Annual report : 2013/2014 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

Contributors

Wellcome Trust (London, England)
Cancer Research UK. Gurdon Institute of Cancer and Developmental Biology
Cancer Research Campaign (Great Britain)
Gurdon Institute of Cancer and Developmental Biology (Great Britain)

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The Wellcome Trust/Cancer Research UK Gurdon Institute

2014 PROSPECTUS / ANNUAL REPORT 2013

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INTRODUCTION

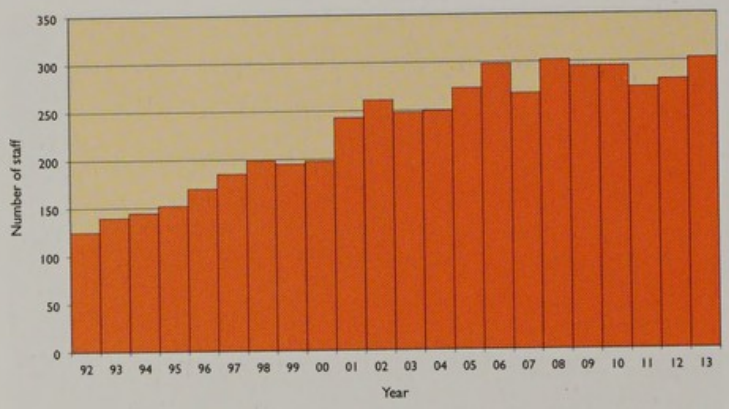
After all of the excitement last year over John Gurdon's Nobel Prize and our 21st anniversary symposium, this year has been a relatively calm one for the Gurdon Institute. Nevertheless, we still have had a number of causes for celebration. Firstly, Tony Kouzarides was awarded the Heinrich Wieland Prize for outstanding research on biologically active molecules and systems in the fields of Chemistry, Biochemistry and Physiology, and the Biochemical Society's Novartis Medal, as well as being elected as the Cancer Research UK Gibb Fellow in recognition of his significant contributions to translating his knowledge of basic cancer biology into the clinic for the benefit of patients. Secondly, Eric Miska was elected as the Herchel Smith Professor of Molecular Genetics and has been promoted to a Senior Group Leader position in the Institute. It has been a very successful year for Eric all round, as he was also awarded the Hooke Medal by the British Society of Cell Biology for his outstanding contribution to UK Cell Biology within the first 10 years of establishing his own lab. Thirdly, Magda Zernicka-Goetz was amongst 44 distinguished medical scientists to be elected a Fellow of the Academy of Medical Sciences this year. It is not only group leaders who have been winning prizes as Dr Jerome Jullien won the BioMed Central Annual Research Award for the best paper in the Molecular and Cellular Science category for his article "HIRA dependent H3.3 deposition is required for transcriptional reprogramming following nuclear transfer to *Xenopus oocytes*".

As well as the scientific awards mentioned above, members of the Institute have excelled in their efforts to reduce our energy consumption, which allowed the Institute to make a clean sweep at the University's green impact awards, winning the Gold awards for Green Impact, Lab Green Impact and Best Energy Saving Idea, as well as the National Award for Best Energy Saving Idea. This success has been masterminded by our Facilities Manager, Kathy Hilton, who fully deserved her award as Environmental Hero for 2012/2013. So far, the Institute has managed to cut its electricity bill by more than 7.5% mainly through simple behavioural changes, resulting in an annual saving of over £30,000, which will go towards renovating our tea room.

As usual, there has been some turnover in the group leaders during the last year. After five very productive years in the Institute, Thomas Down left us in the spring to start his own company and we wish him every success in his new venture. Rafael Carazo-Salas has also moved from his temporary space in the Institute to join his host Department of Genetics. It has been a great pleasure having Rafael as a colleague for the last four years, and we hope that we will still see him regularly now that he has moved to the Pharmacology building just down the road. Finally, we are delighted to have recruited Meritxell Huch as a new group leader. Meri is just finishing a very successful postdoc with Hans Clevers at the Hubrecht Institute in Utrecht, where one of her many projects led to the identification of stem cells in the adult mouse liver that appear after damage. Meri will be joining us in February to start her research group funded by a Wellcome Trust Recruitment Enhancement Award and will focus on the characterisation of these adult liver stem cells and their roles in liver regeneration and disease.

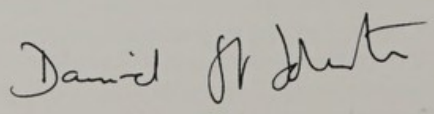
Green Impact Gold Award, 2013

The research in the Institute depends on the generous support of our sponsors, the Wellcome Trust and Cancer Research UK, and group leaders have been particularly successful this year at securing major funding. John Gurdon and Rick Livesey have received Wellcome Trust Senior Investigator Awards to support their work on the "Mechanisms for the reprogramming of somatic cell nuclei by eggs and oocytes" and "Human models of Alzheimer's disease" and Rick also received a large grant from the Alborada Trust for his Alzheimer's research. Congratulations also to Julie Ahringer who renewed her Wellcome Trust Senior Research Fellowship on "The control of chromatin structure and function" and Steve Jackson, who leads a team that secured a Wellcome Trust Strategic Award to study "Mutational signatures of DNA damage and repair processes". Finally, John Gurdon, Tony Kouzarides and Jon Pines were awarded grants by the MRC, BBSRC and the European Union. This year also saw a strengthening of our links with the Wellcome Trust Sanger Institute in Hinxton with the appointment of Eric Miska and Steve Jackson as associated faculty members.



Total number of staff (December 2013)

The strong community spirit of the Gurdon Institute depends on the dedication of the members of the Institute who help to organise events and activities, and two deserve special mention this year. Firstly, I would like to thank Emmanuelle Vire and the members of the Gurdon Institute Postdoc Association committee for all of their hard work during a particularly busy year. In addition to running a postdoc retreat on the topic of "Getting the most out of your postdoc in Cambridge", they also arranged five research seminars by distinguished visiting scientists and seven career path talks from Institute alumni. I am also very grateful to our Institute Outreach Officer, Hélène Doerflinger, and her team of enthusiastic volunteers for organising a number of successful events this year. The highlights were the Institute Open Day on the theme of "All you want to know about cloning" that was attended by more than 300 members of the public, and a stand and presentation as part of European Researchers' Night at the Natural History Museum called "Ask me how cells divide". Hélène's team also gave a number of talks in local schools and hosted six school visits to the Institute. Their goal for the next year is to develop a Mobile Laboratory that they can take into local primary schools, supported by a grant from the Wellcome Trust Institutional Strategic Support Fund. Finally, I would like to thank the social committee for several great parties and all of the Institute core staff for their excellent work in keeping the Institute running so smoothly

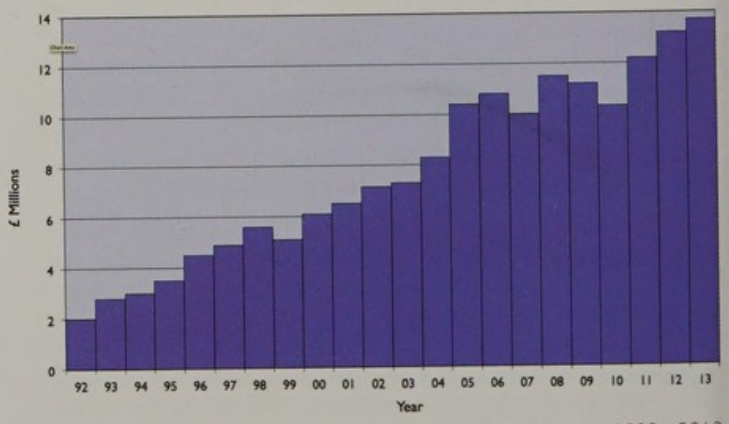


Professor Daniel St Johnston

HISTORICAL BACKGROUND

The Institute was founded in 1989 to promote research in the areas of developmental biology and cancer biology, and is situated in the middle of the area containing the biological science departments of the University of Cambridge, close to the more recently established Wellcome Trust Institute for Stem Cell Research. The Institute hosts a number of independent research groups in a purpose-built building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells, including stem cells, acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intra- and intercellular processes, which need to be analysed at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master, including molecular biology, biochemistry, microarray technology, bioinformatics, cell culture, imaging and embryonic manipulations. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another as is the case in the Institute.

The Institute is an integrated part of Cambridge University, and all group leaders are also members of another University department within the School of Biological Sciences, and contribute to both undergraduate and graduate student teaching.



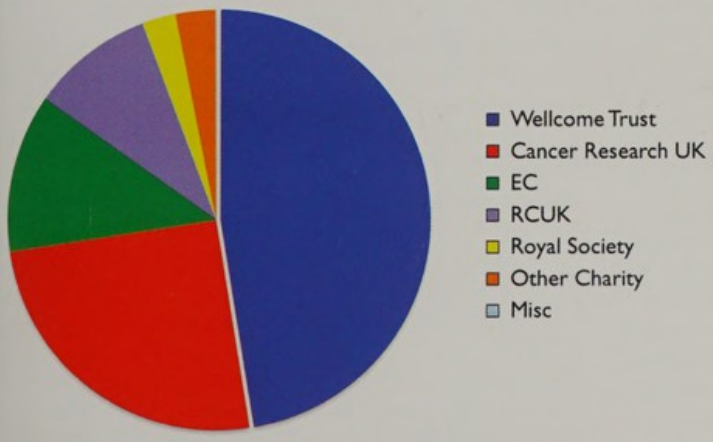
Grant income 1992 - 2013

CENTRAL SUPPORT SERVICES

The Institute's 'core staff' provides essential administrative, technical and computing support to our scientists so that the scientists can spend as much time as possible on their research.

FUNDING

Our two major funding bodies, the Wellcome Trust and Cancer Research UK, continue to offer the Institute vital backing in the form of Fellowships, individual programme, project and equipment grants, in addition to our invaluable core funding.



Sources of funding 2013

Other sources of funding, both direct and indirect, include the European Commission, BBSRC, MRC, the Royal Society, NIH, the European Molecular Biology Organization, HFSP, the Isaac Newton Trust, the Association for International Cancer Research, the Alzheimer's Research Trust, the Federation of European Biochemical Societies, the Japan Society for the Promotion of Science, the Ramon Areces Foundation, the March of Dimes, the Sankyo Foundation of Life Science, the Wenner-Gren Foundation, the Erasmus Programme, the Amgen Scholars Programme, the Croucher Foundation, the Woolf Fisher Trust, the Darwin Trust, the Thai Government, the Liechtenstein Government, the Turkish Government, the Cambridge Cancer Centre, Gates Cambridge Scholarships, Riken, SystemsX.ch, GSK and KAUST.

The University has also been generous in its support of the Institute, particularly through various student schemes and Herchel Smith schemes, and its funding of equipment.

The Institute on retreat, October 2013, held at Dunston Hall, Norfolk

RETREAT

Our Annual Retreat this year was held at Dunston Hall, Norwich on 3rd and 4th October 2013. The event was highly successful. Many Institute members attended and all gained from the experience both scientifically and socially.

Julie Ahringer

The regulation of chromatin structure and function

Co-workers: Alex Appert, Dasha Ausiannikava, Fanelie Bauer, Ron Chen, Mike Chesney, Duccio Conti, Yan Dong, Kenneth Evans, Bruno Fievet, Moritz Herrmann, Jürgen Janes, Djem Kissiov, Alicia McMurchy, Josana Rodriguez, Przemyslaw Stempor, Christine Turner, Eva Zeiser

The regulation of chromatin structure in transcription and other events plays an important role in the determination and expression of cellular identity, and chromatin disregulation is implicated in many diseases, including developmental defects, ageing, and cancer. We use the power of functional genetics and genomics in *C elegans* to address fundamental questions in chromatin regulation and transcriptional control, by analysing epigenetic state and function in wild-type and mutant animals and tissues. *C elegans* is an excellent system for studies of chromatin function due to its small well-annotated genome, powerful RNAi technology, and rich resource of chromatin mutants.

To provide a resource for investigations into transcription control, we determined the genome-wide landscape of RNA polymerase II transcription initiation and elongation in *C elegans*. In addition to mapping transcription start sites for protein coding genes, we discovered extensive transcription of enhancer regions, with transcription elongation often oriented towards the nearest downstream gene. We are investigating functions of enhancer and other non-coding transcription and the relationship between promoters and enhancers and their developmental regulation.

Within chromatin, particular sets of histone modifications and/or chromatin proteins co-occur, and different "chromatin states" are associated with different genomic features. By generating and analysing a *C elegans* chromatin state map, we have found that the genome is organised into blocks of active and inactive chromatin separated by boundary regions. We are studying the formation and function of different types of boundary region and how this global genomic organisation arises.

We also study the functions of *C elegans* counterparts of major chromatin regulatory complexes implicated in human disease, including the histone deacetylase complex NuRD, the retinoblastoma complex DRM, and a TIP60 histone acetyltransferase complex. Our work makes extensive use of high-throughput sequencing and computational methods.

Selected publications:

• Chen RA-J, Down TA, Stempor P, Chen QB, Egelhofer TA, Hillier LW, Jeffers TE and Ahringer J (2013) The landscape of RNA polymerase II transcription initiation in *C elegans* reveals enhancer and promoter architectures, Genome Research, 8, 1339-47.

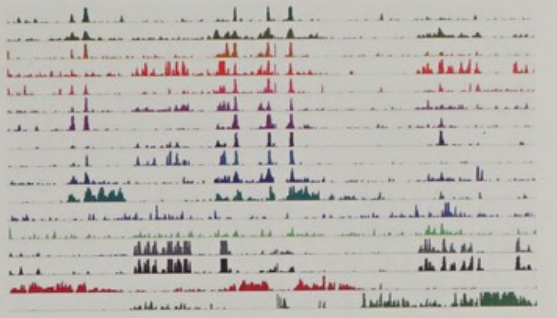
Woods S, Coghlan A, Rivers D, Warnecke T, Jeffries SJ, Kwon T, Rogers A, Hurst L and Ahringer J (2013) Duplication and retention biases of essential and non-essential genes revealed by systematic knockdown analyses, Plos Genetics, 9(5): e1003330. doi:10.1371/journal.pgen.1003330.

• Vielle A, Lang J, Dong Y, Ercan S, Kotwaliwale C, Rechtsteiner A, Appert A, Chen QB, Dose A, Egelhofer T, Stempor P, Dernburg A, Lieb J, Strome S and Ahringer J (2012) H4K20me1 contributes to downregulation of X-linked genes for *C elegans* dosage compensation, Plos Genetics 8(9): e1002933

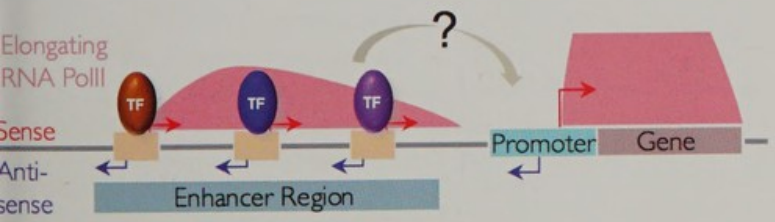
• Gerstein MB, modENCODE Consortium, Ahringer J, Strome S, Gunsalus KC, Micklem G, Liu XS, Reinke V, Kim SK, Hillier LW, Henikoff S, Piano F, Snyder M, Stein L, Lieb JD, Waterston RH. (2010) Integrative Analysis of the *Caenorhabditis elegans* Genome by the modENCODE Project. Science 330, 1775-87

• Kolasinska-Zwierz P, Down T, Latorre I, Liu T, Liu XS and Ahringer J (2009) Differential chromatin marking of introns and expressed exons by H3K36me3. Nature Genetics 41, 376-381

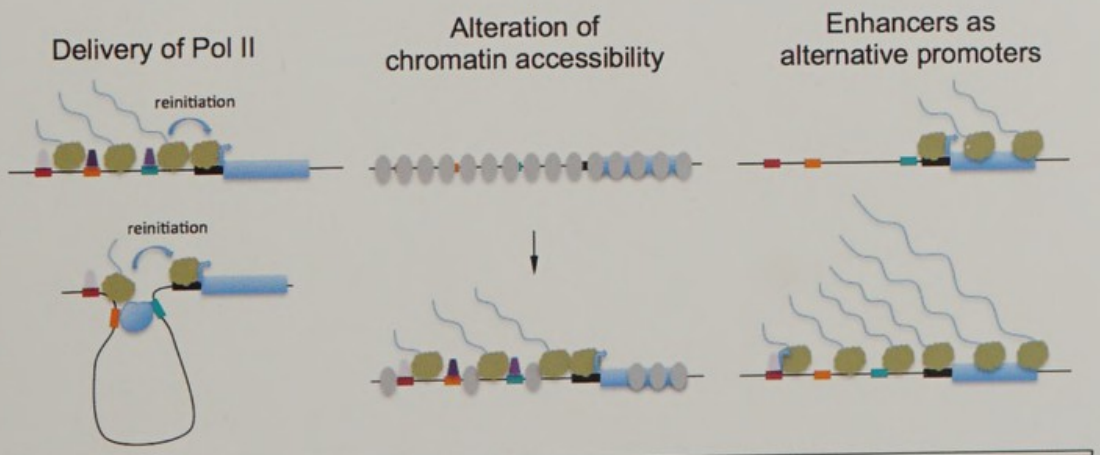
Chromatin states show that genes are organised into active and inactive blocks



Genome-wide mapping of chromatin proteins and histone modifications.



Regulatory architecture of C elegans upstream enhancer regions. Transcription initiates bidirectionally from transcription factor binding sites and elongated transcription is directed towards the nearest downstream gene.



Models of enhancer functions

Andrea Brand

Stem cells to synapses: regulation of self-renewal and differentiation in the nervous system

Co-workers: Janina Ander, Elizabeth Caygill, Seth Cheetham, Esteban Contreras Sepulveda, Melanie Cranston, Abhijit Das, Catherine Davidson, Paul Fox, Katrina Gold, Jun Liu, Owen Marshall, Leo Otsuki, Chloe Shard, Tony Southall, Pauline Spéder, Christine Turner

Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is a key step in the therapeutic use of stem cells to repair tissues after damage or disease. We are investigating the genetic networks that regulate neural stem cells in *Drosophila*. Stem cells can divide symmetrically to expand the stem cell pool, or asymmetrically to self-renew and generate a daughter cell destined for differentiation. The balance between symmetric and asymmetric division is critical for the generation and repair of tissues, as unregulated stem cell division results in tumourous overgrowth. By comparing the transcriptional profiles of symmetrically and asymmetrically dividing stem cells, we identified Notch as a key regulator of the switch from symmetric to asymmetric division.

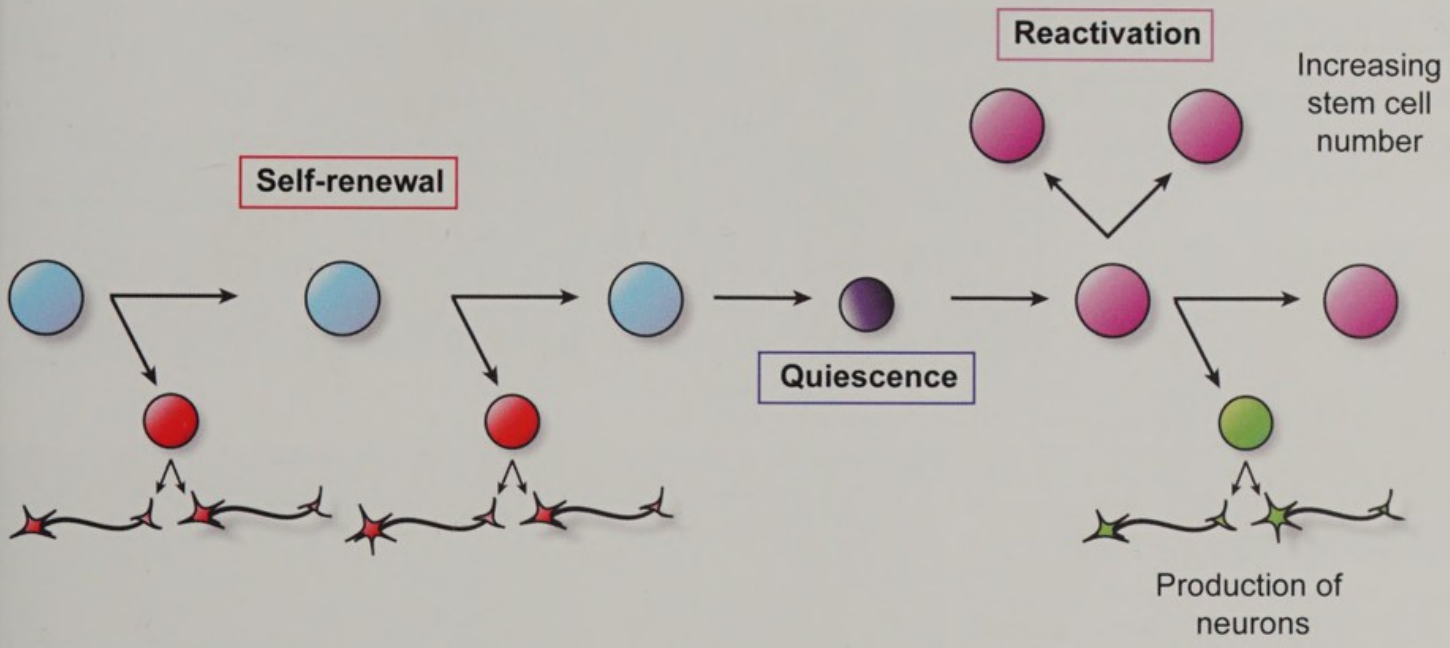
During asymmetric division cell fate determinants, such as the transcription factor Prospero, are partitioned from the neural stem cell to its daughter. We showed that Prospero acts as a binary switch between self-renewal and differentiation. We identified Prospero's targets throughout the genome and showed that Prospero represses genes for self-renewal and activates differentiation genes. In Prospero mutants, differentiating daughters revert to a stem cell-like fate: they express markers of self-renewal, continue to proliferate, fail to differentiate and generate tumours.

Neural stem cells transit through a period of quiescence at the end of embryogenesis. We discovered that insulin signalling is necessary for these stem cells to exit quiescence and reinitiate cell proliferation. We showed that a glial niche secretes the insulin-like peptides that reactivate neural stem cells *in vivo*. We are investigating the systemic and local signals that regulate stem cell growth and proliferation and the role of glia in inducing neural stem cell exit from quiescence.

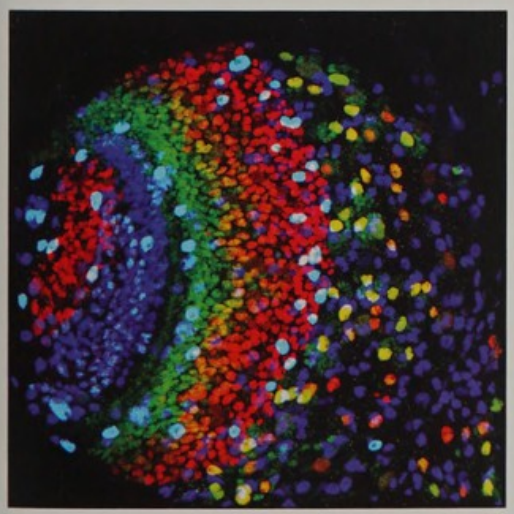
For more information, see the Brand lab home page: http://www.gurdon.cam.ac.uk/~brandlab/

Selected publications:

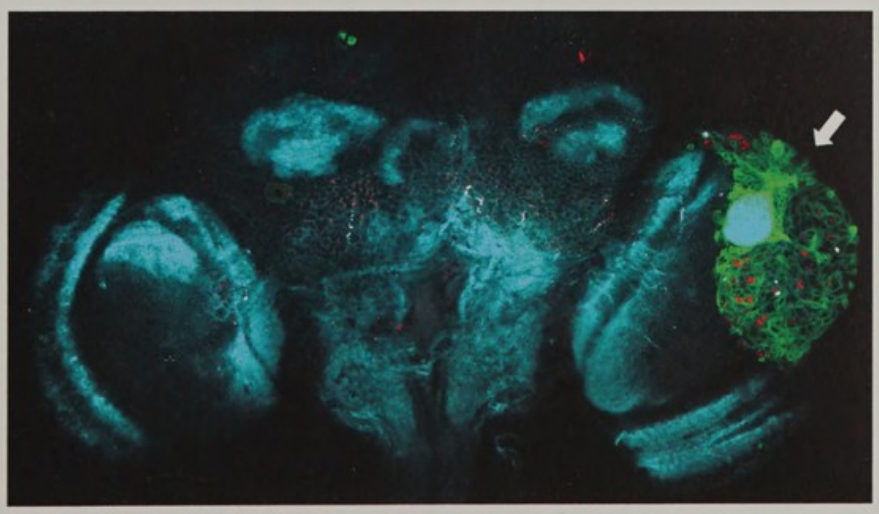
- Southall TD, Gold KS, Egger B, Davidson CM, Caygill EE, Marshall OJ and Brand AH (2013) Cell type-specific profiling of gene expression and chromatin binding without cell isolation: Assaying RNA Pol II occupancy in neural stem cells. **Developmental Cell** 26, 101-112.
- Cheetham SW and Brand AH (2013) Insulin finds its niche. **Science** 340, 817-818
- Wolfram V, Southall TD, Brand AH and Baines RA (2012) The LIM-homeodomain protein Islet dictates motor neuron electrophysiological properties by regulating K+ channel expression. **Neuron** 75, 663-674
- Gold KS and Brand AH (2012) Transcriptome analysis of *Drosophila* neural stem cells. **Methods Mol Biol** 916, 99-110
- Chell JM and Brand AH (2010) Nutrition-responsive glia control exit of neural stem cells from quiescence. **Cell** 143(7), 1161-1173



Drosophila neural stem cells (blue) divide asymmetrically during embryogenesis to self-renew and generate differentiating daughter cells (red). Neural stem cells then enter a period of quiescence (grey) from which they are reactivated to expand the stem cell pool (purple) and generate the neurons of the adult nervous system (green).



Visualising brain organisation: neural stems cells (red) and glial cells (blue) in a Drosophila brain lobe; dividing cells are labelled in green.



Drosophila as a cancer model: We showed that neurons mutant for the gene lola (outlined in green) revert to a stem cell-like fate (red) and cause brain tumours in adults (arrowed; brain outlined in cyan. [Dedifferentiation of neurons precedes tumour formation in lola mutants. Southall et al. (2014) Developmental Cell 28, 685-696.]

Nick Brown

Molecular analysis of morphogenesis

Co-workers: Natalia Bulgakova, Hannah Green, Annabel Griffiths, Sven Huelsmann, Benjamin Klapholz, Tarun Kumar, Miranda Landgraf, Aidan Maartens, Juan Manuel Gomez, John Overton, Paula Rodriguez, Peerapat Thongnuek, Susan Tweedie

Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, receptors, which stick cells together (adhesion) and/or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Our research is currently focused on how adhesion receptors are linked with the cytoskeleton to specify cell shape and movement within the developing animal. This linkage between the adhesion receptors and the major cytoskeletal filaments contains many components, giving it the ability to grow or shrink in response to numerous signals. For example, as the cytoskeleton becomes contractile and exerts stronger force on the adhesion sites, additional linker proteins are recruited in to strengthen adhesion.

