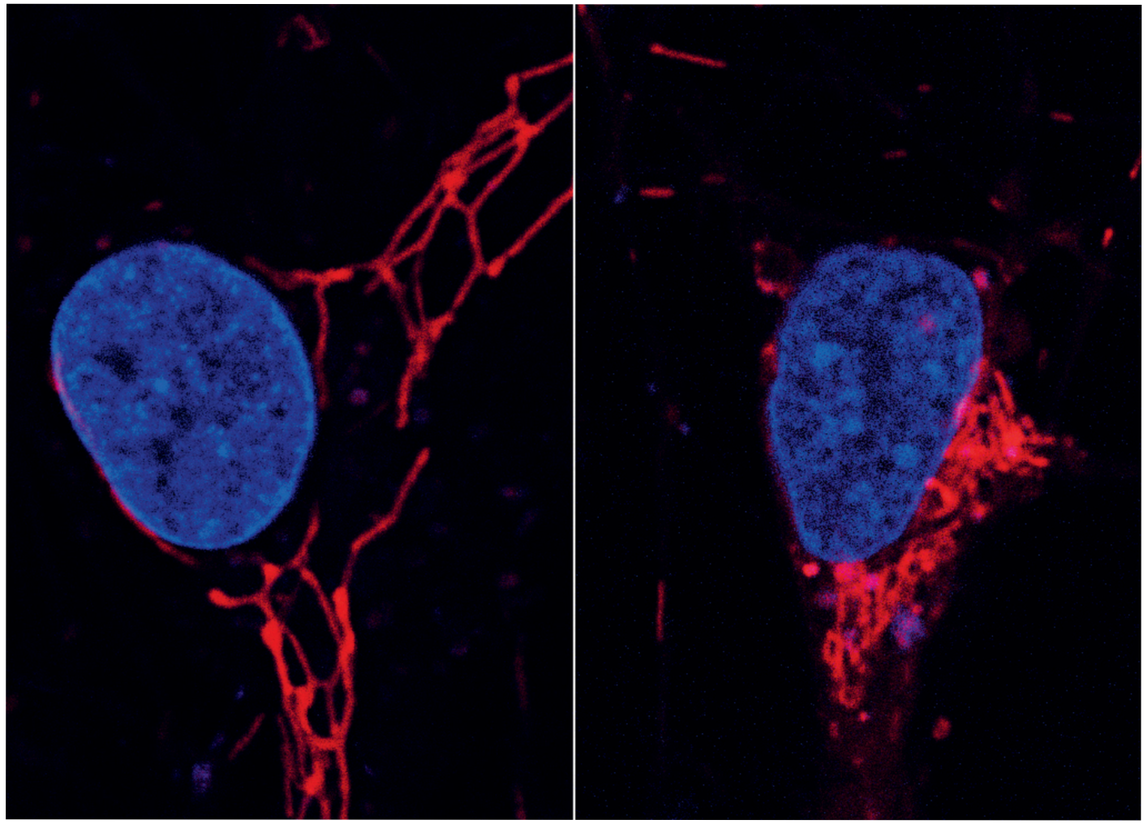


IMAGE BY CHRISTY HUNG.

"Using stem cells from patients with genetic forms of Alzheimer's disease, we have modelled disease pathogenesis in neurons in culture"

Selected publications

> Real R *et al*. (2018) In vivo modeling of human neuron dynamics and Down syndrome. ***Science*** 362: eaau1810.
> Evans LD *et al*. (2018) Extracellular Monomeric and Aggregated Tau Efficiently Enter Human Neurons through Overlapping but Distinct Pathways. ***Cell Rep*** 22: 3612-3624.
> Hung COY & Livesey FJ (2018) Altered γ-Secretase Processing of APP Disrupts Lysosome and Autophagosome Function in Monogenic Alzheimer's Disease. ***Cell Rep*** 25: 3647-3660.e2.

Hansong Ma

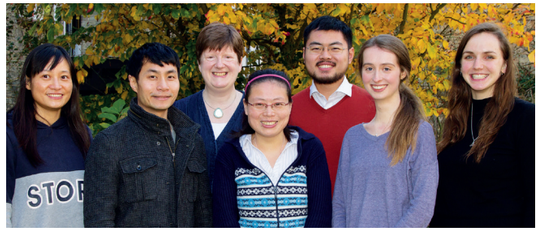
Genetics of mitochondrial DNA in evolution and disease

How are mitochondrial mutations transmitted?

In addition to the nuclear genome, all animals have another genome packed inside the mitochondrion called mtDNA. This maternally inherited genome encodes important proteins for energy production. Pathogenic mitochondrial mutations often arise among the thousands of copies of wild-type genomes in each cell, and beyond a certain threshold the genetic defects will manifest as a disease phenotype. Over 50 such mitochondrial diseases have been described in humans.

Selectivity in the transmission of functional versus pathogenic genomes in somatic cells affects the expression of disease phenotype as we age. Selective transmission in germline cells governs the inheritance of mtDNA mutations from mother to progeny, and in this way its evolution. I have developed genetic tools for mitochondrial studies in Drosophila, which have a mitochondrial genome that is very similar to humans. By artificially mixing different genomes and following their transmission over generations, my lab uses Drosophila to study inheritance of mtDNA mutations to provide insights into human longevity, fertility and disease.

What governs transmission of mitochondrial genomes?>
Top: *The multi-copied mitochondrial genome (mtDNA) is a circular double-stranded DNA molecule encoding 13 essential polypeptides of the oxidative phosphorylation system. It is usually inherited from only the mother.*
Bottom: *Artificial mixing of wild-type and mutant mitochondrial genomes resolves two types of selection that influence the competition between co-existing mitochondrial genomes: 1) a purifying selection, where the genome providing more functions always takes over; and 2) a selfish selection, where a 'bully' genome takes over a 'wimpy' genome if it replicates or transmits better (i.e. independent of function). Occasionally, co-existing mitochondrial genomes recombine to form a new genome.*



Co-workers
Chieh-Yin (Ason) Chiang, Ying (Ivy) Di, Anna Klucnika, Yu Zhi (Andy) Li, Eleanor McCartney, Kathy Oswald

