Annual report : 2012/2013 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

Contributors

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

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The Wellcome Trust/Cancer Research UK Gurdon Institute

2013 PROSPECTUS / ANNUAL REPORT 2012

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INTRODUCTION

2012 has been a year of celebration in the Gurdon Institute. First and foremost, we are delighted that John Gurdon has been awarded this year's Nobel Prize in Physiology or Medicine with Shinya Yamanaka for their pioneering work showing that mature cells can be reprogrammed to become pluripotent. We renamed the Institute in John's honour several years ago to reflect both his outstanding research and the key role that he played in founding the Institute and in establishing its stimulating, friendly, and collaborative atmosphere. This was considered very unusual at the time, because John is still a group leader in the Institute and runs a very active research group, but it is much more common to name institutions after Nobel Prize winners, making us particularly pleased that the Nobel committee have recognised John's achievements.

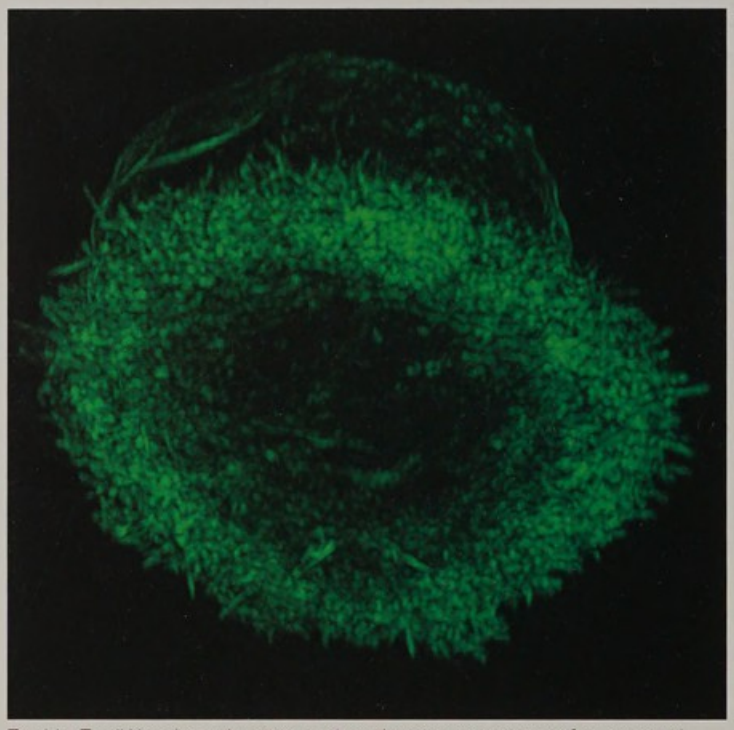
Professor Sir John Gurdon DPhil, DSc, FRS, Nobel Laureate

John Gurdon has also been awarded an honorary degree by the Universidad Andres Bello in Chile, but he is not the only group leader to be congratulated this year. Most importantly, Tony Kouzarides was elected a Fellow of the Royal Society for his work on chromatin modification and its role in transcriptional control and cancer, bringing the tally of FRSs in the Institute to six, four of whom are entirely home-grown. Many congratulations as well to Eric Miska who has been elected as a member of the European Molecular Biology Organization, and to Vincent Pasque, who won a prize in the Wellcome Trust Image Awards for pictures arising from his PhD work with John Gurdon. We are also very happy that Azim Surani and Ben Simons have been

The Brand Group celebrating their success and the Institute's Green Apple Award.

awarded Wellcome Trust Senior Investigator Awards, and that Jon Pines has successfully renewed his Cancer Research UK programme grant. Last but not least, the whole Institute has been awarded a Green Apple Award for environmental best practice for our strategy for reducing our energy consumption. Our energy champion, Kathy Hilton, the Brand lab energy representative, Libby Caygill, Di Foster and Kat Gold were invited to the House of Commons in November to receive a gold award and a cheque for £1,000. Led by Libby's efforts in the Brand lab, the Institute has reduced its electricity bill by £23,000 this year, which we are going to use to refurbish our tea room.

Apart from all of the prizes and awards, the highlight of the year was a symposium to mark the 21st anniversary of the opening of the Institute. More than 400 people attended the talks, including many former group leaders, postdocs and students, as well as our Scientific Advisory Board who visited the Institute immediately before the symposium to provide their usual valuable and constructive advice. Half of the talks were presented by Institute alumni, who were by no means overshadowed by the famous scientists – including two Nobel laureates - whom they spoke alongside. It was a great pleasure to see so many familiar faces and hear how well everyone was doing in their post-Gurdon careers. The event culminated in a party for all our alumni and current members, organised by Tony Kouzarides and the Institute's entertainment committee, which lasted all night and included plenty of exotic cocktails and two live bands, one formed specially for the occasion by members of the Institute. I am very grateful to Vanessa Stefanak for her hard work in organising the symposium and Amanda and Melissa of Zest catering who, as well as serving excellent food in our tea room every day, have excelled themselves at providing themed canapés for the frequent celebrations we have had this year.

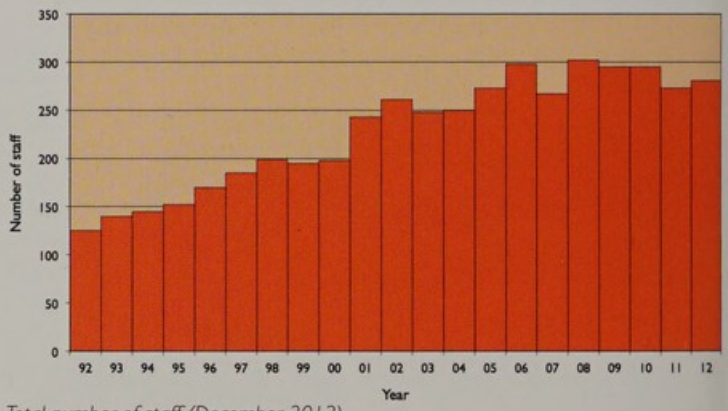


Top Hat T cell. Visualising the actin mesh at the immune synapse of an activated T cell. (Sample prepared by Nele Dieckmann and imaged on the OMX by Nicola Lawrence, Core Group, 2012)

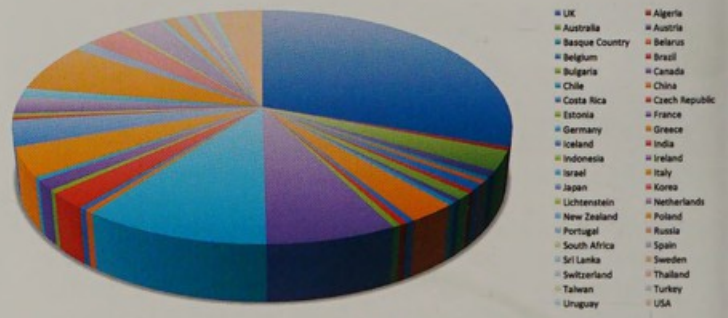
HISTORICAL BACKGROUND

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.



Total number of staff (December 2012)



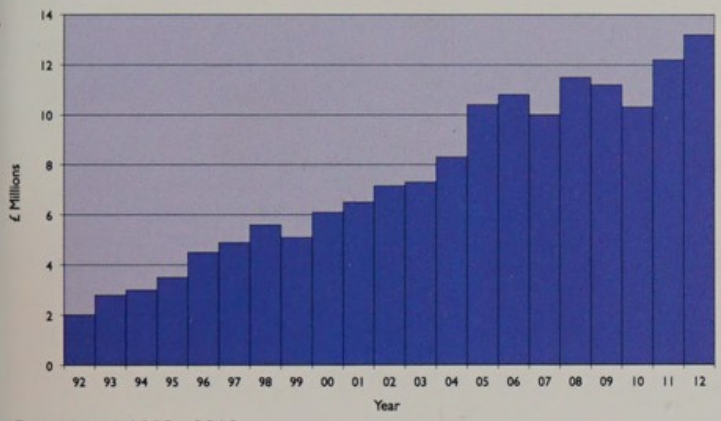
Distribution of staff nationalities 2012. UK is in dark blue; all other nationalities proceed clockwise, sorted alphabetically.

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.

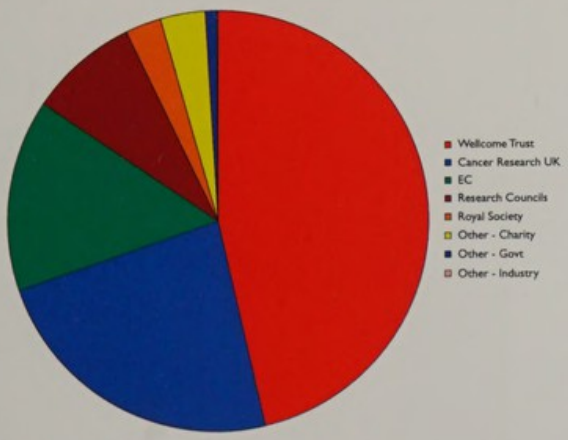
FUNDING

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.



