Annual report : 2010/2011 / 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)

Publication/Creation

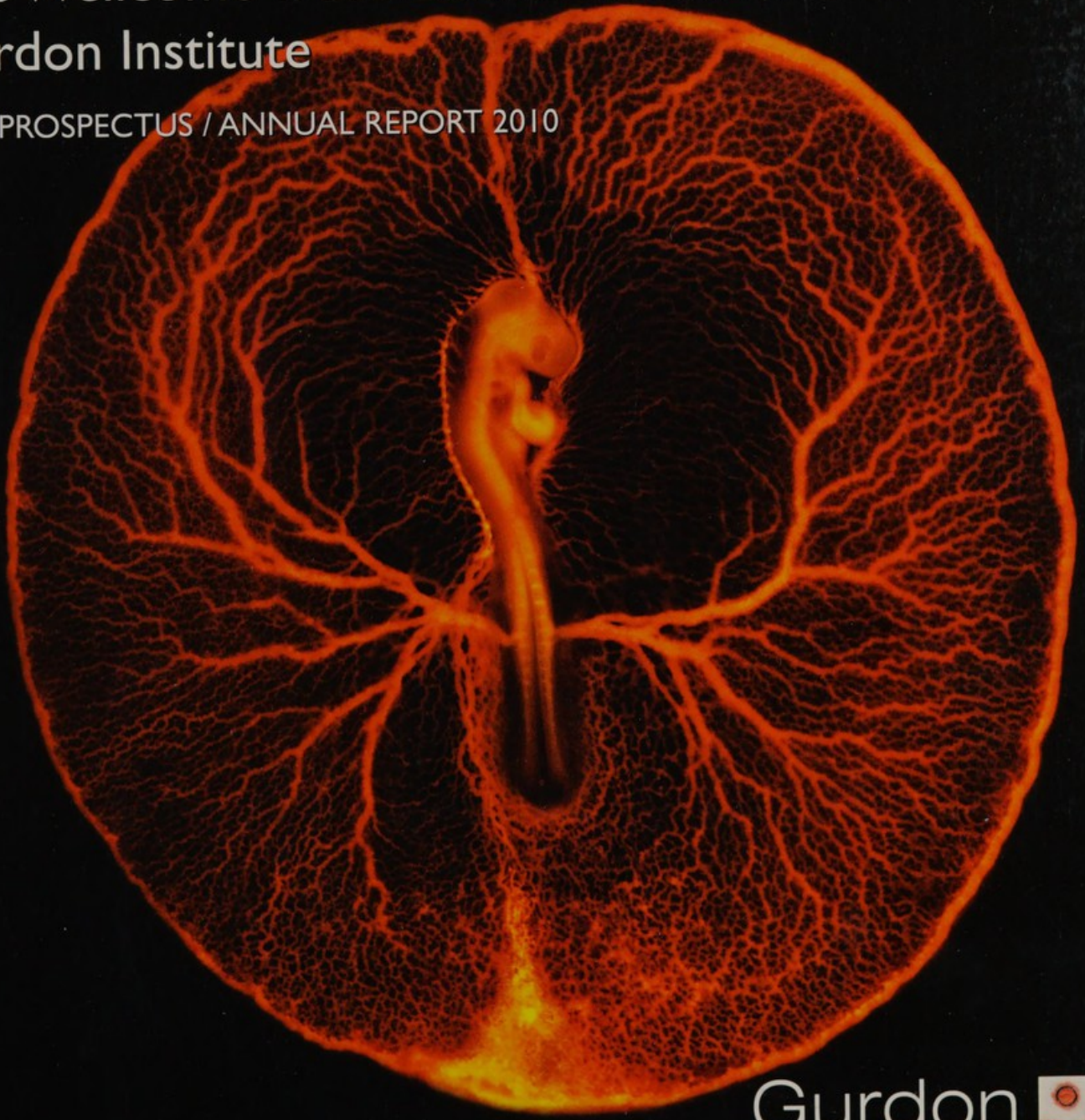
Cambridge : Wellcome Trust / Cancer Research UK Gurdon Institute, 2011

Persistent URL

https://wellcomecollection.org/works/pgnx96e3

The Wellcome Trust/Cancer Research UK Gurdon Institute

2011 PROSPECTUS / ANNUAL REPORT 2010



Gurdon INSTITUTE

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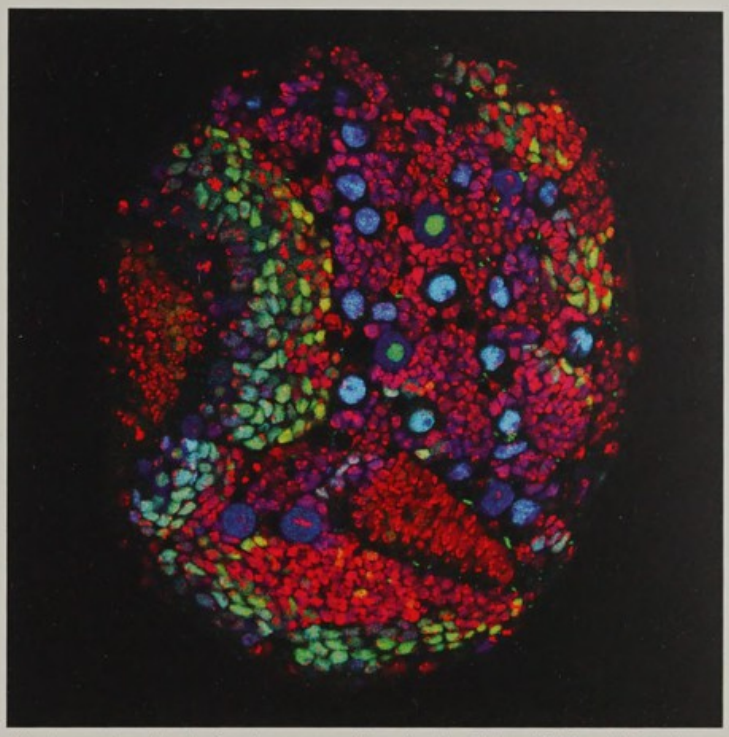
INTRODUCTION

This has been an exciting and successful year for the Institute in a number of ways. First, we have been delighted to welcome two new group leaders to the Gurdon. Eugenia Piddini joined us from Dr Jean-Paul Vincent's group at the National Institute of Medical Research, and has set up a group investigating the role of cell competition in development and cancer. Eugenia has been awarded a Royal Society Research Fellowship and has also obtained a Cancer Research UK programme grant to support her work. She is joined by Rafael Carazo-Salas, who moved with his group from the ETH in Zurich. Rafael is supported by a European Research Council starting grant and is taking systems biology approaches to investigate how fission yeast cells control their shape and microtubule cytoskeleton as they grow. We are also very pleased to have recruited Jenny Gallop, who will join the Gurdon next summer from Marc Kirschner's group at Harvard Medical School. Jenny's arrival will enhance our expertise in super-resolution total internal reflection fluorescence imaging and in vitro reconstitution with her studies on how filopodia form *in vitro* and *in vivo*.

Polarised neural stem cell rosettes derived from human induced pluripotent stem cells. Pax6 Red; Gamma Tubulin Green; DAPI Blue. (Yichen Shi, Livesey Group, 2010)



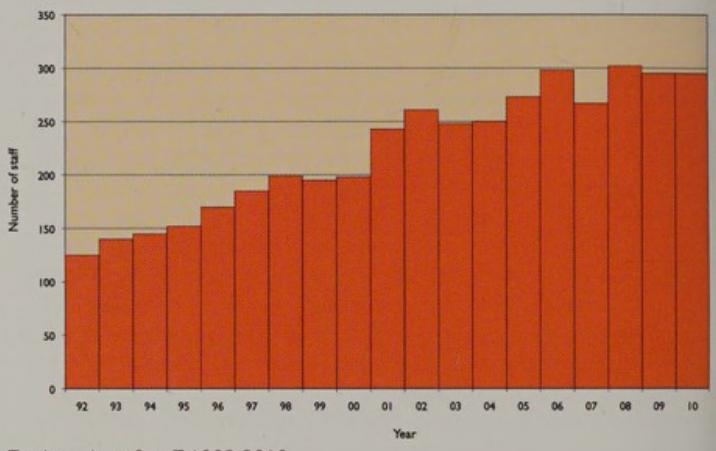
Third instar larval brain. Deadpan green; Neuralised-lacZ blue; DNA red. (Boris Egger, Brand Group, 2010)

Much of my time this year has been taken up by preparations for the five-year review of the Institute by the Wellcome Trust and Cancer Research UK. I am happy to report that we passed with flying colours, and have been awarded £14.5 million over the next five years to fund the core staff and facilities that underpin all of our research. Given the difficult economic climate, we are very grateful for the continuing generous support from our sponsors. Many thanks are due to every one who contributed to our weighty submission, in particular our administrator, Ann Cartwright, and chief technician, Diane Foster.

The renewal of our core funding and Wellcome Trust Centre status is largely due to the international reputation of our group leaders and the outstanding research going on in their groups, as I hope that the rest of this prospectus will reveal. For example, Tony Kouzarides and Steve Jackson were both listed this year as being amongst the 20 most cited authors in the field of Molecular Genetics and Genomics. The achievements of other group leaders have also been recognised in a number of ways. Azim Surani was awarded the Royal Medal of the Royal Society "for his pivotal contributions to the understanding

of early mammalian development". Andrea Brand was elected a Fellow of the Royal Society this year for "her pioneering work on the development of the nervous system". This is particularly pleasing as she is the third group leader in the last five years who began their independent research career in the Institute and has gone on to become an FRS. We are also delighted that Nick Brown has been elected a member of the European Molecular Biology Organisation for his work on integrins. Finally, congratulations are due to Magda Zernicka-Goetz who has been promoted to a Professorship in the University of Cambridge.

Amongst the other notable events this year was a symposium to mark the forthcoming retirement of Ron Laskey, who was one of the founders of the Gurdon Institute nearly twenty years ago. Although Ron left us in 2001 to found the Hutchison/MRC Research Centre in Cambridge, he played a key role in setting up the Institute and recruiting many of the group leaders who are still here, and it was fitting that several of the speakers were present or former members of the Institute. We also hosted the Wellcome Trust governors and senior staff during their recent visit to Cambridge, and appreciated the opportunity to meet them and tell them about our work. Finally, our International Scientific Advisory Board have recently spent two days in the Institute hearing about our research and future plans. As always, Robb Krumlauf and his colleagues provided us with lots of useful advice and support, and we look forward to welcoming them back in the spring of 2012, when we will celebrate our 21st birthday with an anniversary symposium.



Total number of staff, 1992-2010

Distribution of researchers' nationalities (red), September 2010

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 newly-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.

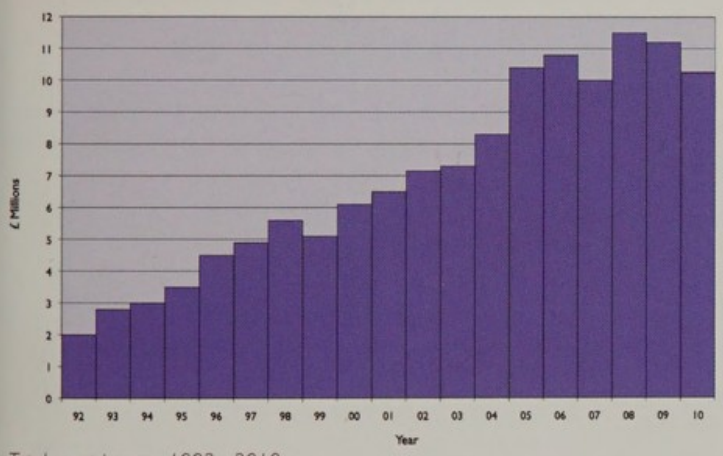
The Institute is an integrated part of Cambridge University, and all group leaders are also members of another University department within the School of Biological Sciences, and contribute to both undergraduate and graduate student teaching.

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

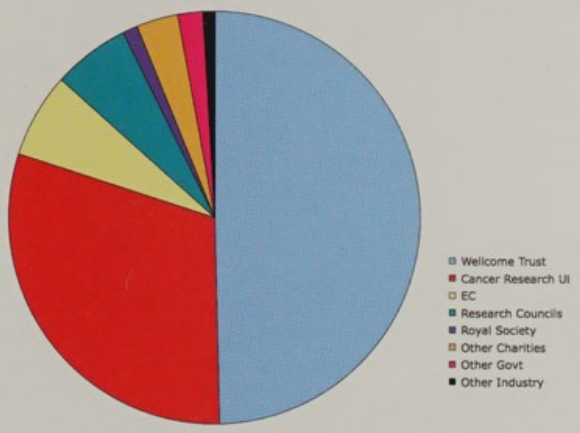
Our two major funding bodies, the Wellcome Trust and Cancer Research UK continue to offer the Institute vital backing in the form of Fellowships, individual programme, project and equipment grants, in addition to our invaluable core funding.



Total grant income 1992 - 2010

Other sources of funding, both direct and indirect, include The European Commission, BBSRC, MRC, the Royal Society, NIH, the European Molecular Biology Organization, HFSP, JDRF, the Isaac Newton Trust, the Association for International Cancer Research, the Alzheimer's Research Trust, the Ernst Shering Foundation, the Federation of European Biochemical Societies, the Japan Society for the Promotion of Science, the Sankyo Foundation of Life Science, the Swiss National Science Foundation, the Wenner-Gren Foundation, the Wiener-Anspach Foundation and Astra Zeneca.

The University has also been very generous in its support of the Institute, particularly in funding equipment.



Grant sources (July 2009 - July 2010)

RETREAT

Our Annual Retreat this year was held at the Five Lakes Hotel, Maldon, Essex on 29th and 30th September 2010. The event was highly successful. Many Institute members attended and all gained from the experience both scientifically and socially.

The Institute on retreat, October 2010 (image by John Overton, Brown Group)

Julie Ahringer

Chromatin regulation in transcription and splicing, and cell polarity establishment and transduction

Co-workers: Anne Vielle, Ron Chen, Michael Chesney, Yan Dong, Sky Feuer, Bruno Fievet, Moritz Herrmann, Paulina Kolasinska-Zwierz, Josana Rodriguez, Przemyslaw Stempor, Christine Turner, Eva Zeiser

Regulation of chromatin structure plays a central role in transcriptional control and also impacts mRNA post-transcriptional events. The small well-annotated genome, powerful RNAi technology, and rich resource of chromatin mutants of *C. elegans* make it an excellent system for studies of chromatin function. To provide a framework for such work, we generated a genome-wide map of 18 histone modifications in *C. elegans*. We found that many modifications are organised into broad chromosomal domains that differentially mark the more recombinagenic distal arm regions and the central regions. In addition, we found that exon and intron sequences are differentially marked by trimethylation of histone H3 K36, a pattern we also found in mouse and human. We are studying the formation and function of the broad domains, and the function of H3K36me3 exon marking and its relationship with splicing. We are also investigating the functions of *C. elegans* counterparts of major chromatin regulatory complexes that are implicated in human disease including the histone deacetylase complex NuRD, the retinoblastoma complex DRM, and a TIP60 histone acetyltransferase complex. We study the function of these proteins in transcriptional control and development using chromatin immunoprecipitation followed by deep sequencing, global mRNA expression analyses and other genetic and genomic methods.

Cell polarity is important for many of the functions of animal cells, such as migration, axis formation, and asymmetric cell division. Many of the known molecules involved in cell polarity are conserved across animals, however, the mechanisms by which these function are not well understood. We use the one-celled *C. elegans* embryo to investigate the polarity cue, its reception, and how polarisation leads to downstream events such as asymmetric spindle positioning. We have completed a large number of genetic interaction RNAi screens that have identified many new cell polarity genes. We are incorporating these into a large cell polarity network and probing their functions using a range of techniques, including live cell imaging, genetics, and biochemistry.

Selected publications:

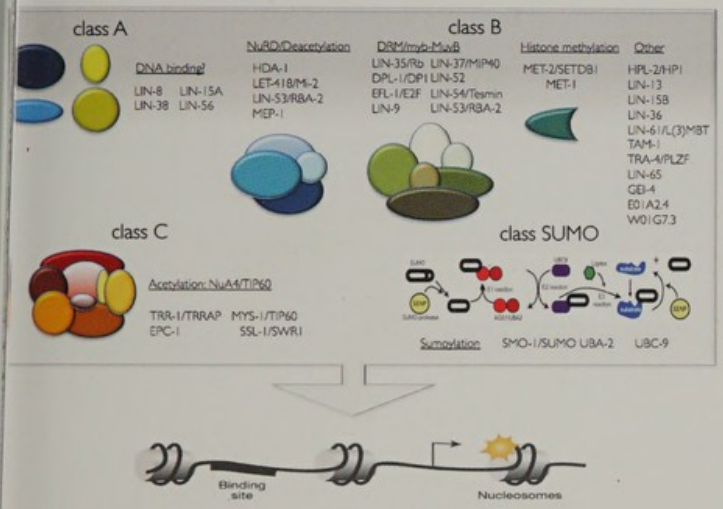
• Liu T, **Ahringer J** et al (2011) Broad chromosomal domains of histone modification patterns in *C. elegans*. Genome Research [in press]

• Gerstein MB, **Ahringer J** et al (2010) Integrative Analysis of the *Caenorhabditis elegans* Genome by the modENCODE Project. Science 330, 1775-1787

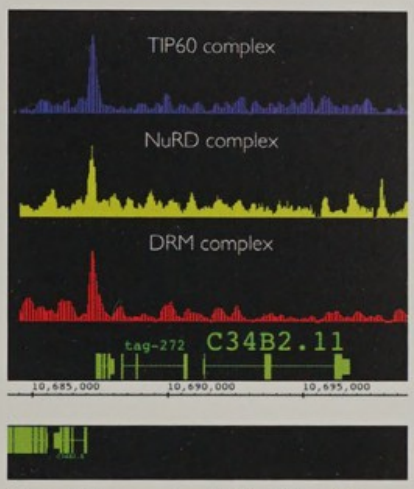
• Egelhofer TA, **Ahringer J** et al (2010) Assessment of histone-modification antibody quality. Nature Structural and Molecular Biology 18, 91-93

• 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

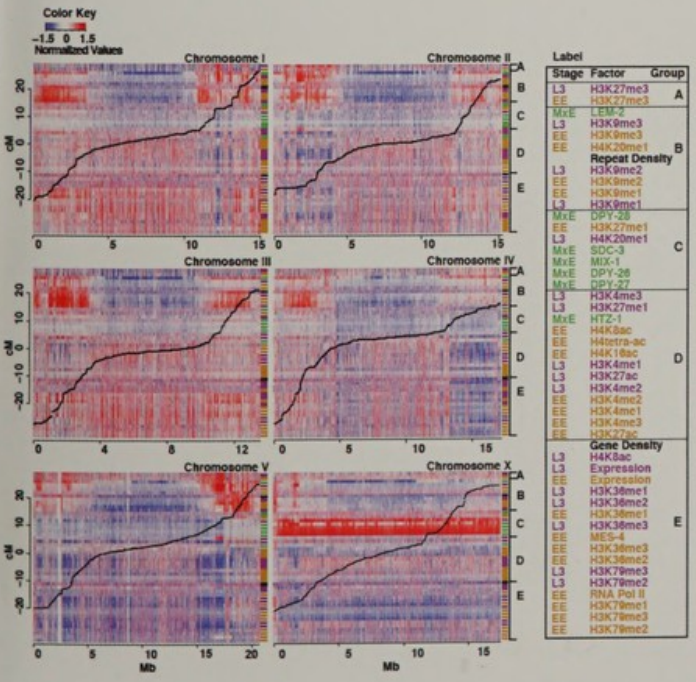
• **St Johnston D** and **Ahringer J** (2010) Cell polarity in eggs and epithelia: parallels and diversity. Cell, 141, 757-774



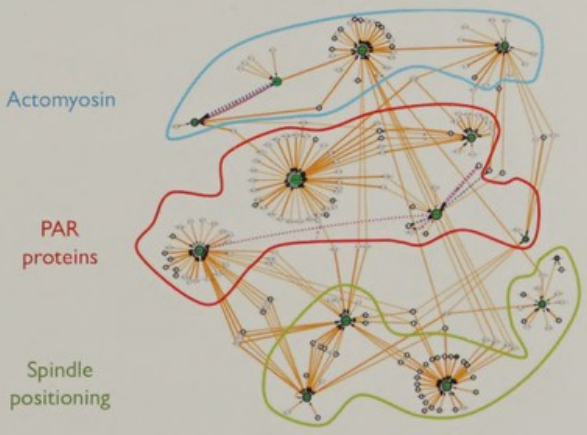
ynMuv proteins encode homologs of chromatin regulators found in omplexes that modify histones or move nucleosomes.



Chromatin immunoprecipitation followed by high-throughput sequencing reveals common sites occupied by different chromatin regulatory complexes



Histone modifications are found in broad chromosomal domains in C. elegans



Interconnected cell polarity network derived from genetic interaction RNAi screening

Andrea Brand

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

Co-workers: Elizabeth Caygill, Esteban Contreras-Sepulveda, Melanie Cranston, Catherine Davidson, Boris Egger, Katrina Gold, Harry Han, Clare Howard, Jun Liu, Tony Southall, Pauline Spéder, Alyson Thompson, Christine Turner, Pao-Shu (Paul) Wu

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. Symmetrically dividing stem cells exist in the optic lobe of the brain, where they convert to asymmetrically dividing neuroblasts. 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. 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.

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. By identifying Prospero's targets throughout the genome we 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.

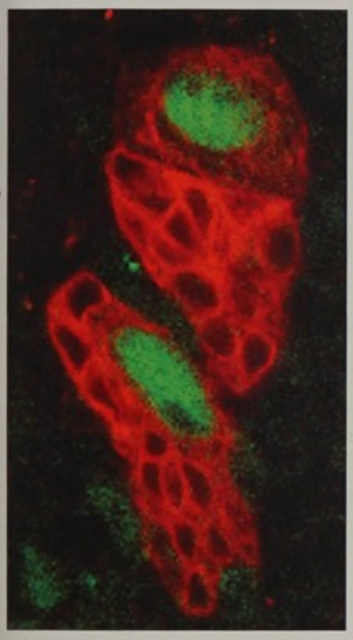
Neural stem cells transit through a period of quiescence at the end of embryogenesis. We showed that insulin signalling is necessary for these stem cells to exit quiescence and reinitiate cell proliferation, we identified nutrition-responsive glial cells as the source of the insulin-like peptides that reactivate neural stem cells *in vivo*.

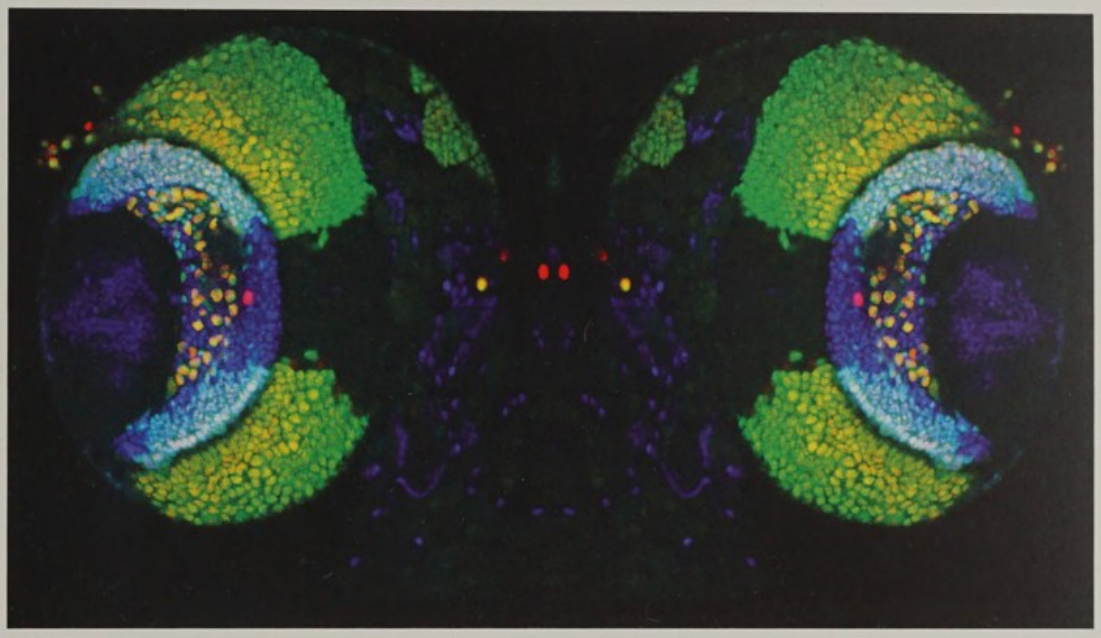
For more information, see the Brand lab home page:

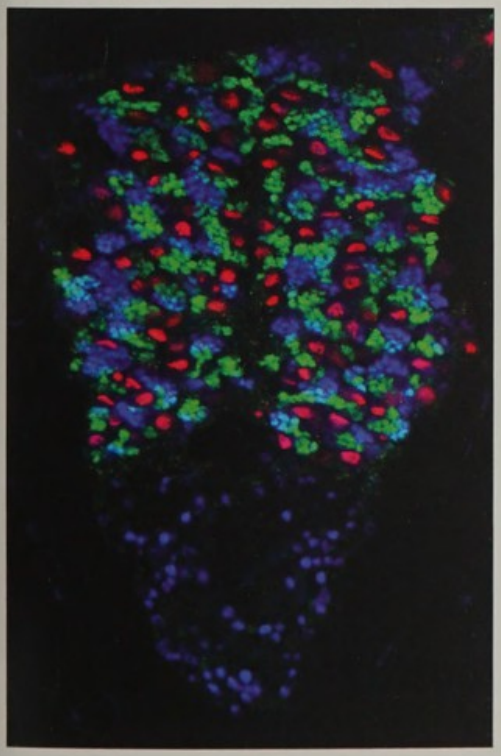
http://www.gurdon.cam.ac.uk/~brandlab/

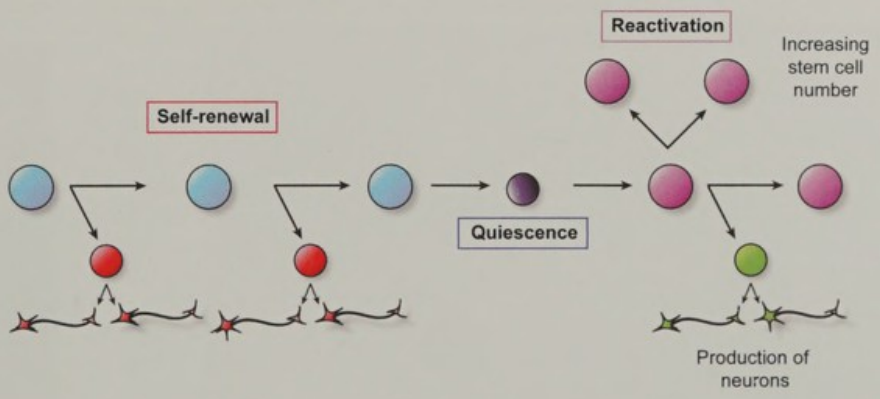
Selected publications:

- Chell JM and **Brand AH** (2010) Nutrition-responsive glia control exit of neural stem cells from quiescence. Cell 143(7), 1161-1173
- Egger B, Gold KS and **Brand AH** (2010) Notch regulates the switch between symmetric and asymmetric neural stem cell division in the *Drosophila* optic lobe. Development, 137, 2981-2987
- Bardin AJ, Perdigoto CN, Southall TD, **Brand AH** and Schweisguth F (2010) Transcriptional control of stem cell maintenance in the *Drosophila* intestine. Development 137, 705-714
- Monier B, Pelissier A, **Brand AH** and Sanson B (2010) An actomyosin-based barrier inhibits cell mixing at compartmental boundaries in *Drosophila* embryos. Nature Cell Biology 12, 60-65
- Southall TD and **Brand AH** (2009) Multiple transcription factor binding identifies neural stem cell gene regulatory networks. EMBO J. 28, 3799-807









Top left: two neural stem cell clones in the larval brain, labelled in red. Neuroblast nuclei are green.