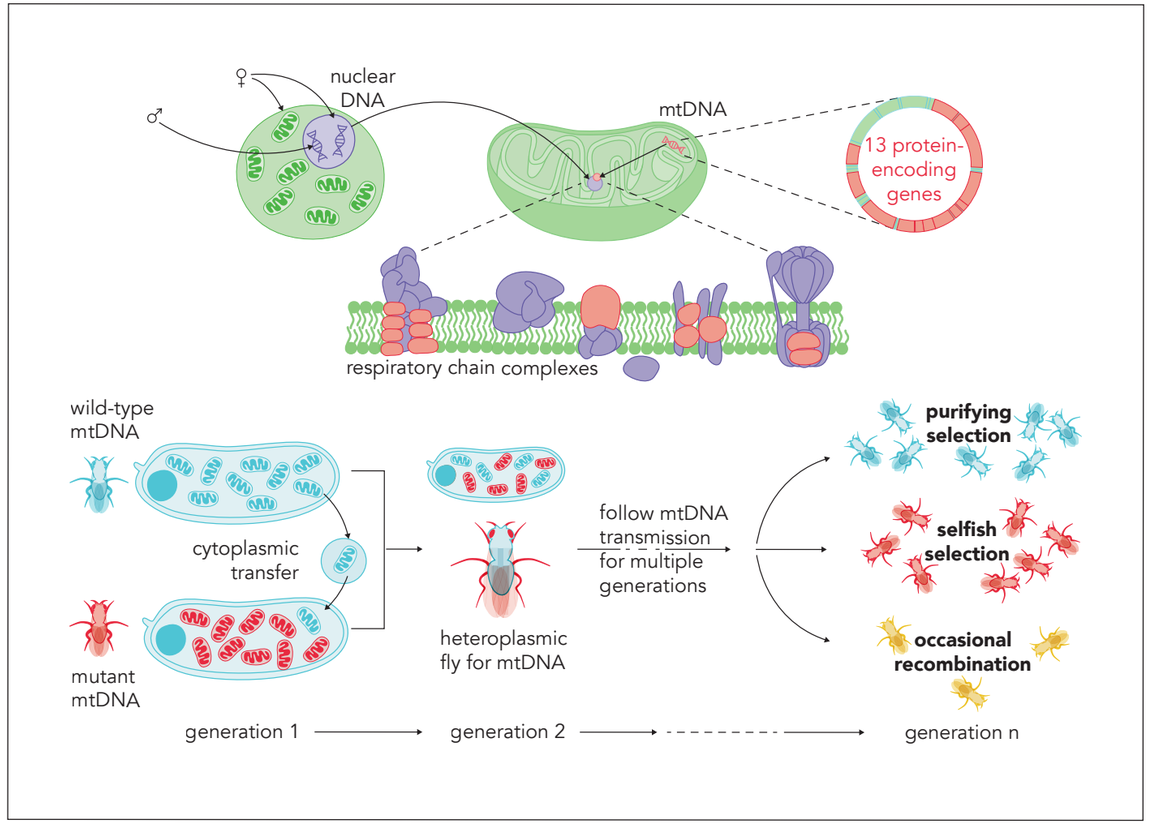


ILLUSTRATION BY CLAUDIA FLANDOLI.

"We aim to establish sensitive genetic screens to identify nuclear genes influencing selective transmission of mtDNA"

Selected publications

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> Ma H & O'Farrell PH (2015) Selections that isolate recombinant mitochondrial genomes in animals. ***Elife*** 4: e07247.
> Ma H *et al.* (2014) Transmission of mitochondrial mutations and action of purifying selection in Drosophila melanogaster. ***Nat Genet*** 46: 393–397.

Eric Miska

Non-coding RNA and genome dynamics

What does non-coding RNA do in development and disease?

Most of the RNA transcribed from the DNA in our genome is not translated into protein but instead has direct functions in regulating biological processes. This paradigm shift in nucleic acid biology has been supported by technical advances in high-throughput sequencing, molecular genetics and computational biology, which can be combined with more traditional biochemical analyses.

Many species and roles of non-coding RNA have been identified. Our goal is to understand how non-coding RNAs regulate development, physiology and disease. We are exploring microRNA in the pathology of cancer and other diseases, RNA interference in viral immunity, Piwi-interacting RNA in germline development and genome integrity, and endogenous small interfering RNA in epigenetic inheritance – where we predict a big impact in understanding human health. Our model organisms are the nematode worm, the cichlid fishes of the Rift Lakes of East Africa, mouse, and human cell culture. More recently we have developed a technology to assess RNA structure and RNA–RNA interactions in living systems. We used this to uncover unexpected biology for the Zika virus.

Ancient transcription factor repurposed for role in genome defence >

Piwi-interacting RNAs (piRNAs) maintain genome integrity and are essential for fertility. In C. elegans we identified an upstream sequence transcription complex (USTC) that is essential for production of piRNAs, specifically those in gene clusters containing thousands of piRNA transcription units.

Co-workers

Alper Akay, Dhiru Bansal, Ahmet Can Berkyurek, Fabian Braukmann, Nicholas Burton, Isabela Cunha Navarro, Benjamin Fisher, Giulia Furlan, Katharina Gapp, David Jordan, Joana Kosalka, Lisa Lampersberger, Miranda Landgraf, Wayo Matsushima, Ragini Medhi, Guillermo Parada, Audrey Putman, Navin Brian Ramakrishna, Cristian Riccio, Marc Ridyard, Grégoire Vernaz, Chengwei (Ulrika) Yuan, Omer Ziv

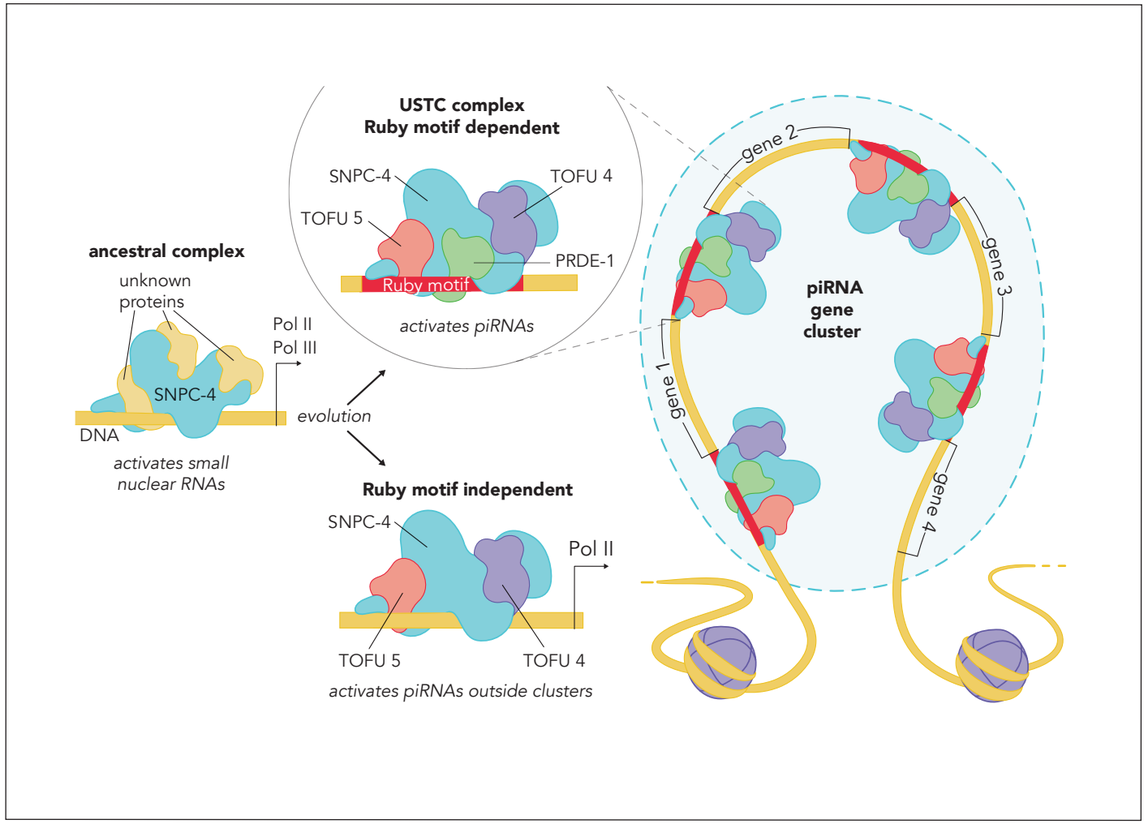

ILLUSTRATION BY CLAUDIA FLANDOLI.

"Our goal is to understand how non-coding RNAs regulate development, physiology and disease"

Selected publications

> Weng C *et al.* (2019) The USTC co-opts an ancient machinery to drive piRNA transcription in C. elegans. ***Genes Dev*** 33: 90-102.

> Malinsky M *et al.* (2018) Whole-genome sequences of Malawi cichlids reveal multiple radiations interconnected by gene flow. ***Nat Ecol Evol*** 2: 1940-1955.

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Emma Rawlins

Stem and progenitor cells in the mammalian lung

How do stem cells build and maintain the lung?
The complicated three-dimensional structure of our lungs is essential for respiration and host defence. Building this structure relies on the correct sequence of division and differentiation events by lung progenitor cells, which also maintain the slowly turning-over airway epithelium in the adult. How is the production of different cell types controlled in embryonic development and adult maintenance? We apply mouse genetics, live imaging, single-cell molecular analysis and mathematical modelling to understand lung stem cells, with a longer-term aim of directing endogenous lung cells to repair, or regenerate, diseased tissue.

In the adult lung we focus on the cellular mechanisms that maintain stem cell quiescence at steady-state, but allow a rapid repair response when needed. In the embryonic lung we study a population of multipotent progenitors that undergo steroid-induced changes in competence during development. In the embryo, we have recently switched our focus to normal human lung development, primarily using an organoid system that we developed. We combine the analysis of fresh human embryonic tissue with gene-targeting in the organoids, to determine the molecular and cellular mechanisms of normal human lung development. This will provide insights into conditions related to premature birth and into the possibility of therapeutic lung regeneration.