Grant income 1992 - 2012

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



Sources of funding 2012

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

RETREAT

The Institute on retreat, October 2012 (image by John Overton, Brown Group)

Our Annual Retreat this year was held at the Five Lakes Hotel, Maldon, Essex on 27th and 28th September 2012. The event was highly successful. Many Institute members attended and all gained from the experience both scientifically and socially.

Professor Daniel St Johnston

Julie Ahringer

Chromatin regulation in transcriptional and post-transcriptional events

Co-workers: Alex Appert, Darya Ausiannikava, Fanélie Bauer, Ron Chen, Mike Chesney, Yan Dong, Bruno Fievet, Moritz Herrmann, Jürgen Jänes, Djem Kissiov, Josana Rodriguez, Przemyslaw Stempor, Christine Turner, Eva Zeiser

Chromatin regulation plays a central role in transcriptional control and genome organisation, and also impacts mRNA post-transcriptional events. *C elegans* is an excellent system for studies of chromatin function due to its small well-annotated genome, powerful RNAi technology, and rich resource of chromatin mutants. We generated and analysed a genome-wide map of 18 histone modifications, finding that modifications are organised into broad domains that differently mark the central and distal regions and that genes are locally organised into active and inactive blocks. We also discovered specific modifications that mark exons and the X-chromosome, and that the latter is important for global downregulation of X-linked gene expression during dosage compensation. We are studying the functions of histone modifications in transcriptional and post-transcriptional processes.

It has recently been shown that RNA Polymerase II transcription is far more extensive than previously thought, much of it not associated with protein-coding genes. To investigate this phenomenon, we recently carried out the first global mapping of transcription initiation and elongation in *C elegans*. We found that transcription initiation is usually bidirectional and that the majority of initiation events occur in regions with enhancer-like chromatin signatures. These regions show a novel regulatory architecture, whereby upstream enhancers are transcribed towards and in the same orientation at that of the nearest downstream gene.

We also study the functions of *C elegans* counterparts of major chromatin regulatory complexes implicated in human disease, including the histone deacetylase complex NuRD, the Retinoblastoma complex DRM, and a TIP60 histone acetyltransferase complex. We investigate 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.

We recently completed 17 systematic genetic interaction RNAi screens for cell polarity genes. In the resulting functional map of 184 genes, 72% were not previously linked to cell polarity and 80% have human homologs. This network should be widely applicable across animals given the conservation known cell polarity mechanisms.

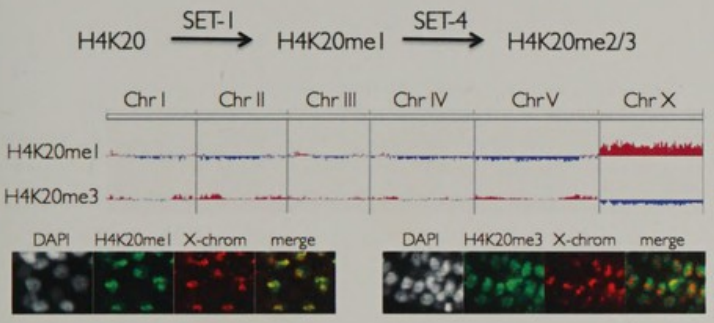
Selected publications:

• Fievet BT*, Rodriguez J*, Naganathan S, Lee C, Zeiser E, Ishidate T, Shirayama M, Grill S and Ahringer J (2012) Systematic genetic interaction screens uncover cell polarity regulators and functional redundancy. Nature Cell Biology 15 (1), 103-112

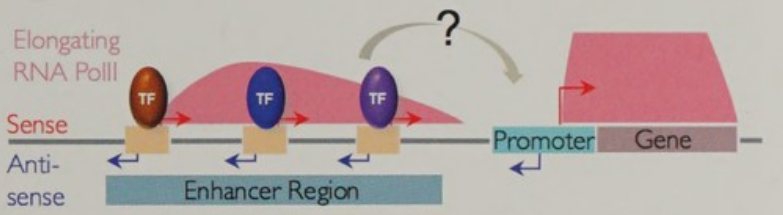
• Vielle A, Lang J, Dong Y, Ercan S, Kotwaliwale C, Rechtsteiner A, Appert A, Chen QB, Dose A, Egelhofer T, Stempor P, Dernburg A, Lieb J, Strome S and Ahringer J (2012) H4K20me1 contributes to downregulation of X-linked genes for *C elegans* dosage compensation, Plos Genetics 8(9): e1002933

• 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

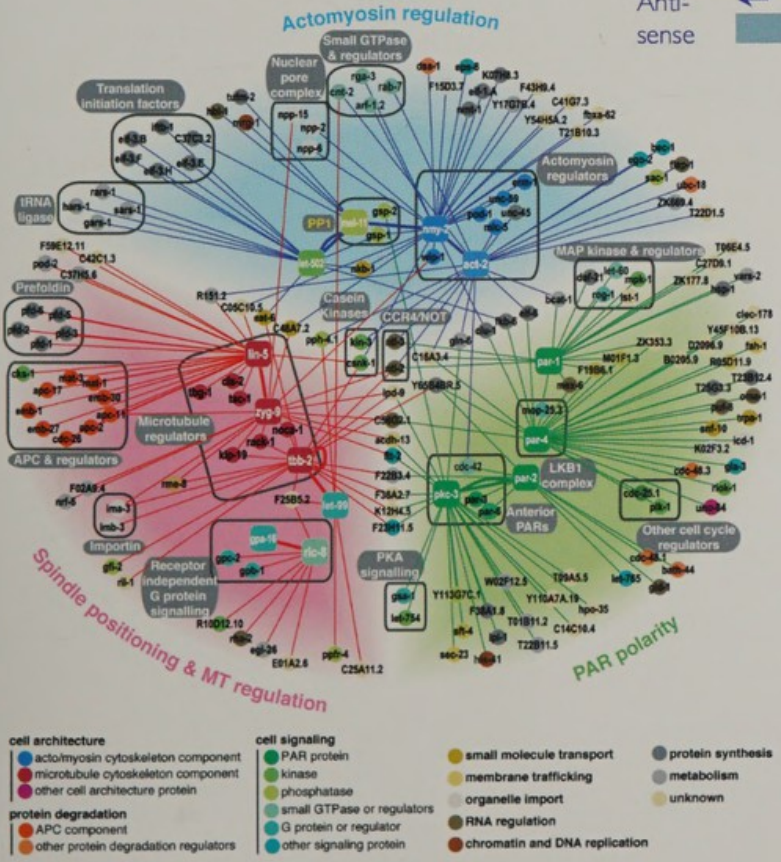
• Gerstein MB, modENCODE Consortium, **Ahringer J**, Strome S, Gunsalus KC, Micklem G, Liu XS, Reinke V, Kim SK, Hillier LW, Henikoff S, Piano F, Snyder M, Stein L, Lieb JD, Waterston RH. (2010) Integrative Analysis of the *Caenorhabditis elegans* Genome by the modENCODE Project. Science 330, 1775-87



H4K20me1 is enriched and H4K20me3 underenriched on the X chromosome.



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



Cell polarity network derived from 17 systematic genetic interaction RNAi screens

cell architecture
- acto/myosin cytoskeleton component
- microtubule cytoskeleton component
- other cell architecture protein

protein degradation
- APC component
- other protein degradation regulators

cell signaling
- PAR protein
- kinase
- phosphatase
- small GTPase or regulators
- G protein or regulator
- other signaling protein

- small molecule transport
- membrane trafficking
- organelle import
- RNA regulation
- chromatin and DNA replication
- protein synthesis
- metabolism
- unknown

Andrea Brand

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

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

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

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

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

For more information, see the Brand lab home page:

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

Selected publications:

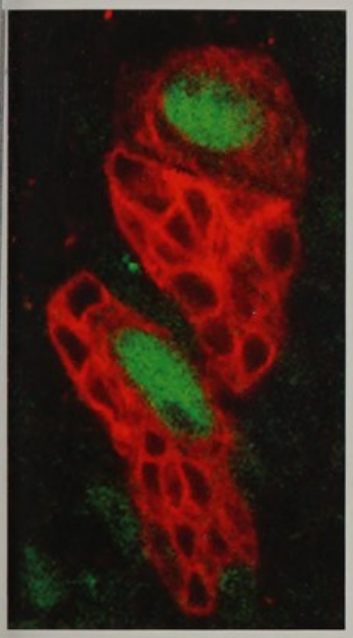
• Chell JM and Brand AH (2010) Nutrition-responsive glia control exit of neural stem cells from quiescence. **Cell** 143(7), 1161-1173