Top right: Lineage tracing in the Drosophila optic lobes of the Drosophila brain, using the Gtrace system. Cells currently expressing the transcription factor Optix express RFP (red); cells descended from Optix-expressing cells express GFP (green). The transcription factor Dachshund (blue) marks the lamina region of the developing visual system.

Left: Expression of temporal transcription factors Castor (green) and Chinmo (blue) in the larval ventral nerve cord. Neuroblasts in red.

Above: 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).

Nick Brown

Molecular analysis of morphogenesis

Co-workers: Natalia Bulgakova, Jonathan Friedlander, Annabel Griffiths, Sven Huelsmann, Yoshiko Inoue, Benjamin Klapholz, Matt Newton, John Overton, Peerapat Thongnuek, Jutta Wellmann, Jari Ylanne

Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, which stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one family of cell surface receptors, called integrins, can perform both of these activities, and therefore provide a molecular link between cell adhesion and signalling. Our research is focused on determining how proteins inside and outside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers, and cell differentiation.

We use the genetics of the fruit fly Drosophila to elucidate integrin function within the developing animal, to identify the proteins that work with integrins and decipher how they function. In this way, we aim to discover how integrins perform such distinct roles at different times and places during development. In the developing embryo a major function of integrins is to attach the ends of the large multinucleate muscles to the epidermal tendon cells (Fig. 1). In the absence of certain integrin-associated proteins, such as talin, integrin-mediated attachment of the muscles fails (Fig. 2), while paxillin controls the number of cell fusions, thus dictating muscle size. In the follicular epithelia, integrins organise dynamic actin structures (Fig. 3) that drive changes in cell shape. Some integrin-associated proteins have multiple tasks, including those that are crucial for integrin function and those within other pathways. We are dissecting out how these molecules act in diverse ways, such as mapping the part of talin that controls the expression of another cell adhesion molecule, which in turn is critical for the earliest polarity in the developing egg (Fig. 4).

Selected publications:

• Delon I and **Brown NH** (2007) Integrins and the actin cytoskeleton. Curr Opin Cell Biol 19, 43-50

• Delon I and **Brown NH** (2009) The integrin adhesion complex changes its composition and function during morphogenesis of an epithelium. J Cell Sci 122, 4363-437

• Bataillé L, Delon I, Da Ponte JP, **Brown NH** and Jagla K (2010) Downstream of identity genes : Muscle-type specific regulation of fusion process. Dev Cell 19, 317-28

• Sabino D, **Brown NH** and Basto R (2011) Ajuba restrict Aurora A activity to the centrosome but it is not an Aurora-A activator. J Cell Sci [in press]

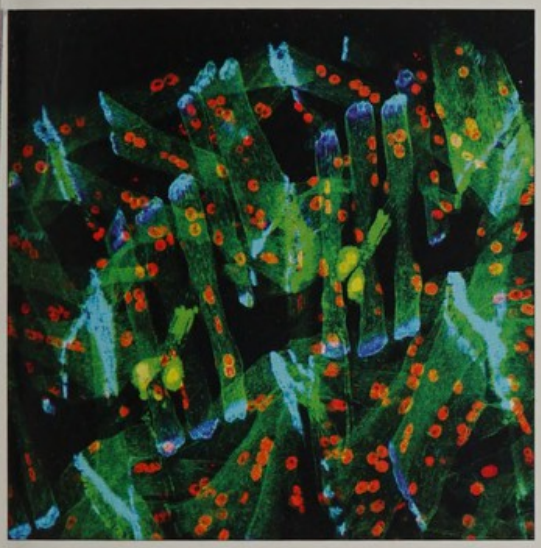


Fig. 1 Live imaging of muscles in the developing embryo. Their outer surfaces are outlined in green (CD8-GFP), and they use integrins and their associated proteins to regulate their size by controlling the number of cell fusion events, visible by the number of nuclei (red, histone-RFP) in each muscle, and by generating specialised attachments sites at the muscle ends, with concentrated integrins (blue, integrin-linked-kinase-BFP)

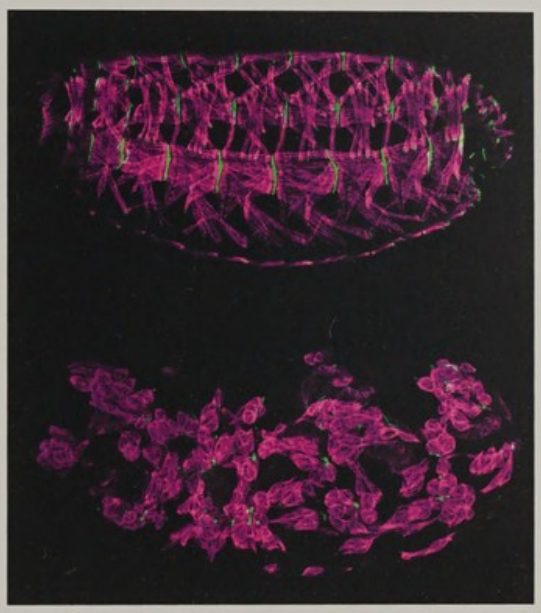


Fig. 2. Wild type embryo (top) and an embryo lacking the integrin-associated protein talin (bottom). Talin is needed for the integrins (green) to attach the ends of the muscles (purple), but not for the concentration of integrins at muscle ends.

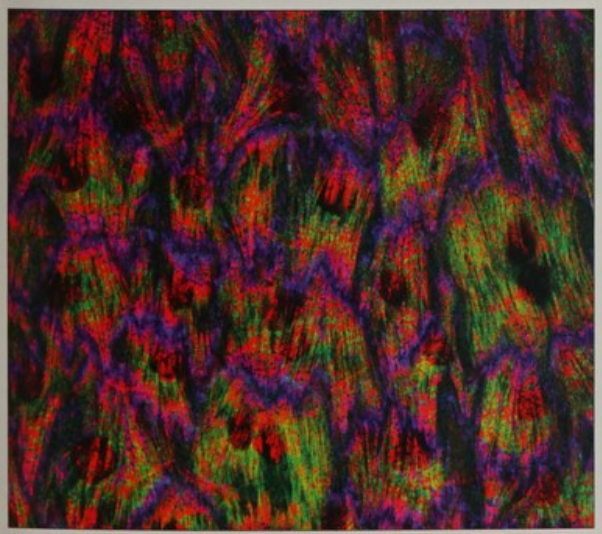


Fig. 3. Integrins (blue) organise contractile stress fibres within the follicle cell epithelium, composed of actin filaments (green) and the motor protein myosin (red).

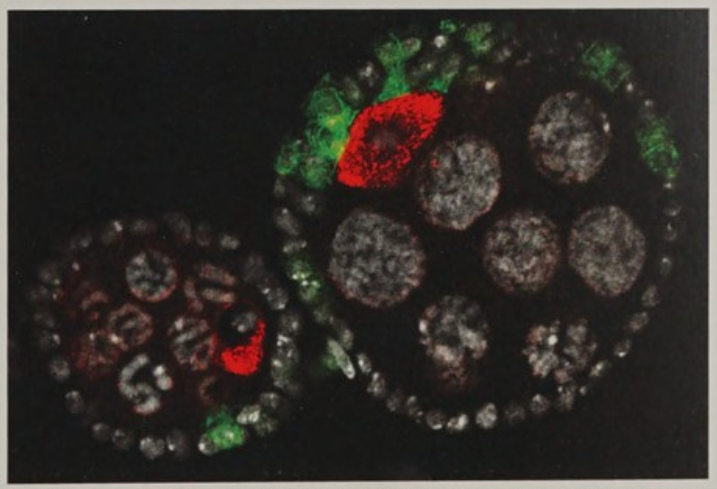


Fig. 4 The lack of talin in a patch of follicle cells (green) from the ovarian egg chamber often causes the oocyte (red) to become attached to the mutant cells, instead of at its normal position at the posterior pole (right side, also visible in the smaller egg chamber). This occurs because the mutant cells increase their synthesis of the cell adhesion molecule cadherin, which sticks the cells to oocyte. Only a fraction of the talin molecule is required for this function. The DNA in the nuclei of the cells is shown in white.

Rafael Carazo Salas

Functional genomics of cell morphogenesis

Co-workers: Anatole Chessel, James Dodgson, Marco Geymonat, Veronika Graml, Yung-Chin Oei, Kathy Oswald, Xenia Studera

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 work seeks to identify the gene and protein networks that regulate these three processes and overall cell morphogenesis, in space and time. To that end we adopt a multi-disciplinary approach combining high-content and quantitative microscopy, genetics, biochemistry and computational methods. We use fission yeast as primary model organism and plan to extend our scope to mammalian cells in the future.

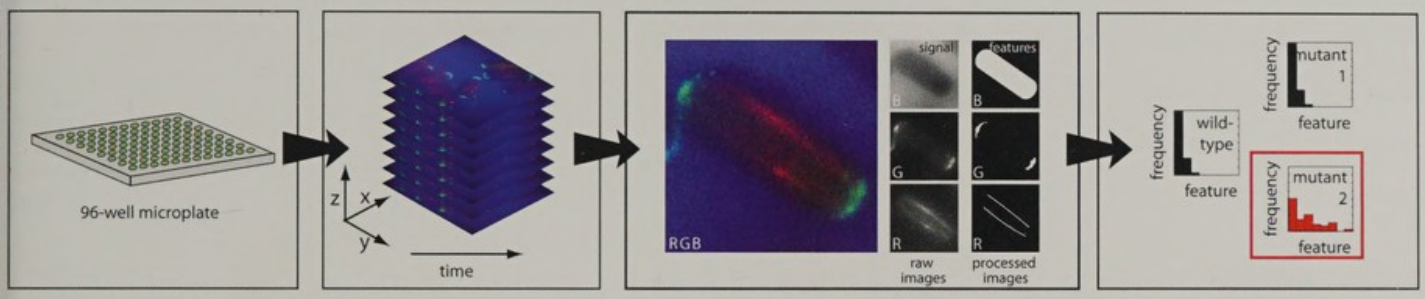
We recently established a high-throughput/high-content microscopy platform for yeast-based functional genomics studies. Using that platform and systematic gene knock-outs, we are about to begin the first comprehensive live cell-based screen for microtubule and cell shape regulators. With this screen we expect to discover many novel regulators and hope to obtain the most exhaustive genomic map and spatiotemporal annotation of such regulators to date.

We have also developed, in collaboration with theoreticians, computational methods to simulate the collective interaction of microtubules and microtubule regulator recipes in 3D over time, in order to clarify the mechanisms that precisely pattern microtubules in cells. We find that, together with regulator abundance, cell geometry is a strong determinant of microtubule pattern, something we are actively investigating experimentally.

Lastly, we have begun characterising the dynamics and structure of the polarity machinery at high spatiotemporal resolution. Using live super-resolution microscopy and custom-made image analysis tools, we find that components of the machinery previously thought to regulate polarity by physically interacting at the cell cortex actually localise to separate, distinct complexes. This suggests novel layers of polarity regulation we are seeking to unravel.

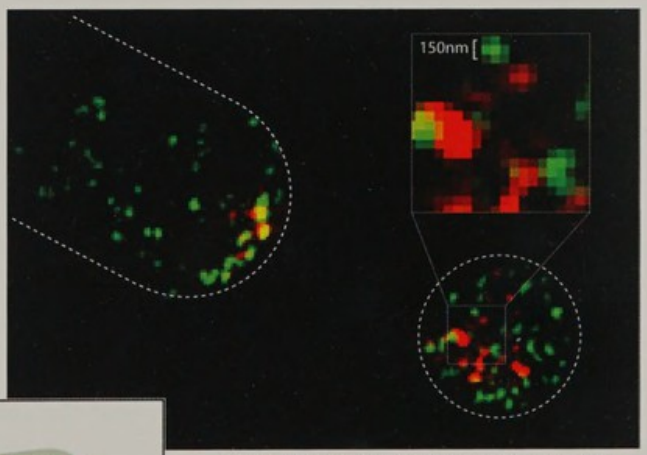
Selected publications:

- **Carazo-Salas RE**, and Nurse P (2007). Sorting out interphase microtubules. Mol Syst Biol 3:95-6.
- Salinas S, **Carazo-Salas RE**, Proukakis C, Schiavo G, Warner TT (2007). Spastin and microtubules: Functions in health and disease. J Neurosci Res 85(12):2778-82.
- **Carazo-Salas RE**, and Nurse P (2006). Self-organization of interphase microtubule arrays in fission yeast. Nat Cell Biol 8(10):1102-7.
- Salinas S, **Carazo-Salas RE**, Proukakis C, Cooper JM, Weston AE, Schiavo G, Warner TT (2005). Human spastin has multiple microtubule-related functions. J Neurochem 95(5):1411-20.
- **Carazo-Salas RE**, Antony C, Nurse P (2005). The kinesin Klp2 mediates polarization of interphase microtubules in fission yeast. Science 309(5732):297-300.

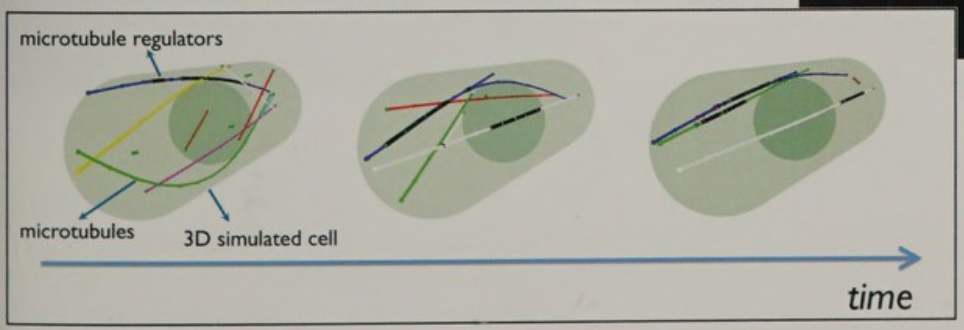


A high-throughput/high-content microscopy workflow used to systematically screen through the genome for novel regulators of cell morphogenesis.

High-resolution image of cells expressing GFP-tubulin, generated with an automated high-throughput spinning disc confocal microscope.



Polarity complexes visualised at superresolution. Live cells expressing two fluorescently-labelled (green:GFP, red: mCherry) polarity factors. Super-resolution reveals that both factors, thought to regulate polarity by physically interacting, belong to separate 150nm-sized complexes. Left: cell visualised 'sideways'. Right: cell visualised 'head on'. Dotted lines: cell contours.



Snapshots from a computer simulation of microtubule organisation in a virtual cell.

Thomas Down

Epigenomics and transcription informatics

Co-workers: Paulina Chilarska, Kenneth Evans, Jing Su

We study the mechanisms by which programs of gene expression are selected and perpetuated during the development of multicellular organisms. Regulatory sequence elements contain clusters of binding sites for transcription factors, most of which interact with some specific DNA sequence motif. By discovering the repertoire of transcription factor binding sites, we can uncover an important part of the cell's regulatory network. We are addressing this question using a new computational motif discovery tool, NestedMICA, to find DNA sequence motifs that are over-represented in larger sets of regulatory sequences from across the genomes of a panel of multicellular organisms.

It has become increasingly clear that the function of regulatory elements depends on their context in terms of nuclear location and chromatin structre. To this end, we are keen to understand the landscape and functions of stable epigenetic modifications - particularly DNA cytosine methylation. High-throughput sequencing technologies allow epigenetic marks to be studied on a genome-wide basis, and we have used a combination of deep sequencing and a new analytical technique to generate the first map of DNA methylation across a complete vertebrate genome. We are now combining this technology with other analysis and data visualisation methods in order to study how DNA methylation interacts with other regulatory and epigenetic mechanisms. We are also investigating how human DNA methylation changes are associated with ageing and complex diseases.

Selected publications:

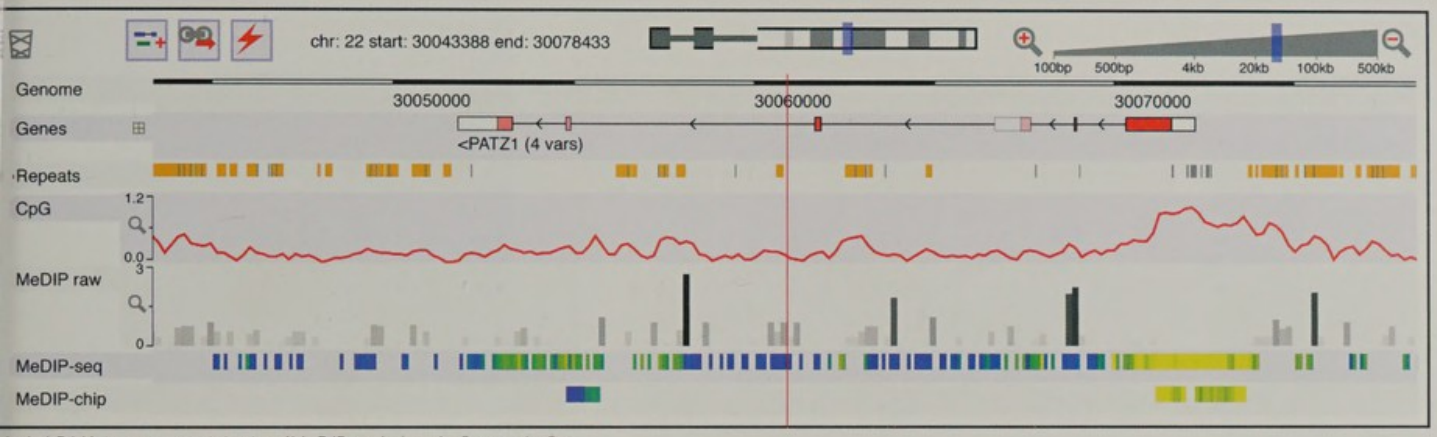
• Rakyan VK, **Down TA**, Maslau S, Andrew T, Yang T-P, Beyan H, Whittaker P, McCann OT, Finer S, Valdes AM, Leslie RD, Deloukas P, and Spector TD (2010) Human aging-associated DNA hypermethylation occurs preferentially at bivalent chromatin domains. Genome Res. 20:434-439

• 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

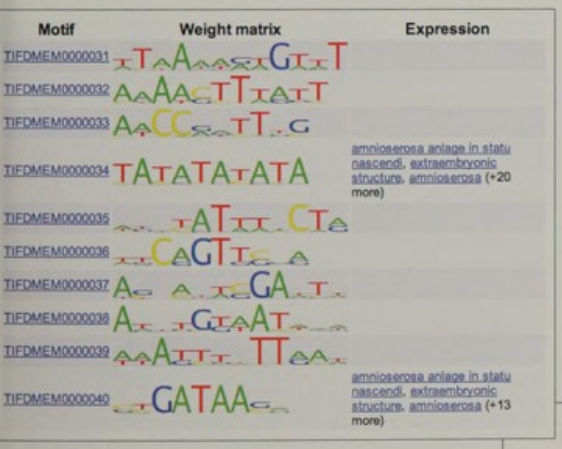
• **Down TA**, Rakyan VK, Turner DJ, Flicek P, Li J, Kulesha E, Graf S, Johnson N, Herrero J, Tomazou EM, Thorne NP, Backdahl L, Herberth M, Howe KL, Jackson DK, Miretti MM, Marioni JC, Birney E, Hubbard TJP, Durbin R, Tavare S and Beck S (2008) A Bayesian deconvolution strategy for immunoprecipitation-based DNA methylome analysis. Nature Biotech 26:779-785

• **Down TA**, Bergman CM, Su J and Hubbard TJP (2007) Large scale discovery of promoter motifs in *Drosophila* melanogaster. PLoS Comput Biol 3:e7

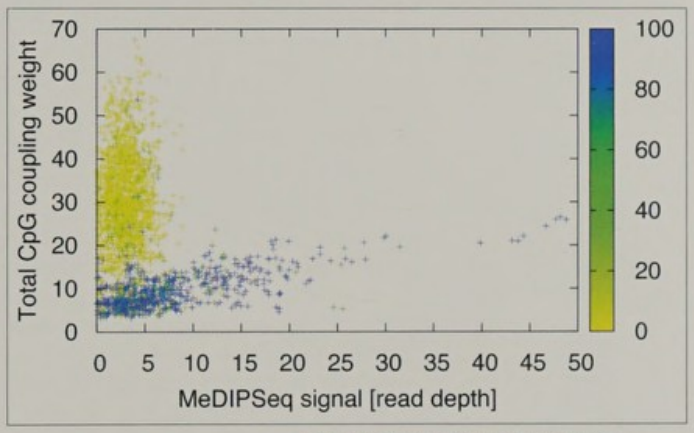
• **Down TA** and Hubbard TJP (2005) NestedMICA: sensitive inference of over-represented motifs in nucleic acid sequences. Nucleic Acids Res 33, 1445-1453



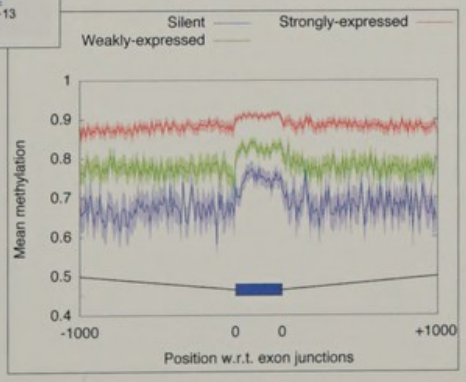
Methyl-DNA immuonprecipitation (MeDIP-seq) data before and after normalisation using the Batman method. Viewed in the Dalliance genome visualisation tool (http://www.biodalliance.org/)



The BioTIFFIN interface for browsing regulatory sequence motifs.



The Methyl DNA Immunoprecipitation (MeDIP) technique can be used to quantify the methylation state of genomic DNA on a large scale. In methylated regions (coloured blue), signal correlates with the density of CpG dinucleotides.



Multiple epigenetic marks "paint" exons in the genome. In the case of DNA methylation (shown here) the marking of exon boundaries is remarkably sharp, and appears to be independent of transcription. (single-base methylation data from Lister et al. Nature AOP 14th October 2009).

Jenny Gallop

Membranes, actin and morphogenesis

Co-workers: Recruitment to the Gallop lab will commence in 2011

Understanding the molecular basis of cell shape and the changes that occur when cells move is vital for understanding the different cell rearrangements that underlie morphogenesis. The actin cytoskeleton is of key importance. The actin cytoskeleton is remodelled in response to changes in the cellular environment, which are transduced through signalling at the plasma membrane. Many actin regulators are recruited to membranes and my lab will study how the organisation of proteins at membranes prompts the formation of distinct actin structures that influence cell shape and movement. We hope to gain a better understanding of how the changes in cell shape lead to morphogenesis in the whole organism.