How does the lung build itself? >
In this 16-weeks-gestation human embryonic lung, a close interaction can be seen between the developing epithelial progenitor cells (green) and the endothelial cells (red) that line the developing blood vessels. Cell nuclei in blue.

Co-workers
Quitz Jeng, Heleen Kool, Florence Leroy, Kyungtae Lim, Shuyu Liu, Vishal Menon, Vanesa Sokleva, Dawei Sun

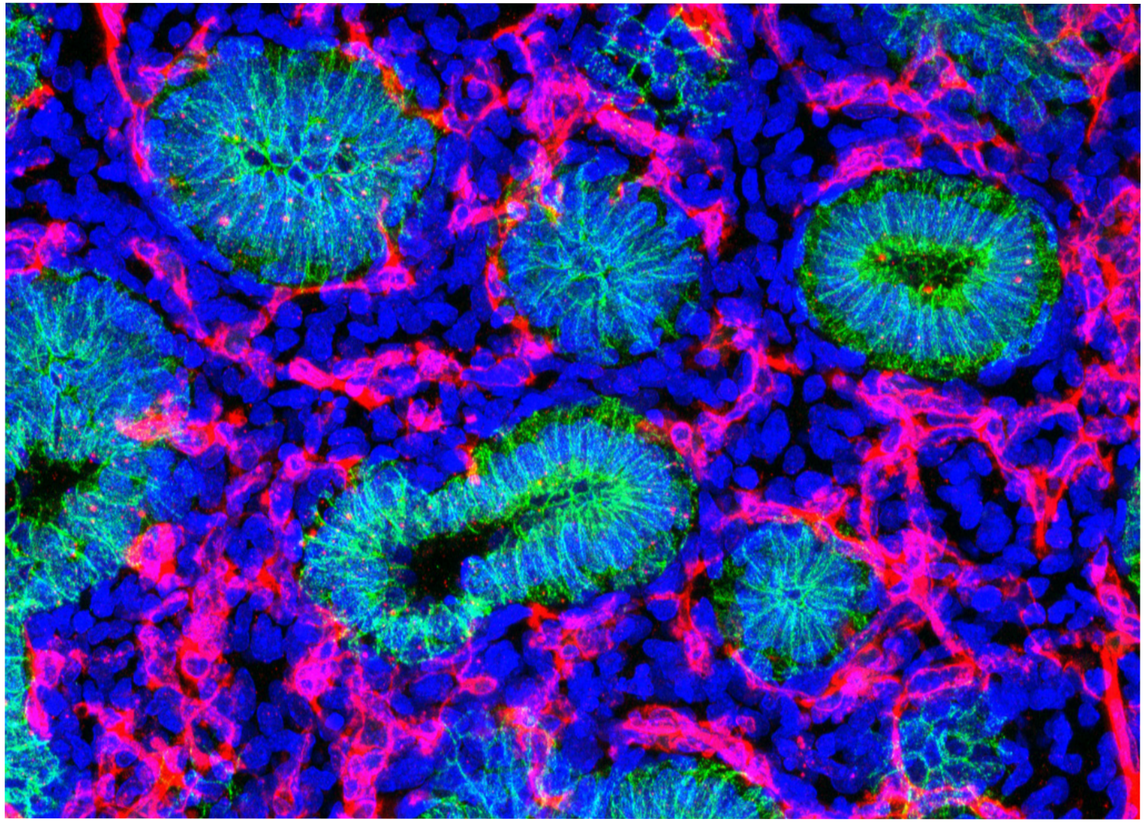


IMAGE BY VALENTIN PICANT.

"We have recently switched our focus to normal human lung development, primarily using an organoid system that we developed"

Selected publications

> Nikolić M *et al.* (2018) Human lung development: recent progress and new challenges. ***Development*** 145: dev163485.
> Nikolić M *et al.* (2017) Human embryonic lung epithelial tips are multipotent progenitors that can be expanded in vitro as long-term self-renewing organoids. ***Elife*** 6: e26575.
> Balasooriya GI *et al.* (2016) An FGFR1-SPRY2 Signaling Axis Limits Basal Cell Proliferation in the Steady-State Airway Epithelium. ***Dev Cell*** 37: 85–97.

Ben Simons

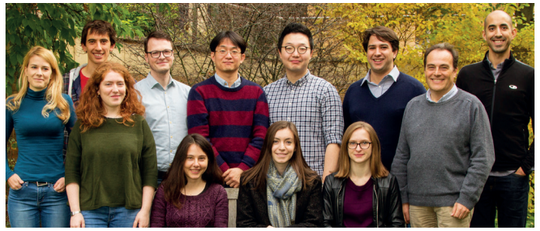
Mechanisms of stem cell fate in tissue development, maintenance and disease

How do stem and progenitor cells regulate their fate behaviour to specify and maintain tissues?

In development, tissue precursors must coordinate proliferation and differentiation with collective cell movements to specify organs of the correct size, pattern and composition. In the adult, stem cells must regulate a precise balance between proliferation and differentiation to maintain tissue homeostasis.

To address the mechanisms that regulate stem and progenitor cell fate, we combine cell lineage-tracing approaches and single-cell gene expression profiling with concepts and methods from statistical physics and mathematics. Applied to epithelial tissues, our studies have shown how common principles of self-organisation and emergence provide predictive insights into the cellular mechanisms that regulate tissue development and maintenance. As well as questioning the basis of stem cell identity and the mechanisms that underpin cell fate stochasticity and state flexibility, these studies establish a quantitative platform to investigate pathways leading to tumour initiation and progression.

The integration of cell fate and patterning >
Short-term BrdU incorporation (green) shows how cell divisions are aligned with local gradients of expansion during postnatal development of mouse tail epidermis.



Co-workers
Roberta Azzarelli, Lemonia Chatzeli, Catherine Debrowska, Adrien Hallou, Seungmin Han, Tom Hiscock, Daniel Kunz, Jamie McGinn, Min Kyu Yum

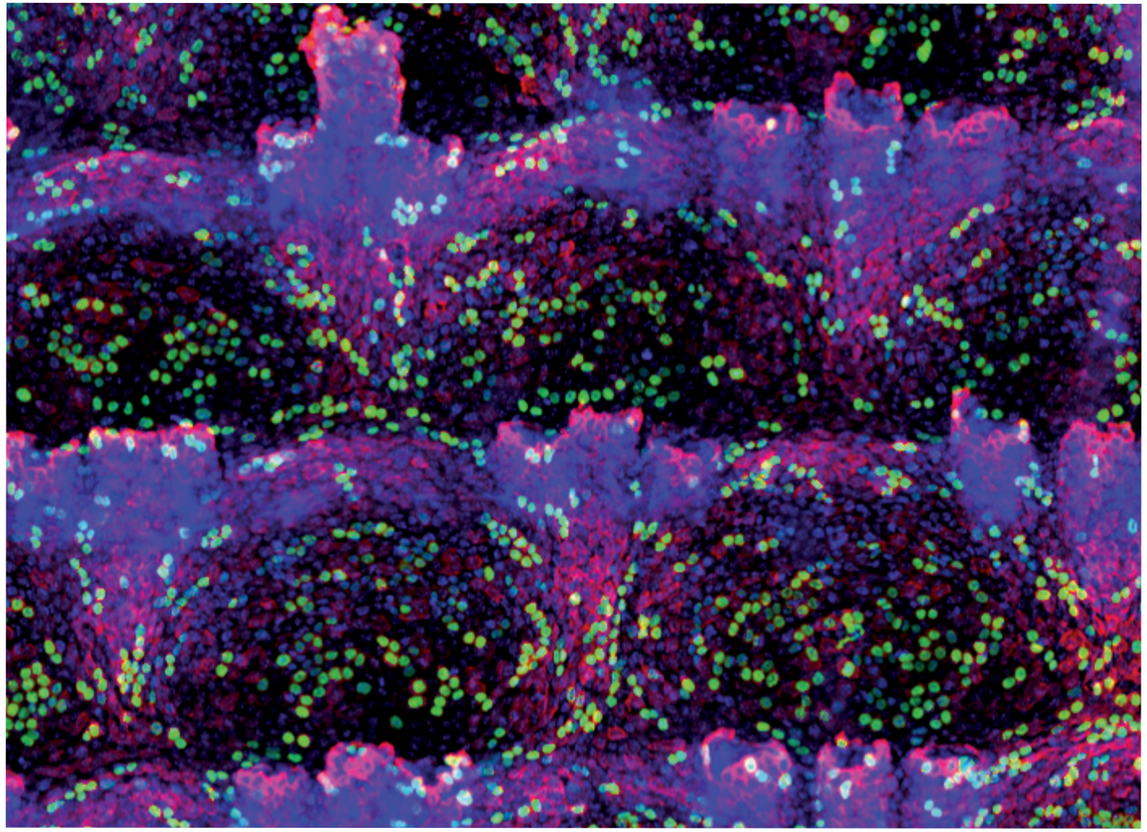


IMAGE BY SOPHIE DEKONINCK, BLANPAIN LAB, BRUSSELS.