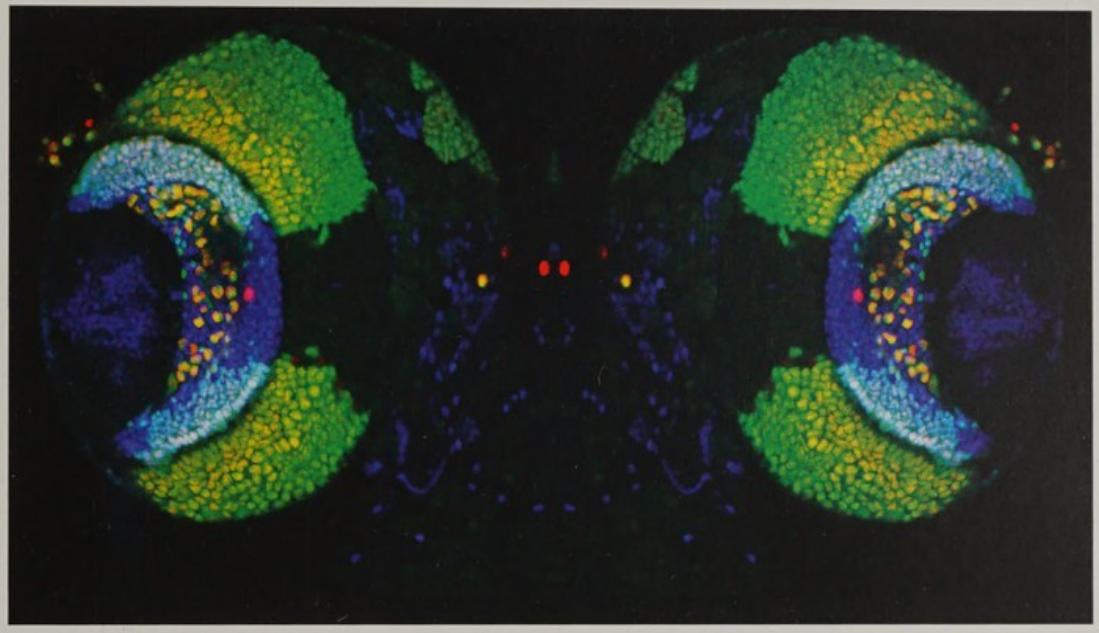
• Wolfram V, Southall TD, Brand AH and Baines RA (2012) The LIM-homeodomain protein Islet dictates motor neuron electrophysiological properties by regulating K+ channel expression. **Neuron** 75, 663-674

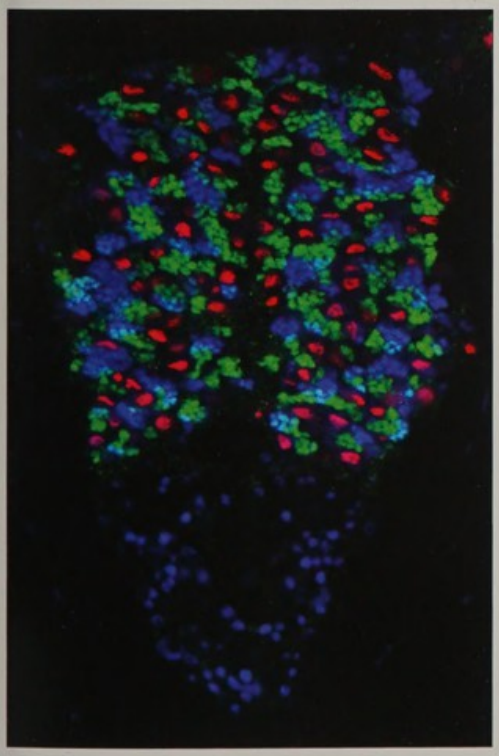
• Gold KS and Brand AH (2012) Transcriptome analysis of *Drosophila* neural stem cells. **Methods Mol Biol** 916, 99-110

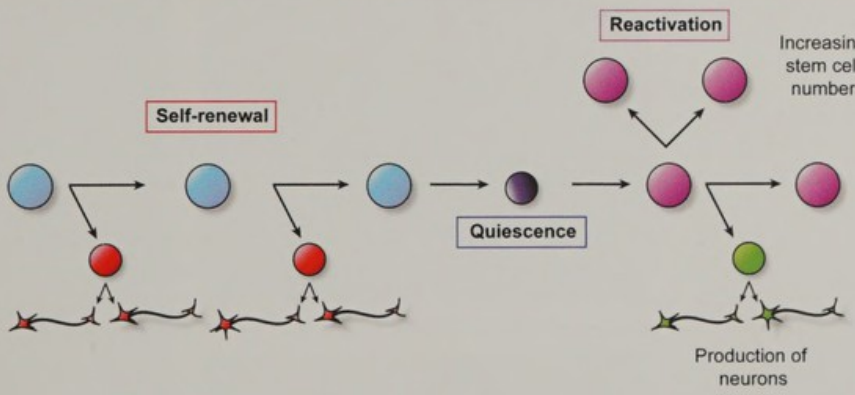
• Caygill EE. Gold KS and Brand AH (2012) Molecular profiling of neural stem cells in *Drosophila melanogaster*. in **The making and un-making of neuronal Circuits in *Drosophila*** Ed. Bassem AH

• Murray MJ, Southall TD, Liu W, Fraval H, Lorensuhewa N, Brand AH and Saint R (2012) Snail dependent repression of the RhoGEF Pebble is required for gastrulation consistency in *Drosophila melanogaster*. **Development, Genes & Evolution**, 222 (6), 361-368









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, Annabel Griffiths, Sven Huelsmann, Yoshiko Inoue, Benjamin Klapholz, Cézary Kucewicz, Aidan Maartens, John Overton, Paula Rodriguez Sanchez, Peerapat Thongnuek, Susan Tweedie

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

We use the fruit fly *Drosophila* as our model organism to discover how the complex machinery linking cell adhesion to the cytoskeleton works, and contributes to morphogenesis. We are seeking to discover how adhesion receptors form contacts of differing strength and longevity, at one point mediating dynamic attachments as the cell moves, and at another point stable connections essential for the functional architecture of the body. At these stable sites of adhesion, such as the integrin-dependent attachments of the muscles, genetic changes to intracellular proteins that work with integrins results in partial or complete loss of integrin adhesion (Fig 1). By combining quantitative imaging with genetics we are discovering the rules that govern the assembly of the integrin adhesion complex. To combine biophysical approaches with genetics, we are developing a method of primary cell culture of embryonic muscles, where we can now generate bipolar muscles with integrin adhesions at each end (Fig 2). Of particular interest are the mechanosensitive properties of cell adhesion, where acto-myosin contraction with the cell exerts force on sites of adhesion, causing the recruitment of proteins like vinculin (Fig 3) to strengthen adhesion. Cell-cell adhesion is regulated by dynamic microtubules, and we have discovered that a novel adhesion subcomplex controlled by microtubules is required to maintain the segmental boundaries that are crucial for the generation of the pattern within the embryonic epidermis (Fig 4).

Selected publications:

- Bulgakova NA, Klapholz B and Brown NH (2012) Cell adhesion in *Drosophila*: versatility of cadherin and integrin complexes during development. **Curr Opin Cell Biol** 24, 702-712
- Brown NH (2011) Extracellular matrix in development: insights from mechanisms conserved between invertebrates and vertebrates. **Cold Spring Harb Perspect Biol**
- Ratheesh A, Gomez GA, Priya R, Verma S, Kovacs EM, Jiang K, Brown NH, Akhmanova A, Stehbens SJ, Yap AS (2012) Centralspindlin and α-catenin regulate Rho signalling at the epithelial zonula adherens. **Nat Cell Biol** 14, 818-828
- Zervas CG, Psarra E, Williams V, Solomon E, Vakaloglou KM and Brown NH (2011) Central multifunctional role of Integrin-Linked Kinase at muscle attachment sites **J Cell Sci** 124, 1316-1327
- Delon I and Brown NH (2009) The integrin adhesion complex changes its composition and function during morphogenesis of an epithelium. **J Cell Sci** 122, 4363-4374.

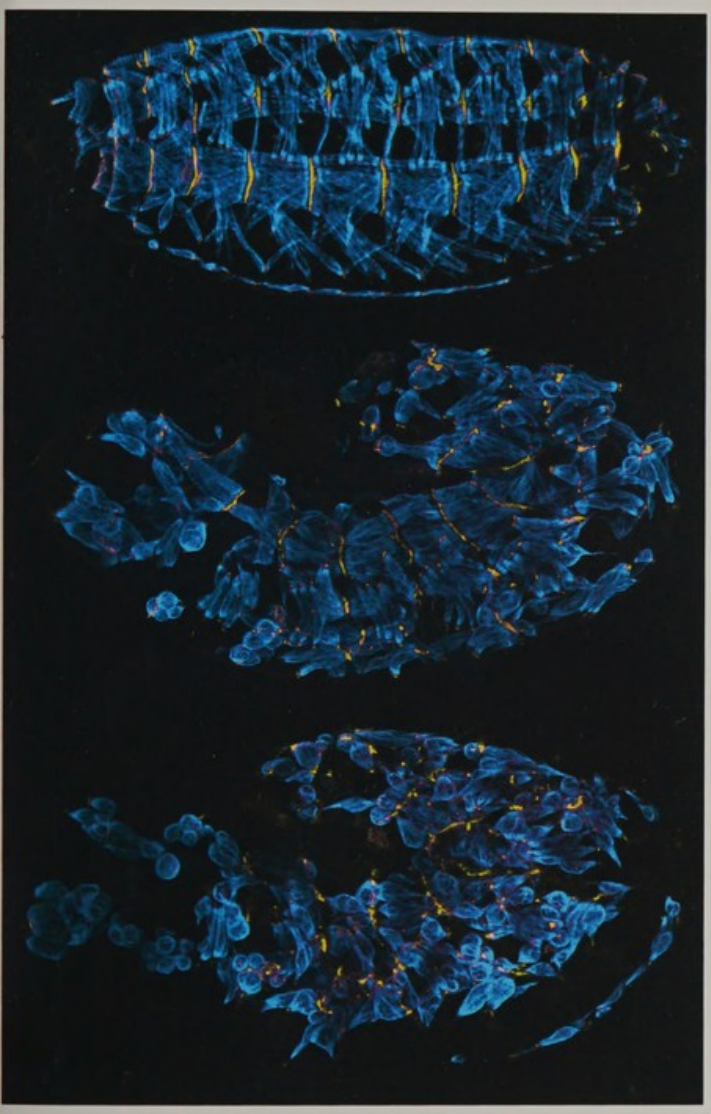
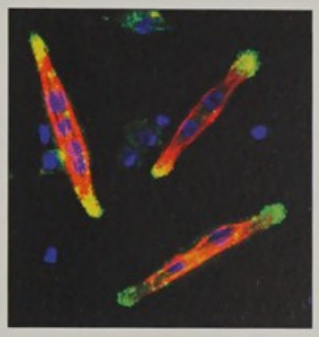