We use the fruit fly *Drosophila* as our model organism to discover how the complex machinery linking cell adhesion to the cytoskeleton works, and contributes to morphogenesis. We are seeking to discover how adhesion receptors form contacts of differing strength and longevity, at one point mediating dynamic attachments as the cell moves, and at another point stable connections essential for the functional architecture of the body. A good example of stable sites of adhesion is the integrin-dependent attachments of the muscles (Fig 1). Using super-resolution microscopy we can visualise the orientation of the proteins with the adhesion site (Fig 2). To combine biophysical approaches with genetics, we are developing a method of primary cell culture of embryonic muscles, where we can now generate bipolar muscles with integrin adhesions at each end (Fig 3). Of particular interest are the mechanosensitive properties of cell adhesion, where acto-myosin contraction with the cell exerts force on sites of adhesion, causing the recruitment of proteins like vinculin to strengthen adhesion, and actin protrusions are capable of pushing the nucleus to one side. Cell-cell adhesion is regulated by dynamic microtubules (Fig 4), and we have discovered that a novel adhesion subcomplex controlled by microtubules is required to maintain segmental boundaries, which are crucial for the generation of the pattern within the embryonic epidermis.

Selected publications:

- Huelsmann S, Ylänne J and Brown NH (2013) Filopodia-like actin cables position nuclei in association with perinuclear actin in *Drosophila* nurse cells. **Dev. Cell** 26, 604-615.
- Bulgakova NA, Grigoriev I, Yap AS, Akhmanova A and Brown NH (2013) Dynamic microtubules produce an asymmetric E-cadherin-Bazooka complex to maintain segment boundaries. **J Cell Biol. 201**, 887-901.
- Bulgakova NA, Klapholz B and Brown NH (2012) Cell adhesion in *Drosophila*: versatility of cadherin and integrin complexes during development. **Curr Opin Cell Biol.** 24, 702-712.
- Zervas CG, Psarra E, Williams V, Solomon E, Vakaloglou KM and Brown NH (2011) Central multifunctional role of Integrin-Linked Kinase at muscle attachment sites **J. Cell Sci.** 124, 1316-1327

Fig 1) Embryonic epidermal cells showing that the apical array of microtubules (red) is well organised into parallel bundles. The ends of these microtubules regulate the levels of the cell adhesion molecule E-cadherin (green) to control cell movement within the layer of cells.

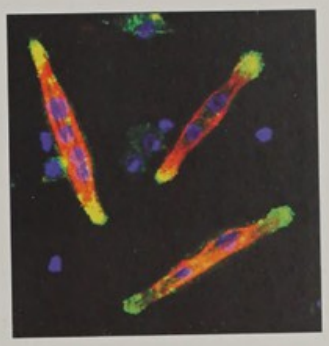


Fig 3) Primary cell culture, showing that embryonic muscles become bipolar on a uniform extracellular matrix substrate, with integrin adhesions in green, connected to red actin filaments, and nuclei in blue.

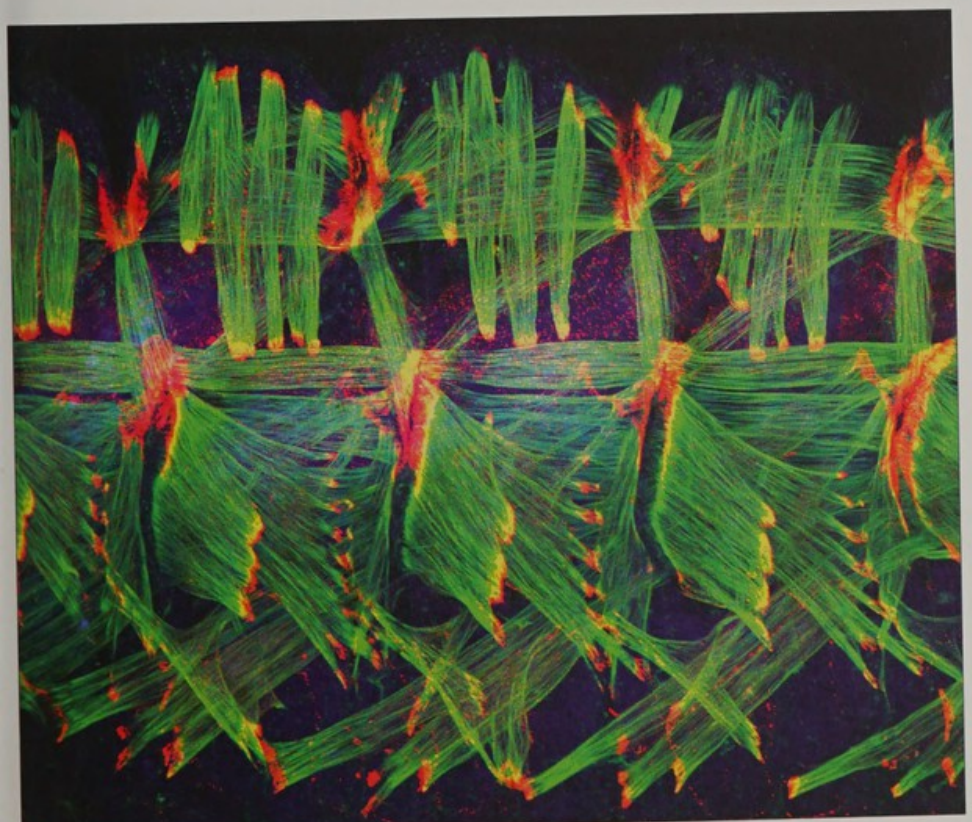


Fig 2) Attachment of muscles in the Drosophila embryo is mediated by integrins, which are linked to the actin cytoskeleton (green) by linker proteins such as vinculin (red).

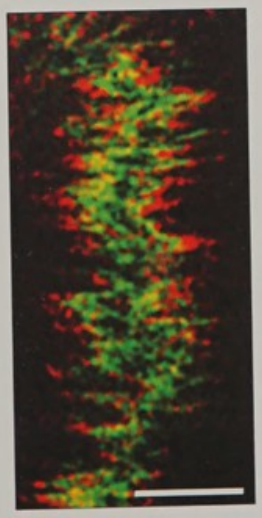
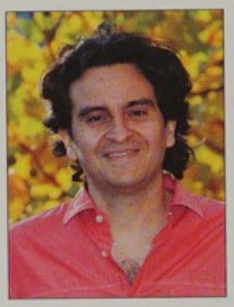


Fig 4) Magnified view of the muscle attachment site by super-resolution microscopy shows that the actin-binding region of the linker protein talin (red) is pulled away from the integrin cytoplasmic tails (green).

Rafael Carazo Salas

Functional genomics of cell morphogenesis

Co-workers: Juan Francisco Abenza Martínez, Bálint Antal, Anatole Chessel, James Dodgson, Marco Geymonat, Joseph Harvey, Jonathan Lawson, Oliver Meacock, Yung-Chin Oei, Kathy Oswald, Hannah Punter



An extraordinary capacity of cells is their ability to modulate their shape, polarity and intracellular cytoskeletal organisation, according to the functions they need to perform. Our lab's goal is to understand how the gene and protein networks that regulate cellular growth, division and morphogenesis operate in space and in time, and how different cell shapes and growth patterns can arise from a single genome.

A large part of our work has focused on pioneering 3D image-based high-throughput/high-content microscopy pipelines for functional genomics studies. Capitalising on this technology a number of projects are ongoing in our group using yeast and, increasingly, human cells.

We recently completed the first live cell-based, multi-process screen for genes that control and link cell shape, the microtubule cytoskeleton and cell cycle progression, and discovered tens of novel candidate regulators - mostly conserved through to humans - which we are validating. In another project, we have begun reconstructing the topology of the cell polarity network and have identified unexpected systems-level feedbacks between different subsets of polarity machineries.

Overall, our vision is to generate an incremental genome annotation resource allowing us to share, analyse and visualise the biological big data sets we are generating, and to provide fundamental new insights into how genes regulate and coordinate multiple biological processes in cells as well as how diverse processes are co-regulated.

In parallel, we seek to dissect how the molecules and pathways we discover spatiotemporally control morphogenesis in live cells, using time-lapse and super resolution microscopy, computational modelling and mechanobiological approaches.

Selected publications:

• Csikász-Nagy A, Sato M, Carazo Salas RE (2013) Projecting cell polarity into the next decade. **Philos Trans R Soc Lond B Biol Sci.** Sep 23;368(1629):20130001.

• Bajpai A, Feoktistova A, Chen JS, McCollum D, Sato M, Carazo-Salas RE, Gould KL, Csikász-Nagy A (2013) Dynamics of SIN asymmetry establishment. **PLoS Comput Biol.** Jul;9(7):e1003147.

• Dodgson J, Chessel A, Yamamoto M, Vaggi F, Cox S, Rosten E, Albrecht D, Geymonat M, Csikasz-Nagy A, Sato M, Carazo-Salas RE (2013) Spatial segregation of polarity factors into distinct cortical clusters is required for cell polarity control. **Nat Commun.** 4:1834.

• Vaggi F, Dodgson J, Bajpai A, Chessel A, Jordán F, Sato M, Carazo-Salas RE and Csikász-Nagy A (2012) Linkers of cell polarity and cell cycle regulation in the fission yeast protein interaction network. **PLoS Comp Biol** 2012 Oct;8(10):e1002732.

• Chessel A, Dodgson J and Carazo-Salas RE (2012) Spherical spatial statistics for 3D fluorescence video-microscopy. **9th IEEE International Symposium on Biomedical Imaging** (ISBI) 1747-50.

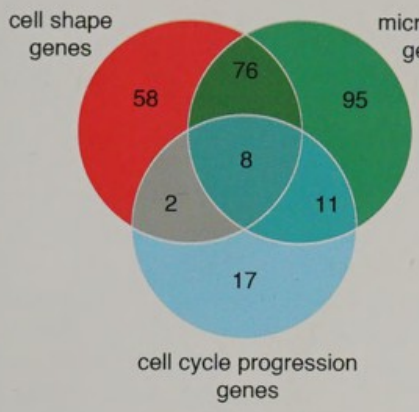


FIgure 1) Genes that control or link cell shape, microtubules and cell cycle progression, identified through a high-throughput/high-content microscopy screen.

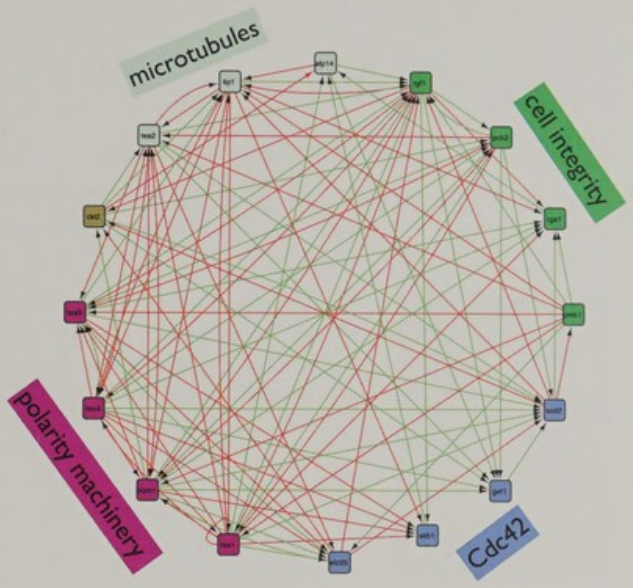


Figure 2) Systems-level feedbacks across polarity regulators, identified by microscopy-based phenotypic profiling.

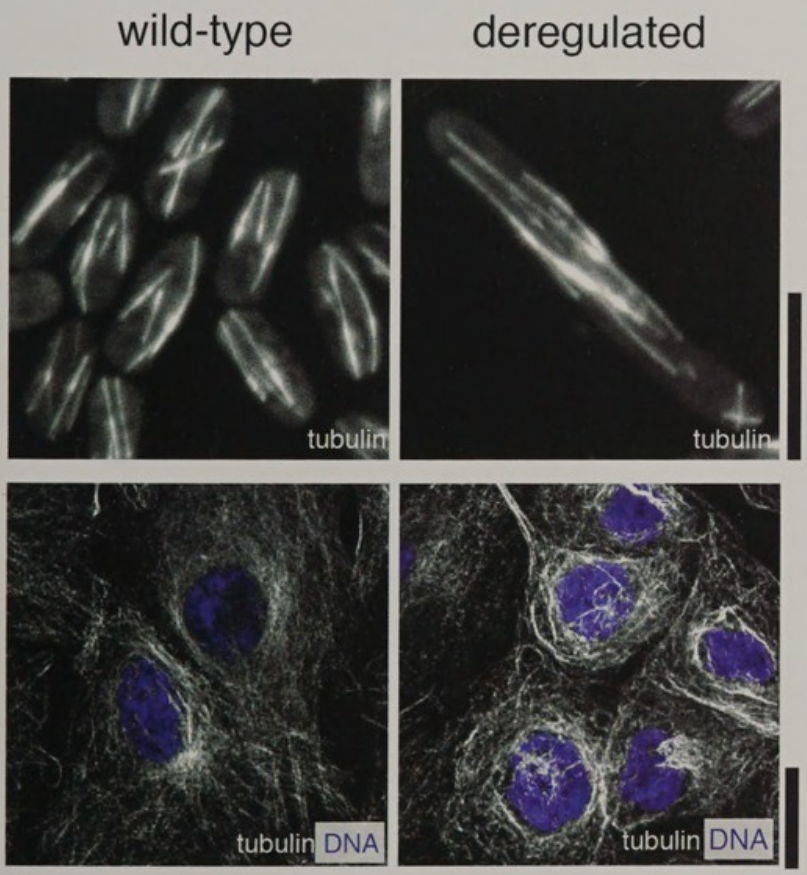


Figure 3) Examples of mutants and treatments that we have identified to induce microtubule phenotypes.

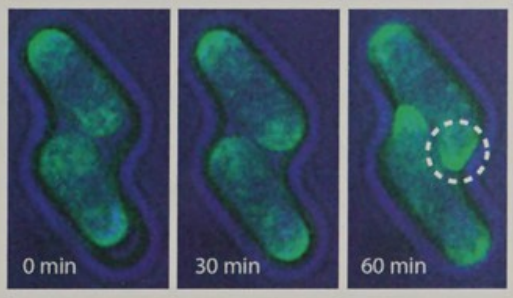


Figure 4) Mechanical confinement in micro-fabricated chambers alters the pattern of cell growth.

Jenny Gallop

Membranes, actin and morphogenesis

Co-workers: Guilherme Correia, Xidi Feng, Helen Fox, Lynn Froggett, Yoshiko Inoue, Julia Mason, Daniel Saxton, Astrid Walrant

We are interested in the molecular basis of cell shape and the changes that occur when cells move and tissues develop. Cell shape is in large part determined by the actin cytoskeleton and remodelling of the cytoskeleton underlies the cell rearrangements that occur during normal morphogenesis and also when morphogenetic programs go wrong, for example in developmental defects and during cancer metastasis. The machinery of the actin cytoskeleton is also hijacked by various pathogens to mediate infection.

Actin filaments are nucleated at cell membranes and are elongated and bundled in different ways to form distinct cytoskeletal structures. We have found that the membrane environment influences which proteins are used to make actin structures. Membranes are interesting to consider in how cells change shape because they are the interface between the outside and inside of the cell and therefore are hubs of signalling activity, as well as being the boundary of the cell that has to be moulded by links to the cytoskeleton.

We are particularly concentrating on how actin is polymerised during filopodia formation and endocytosis (Fig 1). We take a two-pronged approach: (1) reconstitution of actin polymerisation *in vitro* using artificial membranes and *Xenopus* egg extracts (Fig 2) and (2) investigation of how actin regulators are used by cells *in vivo* in *Drosophila melanogaster* and during early development in *Xenopus laevis* (Fig 3). This interdisciplinary approach gives us the possibility of attaining a complete molecular understanding and also testing those models within the natural complement of physiological signals provided by the whole organism.

Selected publications:

- Gallop JL, Walrant A, Cantley LC and Kirschner MW (2013) Phosphoinositides and membrane curvature switch the mode of actin polymerization via selective recruitment of toca-1 and Snx9. **Proc Natl Acad Sci** 110: 7193-7198
- Lee K*, Gallop JL*, Rambani K and Kirschner MW (2010) Self-assembly of filopodia-like structures on supported lipid bilayers. **Science** 329: 1341-1345
- Gallop JL*, Jao CC*, Kent HM, Butler PJ, Evans PR, Langen R and McMahon HT (2006) Mechanism of endophilin N-BAR domain-mediated membrane curvature. **EMBO J** 25: 2898-2910
- Gallop JL, Butler PJ and McMahon HT (2005) Endophilin and CtBP/BARS are not acyl transferases in endocytosis or Golgi fission. **Nature** 438: 675-678
- McMahon HT and Gallop JL (2005) Membrane curvature and mechanisms of dynamic cell membrane remodelling. **Nature** 438: 590-596

(* joint first authors)

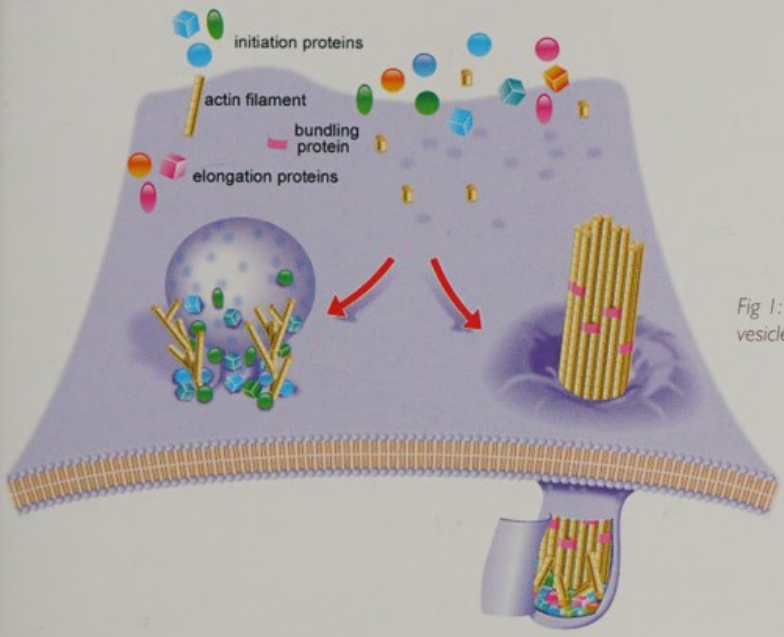


Fig 1: Filopodia protrude from cells and are made of bundled actin, vesicles bud inwards into cells and nucleate branched actin.

Fig 2: Filopodia-like structures formed in vitro, with fluorescently-labelled actin which grow from supported lipid bilayers.

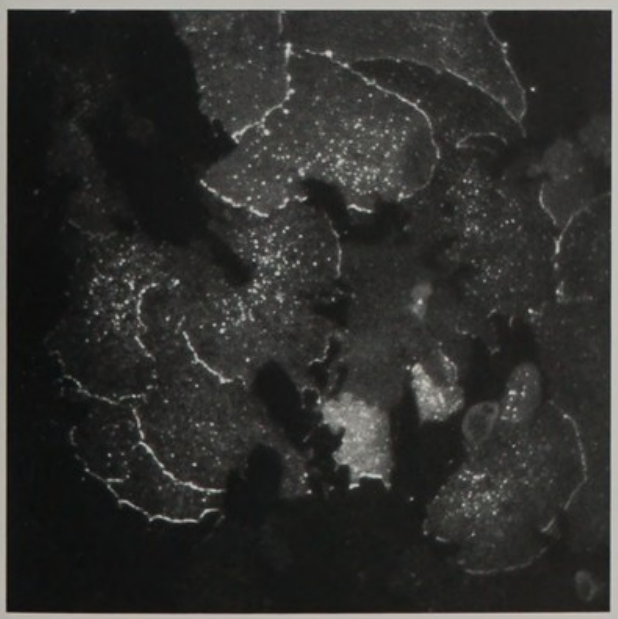
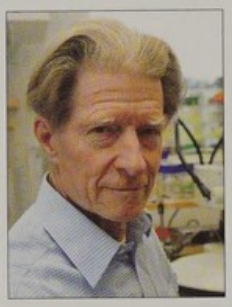


Fig 3: Total internal reflection fluorescence microscopy image of a Keller explant from a Xenopus gastrula, showing that actin regulator Toca-1 localises to lamellipodial edges, filopodia tips and endocytic vesicles.

John Gurdon

Nuclear reprogramming by oocytes and eggs

Co-workers: Dilly Bradford, Nigel Garrett, Richard Halley-Stott, Sarah Herberg, Eva Hormanseder, Jerome Jullien, Magdalena Koziol, Kei Miyamoto, Angela Simeone, Marta Teperek-Tkacz



Amphibian eggs were used for the first somatic cell nuclear transfer experiments carried out over 60 years ago, but they still provide valuable material for analysing the molecular mechanisms of nuclear reprogramming, in which gene expression in a differentiated cell can be reversed to that of an embryonic cell. Our aim is to identify those components of an egg that can bring about this rejuvenation of adult gene expression, and also to identify the molecules in the nuclei of differentiated cells that resist the reprogramming activities of an egg.

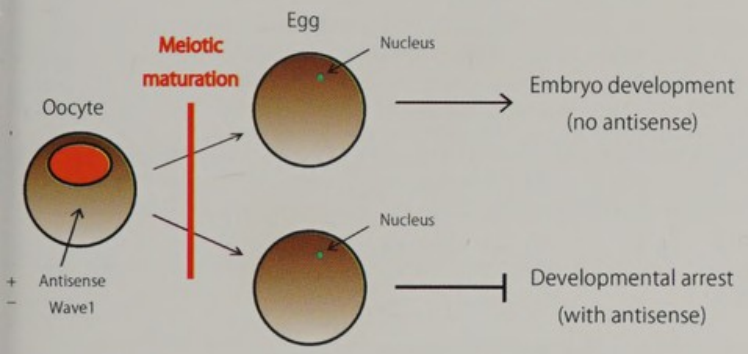
We make use of the oocytes of *Xenopus*. These egg progenitors in the maternal ovary possess an immensely enlarged nucleus (the germinal vesicle) which contains a large supply of molecules required for normal development. We inject a few hundred somatic nuclei of mammals or frogs into this germinal vesicle. Neither the injected nuclei, nor the recipient oocyte replicate DNA or divide, but the nuclei undergo a rapid transformation of structure and function, and within 1-4 days start to transcribe pluripotency genes. As cells become increasingly differentiated in normal development, their nuclei become progressively more resistant to the reprogramming effects of an egg or oocyte, a characteristic that reflects the stability of cell differentiation.

The transcriptional activation of pluripotency genes that have become quiescent during cell differentiation depends on a sequence of events starting with the uptake of an oocyte-specific linker histone, B4, and this is followed by the uptake of another abundant oocyte histone H3.3, the epigenetic modification of histone, and the polymerisation of nuclear actin, culminating with transcriptional activity of elongating polymerase II. The resistance of somatic nuclei to reprogramming depends on DNA methylation, chromatin proteins including macro H2A modified histones, and some other tight binding chromatin components.

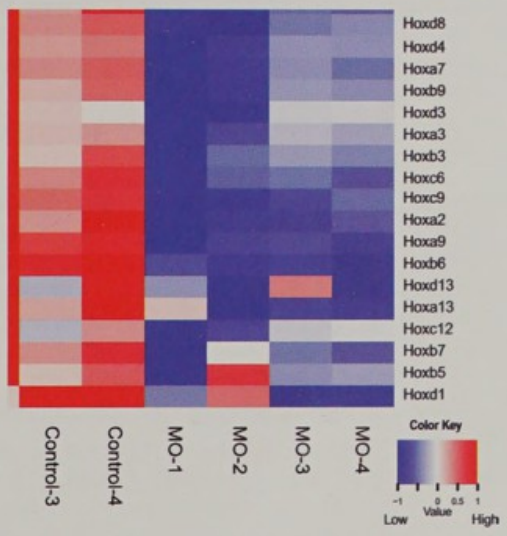
Our long-term hope is to be able to make use of natural egg components to improve the efficiency of somatic cell reprogramming for cell replacement therapy.

Selected publications:

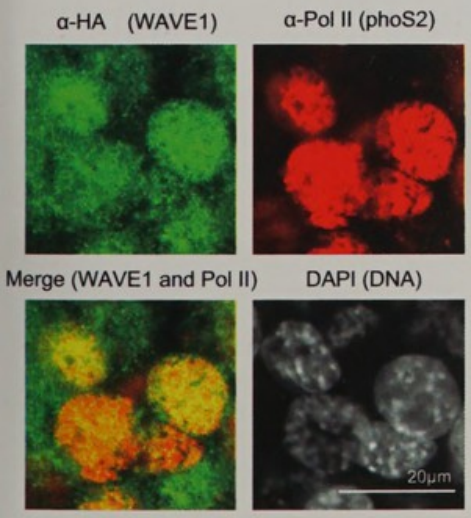
- Halley-Stott RP, Pasque V and Gurdon JB (2013) Nuclear reprogramming. Development 140: 2468-2471.
- Gurdon JB (2013) The egg and the nucleus: a battle for supremacy. Development 140:2449-2456.
- Miyamoto K, Teperek, M, Yusa K, Allen GE, Bradshaw CR and Gurdon JB (2013) Nuclear WAVE1 is required for reprogramming transcription in oocytes and for normal development. Science 341:1002-5.
- Gurdon JB (2013) Secrets in the egg. Cell 153: 1179.
- Pasque V, Jullien J, Miyamoto K, Halley-Stott RP and Gurdon JB (2011) Epigenetic factors influencing resistance to nuclear reprogramming. Trends in Genetics 27(12)516-525.



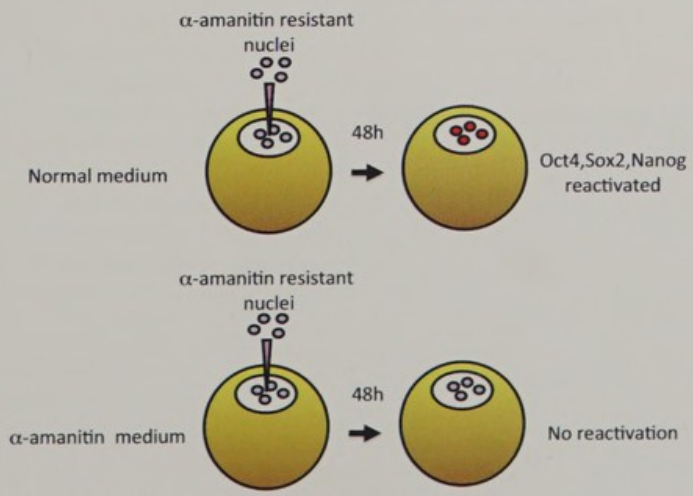
WAVE I (Wiskott-Aldrich syndrome family protein) is required for embryonic gene activation and embryonic development.



RNA-seq analysis of Xenopus embryos.



WAVE I is present in transplanted nuclei that are actively transcribing.



Oocyte derived RNA polymerase II is required for transcriptional reprogramming following nuclear transfer

Steve Jackson

Maintenance of genome stability

Co-workers: Pallavi Agarwal, Gabriel Balmus, Linda Baskcomb, Rimma Belotserkovskaya, Andrew Blackford, Jessica Brown, Will Chiang, Julia Coates, Matt Cornwell,, Mukerrem Demir, Kate Dry, Josep Forment, Yaron Galanty, Nicola Geisler, Mareike Herzog, Satpal Jhujh, Delphine Larrieu, Carlos le Sage, Natalia Lukashchuk, Ryotaro Nishi, Fabio Puddu, Helen Reed, Israel Salguero, Christine Schmidt, Matylda Sczaniecka-Clift, Jon Travers, David Weismann, Paul Wijnhoven

Our work focuses on the DNA-damage response (DDR), the set of events that optimises cell survival and genome integrity by detecting DNA damage, signalling its presence and mediating its repair. As DDR defects are associated with neurodegenerative diseases, immunodeficiencies, premature ageing and cancer, our research is not only providing academic insights but is also suggesting new ways to better understand and alleviate such conditions.