"Common principles of self-organisation and emergence provide predictive insights into the cellular mechanisms"

Selected publications

> Kitadate Y *et al.* (2019) Competition for mitogens regulates spermatogenic stem cell homeostasis in an open niche. ***Cell Stem Cell*** 24: 79-92.e6.
> Pilz G-A *et al.* (2018) Live imaging of neurogenesis in the adult mouse hippocampus. ***Science*** 359: 658–662.
> Hannezo E *et al.* (2017) A unifying theory of branching morphogenesis. ***Cell*** 171: 242–255.

Daniel St Johnston

Polarising epithelial cells and body axes

How do cells know 'up' from 'down'?
Most cells in the body perform different functions at opposite sides of the cell. This cell polarity is essential in development, for example: in determining the head-to-tail axis of many animals, for cell migration and for asymmetric stem-cell divisions. Furthermore, loss of polarity is a hallmark of tumour cells and is thought to contribute to tissue invasion and metastasis.

Our work focuses on epithelia, the sheets of polarised cells that form barriers between compartments and make up most of our organs and tissues. We study the factors that mark different sides of epithelial cells and how these organise the internal cell architecture, using *Drosophila* and intestinal organoids as models. We have recently discovered that the gut epithelium polarises by a fundamentally different mechanism from other fly epithelia, and is much more similar to mammalian epithelia. We are now identifying new polarity factors in the fly gut and are testing whether these play similar roles in mouse intestinal organoids. We are also using live microscopy to visualise polarised secretion in epithelial cells, and quantitative super-resolution microscopy to examine the clustering and co-localisation of polarity proteins.

The special properties of epithelia **>**
A drawing showing how epithelial cells stick together to form epithelial sheets, with their free apical surfaces facing towards the outside or the lumen of an epithelial tube or gland. The lateral junctions (yellow) create a barrier between cells so that fluids, solutes and pathogens cannot leak across the epithelium. Most cancers arise from epithelial tissues and are characterised by a loss of apical–basal polarity (red cells).

Co-workers
Edward Allgeyer, Jia Chen, Hélène Doerflinger, Edo Dzafic, Weronika Fic, Xiao Li He, Florence Leroy, Bohdan Lewkow, Erinn Los, Dmitry Nashchekin, John Overton, Amandine Palandri, Andrew Plygawko, Jennifer Richens, Judy Sayers, George Sirinakis, Iolo Squires, Mihoko Tame, Vivien Tsang, Helen Zenner-Branco

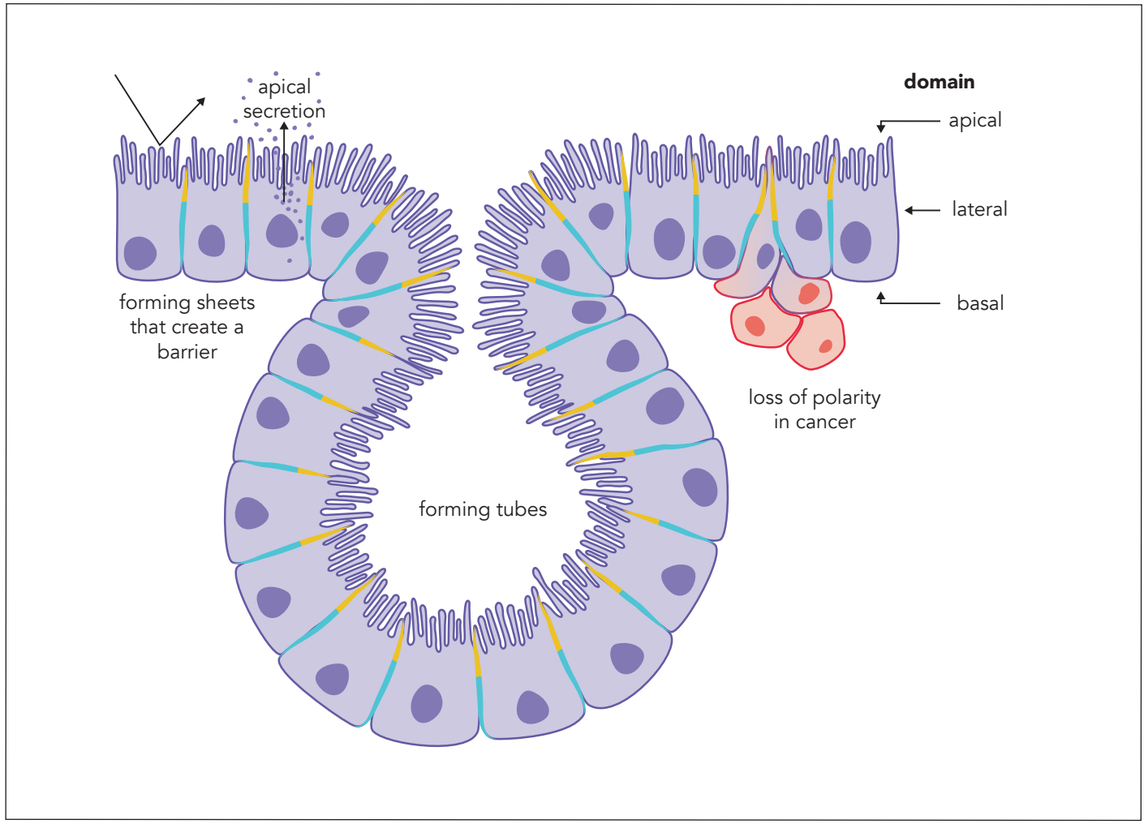


ILLUSTRATION BY CLAUDIA FLANDOLI.

"We have recently discovered that the gut epithelium polarises by a fundamentally different mechanism from other fly epithelia"

Selected publications

> Fic W *et al.* (2019) Drosophila IMP regulates Kuzbanian to control the timing of Notch signalling in the follicle cells. ***Development*** 146: dev168963.
> Chen J *et al.* (2018). An alternative mode of epithelial polarity in the Drosophila midgut. ***PLoS Biol*** 16: e3000041.
> Nieuwburg R *et al.* (2017) Localised dynactin protects growing microtubules to deliver oskar mRNA to the posterior cortex of the Drosophila oocyte. ***Elife*** 6: e27237.

Azim Surani

The human germline

What makes a germline cell?
We study primordial germ cells (PGCs), precursors to eggs and sperm, in the early embryo. We have established principles of early human development with a focus on human PGC specification. A unique epigenetic resetting follows in the germline after hPGC specification. Our work shows that SOX17 is the key regulator of human, but not mouse, germ cell fate. By developing in vitro models, and with authentic hPGCs from human embryos, we have also established how pluripotent stem cells gain competence for germ cell and somatic fates in human. These findings are important for studies on human pluripotent stem cells and regenerative medicine. The inheritance of genetic and epigenetic information from the germline through the totipotent state affects human development and disease for generations.