Fig 1: Partial (middle) or complete (bottom) loss of the function of the integrin-binding protein talin results in different degrees of muscle attachment in the Drosophila embryo. Muscles are labelled cyan and the integrin adhesion receptors are yellow..

Fig 2: Primary cell culture, showing that embryonic muscles become bipolar on a uniform extracellular matrix substrate, with integrin adhesions in green, connected to red actin filaments, and nuclei in blue



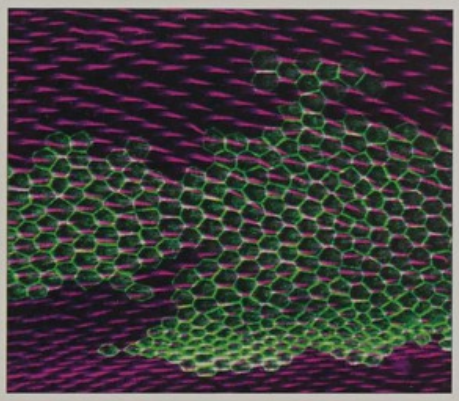


Fig 3: The activated form of the mechanosensitive protein vinculin (green) is efficiently recruited to sites cell-cell adhesion in the developing wing epithelium. Labelling for actin (magenta) reveals the actin rich protrusions formed by each wing cell

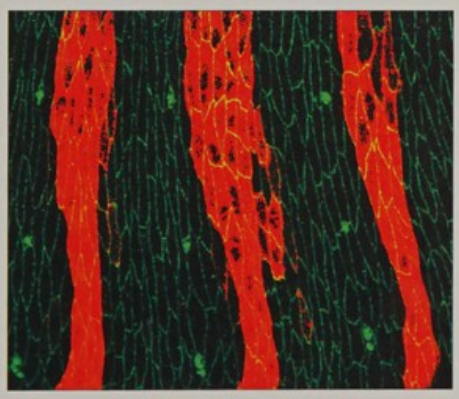
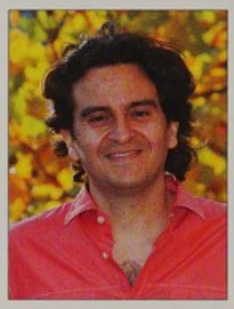


Fig 4: Reduction of a novel dynamic pool of the cell-cell adhesion molecule E-cadherin in the cells of each posterior compartment within the embryo (labelled red), makes it harder for the cells to respect the boundary that keeps them in position, so they cross into the adjacent anterior compartment (to the right) more frequently. Cell outlines are shown in green

Rafael Carazo Salas

Functional genomics of cell morphogenesis

Co-workers: Juan Francisco Abenza Martinez, Anatole Chessel, James Dodgson, Tara Finegan, Marco Geymonat, Veronika Graml, Jonathan Lawson, 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. Work in our lab seeks to elucidate how the gene and protein networks that regulate cellular growth, division and morphogenesis operate in space and in time, and how different cell shapes and growth patterns can arise from a single genome.

We have pioneered the development of 3D image-based high-throughput/high-content microscopy pipelines for yeast-based functional genomics studies. Using that approach, we recently completed the first comprehensive live cell-based screen for microtubule and cell shape regulators and discovered tens of novel candidate regulators - mostly evolutionarily conserved through to humans - which we are validating. Our aim is to generate the most exhaustive genomic map and phenotypic annotation of such regulators, and identify candidate biomedically-relevant targets. Capitalising on this technology, several other microscopy-based functional genomics projects are ongoing in our group.

We also recently discovered that the molecular machinery that regulates cell polarity localises to nanoscopic protein clusters at the cell cortex, with different regulators belonging to different cluster populations. This allows cells to control whether certain polarity regulators interact with others on the cortex, at different points of the cell cycle, revealing a fundamental hitherto ignored layer of cell polarity regulation.

Lastly, a large focus of the lab has shifted to establishing refined biophysical and micro-fabrication technologies to investigate how mechanical inputs modulate cell growth, a fundamental yet very poorly understood aspect of morphogenetic control.

Selected publications:

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

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

• Carazo-Salas RE and Nurse P (2006) Self-organization of interphase microtubule arrays in fission yeast. **Nat Cell Biol** 8(10):1102-7

• Carazo-Salas RE, Antony C and Nurse P (2005) The kinesin Klp2 mediates polarization of interphase microtubules in fission yeast. **Science** 309(5732):297-300

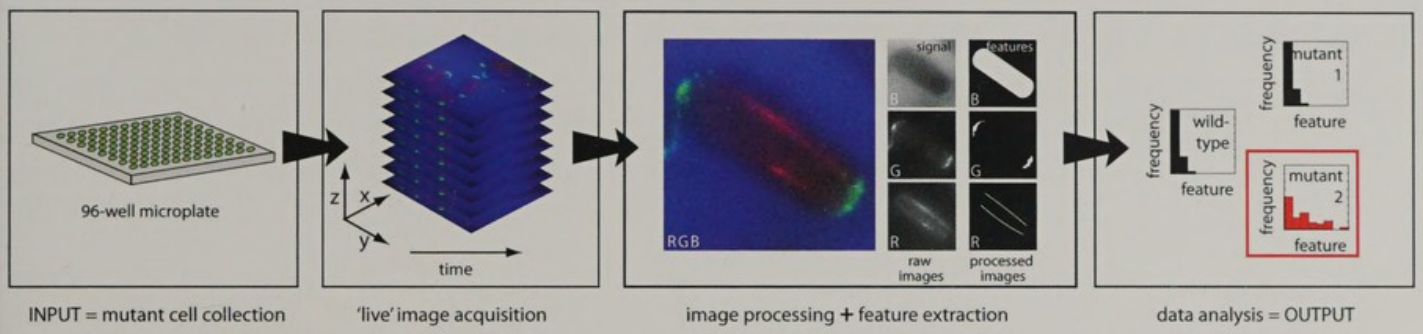


FIgure 1: A high-throughput/high-content microscopy workflow used to screen systematically through the genome for novel regulators of cell morphogenesis.

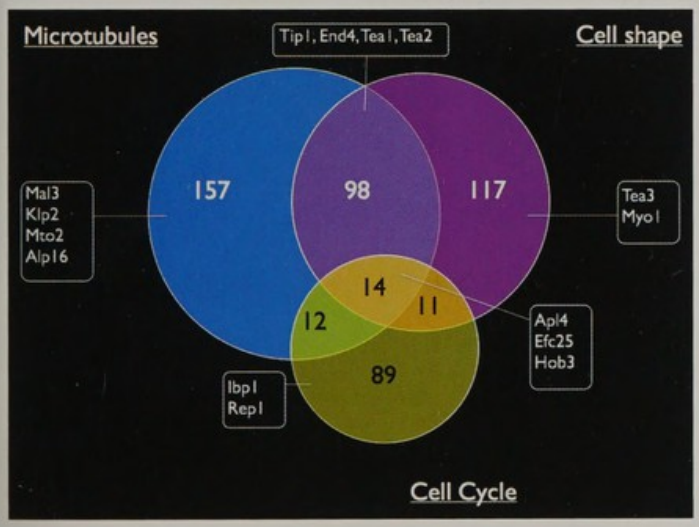


Figure 2: Gene knockouts that coordinately deregulate microtubules, cell shape and the cell cycle, identified through a multiparametric screen.

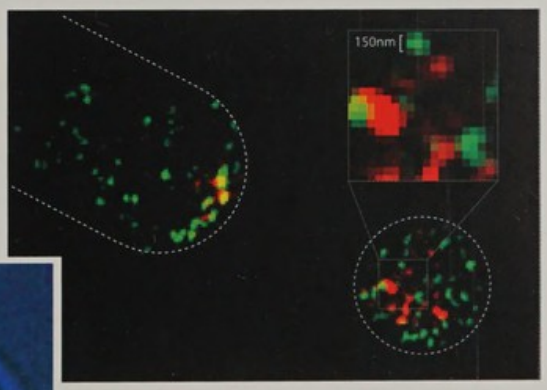


Figure 3: Polarity complexes localise to nanoscopic clusters, when visualised at superresolution.