Over the past year, we have continued to study how the DDR is controlled by protein post-translational modifications. For instance, we established that the SUMO targeted ubiquitin E3 ligase (STUBL) RNF4 promotes DNA double-strand break DSB repair, shedding new light on the molecular dynamics regulating DSB signalling and repair, and highlighting the interplay between ubiquitylation and sumoylation (1,2). We have also determined how the key DSB signalling protein ATM can be activated through chromatin alterations (3). Thus, we established that tyrosine phosphorylation of the protein acetyltransferase KAT5 (Tip60) is mediated by the proto-oncogene c-Abl, and that this modification increases after DNA damage in a manner associated with KAT5 binding to the histone mark H3K9me3. This in turn triggers KAT5-mediated ATM acetylation, DDR checkpoint activation and cell survival (3). Another major recent highlight has been us establishing a method for microscopic visualisation and quantification of the (DSB) repair protein Ku at individual DNA-damage sites (4) – a goal that we and others have sought for the ~20 years since Ku was first identified as a non-homologous end joining (NHEJ) factor.

Selected publications:

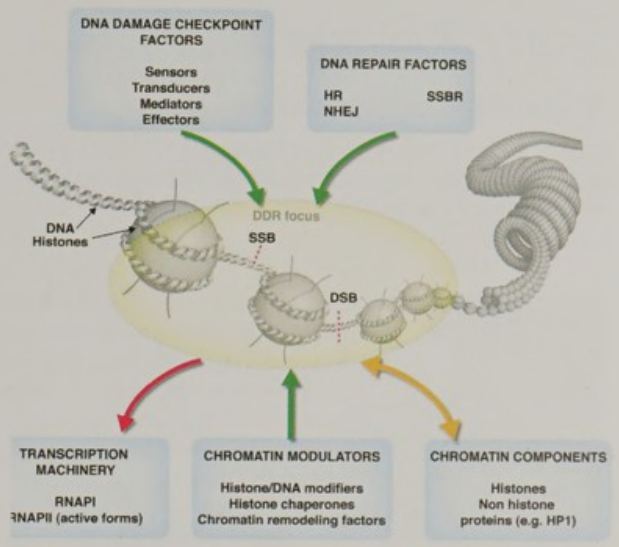
• Jackson SP and Durocher D (2013) Regulation of DNA damage responses by Ubiquitin and SUMO. **Molecular Cell** 49, 795-807.

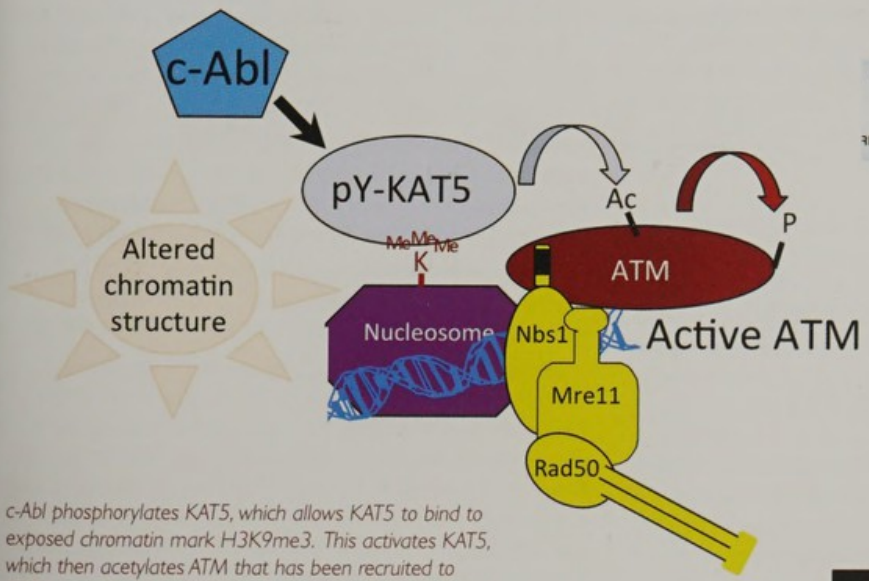
• Kaidi A and Jackson SP (2013) KAT5 tyrosine phosphorylation couples chromatin sensing to ATM checkpoint signalling. **Nature** 498, 70-74.

• Britton S, Coates J and Jackson SP (2013) A new method for high-resolution imaging of Ku foci to decipher mechanisms of DNA double-strand break repair. **Journal of Cell Biology** 202, 579-595.

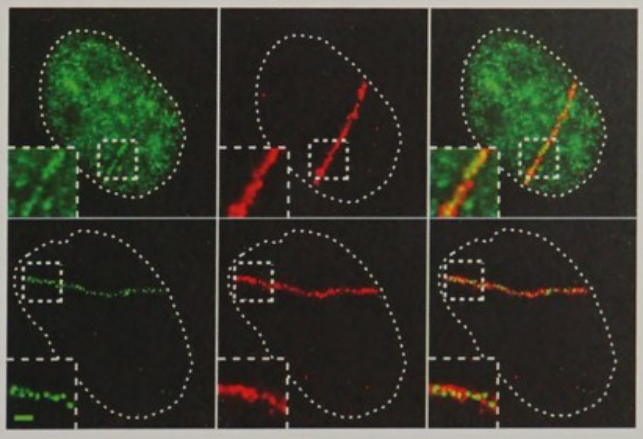
• Galanty Y, Belotserkovskaya R, Coates J and Jackson SP (2012) RNF4, a SUMO-targeted ubiquitin E3 ligase, promotes DNA double-strand break repair. **Genes Dev** 26, 1179-95

Protein dynamics to and from sites of DNA breaks. DNA damage checkpoint and repair factors and modulators of chromatin organisation are recruited (green arrows) to DNA breaks (SSB and DSB), while transcription machineries are excluded (red arrows), and the dynamics of structural chromatin components operate in both directions (orange arrows). HR, homologous recombination; NHEJ, non-homologous end joining. Taken from Polo SE and Jackson SP (2011) Dynamics of DNA damage response at DNA breaks: A focus on protein modifications. **Genes Dev** *25, 409-433*





c-Abl phosphorylates KAT5, which allows KAT5 to bind to exposed chromatin mark H3K9me3. This activates KAT5, which then acetylates ATM that has been recruited to DSB sites by the Mre11-Rad50-Nbs1 complex. ATM then autophosphorylates to become fully active and trigger DNA-damage signalling.



We have developed a new technique to visualise DNA repair proteins at sites of DNA breaks. Ku accumulation is shown at sites of laser micro irradiation (green). γH2AX (red) is used as a marker for DNA double-strand breaks.

Tony Kouzarides

Epigenetic modifications and cancer

Co-workers: Paulo Amaral, Andy Bannister, Isaia Barbieri, Ester Cannizzaro, Ka Hing (Harvey) Che, Ali Cook, Mark Dawson, Chun Yew Fong, Namshik Han, Sri Lestari, Valentina Migliori, Jessica Morison, Nikki Parsons, Sam Robson, Helena Santos Rosa, Peter Tessarz, Emmanuelle Vire, Meike Wiese, Beata Wyspianska

Our group is interested in defining the mechanisms by which modifications of chromatin and non-coding (nc) RNAs regulate cellular processes. Our attention is focused on enzymes which regulate transcription by covalently modifying histones or ncRNAs. We would like to understand what biological processes these enzymes control and the precise mechanism by which modifications act. At the same time we are dissecting how modification pathways are mis-regulated in cancer cells and exploring avenues for treatment.

Our recent work has identified two new modification pathways. The first involves methylation of miRNA145 by a new RNA modifying enzyme BCDN3D. This methylation disrupts the binding of miRNA145 to dicer and therefore controls miRNA maturation. The BCDN3D enzyme is an oncogene with pro-metastatic characteristics, indicating that this pathway may be therapeutically important. The second pathway involves a new class of chromatin modifying enzyme, which is able to methylate a glutamine residue within H2A. This modification is restricted to the rDNA locus and has a role in transcription by RNA polymerase I. In adidition, characterisation of arginine cirtrullination by the Padi4 enzyme, a modification we described some years ago, has revealed a role for this activity in pluripotency.

Our interest in the intervention of epigenetic pathways has identified the acetyl-binding BET proteins as a therapeutic target. A small molecule inhibitor of BETs (I-BET) was used to prevent the binding of BET proteins to acetylated histones and suppress a gene expression program leading to MLL-leukaemia. This small molecule effectively inhibits primary human leukaemias and halts the process of leukaemia in model systems. I-BET is currently in clinical trials.

Selected publications:

• Christophorou M, Castelo-Branco G, Halley-Stott R, Slade Oliveira C, Loos R, Bertone P, Silva J, Zernicka-Goetz M, Nielsen M, Gurdon JB, Radzisheuskaya A, Mowen K and Kouzarides T (2014) Citrullination regulates pluripotency and H1 linker histone binding to chromatin. **Nature** doi: 10.1038/nature12942

• Tessarz P, Santos-Rosa H, Robson SC, Sylvestersen KB, Nelson CJ, Nielsen ML and Kouzarides T (2013) Glutamine methylation in Histone H2A is an RNA Polymerase I dedicated modification. **Nature** doi:10.1038/nature12819

• Xhemalce B, Robson SC and Kouzarides T (2012) Human RNA methyltransferase BCDIN3D regulates microRNA processing. **Cell** 2012 Oct 12;151(2):278-88.

• Dawson MA, Prinjha RK, Dittmann A, Giotopoulos G, Bantscheff M, Chan WI, Robson SC, Chung CW, Hopf C, Savitski MM, Huthmacher C, Gudgin E, Lugo D, Beinke S, Chapman TD, Roberts EJ, Soden PE, Auger KR, Mirguet O, Doehner K, Delwel R, Burnett AK, Jeffrey P, Drewes G, Lee K, Huntly BJ and Kouzarides T (2011) Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. **Nature** 478(7370), 529-533

• Bartke T, Vermeulen M, Xhemalce B, Robson SC, Mann M and Kouzarides T (2010). Nucleosome-interacting Proteins Regulated by DNA and Histone Methylation. **Cell** 143: 470 – 84

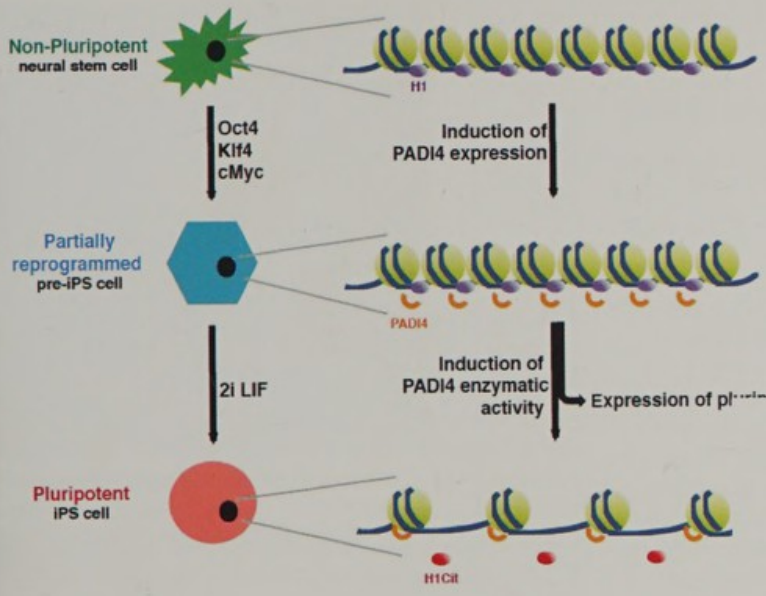


Fig 1 Citrullination by PADI4 regulates pleuripotency by causing chromatin de-compaction

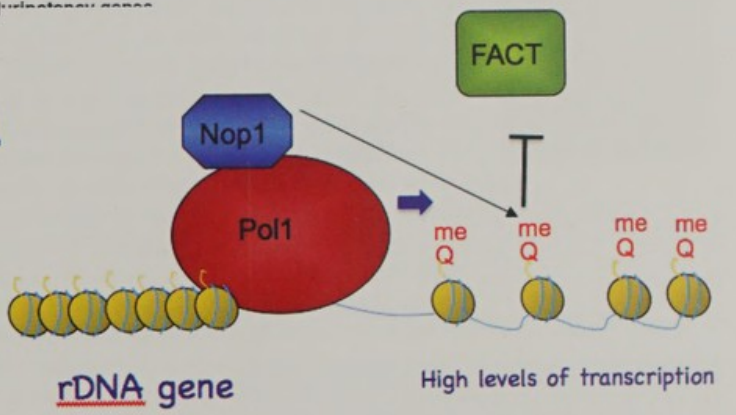


Fig 2 Glutamine methylation displeces the FACT complex and activates transcription by RNA polymerase I

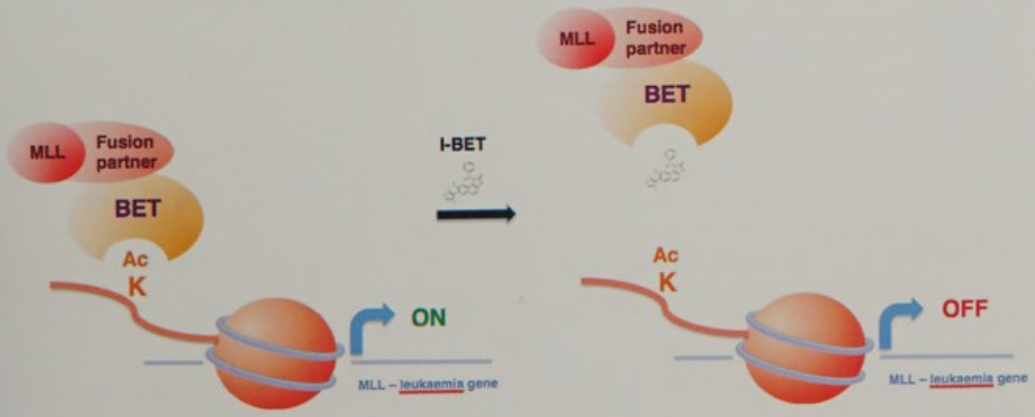


Fig 3 The small molecule I-BET displaces BET proteins and represses genes that cause MLL-leukaemia.

Rick Livesey

Mammalian neural stem cell biology, fundamental and applied

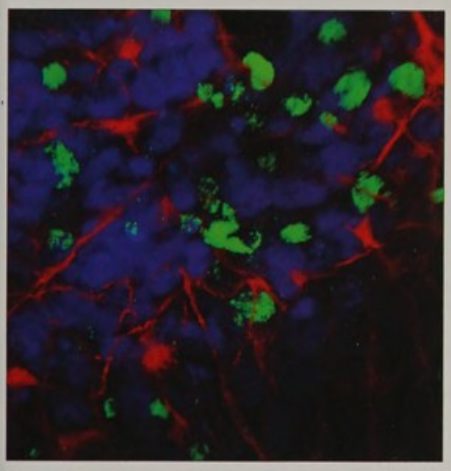
Co-workers: Thérèse Andersson, Roberta Cagnetta, Tatyana Dias, Macushla Hughes, Peter Kirwan, Teresa Krieger, Steven Moore, Tomoki Otani, Nathalie Saurat, Yichen Shi, James Smith, Selina Wray

The cerebral cortex, which makes up three quarters of the human brain, is the part of the nervous system that integrates sensations, executes decisions and is responsible for cognition and perception. Given its functional importance, it is not surprising that diseases of the cerebral cortex are major causes of morbidity and mortality. Understanding the biology of cortical neural stem cells is essential for understanding human evolution, the pathogenesis of human neurodevelopmental disorders and the rational design of neural repair strategies in adults. During embryonic development, all of the neurons in the cortex are generated from a complex population of multipotent stem and progenitor cells. Much of the research in the lab centres on the cell and molecular biology of cortical stem cells. We are particularly interested in the molecular mechanisms controlling multipotency, self-renewal and neurogenesis, and how these are coordinated to generate complex lineages in a fixed temporal order. A number of ongoing projects in the group address the functional importance of transcriptional and epigenetic mechanisms in this system.

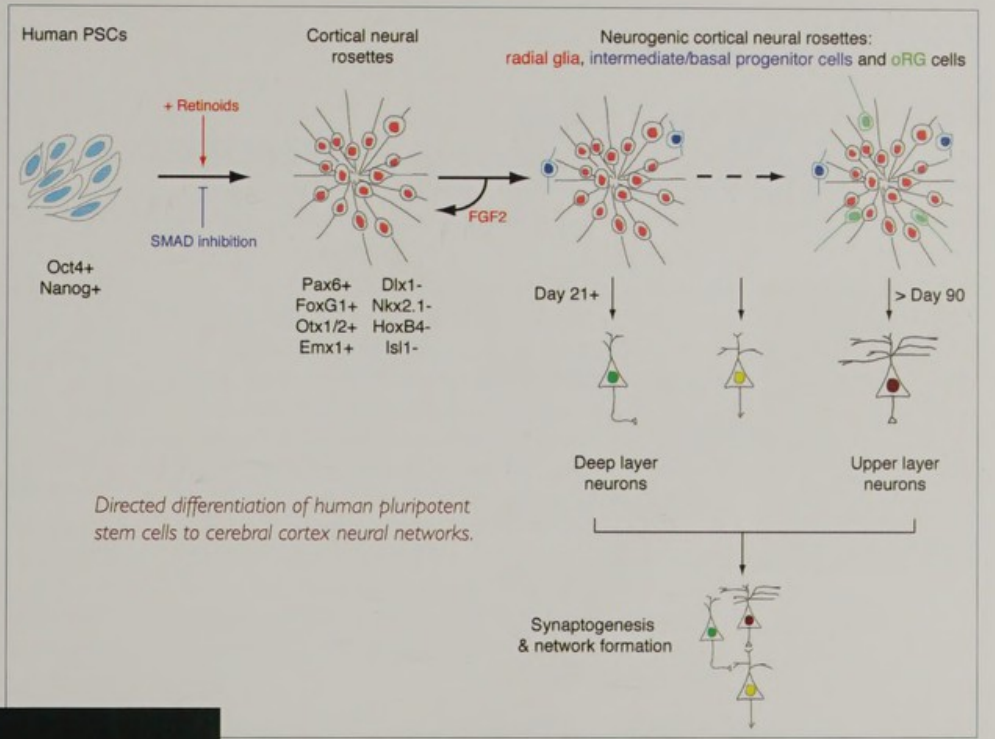
In the other major strand of research in the group, we have developed methods for directing differentiation of human pluripotent stem cells to cortical neurons, via a cortical stem cell stage. Human stem-cell-derived cortical neurons form functional networks of excitatory synapses in culture. We are using this system for studies of human neural stem cell biology and to generate models of cortical diseases. Our initial focus has been on dementia, where we have used stem cells from people with Down syndrome and from patients with familial Alzheimer's disease to create cell culture models of Alzheimer's disease pathogenesis in cortical neurons. We are using these models to study Alzheimer's disease pathogenesis and the efficacy of current therapeutic strategies.

Selected publications:

- **Livesey FJ** (2012) Stem cell models of Alzheimer's disease and related neurological disorders. Alzheimers Res Ther 4, 44
- Shi Y, Kirwan P and **Livesey FJ** (2012) Directed differentiation of human pluripotent stem cells to cerebral cortex neurons and neural networks. Nature Protocols 7, 1836-1846
- Shi Y, Kirwan P, Smith J, Maclean G, Orkin SH and **Livesey FJ** (2012) A human stem cell model of early Alzheimer's disease pathology in Down syndrome. Sci Transl Med 4, 124ra29
- Shi Y, Kirwan P, Smith J, Robinson HP and **Livesey FJ** (2012) Human cerebral cortex development from pluripotent stem cells to functional excitatory synapses. Nat Neurosci 15, 477-486
- Pereira JD, Sansom SN, Smith J, Dobenecker MW, Tarakhovsky A and Livesey FJ (2010) Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. Proc Natl Acad Sci USA 107, 15957-15962.



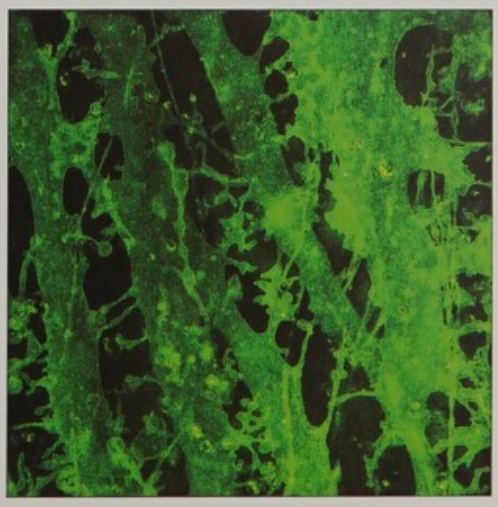
Extracellular aggregates (green) of the Alzheimer's disease pathogenic peptide Aβ42 in cultures of human cortical neurons generated from Down syndrome iPS cells.



Directed differentiation of human pluripotent stem cells to cerebral cortex neural networks.

Human cortical stem cells formed polarised neuroepithelial rosettes in culture, with centrosomes (red) located apically at the centre of the rosette.

Super-resolution microscopy image of DiO-labelled human iPS cell-derived cortical neurons



Eric Miska

Small regulatory RNA

Co-workers: Alper Akay, Alyson Ashe, Amy Cording, Miranda Landgraf, Jéremie le Pen, Nic Lehrbach, Milan Malinsky, Sylviane Moss, Kenneth Murfitt, Alexandra Sapetschnig, Peter Sarkies, Mélanie Tanguy, Eva-Maria Weick

microRNAs (miRNAs), a large class of short non-coding RNAs found in many plants and animals, often act to inhibit gene expression post-transcriptionally. Approximately 3% of all known human genes encode miRNAs. Important functions for miRNAs in animal development and physiology are emerging. A number of miRNAs have been directly implicated in human disease. We have generated loss-of-function mutations in almost all of the 112 known miRNA genes in the nematode *Caenorhabditis elegans*. This collection provides the only comprehensive resource for the genetic analysis of individual miRNAs to date. Our main goal is to understand the genetic networks underlying miRNA-dependent control of development.

We are also studying other short RNA (sRNA) species, their biology and mechanism of action. For example, we recently identified the piRNAs of *C elegans*. piRNAs are required for germline development and maintenance in worms, flies and mammals. Neither the biogenesis nor the mechanism of action is understood for this class of small RNAs. We are using genetic screens, biochemical and molecular biology approaches to address basic questions about sRNA biology. Of particular interest is how small RNA regulatory networks interact with the genome and the environment.

In addition, we have developed tools for the analysis of miRNA expression in human disease and have discovered miRNAs that have potential as molecular markers for diagnosis and prognosis.

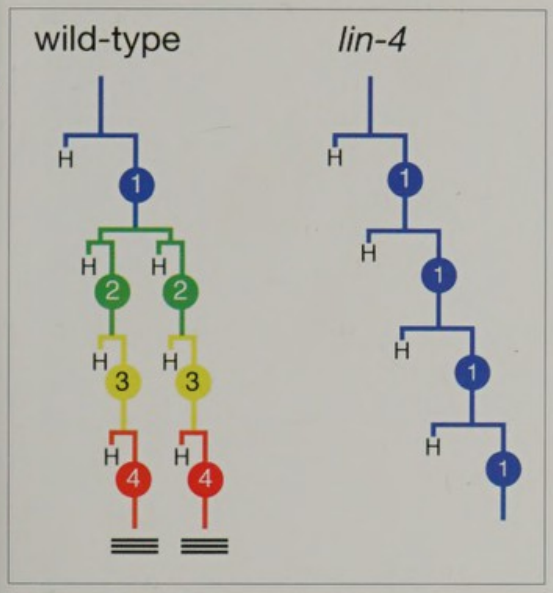
Selected publications:

• Ashe A, Bélicard T, Le Pen J, Sarkies P, Frézal L, Lehrbach NJ, Félix MA, **Miska EA** (2013) A deletion polymorphism in the *Caenorhabditis elegans* RIG-I homolog disables viral RNA dicing and antiviral immunity. E-Life 2:e00994

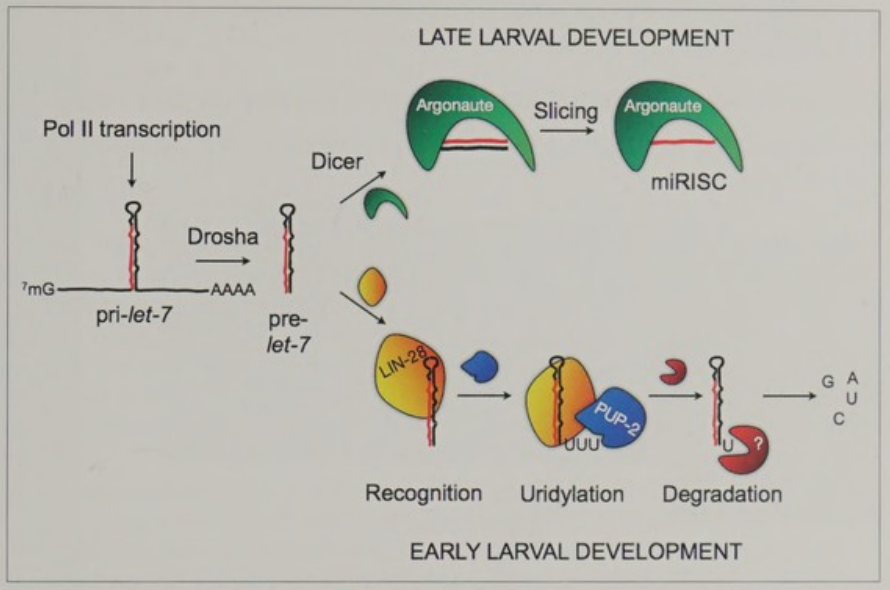
• Sarkies P and **Miska EA** (2012) Molecular biology. Is there social RNA? Science 341(6145), 467 - 468

• Ashe A, Sapetschnig A, Weick EM, Mitchell J, Bagijn MP, Cording AC, Doebley AL, Goldstein LD, Lehrbach NJ, Le Pen J, Pintacuda G, Sakaguchi A, Sarkies P, Ahmed S and **Miska EA** (2012) piRNAs can trigger a multigenerational epigenetic memory in the germline of *C. elegans*. Cell 150, 88-99

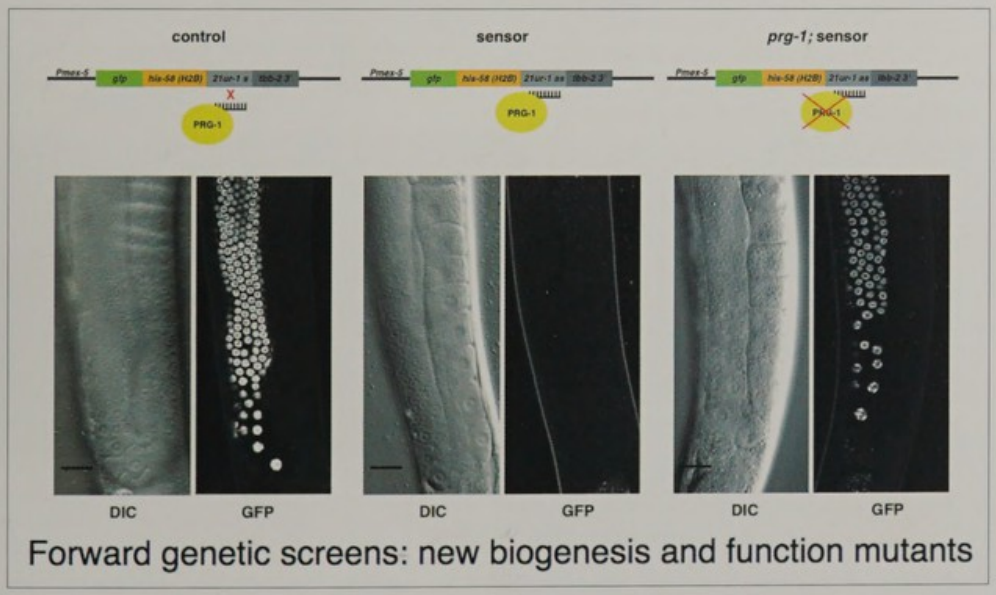
• Bagijn MP, Goldstein LD, Sapetschnig A, Weick EM, Bouasker S, Lehrbach NJ, Simard MJ and **Miska EA** (2012) Function, targets, and evolution of *Caenorhabditis elegans* piRNAs. Science 337, 574 - 578



The first miRNA to be identified was the product of the C elegans gene lin-4. Loss of function of ***lin-4*** *leads to the failure of a stem cell lineage to differentiate.*



We have discovered that let-7, LIN-28 and the poly(U) polymerase form an ultraconserved switch that regulates stem cell decisions in C elegans



An in-vivo assay for piRNA function in the germline. piRNAs and Piwi proteins protect the germline. We are using molecular genetics, cell biology and high-throughput sequencing to discover miRNA biogenesis and mechanisms.