Whereas SOX17–BLIMP1 apparently initiate the epigenetic programme in early human germline, BLIMP1–PRDM14 play a similar role in mouse germline, resulting in the comprehensive erasure of DNA methylation (except for some resistant loci), X-reactivation and imprints erasure, followed by re-establishment of sperm- and oocyte-specific imprints. Defects in these gamete-specific imprints lead to a variety of human disease syndromes. We have also examined mitochondrial DNA (mtDNA) in PGCs, showing evidence for selection against mitochondria that harbour mutations. This mechanism is imperfect and can account for inherited mtDNA disorders.

What we know about primordial germ cell development >
Primordial germ cells are the first cell type to be specified in vivo in early human development. We have developed a protocol using specific signalling molecules to generate primordial germ cell-like cells in vitro from human pluripotent stem cells. We found that SOX17 is a critical determinant of human germ cell fate.

Co-workers
João Alves Lopes, Aracely Castillo Venzor, Elena Drousioti, Lynn Froggett, Wolfram Gruhn, Mei Gu, Nadia Gueorguieva, Naoko Irie, Yong-Hee Kim, Sun Min Lee, Merrick Pierson Smela, Anastasiya Sybirna, Walfred Tang, Frederick Wong, Qi Yin

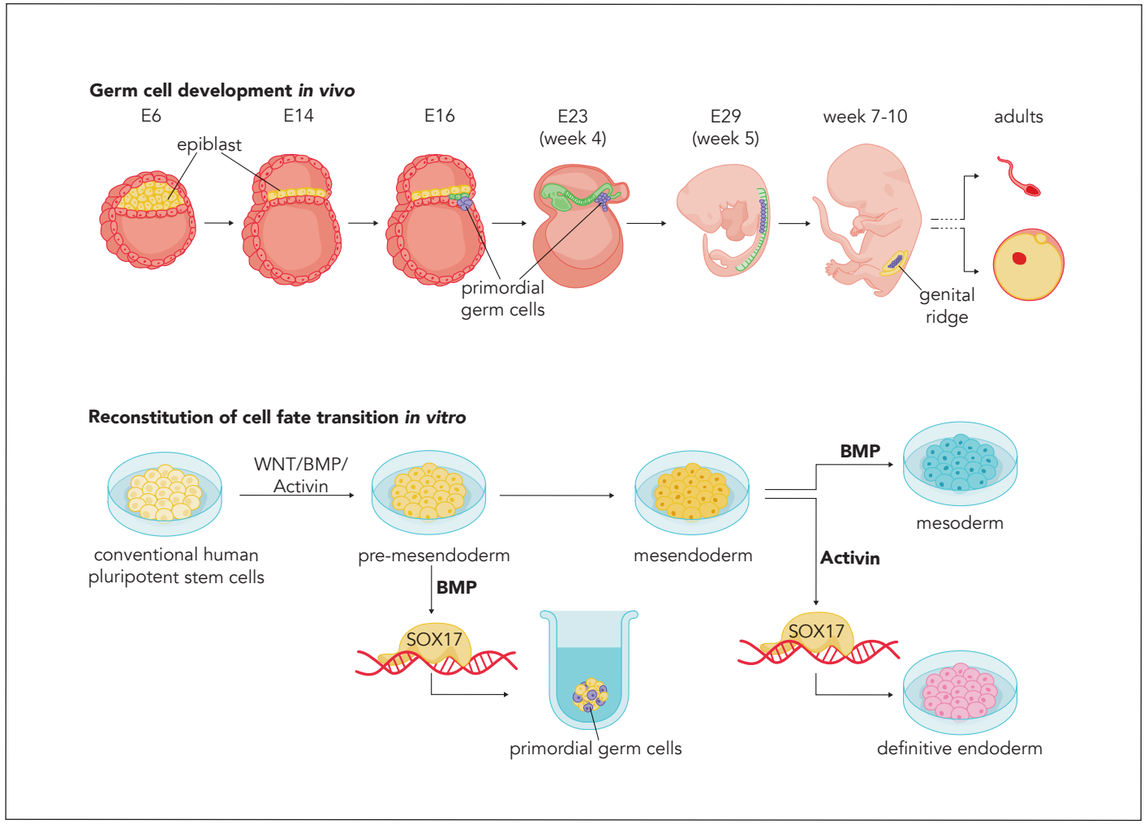


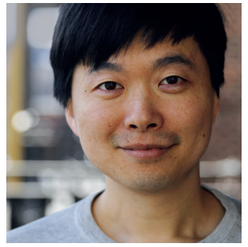
ILLUSTRATION BY CLAUDIA FLANDOLI.

"We have established principles of early human development with a focus on human PGC specification"

Selected publications

> Floros VI *et al.* (2018) Segregation of mitochondrial DNA heteroplasmy through a developmental genetic bottleneck in human embryos. ***Nat Cell Biol*** 20: 144–151.
> Kobayashi T *et al.* (2017) Principles of early human development and germ cell program from conserved model systems. ***Nature*** 546: 416–420.
> Irie N *et al.* (2015) SOX17 Is a Critical Specifier of Human Primordial Germ Cell Fate. ***Cell*** 160: 253–268.

Fengzhu Xiong



Tissue morphogenesis by mechanics and cell dynamics

What forces drive tissue morphogenesis?
Embryos are made of soft materials consisting of cells with limited mechanical capacities, yet they develop in a robust and coordinated manner and produce large-scale deformations (morphogenesis). We are interested in the ways in which developing tissues produce and respond to mechanical forces in order to achieve the correct shape and pattern. This knowledge is useful for understanding complex birth defects and engineering stem or reprogrammed cells into tissues, as well as interpreting the changes in diseased tissues such as tumours.

We use early avian embryos as a model system. The large size and accessibility of these embryos allow us to image cell and tissue dynamics, perform molecular genetic perturbations, and deploy novel mechanical tools such as soft gels and cantilevers to measure and apply forces. By integrating cell and tissue dynamics, we found that the paraxial mesoderm and axial tissues coordinate their elongation through mechanical feedback. We are currently investigating if the identified forces are also important for the straightness (bilateral symmetry) of the tissues and the folding of the neural tube.

Cell dynamics in a chicken embryo >
Left: A ubiquitous transgenic green fluorescent chicken embryo (ventral view) at 4-somite stage, head to the top. Progenitors clusters (bright spots) were labelled with DiI for cell tracking.
Right: Single cell trajectories (coloured lines) around the body axis (black).