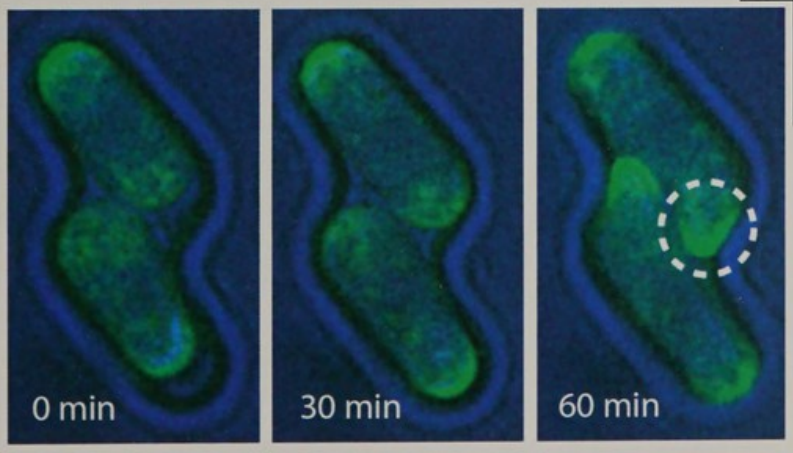


Figure 4: Mechanical confinement alters the pattern of cell growth.

Thomas Down

Epigenomics and transcription informatics

Co-workers: Paulina Chilarska, Kenneth Evans

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:

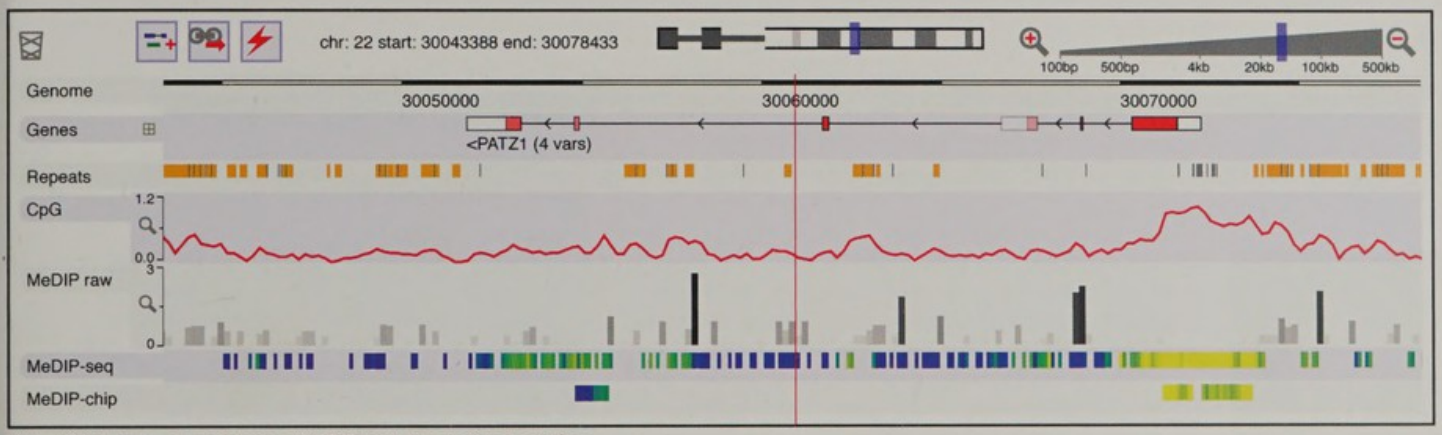
• Rakyan VK, Down TA, Maslau S, Andrew T, Yang T-P, Beyan H, Whittaker P, McCann OT, Finer S, Valdes AM, Leslie RD, Deloukas P and Spector TD (2010) Human ageing-associated DNA hypermethylation occurs preferentially at bivalent chromatin domains. **Genome Res** 20:434-439

• 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

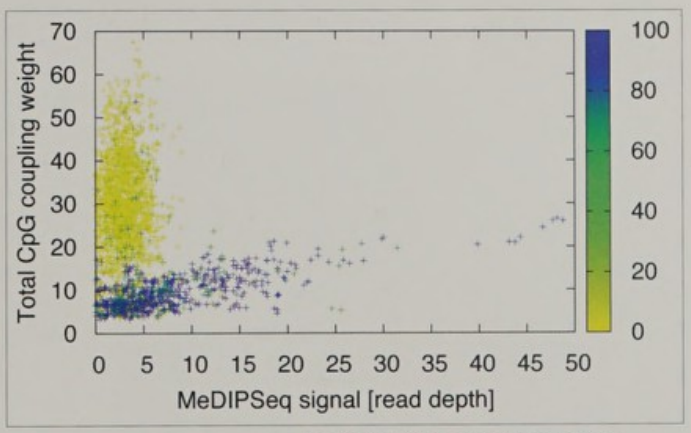
• Down T, Rakyan VK, Turner DJ, Flicek P, Li J, Kulesha E, Graf S, Johnson N, Herrero J, Tomazou EM, Thorne NP, Backdahl L, Herberth M, Howe KL, Jackson DK, Miretti MM, Marioni JC, Birney E, Hubbard TJP, Durbin R, Tavare S and Beck S (2008) A Bayesian deconvolution strategy for immunoprecipitation-based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

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

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

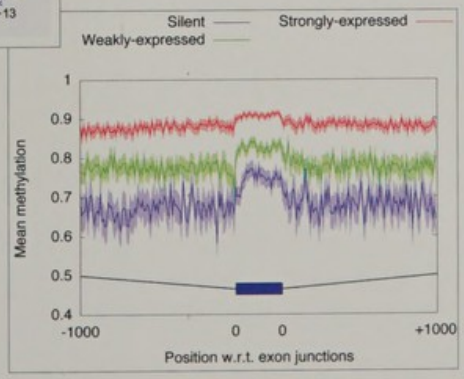


Methyl-DNA immuonprecipitation (MeDIP-seq) data before and after normalisation using the Batman method. Viewed in the Dalliance genome visualisation tool (http://www.biodalliance.org/)



The 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.

The BioTIFFIN interface for browsing regulatory sequence motifs.



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: Guilherme Correia, Lynn Froggett, Julia Mason, Astrid Walrant

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

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

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

Particular questions occupying us at the moment are:

- What defines when and where a filopodium is formed?
- How are endocytic actin structures generated differently from actin in filopodia?
- How are proteins that regulate actin employed during morphogenesis?

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)

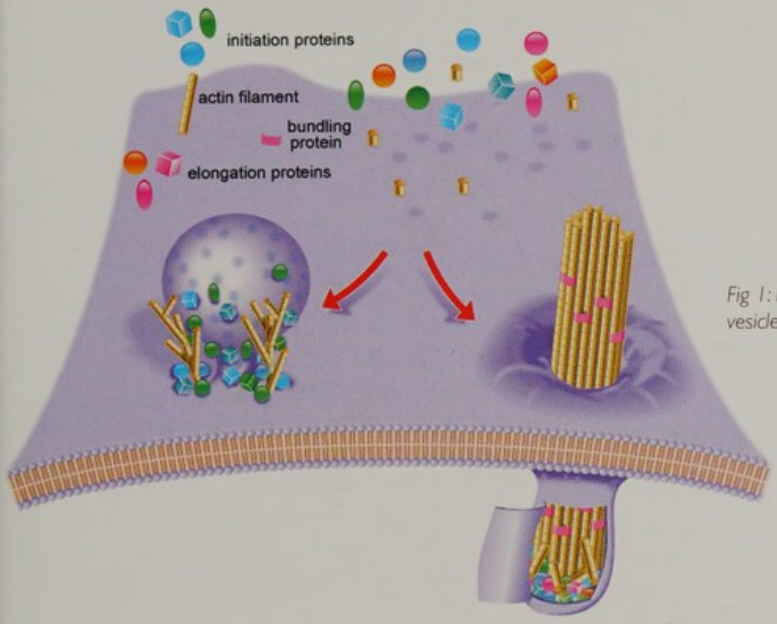


Fig 1: Filopodia protrude from cells and are made of bundled actin, vesicles bud inwards into cells and nucleate branched actin.