We will particularly concentrate on how actin is polymerised during filopodia formation and endocytosis. Filopodia are finger-like actin-rich protrusions that are thought to be sensory structures. In previous work I established an *in vitro* reconstitution system using supported lipid bilayers and *Xenopus* egg extracts that recapitulates the formation of actin structures resembling filopodia (Fig 1), and proposed a model for how filopodia form in cells (Fig 2). The role of actin in endocytosis is somewhat unclear, but there are many molecular links that suggest it is important. Endocytic actin structures can also be recapitulated using reconstitution systems and key actin regulator, toca, found using this approach, appears to be involved in endocytosis and gastrulation in *Xenopus* (Fig 3).

Specifically we will ask: how are filopodia formed? How are endocytic actin structures generated at the membrane and in what ways is this different from filopodia formation? How are the proteins that regulate actin structures used during morphogenesis? To answer these questions we will take a two-pronged approach: (1) reconstitution of actin polymerisation *in vitro* using artificial membranes and *Xenopus* egg extracts combined with advanced microscopy and (2) investigation of how actin regulators are used by cells *in vivo* during early development in the frog, *Xenopus laevis*. This interdisciplinary approach has two main strengths: (1) The possibility of attaining a complete molecular understanding using the *in vitro* systems and (2) study of cell biological events within the natural complement of physiological signals provided by the whole organism.

Selected publications:

• Lee K*, **Gallop JL***, Rambani K and Kirschner MW (2010) Self-assembly of filopodia-like structures on supported lipid bilayers. Science 329: 1341-1345

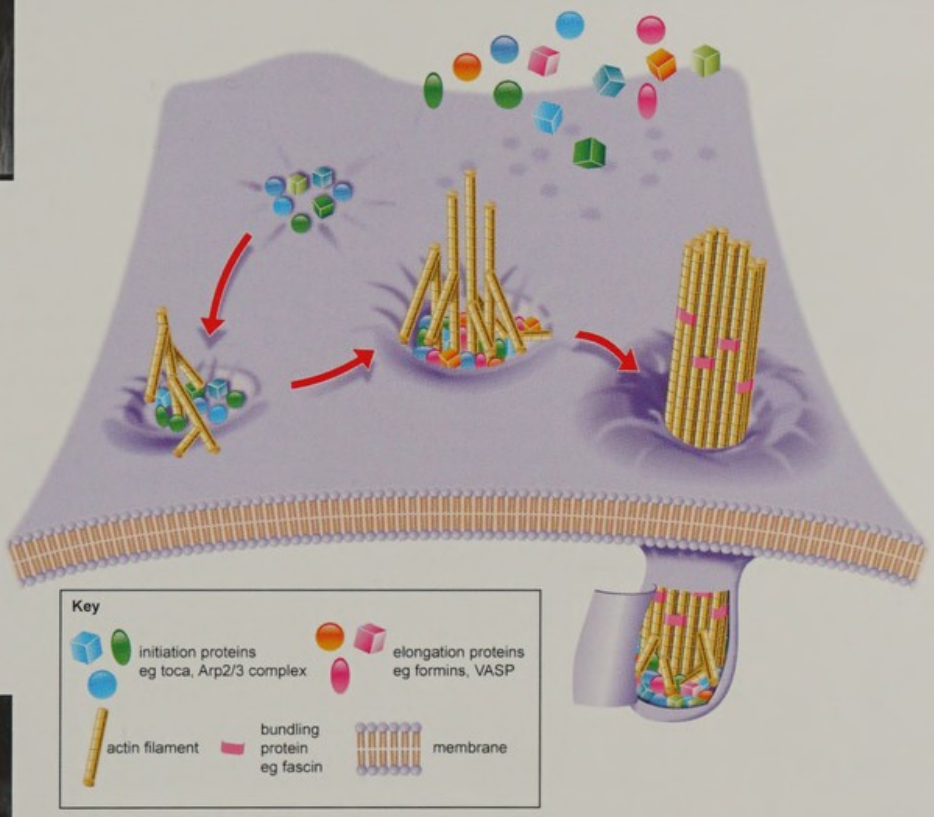
• **Gallop JL***, Jao CC*, Kent HM, Butler PJ, Evans PR, Langen R and McMahon HT (2006) Mechanism of endophilin N-BAR domain-mediated membrane curvature. EMBO J 25: 2898-2910

• **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

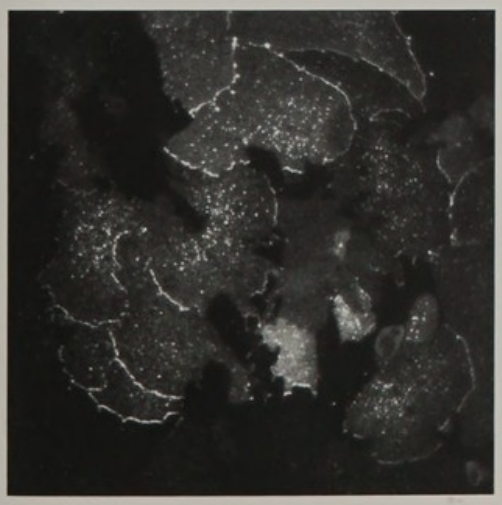
• McMahon HT and **Gallop JL** (2005) Membrane curvature and mechanisms of dynamic cell membrane remodelling. Nature 438: 590-596

(* joint first authors)

(1) Filopodia-like structures made of fluorescently-labelled actin which grow from supported lipid bilayers (at the base of the picture).



(2) Model for filopodia formation from the study of filopodia-like structures, with an initial clustering step followed by actin polymerisation at the membrane surface then elongation of actin filaments to cause outgrowth of the filopodium.

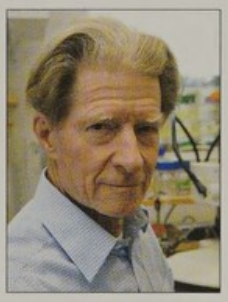


(3) Toca localisation to lamellipodial edges, filopodia tips and endocytic vesicles in cells within a Keller explant from a Xenopus gastrula.

John Gurdon

Chromatin regulation in transcription and splicing, and cell polarity establishment and transduction

Co-workers: Dilly Bradford, Nigel Garrett, Richard Halley-Stott, Jerome Jullien, Kei Miyamoto, Patrick Narbonne, Maryna Panamarova, Vincent Pasque, Marta Teperek-Tkacz



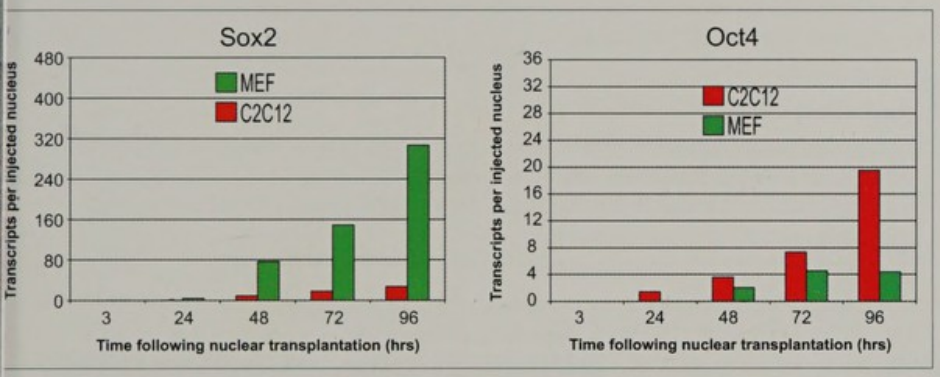
Our aim is to understand two aspects of somatic cell nuclear transfer to eggs and oocytes. First, we aim to identify the components of amphibian eggs and oocytes that can reprogram the nuclei of differentiated cells so that embryonic genes are re-expressed. This makes it possible, in some cases, to derive a normal adult animal by transplanting the nucleus of a specialised cell to an enucleated egg. Second, we wish to understand what components of specialised cell nuclei resist the reprogramming factors of eggs and oocytes. This would explain the dramatic reduction in the efficiency of reprogramming when donor nuclei are taken from progressively more differentiated cells. As we identify important components of eggs and oocytes, and those of the chromatin of specialised cells, we analyse the mechanisms by which these components have their effect.

To analyse the basis of both the ability of eggs to reprogram nuclei and the resistance of the nuclei of specialised cells to this activity, we transplant nuclei from differentiated cells of both amphibia and mammals to the germinal vesicle of oocytes of *Xenopus*. Oocytes have the special property of directly switching the transcriptional profile of an adult somatic cell nucleus to that of an embryo or stem cell. They do this directly with no DNA synthesis or cell division and in the absence of protein synthesis; within a few hours, transcripts of Oct4, Nanog, and other stem cell marker genes increase by a factor of up to 100 times. We use antibodies to reduce the content of individual proteins of an oocyte to test the function of these proteins. We remove proteins from somatic nuclei before transplantation to identify gene repressors in somatic cells. We find that the oocyte can activate a wide range of genes in different lineages, and has a general gene derepressing activity likely to be characteristic of very early embryos.

This identification of natural molecules and mechanisms that promote and inhibit gene reprogramming in somatic cells may eventually contribute to procedures for cell replacement in humans.

Selected publications:

- **Gurdon JB** and Melton DA (2008) Nuclear reprogramming in cells. Science 322, 1811-1815
- Murata K, Kouzarides T, Bannister AJ and **Gurdon JB** (2010) Histone H3 lysine 4 methylation is associated with the transcriptional reprogramming efficiency of somatic nuclei by oocytes. Epigenetics & Chromatin 3, 4
- Jullien J, Astrand C, Halley-Stott RP, Garrett N, and **Gurdon JB** (2010) Characterization of somatic cell nuclear reprogramming by oocytes in which a linker histone is required for pluripotency gene reactivation. PNAS 107, 5483-5488
- Halley-Stott RP, Pasque V, Astrand C, Miyamoto K, Simeoni I, Jullien J and **Gurdon JB** (2010) Mammalian Nuclear Transplantation to Germinal Vesicle stage *Xenopus* Oocytes – A method for Quantitative Transcriptional Reprogramming. Methods 51, 56-65
- Pasque V, Miyamoto K and **Gurdon JB** (2010) Efficiencies and mechanisms of nuclear reprogramming. Cold Spring Harbor Symposia on Quantitative Biology (online version 4 Nov 2010)



Transcriptional activation by oocytes differs dramatically according to donor cells used

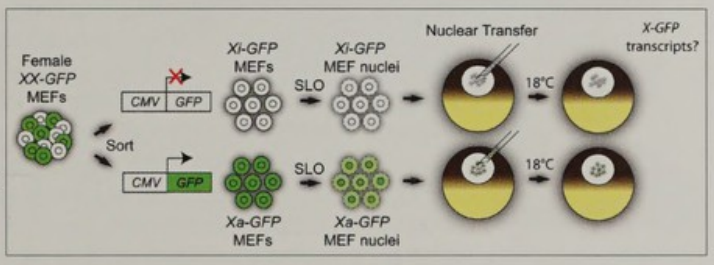
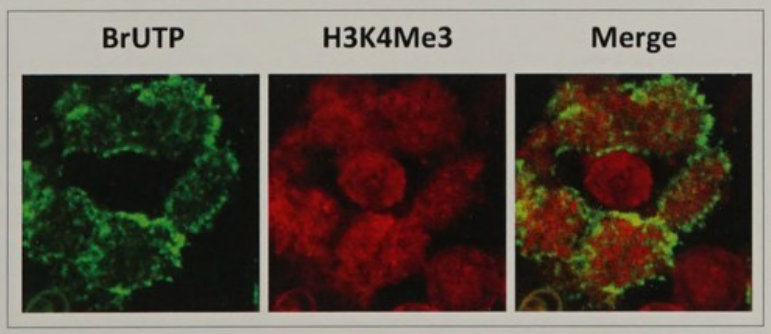
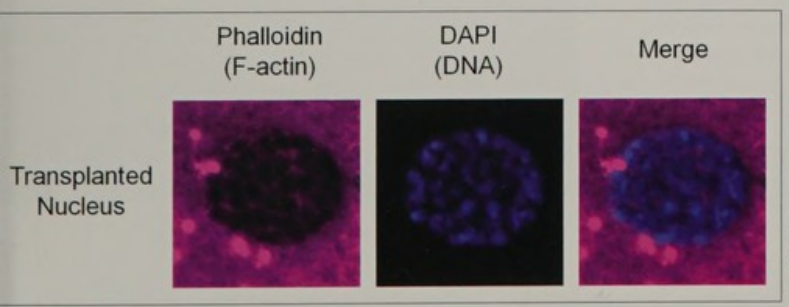


Diagram to explain the design of experiment testing the reprogramming of the female mammalian inactive X chromosome after nuclear transfer to oocytes



New transcripts from transplanted nuclei seen by incorporation of BrUTP into newly produced RNA



Filamentous actin marked by Phalloidin, enters somatic nuclei transplanted to oocytes

Steve Jackson

Maintenance of genome stability

Co-workers: Linda Baskcomb, Rimma Belotserkovskaya, Melanie Blasius, Sébastien Britton, Jessica Brown, Julia Coates, Kate Dry, Josep Forment, Yaron Galanty, Ilaria Guerini, Jeanine Harrigan, Xavier Jacq, Louise Jones, Kamila Jozwik, Abderrahmane Kaidi, Charlotte Knights, Delphine Larrieau, Carlos le Sage, Natalia Lukashchuk, Kyle Miller, Ryotaro Nishi, Tobias Oelschlägel, Helen Reed, Lisa Smith, Neha Thakkar, Jorrit Tjeertes, Paul Wijnhoven

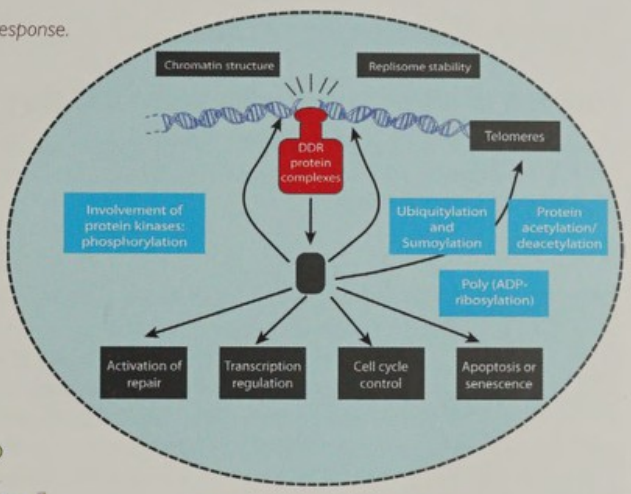
Our work focuses on the DNA-damage response (DDR): the set of events that optimises cell survival and genomic integrity by detecting DNA damage, signalling its presence and mediating its repair. The importance of the DDR is underscored by defects in it being associated with various pathologies, including neurodegenerative disease, immunodeficiency, premature ageing, infertility and cancer.

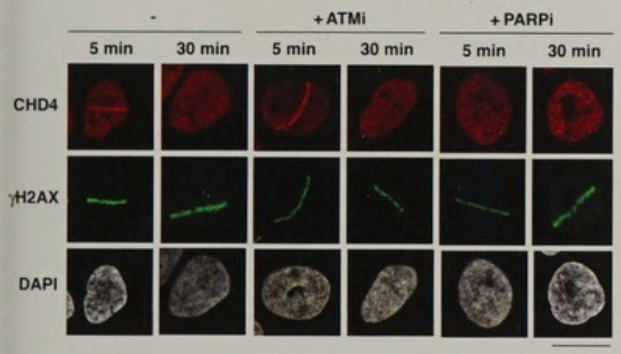
By working with both yeast and human cells, we are identifying new DDR factors, defining the functions of known DDR components, assessing how the DDR is affected by chromatin structure, and learning how DDR events are regulated. Much of this work is focused on how the DDR is controlled by protein post-translational modifications. For example, we have established that the mammalian SUMO E3 ligases PIAS1 and PIAS4 accumulate at sites of DNA double strand breaks (DSBs) and promote cellular responses to DSBs by mediating SUMOylation of various DDR factors. Furthermore, we recently discovered that the histone deacetylase enzymes HDAC1 and HDAC2 accumulate at DSB sites to facilitate repair by non-homologous end-joining. Additionally, we established that the human NAD-dependent protein deacetylase, SIRT6, controls DSB signalling and repair by homologous recombination by bringing about DNA-damage induced deacetylation and activation of the key DSB-resection factor CtIP. Another highlight of the past year has been our discovery that chromatin remodelling complexes containing the CHD4 protein are recruited to DNA damage sites by mechanisms that require PARP1 activity and promote DSB repair. Finally, we have recently extended our work defining how DSB responses are controlled during the cell cycle by showing that, while cells entering mitosis with DSBs trigger apical DDR events, downstream signalling events do not operate, thus allowing cells to progress through mitosis to repair DSBs in the subsequent G1 phase.

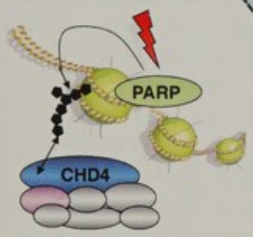
Selected publications:

- Galanty Y, Belotserkovskaya R, Coates J, Polo S, Miller KM and **Jackson SP** (2009) Mammalian SUMO E3-ligases PIAS1 and PIAS4 promote responses to DNA double-strand breaks. Nature 462, 935-939
- Miller KM, Tjeertes JV, Coates J, Legube G, Polo SE, Britton S and **Jackson SP** (2010) Human HDAC1 and HDAC2 function in the DNA-damage response to promote DNA non-homologous end-joining. Nature Structural and Molecular Biology 17, 1144-1151.
- Kaidi A, Weinert BT, Choudhary C and **Jackson SP** (2010) Human SIRT6 promotes DNA end resection through CtIP deacetylation. Science 329, 1348-1353.
- Polo SE, Kaidi A, Baskcomb L, Galanty Y and **Jackson SP** (2010) Regulation of DNA damage responses and cell cycle progression by the chromatin remodeling factor CHD4. EMBO Journal 29, 3130-3139.
- Giunta S, Belotserkovskaya R and **Jackson SP** (2010) DNA damage signaling in response to double-strand breaks during mitosis. Journal of Cell Biology 190, 197-207.

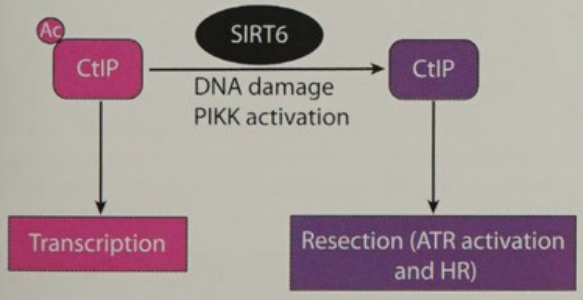
Model for the DNA damage response.



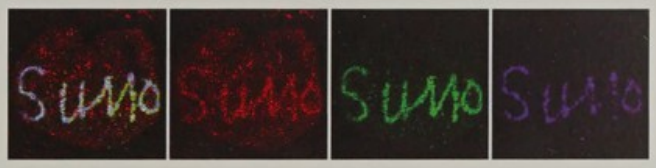


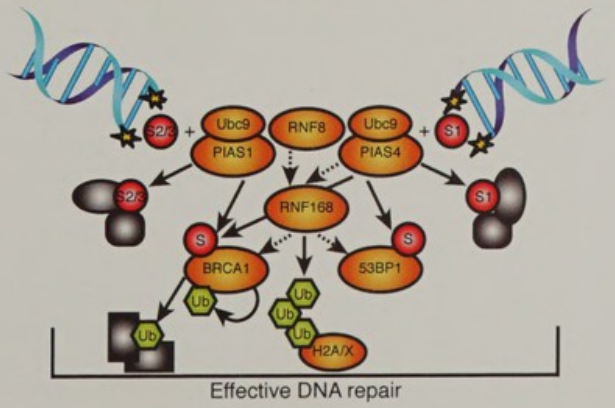


PARP-dependent recruitment of CHD4 to sites of DNA damage



Human SIRT6 promotes DNA end resection through CtIP deacetylation.





Co-localisation of SUMO2/3 (red) with DDR proteins MDC1 (green) and 53BP1 (blue) at laser-lines, indicative of DSBs (merge, white). Model in which PIAS1 and PIAS4 act in parallel, but overlapping, SUMO-conjugation pathways to control the DDR.

Tony Kouzarides

Function of chromatin modifications and their role in cancer

Co-workers: Hatice Akarsu, Paolo Amaral, Andrew Bannister, Isaia Barbieri, Till Bartke, Gonçalo Castelo-Branco, Maria Christophorou, Alistair Cook, Mark Dawson, Miranda Landgraf, Nikki Parsons, Sam Robson, Helena Santos-Rosa, Marc Schneider, Peter Tessarz, Emmanuelle Viré, Beata Wyspianska, Blerta Xhemalce

Our group is interested in defining the mechanisms by which chromatin modifications function regulate cellular processes. Our attention is focussed on a set of enzymes (acetylases, deacetylases, methylases and kinases), which regulate transcription by covalently modifying histories. We would like to understand what biological processes these enzymes control and the precise role of each modification on chromatin dynamics. In addition, a number of chromatin modifying enzymes have been implicated in the genesis of cancer so we are dissecting as far as possible, in the pathways misregulated in cancer cells.

Histones are very highly modified. Despite their abundance, we believe that more modifications are likely to exist on histones. This complexity is probably necessary because histones integrate many signalling pathways with biological processes involving DNA manipulation. We are taking a number of complementary approaches to characterise the function of chromatin modifications. We use yeast as a model system whenever possible to define pathways. We use human cells to characterise function in higher organisms and probe connections to cancer.

One of the major ways in which modifications work is by the recruitment of proteins. We have developed an assay for capturing such modification-binding proteins, which we call SNAP (Silac Nucleosome Affinity Purification). This involves making modified nucleosomes *in vitro* and pulling out of nuclear extracts interacting proteins. This approach has been successfully used to identify proteins recruited by histone and DNA methylation and to find a 'cross talk' between these two distinct classes of modification.

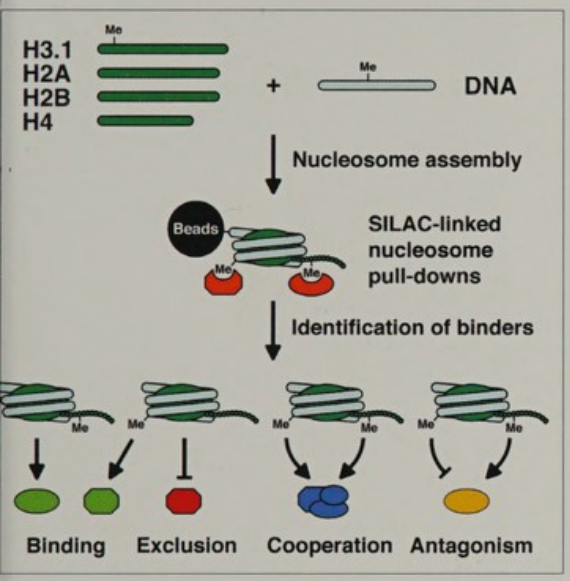
A major drive for us in recent years has been to identify new histone modifications, as the pathways that control them may well be deregulated in cancer. We have identified several novel pathways that modify chromatin such as arginine deimination, proline isomerisation, tyrosine phosphorylation and histone clipping. In the case of tyrosine phosphorylation by the JAK2 enzyme, we uncovered a novel pathway which takes place in the nucleus. We showed that phosphorylation of H3 by JAK2 can displace a repressor, HP1, from a gene implicated in leukaemia. Misregulation of this pathway may explain the cancer-inducing potential of JAK2 mutations frequently found in leukaemia.