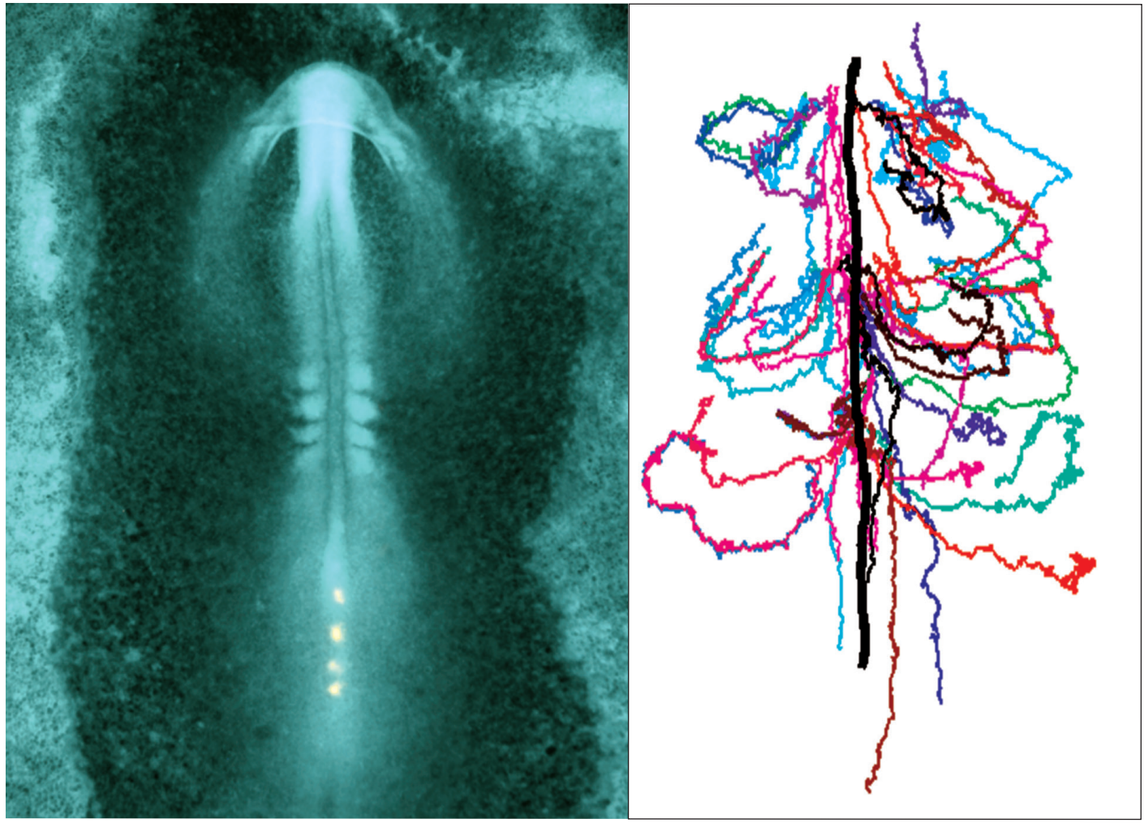


IMAGE BY FENGZHU XIONG

"We are interested in the ways in which developing tissues produce and respond to mechanical forces"

Selected publications

> Xiong F & Megason SG (2015) Abstracting the Principles of Development Using Imaging and Modeling. ***Integr Biol*** 7: 633-642.
> Xiong F *et al.* (2014) Interplay of Cell Shape and Division Orientation Promotes Robust Morphogenesis of Developing Epithelia. ***Cell*** 159: 415-427.
> Xiong F *et al.* (2013) Specified Neural Progenitors Sort to Form Sharp Domains After Noisy Shh Signaling. ***Cell*** 153: 550-561.

Philip Zegerman

The regulation of DNA replication initiation in eukaryotes

How is DNA replication controlled?
A fundamental requirement for all life on earth is that an exact copy of the entire genome must be made before cell division. DNA replication is therefore tightly regulated because failures in this process cause genomic instability, which is a hallmark of many diseases, most notably cancers. In addition, inhibition of DNA replication is the primary mode of action of many anti-tumour therapies. Therefore, investigating DNA replication control is important for finding new ways to diagnose and treat cancers. The evolutionary conservation of DNA replication mechanisms allows us to study this process in multiple systems, facilitating the translation of findings to humans.

We have shown that the levels of several key replication factors are critical to control the rate of genome duplication, not only in the single-celled organism, budding yeast, but also during vertebrate development in frog embryos. Our studies demonstrate that regulation of the levels of these factors is vital not only for normal cell division, but also for regulating the rate of cell proliferation in animal tissue. This has important implications for the deregulation of cell proliferation, which occurs in cancers.

Studying life's central process >
Regulation of replication initiation is critical for normal cell division.

Co-workers
Esther Cabañas Morafraile, Geylani Can, Vincent Gaggioli, Andreas Hadjicharalambous, Fiona Jenkinson, Mark Johnson, Manuela Kieninger, Florence Leroy, Miguel Santos, Shannon Smyly, Kang Wei Tan

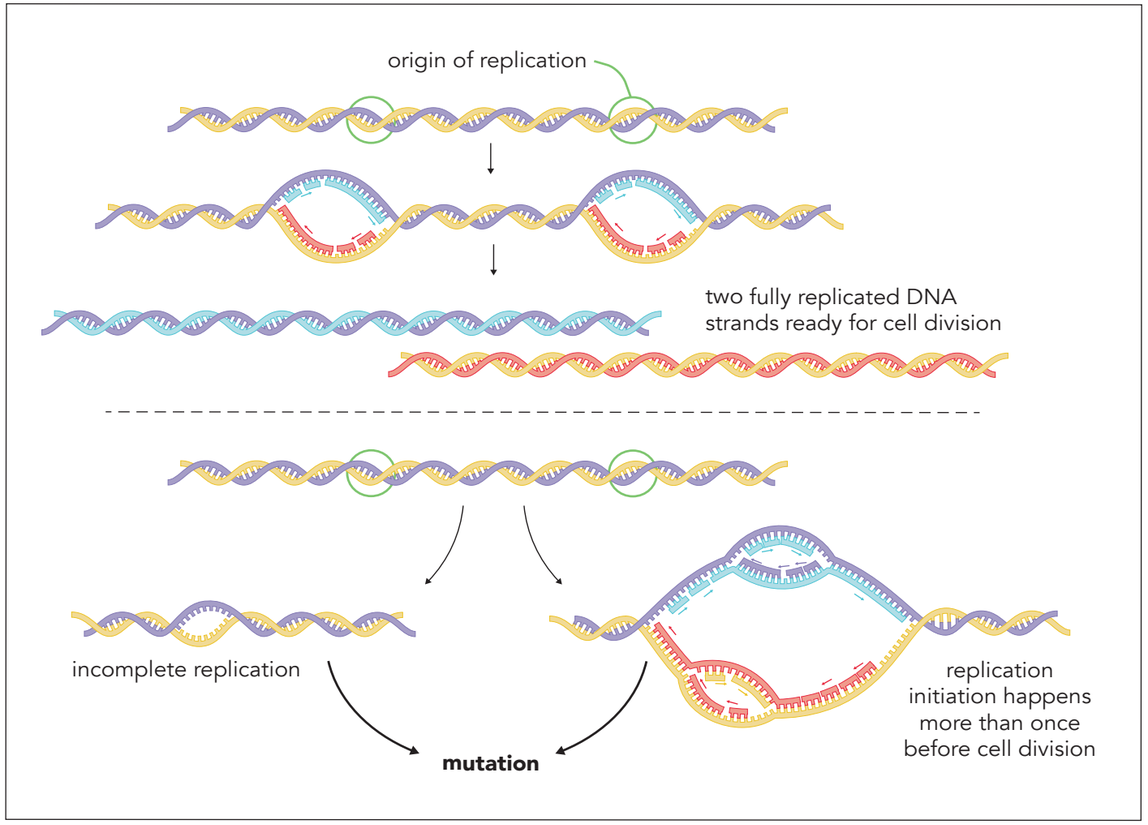


ILLUSTRATION BY CLAUDIA FLANDOLI.

"Investigating DNA replication control is important for finding new ways to diagnose and treat cancers"

Selected publications

> Can G *et al.* (2019) Helicase Subunit Cdc45 Targets the Checkpoint Kinase Rad53 to Both Replication Initiation and Elongation Complexes after Fork Stalling. ***Mol Cell*** 73: p562–573.e3
> Collart C *et al.* (2017) Chk1 Inhibition of the Replication Factor Drf1 Guarantees Cell-Cycle Elongation at the *Xenopus* laevis Mid-blastula Transition. ***Dev Cell*** 42: 82–96.
> Collart C *et al.* (2013) Titration of four replication factors is essential for the *Xenopus* laevis midblastula transition. ***Science*** 341: 893–896.

Martin Hemberg

Computational analysis of large genomic datasets

What can sequencing data tell us about disease?

To create the different cell types in an organism, different genes are expressed at different times as transcripts of RNA. Understanding how, why, when and where genes are expressed is crucial for understanding not just development but also many diseases. High-throughput sequencing of RNA from different tissues can now provide quantitative information about gene expression from individual cells. However, the experimental datasets are large, high-dimensional and noisy, and efficient computational methods are required for the analysis.

Our group uses computational and mathematical methods to develop quantitative models of gene expression and gene regulation. In particular, we are exploring single-cell RNA sequencing, which can reveal insights that are inaccessible through traditional bulk experiments; for example, to estimate the number of differentiated cell types in the body. Another strand of research aims to further our understanding of gene regulation and to understand how non-coding sequences determine gene expression levels.