Eugenia Piddini

Competitive cell interactions in normal physiology and cancer

Co-workers: Adam Benabid, Maja Goschorska, Lea Hampton-O'Neil, Golnar Kolahgar, Iwo Kucinski, Kathy Oswald, Saskia Suijkerbuijk, Silvia Vivarelli, Laura Wagstaff

The elimination of suboptimal cells from tissues is an important process that helps preserve tissue integrity and function. Cell competition is a quality control mechanism that achieves exactly that: when suboptimal cells are present they are recognised by surrounding fitter cells, which eliminate them through competition. Much of the work in our lab focuses on investigating the mechanisms and the physiological role of this phenomenon.

The molecular mechanisms of cell competition are not well understood. In particular it is currently unknown how weaker cells are recognised so that cell competition can be initiated. Our lab is currently tackling this question using both *Drosophila in vivo* models and mammalian *in vitro* models of cell competition. Through transcriptional profiling we have identified a molecular signature common to cells that are normally outcompeted and are currently investigating its significance.

Cell competition has been studied mostly in developing tissues and currently it is little explored to what extent this phenomenon is relevant to adult tissues. This would have important implications, as selection of fitter cells during adult tissue maintenance could lead to improved health and slower tissue ageing. Our model system for these studies is the adult *Drosophila* gut, a simple epithelial layer with high cellular turnover, maintained by a pool of stem cells. Recently, we found that in adult tissues weaker cells are detected and eliminated through apoptosis, while fitter cells increase their tissue colonisation properties, through an increase in their proliferation rate and self-renewal capacity.

In addition the lab investigates the role of cell competition in cancer. Indeed it has been suggested that precancerous cells could act as supercompetitors and kill surrounding normal cells. For these purposes we use a fly model of adult intestinal adenoma, as well as human cancer cell lines.

Selected publications:

• Wagstaff L, Kolahgar G and Piddini E (2013) Competitive cell interactions in cancer: a cellular tug of war. **Trends in Cell Biology** 23(4):160-167

• Vivarelli S, Wagstaff L and Piddini E (2012) Cell wars: regulation of cell survival and proliferation by cell competition. (Review) **Essays Biochem** 10;53(1):69-82

• Vincent JP*, Kolahgar G, Gagliardi M and Piddini E* (2011) Steep differences in Wingless signalling trigger Myc-independent competitive cell interactions. **Dev Cell** 21, 366-374 * Corresponding authors

• Piddini E and Vincent JP (2009) Interpretation of the Wingless gradient requires signalling-induced self-inhibition. **Cell** 136, 296-307

• Hogan C, Dupré-Crochet S, Norman M, Kajita M, Zimmermann C, Pelling AE, Piddini E, Baena-López LA, Vincent JP, Itoh Y, Hosoya H, Pichaud F, Fujita Y (2009) Characterisation of the interface between normal and transformed epithelial cells. **Nat Cell Biol** 11(4):460-7

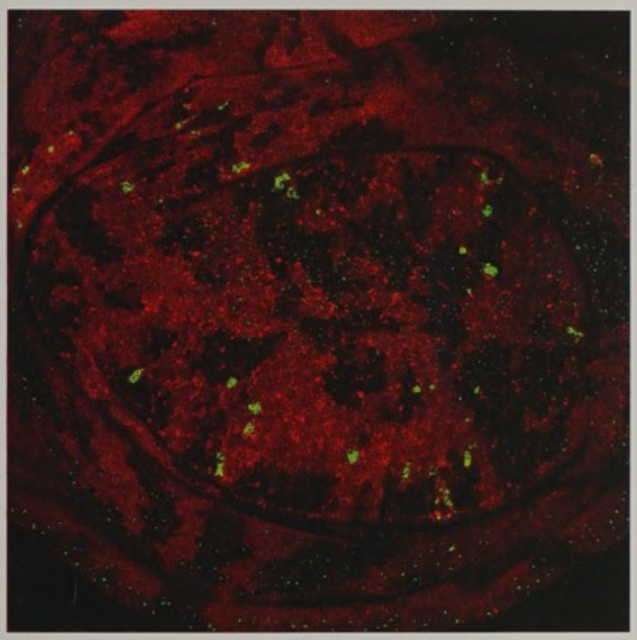


Figure 1: Cell competition in wing imaginal discs. Minute mutant cells (red) are outcompeted by fitter wild-type cells and become apoptotic (green).

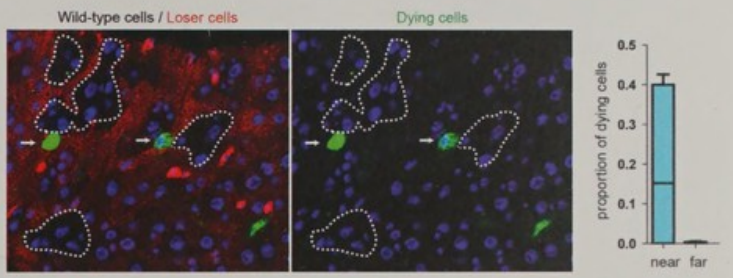


Figure 2: Minute mutant cells are outcompeted by fitter wild-type cells in the adult fly intestine. Minute cells (labelled in red) display increased apoptosis (marked in green), if they are in proximity of fitter wild type clones. Right: quantification of apoptosis frequency in Minute cells next to or far away from wild-type clones.

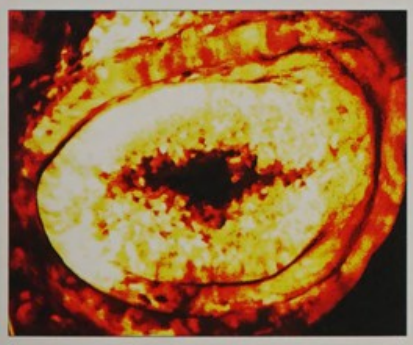


Figure 3: A wing imaginal disc showing expression of a gene upregulated in Minute cells.

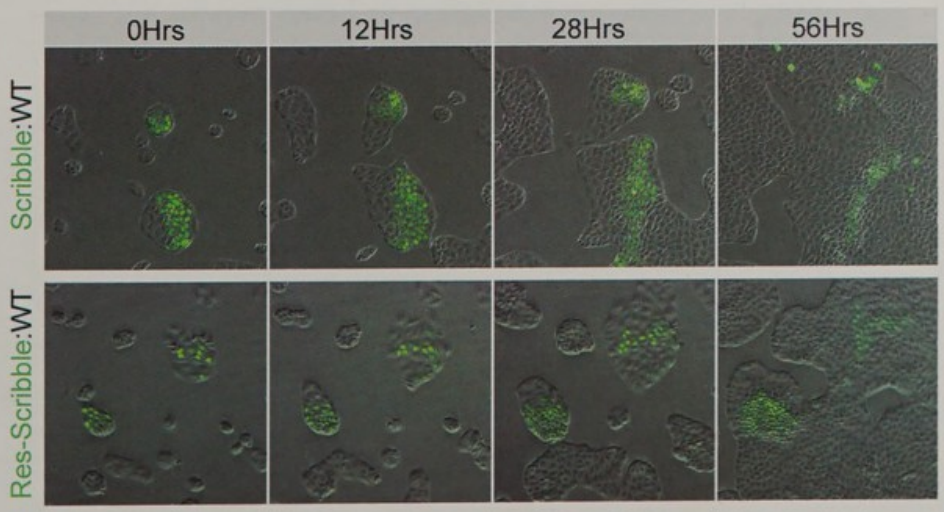


Figure 4: Scribble deficient cells, labelled in green, are outcompeted (top). We have isolated a population of Scribble deficient cells that instead is resistant to cell competition (bottom).

Jonathon Pines

How do cells control mitosis?

Co-workers: Philippe Collin, Barbara Di Fiore, Anja Hagting, Daisuke Izawa, Mark Jackman, Agata Lichawska, Paola Marco Casanova, Chiara Marcozzi, Takahiro Matsusaka, Oxana Nashchekina, Bernhard Strauss, Jill Temple, Samuel Wieser, Claudia Wurzenberger

How do cells regulate entry to mitosis? And, once in mitosis, how do cells coordinate chromosome segregation with cell separation to ensure that the two daughter cells receive an equal and identical copy of the genome? The answers to both questions lie in the interplay between protein kinases, protein phosphatases, and APC/C-mediated proteolysis; this is the focus of our research. To understand the rapid and complex dynamics of mitosis it is essential to do this in living cells, complemented by biochemical analyses. Our recent innovation is to introduce fluorescent tags into the genes encoding our proteins of interest by homologous recombination; this enables us to measure protein numbers and kinetics *in vivo*, which we can use to inform molecular models.

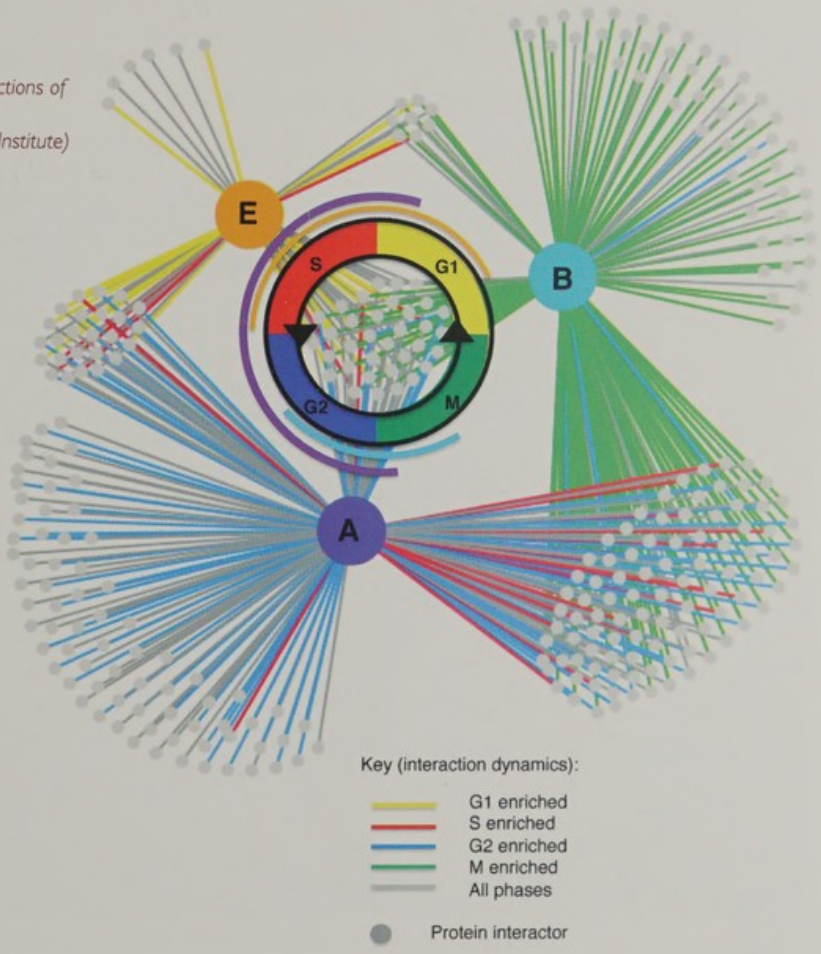
To understand how cells trigger mitosis we are analysing the behaviour of the key mitotic kinases and their regulators. We developed a FRET biosensor to assay the dominant mitotic kinase, Cyclin B1-Cdk1, *in vivo* and are using this to define the pathways that regulate the timing of mitosis. To identify the proteins responsible for regulating the Cyclin-Cdks, and provide insights into Cyclin-Cdk substrates, we have analysed protein complexes through the cell cycle by SILAC mass spectrometry and are following up some of the exciting results from this screen.

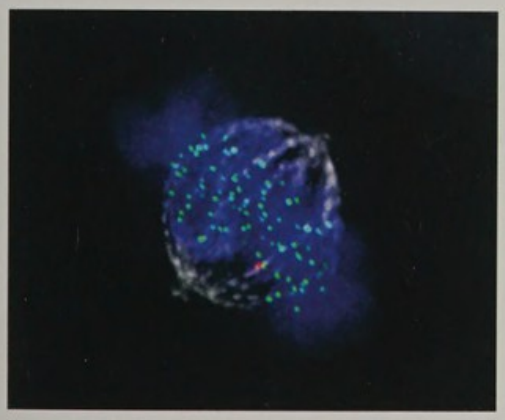
To understand how proteolysis regulates progress through mitosis we complement the analysis of APC/C-dependent degradation in living cells with biochemical analyses of protein complexes and ubiquitination activity. These studies are revealing how the APC/C is activated and how it is able to select a particular protein for destruction at a specific time. The intimate coupling of the APC/C with the spindle assembly checkpoint that is essential to regulate chromosome segregation has meant that our recent work has elucidated the mechanisms that control some of the key steps in the checkpoint pathway.

Selected publications:

- Collin P, Nashchekina O, Walker R and Pines J (2013) The spindle assembly checkpoint works like a rheostat not a toggle-switch **Nat. Cell Biol.** 15, 1378-1385
- Izawa D and Pines J (2012) Mad2 and the APC/C compete for the same site on Cdc20 to ensure proper chromosome segregation. **J Cell Biol** 199, 27-37
- Mansfeld J, Collin P, Collins MO, Choudhary J and Pines J (2011) APC15 drives the turnover of MCC-Cdc20 to make the spindle assembly checkpoint responsive to kinetochore attachment. **Nat Cell Biol** 13, 1234-1244.
- Pagliuca F, Collins MO, Lichawska A, Zegerman P, Choudhary JS and Pines J (2011) Quantitative proteomics reveals the basis for the biochemical specificity of the cell cycle machinery. **Mol Cell** 43, 406-417.
- Gavet O and Pines J (2010) Progressive activation of Cyclin B1-Cdk1 coordinates entry to mitosis. **Dev Cell** 18, 533-543.
- Nilsson J, Yekezare M, Minshull J and Pines J (2008) The APC/C maintains the spindle assembly checkpoint by targeting Cdc20 for destruction. **Nat Cell Biol** 10, 1411-1420

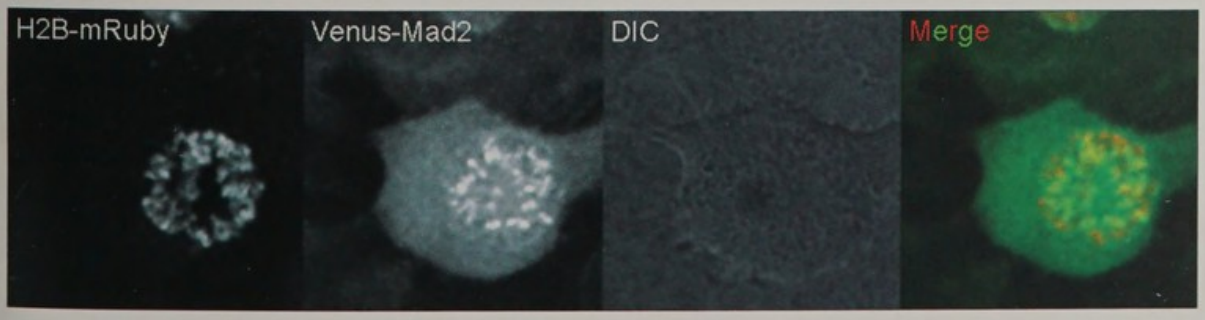
Mass spectroscopy analysis reveals the dynamic interactions of the different cyclins through the cell cycle.
Credit: Felicia Walton-Pagliuca & Mark Collins (Sanger Institute)





Mitotic RPE-1 cell with a single unattached chromosome. Mad2 in red, Hec1 in green, DNA in blue and spindle MTs in white. (Philippe Collin)

Montage of a prometaphase cell in which the Venus fluorescent protein has been knocked into the Mad2 locus. Mad2 binds to unattached kinetochores.The chromosomes are labelled with ectopically expressed Histone H2B-mRuby. (Philippe Collin)



Emma Rawlins

Stem and progenitor cells in the mammalian lung

Co-workers: Gayan Balasooriya, Christoph Budjan, Angelene Huffman, Jo-Anne Johnson, Usua Laresgoiti Garay, Marco Nikolic, Chandrika Rao

Our lungs have a complex three-dimensional structure which facilitates respiration and host defence. Building this structure requires that lung embryonic progenitor cells produce the correct types and numbers of cells in the correct sequence. How is this controlled? And how is the final structure maintained in the adult? Our lab investigates the cellular and molecular mechanisms which control stem and progenitor cell fate decisions in the developing and adult lungs. Key unanswered questions include what mechanisms control the decision of lung progenitors to self-renew or to differentiate? Which pathways are required for cell lineage specification in the lung? Our approach is to use the power of mouse genetics to understand the control of lung progenitor cell behaviour at the single cell level. This allows individual cells to be analysed quantitatively *in vivo*, or by live-imaging in organ culture systems.

We have previously shown that in the embryonic lung there is a population of Id2+ multipotent epithelial progenitor cells located at the distal tips of the budding epithelium. The developmental potential, or competence, of these cells changes during embryogenesis. At the same time the cells undergo a change in gene expression pattern. We are currently exploring the cellular and molecular basis of this change in competence.

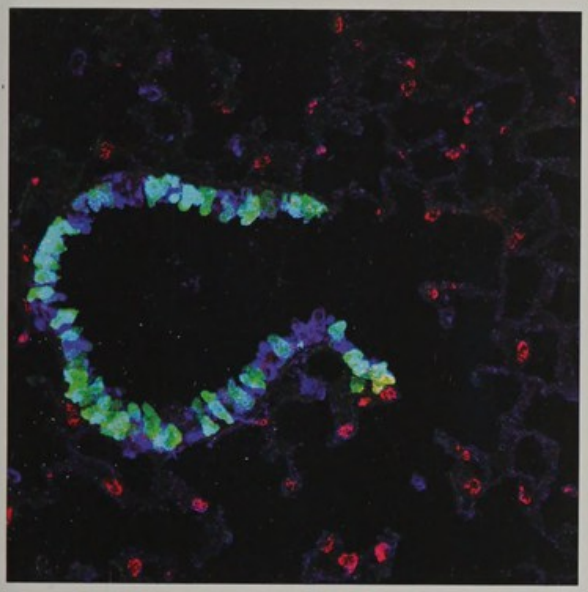
The identity of the epithelial stem and progenitor cells in the postnatal lung remains controversial. Our previous work has shown that each anatomical region (trachea, bronchioles, alveoli) has its own progenitor cell population and that the behaviour of these progenitors can change in response to local conditions. Our current postnatal work focuses on:

- Better characterising the adult lung progenitor cells. This includes testing whether progenitor cell behaviour is widespread or there are stem cells.
- Understanding the genetic regulation of the progenitors under several different physiologically-relevant conditions. In particular, we are focusing on genes that are hypothesised to control the decision to self-renew or differentiate.

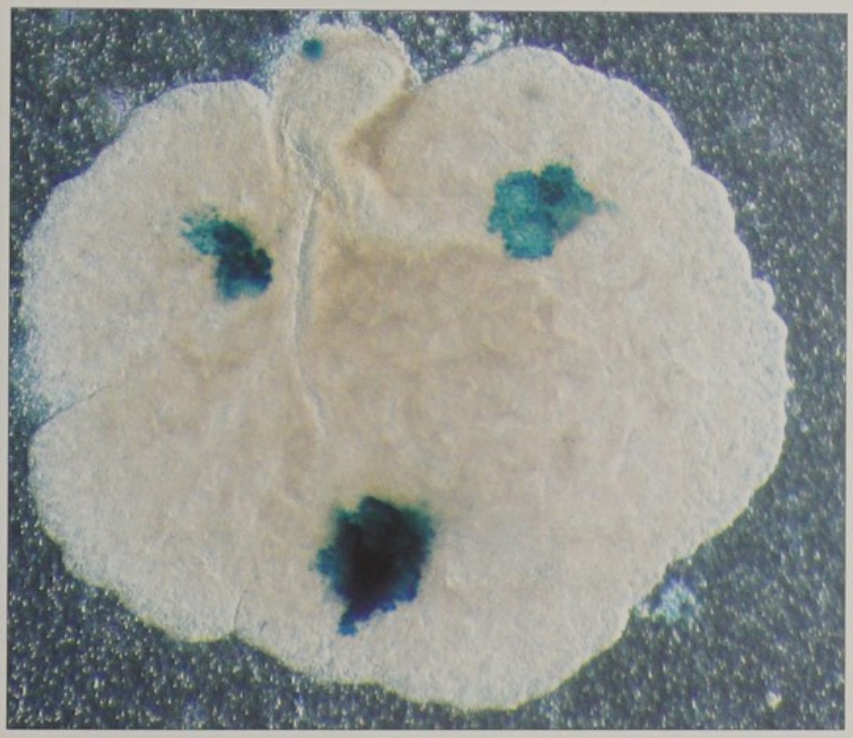
Our long-term vision is to combine the developmental and homeostatic aspects of our work to develop new approaches to ameliorate human pulmonary disease. In particular, we are working towards being able specifically to direct endogenous lung stem cells to generate any lung epithelial cell type.

Selected publications:

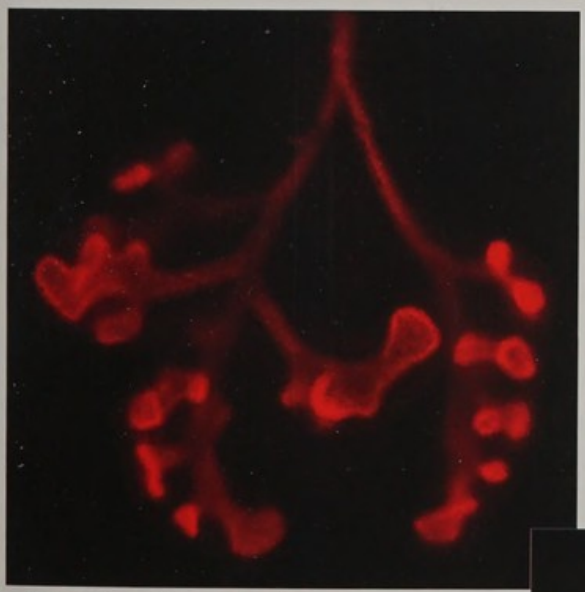
- Rawlins EL (2011) The building blocks of mammalian lung development. Developmental Dynamics 240 463-76
- Onaitis M, D'Amico TA, Clark C, Guinney J, Harpole DH and Rawlins EL (2011) A 10-gene progenitor cell signature predicts prognosis in lung adenocarcinoma. Annals of Thoracic Surgery 91 1046-50
- Rawlins EL, Okubo T, Xue Y, Brass DM, Auten RL, Hasegawa H, Wang F and Hogan BLM (2009) The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. Cell Stem Cell 4 525-534
- Rawlins EL, Clark CP, Xue Y and Hogan BLM (2009) The Id2 distal tip lung epithelium contains individual multipotent embryonic progenitor cells. Development 136 3741-3745



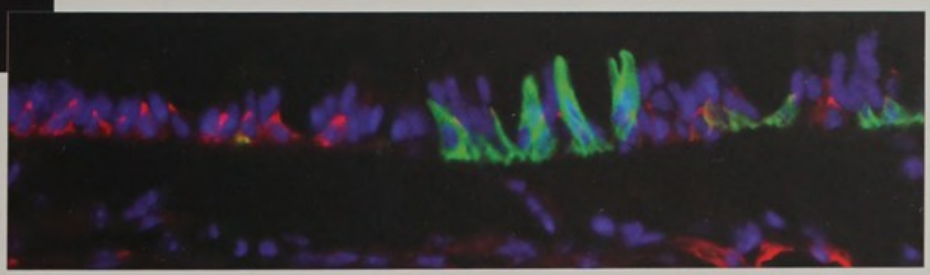
Adult mouse lung section showing lineage-labelled secretory cells (green) in the conducting airways.



Mouse embryonic lung growing in culture. Blue (X-gal staining) shows grafted stem cells which have been incorporated into the lung structure.



Mouse embryonic lung undergoing branching morphogenesis, stained to show the epithelium (E-cadherin).



A clone of mutant tracheal epithelial cells labelled with GFP (green).

Ben Simons

Patterns of stem cell fate in adult and developing tissues

Co-workers: Teresa Krieger

The coordination of cell proliferation and fate specification is central to the development and maintenance of tissues. In development, systems must be tightly-regulated to ensure that precise numbers of lineage-specified cells are generated in the correct sequence whilst, in adult, a delicate balance between proliferation and differentiation is essential for homeostasis. Through a programme of interdisciplinary and collaborative research, our group is interested in establishing unifying principles of stem cell regulation in the development and maintenance of tissues, and to use them to resolve pathways leading to dysregulation in diseased states.

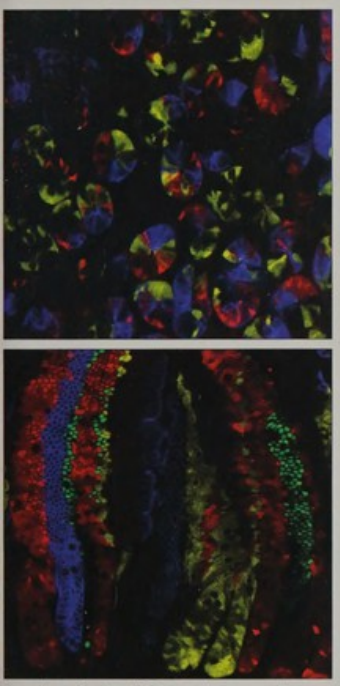
Theories of tissue maintenance place stem cells at the apex of proliferative hierarchies, possessing the lifetime property of self-renewal. In homeostasis the number of stem cells remains fixed imposing an absolute requirement for fate asymmetry in the daughters of dividing cells, such that only half are retained. Fate asymmetry can be achieved either by being the invariant result of every division or by being orchestrated from the whole population, where cell fate following stem cell division is specified only up to some probability. These alternative models suggest different mechanisms of fate regulation, yet their identification in most tissues has remained elusive.