Selected publications:

• Dawson MA, Bannister AJ, Gottgens B, Foster SD, Bartke T, Green AR and **Kouzarides T** (2009) JAK2 phosphorylates histone H3Y41 and excludes HP1 from chromatin. Nature 461, 819-822

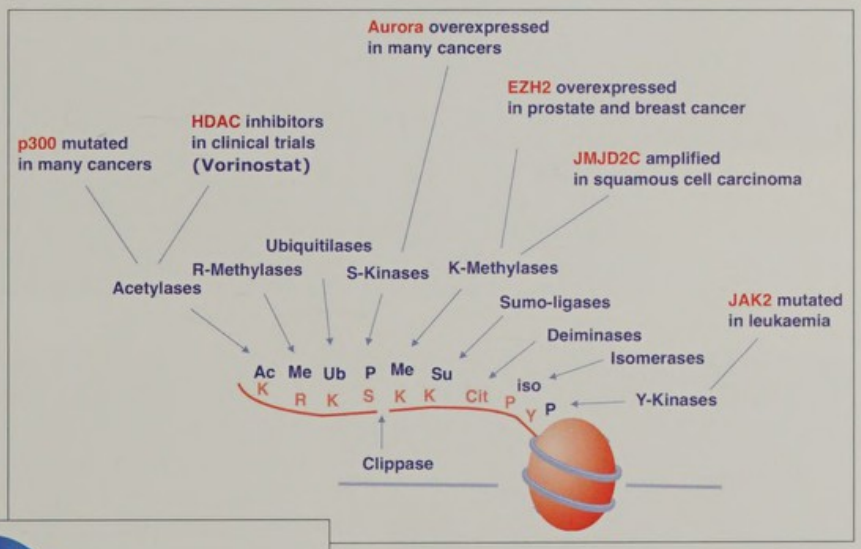
• Xhemalce B and **Kouzarides T** (2010) A chromodomain switch mediated by Histone H3 Lysine 4 Acetylation regulates heterochromatin assembly. Genes Dev 24(7), 647-652

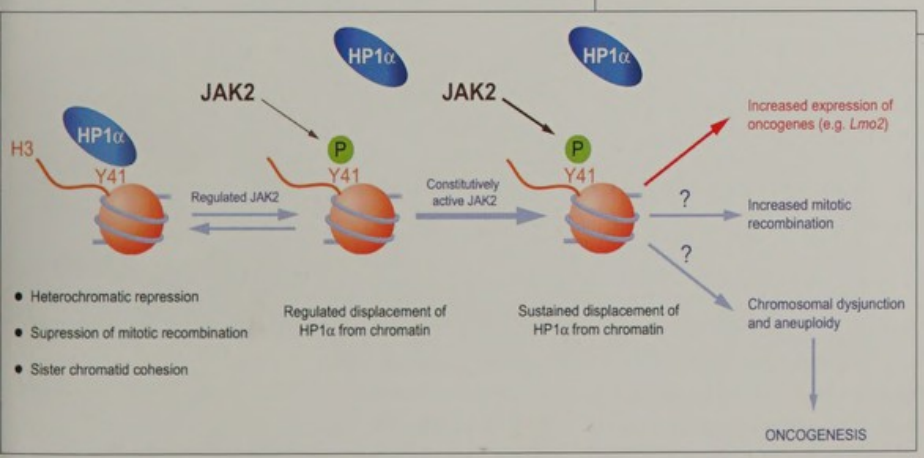
• Bartke T, Vermeulen M, Xhemalce B, Robson SC, Mann M and **Kouzarides T** (2010) Nucleosome-interacting Proteins Regulated by DNA and Histone Methylation. Cell 143: 470 – 84



The SNAP approach identifies 'cross-talk' between modifications in nucleosomes.

Model for the nuclear role of JAK2 in normal cells and in leukaemias containing JAK2 mutations.





Chromatin-modifying enzymes are deregulated in cancer.

Rick Livesey

Neural stem cell biology, fundamental and applied

Co-workers: Jessica Alsio, Therese Andersson, Juliet Barrows, Chibawanye Ene, Peter Kirwan, Moyra Lawrence, João Pereira, Stephen Sansom, Nathalie Saurat, Yichen Shi, James Smith, Uruporn Thammongkol

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 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, using mouse as a model system. 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, including microRNAs and the polycomb chromatin-modifying complexes. In the other major strand of research in the group, we have used our understanding of murine cortical stem cells to develop methods for directing differentiation of human pluripotent stem cells to cortical neurons, via a cortical stem cell stage. We are using this system for basic studies of human cortical neurogenesis and to generate models of cortical diseases, with an initial focus on Down syndrome and Alzheimer's disease.

Selected publications:

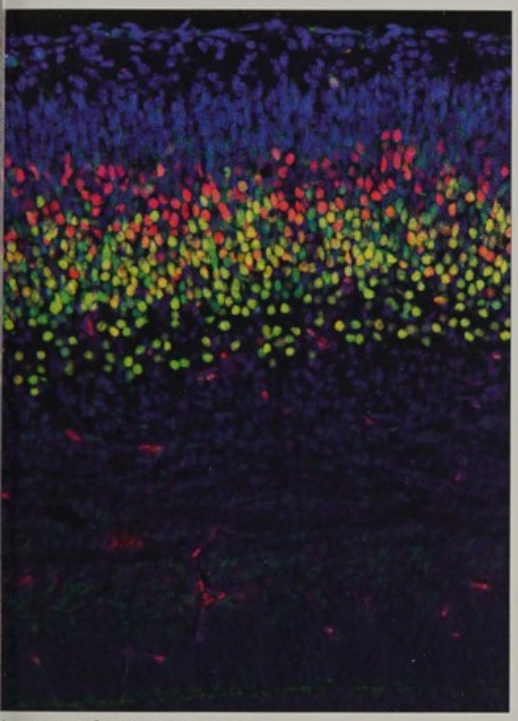
• Pereira JD, Sansom SN, Smith J, Dobenecker MW, Tarakhovsky A and **Livesey FJ** (2010) Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. Proc Natl Acad Sci USA 107, 15957-15962.

• Andersson T, Rahman S, Sansom SN, Alsio JM, Kaneda M, Smith J, O'Carroll D, Tarakhovsky A and **Livesey FJ** (2010) Reversible block of mouse neural stem cell differentiation in the absence of dicer and microRNAs. PLoS ONE 5, e13453

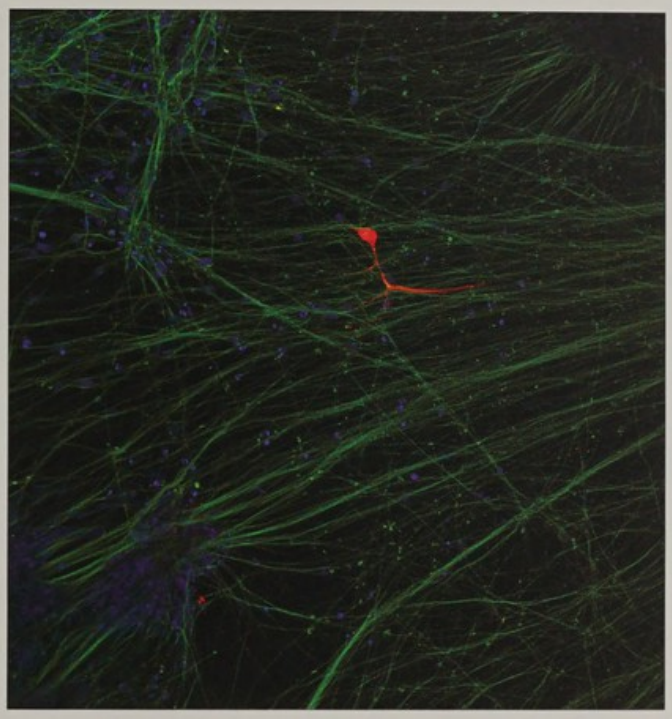
• Subkhankulova T, Yano K, Robinson HP and **Livesey FJ** (2010) Grouping and classifying electrophysiologically-defined classes of neocortical neurons by single cell, whole-genome expression profiling. Front Mol Neurosci 3, 10

• Sansom SN, Griffiths DS, Faedo A, Kleinjan DJ, Ruan Y, Smith J, van Heyningen V, Rubenstein JL and **Livesey FJ** (2009) The level of the transcription factor Pax6 is essential for controlling the balance between neural stem cell self-renewal and neurogenesis. PLoS Genetics 5, e1000511

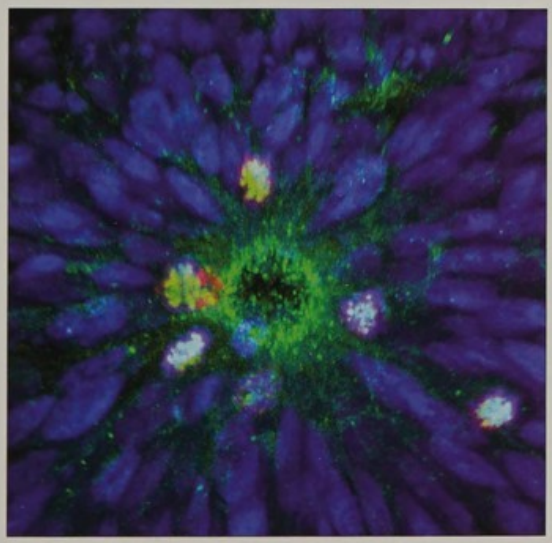
• Sansom SN and **Livesey FJ** (2009) Gradients in the brain: the control of the development of form and function in the cerebral cortex. Cold Spring Harb Perspect Biol 1:a002519



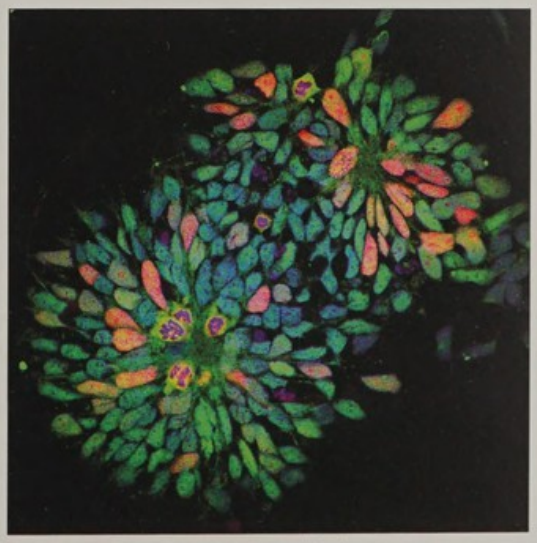
Layer-specific gene expression in neurons of different layers (red, green and yellow) of the cerebral cortex.



A single astrocyte (red) in a culture of human cortical neurons (green).



A human cortical neural stem cell rosette, with stem cells (red) dividing at the apical surface (green).

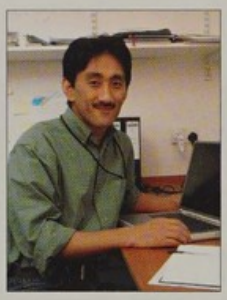


Human stem cell-derived neuroepithelial rosettes expressing cerebral cortex transcription factors

Masanori Mishima

Molecular mechanism of cytokinesis

Co-workers: Tim Davies, Lynn Froggett, Nimesh Joseph, Kian-Yong Lee, Julia Mason, Eva Pablo-Hernando



Cytokinesis is essential for cell proliferation. Its failure leads to aneuploidy, which is often associated with cancer. In spite of its importance, the molecular mechanism of cytokinesis has not yet been fully clarified. We would like to understand cytokinesis more fully, in terms of how molecular machines assemble dynamically. The central spindle is a microtubule-based molecular assembly that forms between the segregating chromosomes during anaphase. During telophase, it associates with the ingressing cleavage furrow and matures into the midbody. These microtubule-based structures play crucial roles in all stages of cytokinesis from initiation to completion. We will address the following questions:

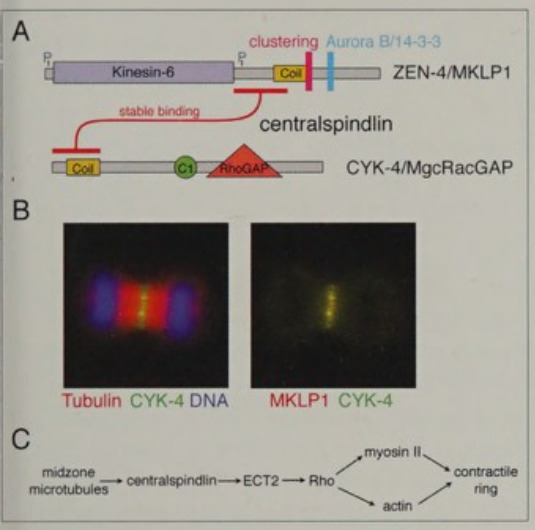
- How is the central spindle/midbody assembled?
- How does the central spindle/midbody contribute to the progression of cytokinesis?

To address these questions, we have been combining various approaches including genetics in *Caenorhabditis elegans*, biochemistry and live observation in mammalian cultured cells and observation at the single molecule level by total internal reflection fluorescence microscopy (TIRF).

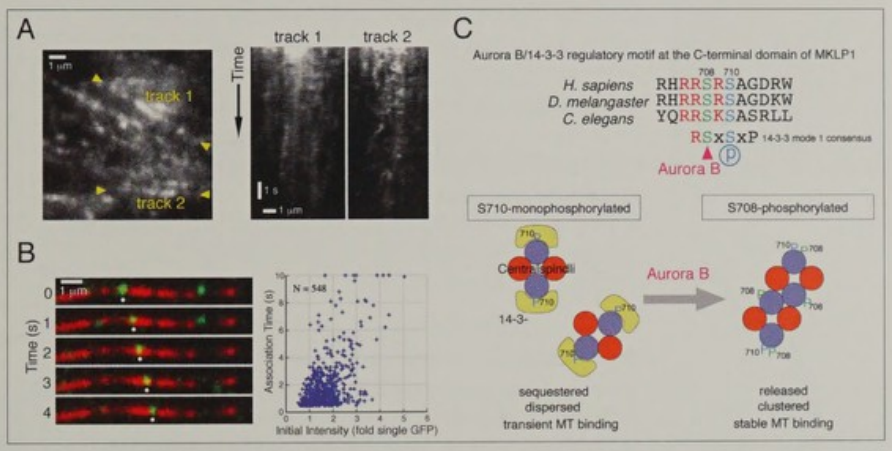
Centralspindlin, a stable protein complex of a kinesin and a RhoGAP, is crucial for the assembly of the central spindle and midbody, and for signalling cleavage furrow formation. We have discovered that centralspindlin travels along microtubules of the central spindle as higher-order clusters and that clustering is essential for both microtubule-bundling and motility along microtubules *in vitro*, and midbody formation *in vivo*. Based on these findings, we have proposed a positive feedback loop model to explain the distinct localisation pattern of centralspindlin during cytokinesis. Furthermore, we have revealed that the clustering of centralspindlin is regulated by Aurora B kinase and 14-3-3 protein. This adds another layer of regulation to the positive feedback loop, ensuring co-ordination of cytokinesis with chromosome segregation.

Selected publications:

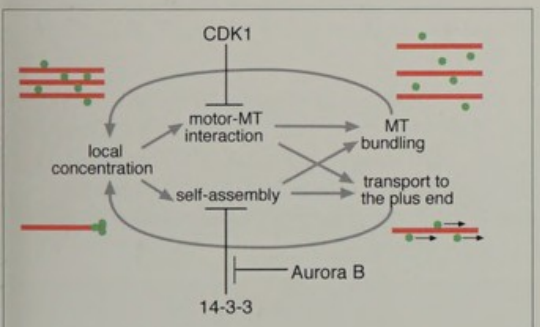
- Douglas ME, **Mishima M** (2010) Still entangled: assembly of the central spindle by multiple microtubule modulators. Semin Cell Dev Biol 21, 899-908
- Douglas ME, Davies T, Joseph N, **Mishima M** (2010) Aurora B and 14-3-3 coordinately regulate clustering of centralspindlin during cytokinesis. Curr Biol 20, 927-33
- Hutterer A, Glotzer M, **Mishima M** (2009) Clustering of centralspindlin is essential for its accumulation to the central spindle and the midbody. Curr Biol 19, 2043-9

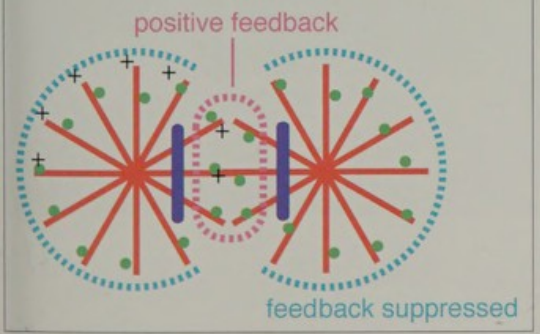


Centralspindlin is an evolutionarily-conserved microtubule-bundling protein complex (A). Both Kinesin-6 and RhoGAP components are essential for in vivo formation of the central spindle and for in vitro microtubule-bundling activity. During early cytokinesis, centralspindlin sharply accumulates to the centre of the central spindle (B). This is critical for proper cleavage furrow positioning since centralspindlin is the most upstream molecule in a signalling pathway for contractile ring assembly (C).



Using total internal reflection fluorescence (TIRF) microscopy, we have succeeded in directly observing the movement of particles of centralspindlin in vivo (A). In vitro motility analysis indicated that clustering promotes continuous movement of centralspindlin along a microtubule track (B). Furthermore, we have discovered that clustering of centralspindlin is regulated by 14-3-3 protein and phosphorylation by Aurora B kinase (C).





We have proposed a novel positive feedback mechanism to explain the distinct localisation pattern of centralspindlin. Centralspindlin accumulates to the anti-parallel overlap of microtubules at the equatorial region of a dividing cell. Regulation by 14-3-3 protein and Aurora B ensures spatial co-ordination of this process with chromosome segregation as Aurora B kinase activity peaks between segregating chromosomes.

Eric Miska

Small regulatory RNA

Co-workers: Javier Armisen Garrido, Alyson Ashe, Alejandra Clark, Leonard Goldstein, Ethan Kaufman, Nic Lehrbach, Helen Lightfoot, Kenneth Murfitt, Nicola Parsons, Alexandra Sapetschnig, Funda Sar, Eva-Maria Weick, Julie Woolford

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.

We also 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:

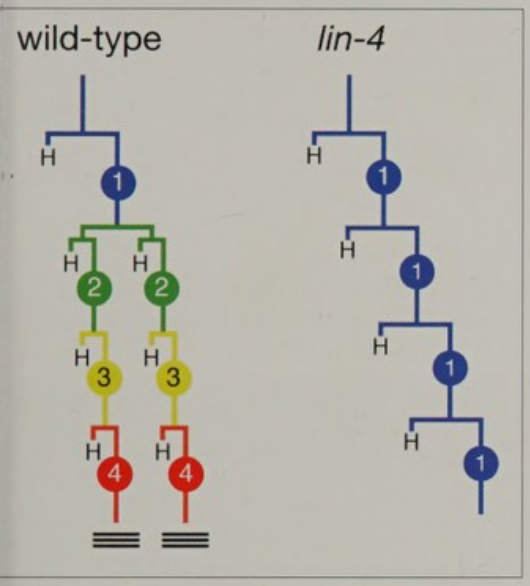
• Lehrbach N, Armisen J, Lightfoot H, Murfitt K, Bugaut A, Balasubramanian S, **Miska EA** (2009) LIN-28 and the poly(U) polymerase PUP-2 regulate let-7 microRNA processing in *Caenorhabditis elegans*. Nature Struct Mol Biol 16, 1016-1022

• Armisen J, Gilchrist MJ, Wilczynska A, Standart N and **Miska EA** (2009) Abundant and dynamically expressed miRNAs, endo-siRNAs and piRNAs in the African clawed frog *Xenopus tropicalis*. Genome Research 19, 1766-1755

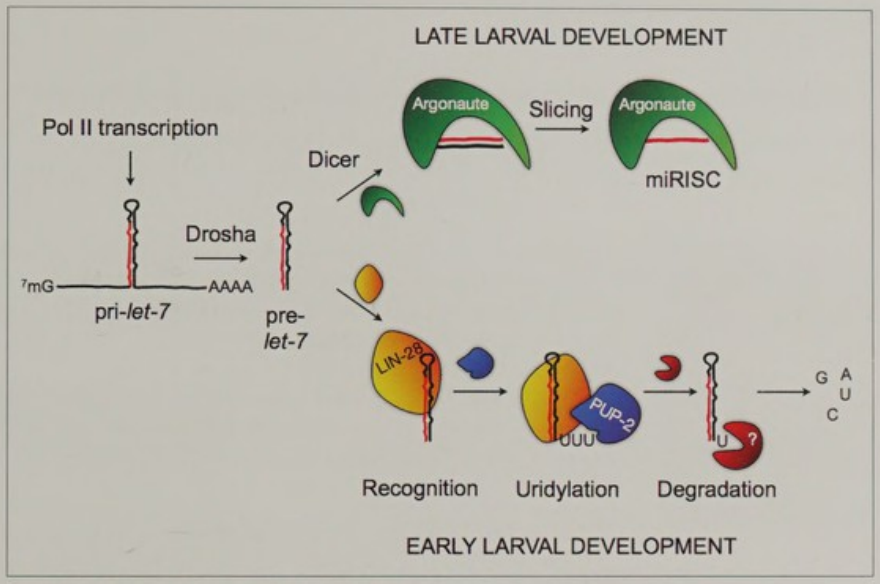
• Das PP, Bagijn MP, Goldstein LD, Woolford JR, Lehrbach NJ, Sapetschnig A, Buhecha HR, Gilchrist MJ, Howe KJ, Stark R, Berezikov E, Ketting RF, Tavaré S, **Miska EA** (2008) Piwi and piRNAs act upstream of an endogenous siRNA pathway to suppress Tc3 transposon mobility in the *Caenorhabditis elegans* germline. Mol Cell 31, 79-90

• **Miska EA**, Alvarez-Saavedra E, Abbott AL, Lau NC, Hellman AB, Bartel DP, Ambros VR, Horvitz HR (2007) Most *Caenorhabditis elegans* microRNAs are individually not essential for development or viability. PLoS Genet 3, e215

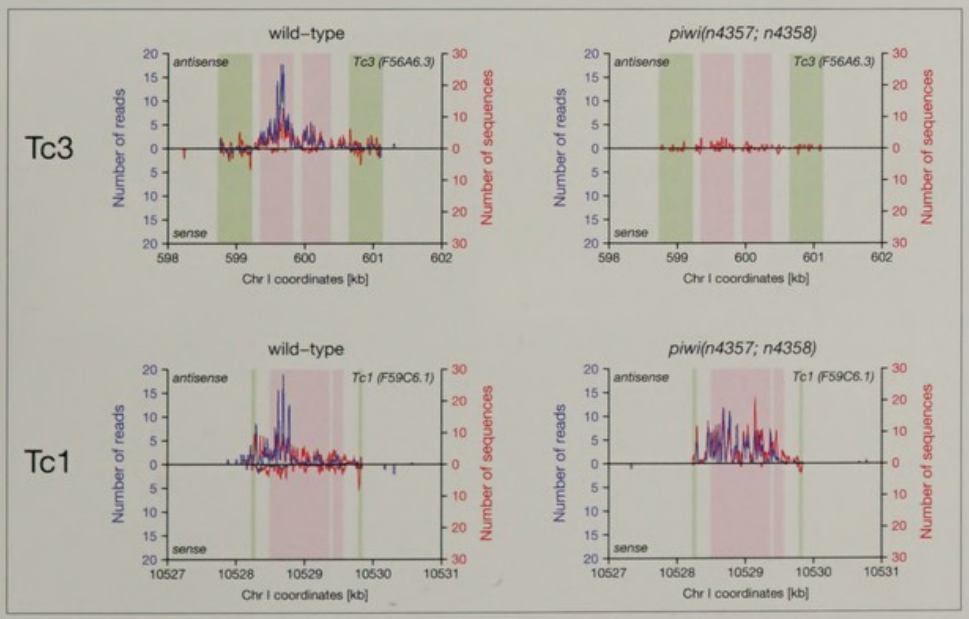
• Blenkiron C, Goldstein LD, Thorne NP, Spiteri I, Chin SF, Dunning M, Barbosa-Morais NL, Teschendorff A, Green AR, Ellis IO, Tavaré S, Caldas C, **Miska EA** (2007) MicroRNA expression profiling of human breast cancer identifies new markers of tumour subtype. Genome Biology 8, R214



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



piRNAs *and* ***Piwi*** *proteins are required to generate endogenous siRNAs that silence the Tc3 DNA transposon in the germline.*

Eugenia Piddini

Competitive cell interactions in normal physiology and cancer

Co-workers: Golnar Kolahgar, Kathy Oswald, Silvia Vivarelli, Laura Wagstaff

Cell interactions are at the basis of all multi-cellular life. They allow cells to coordinate decisions such as whether to proliferate, differentiate or die and are therefore essential to generate and maintain healthy tissues and organs. Our lab studies the mechanisms and the physiological role of competitive cell interactions. These interactions were first discovered in *Drosophila* when it was found that, within tissues, cells compete for survival and less fit cells are induced to die.

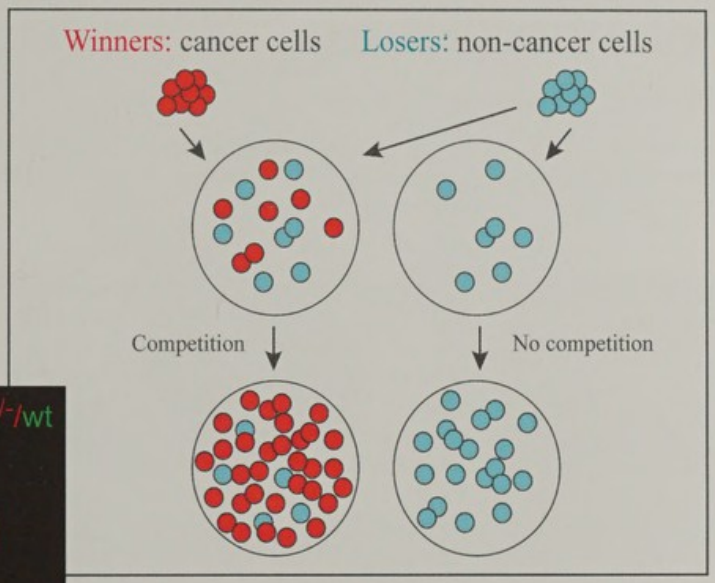
We have recently found that, in *Drosophila,* cells with different signalling levels of the growth factor Wingless (the *Drosophila* homolog of the mammalian Wnt family oncogene Wnt-1) engage in cell competition and, in particular, that cells with abnormally high signalling levels induce the death of neighbouring wild-type cells. Since Wnt signalling is overactivated in a variety of cancers, Wnt-induced cell competition could allow cancer cells to kill surrounding normal cells during early tissue colonisation.