Analysing RNA, one cell at a time >
Left: *The scmap method is used to project cells obtained in a single-cell RNA-seq experiment from a query on to a reference. This facilitates the analysis of new experiments by allowing researchers to determine cell type by comparing with existing datasets.*
Right: *We applied scmap-cell to a differentiation trajectory to identify the most similar cell (as calculated through exhaustive search) and measured the accuracy based on how often it was found among the 5 or 10 nearest neighbours (in expression space).*

Co-workers
Tallulah Andrews, Louis-François Handfield, Jacob Hepkema, Nicholas Keone Lee, Guillermo Parada (joint with Eric Miska), Cristian Riccio (joint with Eric Miska), Xiaojuan Shen

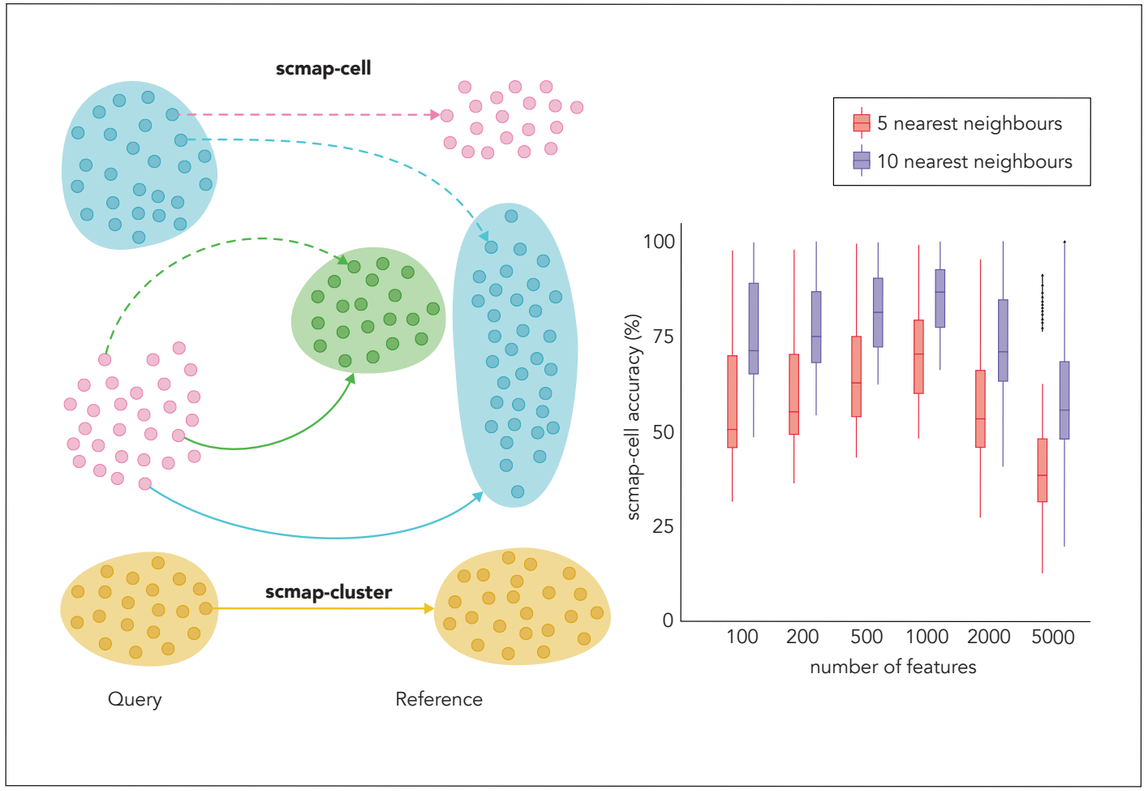


ILLUSTRATION BY CLAUDIA FLANDOLI.

"We are exploring single-cell RNA sequencing, which can reveal insights that are inaccessible through traditional bulk experiments"

Selected publications

> Kiselev VY *et al.* (2018) scmap: projection of single-cell RNA-seq data across data sets. ***Nat Methods*** 15: 359–362.
> Bergiers I *et al.* (2018) Single-cell transcriptomics reveals a new dynamical function of transcription factors during embryonic hematopoiesis. ***Elife*** 7: e29312.
> Kiselev VY *et al.* (2017) SC3: consensus clustering of single-cell RNA-seq data. ***Nat Methods*** 14: 483–486.

Facilities

In addition to the selection of facilities and services described below, the Institute benefits from dedicated support teams such as administration and stores, listed overleaf. Our aim is to enable scientists to focus on research.

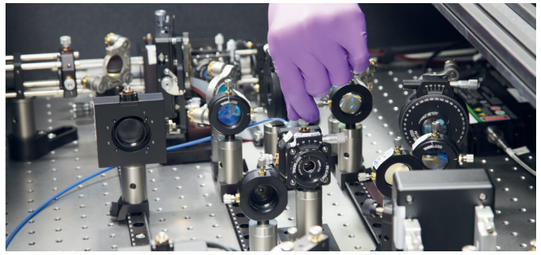
Media/glasswashing service

The media team provide quality-controlled buffers, growth media, worm plates, bacterial plates, fly vials, and standard and custom solutions. They collect and wash used glassware and provide sterile supplies.

Typical annual production of media includes 400,000 vials of Iberian fly food, 300,000 nematode worm plates and over 100 different recipes for buffers, media and solutions.

Find out more about the media team in the video for our YouTube series: ‘A Year in Institute Life’.

Microscopy and image analysis

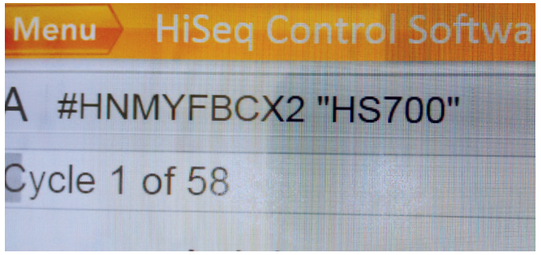


The team run the technical support for a wide range of the latest imaging technologies, as well as providing training, research contributions and custom software development.

Researchers have access to confocal, light-sheet and super-resolution (STORM, PALM, STED, SIM) microscopes. We also have a cell-sorting core.

The team building our new super-resolution microscopes describe their work in a video in our YouTube series: ‘A Year in Institute Life’.

Next-generation sequencing and bioinformatics



On-site sequencing allows researchers to access results with a quick turnaround. Bioinformatics expertise is provided by core posts as well as by research-group-based posts. A High Performance Computer cluster offers researchers the capability to process sequencing data in-house. These services are backed up by locally available courses in a variety of programming and analysis tools.

The sequencing service is featured in a video in our YouTube series: ‘A Year in Institute Life’.

IT/computing

The computing team provides flexible and high-quality infrastructure, services and support for all research and administrative computing activities within the Institute. Responsibilities include maintenance of a very large filestore and high-bandwith internal networking to ensure the efficient movement, secure storage, and future accessibility and re-use of a large volume of research data.

Institute staff can also access a wide range of University training courses in all the major software applications.

Support staff

Administration

Helen Lonergan BSc PGDip
Business and Operations Manager
Suzanne Campbell BSc
HR/Grants Manager
Naomi Clements-Brod BA
Public Engagement Assistant
Jane Course
Finance Manager
Hélène Doerflinger PhD
Public Engagement Manager
Jayne Fisher
HR Admin Support
Diane Foster
Deputy Business and Operations Manager
Lynda Lockey
Office Manager
Jessica Meyer BSc
Core Technical Co-ordinator
Sylviane Moss PhD
Safety and Compliance Manager
Dermot Nolan MA
Receptionist
Claire O'Brien PhD
Information and Communications Officer
Isabel Phelan
Receptionist

IT/computing

Alastair Downie
Computer Systems Manager
Nigel Smith
Computer Associate
Peter Williamson BSc
Computer Associate

Imaging

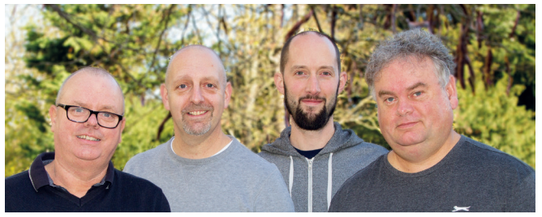
Alex Sossick BSc
Head of Microscopy and Scientific Facilities Co-ordinator, Laser Safety Officer
Richard Butler PhD
Research Associate (Imaging)
Nicola Lawrence PhD
Computer Imaging Associate, Laser Safety Officer