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

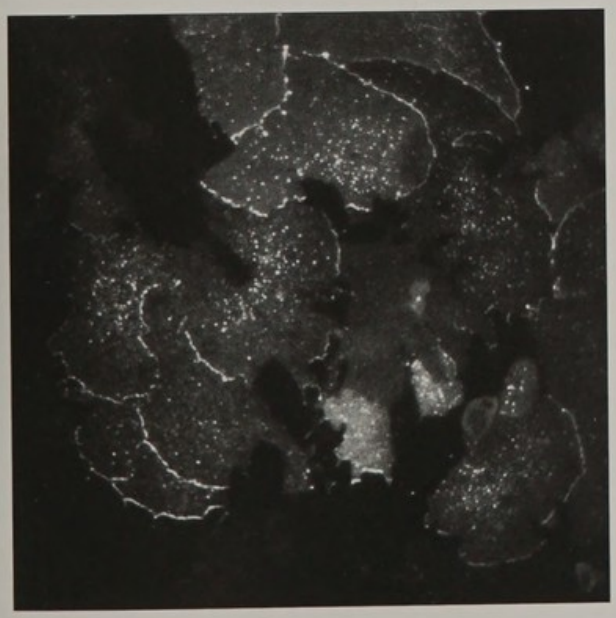
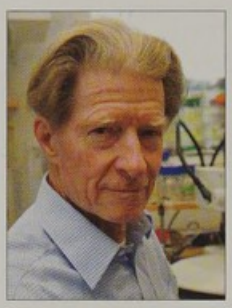


Fig 3: Total internal reflection fluorescence microscopy image of a Keller explant from a Xenopus gastrula, showing that actin regulator Toca-1 localises to lamellipodial edges, filopodia tips and endocytic vesicles.

John Gurdon

Nuclear reprogramming by oocytes and eggs

Co-workers: Dilly Bradford, Celia Delahaye, Sally Fenn, Richard Halley-Stott, Eva Hörmanseder, Jerome Jullien, Kei Miyamoto, Marta Teperek-Tkacz, Stan Wang



The differentiated state of adult cells is remarkably stable, and ensures the normal function of our body tissues and organs. Hardly ever does a cell of one kind change into a different kind of cell. However, there are certain experimental procedures by which gene expression of a specialised adult cell can be reversed to that of an embryonic cell. This opens the way to provide therapeutically useful replacement cells of any kind from other readily available cells of another kind, such as skin.

One procedure for reversing the differentiated state of a cell is by transplanting its nucleus (frog or mammal) to an egg or oocyte. Our aim is to understand how eggs or oocytes achieve this, so as to identify the reprogramming molecules involved, and thus, eventually, to improve the efficiency of this route towards cell replacement without immunosuppression.

We use the growing eggs ("oocytes") of amphibia to activate embryo-expressing genes in the transplanted nuclei of adult mammalian cells. We have recently identified polymerised actin and its cofactors as a significant component of this oocyte transcriptional apparatus for reprogramming somatic nuclei. A question of at least as much importance is how the differentiated state of a cell makes its nucleus resistant to the reprogramming activities of an oocyte. Genes that become transcriptionally repressed in normal development are of this kind. Some genes show an epigenetic memory of their active state. We have identified macroH2A as one chromatin protein that helps to confer an inactive state of genes on the inactive X chromosome of female mammals. We have recently developed a procedure by which chromosomal proteins can be progressively removed from somatic cell nuclei to improve embryonic gene reactivation. This can lead to the identification of chromosomal components that resist reprogramming by oocytes. The removal of these could greatly improve the efficiency of nuclear reprogramming.

Selected publications:

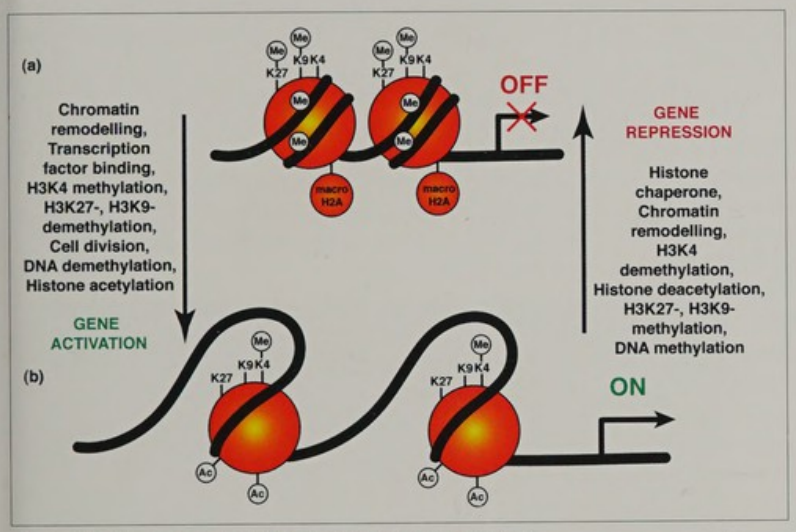
• Gurdon JB (2006) From nuclear transfer to nuclear reprogramming: the reversal of cell differentiation. **Ann Rev Cell Dev Biol** 22, 1-22. PMID: 16704337

• Jullien J, Halley-Stott RP, Miyamoto K, Pasque V and Gurdon JB (2011) Mechanisms of nuclear reprogramming by eggs and oocytes: a deterministic process? **Nature Reviews Molecular & Cell Biology**, 12, 453-459

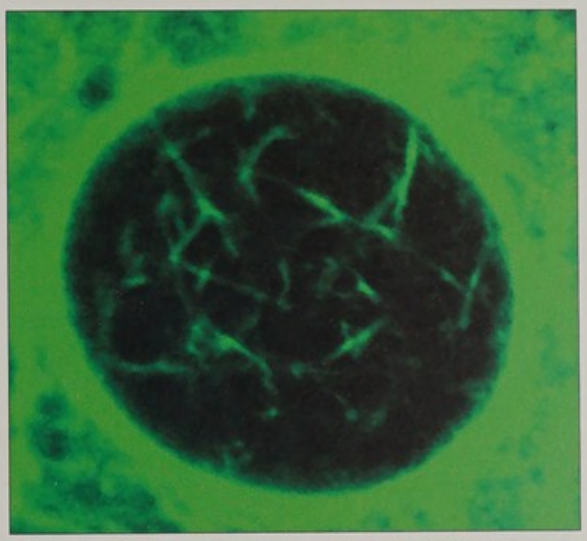
• Pasque V, Jullien J, Miyamoto K, Halley-Stott RP and Gurdon JB (2011) Epigenetic factors influencing resistance to nuclear reprogramming. **Trends in Genetics** 27(12)516-525.

• Narbonne P, Miyamoto K and Gurdon JB (2012) Reprogramming and development in nuclear transfer embryos and in interspecific systems. **Current Opinion in Genetics & Development** 22:450-458.

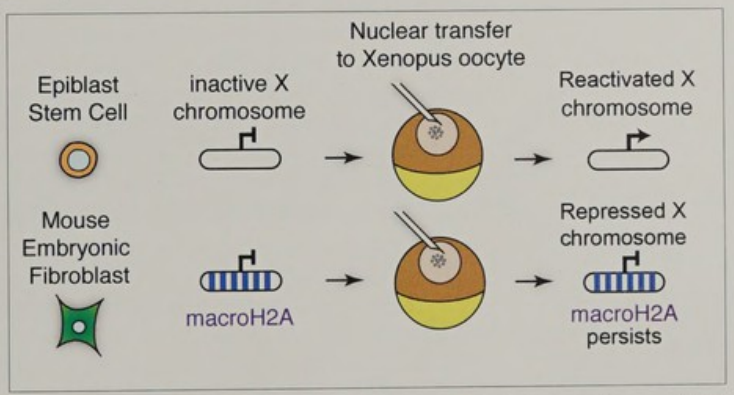
• Jullien J, Astrand C, Szenker E, Garrett N, Almouzni G and Gurdon JB (2012) HIRA dependent H3.3 deposition is required for transcriptional reprogramming following nuclear transfer to *Xenopus* oocytes. **Epigenetics and Chromatin** 5:17



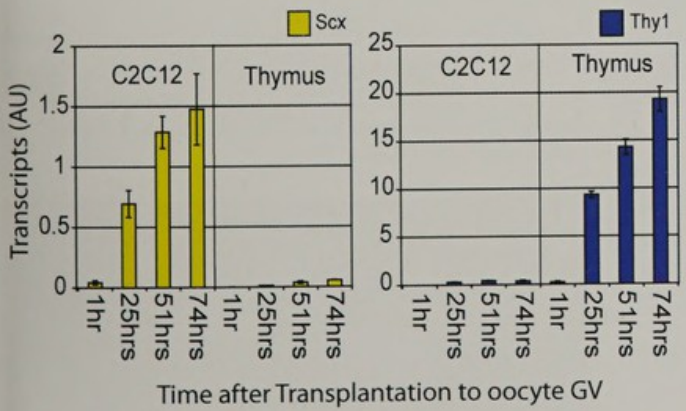
A model of changes in chromatin state during reprogramming.



Polymerised nuclear actin enhances nuclear reprogramming.



Transcription of an inactive X chromosome of mice is inhibited in part by macroH2A.

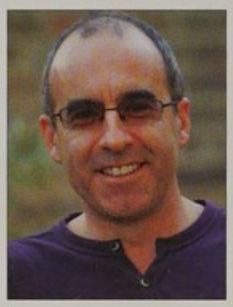


A dramatic difference exists in the ability of an oocyte to activate Scleraxis (Scx) or Thy1 genes in different cell types.