By drawing upon concepts from physics and mathematics, we have shown that strategies of stem cell self-renewal can be classified according to whether fate is specified by internal or extrinsic factors, and whether it leads to invariant asymmetric self-renewal or population asymmetry. As well as achieving a functional classification of stem cell types, this identification provides a general framework that we are using to interpret lineage tracing data. To develop this programme, we are involved in multiple collaborations, addressing different tissue types from epidermis and gut, to retina and germline. Current collaborators include Cedric Blanpain, Hans Clevers, Philip Jones, Emma Rawlins, Shosei Yoshida, and Jochen Wittbrodt.

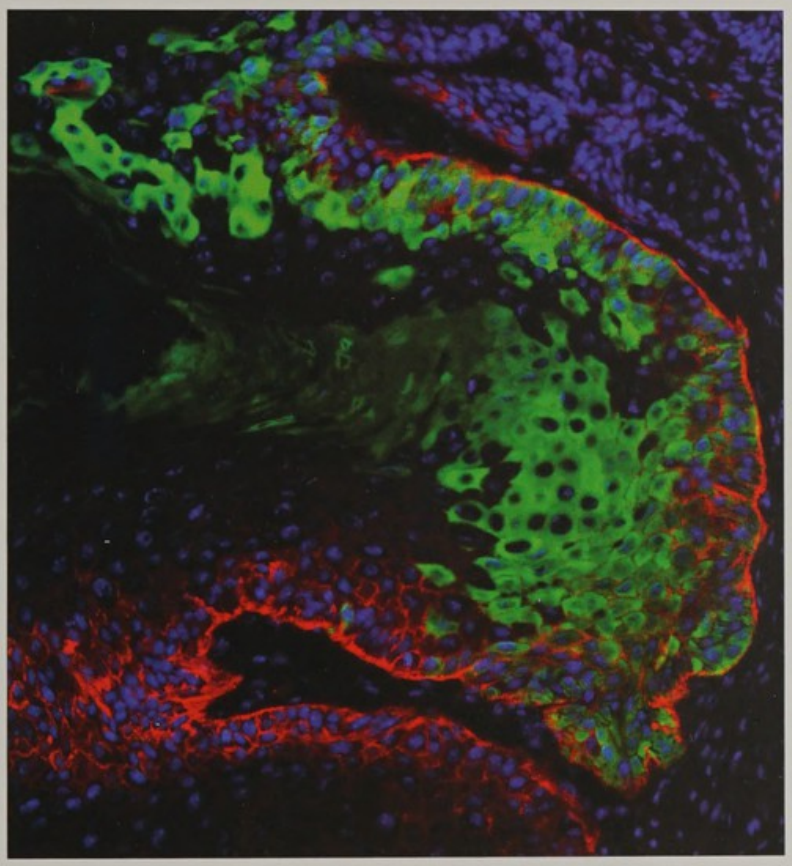
In a related programme, we are also using lineage tracing methodologies to elucidate patterns of progenitor cell fate in the late-stage development of tissues. Current collaborators include Rick Livesey and Magdalena Zernicka-Goetz (cortex), Cedric Blanpain (prostate and heart), Bill Harris and Michel Cayouette (retina), and Fiona Watt (dermis). Finally, we are also making use of lineage-tracing methods to investigate how stem and progenitor cells become subverted in tumour-initiation. Current collaborators include Hans Clevers (intestinal adenomas), Cedric Blanpain and Philip Jones (skin tumours), and Tony Green (leukaemia).

Selected publications:

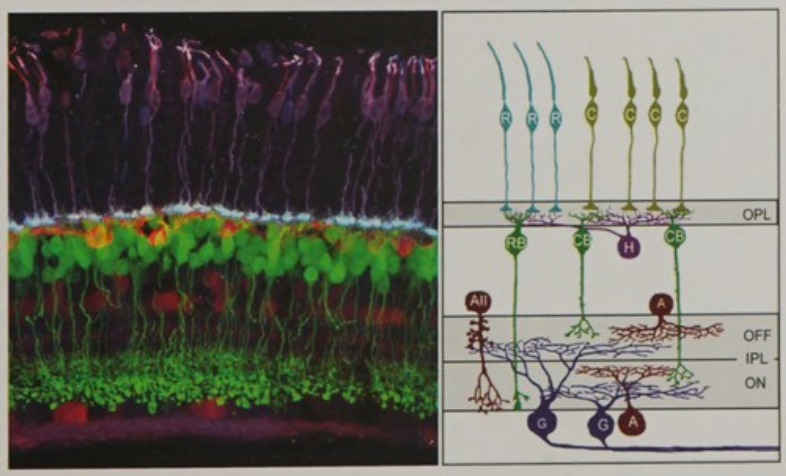
- Mascre G, Dekoninck S, Drogat B, Youssef KK, Brohee S, Sotiropoulou PA, Simons BD and Blanpain C (2012) Distinct contribution of stem and progenitor cells to epidermal maintenance. Nature 489, 257-62
- Driessens G, Beck B, Caauwe A, Simons BD and Blanpain C (2012) Defining the mode of tumour growth by clonal analysis. Nature 488, 527-30
- Doupé DP, Alcolea MP, Roshan A, Zhang G, Klein AM, Simons BD and Jones PH (2012) A single progenitor population switches behavior to maintain and repair esophageal epithelium. Science 337, 1091-3
- Simons BD and Clevers H (2011) Strategies for homeostatic stem cell self-renewal in adult tissues. Cell 145, 851-62
- Snippert HJ, van der Flier LG, Sato T, van Es JH, van den Born M, Kroon-Veenboer C, Barker N, Klein AM, van Rheenen J, Simons BD and Clevers H (2010) Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell 143, 134-144



Studies of clonal fate using a multi-colour inducible genetic labelling system provide a vivid demonstration of neutral drift dynamics and the progession towards monoclonality in crypt. The top image shows a section through the base of the crypt showing the clonal progeny of the stem/paneth cell compartment at 7 days post-induction. The bottom image shows the migration streams of differentiated cells moving up (fully-clonal crypts) and onto villi.



Inducible genetic labelling allows the fate of progenitor cells and their progeny to be traced in epidermis both in normal and diseased states. The figure shows the progeny of a GFP labelled cell in a squamous tumour in mouse. Such lineage tracing assays allows for the in vivo characterisation of the tumour-initiating potential of tumour cells, and the study of the progression from benign papilloma to invasive squamous carcinoma.



Lineage-tracing studies show that mechanisms of stochastic stem cell fate play a central role in the homeostasis of adult tissues. However, it remains unclear whether such patterns of fate play a role in the development of tissue. Currently, we are working with experimentalists to resolve the pattern of progenitor cell fate in retina, where retinal precursors must coordinate to give rise to multiple differentiated cell types.

Daniel St Johnston

The control of cell polarity in eggs and epithelia

Co-workers: Dan Bergstralh, Jia Chen, Hélène Doerflinger, Artur Fernandes, Weronika Fic, Jackie Hall, Timm Haack, Holly Lovegrove, Nick Lowe, Avik Mukherjee, Dmitry Nashchekin, Aram Sayadian, Vanessa Stefanak, Vitor Trovisco, Helen Zenner

Cell polarity is essential for normal cell function and for several key developmental processes, such as cell migration, axis determination and asymmetric stem cell divisions, whereas loss of polarity is a critical step in the formation of tumours. We are using *Drosophila* and mammalian tissue culture cells to analyse how polarity arises and how cortical polarity factors regulate other polarised aspects of cell behaviour.

Most organs in the body are composed of epithelial cells that are polarised along their apical-basal axes so that they can adhere to each other to form sheets of cells that act as barriers between compartments. We use the follicular epithelium that surrounds the developing *Drosophila* egg chamber as a model secretory epithelium, because it can be imaged along its apical-basal axis and is continuously generated from stem cells, making it easy to produce mutant clones in the adult. We are investigating how apical-basal polarity is established and how polarity factors control polarised secretion and the organisation of the microtubule cytoskeleton. For example, we are analysing how the mitotic spindle is oriented in epithelia to ensure that both daughter cells remain within epithelium, as mis-oriented spindles have been proposed to contribute to tumour development. Almost all well-characterised epithelia are secretory, and we are also using the adult midgut as a model for an absorptive epithelium. We have found that the polarity of midgut cells relies on different polarity factors from secretory epithelia, and are now investigating how this relates to their inverted arrangement of intercellular junctions.

Another major goal of the group is to understand how the *Drosophila* oocyte is polarised to define the anterior-posterior axis of the embryo. This requires the microtubule-dependent transport of bicoid and oskar mRNAs to opposite ends of this very large cell, and we are using a range of live imaging techniques to visualise moving mRNA particles and growing microtubules in wildtype and mutant oocytes.

Selected publications:

- Morais-de-Sa E, Vega-Rioja A, Trovisco V and St Johnston D (2013) Oskar is targeted for degradation by the sequential action of Par-1, GSK-3, and the SCF-Slimb ubiquitin ligase. **Developmental Cell** 26: 303-314
- Bergstralh DT, Lovegrove HE and St Johnston D (2013) Discs large links spindle orientation to apical-basal polarity in *Drosophila* epithelia. **Current Biology** 23: 1707-1712
- Haack T, Bergstralh DT and St Johnston D (2013) Damage to the *Drosophila* follicle cell epithelium produces "false clones" with apparent polarity phenotypes. **Biology Open** 2: 1313-1320
- St Johnston D (2013) Using mutants, knockdowns, and transgenesis to investigate gene function in *Drosophila*. **Wiley Interdisciplinary Reviews Developmental Biology** 2: 587-613
- Bergstralh DT, Haack T and St Johnston D (2013) Epithelial polarity and spindle orientation: intersecting pathways. **Philosophical Transactions of the Royal Society of London** 368: 20130291
- Zhao T, Graham O, Raposo A and St Johnston D (2012) Growing microtubules push the oocyte nucleus to polarize the *Drosophila* dorsal-ventral axis. **Science**, 336, 999-1003.

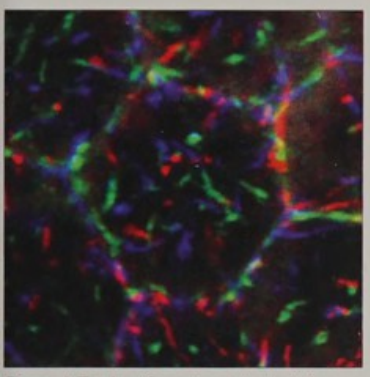


Figure 1. Tracks of growing microtubules on the apical side of the follicular epithelium over a two minute period

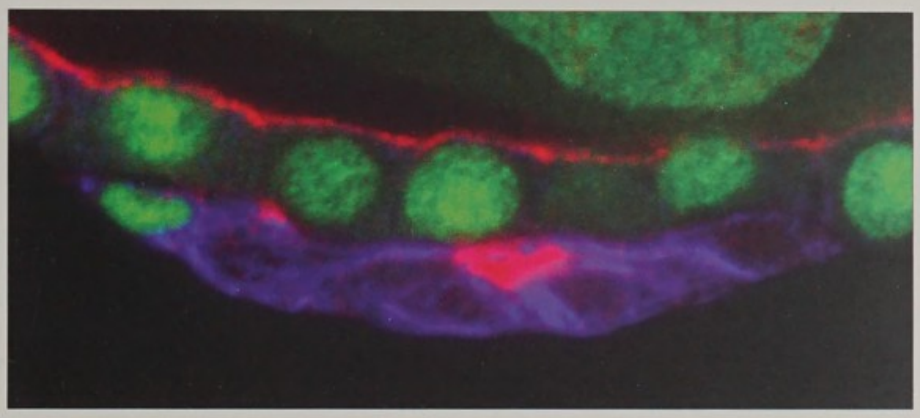


Figure 2. A clone of mutant follicle cells (marked by the loss of nuclear GFP) that have lost their apical-basal polarity and been extruded from the basal side of the epithelium.

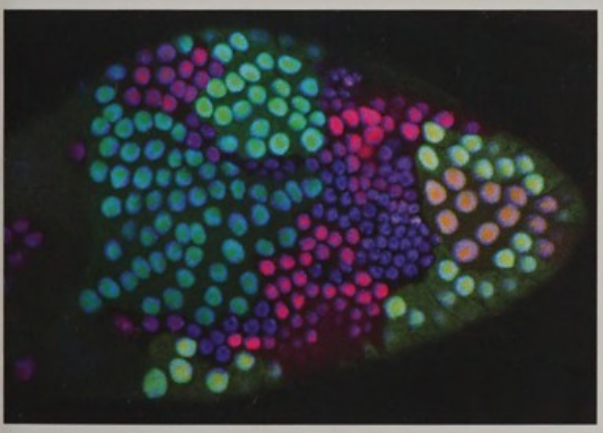


Figure 3. An egg chamber containing two types of follicle cell clones homozygous for mutations that delay the switch between proliferation and differentiation. One class of clones is marked by the loss GFP (green), the other by the loss of RFP (red) and the nuclei have been counterstained for DNA (blue). The two mutations are additive as the cells in the double mutant clones (blue only) are smaller than either single mutant.

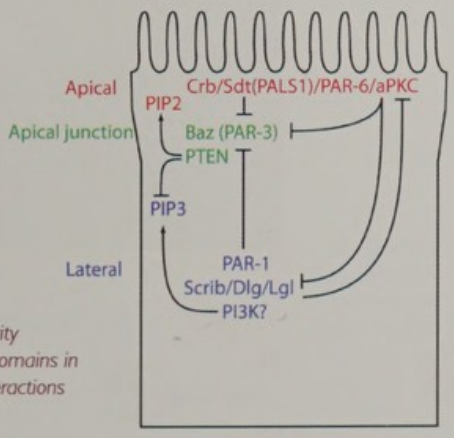


Figure 4. A model showing the polarity factors that mark different cortical domains in epithelial cells and the inhibitory interactions between them.

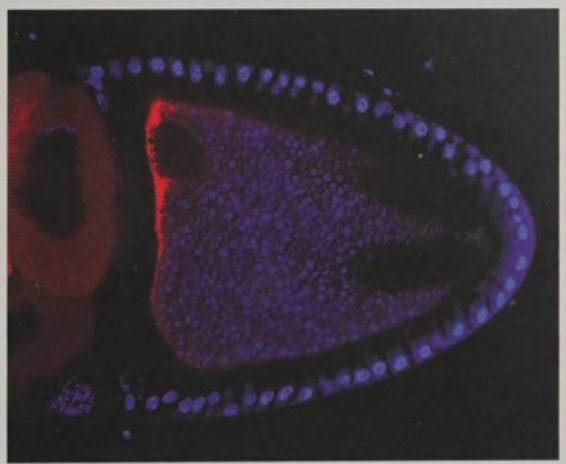
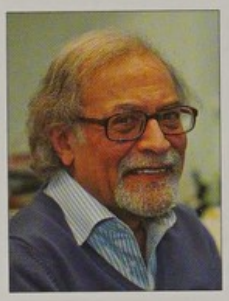


Figure 5. A stage 10 egg chamber expressing a marker for the microtubule minus ends fused to Cherry fluorescent protein (red), counterstained for DNA (blue). The minus ends of the microtubules are anchored to the anterior cortex of the oocyte and direct the localisation of bicoid mRNA.

Azim Surani

Germline - specification and programming for totipotency and development

Co-workers: Delphine Cougot, Dang Vinh Do, Lynn Froggett, Wolfram Gruhn, Ufük Günesdogan, Jamie Hackett, Yun Huang, Naoko Irie, Elena Itskovich, Shinseog Kim, Toshihiro Kobayashi, Caroline Lee, Roopsha Sengupta, Walfred Tang, Thor Theunissen, Julia Tischler, Mark Ziats, Jan Zylicz



Specification of primordial germ cells (PGCs) occurs after the development of equipotent post implantation epiblast cells, which also give rise to all the somatic cells in mice. Recent studies show that that BLIMP1, PRDM14 and AP2γ are necessary and sufficient for PGC specification (Fig 1). This mutually interdependent tripartite genetic network initiates PGC specification by repressing the somatic programme but induces pluripotency genes and the germ cell programme (Fig 2). These events can be captured *in vitro* under specific conditions after they undergo priming and gain competence for the specification of cell fates. The network also initiates sequential and dynamic changes in histone modifications, reactivation of the X chromosome and comprehensive global DNA demethylation, including imprints erasure (Fig 3). The latter is important for the initiation of the imprinting cycle in the germ line, and subsequently, establishment of parent of origin specific imprints (Fig 4). The inheritance of these epigenetic modifications after fertilisation results in functional differences between parental genomes, which following fertilisation is critical for the establishment of totipotency. We are interested in the wider applications of the knowledge gained from the specification of PGCs and epigenetic reprogramming for the manipulation of pluripotent state and cell fates

Selected publications:

• Magnusdottir E, Dietmann S, Murakami K, Gunesdogan U, Tang F, Bao S, Diamanti E, Lao K, Gottens B, Surani MA (2013) A tripartite transcription factor network regulates primordial germ cell specification in mice. Nature Cell Biology 15, 906-915

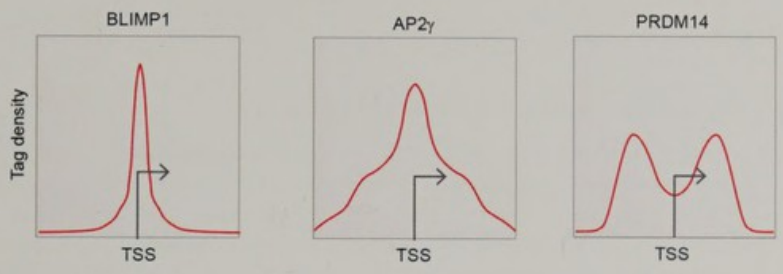
• Hackett JA, Sengupta R, Zylicz JJ, Murakami K, Lee C, Down TA and Surani MA (2012) Germline DNA demethylation dynamics and imprint erasure through 5-hydoxymethylcytosine. Science 339, 448-452

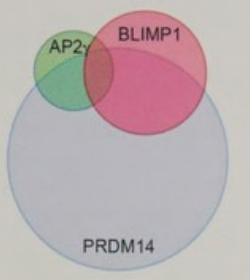
• Gillich A, Bao S, Grabole N, Hayashi K, Trotter MW, Pasque V, Magnusdottir E and Surani MA (2012) Epiblast stem cell-based system reveals reprogramming synergy of germline factors. Cell Stem Cell 10, 425-439

• Tang F, Barbacioru C, Bao S, Lee C, Nordman E, Wang X, Lao K, Surani MA (2010) Tracing the derivation of embryonic stem cells from the inner cell mass by single-cell RNA-Seq analysis. Cell Stem Cell 6, 468-478

E 7.25 Mouse Embryo

Fig 1. Founder population of PGCs at E7.5 detected by STELLA.





Overlap of genes bound by BLIMP1, PRDM14 and AP2γ

Fig 2a. Differential occupancy and combinatorial roles of BLIMP1, PRDM14 and AP2γ : BLIMP1 occupies promoters, PRDM14, distal regulatory elements and AP2γ bind both. Venn diagram depicts genes bound by the three factors

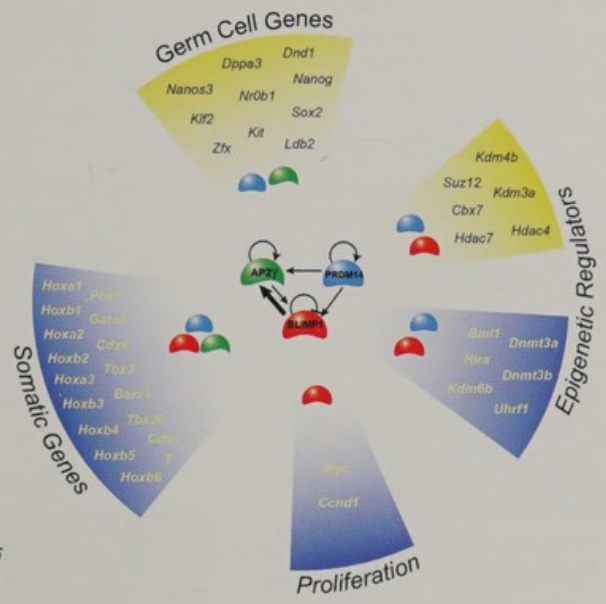


Fig 2b. The tripartite genetic network regulates expression of genes at PGC specification

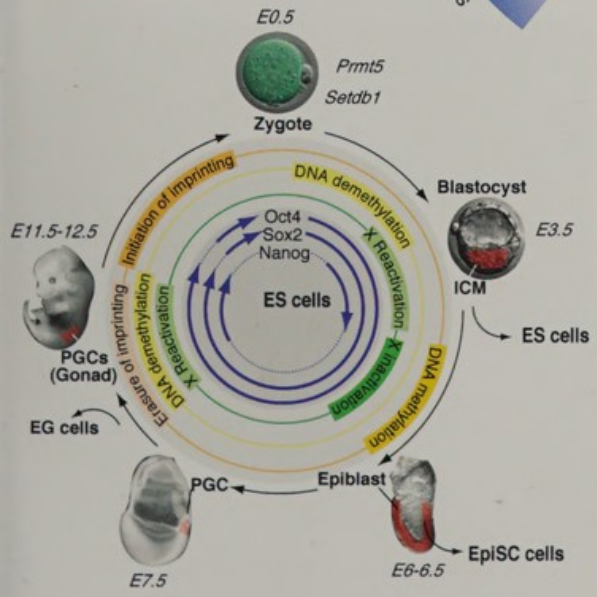


Fig 3. Parallel routes to reprograming and the establishment of the epigenetic ground state in primordial germ cells

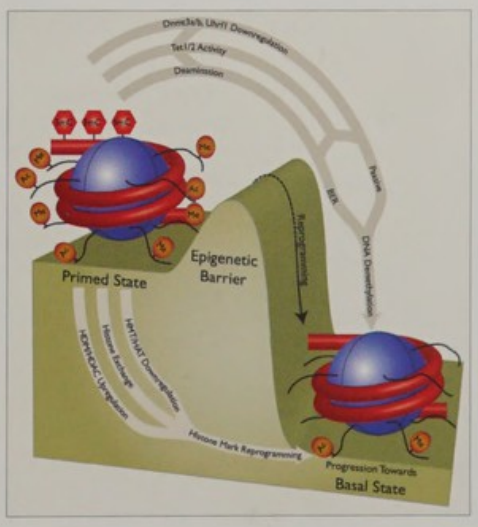


Fig4. Germline – Imprinting cycle generates the totipotent/ pluripotent states with parent of origin specific DNA methylation imprints for the transmission of epigenetic information.

Philip Zegerman

The regulation of DNA replication initiation in eukaryotes

Co-workers: Geylani Can, Vincent Gaggioli, Christine Hänni, Mark Johnson, Oleg Kovalevskiy, Barbara Schöpf

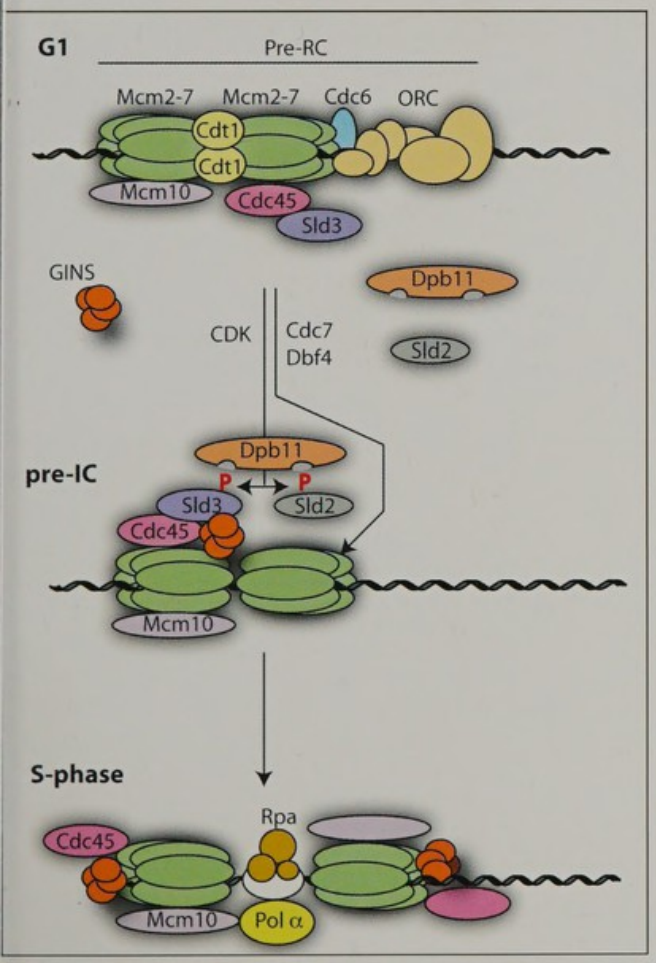
To successfully pass on their genetic information, every organism must make a perfect duplicate of their genome in every cell cycle. Failure to copy every chromosome faithfully leads to genomic instability, which is the root cause of cancer. As a result, the process of DNA replication must be strictly regulated, within the normal cell cycle, after DNA damage and during development. Our research takes advantage of a wide variety of organisms to understand the molecular mechanism of how this strict regulation of DNA replication is achieved.

Perfect genome duplication in eukaryotes is achieved by coupling the assembly of the DNA replication apparatus with the cell cycle. The fundamental regulator of the cell cycle, Cyclin-Dependent Kinase (CDK) plays a pivotal role in ensuring that replication initiation can only occur once before cell division. We have previously shown that CDK phosphorylates the two essential replication initiation factors Sld2 and Sld3, which in turn allows binding to another essential initiation factor called Dpb11. How CDK phosphorylation of these targets facilitates replication initiation is not known, but the transient association of these factors at origins produces a switch that only allows replication initiation in S-phase of the cell cycle.

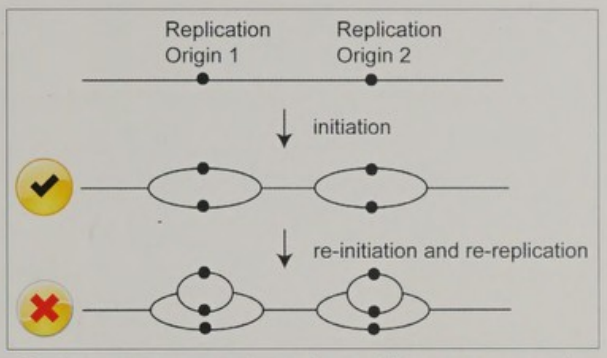
Interestingly, the time it takes to copy the genome changes during development. For example in many organisms S-phase is fast in the embryo, but greatly slows down in somatic cells. We have shown that it is the level of the key CDK targets that determines the rate of genome duplication in early vertebrate embryogenesis. Our work has therefore pinpointed a fundamental step in replication initiation that determines both the fidelity and the rate of DNA replication across eukaryotes.