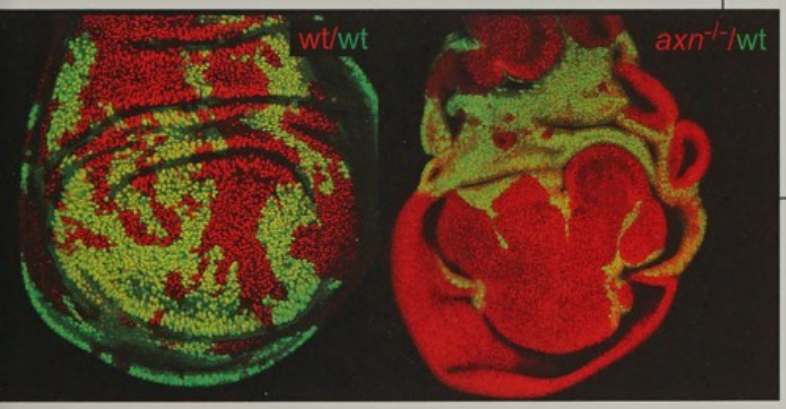
Based on these observations, our current work is expanding in two main directions. First, we want to understand at the molecular level how this newly-discovered type of competition is brought about. To this end, we are using the power of *Drosophila* genetics to investigate how cells sense differential Wingless signalling levels among them, and what molecules they exchange that lead to the selective elimination of low Wingless signalling cells. Secondly, we want to investigate the relevance of this phenomenon in Wnt-induced cancers. For that purpose, we are working towards reconstituting Wnt-induced cell competition between normal cells and Wnt-induced tumour cells in culture. This will allow us to translate our findings from *Drosophila* to mammals and to identify novel mediators of cell competition of potential therapeutic relevance.

Selected publications:

- 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 Apr;11(4):460-7
- **Piddini E** and Vincent JP (2009) Interpretation of the Wingless gradient requires signalling-induced self-inhibition. Cell Jan 136, 296-307
- **Piddini E***, Marshall F*, Dubois L, Hirst E, Vincent JP (2005) Arrow (LRP6) and Frizzled2 cooperate to degrade Wingless in *Drosophila* imaginal discs. Development Dec;132(24):5479-89. * equal contribution
- Franch-Marro X, Marchand O, **Piddini E**, Ricardo S, Alexandre C, Vincent JP (2005) Glypicans shunt the Wingless signal between local signalling and further transport. Development Feb;132(4):659-66

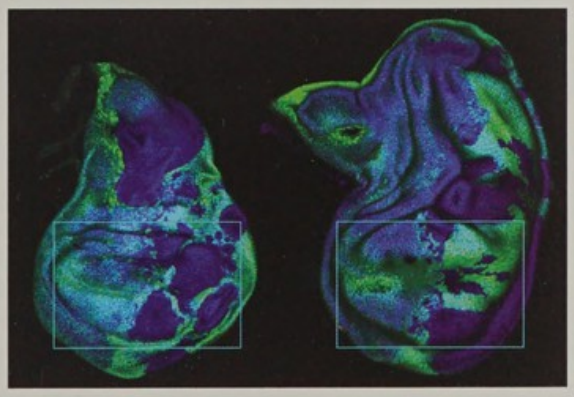
We are working towards reconstituting cell competition among tumour cells and normal cells in vitro. We do so by mixing them in culture and analysing how this affects the proliferation and survival of normal cells.

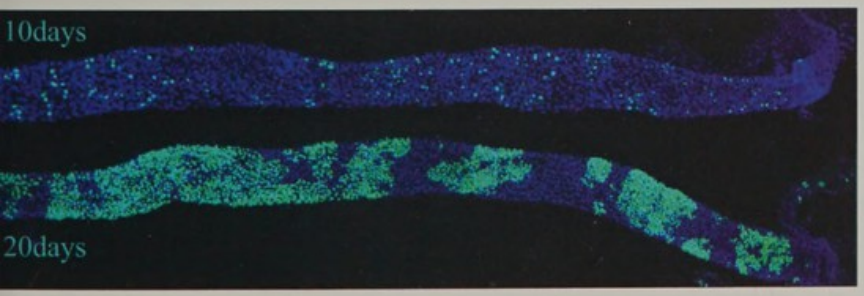




In a control disc, where both GFP-positive and GFP-negative cells are wild-type, they colonise the tissue equally (left panel). However when GFP-negative cells have high-Wnt signalling they outcompete wild-type GFP-positive cells (right panel).

Left panel: High Wnt signaling cells (GFP-negative) generated in the Posterior compartment of a wing pouch (boxed area) colonise the tissue at the expense of wild-type cells. Right panel: By contrast, in a notum mutant background outcompetition by high Wnt signaling cells is inhibited.





Like in the mammalian colon, overactivation of Wnt signaling leads to adenomas in the Drosophila gut. High-Wnt cells (green) overproliferate and form extensive adenomas 20 days after induction. The top gut was fixed 10 days after high-Wnt cells generation. The bottom gut was fixed 20 days after high-Wnt cells generation.

Jonathon Pines

How do cells control mitosis?

Co-workers: Philippe Collin, Barbara Di Fiore, Anja Hagting, Daisuke Izawa, Mark Jackman, Agata Lichawska, Jörg Mansfeld, Paola Marco, Takahiro Matsusaka, Oxana Nashchekina, Jackie Simcox, Bernhard Strauss, Samuel Wieser

How do cells regulate entry to mitosis? And, once in mitosis, how do cells coordinate chromosome segregation with cell division itself (cytokinesis) to ensure that the two daughter cells receive an equal and identical copy of the genome? The answer lies in the interplay between protein kinases, protein phosphatases, and APC/C-mediated proteolysis, and this is the focus of our research. Because mitosis is a highly dynamic process we study living cells by time-lapse fluorescence microscopy but to complement this with biochemical analyses we are using somatic cell recombination to knock-out and mutate specific mitotic regulators. This has given us remarkably accurate and precise *in vivo* kinetics for protein degradation.

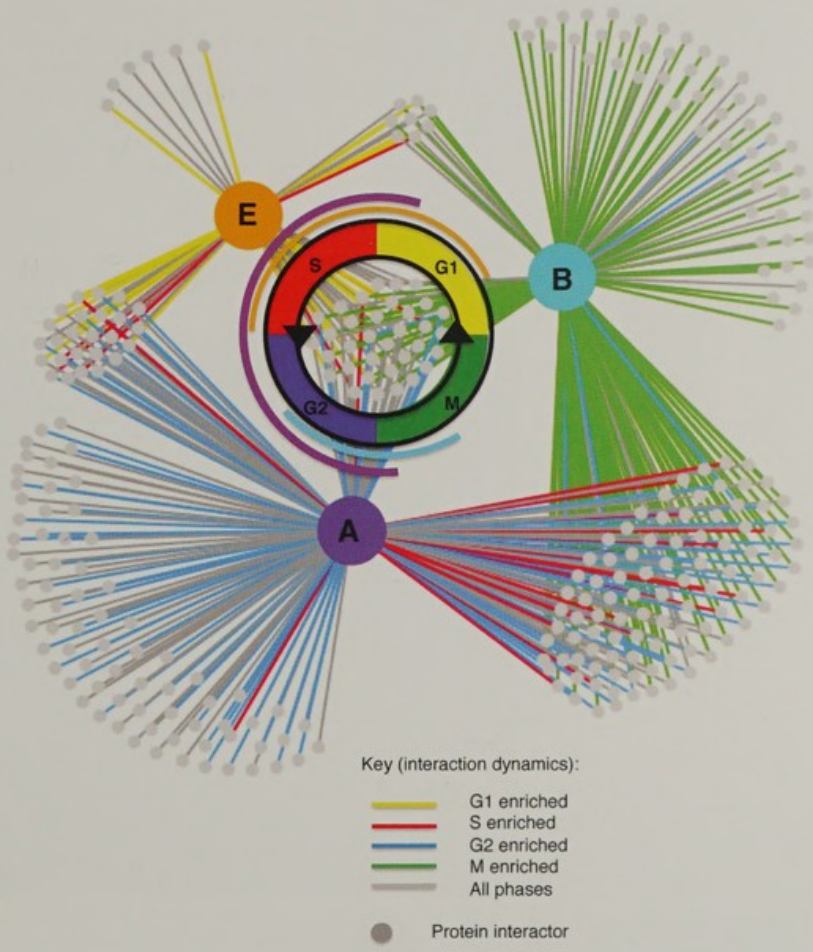
To understand how cells initiate mitosis we are analysing the behaviour of the key mitotic kinases, the Cyclin A- and B-dependent kinases, and their regulation by phosphorylation and dephosphorylation. We recently developed a FRET biosensor to assay Cyclin B1-Cdk1 activity *in vivo* and are using this to define the events that link DNA replication with the initiation of mitosis. To identify the proteins responsible for regulating the Cyclin-Cdks, and provide insights into their 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, how it is able to select a particular protein for destruction at a specific time, and how its activity is regulated by the spindle assembly checkpoint that is essential to the control of chromosome segregation and cytokinesis.

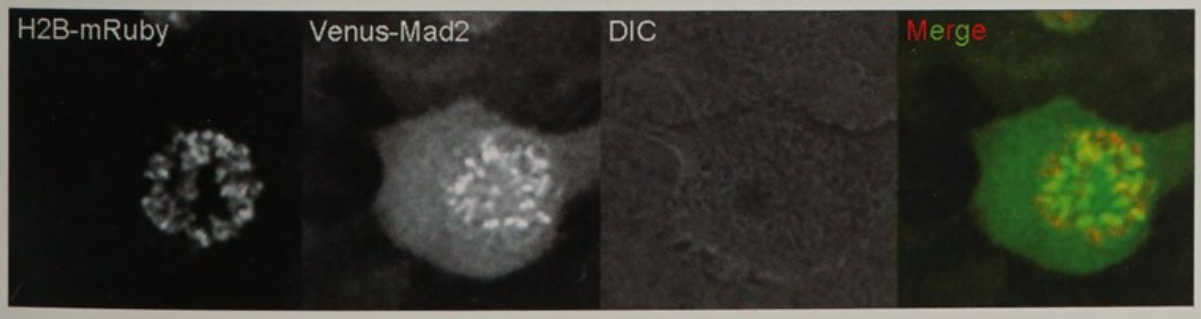
Selected publications:

- Di Fiore B and **Pines J** (2010) How Cyclin A destruction escapes the Spindle Assembly Checkpoint. J Cell Biol 190, 501-509
- Gavet O and **Pines J** (2010) Progressive activation of Cyclin B1-Cdk1 coordinates entry to mitosis. Dev Cell 18, 533-543.
- Gavet O and **Pines J** (2010) Activation of Cyclin B1-Cdk1 synchronizes events in the nucleus and the cytoplasm at mitosis. J Cell Biol 189, 247-259
- 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
- Wolthuis R, Clay-Farrace L, van Zon W, Yekezare M, Ogink J, Medema R and **Pines J** (2008) Cdc20 and Cks Direct the Spindle Checkpoint-Independent Destruction of Cyclin A. Mol Cell 30, 290-302

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



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, 2010)



Emma Rawlins

Stem and progenitor cells in the mammalian lung

Co-workers: Gayan Balasooriya, Juliet Barrows

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: which cells are the stem and progenitor populations? And what mechanisms control the decision of lung progenitors to self-renew or to differentiate? 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.

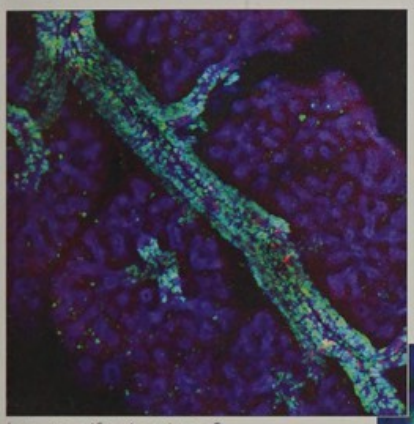
We have previously shown that in the embryonic lung there is a population of Id2+ multipotent epithelial progenitor cells located at the distal tips of the budding epithelium. The developmental potential, or competence, of these cells changes during embryogenesis. At the same time the cells undergo a change in gene expression pattern. Currently we are testing the function of some of these genes, which are hypothesised to regulate the sequence of descendents produced by the progenitors.

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 focusses 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 focussing on genes that are hypothesised to control the decision to self-renew or differentiate.

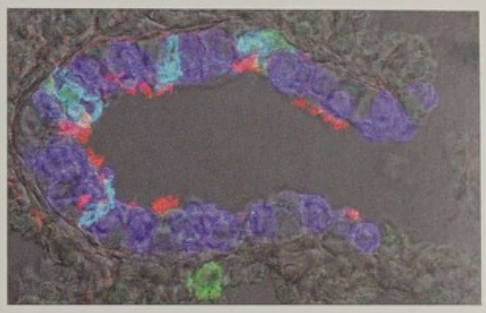
Selected publications:

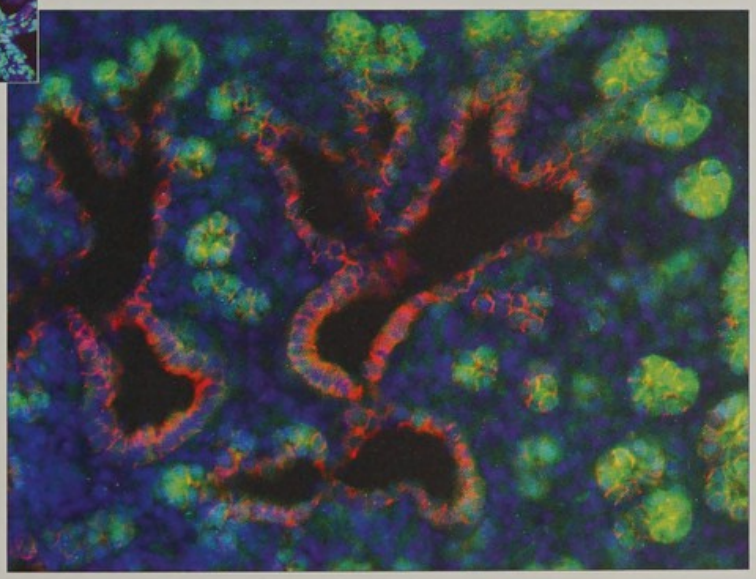
- **Rawlins EL**, Clark CP, Xue Y and Hogan BLM (2009) The Id2 distal tip lung epithelium contains individual multipotent embryonic progenitor cells. **Development** 136 3741-3745
- **Rawlins EL**, Okubo T, Xue Y, Brass DM, Auten RL, Hasegawa H, Wang F and Hogan BLM (2009) The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. **Cell Stem Cell** 4 525-534
- **Rawlins EL** and Hogan BLM (2008) Ciliated epithelial cell lifespan in the mouse trachea and lung. **American Journal of Physiology: Lung Cell Molecular Physiology** 295 L231-234
- **Rawlins EL**, Ostrowski LE, Randell SH and Hogan BLM (2007) Lung development and repair: contribution of the ciliated lineage. **Proc Natl Acad Sci USA** 104 410-417



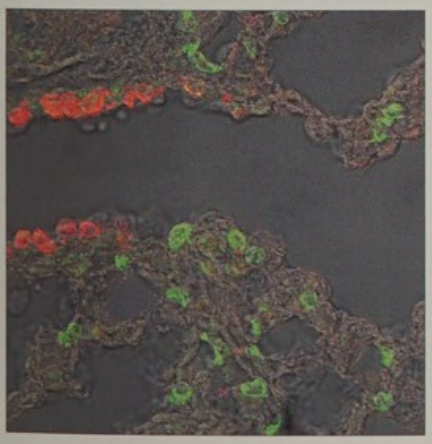
Low magnification view of the embryonic mouse lung showing the branching airways (blue) and differentiating bronchiolar cells (red and green).

Lineage-labelled bronchiolar cells (green) in the growing mouse lung. These cells are descended from an embryonic-specific progenitor cell population.

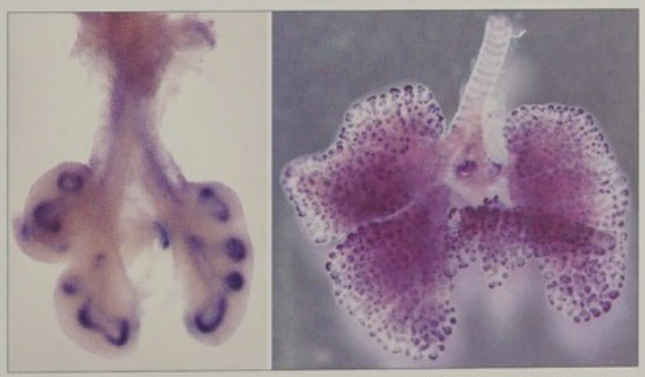




Higher magnification view of a section of the late-stage embryonic lung. Id2+ progenitor cells (green) are located at the tips of the branching airways (red).



Lung bronchiolar cells (red) and alveolar cells (green) are located in close proximity. However, we have shown that these lung compartments are maintained by separate progenitor cells.



Wholemount early stage embryonic lungs stained for Id2 mRNA (purple), which is located at the distal tips of the budding epithelium. The lungs form by progressive branching of an epithelial tube, which is surrounded by loosely packed mesenchymal cells.

Ben Simons

Patterns of stem cell fate in adult and developing tissues

Co-workers: John Biggins (Harvard), Allon Klein (Harvard), Gen Zhang

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 stem cells, such that only half are retained as stem cells. 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 remains elusive.

In recent years, much emphasis has been placed on resolving the extrinsic factors controlling stem cell fate and the spatial organisation associated with the stem cell niche. Guided by the paradigm of invariant asymmetry, many studies have sought to identify factors that provide proliferative control, and ensure stem cell longevity. However, by addressing long-term lineage tracing studies involving several adult tissue types, from interfollicular epidermis and intestine to germ line, we have found that stem cell loss, leading to population asymmetric renewal, is central to homeostasis.

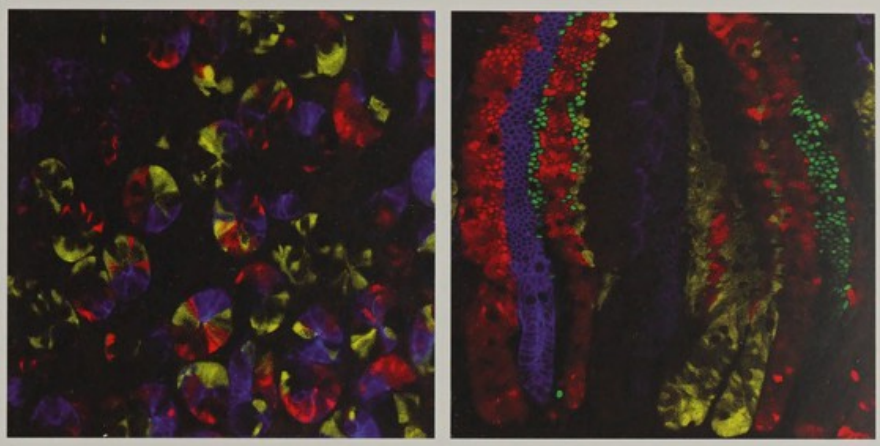
By drawing upon concepts from the statistical physics and mathematical literature, we have shown that tissue homeostasis permits just three classes of stem cell behaviour, discriminated by universal patterns of long-term clonal evolution. As well as achieving a functional classification of tissue stem cell types, this identification provides a general framework that we are using to interpret lineage tracing and mosaic-chimera studies, and to explore mechanisms of dysregulation. Current collaborators include Hans Clevers, Phil Jones, Alfonso Martinez-Arias, Michael Shen, Colin Watts, Doug Winton, and Shosei Yoshida.

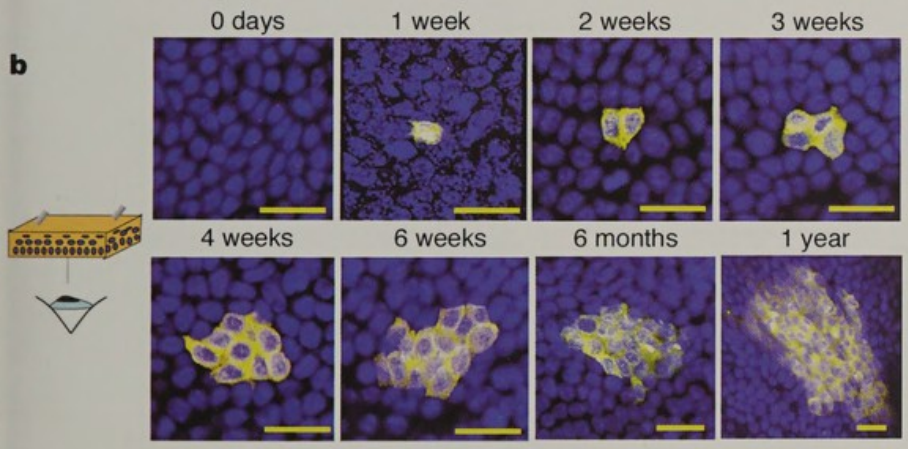
In a separate but related programme of research we are also using these general concepts and lineage tracing methodologies to elucidate patterns of progenitor cell fate in the late stage development of retina and spinal cord. Current collaborators include James Briscoe, Bill Harris, and Michel Cayouette.

Selected publications:

- Snippert H J, van der Flier L G, Sato T, van Es J H, van den Born M, Kroon-Veenboer C, Barker N, Klein A M, 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
- Lopez-Garcia C, Klein AM, **Simons BD**, and Winton DJ (2010) Intestinal stem cell replacement follows a pattern of neutral drift. Science 330, 822-825
- Klein AM, Nakagawa T, Ichikawa R, Yoshida S, and **Simons BD** (2010) Mouse germ line stem cells undergo rapid and stochastic turnover. Cell Stem Cell 7, 214-224
- Klein AM, Brash DE, Jones PH, and **Simons BD** (2010) Stochastic fate of p53-mutant epidermal progenitor cells is tilted toward proliferation by UV B during preneoplasia. Proceedings of the National Academy of Sciences 107, 270-275
- Clayton E, Doupe DP, Klein AM, Winton D, **Simons BD**, and Jones PH (2007) A single type of progenitor cell maintains the epidermis. Nature 446, 185-189

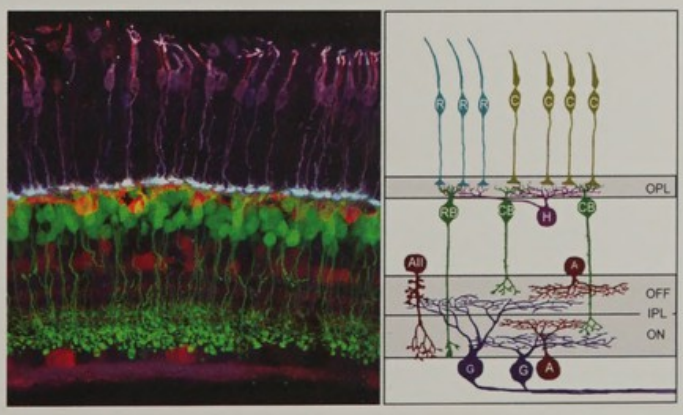
Studies of clonal fate using a multi-colour inducible genetic labelling system provide a vivid demonstration of neutral drift dynamics and the progession towards monoclonality in crypt. The left-hand image shows a section through the base of the crypt showing the clonal progeny of the stem/paneth cell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





The confocal sections through the basal layer of interfollicular epidermis show the clonal progression of a set of progenitor cells induced at a sequence of timepoints. The data show the continual expansion of clones from an ever-diminishing clone population. A detailed analysis of the lineage-tracing data show that tissue is maintained by a single progenitor cell population following a pattern of balanced stochastic fate in which stem cell loss is compensated by self-renewal.

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

Cell polarity, the cytoskeleton and mRNA localisation

Co-workers: Rebecca Bastock, Dan Bergstralh, Hélène Doerflinger, Celia Faria, Alejandra Gardiol, Timm Haack, Jackie Hall, Nick Lowe, Dmitry Nashchekin, Ross Nieuwburg, Aram Sayadian, Vanessa Stefanak, Vitor Trovisco, Antonio Vega Rioja, Lucy Wheatley, Tongtong Zhao

Cell polarity is essential both for cell function and for several key developmental processes, such as cell migration, axis determination and asymmetric cell division, whereas loss of polarity is a critical step in the formation of tumours. We use *Drosophila* and mammalian tissue culture cells to analyse how polarity is established, taking a combination of cell-biological, genetic and molecular approaches.

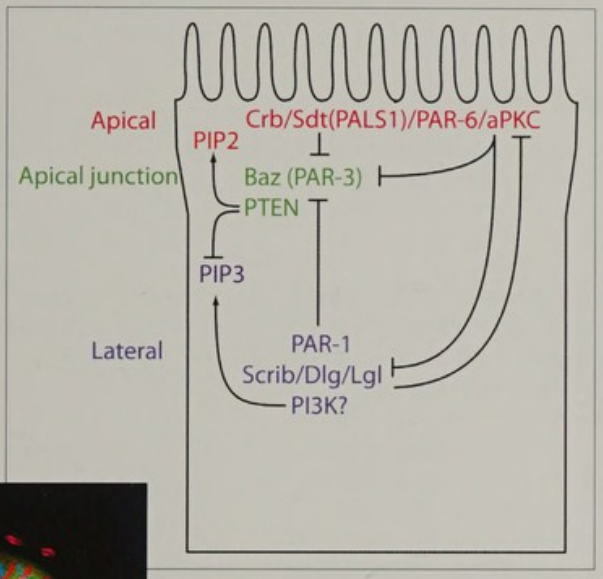
Much of our work focuses on how epithelial cells become polarised along their apical-basal axis, using the follicle cells as a typical secretory epithelium and the adult midgut as model absorptive epithelium. We have recently discovered that the tumour suppressor, LKB1, and the energy sensor, AMPK, are required for epithelial polarity under conditions of energetic stress, revealing the existence of a distinct low energy polarity pathway. We have identified several other components of this pathway in *Drosophila* and mammals, all of which have been implicated in cancer. We are currently analysing the functions of these factors and are performing genetic screens for new genes required for epithelial polarity under either high or low energy conditions.