Bioinformatics

Charles Bradshaw PhD
Bioinformatician

Sequencing

Kevin (Kay) Harnish MSc
Wellcome Research Assistant (Sequencing Facility)



Accounts/purchasing/stores

Ian Fleming
Stores/Purchasing Manager
Simon Aldis
Purchasing/Accounts Assistant
David Cooper
Stores Technician
Andy Vincent
Senior Stores Technician
Mick Woodroofe
Purchasing/Accounts Assistant

Media/glasswashing

Juanita Baker-Hay
Media/Glass Washing Manager
Lisa Baker
Laura Carlton BA
Vince Dams
Sandra Human
Miguel Leon Salvador
Tracy Mitchell
Luciano Trevisan Moraes MSc
Nathy Villalobos MA

Combined building & services group

Alan Rix
Building Services Manager
Clive Bennett
Katherine Bennett
John Lyons
Joel Shubrooks
Paul Turrell

Super-resolution microscopy

Edward Allgeyer PhD
Wellcome Senior Research Associate
George Sirinakis PhD
Wellcome Senior Research Associate

Technical support

Polly Attlesey RAnTech MIAT
Facility Manager
Therese Jones-Green BSc
Manager of Aquatic Services

Zest catering

Amanda Harris
Melissa Plowden Roberts

Seminars, events and publications in 2018

Seminars

The Gurdon Institute Seminar Series

brings high-profile international scientists in front of an audience drawn from across the University biological sciences departments. Our 2018 speakers are listed below:

16 January
Johanna Ivaska, Turku Centre for Biotechnology, University of Turku, Finland
Imaging cancer invasion and pluripotency

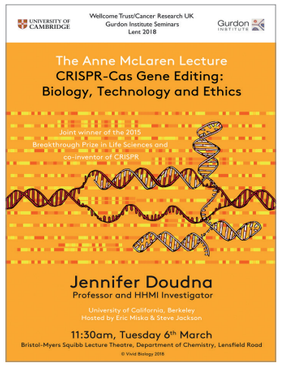
30 January
Eduard Batlle, Institute for Research in Biomedicine (IRB), Barcelona, Spain
Immune evasion and metastasis in colorectal cancer

6 February
Carla F. Kim, Boston Children's Hospital, USA
Regulation of progenitor cells in adult lung and in lung cancer

6 March
Jennifer Doudna, University of California, Berkeley, USA. **The Anne McLaren Lecture**: *CRISPR-Cas Gene Editing: Biology, Technology and Ethics*

20 March
Jan Huisken, Morgridge Institute for Research, Madison, USA
Smart light sheet microscopes for you and me

15 May
Danny Reinberg, Howard Hughes Medical Institute, NYU Langone School of Medicine at Smilow Research Center, New York, USA
Epigenetics: One Genome, Multiple Phenotypes
and
Rob Martienssen, Cold Spring Harbor Laboratory, New York, USA
Modified small RNA regulate chromosome dosage and segregation



POSTER BY CLAUDIA STOCKER.

5 June
Joanna Wysocka, Stanford University School of Medicine, USA
Regulatory principles in human development and evolution

19 June
Helen Blau, Baxter Laboratory for Stem Cell Biology, Stanford University, USA
Regulators of Muscle Stem Cell Fate and Function

10 July
Yi Zhang, Dept Genetics & Dept of Pediatrics, Harvard Medical School, USA
Role of H3K27me3-mediated genomic imprinting in development and somatic cell nuclear transfer reprogramming

15 November
Melissa Little, Murdoch Children's Research Institute, Victoria, Australia
Generating human kidney tissue from pluripotent stem cells

27 November
Ben Lehner, Centre for Genomic Regulation (CRG), Barcelona, Spain
Towards in vivo structural biology: solving protein structures using deep mutagenesis

Seminars for the local academic community

Beyond our own Gurdon Institute Seminars, our members organise, host and support several series of seminars for the local academic community:
Cambridge 3Rs (replication, repair and recombination), Cambridge Epigenetics Club, Cambridge Fly Meeting, Cambridge RNA Club, Developmental Biology Seminars, Life Science Masterclasses and Worm Club.

Events

Science and celebrations for staff

We have a long-established Postdoc Association and a newer PhD Student Association, regular social and sports activities, and plenty of special celebrations to bring all staff together. Below is a selection from 2018.

27 February: Gurdon Institute Postdoc Association (GIPA) **pub night**.

28 Febuary: The Institute's **Basketball team** finished the season undefeated to become College League Champions.

29 March: **Easter Egg Hunt** around the building.

29 March: **GIPA-hosted seminar** by Bart De Strooper, Director of the UK Dementia Research Institute, on 'The cellular phase of Alzheimer's disease'.

4 May: **Special Happy Hour** by the Surani lab, on Flavours of the World.

15 May: **GIPA joint-hosted seminar** by Danny Reinberg, NYU Langone School of Medicine, on 'Epigenetics: One genome, multiple phenotypes'.

8 June: **Special Happy Hour** by the Ahringer lab on a theme of The Wild West.

25 June: **GIPA held a half-day retreat** at Hughes Hall with the theme '(In)equality in Science', followed by informal drinks and BBQ. Session topics included unconscious bias, the emotional impact of racism, 'standing up for ourselves', interviews in academia, appraisals and disability. GIPA also ran a **board-games night**, and throughout the year ran a mentoring scheme for students and postdocs.

ILLUSTRATION BY FEDERICA MARINARO.

5 July: **Athena SWAN Garden Party** to celebrate renewal of our Bronze Award.

20 July: **Special Happy Hour** by the Miska lab, featuring games and a paddling pool.

27 & 28 September: **The 2018 Institute Retreat** for scientific staff was held at the Crowne Plaza Resort Colchester Five Lakes. Guest speaker was Professor Dame Ottoline Leyser, Director of the Sainsbury Laboratory, University of Cambridge.

Talks from group leaders were followed by the 'Treasure hunt' (meaning games in the sunshine), poster session, dinner and disco. Prizes were announced for **four best posters** (Fiona Jenkinson & Kang Wei Tan [Zegerman lab], Jelle van den Ameele & Robert Krautz [Brand], Gianmarco Mastrogiovanni [Huch] and Kyungtae Lim [Rawlins]), best research image (Jelle van den Ameele, Brand) and best research video (Mewanthi Flaminia Kaluthantrige Don & Nicole Prior [Huch]). **Other award winners:** Public Engagement Champion (Nicola Lawrence, Imaging);

Treasure hunt games at the Institute Retreat.

David Dunbar Sports Trophy (Valentina Migliori, Kouzarides lab, for organising weekly volleyball); Martin Evans Award for the greatest contribution to Institute social life (GIPA, for their excellent retreat); and the Ann Cartwright Good Citizen (Sylviane Moss, Safety and Compliance Manager).

5 October: **Special Happy Hour** by Ma and Rawlins labs for the Chinese Mid-Autumn Festival, with chopstick games, making paper lanterns and steamed dumplings.

19 October: **Special Happy Hour** by the Public Engagement team to showcase outputs of the 'Experiments in Art & Science' project. Captured on video for our YouTube series 'A Year in Institute Life'.

17 November: **Opening night party at the LAB**, Tony Kouzarides' science-themed bar around the block on Regent Street.

11 December: **Children's Christmas party** with entertainer, games, dancing and food. Captured on video for our YouTube series 'A Year in Institute Life'.

13 December: **Institute Christmas party** with fancy dress theme of 'Gene names', bake-off competition (including, of course, a Hedgehog entry!), lab sketches and live band.

Publications

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The Wellcome Trust/Cancer Research UK Gurdon Institute
The Henry Wellcome Building of Cancer and Developmental Biology
University of Cambridge
Tennis Court Road
Cambridge CB2 1QN, UK

Tel: +44 (0)1223 334088
Fax: +44 (0)1223 334089
www.gurdon.cam.ac.uk
contact@gurdon.cam.ac.uk
@GurdonInstitute