Selected publications:

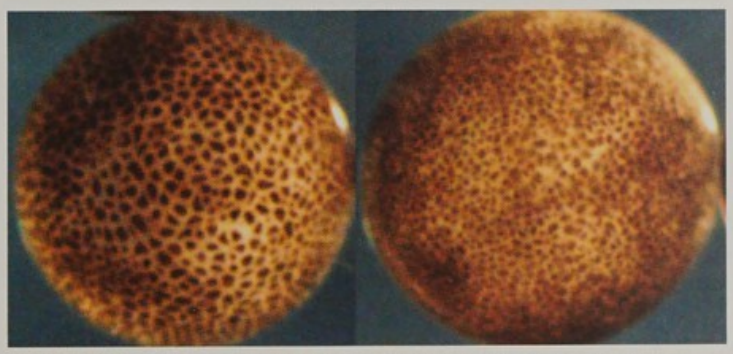
- Collart C, Allen GE, Bradshaw CR, Smith JC and Zegerman P (2013) Titration of four replication factors is essential for the *Xenopus laevis* midblastula transition. Science doi:10.1126/science.1241530
- Mantiero D, Mackenzie A, Donaldson A and Zegerman P (2011) Limiting factors execute the temporal programme of origin firing in budding yeast. EMBO J 23, 4805-4814
- Pagliuca FW Collins M, Zegerman P, Choudhary J and Pines J (2011) Quantitative proteomics reveals the basis for the biochemical specificity of the cell cycle machinery. Mol Cell 43, 406-417
- Zegerman P and Diffley JF (2010) Checkpoint dependent inhibition of DNA replication initiation via phosphorylation of Sld3 and Dbf4. Nature 467, 474-478
- Zegerman P and Diffley JF (2007) Phosphorylation of Sld2 and Sld3 by cyclin-dependent kinases promotes DNA replication in budding yeast. Nature 445, 281-285



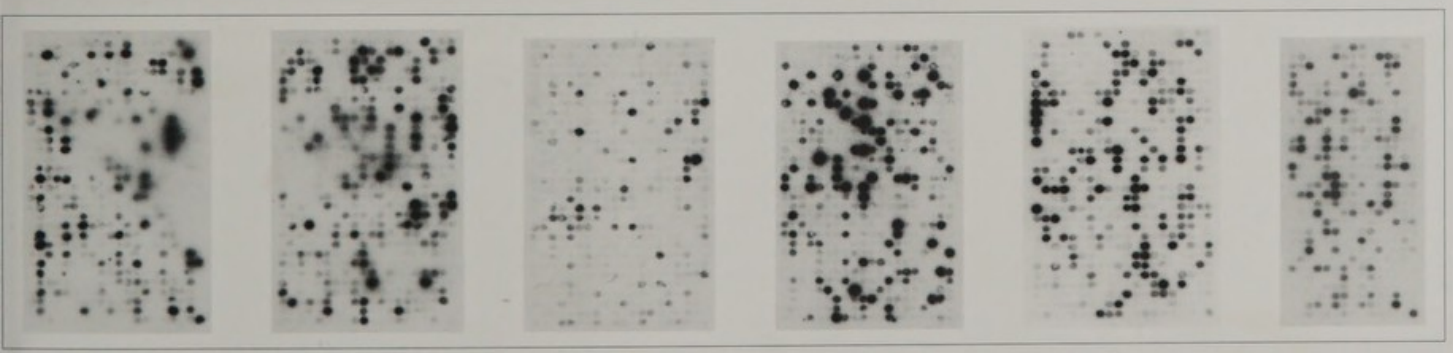
The sequence of eukaryotic replication initiation



Replication initiation must be strictly controlled to occur once, and only once, in every cell cycle.



Xenopus laevis embryos at the Midblastula Transition. Left is a normal embryo, right is an embryo over-expressing limiting replication factors.



Phospho-peptide array analysis of replication initiation factors.

Magdalena Zernicka-Goetz

Developmental plasticity, fate and morphogenesis in the mouse embryo

Co-workers: Agnieszka Jedrusik, Monika Bialecka, Paula Coelho, Ivan Bedzhov, Andy Cox, Maryna Panamarova, Sarah Graham, Chuen Yan Leung, Mubeen Goolam, Leah Bury, John Crang

We investigate mechanisms underlying the specification of cell fate and patterning, using mouse embryos as our major model because this allows us to combine cell biological and molecular genetic approaches with live imaging in a system that is close to human development.

Plasticity and Cell Fate acquisition: Embryonic cells in mouse and human are flexible and how their fate becomes restricted is unclear. To determine the molecular steps that mediate the transition from the egg totipotency towards either differentiation or pluripotency, we have isolated a number of regulatory genes essential for lineage determination and follow the interplay between cell polarity, position and developmental history of cells on fate specification.

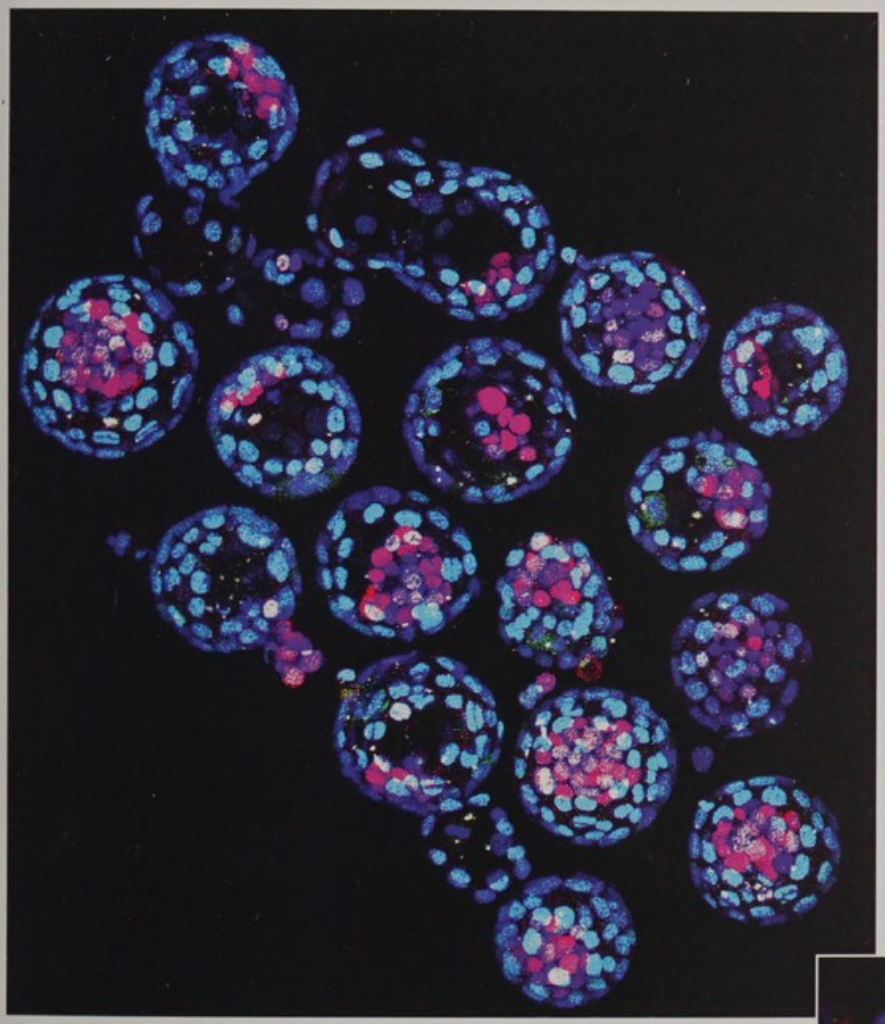
Asymmetric and Symmetric divisions: Development begins with the asymmetric divisions of the oocyte, following fertilisation cells divide symmetrically until the 8-cell stage when division asymmetry is again important. To understand the processes that break symmetry, we study the events that lead to cell polarisation and spindle orientation.

Maternal to Zygotic Transition: To understand the factors essential for the correct development, we have established a non-invasive method to forecast already at fertilisation which eggs have the highest chance of development to birth. We collaborate with IVF clinics to select with this approach the best quality eggs for transfer to would-be-mothers.

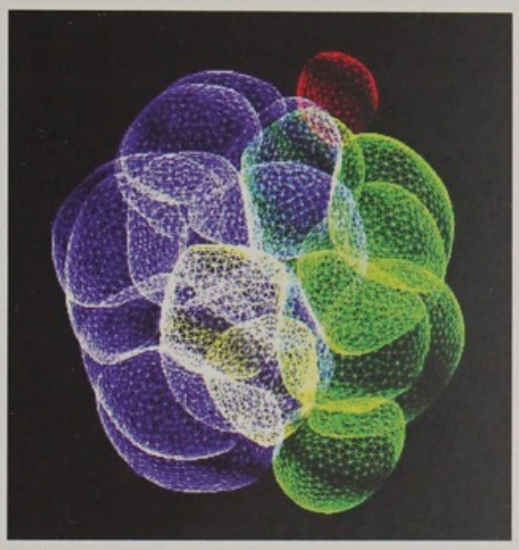
Self-organisation of pattern: We wish to understand how the embryo integrates the development of different cell types into an organism. To address this, we have developed *in vitro* system to culture and image development at implantation stages outside the mother and to mimic several of the key morphogenetic steps using ES cells.

Selected publications:

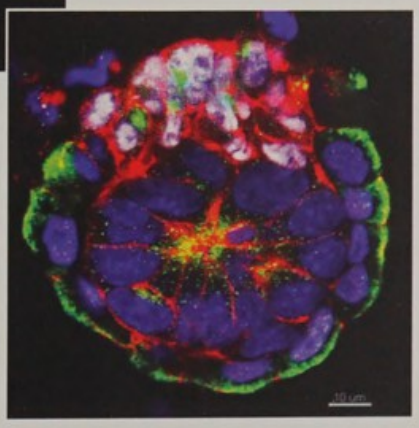
- Bedzhov, I; **Zernicka-Goetz, M** (2014) Self-organizing properties of mouse pluripotent cells initiate morphogenesis upon implantation. **Cell**, 2014 vol. 156(5) pp. 1032-44
- Leung CY, Zernicka-Goetz M (2013) Angiomotin prevents pluripotent lineage differentiation in mouse embryos via Hippo pathway-dependent and -independent mechanisms. **Nat Commun**. 2013;4:2251. doi: 10.1038/ncomms3251
- Skamagki M, Wicher KB, Jedrusik A, Ganguly S, Zernicka-Goetz M. (2013). Asymmetric localization of Cdx2 mRNA during the first cell-fate decision in early mouse development. **Cell Reports** doi:pii: S2211-1247(13)00013-2. 10.1016/j.celrep.2013.01.006
- Morris S, Guo A and Zernicka-Goetz M (2012). Developmental plasticity is bound by pluripotency and the fgf and wnt signaling pathways. **Cell Reports**: S2211-1247(12)00269
- Morris SA, Grewal S, Barrios F, Patankar SN, Strauss B, Buttery L, Alexander M, Shakesheff KM and Zernicka-Goetz M (2012) Dynamics of anterior-posterior axis formation in the developing mouse embryo. **Nature Commun**, 3:673.



Cultured mouse embryos at the blastocyst stage, just before implantation, stained with fluorescent antibodies to identify the different cell lineages. The blue cells are the trophectoderm which will form part of the placenta, The white cells are the pluripotent epiblast which will go on to form all the cells of the embryo proper, and the pink cells are the primitive endoderm which will differentiate into the yolk sac. (Mubeen Goolam)



3D reconstruction of mouse embryo



E5.0 mouse embryo stained for Rab11a (green), Phalloidin (red), Eomes (white) and DAPI (blue) at the onset of proamniotic cavity formation. (Ivan Bedzhov)

CATEGORIES OF APPOINTMENT

SENIOR GROUP LEADER
Professor, Director of Research or Reader

GROUP LEADER
5-year grant-funded appointment (maximum 10 years)

CAREER DEVELOPMENT FELLOW
4-year grant-funded appointment

INDEPENDENT SENIOR RESEARCH ASSOCIATE
3-year grant-funded appointment within individual groups

RESEARCH ASSOCIATE/FELLOW
Postdoctoral Fellow within individual groups, appointed by group leader

RESEARCH ASSISTANT
Postgraduate within individual groups, mainly grant-funded

GRADUATE STUDENT
3 or 4 year studentship within individual groups, mainly grant-funded

RESEARCH TECHNICIAN
Within individual groups, mainly grant-funded

LABORATORY ASSISTANT / TECHNICIAN
Within individual groups or part of core support, grant-funded

ITALICS: LEAVERS DURING THE LAST YEAR

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are funded from a variety of sources, including government research councils, the Wellcome Trust and Cancer Research UK. Applicants should write, in the first instance, to the leader of the group they wish to join.

DANIEL ST JOHNSTON PhD FRS FMedSci, Director

Wellcome Trust Principal Research Fellow
Professor of Developmental Genetics
Member, European Molecular Biology Organization
Director, Company of Biologists
(Member of the Department of Genetics)

DAN BERGSTRALH PhD
Wellcome Trust Research Associate

JIA CHEN PhD
Royal Society KC Wong Fellow

HÉLÈNE DOERFLINGER PhD
Wellcome Trust Research Associate/Institute Outreach Officer

ARTUR FERNANDES MPhil
School of Biological Sciences PhD Student

WERONIKA FIC PhD
Wellcome Trust Research Associate

ALEJANDRA GARDIOL PhD
Wellcome Trust Research Associate

TIMM HAACK MPhil
Wellcome Trust PhD Student

JACKIE HALL MSc
Wellcome Trust Senior Research Technician

HOLLY LOVEGROVE MSc
Herchel Smith PhD Student

NICK LOWE PhD
Wellcome Trust Research Associate

AVIK MUKHERJEE MSc
CISS PhD Student

DMITRY NASHCHEKIN PhD
Wellcome Trust Research Associate

ARAM SAYADIAN MPhil
Wellcome Trust PhD Student (Formerly Wellcome Trust Developmental Biology Student)

VANESSA STEFANAK PhD
Administration Manager for the Office of the Director

VITOR TROVISCO PhD
Wellcome Trust Research Associate

YU YE PhD
Henslow Research Fellow/Wellcome Trust Research Associate

HELEN ZENNER-BRANCO PhD
Wellcome Trust Research Associate

JULIE AHRINGER PhD FMedSci

Wellcome Trust Senior Research Fellow
Member, European Molecular Biology Organization,
Director of Research in Genetics and Genomics
(Member of the Department of Genetics)

ALEX APPERT PhD
Wellcome Trust Research Associate

DARYA AUSIANNIKAVA BSc
Darwin Trust PhD Student

FANÉLIE BAUER PhD
Wellcome Trust Research Associate/Herchel Smith Fellow

RON CHEN PhD
Wellcome Trust Research Associate

MIKE CHESNEY PhD
Wellcome Trust Research Associate

YAN DONG MSc
Wellcome Trust Research Assistant

KENNETH EVANS PhD
Wellcome Trust Research Associate

BRUNO FIEVET BSc
Wellcome Trust Research Associate

MORITZ HERRMANN BSc
BBSRC PhD Student

JÜRGEN JÄNES MSc
Wellcome Trust Mathematical Biology PhD Student

DJEM KISSIOV BA
Wellcome Trust Research Assistant

ALICIA McMURCHY PhD
Wellcome Trust/CIHR Research Associate

JOSANA RODRIGUEZ PhD
Wellcome Trust Research Associate

PRZEMYSLAW STEMPOR PhD
Wellcome Trust Research Associate

CHRISTINE TURNER
PA/Secretary

EVA ZEISER BSc
Wellcome Trust Research Assistant

ANDREA BRAND PhD FRS FMedSci

Herchel Smith Professor of Molecular Biology,
Member, European Molecular Biology Organization
(Member of the Department of Physiology, Development and Neuroscience)

JANINA ANDER BSc
BBSRC PhD Student

JORGE BUENDIA BUENDIA BSc
CONACYT MPhil Student

ELIZABETH CAYGILL PhD
Herchel Smith Fellow/Wellcome Trust Research Associate

SETH CHEETHAM BSc
Herchel Smith Research Student

ESTEBAN CONTRERAS SEPULVEDA MPhil
Wellcome Trust PhD Student

MELANIE CRANSTON BA
Wellcome Trust Research Assistant

ABHIJIT DAS PhD
Wellcome Trust Research Associate

CATHERINE DAVIDSON BSc
Wellcome Trust Research Associate

DAVID DOUPÉ PhD
Sidney Sussex College Junior Research Fellow

PAUL FOX PhD
EMBO Fellow

KATRINA GOLD PhD
Wellcome Trust Research Associate

JUN LIU BA
Dr Herchel Smith Graduate Fellow

OWEN MARSHALL PhD
EMBO Fellow

LEO OTSUKI MPhil
Wellcome Trust Developmental Biology PhD Student

CHLOE SHARD BSc
Cambridge Australia McCrum Scholarship Student

TONY SOUTHALL PhD
Wellcome Trust Research Associate

PAULINE SPÉDER PhD
Sir Henry Wellcome Postdoctoral Fellow

CHRISTINE TURNER
PA/Secretary

NICK BROWN PhD

Reader in Cell Biology,
Member, European Molecular Biology Organization,
(Member of the Department of Physiology, Development and Neuroscience)

NATALIA BULGAKOVA PhD
BBSRC Research Associate

JUAN MANUEL GOMEZ PhD
BBSRC Research Associate

HANNAH GREEN MPhil
Wellcome Trust Developmental Biology PhD Student

ANNABEL GRIFFITHS BA
MRC PhD Student

SVEN HUELSMANN PhD
University of Jyväskulä Research Associate

YOSHIKO INOUE PhD
Wellcome Trust Research Associate

BENJAMIN KLAPHOLZ PhD
Wellcome Trust Research Associate

TARUN KUMAR BSc
Commonwealth PhD Student

MIRANDA LANDGRAF MA
PA/Secretary

AIDAN MAARTENS PhD
Wellcome Trust Research Associate

JOHN OVERTON HNC
Wellcome Trust Chief Research Technician

PAULA RODRIGUEZ SANCHEZ MSc
Wellcome Trust Research Assistant

PEERAPAT THONGNUEK MRes in Regenerative Medicine
Thai Government PhD Student

JOHN GURDON Kt DPhil DSc FRS

Distinguished Group Leader,
Nobel Laureate in Physiology or Medicine 2012,
Wellcome Trust Senior Investigator,
Member, European Molecular Biology Organization
(Member of the Department of Zoology)

DILLY BRADFORD
PA/Secretary

SALLY FENN BSc
PA/Secretary

RICHARD HALLEY-STOTT PhD
MRC Research Associate

EVA HÖRMANSEDER PhD
Research Associate

JEROME JULLIEN PhD
Wellcome Trust Research Associate

MAGDALENA KOZIOL PhD
Postdoctoral Researcher

KEI MIYAMOTO PhD
Herchel Smith Research Associate

ANGELA SIMEONE PhD
Wellcome Trust/MRC Research Associate (Bioinformatics)

MARTA TEPEREK-TKACZ MSc
Wellcome Trust Developmental Biology Student PhD Student/MRC Research Assistant

STAN WANG BS
NIH/Gates MD-PhD Student

STEVE JACKSON PhD FRS FMedSci

Frederick James Quick Professor of Biology,
Head of Cancer Research UK Labs,
Member, European Molecular Biology Organization,
ERC Advanced Researcher,
(Member of the Department of Biochemistry)

PALLAVI AGARWAL PhD
Cancer Research UK Research Associate

GABRIEL BALMUS PhD
Cancer Research UK Research Associate

LINDA BASKCOMB MSc
Cancer Research UK Chief Research Laboratory Technician

RIMMA BELOTSERKOVSKAYA PhD
Cancer Research UK Research Associate

ANDREW BLACKFORD PhD
Cancer Research UK Research Associate

SÉBASTIEN BRITTON PhD
Cancer Research UK Research Associate

JESSICA BROWN MB Bchir
Wellcome Trust Clinical Fellow/PhD Student

TING-WEI (Will) CHIANG MSc
Cambridge Overseas Trust PhD Student

JULIA COATES MA
Cancer Research UK Research Assistant

MATTHEW CORNWELL MChem
Dept Chemistry/CCC/School of Physical Sciences PhD Student (joint with Department of Chemistry)

MUKERREM DEMIR BSc
ERC Senior Research Technician

SENIOR GROUP LEADERS

KATE DRY PhD
Cancer Research UK Information Specialist

JOSEP FORMENT PhD
A-T Society/Cancer Research UK Research Associate

YARON GALANTY PhD
ERC Senior Research Associate

NICOLA GEISLER BSc
Cancer Research UK/Wellcome Trust Senior Research Technician

MAREIKE HERZOG BA
Wellcome Trust PhD Student (joint with Sanger Institute)

SATPAL JHUJH MSc
ERC Research Technician

ABDERRAHMANE KAIDI PhD
ERC Research Associate

DELPHINE LARRIEU PhD
EMBO Fellow and Cancer Research UK Research Associate

CARLOS LE SAGE PhD
ERC Research Associate

NATALIA LUKASHCHUK PhD
Cancer Research UK Research Associate

RYOTARO NISHI PhD
Cancer Research UK Research Associate

FABIO PUDDU PhD
EMBO Fellow

HELEN REED
PA/Secretary

ISRAEL SANGUERO CORBACHO PhD
Wellcome Trust Research Associate

CHRISTINE SCHMIDT PhD
FEBS Research Fellow/ERC Research Associate

MATYLDA SCZANIECKA-CLIFT PhD
ERC Research Associate

JON TRAVERS PhD
EU Research Associate

DAVID WEISMANN PhD
EU Research Associate

PAUL WIJNHOVEN BSc
Cancer Research UK Research Assistant/PhD Student

TONY KOUZARIDES PhD FRS FMedSci

Deputy Director
Professor, Cancer Research UK Gibb Fellow, Member, European Molecular Biology Organization, ERC Advanced Researcher, (Member of the Department of Pathology)

PAULO AMARAL PhD
Royal Society Newton International Fellow

ANDREW BANNISTER PhD
Cancer Research UK Senior Research Associate, Senior Radiation Protection Supervisor

ISAIA BARBIERI PhD
Leukaemia & Lymphoma Research, Research Associate

ESTER CANNIZZARO MSc
Cancer Research UK PhD Student

KA HING CHE PhD
Cancer Research UK Research Associate

MARIA CHRISTOPHOROU PhD
Cancer Research UK Research Associate

ALISTAIR COOK GIBiol
ERC Chief Research Technician

MARK DAWSON MBBS (HONS) BMEDSci FRACP FRCP
Wellcome Beit Intermediate Clinical Fellow

CHUN YEW FONG MBBS BMedSci
Visiting Leukaemia Foundation of Australia/ Haematology Society of Australia & New Zealand/ Royal Australasian College of Physicians Clinical Fellow

NAMSHIK HAN PhD
Cancer Research UK Research Associate (Bioinformatics)

SRI LESTARI MSc
Cancer Research UK Senior Research Laboratory Technician

VALENTINA MIGLIORI PhD
EMBO Fellow/King's College Junior Research Fellow

JESSICA MORISON PhD
Visiting Researcher

NIKKI PARSONS BA
PA/Secretary

SAM ROBSON PhD
ERC Research Associate (Bioinformatics)

HELENA SANTOS ROSA PhD
Cancer Research UK Senior Research Associate

PETER TESSARZ PhD
Cancer Research UK/BBSRC Research Associate

EMMANUELLE VIRÉ PhD
ERC/Cancer Research UK Research Associate

MEIKE WIESE MSc
Cancer Research UK PhD Student

BEATA WYSPIANSKA MSc
BBSRC Case PhD Student

ERIC MISKA PhD

Herchel Smith Professor of Molecular Genetics, Cancer Research UK Senior Research Fellow, Member, European Molecular Biology Organization, ERC Independent Starting Researcher, (Member of the Department of Genetics)

ALPER AKAY PhD
Cancer Research UK Research Associate

ALYSON ASHE PhD
Herchel Smith Fellow/ERC Research Associate

FABIAN BRAUKMANN MSc
ERC Research Assistant

AMY CORDING BSc
CRUK Research Assistant

SABRINA HUBER MSc
Cambridge PhD Training Programme in Chemical Biology and Molecular Medicine

MIRANDA LANDGRAF MA
PA/Secretary

JÉREMIE LE PEN MPhil
Wellcome Trust Developmental Biology PhD Student

NIC LEHRBACH PhD
ERC Research Associate

MILAN MALINSKY MPhil
Wellcome Trust Mathematical Biology PhD Student

SYLVIANE MOSS PhD
Cancer Research UK Research Associate/Lab Manager

KENNETH MURFITT MPhil
ERC PhD Student

ALEXANDRA SAPETSCHNIG PhD
HFSP Research Fellow/ERC Senior Research Associate

PETER SARKIES PhD
Gonville and Caius Research Fellow/CRUK Research Associate

MÉLANIE TANGUY PhD
Cancer Research UK Research Associate

EVA-MARIA WEICK BSc
Herchel Smith/ERC PhD Student

JONATHON PINES PhD FMEDSci

Director of Research in Cell Division,
Cancer Research UK Senior Research Fellow,
Member, European Molecular Biology Organization,
(Member of the Department of Zoology)

PHILIPPE COLLIN PhD
BBSRC Research Associate

BARBARA DI FIORE PhD
Cancer Research UK Research Associate

ANJA HAGTING PhD
Cancer Research UK Research Associate
Biological Safety Officer

DAISUKE IZAWA PhD
Cancer Research UK Research Associate

MARK JACKMAN PhD
Cancer Research UK Research Associate,
Chemical Safety Officer

AGATA LICHAWSKA PhD
Herchel Smith PhD Student

PAOLA MARCO CASANOVA PhD
MRC Research Associate

CHIARA MARCOZZI MSc
Boehringer Ingelheim Fonds/BBSRC CASE PhD Student

TAKAHIRO MATSUSAKA PhD
Cancer Research UK Research Associate

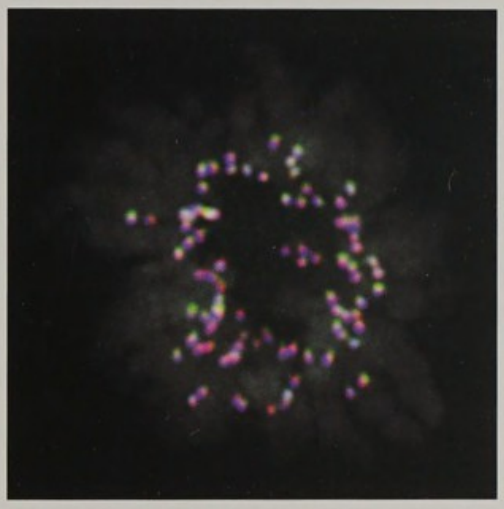
OXANA NASHCHEKINA MSc
Cancer Research UK Chief Research Technician

BERNHARD STRAUSS PhD
MRC Research Associate

JILL TEMPLE MSc
MRC Research Assistant

SAMUEL WIESER MSc
Liechtenstein Government PhD Student

CLAUDIA WURZENBERGER PhD
EMBO Fellow



Human RPE1 cell in prometaphse: Chromosomes in grey, kinetochores in red, centromeres in blue and Checkpoint protein Mad2 in green (Philippe Collin, Pines Lab)

AZIM SURANI PhD CBE FRS FMEDSci

Director of Germline and Epigenomics Research,
Head of Wellcome Trust Labs,
Wellcome Trust Senior Investigator,
Chairman of the Scientific Advisory Board of the Centre for Trophoblast Research, University of Cambridge,
Member, European Molecular Biology Organization,
(Member of the Department of Physiology, Development and Neuroscience)