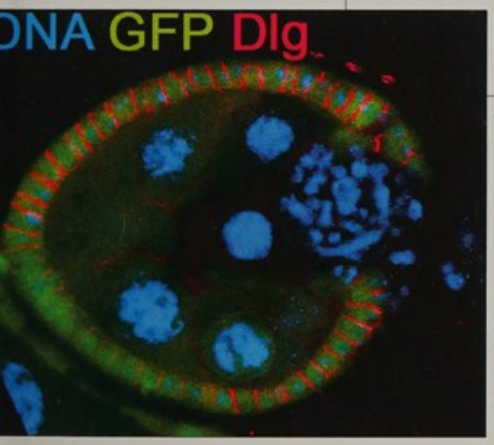
In parallel, we are examining how the *Drosophila* oocyte is polarised, since the localisation of *bicoid* and mRNAs to opposite ends of this very large cell defines the anterior-posterior axis of the embryo. We are using proteomic and biochemical approaches to elucidate how conserved polarity proteins regulate the organisation of the microtubule cytoskeleton in the oocyte, and we are investigating the mechanisms of mRNA transport by making time-lapse films of moving mRNA particles in wildtype and mutant oocytes. In addition, we are performing genetic screens for mutants that affect the localisations of *bicoid* and *oskar* mRNAs, and are analysing the novel polarity and mRNA localisation factors that these identify.

Selected publications:

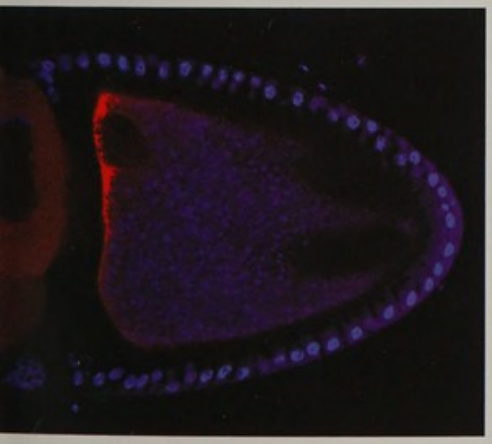
- Doerflinger H, Vogt N, Torres IL, Mirouse V, Koch I, Nusslein-Volhard C and **St Johnston D** (2010) Bazooka is required for polarisation of the *Drosophila* anterior-posterior axis. Development 137, 1765-73
- Morais-de-Sa E, Mirouse V and **St Johnston D** (2010) aPKC phosphorylation of Bazooka defines the apical/lateral border in *Drosophila* epithelial cells. Cell 141, 509-23
- **St Johnston D** and **Ahringer J** (2010) Cell polarity in eggs and epithelia: parallels and diversity. Cell 141, 757-774
- Mirouse V, Christoforou CP, Fritsch C, **St Johnston D** and Ray R (2009) Dystroglycan and Perlecan provide a basal cue that is required for epithelial polarity during energetic stress. Dev Cell 16, 83-92
- Zimaynin VL, Belaya K, Pecreaux J, Gilchrist MJ, Clark A, Davis I and **St Johnston D** (2008) *In vivo* imaging of *oskar* mRNA transport reveals the mechanism of posterior localization. Cell 134, 843-853

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

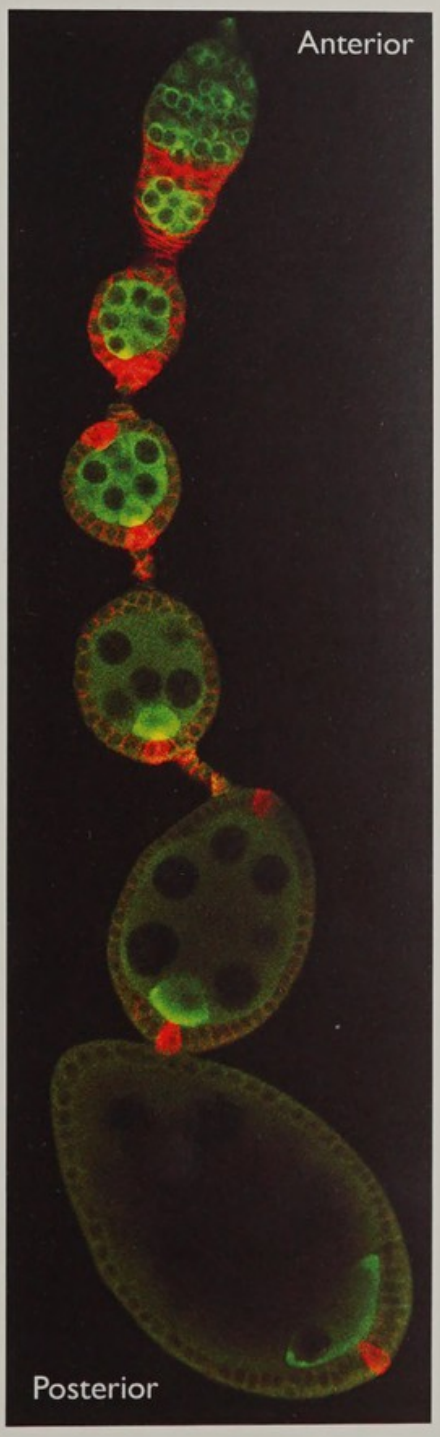




Removal of the AMP-dependent protein kinase from clones of follicle cells (marked by the absence of GFP; green) causes the cells to lose their polarity and over-proliferate, resulting in small tumours.



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.



A Drosophila ovariole containing a series of germline cysts that progress through oogenesis as they move posteriorly. The cysts are born at the anterior of the ovariole, and become surrounded by somatic follicle cells (red, FasIII). Each cyst contains 16 germ cells, one of which becomes the oocyte and accumulates higher levels of BicD protein (green).

Azim Surani

Mammalian germ cells, pluripotency and epigenesis

Co-workers: Delphine Cougot, Lynn Froggett, Astrid Gillich, Nils Grabole, Ufük Günesdogan, Jamie Hackett, Shinseog Kim, Caroline Lee, Harry Leitch, Erna Magnúsdóttir, Roopsha Sengupta, Qin Si, Katarzyna Wilczynska

The primary objective of our research is to elucidate the mechanism of primordial germ cell (PGC) specification, and to investigate the mechanism of extensive epigenetic reprogramming in early germ cells, including that conferred by maternally inherited factors in oocytes. Building on our previous work on germ cell determinants, we aim to resolve comprehensively the molecular foundations of specification of the mammalian germ cell lineage. Specification of PGCs is accompanied by the repression of the somatic programme, and epigenetic modifications that erase the epigenetic memory of their trajectory towards the somatic fate, while restoring an underlying pluripotency. Whereas a repressive complex maintains unipotency of germ cells, dedifferentiation of unipotent PGCs to pluripotent stem cells *in vitro* is accompanied by the reversal of the PGC specification process. Early germ cells also exhibit unprecedented genome-wide DNA demethylation and chromatin remodelling, which are essential towards the establishment of totipotency. These events together with the maternal inheritances of genetic and epigenetic regulators in oocyte are critical towards the establishment of the pluripotent state. We are gathering insight into the mechanisms involved, and continuing to identify the key factors that are crucial at these times. We are interested in exploiting the knowledge gained from studies on germ cells by creating *in vitro* models for induced epigenetic reprogramming, and using these models towards attempts at rejuvenation of somatic cells.

Selected publications:

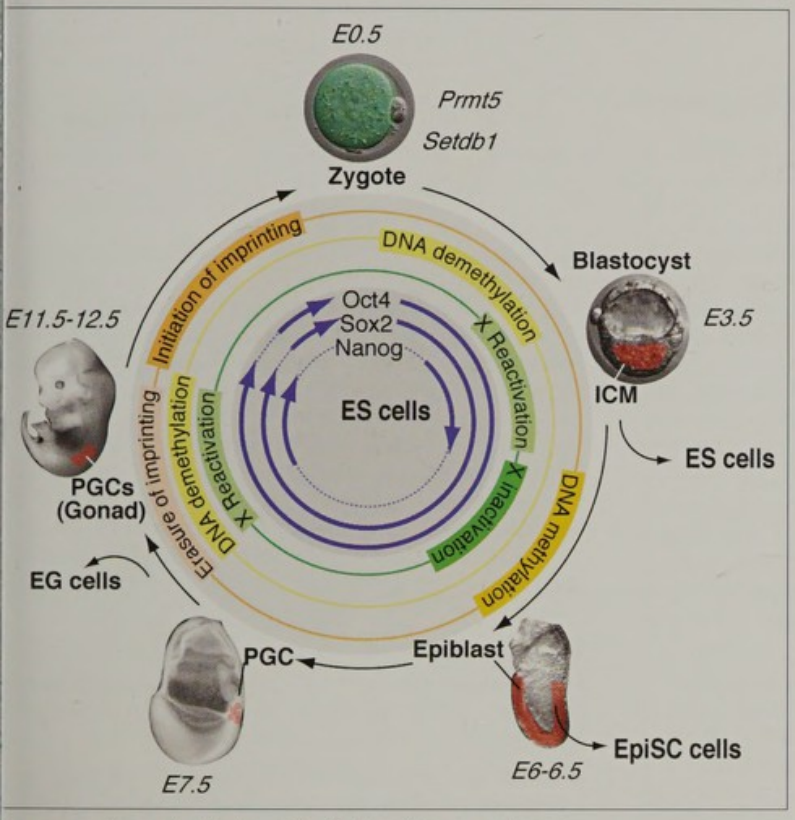
• **Surani MA** and Hajkova P. (2010) Epigenetic reprogramming of mouse germ cells towards totipotency. Cold Spring Harbor Symposium on Nuclear Organisation and Function, Volume LXXV

• Hajkova P, Jeffries SJ, Lee C, Miller N, **Jackson SP**, **Surani MA**. (2010) Genome-wide reprogramming in the mouse germ line entails the base excision repair pathway Science 329, 78-82

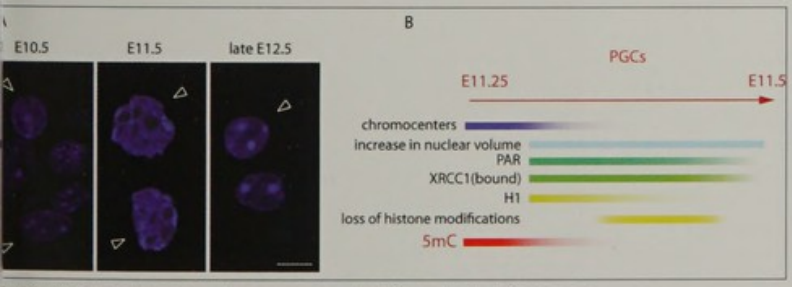
• Tang F, Barbacioru C, Bao S, Lee C, Nordman E, Wang X, Lao K, **Surani MA**. (2010) Tracing the derivation of embryonic stem cells from the inner cell mass by single cell RNA-Seq analysis. Cell Stem Cell 6, 468-478

• Bao S, Tang F, Li X, Hayashi K, Gillich A, Lao K, **Surani MA**. (2009) Epigenetic reversion of postimplantation epiblast to pluripotent embryonic stem cells . Nature 461, 1292-1295

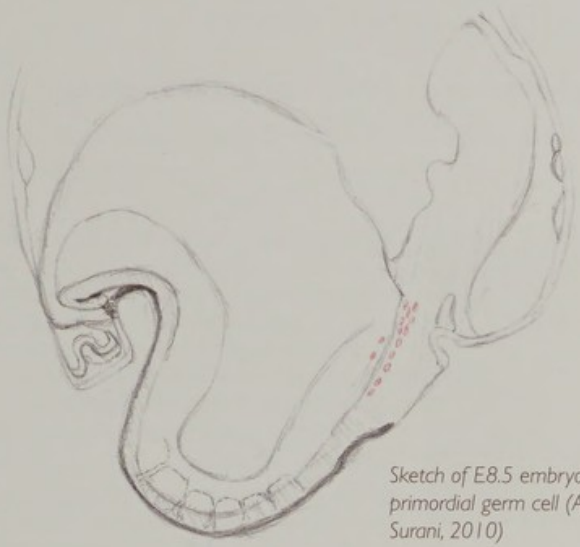
• Hajkova P, Ancelin K, Waldmann T, Lacoste N, Lange UC , Cesari F, Lee C, Almouzni G, Schneider R, **Surani MA**. (2008) Chromatin dynamics during epigenetic reprogramming in the mouse germ line. Nature 452, 877-881



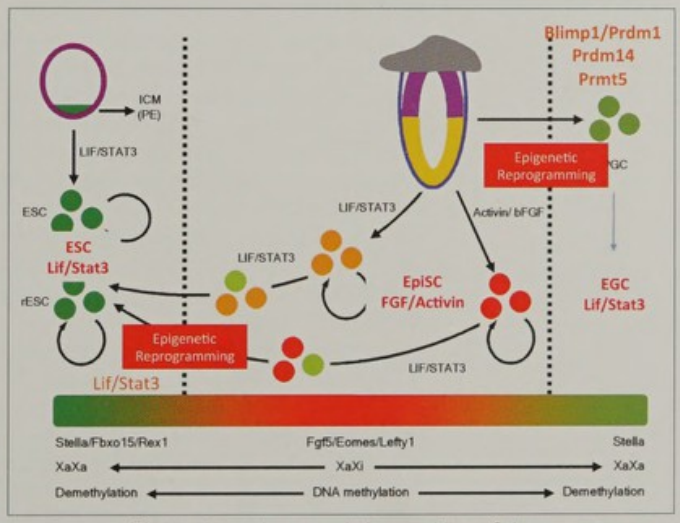
Mouse germ line cycle with the origin of primordial germ cells and pluripotent stem cells. Epigenetic changes in gonadal PGCs include genome-wide DNA demethylation and chromatin remodelling. Maternal inheritance of epigenetic modifiers in the zygote is critical for the establishment of the pluripotent state



Epiblast stem cells can undergo reversion to ESC or to specification as PGCs, accompanied by epigenetic reprogramming events



Sketch of E8.5 embryo with primordial germ cell (Azim Surani, 2010)



Changes in nuclear morphology and loss of chromocenteres in gonadal PGCs. B. Genome-wide DNA demethylation is accompanied by base excision repair.

Philip Zegerman

The regulation of DNA replication initiation in eukaryotes

Co-workers: Juliet Barrows, Vincent Gaggioli, Davide Mantiero, Barbara Schöpf

To successfully pass on its genetic information, every cell must make a perfect duplicate of the genome in every cell cycle. Failure to copy every chromosome faithfully leads to genomic instability, which is the cause of cancer. As a result, replication initiation is strictly regulated, both within the normal cell cycle and after DNA damage. We are interested in how this regulation of DNA replication is achieved in eukaryotes during the cell cycle and when replication forks stall.

Unlike prokaryotes, eukaryotes replicate their genomes from multiple origins. This has the advantage of facilitating the evolution of much larger and more complex genomes, but it does create a problem: If there are multiple origins in the genome, how is origin firing coordinated to make sure that no origin fires more than once?

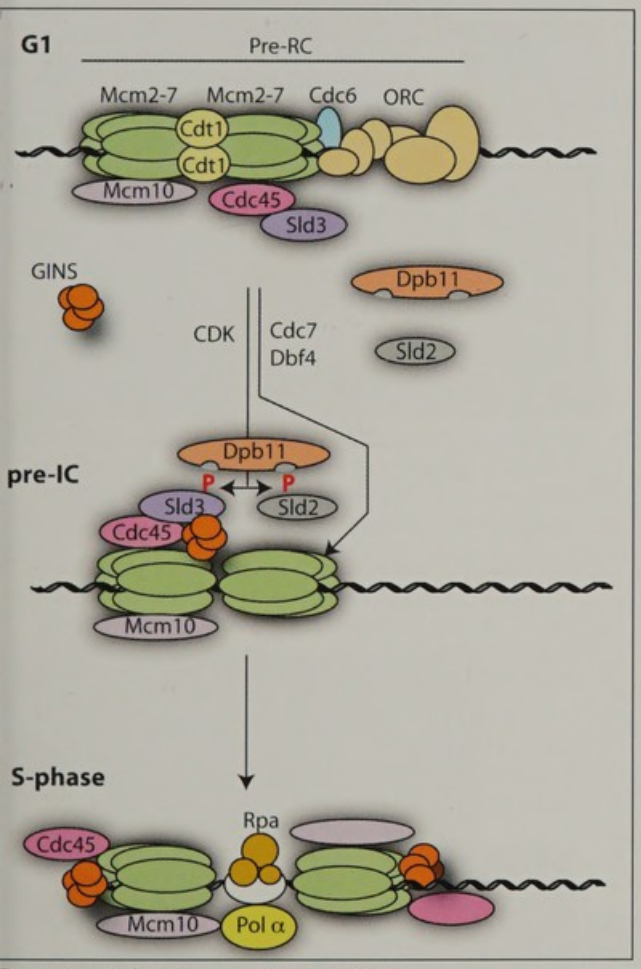
The assembly of the eukaryotic replication apparatus at origins is tightly regulated in two critical steps. The first step, pre-replicative complex (pre-RC) formation, involves the loading of the replicative helicase Mcm2-7 in an inactive form at origins. This complex can only form in G1 phase of the cell cycle when the APC/C is active and CDK activity is low. This is because CDKs and other APC/C targets such as Geminin are potent inhibitors of pre-RC formation. Once cells enter S-phase, the APC/C is inactivated, CDK activity (and also Geminin) rises and any further pre-RC formation is blocked.

In addition to its role as an inhibitor of pre-RC formation, CDK, together with a second kinase - DDK (Cdc7/Dbf4), are essential for the second step in replication initiation, which involves the activation of the Mcm2-7 helicase and the recruitment of DNA polymerases to origins. We have previously shown that CDK phosphorylates the two essential 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 has been termed the pre-initiation complex (pre-IC). Since CDK activity both inhibits pre-RC formation and is essential to initiate replication, this produces a switch that only allows replication initiation in S-phase.

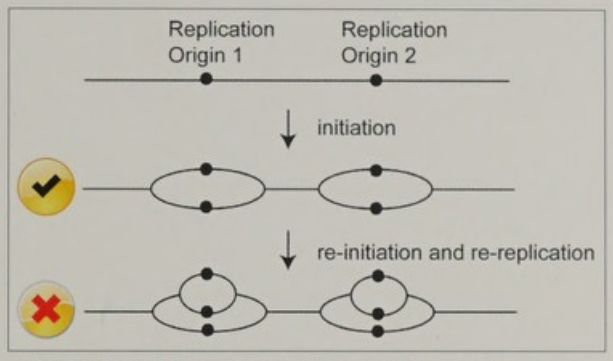
Our research is focused on the pre-initiation complex step in the replication reaction. This step is the key CDK regulatory step, but the function of this intermediate is not known. Furthermore, the pre-IC also integrates information from other kinases, such as the DNA damage checkpoint and may be responsible for regulating how efficiently and when an origin fires during S-phase. Much of our understanding of the pre-IC in eukaryotes comes from studies in budding yeast, but how replication initiation is regulated in other eukaryotes is largely unknown. Our aim is to take advantage of the expertise in the wide variety of organisms within the institute and extend these budding yeast studies to the nematode *C.elegans* and to mammalian cells.

Selected publications:

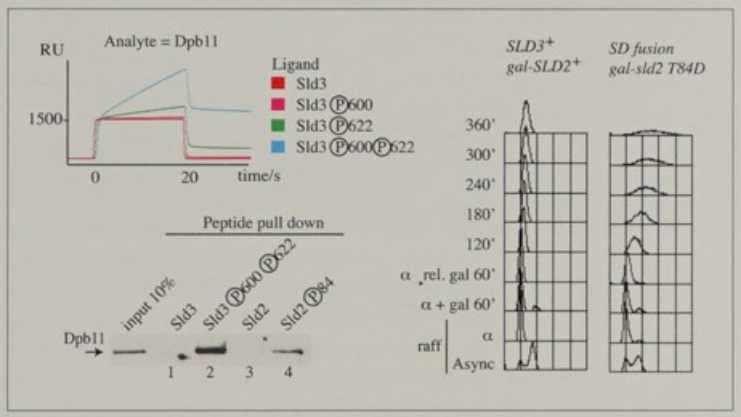
- **Zegerman P** and Diffley JF (2010) Checkpoint dependent inhibition of DNA replication initiation via phosphorylation of Sld3 and Dbf4. Nature 467, 474-478
- **Zegerman P** and Diffley JF (2009) DNA replication as a target of the DNA damage checkpoint. DNA repair 8,1077-88
- **Zegerman P** and Diffley JF (2007) Phosphorylation of Sld2 and Sld3 by cyclin-dependent kinases promotes DNA replication in budding yeast. Nature 445, 281-5
- **Zegerman P** and Diffley JF (2003) Lessons in how to hold a fork. **Nature Struct Biol** 10, 778-9



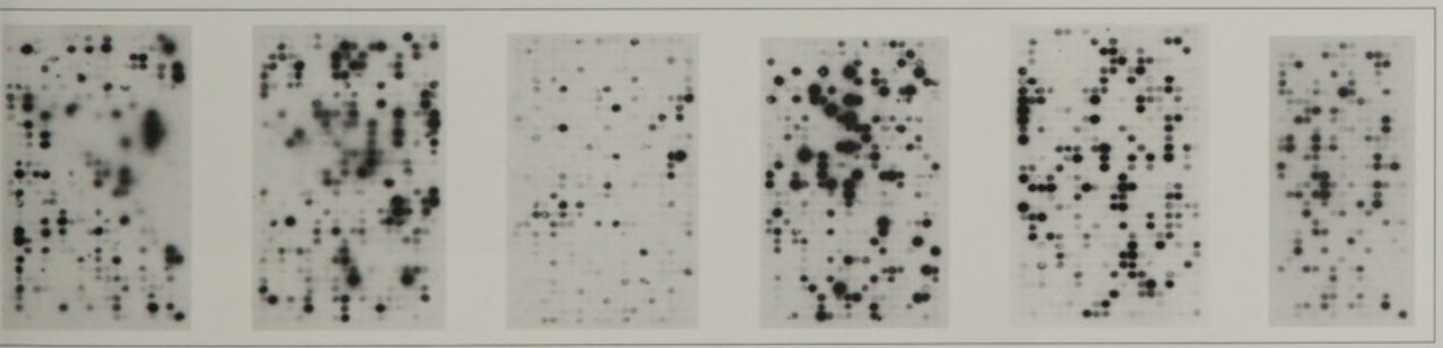
The sequence of eukaryotic replication initiation



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



Interactions between Dpb11 and phospho-Sld2/Sld3 in vitro (left panel) are confirmed to be essential for replication initiation in vivo (right panel).



Phospho-peptide array analysis of replication initiation factors.

Magdalena Zernicka-Goetz

Cell polarity, cell position and gene expression in the first cell fate decisions in the mouse embryo

Co-workers: Anna Ajduk, Stoyana Alexandrova, Paula Almeida Coelho, Florencia Barrios, Helen Bolton, John Crang, Sarah Graham, Agnieszka Jedrusik, Manuela Monti, Samantha Morris, Bedra Sharif, Maria Skamagki, Bernhard Strauss, Krzysztof Wicher

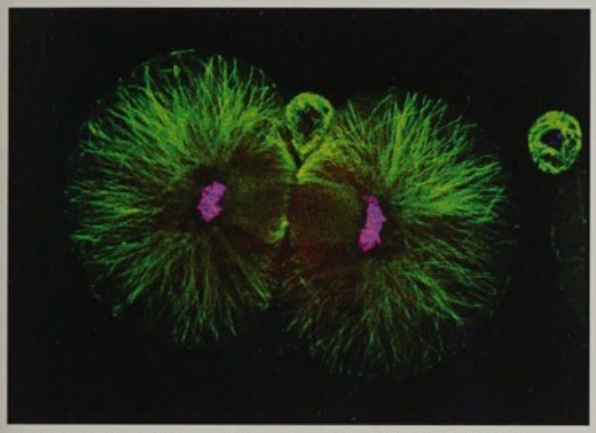
Setting aside the pluripotent cells that give rise to the future body from the extra-embryonic tissues is key to early mammalian development. It requires that some blastomeres divide asymmetrically to direct cells to the inside of the embryo, where they retain pluripotency. Is this regulated or does it occur at random and then what makes inside and outside cells different from each other? To address these questions, we have traced the origins and followed the division orientations and fates of every single cell in three-dimensional space throughout the first four days of development of mouse embryos. This revealed a spatial and temporal pattern of symmetric versus asymmetric cell divisions that depends on a cell's history and defines the orientation of the embryonic-abembryonic axis of the embryo. Our findings suggest that the first cell fate decision of the mouse embryo is a result of the generation of heterogeneity among blastomeres and this affects whether blastomeres undertake symmetric or asymmetric divisions. Our recent studies show that second fate decision that leads to the formation of the second extra-embryonic tissue is bound up with the later asymmetric divisions. Currently we are addressing:

- The role of epigenetic modifications at very early stages, specifically histone H3 arginine 26 methylation that we found affects the extent of cell pluripotency.
- The cellular mechanisms regulating asymmetric divisions.
- The contributions of cell polarity and cell position in determining specific patterns of gene expression in both fate decisions.
- How the first signalling centres arise in the two extra-embryonic tissues and function immediately after implantation.