Steve Jackson

Maintenance of genome stability

Co-workers: Linda Baskcomb, Rimma Belotserkovskaya, Andrew Blackford, Sébastien Britton, Jessica Brown, Julia Coates, Mukerrem Demir, Kate Dry, Josep Forment, Yaron Galanty, Nicola Geisler, Abderrahmane Kaidi, Delphine Larrieu, Carlos le Sage, Natalia Lukashchuk, Ryotaro Nishi, Helen Reed, Christine Schmidt, Matylda Sczaniecka-Clift, Jon Travers, Paul Wijnhoven



Our work focuses on the DNA-damage response (DDR), which optimises cell survival and genome integrity by detecting DNA damage, signalling its presence and mediating its repair. As DDR defects are associated with neurodegenerative diseases, immunodeficiencies, premature ageing, infertility and cancer, our research might suggest new ways to alleviate such conditions.

Over the past year, we have obtained important new insights into DDR processes. For example, we have used super-resolution microscopy to visualise the spatial and temporal distribution of the DDR proteins BRCA1 and 53BP1, enhancing our understanding of how the activities of these factors are coordinated (1). In addition, we have identified human hnRNPUL proteins 1 and 2 as binding partners for the double-strand break (DSB) sensor complex MRN (MRE11-RAD50-NBS1), work that provides new insights into how cells respond to DSBs (2). Furthermore, this work together with proteomics-based studies that we carried out in collaboration with Dr C Choudhary (Denmark; 3) have highlighted crucial connections between RNA metabolism and DNA repair.

We have also continued to focus on how the DDR is controlled by protein post-translational modifications. For instance, we established how the SUMO targeted ubiquitin E3 ligase (STUBL) RNF4 promotes DSB repair, shedding new light on the molecular dynamics regulating DSB signalling and repair, and highlighting the interplay between ubiquitylation and SUMOylation (4). Finally, with Prof S Balasubramanian (Department of Chemistry), we used a synthetic small molecule that targets G-quadruplexes – four-stranded non-Watson-Crick DNA structures – to map the locations of these structures in the human genome, define how they impact on transcription, and show how they can be targeted to inhibit cancer cell growth (5).

Selected publications:

1) Chapman JR, Sossick AJ, Boulton SJ and Jackson SP (2012) BRCA1-associated exclusion of 53BP1 from DNA damage sites underlies temporal control of DNA repair. J Cell Sci 125, 3529-3534

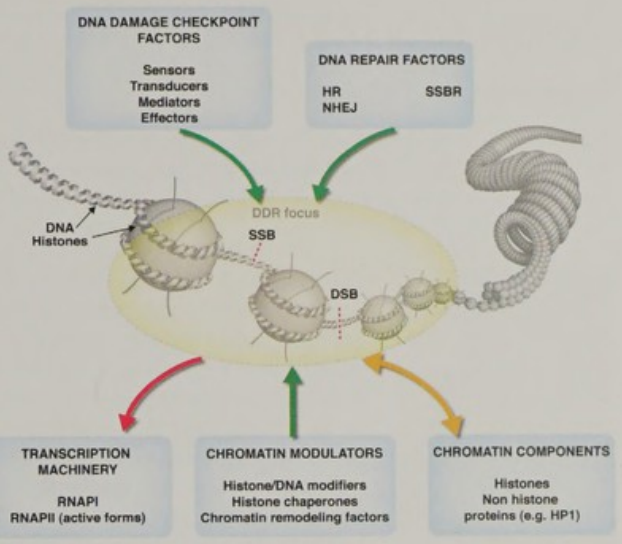
2) Polo SE, Blackford AN, Chapman JR, Baskcomb L, Gravel S, Rusch A, Thomas A, Blundred R, Smith P, Kzhyshkowska J, Dobner T, Taylor AMR, Turnell AS, Stewart GS, Grand RJ and Jackson SP (2012) Regulation of DNA-End Resection by hnRNPU-like proteins promotes DNA double-strand break signalling and repair. Mol Cell 45, 505-516

3) Beli P, Lukashchuk N, Wagner SA, Weinert BT, Olsen JV, Baskcomb L, Mann M, Jackson SP and Choudhary C (2012) Proteomic investigations reveal a role for RNA processing factor THRAP3 in the DNA damage response. Mol Cell 46, 212-25

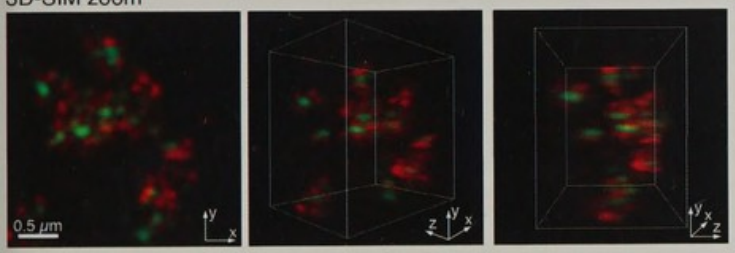
4) Galanty Y, Belotserkovskaya R, Coates J and Jackson SP (2012) RNF4, a SUMO-targeted ubiquitin E3 ligase, promotes DNA double-strand break repair. Genes Dev 26, 1179-95

5) Rodriguez R, Miller KM, Forment JV, Bradshaw CR, Nikan M, Britton S, Oelschlaegel T, Xhemalce B, Balasubramanian S and Jackson SP (2012) Small-molecule-induced DNA damage identifies alternative DNA structures in human genes. Nat Chem Biol 8, 301-10

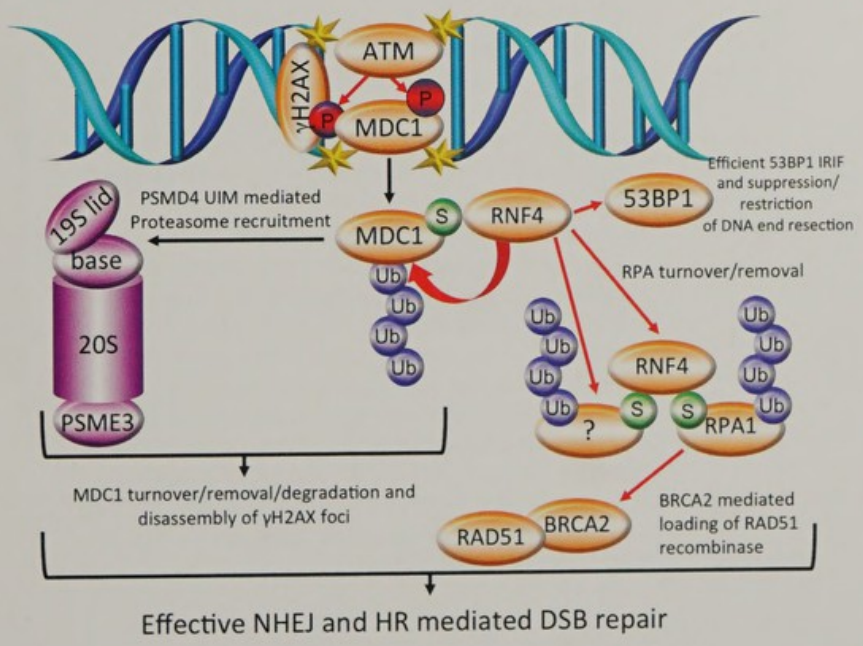
Protein dynamics to and from sites of DNA breaks. DNA damage checkpoint and repair factors and modulators of chromatin organisation are recruited (green arrows) to DNA breaks (SSB and DSB), while transcription machineries are excluded (red arrows), and the dynamics of structural chromatin components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



3D-SIM zoom



Subdiffraction-limit imaging of BRCA1 and 53BP1 in ionising-radiation-induced foci (IRIF). Image of BRCA1 (green) and 53BP1 (red) in IRIF. Human RPE1 cells were irradiated, stained and imaged using 3D-structural illumination microscopy (3D-SIM). Shown are projected images (left) and 3D-rendered images (other panels) constructed from Z-series images. Taken from (1).



Tony Kouzarides

Epigenetics and cancer

Co-workers: Paulo Amaral, Andrew Bannister, Isaia Barbieri, Ester Cannizzaro, Maria Christophorou, Alistair Cook, Mark Dawson, Miranda Landgraf, Sri Lestari, Valentina Migliori, Nikki Parsons, Sam Robson, Helena Santos Rosa, Peter Tessarz, Emmanuelle Viré, Meike Wiese, Beata Wyspianska

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

Our recent work has identified two new modification pathways that are implicated in cancer. The first pathway involves phosphorylation of tyrosine 41 of histone H3 by the JAK2, an enzyme found mutated in leukaemia. This modification functions by displacing the HP1 repressor protein from a key gene, LMO2, whose up-regulation is sufficient to cause leukaemia. The second pathway involves methylation of miRNA 145 by a new RNA enzyme BCDN3D. This modification disrupts the binding of miRNA 145 to dicer and therefore controls miRNA maturation. The BCDN3D enzyme is an oncogene with pro-metastatic characteristics, indicating that this pathway may be therapeutically important.