FLORENCIA BARRIOS PhD
Royal Society Newton International Fellow

DELPHINE COUGOT PhD
Wellcome Trust Research Associate

DANG VINH DO PhD
Wellcome Trust Research Associate

LYNN FROGGETT
PA/Secretary

NILS GRABOLE BSc
Wellcome Trust PhD Student

WOLFRAM GRUHN PhD
Wellcome Trust Research Associate

UFUK GÜNESDOGAN PhD
Wellcome Trust Research Associate/Marie Curie Intra-European Fellow

JAMIE HACKETT PhD
HFSP Research Associate

YUN HUANG BA
MB-PhD Student

NAOKO IRIE PhD
BIRAX Research Associate

ELENA ITSKOVICH MSc
Wellcome Trust PhD Student

SHINSEOG KIM PhD
Wellcome Trust Research Associate

TOSHIHIRO KOBAYASHI PhD
JSPS Fellow

CAROLINE LEE ONC
Wellcome Trust Chief Research Technician,
Radiation Protection Supervisor

HARRY LEITCH MA (Cantab) PhD
MB/PhD Student

KAZUHIRO MURAKAMI PhD
Wellcome Trust Research Associate

ROOPSHA SENGUPTA PhD
Wellcome Trust Research Associate

WALFRED TANG MPhil
Croucher Cambridge International PhD Student

THOR THEUNISSEN
Sir Henry Wellcome Postdoctoral Fellow

JULIA TISCHLER PhD
APART Research Fellow

MARK ZIATS BS
NIH PhD Student

JAN ZYLICZ MSc
Wellcome Trust PhD Student

RAFAEL CARAZO SALAS PhD

ERC Starting Independent Researcher
(Member of the Department of Genetics)

JUAN FRANCISCO ABENZA MARTINEZ PhD
Ramón Areces Foundation Research Fellow/Herchel Smith Fellow

BÁLINT ANTAL PhD
ERC Research Associate (Bioinformatics)

ANATOLE CHESSEL PhD
BBSRC Research Associate (Bioinformatics)

JAMES DODGSON PhD
BBSRC/ERC Research Associate

GROUP LEADERS

TARA FINEGAN MPhil
Clare Hall MPhil Student/School of Biological Sciences PhD Student

MARCO GEYMONAT PhD
ERC/BBSRC Research Associate

VERONIKA GRAML MSc
SystemsX.ch PhD Student

JOSEPH HARVEY BA
Wellcome Trust Mathematical Genomics and Medicine PhD Student

JONATHAN LAWSON MPhil
Wellcome Trust Developmental Biology PhD Student

YUNG-CHIN OEI MSc
Cancer Research UK PhD Student

KATHY OSWALD MA
PA/Secretary

XENIA STUDERA MSc
ERC Research Assistant/PhD Student

THOMAS DOWN PhD

Wellcome Trust Career Development Fellow, (Member of the Department of Genetics)

PAULINA CHILARSKA BSc
Wellcome Trust PhD Student

KENNETH EVANS PhD
Wellcome Trust Bioinformatics Research Associate

JENNIFER GALLOP PhD

Wellcome Trust Career Development Fellow, ERC Independent Starting Researcher, (Member of the Department of Biochemistry)

GUILHERME CORREIA MSc
Wellcome Trust Research Assistant/PhD Student

HELEN FOX MPhil
Wellcome Trust Developmental Biology PhD Student

LYNN FROGGETT
PA/Secretary

YOSHIKO INOUE PhD
ERC Research Associate

JULIA MASON BSc
ERC Research Assistant

DANIEL SAXTON BSc
ERC Research Assistant

ASTRID WALRANT PhD
ERC Research Associate

RICK LIVESEY MB BChir PhD

Wellcome Trust Senior Investigator, University Reader in Molecular Neuroscience, (Member of the Department of Biochemistry)

SIAN ALEXANDER DPhil MRCP
Visiting Academic Clinical Fellow

THERESE ANDERSSON PhD
Wenner-Gren Foundation Research Fellow

PHILIPP BERG
Wellcome Trust PhD Student

LAURA BRIGHTMAN BA
Stem Cell Centre Seed Funding Research Assistant

TATYANA DIAS PhD
Alzheimer's Research UK Research Associate

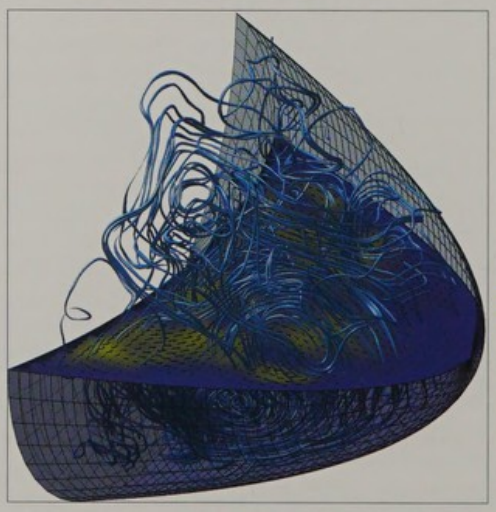
ALBERTO FRANGINI PhD
Wellcome Trust Research Associate

MACUSHLA HUGHES BA
PA/Secretary

PETER KIRWAN BSc
Wellcome Trust/ART PhD Student (Formerly Wellcome Trust Developmental Biology PhD Student)

TERESA KRIEGER MSci
EPSRC PhD Student (Joint with Ben Simons)

AMELIA McGLADE BSc
Innovative Medicines Initiative Research Assistant



Theoretically computed three-dimensional flow field of slow cytoplasmic streaming in a stage 9 Drosophila oocyte. Philipp Khuc Trong, St Johnston Lab

AYIBA MOMOH MSc
Wellcome Trust Research Assistant

STEVEN MOORE PhD
Alzheimer's Research UK Research Associate

TOMOKI OTANI MPhil
Wellcome Trust Developmental Biology PhD Student

NATHALIE SAURAT BSc
Woolf Fisher PhD Student

YICHEN SHI BSc
PhD Student

JAMES SMITH BSc
MRC/Innovative Medicines Initiative Research Assistant

SELINA WRAY PhD
Visiting Researcher

EUGENIA PIDDINI PhD

Royal Society Research Fellow (Member of the Department of Zoology)

MAJA GOSCHORSKA BSc
Cambridge Cancer Centre PhD Student

LEA HAMPTON-O'NEIL, BSc
MPhil Student

GOLNAR KOLAHGAR PhD
Cancer Research UK Research Associate

IWO KUCINSKI MPhil
Wellcome Trust Developmental Biology PhD Student

KATHY OSWALD MA
PA/Secretary

SASKIA SUIJKERBUIJK PhD
EMBO Fellow/Rubicon Research Associate

SILVIA VIVARELLI PhD
Cancer Research UK Research Associate

LAURA WAGSTAFF PhD
Cancer Research UK Research Associate

EMMA RAWLINS PhD

MRC Research Fellow (Member of the Department of Pathology)

GAYAN BALASOORIYA BSc
MRC Research Technician/PhD Student

CHRISTOPH BUDJAN MPhil
Wellcome Trust Developmental Biology PhD Student

MACUSHLA HUGHES BA
PA/Secretary

Reflection interference contrast microscopy image of MDCK cells, (Laura Wagstaff, Piddini Lab)

O-ANNE JOHNSON MB ChB MRCPCH
Wellcome Trust Clinical Fellow/PhD Student

ANGELENE HUFFMAN
PA/Secretary

JSUA LARESGOITI GARAY PhD
Wellcome Trust Research Associate

MARCO NIKOLIC MA MB BChir MRCP
Wellcome Trust Clinical Fellow/PhD Student

CHANDRIKA RAO MSc
March of Dimes/Wellcome Trust Chief Research Technician

PHILIP ZEGERMAN PhD

Association for International Cancer Research, Research Fellow
(Member of the Department of Zoology)

GEYLANI CAN MSc
Turkish Government/Sackler PhD Student

VINCENT GAGGIOLI PhD
Association for International Cancer Research, Research Associate

CHRISTINE HÄNNI MSc
Cambridge Cancer Centre PhD Student

MARK JOHNSON PhD
Association for International Cancer Research, Research Assistant

OLEG KOVALEVSKIY PhD
Cancer Research UK Research Associate

JESSICA BLACK
PA/Secretary

ANGELENE HUFFMAN
PA/Secretary

BARBARA SCHÖPF PhD
EMBO Fellow/Association for International Cancer Research, Research Associate

MAGDALENA ZERNICKA-GOETZ PhD, FMED Sci

Wellcome Trust Senior Research Fellow,
Professor of Developmental Biology,
Member, European Molecular Biology Organization,
Member of the Academy of Medical Sciences
(Member of the Department of Physiology, Development and Neuroscience)

FRANCESCO ANTONICA PhD
Wellcome Trust Research Associate

STOYANA ALEXANDROVA BA
MRC PhD Student

PAULA ALMEIDA COELHO PhD
Visiting Academic

IVAN BEDZHOV PhD
Wellcome Trust Research Associate

MONIKA BIALECKA PhD
Wellcome Trust Research Associate

HELEN BOLTON BSc MB BS MRCOG
Wellcome Trust Clinical Fellow/PhD Student

LEAH BURY Diplom Mol Med
Cambridge Cancer Centre PhD Student

ANDY COX PhD
Wellcome Trust Research Assistant

JOHN CRANG DPhil
PA

MOHAMMED GOOLAM MSc
St John's College Mary Gray PhD Student

SARAH GRAHAM MSc
PhD Student

AGNIESZKA JEDRUSIK PhD
Wellcome Trust Research Associate (Formerly Wellcome Trust Developmental Biology PhD Student)

CHUEN YAN LEUNG BSc
PhD Student

MARYNA PANAMAROVA BSc
Darwin Trust PhD Student

KRZYSZTOF WICHER PhD
Wellcome Trust Research Associate

BEN SIMONS PhD

Herchel Smith Professor of Theoretical Physics, Cavendish Laboratory

TERESA KRIEGER BA MSci
EPSRC PhD Student (Joint with Rick Livesey)

Sabbatical Researchers

URI ABDU
Senior Lecturer, BGU, Israel (St Johnston Lab)

LOUIS LEFEBVRE
Associate Professor, UBC, Canada (Surani Lab)

Visiting Students/Researchers

BILGE ASKSU: BSc: ENS de Cachan, Cachan, France (Visiting Master's Student, Carazo Salas Lab)

JOE BAXTER: Undergraduate Student, University of Cambridge (Visiting Wellcome Trust Vacation Student, Surani Lab)

ROBERTA CAGNETTA: BBSRC DTP Student, Department of Plant Sciences, University of Cambridge (Erasmus Student, Livesey Lab)

CELIA DELAHAYE: BSc: PhD Student, Department of Genetics, University of Cambridge (Visiting Student ENSTBB, Bordeaux University, Gurdon Lab)

JOSEP DUATO BOTAM: Undergraduate Student, Zaragoza University, Spain
(Erasmus Student, Brown Lab)

KANAT DUKENBAYEV PhD: Postdoctoral Fellow, Cavendish Laboratory, University of Cambridge (Visiting Researcher, Carazo Salas Lab)

XIDI FENG: Undergraduate Student, Chinese University, Hong Kong,
(Visiting CSSS Student, Gallop Lab)

SARAH HERBERG BSc:
(Visiting Master's Student, Gurdon Lab)

MARKUS HESS: Undergraduate Student, University of Würzburg, Germany
(Visiting Student, St Johnston Lab)

LOH CHET HONG: Undergraduate Student, Nanyang Technological University, Singapore
(Visiting CSSS Student, Brand Lab)

PABLO HURTADO: Master's Student, Human Reproductive Science, UCL, London
(Erasmus Student, St Johnston Lab)

ZIVOJIN JEVTIC: Undergraduate Student, University of Belgrade, Serbia (Visiting Student, St Johnston Lab)

HE MING LAI: Undergraduate Student
(Visiting CSSS Student, Miska Lab)

EMILY LINGEMAN: Undergraduate Student, University of Wisconsin, USA
(SCORE Visiting Student, Livesey Lab)

ZHU MENG: Undergraduate Student, School of Life Sciences, Tsinghua University, Beijing, China
(Visiting CSSS Student, St Johnston Lab)

MOHAMMED MOFATTEH: Undergraduate Student, King's College, London
(Amgen Scholar, St Johnston Lab)

NAVIN BRIAN RAMAKRISHNA: Undergraduate Student, University of Oxford,
(Amgen Scholar, Pines Lab)

CAROL READHEAD PhD: Ongoing collaborative Project (Visiting Academic, Surani Lab)

CLARA SLADE OLIVEIRA MVB: Research Analyst, Embrapa Gado de Leite, Brazil
(Visiting Academic, Zernicka-Goetz Lab)

ALESSIO STRANO: Undergraduate Student, University of Cambridge,
(Visiting Student, Livesey Lab)

YULIANG SUN: Undergraduate Student, University of Wisconsin, (SCORE Visiting Student, Ahringer Lab)

VASANTH THAMODARAN MSc: University of South Bohemia, Czech Republic
(Visiting PhD Student, Zernicka-Goetz Lab)

DENIS TORRE: Undergraduate Neuroscience Student, University of Trieste, Italy
(Wellcome Trust Vacation Student, Livesey Lab)

ABELLONA U: Undergraduate Student, Imperial College, London (Visiting Student, Brown Lab)

ANOESKA VAN DE MOOSDIJK: Graduate Student, Utrecht University, Netherlands (Erasmus Student, Zernicka-Goetz Lab)

ANTOINETTE van OUWERKERK BSc: (Visiting Student, Surani Lab)

JASMINE WANG: Undergraduate Student, School of Life Sciences, Peking University, Beijing, China (Visiting CSSS Student, Jackson Lab)

ISABEL WILKINSON: Undergraduate Student, University of Cambridge (Amgen Scholar, Miska Lab)

HAOCHEN YU PhD: Researcher, ETHZ, Switzerland
(Visiting Postdoctoral Researcher, Carazo Salas Lab)

ADMINISTRATION

ANN CARTWRIGHT MPhil
Institute Administrator

JESSICA BLACK
Receptionist

GEORGE BROWN
Accounts Manager

SUZANNE CAMPBELL BSc
HR/Grants Manager

JANE COURSE
Accounts Manager

DIANE FOSTER
Deputy Administrator

EMILIE HAINE BA
Receptionist

KATHY HILTON DipMgm
CBSG Manager

ANGELENE HUFFMAN
Receptionist

CEZARY KUCEWICZ MA
Accounts/Clerical Assistant

LYNDA LOCKEY
Office Manager

JANET MOORE PhD
Receptionist

COMPUTING

ALASTAIR DOWNIE
Computer Systems Manager

RICHARD BUTLER PhD
Research Associate (Imaging)

NICOLA LAWRENCE PhD
Computer Imaging Associate, Laser Safety Officer

NIGEL SMITH
Computer Associate

ALEX SOSSICK BSc
Computer Imaging Associate, Laser Safety Officer

PETER WILLIAMSON BSc
Computer Associate

BIOINFORMATICS

CHARLES BRADSHAW PhD
Computer Associate (Bioinformatics)

GEORGE ALLEN PhD
Research Associate (Bioinformatics)

ACCOUNTS/PURCHASING/STORE

IAN FLEMING
Stores/Purchasing Manager

SIMON ALDIS
Purchasing/Accounts Assistant

DAVID COOPER
Stores Technician

RICHARD ETTERIDGE MA
Purchasing/Accounts Assistant

ANDY VINCENT
Senior Stores Technician

MICK WOODROOFE
Purchasing/Accounts Assistant

TECHNICAL SUPPORT

POLLY ATTLESEY
Unit Manager

RYAN ASBY
CAROLINE BLAKE
NICOLA EVANS-BAILEY
RICHARD HARPER
LUKE ATTLESEY
ELEANOR DALE
MARK GILLILAND
JACK HARRIS

GILLIAN HYNES
WEN JIN
THERESE JONES-GREEN
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DAVID SIMPSON
DANIEL WATTS
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NIGEL BARNETT
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CLIVE BENNETT
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STUART TURNER
SIMON WILSON

MEDIA/GLASS WASHING

JUANITA BAKER-HAY
Media/Glass Washing Manager

SUE HUBBARD
Deputy Media/Glass Washing Manager

JANIS ABBOTT
KAZUKO COLLINS
SANDRA HUMAN
TRACY MITCHELL
DANIEL WATTS
LISA BAKER
VINCE DAMS
MARK JOHNS
HANNAH RULE

ZEST CATERING

AMANDA HARRIS
MELISSA PLOWDEN ROBERTS
REECE WEISSFLOG

The following is a list of articles by members of the Institute that were either published or accepted for publication, since the date of publication of the last Annual Report.

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INSTITUTE PUBLICATIONS

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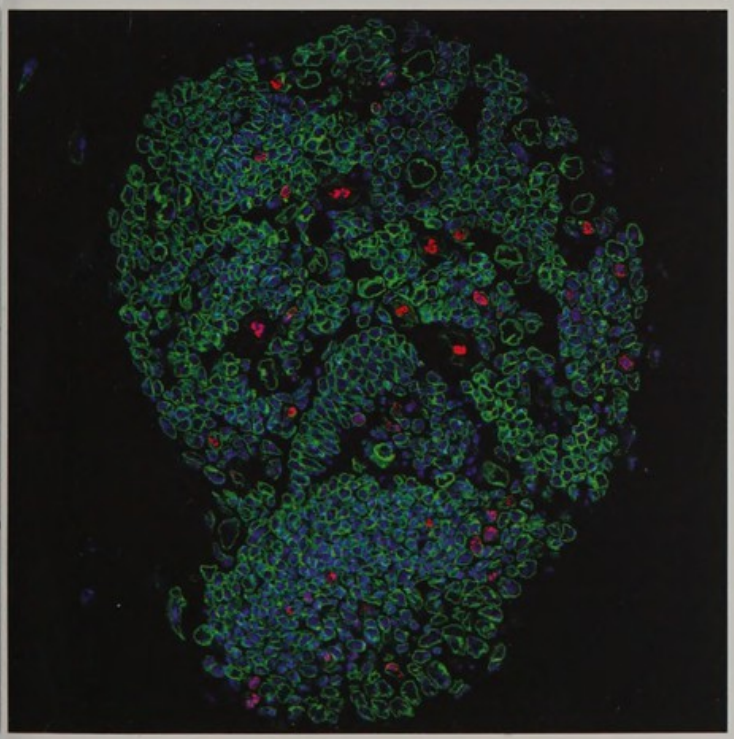

Nuclei in fly brain. Green: anti-Lamin; Blue: DAPI; Red: Phospho-histone3 (Abhijit Das, Brand Lab)

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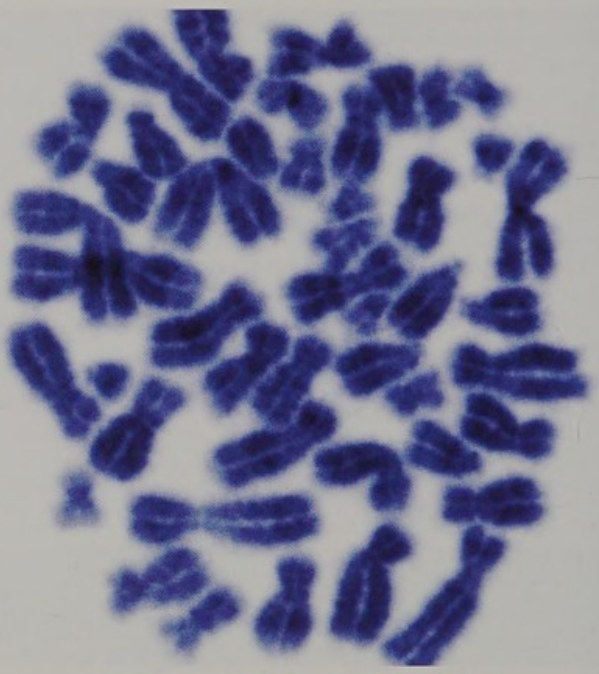

Visualisation of metaphase chromosomes (Carlos le Sage, Jackson lab)

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INSTITUTE PUBLICATIONS

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A cluster of human stem cell derived neurons 62 days after neural induction. Red stain (tuj1) labels all neurons whereas the green (gad6) labels gabaergic inhibitory neurons. Ctip2 positive deep layer cortical neurons are stained in blue. (Steven Moore, Livesey Lab)

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106 Zenner HL, Mauricio R, Banting G, Crump CM (2013) Herpes simplex virus type-1 counteracts tetherin restriction via its virion host shutoff activity. J Virol 87,24: 13115-23. [St Johnston Group]

107 **Zernicka-Goetz M** (2013) Development: do mouse embryos play dice? Curr Biol 23, 1: R15-R17.

Drosophila larva under polarised light (Peerapat Thongnuek, Brown Lab)

TALKS BY INSTITUTE RESEARCHERS

JANUARY

JULIE AHRINGER: Stowers Institute for Medical Research, Kansas City, USA
ANDREA BRAND: Peter Thorogood Memorial Lecture, University College London, UK
JOHN GURDON: Leys School, Cambridge, UK
JOHN GURDON: Hinxton, Cambridge, UK
JOHN GURDON: King's College, Cambridge, UK
TONY KOUZARIDES: Massachusetts General Hospital, Boston, USA
TONY KOUZARIDES: Stowers Institute for Medical Research, Kansas City, USA
RICK LIVESEY: MRC Developmental Neurobiology Centre, London, UK
ERIC MISKA: University of Regensburg, Germany
ERIC MISKA: Biochemistry Society, Edinburgh, UK
JON PINES: EMBO Workshop, Obergurg, Austria
PETER SARKIES: Biochemistry Society, Edinburgh, UK
CHRISTINE SCHMIDT: Newnham College, Cambridge, UK
CHRISTINE SCHMIDT: Robinson College, Cambridge, UK
DANIEL ST JOHNSTON: University of Manchester, UK
JAN ZYLICZ: The British Israel Research and Academic Exchange Partnership (BIRAX), Haifa, Israel

FEBRUARY

ANDREA BRAND: Keystone Symposium, Santa Fe, New Mexico, USA
ANDREA BRAND: British Embassy, Tokyo, Japan
JOHN GURDON: Cold Spring Harbor Laboratories: 60th Anniversary of the Discovery of the Double Helix, New York, NY, USA
STEVE JACKSON: DD Response Meeting, Brussels, Belgium
JON PINES: Institute for Molecular and Cell Biology, Porto, Portugal
AZIM SURANI: Babraham Institute, Cambridge, UK

MARCH

JULIE AHRINGER: Harvard Medical School, Boston, USA
MARK DAWSON: CCRCB Queen's University Belfast, Belfast, Ireland
MARK DAWSON: Peter MacCallum Cancer Centre, Melbourne, Australia
JENNY GALLOP: British Society of Cell Biology, Warwick, UK
JOHN GURDON: CIRA, Kyoto, Japan
STEVE JACKSON: Keystone Symposium Genomic Instability and DNA Repair, Alberta, Canada
TONY KOUZARIDES: Keystone Symposium, Epigenetic Marks & Cancer Drugs, Santa Fe, New Mexico, USA
RICK LIVESEY: SCC Minisymposium, Lund University Stem Cell Center, Lund, Sweden
ERIC MISKA: British Society for Cell Biology, Warwick, UK
ERIC MISKA: RNA Silencing Meeting, Whistler, British Columbia, Canada
EMMA RAWLINS: Royal Society International Scientific Seminar, Milton Keynes, UK
DANIEL ST JOHNSTON: EMBL, Heidelberg, Germany
PHILIP ZEGERMAN: Keystone Symposium, Banff, Alberta, Canada

APRIL

ANDREA BRAND: Genetics Society of America, Washington DC, USA
ANDREA BRAND: Instituto de Neurosciencias, Alicante, Spain
MARK DAWSON: Gordon Research Conference, Switzerland
JOHN GURDON: Vatican Adult Stem Cell Conference, Vatican City, Rome, Italy
STEVE JACKSON: CeMM, Vienna, Austria
TONY KOUZARIDES: Pfizer, New York, NY, USA
TONY KOUZARIDES: University of Pennsylvania, Philadelphia, Pennsylvania, USA
RICK LIVESEY: British Festival of Neuroscience, The Barbican Centre , London, UK
RICK LIVESEY: Oxford Cortex Club, University of Oxford, UK
ERIC MISKA: EMBO Practical Course, Heidelberg, Germany
ERIC MISKA: Abcam Conference, Cambridge, UK
ERIC MISKA: HGMS - Human Genome Meeting, Singapore, Singapore
JON PINES: 3rd Cell Cycle and Cancer Meeting, Montpellier, France
JON PINES: Warwick Medical School, University of Warwick, UK
DANIEL ST JOHNSTON: London Royal Society Cellular Polarity: From Mechanisms to Disease Meeting, London, UK
PETER TESSARZ: Graduate School of University Essen/Duisburg, Ostbeveren, Germany
MAGDA ZERNICKA-GOETZ: Wellcome Trust, London, UK

MAY

ANATOLE CHESSEL: 13th International ELMI Meeting, Arcachon, France
JULIE AHRINGER: Center for Integrative Genomics, University of Lausanne, Switzerland
JULIE AHRINGER: School of Medicine, University of Geneva, Switzerland
ANDREA BRAND: School of Biological Sciences, University of Edinburgh, UK
ANDREA BRAND: Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany
JOHN GURDON: University of California, Southern California, USA
JOHN GURDON: Anne Rowling Regenerative Neurology Clinic/University of Edinburgh, UK
STEVE JACKSON: Technion-Israel Institute of Technology 60th Anniversary conference, Haifa, Israel
TONY KOUZARIDES: EMBO, Chromatin and Epigenetics, Heidelberg, Germany
ERIC MISKA: IMBA Micro-symposium, Vienna, Austria

ROOPSHA SENGUPTA: Jawaharial Nehru Centre for Advanced Scientific Research, Bangalore, India

AZIM SURANI: King's College, London, UK

MAGDA ZERNICKA-GOETZ: Wstepny Conference, Zakopane, Poland

JUNE

ANDREA BRAND: COS Symposium, Heidelberg, Germany

MARK DAWSON: Memorial Sloan Kettering Cancer Centre, New York, USA

MARK DAWSON: Karolinska Institute, Stockholm, Sweden

MARK DAWSON: European Haematology Association Annual Conference, Stockholm, Sweden

TARA FINEGAN: 7th International Fission Yeast Meeting (EMBO Conference), London, UK

DIANE FOSTER: S-lab, Liverpool, UK

JOHN GURDON: Friedrich Meischer Lecture, Basel, Switzerland

JOHN GURDON: ISDB Meeting and Harrison Medal, Cancun, Mexico

JOHN GURDON: Institute of Molecular Biotechnology, Vienna, Austria

KATHY HILTON: S-lab, Liverpool, UK

STEVE JACKSON: Sanger Institute, Hinxton, UK

TONY KOUZARIDES: FASEB Chromatin & Transcription, Nassau, Bahamas

ERIC MISKA: IMB, Mainz, Germany

JON PINES: Cell Cycle Meeting, Salk Institute, La Jolla, California, USA

JON PINES: EMBO Workshop, Breukelen, Netherlands

EMMA RAWLINS: EU COST Meeting: Developmental mechanisms of lung disease, Munich, Germany

ALEXANDRA SAPETSCHNIG: Genetics Society of America, Los Angeles, California, USA

CHRISTINE SCHMIDT: EMBO Workshop, Breukelen, Netherlands

SASKIA SUIJKERBUIJK: Gut Club Meeting, UCL, London, UK

JULIA TISCHLER: ESHG, Paris, France

PHILIP ZEGERMAN: Cold Spring Harbor, Rome, Italy

MAGDA ZERNICKA-GOETZ: ISDB Meeting, Cancun, Mexico

JULY

STEVE JACKSON: International Workshop on A-T/ATM, Birmingham, UK

ERIC MISKA: CRUK Retreat, Manchester, UK

AZIM SURANI: FEBS (Federation of the Societies of Biochemistry and Molecular Biology), St Petersburg, Russian Federation