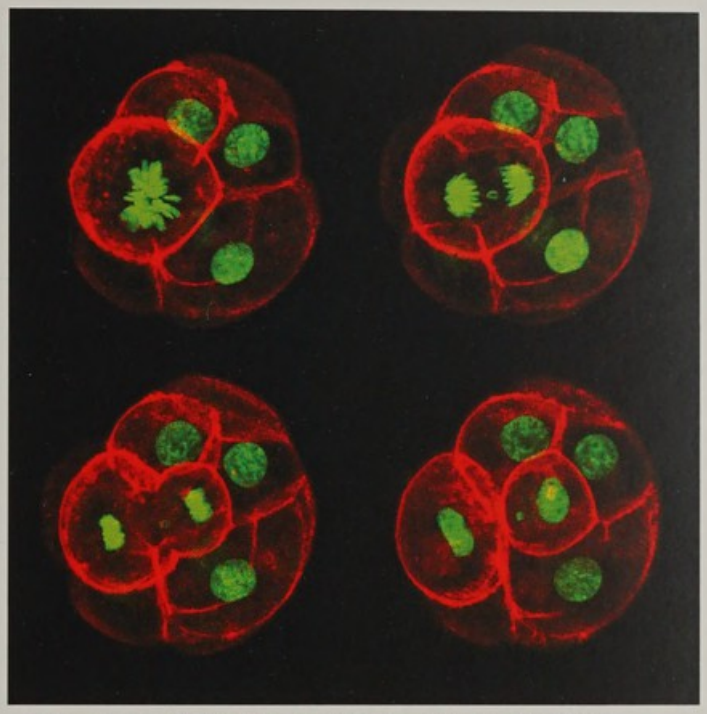
To address these questions we combine methods of classical experimental embryology with modern 4D time-lapse microscopy and molecular cell biology techniques that we have previously developed or optimised in the lab.

Selected publications:

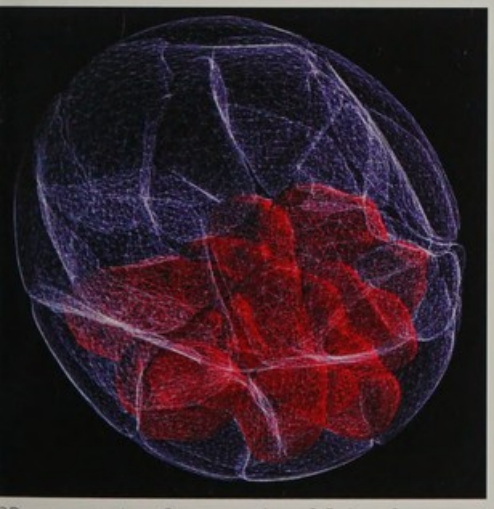
- **Zernicka-Goetz M**, Morris S and Bruce A (2009) Making a firm decision: layers of regulation in early mouse embryo. Nature **Rev Genet** 10, 467-77
- Jedrusik A, Parfitt DE, Guo G, Skamagki M, Grabarek JB, Johnson MH, Robson P and **Zernicka-Goetz M** (2008) Role of Cdx2 and cell polarity in cell allocation and specification of trophectoderm and inner cell mass in the mouse embryo. Genes Dev 22, 2692-706
- Bischoff M, Parfitt DE, **Zernicka-Goetz M** (2008) Formation of the embryonic-abembryonic axis of the mouse blastocyst: relationships between orientation of early cleavage divisions and pattern of symmetric/asymmetric divisions. Development 135, 953-62
- Torres-Padilla ME, Parfitt DE, Kouzarides T and **Zernicka-Goetz M** (2007) Histone arginine methylation regulates pluripotency in the early mouse embryo. Nature 445, 214-218



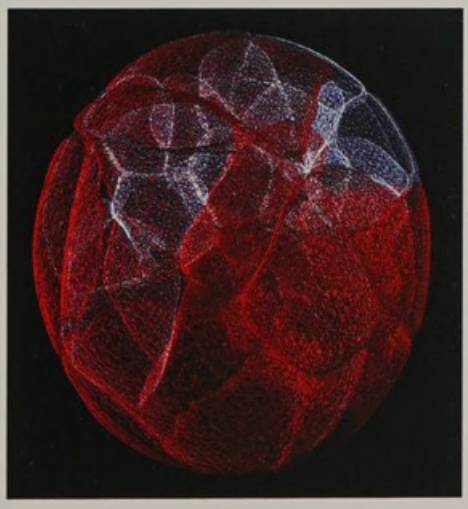
2-cell stage mouse embryo after the division. Microtubules in green, chromatin in magenta. (Image by Bedra Sharif)



Time course of an 8-16 cell stage embryo in which one cell is dividing asymmetrically, giving rise to an outside and inside cell. Chromosomes visualised in green, cell membranes in red. (Image by Sam Morris)



3D reconstruction of mouse embryo 3.5 day after fertilisation; pluripotent cells (ICM) in red, trophectoderm in blue (Image by Agnieszka Jedrusik)



3D reconstruction of an early mouse blastocyst. Cdx2 was over-expressed in half the embryo at the 2-cell stage. The resulting cells contribute disproportionally to the trophectoderm (red cells) of the blastocyst. Cells from the non-injected cell are in blue. (Image by Agnieszka Jedrusik)

CATEGORIES OF APPOINTMENT

SENIOR GROUP LEADER
Professor, Reader, Director of Research, Assistant Director of Research or equivalent

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

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 supported mainly by the Wellcome Trust or Cancer Research UK but additional sponsorship may be solicited from a variety of sources, including government research councils. Applicants should write, in the first instance, to the leader of the group they wish to join.

DANIEL ST JOHNSTON PhD FRS FMedSci, Chairman

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

REBECCA BASTOCK PhD
Wellcome Trust Research Associate

KATSIARYNA BELAYA PhD
Wellcome Trust Research Associate

DAN BERGSTRALH PhD
Marie Curie Research Fellow

EURICO de SA PhD
Graduate Student/Wellcome Trust Research Associate

HÉLÈNE DOERFLINGER PhD
Wellcome Trust Research Associate

CELIA FARIA BSc
Graduate Student

ALEJANDRA GARDIOL PhD
Wellcome Trust Research Associate

TIMM HAACK BSc
Wellcome Trust Graduate Student

JACKIE HALL MSc
Wellcome Trust Senior Research Technician

NICK LOWE PhD
Wellcome Trust Research Associate

DMITRY NASHCHEKIN PhD
Wellcome Trust Research Associate

ROSS NIEUWBURG BSc
Graduate Student

JENNY PESTEL
Visiting Student from Heidelberg

JOHANNA REES PhD
Wellcome Trust Research Associate

HANNA REUTER
Erasmus Student

ARAM SAYADIAN BSc
Wellcome Trust Graduate Student

VANESSA STEFANAK
PA

VITOR TROVISCO PhD
Marie Curie Intra-European Fellow

ANTONIO VEGA RIOJA PhD
FEBS Fellow

LUCY WHEATLEY BSc
Wellcome Trust Research Assistant

TONGTONG ZHAO BSc
Graduate Student

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)

ANNE VIELLE MSc
NIH Research Assistant

RON CHEN PhD
Wellcome Trust Research Associate

MICHAEL CHESNEY PhD
Wellcome Trust Reseach Associate

NICOLE CHEUNG PhD
Wellcome Trust/NIH Research Associate

YAN DONG MSc
Wellcome Trust Research Assistant

SKY FEUER MPhil
Gates Scholarship Graduate Student

BRUNO FIEVET PhD
Wellcome Trust Research Fellow

MORITZ HERRMANN BSc
BBSRC Graduate Student

PAULINA KOLASINSKA-ZWIERZ MSc
Gates Scholarship Graduate Student

SONJA KROSCHWALD
Visiting Student from Max Planck Institute in Dresden

ISABEL LATORRE PhD
NIH Research Associate

DAVID RIVERS PhD
Research Associate

JOSANA RODRIGUEZ PhD
Herchel Smith Research Fellow

PRZEMYSLAW STEMPOR MSc
Wellcome Trust Bioinformatics Research Associate

CHRISTINE TURNER
Secretary

EVA ZEISER BSc
Wellcome Trust Research Assistant

NDREA BRAND PhD FRS FMedSci

rchel Smith Professor of Molecular Biology
mber, European Molecular Biology Organization
ember of the Department of Physiology,
velopment and Neuroscience)

ZABETH CAYGILL PhD
llcome Trust Research Associate

MES CHELL PhD
llcome Trust Research Associate

TEBAN CONTRERAS SEPULVEDA MPhil
llcome Trust Graduate Student

LANIE CRANSTON BA
llcome Trust Research Assistant

THERINE DAVIDSON BSc
llcome Trust Research Associate

MES DODS PhD
llcome Trust Research Associate

RIS EGGER PhD
ss National Science Foundation Fellow

TRINA GOLD MPhil
llcome Trust Graduate Student

RRY HAN
Broad Rice Exchange Fellow

ARE HOWARD BSc
es Scholarship Graduate Student

N LIU BA
Herchel Smith Graduate Fellow

OMI MORIS
ation Student

IA OSWALD
B Vacation Student

INE PELISSIER PhD
BO Fellow

NY SOUTHALL PhD
rchel Smith Research Fellow

JLINE SPÉDER PhD
Henry Wellcome Postdoctoral Fellow

YSON THOMPSON BSc
C Graduate Student

RISTINE TURNER
retary

OB von TROTHA BSc
AD Graduate Student

D-SHU (PAUL) WU MA MD
mbridge Overseas Trust Graduate Student

NICK BROWN PhD

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

NATALIA BULGAKOVA PhD
HFSP Research Associate

JONATHAN FRIEDLANDER MA
Gates Scholarship and BBSRC Graduate Student

ANNABEL GRIFFITHS BA
MRC Graduate Student

SUSANNA HEMPEL
Visiting Masters Student from University of Göttingen, Germany

QIN HU PhD
Visiting Academic

SVEN HUELSMANN PhD
Wellcome Trust Research Associate

YOSHIKO INOUE PhD
Wellcome Trust Research Associate

BENJAMIN KLAPHOLZ PhD
Wellcome Trust Research Associate

SUSHMITA MAITRA PhD
Visiting Academic

MATT NEWTON
Volunteer Researcher

JOHN OVERTON HNC
Wellcome Trust Chief Research Technician

PEERAPAT THONGNUEK MRes in Regenerative Medicine
Thai Government Graduate Student

JUTTA WELLMANN MPhil
Herchel Smith and BBSRC Graduate Student

JARI YLANNE PhD
Sabbatical Visitor from the University of Jyväskylä, Finland

JOHN GURDON Kt DPhil DSc FRS

Distinguished Group Leader
Foreign Associate, US National Academy of Sciences
Foreign Associate, US National Academy of Sciences Institute of Medicine
Foreign Associate, French National Academy of Sciences
Member, European Molecular Biology Organization
Member, Academia Europaea
Honorary Member of American Anatomical Society
Honorary Member of Anatomical Society of Great Britain
Chairman, Company of Biologists
(Member of the Department of Zoology)

CAROLINA ÅSTRAND PhD
Academic Visitor

DILLY BRADFORD
Secretary

NIGEL GARRETT MIBiol
Isaac Newton Trust Research Associate

RICHARD HALLEY-STOTT BSc
Graduate Student

JEROME JULLIEN PhD
Wellcome Trust Research Associate

JOE KUO
Genetics Society Summer Student

KEI MIYAMOTO PhD
Japan Society for the Promotion of Science Research Fellow

PATRICK NARBONNE PhD
HSFP Research Fellow

MARYNA PANAMAROVA Bsc Hons
Darwin Trust Graduate Student

VINCENT PASQUE BSc
Graduate Student

MARTA TEPEREK-TKACZ BSc
Wellcome Trust Graduate Student

MIKIKO TOKORO
Visiting Student from Japan

SENIOR GROUP LEADERS

STEVE JACKSON PhD FRS FMedSci

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

LINDA BASKCOMB MSc
Cancer Research UK Senior Chief Research Laboratory Technician

RIMMA BELOTSERKOVSKAYA PhD
Cancer Research UK Research Associate

MELANIE BLASIUS PhD
Swiss National Foundation Research Fellow

SEBASTIEN BRITTON PhD
EMBO Research Fellow

JESSICA BROWN MB BChir
Wellcome Trust Clinical Fellow/Graduate Student

PHILIP BURN
Biochemical Society Vacation Student

ROSS CHAPMAN BSc
Cancer Research UK Research Assistant

JULIA COATES MA
Cancer Research UK Research Assistant

KATE DRY PhD
Cancer Research UK Information Specialist

SONJA FLOTT PhD
Ernst Schering Foundation Fellow

JOSEP FORMENT PhD
Cancer Research UK Research Associate

YARON GALANTY PhD
Cancer Research UK Senior Research Associate

SIMONA GIUNTA BSc
BBSRC CASE Graduate Student

ILARIA GUERINI PhD
EU Research Associate

JEANINE HARRIGAN PhD
Cancer Research UK Research Associate

PABLO HUERTAS PhD
BBSRC Research Associate

XAVIER JACQ PhD
Research Associate

LOUISE JONES BSc
Research Assistant

KAMILA JOZWIK BSc
Graduate Student (part funded by the Corbridge Trust)

ABDERRAHMANE KAIDI PhD
Herchel Smith Research Fellow

CHARLOTTE KNIGHTS BSc
Research Assistant

DELPHINE LARRIEAU PhD
Research Associate

CARLOS LE SAGE PhD
Cancer Research UK Research Associate

NATALIA LUKASHCHUK PhD
Cancer Research UK Research Associate

KYLE MILLER PhD
Wellcome Trust Research Associate

RYOTARO NISHI PhD
Sankyo Foundation of Life Science Research Fellow

TOBIAS OELSCHLÄGEL PhD
EU Research Associate

SOPHIE POLO PhD
HFSP Research Fellow

HELEN REED
Secretary

LISA SMITH PhD
Research Assistant

NEHA THAKKAR MSc
Cancer Research UK Senior Research Laboratory Technician

JORRIT TJEERTES MSc
BBSRC CASE Graduate Student

PAUL WIJNHOVEN BSc
Cancer Research UK Senior Research Laboratory Technician

TONY KOUZARIDES PhD FMedSci

Deputy Director
Royal Society Napier Professor
Member, European Molecular Biology Organization
(Member of the Department of Pathology)

HATICE AKARSU PhD
EU Research Associate

PAOLO AMARAL Msc
Visiting Graduate Student from the University of Queensland, Australia

ANDREW BANNISTER PhD
Cancer Research UK Senior Research Associate

ISAIA BARBIERI BSc
Visiting Graduate Student from the University of Turin

TILL BARTKE PhD
Cancer Research UK Research Associate

GONÇALO CASTELO-BRANCO PhD
Marie Curie Research Fellow

MARIA CHRISTOPHOROU PhD
EU Research Associate

ALISTAIR COOK GIBiol
Cancer Research UK Chief Research Technician

MARK DAWSON MBBS (Hons); BMEDSci; FRACP; FRCPA; PhD
WELLCOME-BEIT Intermediate Clinical Fellow

CYNTHIA HILL MSc
NIH Senior Research Technician

ANTONIS KIRMIZIS PhD
EU Research Associate

MIRANDA LANDGRAF MA
PA/Secretary (maternity cover)

NIKKI PARSONS BA
PA/Secretary (currently on maternity leave)

SAM ROBSON PhD
Cancer Research UK Research Associate (Bioinformatics)

HELENA SANTOS ROSA PhD
Cancer Research UK Senior Research Associate

MARC SCHNEIDER PhD
EMBO Research Associate

PETER TESSARZ PhD
Cancer Research UK Research Associate

EMMANUELLE VIRÉ PhD
Wiener-Anspach Foundation Research Fellow

BEATA WYSPIANSKA MSc
BBSRC Case Graduate Student

BLERTA XHEMALCE PhD
EU Research Associate

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

FABIEN CUBIZLLES PhD
Collaborating Researcher from Erich Nigg's lab in Basel, Switzerland

BARBARA DI FIORE PhD
Cancer Research UK Research Associate

ANJA HAGTING PhD
Cancer Research UK Research Associate

DAISUKE IZAWA PhD
AICR Research Associate

MARK JACKMAN PhD
Cancer Research UK Research Associate

AGATA LICHAWSKA MSc
Herchel Smith Graduate Student

JÖRG MANSFELD PhD
FEBS Research Fellow

PAOLA MARCO BSc
BBSRC CASE Graduate Student

TAKAHIRO MATSUSAKA PhD
Cancer Research UK Research Associate

OXANA NASHCHEKINA MSc
Cancer Research UK Chief Research Technician

EMILIE RUSSE
Visiting Student from Ecole Normale Superior, Paris

JACKIE SIMCOX
Secretary

BERNHARD STRAUSS PhD
MRC Research Associate (joint with Dr M Zernicka-Goetz)

ELIANA TACCONI BA
Volunteer Researcher

FELICIA WALTON
NSF Graduate Student

SAMUEL WIESER
Graduate Student

MONA YEKEZARE
Yousef Jameel Graduate Student

AZIM SURANI PhD CBE FRS FMedSci

Mary Marshall & Arthur Walton Professor of Physiology and Reproduction
Head of Wellcome Trust Labs
Member, European Molecular Biology Organization
Member Academia Europaea
Associate Fellow, Third World Academy of Sciences
(Member of the Department of Physiology, Development and Neuroscience)

SUZAN BER PhD
Wellcome Trust Research Associate

ANTONIO CAMPOS CARO PhD
Visiting Academic from University of Cadiz

DELPHINE COUGOT PhD
Wellcome Trust Research Associate

LYNN FROGGETT
Secretary

ASTRID GILLICH MSc
Wellcome Trust Graduate Student

NILS GRABOLE BSc
Wellcome Trust Graduate Student

UFÜK GÜNESDOGAN PhD
Wellcome Trust Research Associate

JAMIE HACKETT PhD
Wellcome Trust Research Associate

SOPHIE HANINA BA
Graduate Student

SHINSEOG KIM PhD
Wellcome Trust Research Associate

CAROLINE LEE ONC
Wellcome Trust Chief Research Technician

HARRY LEITCH MA (Cantab)
MB/PhD Graduate Student

ERNA MAGNÚSDÓTTIR PhD
Marie Curie Research Fellow

WILLIAM MIFSUD MD MPhil
Graduate Student

ROOPSHA SENGUPTA PhD
Wellcome Trust Research Associate

QIN SI PhD
Wellcome Trust Research Associate

FUCHOU TANG PhD
Wellcome Trust Research Associate

WEE WEI TEE MPhil
Graduate Student

KATARZYNA WILCZYNSKA PhD
EMBO Research Fellow

GROUP LEADERS

RAFAEL CARAZO SALAS PhD

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

ANATOLE CHESSEL PhD
HFSP Research Associate

JAMES DODGSON PhD
HFSP Research Associate

MARCO GEYMONAT PhD
ERC Research Associate

VERONIKA GRAML BSc
SystemsX.ch Graduate Student

YUNG-CHIN OEI BSc
Cancer Research UK Graduate Student

KATHY OSWALD MA
Secretary/PA

XENIA STUDERA BSc
Swiss National Science Foundation Graduate Student

THOMAS DOWN PhD

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

PAULINA CHILARSKA BSc
Wellcome Trust Graduate Student

KENNETH EVANS PhD
Wellcome Trust Bioinformatics Research Associate

SIARHEI MASLAU PhD
Juvenile Diabetes Research Fund (JDRF) Research Associate

JING SU
Visiting Researcher from LMB

RICK LIVESEY MB BChir PhD

Wellcome Trust Group Leader
Senior Lecturer
(Member of the Department of Biochemistry)

SARRITA ADAMS BSc
Graduate Student

JESSICA ALSIO BSc
Wellcome Trust Graduate Student

THERESE ANDERSSON PhD
Wenner-Gren Foundation Research Fellow

JULIET BARROWS BA
Secretary

CHIBAWANYE ENE BSc
NIH-Cambridge Graduate Student

PETER KIRWAN BSc
Wellcome Trust Graduate Student

MOYRA LAWRENCE BSc
WT/MRC Stem Cell Biology Graduate Student (The Livesey Lab is a member of the Cambridge Stem Cell Initiative)

JOAO PEREIRA BSc
Fundação para a Ciência e Tecnologia Graduate Student

STEPHEN SANSOM PhD
Wellcome Trust Research Associate

NATHALIE SAURAT BSc
Woolf Fisher Graduate Student

YICHEN SHI BSc
Dorothy Hodgkin Postgraduate Student

JAMES SMITH BSc
Wellcome Trust Research Assistant

URUPORN THAMMONGKOL BSc
Graduate Student

MASANORI MISHIMA PhD

Cancer Research UK Group Leader
(Member of the Department of Biochemistry)

TIM DAVIES BSc
BBSRC Graduate Student

MAX DOUGLAS MBiochem
BBSRC Graduate Student

LYNN FROGGETT
Secretary

ANDREA HUTTERER PhD
HFSP Research Fellow

NIMESH JOSEPH PhD
Cancer Research UK Research Associate

KIAN-YONG LEE BSc
Cancer Research UK Graduate Student

JULIA MASON BSc
Cancer Research UK Research Assistant

EVA PABLO-HERNANDO PhD
Isaac Newton Trust Research Associate

ERIC MISKA PhD

Cancer Research UK Group Leader
(Member of the Department of Biochemistry)

JAVIER ARMISEN GARRIDO PhD
EU Research Associate

ALYSON ASHE PhD
Herchel Smith Research Fellow

MARLOES BAGIJN MSc
Graduate Student

ALEJANDRA CLARK PhD
Cancer Research UK Research Associate

LEONARD GOLDSTEIN PhD
Cancer Research UK Research Associate

ETHAN KAUFMAN BSc
Gates Graduate Student

NIC LEHRBACH MPhil
Graduate Student

HELEN LIGHTFOOT BSc
Cancer Research UK Graduate Student (joint with Dept of Chemistry)

SYLVIANE MOSS PhD
Cancer Research UK Chief Research Technician

KENNETH MURFITT BSc
Wellcome Trust Graduate Student

NICOLA PARSONS BA
PA/Secretary (currently on maternity leave)

ALEXANDRA SAPETSCHNIG PhD
Herchel Smith Research Fellow

FUNDA SAR PhD
Cancer Research UK Research Associate

ROBERT SHAW BA MPhil
Graduate Student/Cancer Research UK Research Assistant

EVA-MARIA WEICK BSc
Herchel Smith/BBSRC Graduate Student

JULIE WOOLFORD MPhil
Cancer Research UK Graduate Student

EUGENIA PIDDINI PhD

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

GOLNAR KOLAHGAR PhD
Research Associate

CATHY OSWALD MA
PA/Secretary

SILVIA VIVARELLI PhD
MRC Research Associate

LAURA WAGSTAFF PhD
MRC Research Associate

EMMA RAWLINS PhD

MRC Research Fellow
(Member of the Department of Pathology)

GAYAN BALASOORIYA BSc
MRC Research Technician/Laboratory Manager

JULIET BARROWS BA
Secretary

SMAHAN SULEIMAN MSc
Visiting MPhil Student

PHILIP ZEGERMAN PhD

CRUK Research Fellow
(Member of the Department of Zoology)

JULIET BARROWS BA
Secretary

VINCENT GAGGIOLI PhD
CRUK Research Associate

DAVIDE MANTIERO PhD
EMBO Research Fellow

BARBARA SCHÖPF PhD
CRUK Research Associate

SANDRA VÖLS
Visiting Student from University of Marburg, Germany

MAGDALENA ZERNICKA-GOETZ PhD

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

ANNA AJDUK PhD
Wellcome Trust Research Associate

STOYANA ALEXANDROVA BA
Graduate Student

PAULA ALMEIDA COELHO PhD
Visiting Academic

FLORENCIA BARRIOS PhD
Wellcome Trust Research Associate

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

ALEX BRUCE PhD
Wellcome Trust Research Associate

JOHN CRANG DPhil
PA

SARAH GRAHAM MSc
Graduate Student

SEEMA GREWAL PhD
Wellcome Trust Research Associate

AGNIESZKA JEDRUSIK MSc
Graduate Student

MANUELA MONTI PhD
Academic Visitor from the University of Pavia, Italy

SAMANTHA MORRIS PhD
Wellcome Trust Research Associate

SAMEER PATANKAR BSc
Visiting Student from University of Nottingham

MATTHIAS ROMAUCH Dr med univ
Visiting Student from University of Graz

BEDRA SHARIF BSc
Gates Graduate Student

MARIA SKAMAGKI BSc
Greek State Scholarship Graduate Student

BERNHARD STRAUSS PhD
MRC Research Associate (joint with Dr J Pines)

CHLOE SWORDS
Wellcome Trust Vacation Student

ROY (TANG YI) TEO
A* Graduate Student

KRZYSZTOF WICHER PhD
Wellcome Trust Research Associate

KATHRIN BRUNK PhD

Cancer Research UK Research Associate

BEN SIMONS PhD

Academic Visitor (Professor of Theoretical Condensed Matter Physics at the Cavendish Laboratory)

ADMINISTRATION

ANN CARTWRIGHT MPhil
Institute Administrator
GEORGE BROWN
Accounts Manager
SUZANNE CAMPBELL BSc
HR/Grants Manager
JANE COURSE
Accounts/Admin Assistant
JOHN CRANG DPhil
HR/Grants Manager (Temporary)
SUE CROYSDALE
Receptionist (maternity cover)
DIANE FOSTER
Deputy Administrator
KATHY HILTON DipMgm
CBSG Manager
SOPHIE LEGGETT
HR/Grants Manager (Temporary)
LYNDA LOCKEY
Office Manager
NICOLA PARSONS BA
Receptionist (currently on maternity leave)
JACKIE SIMCOX
Receptionist

COMPUTING

ALASTAIR DOWNIE
Computer Associate
NICOLA LAWRENCE PhD
Computer Associate
NIGEL SMITH
Computer Associate
ALEX SOSSICK BSc
Computer Imaging Associate
PETER WILLIAMSON BSc
Computer Associate

BIOINFORMATICS

CHARLES BRADSHAW PhD
Computer Associate (Bioinformatics)

ACCOUNTS/PURCHASING/STORES

IAN FLEMING
Stores/Purchasing Manager
SIMON ALDIS
Purchasing/Accounts Assistant
DAVID COOPER
Stores Technician
RICHARD ETTERIDGE MA
Purchasing/Accounts Assistant
ANDY VINCENT
Stores Technician
MICK WOODROOFE
Purchasing/Accounts Assistant

TECHNICAL SUPPORT

KEITH SAVILL
Senior Technical Officer
RYAN ASBY
NIGEL BARNETT
ANNABELLE CURRY
MARK GILLILAND
GEMMA HORTON
WEN JIN
MARIA JUHL LARSEN
FALLON MILLER
JASON RISEBOROUGH
RACHEL SMITH-MILLER
LISA WRIGHT
POLLY ATTLESEY
ROBERT BRETT
GARY GARNER
RICHARD HARPER
GILLIAN HYNES
SHANE JOHNSON
URSZULA KOKOT
JENNIE PIDGEN
DAVID SIMPSON
KATIE WOODHOUSE

COMBINED BUILDING SERVICES GROUP (CBSG)

CLIVE BENNETT
GARY HAWKINS
ALAN RIX
JAMES SMITH (JT)
KATHERINE BENNETT
CHRIS HAYLOCK
STEPHEN SALT
PAUL TURRELL

MEDIA/GLASS WASHING

JUANITA BAKER-HAY
Media/Glass Washing Manager
JANIS ABBOTT
LISA BAKER
BEVERLEY CORNELL
VINCE DAMS
SANDRA HUMAN
TRACY MITCHELL
AGNES ASSELIN LE FOLL
BETTINA CASHIN
KAZUKO COLLINS
BETTY HUDSON
MARK JOHNS

ZEST CATERING

AMANDA HARRIS
MELISSA PLOWDEN ROBERTS
DARIA SKRODZKA

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.