AZIM SURANI: Society for Reproduction and Fertility, Cambridge, UK

DANIEL ST JOHNSTON: RNA Localization and Localized Translation Meeting, Niagara on the Lake, Ontario, Canada

MAGDA ZERNICKA-GOETZ: IBD, Vienna, Austria

AUGUST

ALYSON ASHE: Gordon Research Conference, Bryant, Australia

USUA LARESGOITI: Research Seminar, Proctor Academy, Andover, New Hampshire, USA

EUGENIA PIDDINI: Junior European *Drosophila* Investigator Meeting, Windsor, UK

SEPTEMBER

JULIE AHRINGER: EMBO, Oxford, UK

PAULO AMARAL: FAPESP-Brazil, Royal Society, London, UK

PAULO AMARAL: Karolinska Institutet/Uppsala University, Stockholm, Sweden

MARK DAWSON: Université Libre de Bruxelles, Brussels, Belgium

JENNY GALLOP: BSCB Autumn Meeting, Cumbria, UK

JOHN GURDON: Cardiff University, UK

JOHN GURDON: St Catherine's College, Oxford University, UK

STEVE JACKSON: 2nd Gray Institute Symposium,, Oxford, UK

STEVE JACKSON: EMBO Meeting, Amsterdam, Netherlands

ERIC MISKA: Institut Pasteur, Paris, France

ERIC MISKA: Karolinska Institute, Stockholm, Sweden

JON PINES: The IGC (Instituto Gulbenkian de Ciencia), Oeiras, Portugal

CHRISTINE SCHMIDT: NANO 2013 Meeting, Beijing, China

CHRISTINE SCHMIDT: Wuhan University School of Pharmaceutical Science, Wuhan, China

AZIM SURANI: SKMB (Swiss Committee for Molecular Biology), Lausanne, Switzerland

AZIM SURANI: Wellcome Trust, Hinxton, Cambridge, UK

DANIEL ST JOHNSTON: Molecular Mechanism of Development, David Ish-Horowitz Symposium, Cancer Research UK London, London, UK

PHILIP ZEGERMAN: Cold Spring Harbor, New York, UK

MAGDA ZERNICKA-GOETZ: Wydzial Biologii Uniwersytetu, Gdansk, Poland

MAGDA ZERNICKA-GOETZ: Roslin Institute, Edinburgh, Edinburgh, UK

OCTOBER

JULIE AHRINGER: John Innes Centre, Norwich, UK

JULIE AHRINGER: Wellcome Trust Sanger Institute, Cambridge, UK

ANDREA BRAND: European Drosophila Research Conference, Barcelona, Spain

RAFAEL CARAZO SALAS: Centre for Genomic Regulation (CRG), Barcelona, Spain

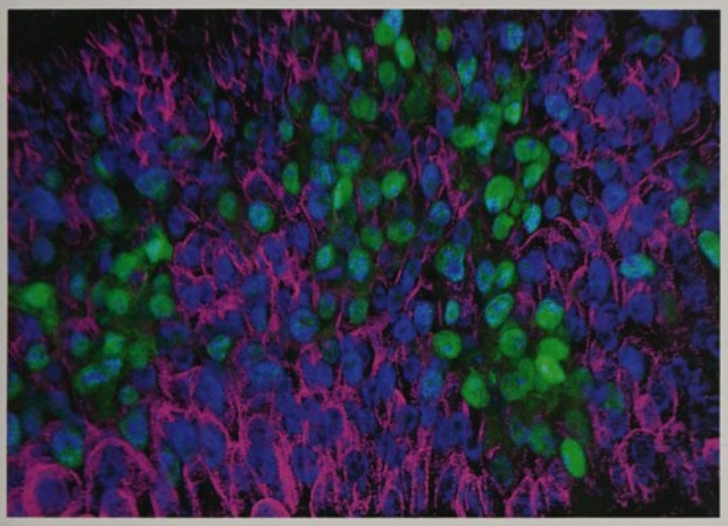
JENNY GALLOP: EMBL, Heidelberg, Germany

JOHN GURDON: Peterhouse College Kelvin Club, Cambridge, UK

JOHN GURDON: Wellcome Trust Conference: Regenerative Medicine: from Biology to Therapy, Hinxton, Cambridge, UK

JOHN GURDON: Eton College Medical Society, Eton, London, UK

TALKS BY INSTITUTE RESEARCHERS



3D reconstruction of Drosophila adult posterior midgut with APC mutant clones and stained for Armadillo (magenta) and DNA (blue) (Saskia Suijkerbuijk, Piddini lab)

STEVE JACKSON: EMBO Conference, Cape Sounio, Greece

TONY KOUZARIDES: Cell Symposia, Sitges, Spain

TONY KOUZARIDES: Heinrich Wieland Prize 2013, Munich, Germany

DELPHINE LARRIEU: EMBO Meeting, Isle sur la Sorgue, France

ERIC MISKA: EMBO Members' Meeting Heidelberg, Germany

EUGENIA PIDDINI: 23rd European *Drosophila* Research Conference, Barcelona, Spain

JON PINES: 108th International Titisee Conference, Titisee, Germany

PETER SARKIES: EMBO Non-coding Genome Meeting, Heidelberg, Germany

ROOPSHA SENGUPTA: Nuclear Structure and Dynamics meeting, European Molecular Biology Organisation (EMBO), L'Isle sur la Sorgue, France

ALEX SOSSICK: Wellcome Trust, London, UK

AZIM SURANI: Weizmann Institute of Science, Rehovot, Israel

AZIM SURANI: Hebrew University, Jerusalem, Israel

AZIM SURANI: School of Medicine, University of Zagreb, Zagreb, Croatia

AZIM SURANI: National Centre for Biological Sciences (NCBS), Bangalore, India

DANIEL ST JOHNSTON: ABCD Congress, Ravenna, Italy

PETER TESSARZ: Faculty of Biology, HU Berlin, Berlin, Germany

PETER TESSARZ: MPI Immunobiology and Epigenetics, Freiburg, Germany

EVA MARIA WEICK: EMBO Non-coding Genome Meeting, Heidelberg, Germany

PHILIP ZEGERMAN: MPI, Munich, Germany

MAGDA ZERNICKA-GOETZ: Mammalian Embryology Conference, University of Warsaw, Poland

NOVEMBER

JULIE AHRINGER: Dunn School of Pathology, University of Oxford, UK

PAULO AMARAL: Stephen Hales Society, Corpus Christi College, Cambridge, UK

RAFAEL CARAZO SALAS: Cell Biology of Yeasts Meeting, Cold Spring Harbor, USA

MARK DAWSON: NCRI Conference, Liverpool, UK

JOHN GURDON: Research Institute of Molecular Pathology (IMP), Vienna, UK

KATHY HILTON: Lux Review Magazine, London, UK

TONY KOUZARIDES: IMPPC, Barcelona, Spain

TONY KOUZARIDES: Abcam Meeting, Cayman Islands

RICK LIVESEY: Neurological and Psychiatric Diseases: Model Systems and Talk Treatment Symposium, Brown University, Providence, Rhode Island, USA

ERIC MISKA: Copenhagen Biosciences Conferences, Copenhagen, Denmark

JON PINES: Vienna Biocenter PhD Symposium, Vienna, Austria

ALEX SOSSICK: Hauser Forum, Cambridge, UK

BERNHARD STRAUSS: Hauser Forum, Cambridge, UK

AZIM SURANI: MRC Clinical Sciences Centre, London, UK

PETER TESSARZ: ZMBH, University of Heidelberg, Germany,

PETER TESSARZ: EMBL, Heidelberg, Germany

ASTRID WALRANT: GEM/GERLI, Saint-Jean-Cap-Ferrat, France

DECEMBER

MARK DAWSON: Abcam Meeting, London, UK

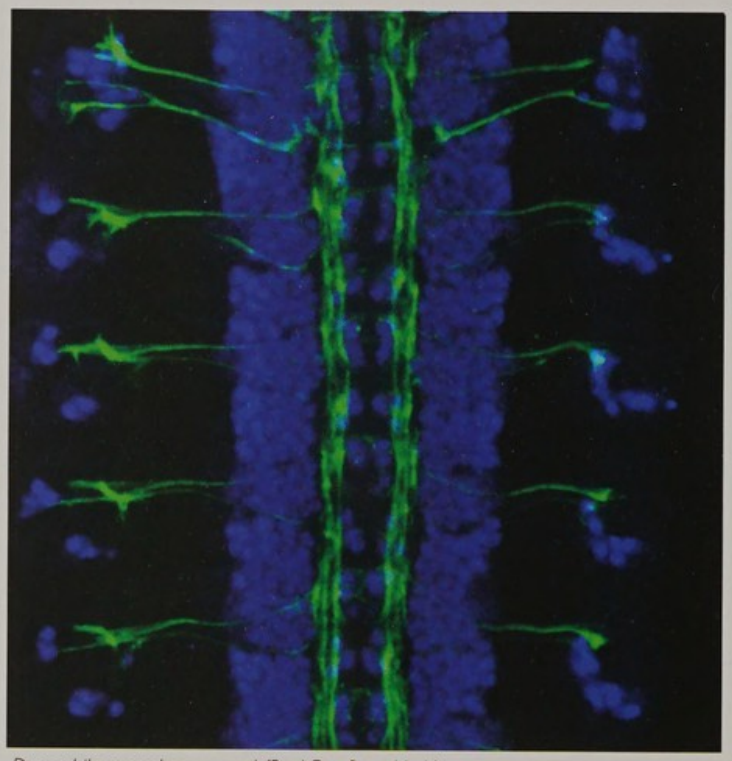
JOHN GURDON: Hong Kong University Faculty of Medicine + Centre for Reproduction, Development and Growth and Stem Cell & Regenerative Medicine Consortium, Hong Kong

AZIM SURANI: Babraham Institute, Cambridge, UK

AZIM SURANI: Wellcome Trust, London, UK

MAGDA ZERNICKA-GOETZ: Institute for Reproductive Sciences, Oxford, UK

MAGDA ZERNICKA-GOETZ: Wellcome Trust Researcher Meeting, Ashridge, Berkhamsted, UK



Drosophila ventral nerve cord (Paul Fox, Brand Lab)

LENT TERM

21 January, Randy Schekman, HHMI, University of California, Berkeley: "Transport vesicle assembly - lessons from yeast applied to mammalian development"

22 January, Amanda Fisher, Imperial College, London: "Reprogramming and cellular dominance" (The Anne McLaren Lecture)

5 February, Nadia Rosenthal, Imperial College London; Monash University; EMBL Australia: "Immune regulation and vertebrate regeneration"

26 February, Alexander van Oudenaarden, Hubrecht Institute-KNAW & University Medical Center Utrecht, Netherlands: "Controlling gene expression fluctuations during development"

5 March, Christof Niehrs, Institute of Molecular Biology (IMB), Mainz, Germany: "Mechanisms of Wnt signal transduction"

19 March, Jiri Lukas, Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Denmark: "Spatial and temporal regulation of the DNA damage response"

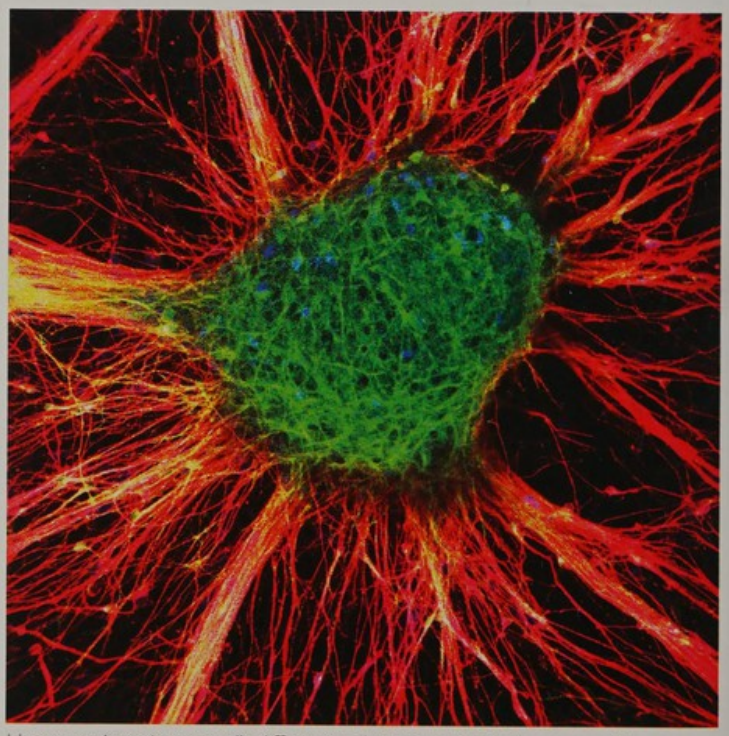
MICHAELMAS TERM

15 October, Ken Zaret, Institute for Regenerative Medicine and Perelman School of Medicine, University of Pennsylvania, USA: "Mechanisms of cellular programming and reprogramming"

5 November, Yoshiki Sasai, RIKEN Center for Developmental Biology, Kobe, Japan: "Self-regulatory mechanism of multicellular systems: tissue self-organization and scaling"

19 November, Tian Xu, HHMI/Yale University, USA: "Growth and size regulation in development and disease"

3 December, Scott Waddell, Centre for Neural Circuits and Behaviour, University of Oxford: "Bending the not so simple mind of the fruit fly"



Human embryonic stem cells differentiated to ventral forebrain neurons (Steven Moore, Livesey Group)

OTHER INFORMATION

STAFF AFFILIATIONS

JULIE AHRINGER is a member of the Scientific Advisory Boards of the MRC Clinical Sciences Centre, Reactome and Wormbase.

ANDREA BRAND is a member of Council of The Royal Society, member of The Royal Society/Wellcome Trust Sir Henry Dale Fellowship Committee, Reviewing Editor for elife, Founding Board Member of The Rosalind Franklin Society (USA). She was a member of The Royal Society Schools Partnership Committee and member of the Evaluation Committee, Universite Pierre et Marie Curie, Paris, France. She is also on the Board of Directors of The Cambridge Science Centre, a Patron of the Cambridge Science Festival, and was a Guest Judge of ReelLife Science, Schools Science Communication Video Competition.

JOHN GURDON is an honorary member of the British and American Anatomical Societies, a Foreign Associate for the US National Academy of Sciences, the US National Academy of Sciences Institute of Medicine, and the French National Academy of Sciences, a Member of Academia Europaea, an Honorary Member of the American Anatomical Society, and the Anatomical Society of Great Britain, an Honorary Fellow UK Academy of Medical Sciences,

STEVE JACKSON is an Associate Faculty Member of the Wellcome Trust Sanger Institute and is founding Scientist and Chief Scientific Officer of MISSION Therapeutics Ltd. He is a member of the Scientific Advisory Boards for the MRC Protein Phosphorylation and Ubiquitylation Unit (Dundee), the Beatson Institute (Glasgow), the MRC Toxicology Unit (Leicester), the Radiation Oncology and Biology Institute (Oxford), the MRC Clinical Sciences Centre and the Netherlands Cancer Institute. He is on the Steering Committee for the Cambridge Cancer Centre, and is a member of the CRUK Science Committee.

TONY KOUZARIDES is a member of the Cancer Research UK Science and Strategy Advisory Group, part of the Scientific Advisory Board for the Centre for Genomic Research (Spain), the Institute of Molecular Biology (Crete) and the Centre for Epigenetics and Biology (Spain). He is the founder and director of a Spanish cancer charity Vencer el Cancer (Conquer Cancer) and a founder of Chroma Therapeutics and Abcam Plc. He is a Director of Abcam Plc and on the Scientific Advisory Board of Glaxo Smith Kline and Cellzome

JONATHON PINES is a member of the Cancer Research UK Fellowship Committee, a member of the Scientific Evaluation Committee of the French National Cancer Institute, INCa, and a member of the Scientific Advisory Board for the Institute of Biology, Paris Seine, and the Evaluation Panel of the Institute of Biochemistry, ETH, Zurich.

DANIEL ST JOHNSTON is a Director of the Wellcome Trust Four-Year PhD programme in Developmental Biology at the University of Cambridge, a non-executive Director of the Company of Biologists, and acting Editor of Disease Models and Mechanisms.

AZIM SURANI is a member of the Steering Committee of the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute, and theme leader of the Pluripotency Programme. He is also a member of the Cambridge-India Partnership Advisory Group, founder and Chief Scientific Advisor for CellCentric Ltd, a member of the Steering Committee for the UK Stem Cell Bank, and a member of the Royal Society Hooke Committee. He is also a member of the Scientific Advisory Board of the Institute of Stem Cell Biology and Regenerative Medicine, Bangalore, India. the Academia Europaea, and Associate Fellow of the Third World Academy of Sciences,

MAGDALENA ZERNICKA-GOETZ is a Fellow of The Academy of Medical Sciences and EMBO

HONOURS AND AWARDS

JOHN GURDON – Honorary Degree, University of Southern California; Honorary Fellowship of the Anatomical Society; Honorary Member of the Biochemical Society; Honorary Fellowship of the American Association for Cancer Research; Honorary Fellowship of the Royal College of Physicians, and Asian College of Knowledge Management

TONY KOUZARIDES – Gibb Fellow; Heinrich Wieland Prize; Novartis Medal and Prize

MAGDALENA ZERNICKA-GOETZ – Anne McLaren International Award

EDITORIAL BOARDS OF JOURNALS

JULIE AHRINGER – eLife; Public Library of Science Biology; Molecular Systems Biology

ANDREA BRAND – eLife; Neural Development; Fly; Biology Image Library

JOHN GURDON – Current Biology; Development; Faculty of 1000; Growth and Differentiation; International Journal of Developmental Biology

STEVE JACKSON – Aging; Biomolecules; Carcinogenesis; Current Biology; DNA Repair ; EMBO Journal ; Genes and Development; PLoS Biology; The Scientist; Science Signaling (Board of Reviewing Editors)

RICK LIVESEY – BMC Developmental Biology; Molecular Autism

EMMA RAWLINS – Pediatric Research, Faculty of 1000

JON PINES – EMBO Journal; EMBO Reports; Open Biology; eLife

DANIEL ST JOHNSTON – Development; Faculty of 1,000

AZIM SURANI – Cell; Nature Communications; Cell Stem Cell; BMC Epigenetics and Chromatin; Epigenome; Epigenomics; Epigenetic Regulators; Regenerative Medicine; Differentiation; Stem Cell Research and Therapy; Faculty of 1,000

MAGDALENA ZERNICKA-GOETZ – Development; Differentation; Developmental Dynamics; Cells

INTERNATIONAL SCIENTIFIC ADVISORY BOARD

DR GENEVIEVE ALMOUZNI, Institut Curie, Paris, France

DR ADRIAN BIRD, Wellcome Trust Centre for Cell Biology, University of Edinburgh

DR STEVE COHEN, Institute of Molecular and Cell Biology, Singapore

DR JUDITH KIMBLE, Department of Biochemistry, University of Wisconsin-Madison, USA

DR ELISABETH KNUST, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

DR ROBB KRUMLAUF (Chairman), Stowers Institute for Medical Research, Kansas City, USA

DR MATTHIAS PETER, ETH Zurich

CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR DUNCAN MASKELL, Department of Veterinary Medicine and Chair of the School of Biological Sciences, University of Cambridge, UK

GROUP LEADERS

RAFAEL CARAZO SALAS: Group Leader, Department of Genetics, University of Cambridge

THOMAS DOWN: Creator and Lead Developer for Biodalliance, supported by BBSRC Tools and Resources Development Fund

POSTDOCTORAL RESEARCHERS

JUAN FRANCISCO ABENZA MARTINEZ: Herchel Smith Fellow, Department of Genetics, University of Cambridge (Carazo Salas Lab)

THERESE ANDERSSON: Group Leader, The WennerGren Institute, Stockholm University, Sweden (Livesey Lab)

BÁLINT ANTAL: ERC Research Associate, Department of Genetics, University of Cambridge (Carazo Salas Lab)

FLORENCIA BARRIOS: Assistant Professor of Histology and Embryology, University of Rome Tor Vergata, Research Associate, University of Rome Sapeienza (Surani Lab)

SÉBASTIEN BRITTON: Senior Postdoctoral Researcher, CNRS, France (Jackson Lab)

ANATOLE CHESSEL: BBSRC Research Associate, Department of Genetics, University of Cambridge (Carazo Salas Lab)

MARK DAWSON: Consultant Haematologist and Group Leader, Peter MacCallum Hospital, University of Melbourne, Australia (Kouzarides Lab)

JAMES DODGSON: BBSRC/ERC Research Associate, Department of Genetics, University of Cambridge (Carazo Salas Lab)

DAVID DOUPÉ: Postdoctoral Fellow, Dept of Genetics, Harvard Medical School (Brand Lab)

BRUNO FIEVET: Scientist, Fahy Gurteen, Cambridge, UK (Ahringer Lab)

ALEJANDRA GARDIOL: Imaging Specialist at Olympus KeyMed, UK (St Johnston Lab)

MARCO GEYMONAT: BBSRC Research Associate, Department of Genetics, University of Cambridge (Carazo Salas Lab)

YOSHIKO INOUE: Transferred to Gallop Research Group (Brown Lab)

ABDERRAHMANE KAIDI: Lecturer, School of Cellular and Molecular Medicine, Bristol University (Jackson Lab)

KAZUHIRO MURAKAMI: Assistant Professor, Hokkaido University, Japan (Surani Lab)

KRZYSZTOF WICHER: Research Scientist, MedImmune, Cambridge UK (Zernicka-Goetz Lab)

SELINA WRAY: Research Associate, UCL, London (Livesey Lab)

YU YE: Sir Henry Wellcome Research Fellow, Department of Chemistry, University of Cambridge (St Johnston Lab)

RESEARCH ASSISTANTS/TECHNICIANS

XENIA STUDERA Consultant, PriceSpective, London (Carazo Salas Lab)

PhD/MPhil STUDENTS

STOYANA ALEXANDROVA: PhD Student, Stem Cell Institute, University of Cambridge (Zernicka-Goetz Lab)

HELEN BOLTON: Clinician, Department of Obstetrics and Gynaecology at Addenbrooke's Hospital (Zernicka-Goetz Lab)

JORGE BUENDIA BUENDIA: Research Student, Wellcome Trust Centre for Cell Biology, University of Edinburgh (Brand Lab)

TARA FINEGAN: School of Biological Sciences, PhD Student, Gurdon Institute (Carazo Salas Lab)

NILS GRABOLE: Postdoctoral Fellow, Roche Pharmaceuticals, Basel, Switzerland (Surani Lab)

VERONIKA GRAML Consultant, Analytics, Deloitte Consulting AG, Zürich, Switzerland (Carazo Salas Lab)

JOSEPH HARVEY: Wellcome Trust Mathematical Genomics and Medicine PhD Student, Department of Genetics, University of Cambridge (Carazo Salas Lab)

JONATHAN LAWSON: Wellcome Trust PhD Student, Department of Genetics, University of Cambridge (Carazo Salas Lab)

NIC LEHRBACH: Postdoctoral Researcher, Ruvkun Lab, Department of Molecular Biology, Massachusetts General Hospital, USA (Miska Lab)

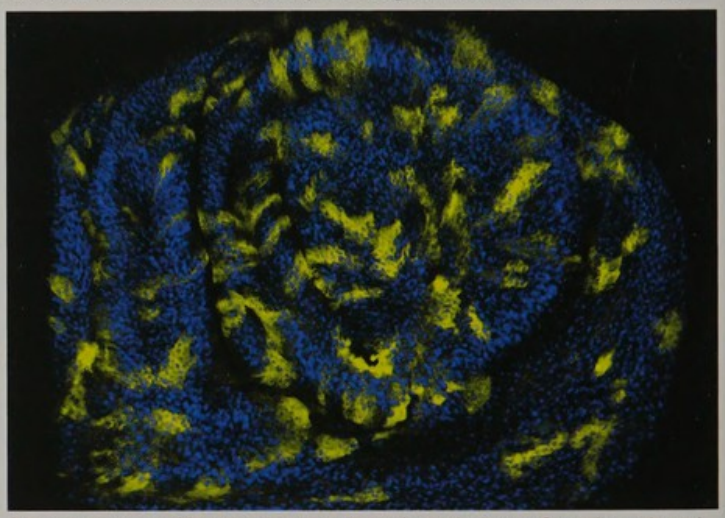
HARRY LEITCH: MB/PhD Student Clinical School, Addenbrooke's, Cambridge (Surani Lab)

PAOLA MARCO CASANOVA: Postdoctoral Researcher, David Komander Lab, MRC LMB, Cambridge (Pines Lab)

YUNG-CHIN OEI: Cancer Research UK PhD Student, Department of Genetics, University of Cambridge (Carazo Salas Lab)

YICHEN SHI: Managing Director, Axol Bioscience, Cambridge UK (Livesey Lab)

MARK ZIATS: Medical Student, Baylor College of Medicine, USA (Surani Lab)



3D reconstruction of Drosophila imaginal wingdisc with clones of membrane bound Venus (yellow) and DNA (blue) (Saskia Suijkerbuijk, Piddini lab)

A happy bunch! The Institute on retreat in Dunston Hall, Norfolk, in September 2013. (photo by James Smith, Livesey Group)

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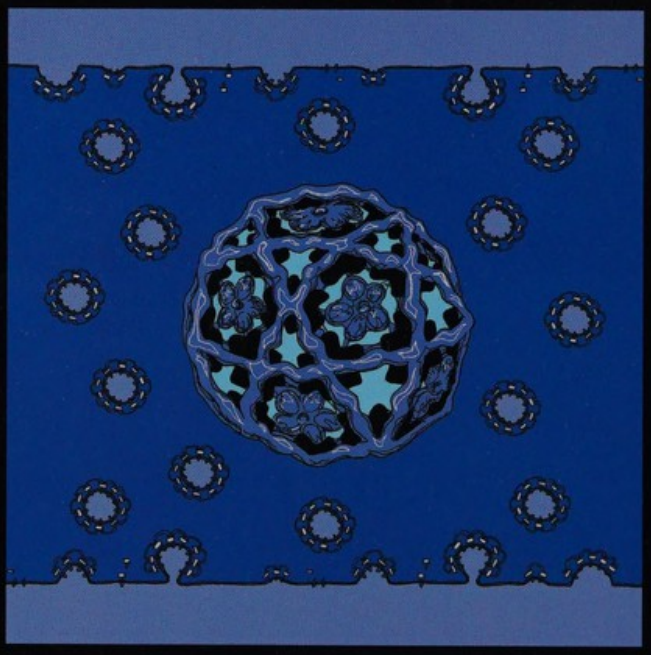
Front cover: Drosophila hemocytes (migratory cells with both immune and matrix remodelling functions) in the lumen formed between the layers of the Drosophila pupal wing. Apical hairs (green) overlay basal actin (red). (Aidan Maartens, Brown Group, 2013)

Back cover: Poster illustration for Randy Schekman (2013 Nobel Laureate) seminar in January. (Claudia Stocker, Carazo Salas Group, 2012, www.claudiastocker.com)



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, United Kingdom

Telephone: +44 (0)1223 334088
Fax: +44 (0)1223 334089
http://www.gurdon.cam.ac.uk
e-mail: info@gurdon.cam.ac.uk