* Indicates equal priority.

1 Ahel D, Hofejsi Z, Wiechens N, Polo SE, Garcia-Wilson, E, Ahel I, Flynn H, Skehel M, West SC, **Jackson SP**, Owen-Hughes T and Boulton SJ (2009) Poly (ADP-ribose)-dependent regulation of DNA repair by the chromatin remodeling enzyme ALC1. Science 325, 1240-1243

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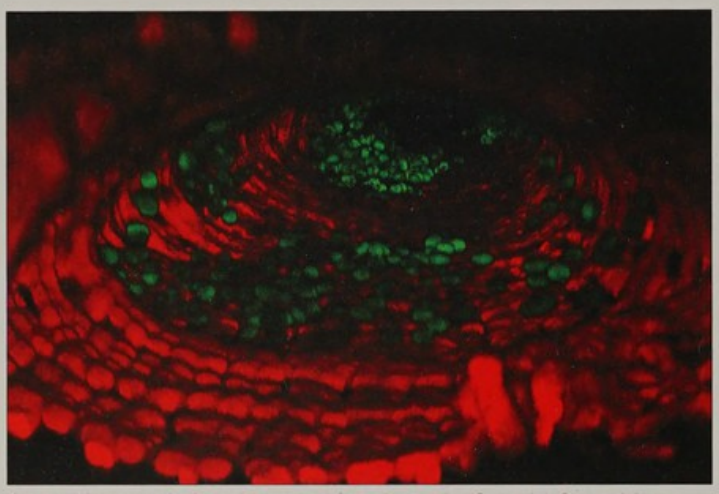

Overproliferating cells (green) observed from the inside of an adult Drosophila gut (red). (Golnar Kolahgar, Piddini Group, 2010)

27 Geymonat M, Spanos A, Jensen S and Sedgwick SG (2010) Phosphorylation of LTE1 By CDK prevents polarised growth during mitotic arrest in *S. Cerevisiae*. Journal of Cell Biology [In press] [**Carazo-Salas** group]

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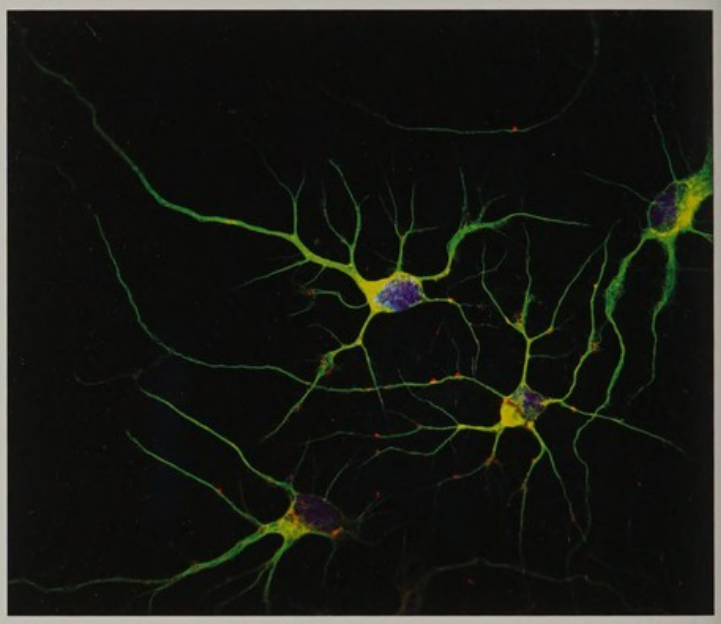

Cultured mouse cortical neurons forming synapses with each other as shown by the red punctae of PSD95. Neurons are labelled in green with beta-III-tubulin. DAPI in blue. (Peter Kirwan, Livesey Group, 2010)

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The following is a list of speakers invited to give talks to the Institute as part of the Gurdon Institute Seminar Series and the Developmental Biology Seminar Series, since the date of publication of the last Annual Report.

1 **Wilhelm Krek** (ETH-Hönggerberg, Institute of Cell Biology, Zurich, Switzerland): "VHL tumor suppressor mechanisms: from maintenance of the primary cilium to promotion of error-free mitosis" 12/01/2010

2 **Bill Harris** (PDN, University of Cambridge): "What are the cells in the developing vertebrate retina doing?" 22/01/2010

3 **Andrea Musacchio** (Department of Experimental Oncology, IFOM-IEO Milan, Italy): "Feedback control of mitosis" 26/01/2010

4 **Katrin Ottersbach** (Cambridge Institute for Medical Research): "The role of Gata3 in the emergence of hematopoietic stem cells - a link between the hematopoietic and sympathetic nervous system" 05/02/2010

5 **Rene Medema** (Laboratory of Experimental Oncology, UMC Utrecht, The Netherlands): "Mitotic entry following a DNA damage-induced arrest" 09/02/2010

6 **Steve Wilson** (Department of Cell and Developmental Biology, University College London): "The development of brain asymmetry - from genes to circuits" 12/02/2010

7 **Octavian Voiculescu** (PDN, University of Cambridge): "Shaping and patterning the embryo: Gastrulation in higher vertebrates" 19/02/2010

8 **Emma Rawlins** (Gurdon Institute, University of Cambridge): "Lung epithelial progenitor cells in development and repair" 26/02/2010

9 **David Ron** (Institute of Metabolic Sciences, University of Cambridge): "Coupling organelle capacity to the cell's needs" 05/03/2010

10 **Peter Sicinski** (Harvard Medical School, Department of Cancer Biology, Dana-Farber Cancer Institute. Boston, USA): "Cell cycle machinery in mouse development and in cancer" 23/03/2010

11 **Kristi Wharton** (Brown University): "Fine-tuning BMP signaling during cell fate specification 23/04/2010

12 **Jose Silva** (Wellcome Trust Centre for Stem Cell Research University of Cambridge): "Dissecting the role of signalling inhibition during the induction of pluripotency" 30/04/2010

13 **Susan Gasser** (Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland): **The Anne McLaren Lecture**: "Remodeling the nucleus through development" 04/05/2010

14 **Rick Livesey** (Gurdon Institute University of Cambridge): "Epigenetic mechanisms in mammalian neurogenesis" 07/05/2010

15 **Petra Hajkova** (MRC Clinical Sciences Centre Imperial College London): "Epigenetic reprogramming in the mouse germ line: the repair connection" 14/05/2010

16 **Barry Thompson** (LRI Lincoln's Inn Fields Laboratories London): "Control of tissue size and shape in Drosophila" 21/05/2010

17 **Nancy Papalopulu** (Faculty of Life Sciences, University of Manchester): "Region-specific regulation of neurogenesis by mir-9" 28/05/2010

18 **Eugenia Piddini** (Gurdon Institute University of Cambridge): "Cell wars: competition through growth factor signalling" 04/06/2010

19 **Ilan Davis** (Department of Biochemistry, University of Oxford, UK): "The mechanism of mRNA transport and localized translation in *Drosophila* oocytes and neurons" 05/10/2010

20 **Roger Pedersen** (The Anne McLaren Laboratory for Regenerative Medicine, University of Cambridge): "Modelling early human cell fate decisions using pluripotent stem cells" 15/10/2010

21 **Gerard Evan** (Head of Department of Biochemistry, University of Cambridge, UK): "Using switchable genetically engineered mice to model cancer therapies" 19/10/2010

22 **Guy Blanchard** (PDN, University of Cambridge): "Tracking cell and cytoskeletal behaviour to understand tissue morphogenesis in fish and fly embryos" 22/10/2010

23 **Rob White** (PDN, University of Cambridge): "Hox targets in Drosophila" 29/10/2010

24 **Wendy Bickmore** (MRC Human Genetics Unit, Edinburgh, UK): "Does epigenetic gene regulation extend beyond histone modifications?" 02/11/2010

25 **Francois Guillemot** (Division of Molecular Neurobiology, National Institute for Medical Research): "Coordinated regulation of cell divisions, migration and differentiation in the developing mouse brain" 05/11/2010

26 **Alan Colman** (Director, Stem Cell Research, King's College London, UK, Singapore Stem Cell Consortium and A*Star Institute of Medical Biology, Singapore): "Human disease in a dish: modelling premature aging and neurological disorders using induced pluripotent stem cells" 09/11/2010

27 **Andrea Münsterberg** (Biological Sciences, University of East Anglia, Norwich): "The regulation of skeletal muscle development by signaling molecules and microRNAs" 12/11/2010

28 **Anton Wutz** (Centre for Stem Cell Research, University of Cambridge): "Regulation of chromatin organization and epigenetic modifications in embryonic stem cells" 19/11/2010

29 **Richard Wingate** (MRC Centre for Developmental Neurobiology, King's College London): "Your inner frog - Can clues from evolution unlock the molecular development of the cerebellum?" 26/11/2010

30 **Yohanns Bellaiche** (Institut Curie, Paris, France): "Mitotic spindle orientation from cell fate specification to tissue morphogenesis in *Drosophila*" 30/11/2010

31 **Marc Kirschner** (John Franklin Enders Professor, Chair and Professor of Systems Biology, Harvard Medical School, Boston, USA): "Size control in mammalian cells" 08/12/2010

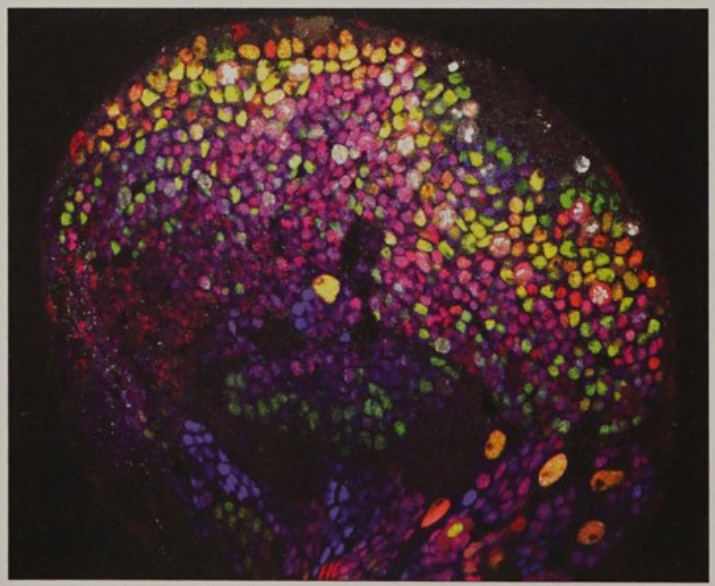
STAFF AFFILIATIONS

JULIE AHRINGER is a member of the MRC Career Development Panel and a mamber of the Scientific Advisory Board of Reactome.

ANDREA BRAND is a Founding Board Member of The Rosalind Franklin Society (USA), member of the Royal Society Research Appointment Panel Bi, member of the Sectional Committee of the Academy of Medical Sciences, member of the EMBO Young Investigator Committee, Chair of the Selection Committee, Genetics and Developmental Biology Unit, Institut Curie (Paris, France), member of the Review Panel of the Developmental Biology Unit, EMBL (Heidelberg, Germany), member of the Scientific Advisory Board for the MRC Centre for Developmental Neurobiology (King's College London) and external advisor to the Management Board of the National Centre for Biological Sciences (Bangalore, India). She is also a member of the University of Cambridge Neuroscience Committee, the steering group of the Cambridge Women in Science, Engineering and Technology Initiative, Patron of the Cambridge Science Festival, and member of Council, Jesus College.

JOHN GURDON is a member of the Scientific Advisory Board of the Harvard Stem Cell Institute (USA) and the Rambam Medical Center (Israel), a member of the British and American Anatomical Societies, Chairman of the Company of Biologists, and a board member of Diagnostics for the Real World

STEVE JACKSON is Chairman of the Board of the Scottish Centre for Cell Signalling (SCILLS), a member of the Cancer Research UK Drug Discovery Advisory Group, the Strategic Board of the Drug Discovery Program (IFOM-IEO, Milan, Italy), the Radiation Oncology and Biology External Advisory Board and the Scientific Advisory Board for the Beatson Institute



Transcription factors stained in red, green and blue colocalise in different cells to act combinatorially in the Drosophila brain to regulate neural stem cell differentiation. (Alyson Thompson, Brand Group, 2010)

The prospective wing area (wing pouch) of a Drosophila wing imaginal disc. Anterior cells are labeled in red. (Eugenia Piddini, 2010)

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 was the Membership Secretary of the British Society for Cell Biology, (2002-2008) and is a member of the Association for International Cancer Research Grants Committee.

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

AZIM SURANI is Chairman of the Scientific Advisory Board of the Centre for Trophoblast Research, University of Cambridge; Member of the Steering Committee of the Cambridge Stem Cell Initiative, and Leader of the Pluripotency Programme; Member of the Cambridge India Partnership Advisory Group; Founder and Chief Scientific Advisor for CellCentric Ltd; Member of the Steering Committee for the UK Stem Cell Bank; Member of the Royal Society Nominations Committee; Visiting Professor, University of Kyoto, Japan

MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Senior Research Fellow at Sidney Sussex College and Board Member of the Cambridge Philosophical Society.

HONOURS AND AWARDS

ANDREA BRAND - Fellowship of the Royal Society

NICK BROWN - Membership of the European Molecular Biology Organization

JOHN GURDON - Hon. Fellowship of the Cambridge Philosophical Society

AZIM SURANI - Awarded Royal Medal of the Royal Society

MAGDALENA ZERNICKA-GOETZ - Professorship in University of Cambridge

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DANIEL ST JOHNSTON – Development, Faculty of 1,000.

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

MAGDALENA ZERNICKA-GOETZ – Developmental Dynamics, BMC Developmental Biology, Reproduction, Development, Differentiation

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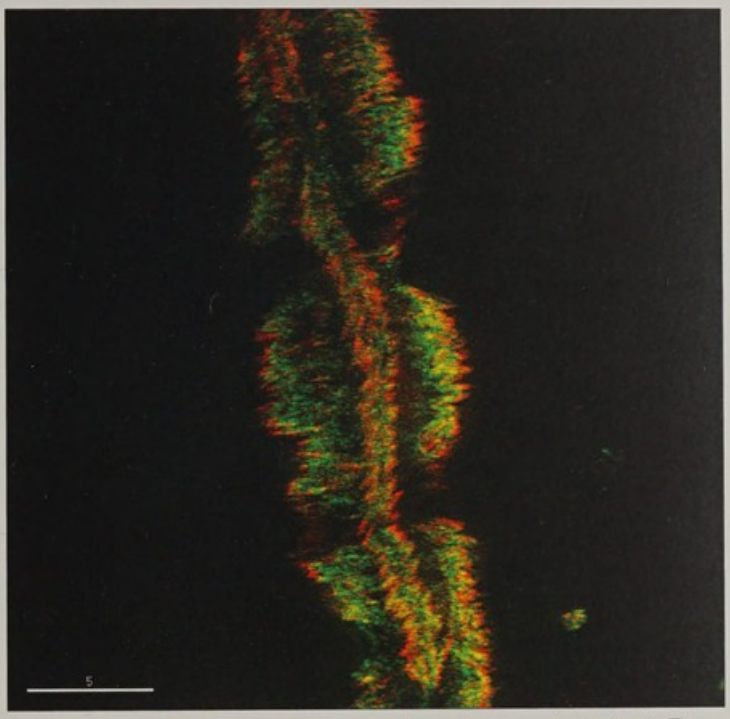


3D reconstruction of Drosophila somatic muscle attachment to the epidermis. The adhesion is mediated by integrin transmembrane receptors and a complex of associated proteins. The larvae express an integrin beta subunit fused to GFP (green) and the adhesion protein vinculin fused to RFP (red). Even though both proteins are part of the same adhesion structure, they localise differentially at attachment sites. (Jutta Wellmann, Brown Group, 2010)

CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR CHRIS GILLIGAN, Department of Plant Sciences and Chair of the School of Biological Sciences, University of Cambridge, UK

DESTINATIONS OF LEAVERS DURING 2010

SARRITA ADAMS transferred to University of California

CAROLINA ÅSTRAND returned to the Karolinska Institute, Sweden

KATSIARYNA BELAYA now working at the Weatherall Institute of Molecular Medicine, Oxford in the Neurosciences Group

ALEX BRUCE moved to the Czech Republic to set up his own group at the University of South Bohemia

ANTONIO CAMPOS CARO completed sabbatical and returned to the University of Cadiz

ROSS CHAPMAN is now a Sir Henry Wellcome Postdoctoral Fellow, Simon Boulton's lab at the London Research Institute, Clare Hall

JAMES CHELL is now a Post Doctoral Fellow in Jonas Frisen's group at the Karolinska Institute, Stockholm, Sweden

NICOLE CHEUNG is now a Senior Bioinformatician at Novartis in Switzerland

FABIEN CUBIZOLLES returned to Erich Nigg's lab in Basel, Switzerland

EURICO DE SA completed his PhD and took up a postdoctoral position at the Sunkel lab, Institute for Molecular and Cellular Biology in Porto, Portugal

JAMES DODS accepted a position at Oliver Wyman, London

MAX DOUGLAS completed his PhD and took up a postdoctoral position in John Diffley's lab at CRUK's London Research Institute, Clare Hall

SONJA FLOTT is now Business Development Associate for Chromatin and Nuclear Signalling at AbCam

SIMONA GIUNTA completed her PhD and is pursuing postdoctoral opportunities

SEEMA GREWAL is now reviews Editor at Development

SOPHIE HANINA was awarded her PhD and returned to Oxford to complete a medical degree

CYNTHIA HILL moved to the US and started a PhD at Tufts University, Massachusetts

PABLO HUERTAS left to set up his own Research Group at CABIMER, University of Seville

ANDREA HUTTERER is now working in science management at the MRC

ANTONIS KIRMIZIS moved to the University of Cyprus to take up an Assistant Professor and group leader post

SONJA KROSCHWALD is now a PhD student at MPI, Dresden

ISABEL LATORRE is now a Project Manager at the Broad institute in Boston

SUSHMITA MAITRA completed her project and moved to Durham

SIARHEI MASLAU moved to the University of Oxford to take up a new position in the Research Group of Prof Chris Ponting

WILLIAM MIFSUD completed his PhD and took up a position at Addenbrooke's Hospital

ANNE PELISSIER (MONIER) is now a Post Doctoral Fellow at the Development Biology Institute of Marseille Luminy, France

JENNY PESTEL returned to Heidelberg to complete her degree course

SOPHIE POLO took up a new position at the Institut Curie in Paris

DAVID RIVERS moved to work in the Zegerman Group then left to set up his own Research Group at Syracuse University, New York, USA

EMILIE RUSSE returned to Ecole Normale Superior, Paris to complete her full-time degree

ROBERT SHAW completed his PhD and is now a postdoc at Imperial College.

ISMAHAN SULEIMAN completed her placement, was awarded an MPhil in Translational Medicine and Therapeutics and is now continuing with a PhD in Cambridge

FUCHOU TANG has moved to China to take up an Assistant Professor position at Beijing University

WEE WEI TEE has moved to the US to take up a postdoctoral position at NYU

ROY (TANG-YI) TEO returned to Singapore to continue his PhD at the University of Singapore

JAKOB VON TROTHA is now a Post Doctoral Fellow in Laure Bally-Cuif's group at the Laboratory of Neurobiology & Development, CNRS, Gif-sur-Yvette, France

FELICIA WALTON-PAGLIUCA is now a Post Doctoral Fellow in Doug Melton's group, at Harvard University

MONA YEKEZARE is now a Post Doctoral Fellow in John Diffley's group, at the Cancer Research UK Clare Hall Labs

The Institute encourages expression of new ideas. Here, Becky Bastock proposes that human developmental biology is a myth; people are in fact carried to the Earth on rays of light from the Sun, causing danger to passing aircraft before landing softly in trees, apparently. All good fun at the Institute retreat. (photo by John Overton)

ACKNOWLEDGEMENTS

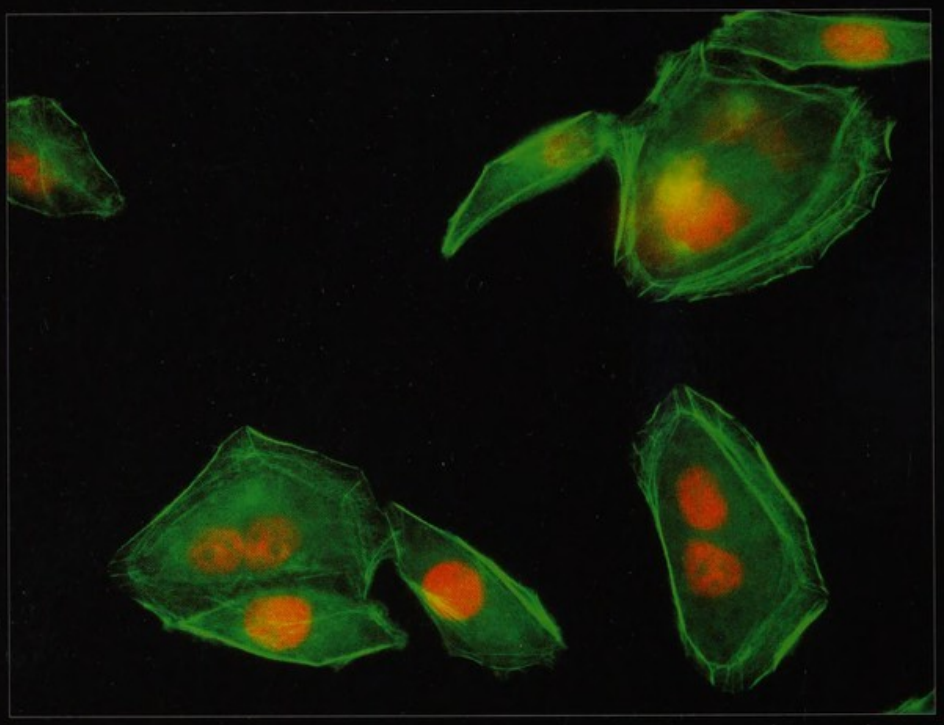
Prospectus produced in the Wellcome Trust/Cancer Research UK Gurdon Institute. Edited by Ann Cartwright, production by Alastair Downie

Group photographs by James Smith, Livesey Group.

Print management by H2 Associates, Cambridge

Front cover: Chicken embryo vascular system revealed by fluorescent dextran injection (Vincent Pasque, Gurdon Group, 2010)

Back cover: Multinucleated HeLa cells due to cytokinesis failure (Masanori Mishima, 2010)



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