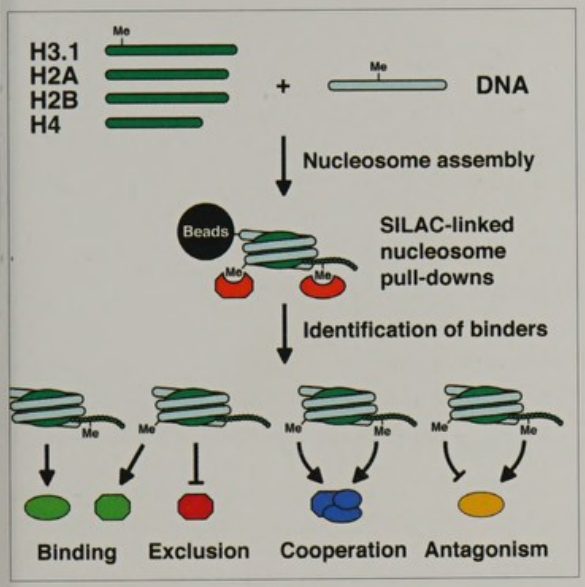
Recently we identified a histone acetylation pathway as being a good target for therapeutic intervention. The BET bromodomain proteins were shown to be involved in activating genes regulated by MLL-fusions, gene products responsible for MLL-leukaemias. A small molecule inhibitor of BETs (I-BET) was used to prevent the binding of BET proteins to acetylated histones and suppress this gene program. The I-BET molecule effectively inhibits primary human leukaemias and halts the process of leukaemia in model systems. Together these data give hope for the development of a therapeutic agent against MLL-leukaemias.

Selected publications:

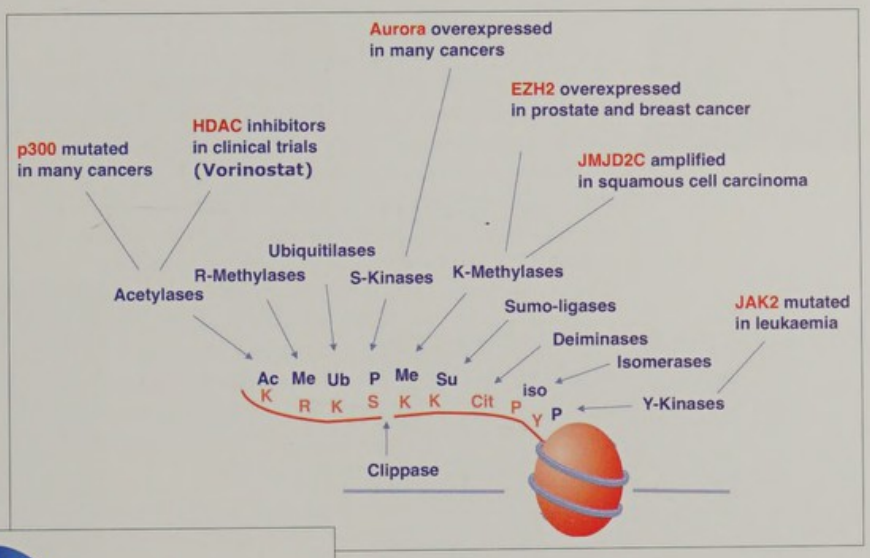
• Xhemalce B, Robson SC and Kouzarides T (2012) Human RNA methyltransferase BCDIN3D regulates microRNA processing. **Cell** 2012 Oct 12;151(2):278-88.

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

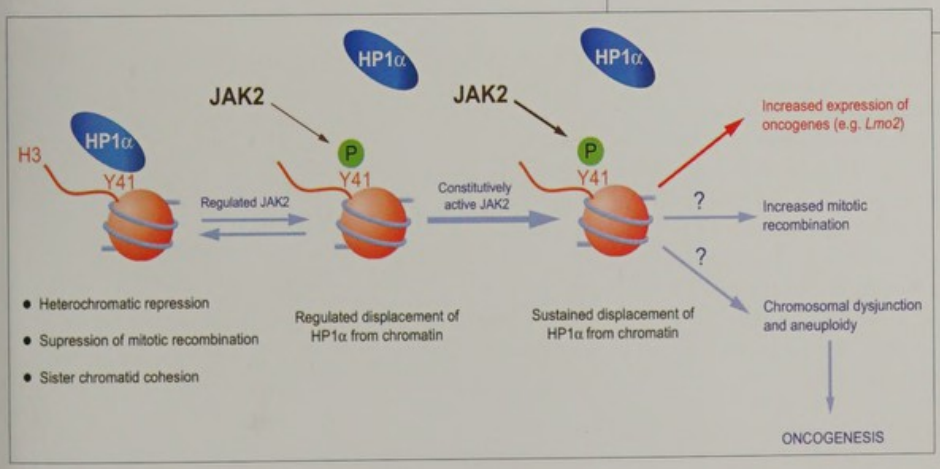
• Bartke T, Vermeulen M, Xhemalce B, Robson SC, Mann M and Kouzarides T (2010). Nucleosome-interacting Proteins Regulated by DNA and Histone Methylation. **Cell** 143: 470 – 84



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

Mammalian neural stem cell biology, fundamental and applied

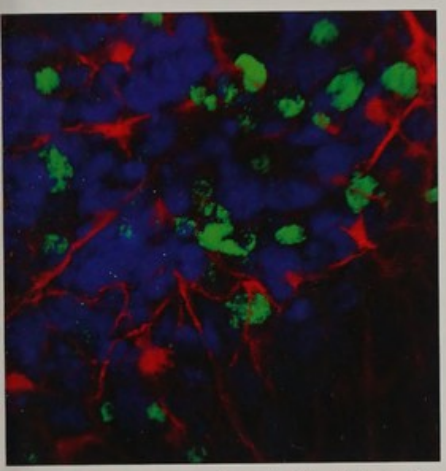
Co-workers: Thérèse Andersson, Roberta Cagnetta, Tatyana Dias, Macushla Hughes, Peter Kirwan, Teresa Krieger, Steven Moore, Tomoki Otani, Nathalie Saurat, Yichen Shi, James Smith, Selina Wray

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

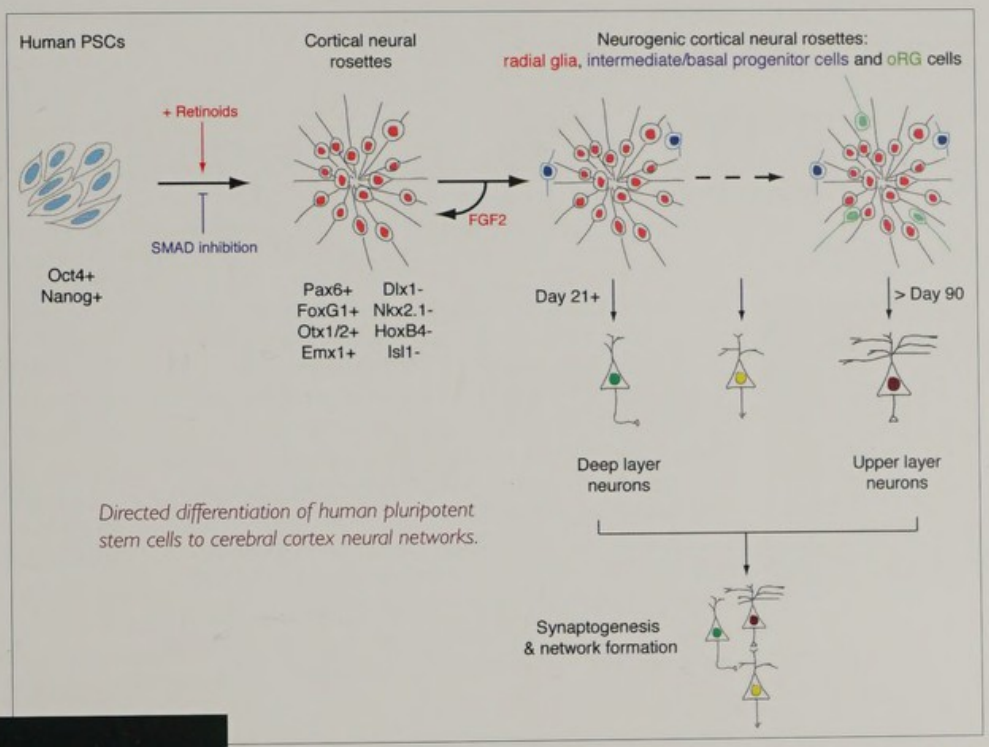
In the other major strand of research in the group, we have developed methods for directing differentiation of human pluripotent stem cells to cortical neurons, via a cortical stem cell stage. Human stem-cell-derived cortical neurons form functional networks of excitatory synapses in culture. We are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

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.
- **Livesey FJ** (2012) Stem cell models of Alzheimer's disease and related neurological disorders. **Alzheimers Res Ther** 4, 44
- Shi Y, Kirwan P and **Livesey FJ** (2012) Directed differentiation of human pluripotent stem cells to cerebral cortex neurons and neural networks. **Nature Protocols** 7, 1836-1846
- Shi Y, Kirwan P, Smith J, Maclean G, Orkin SH and **Livesey FJ** (2012) A human stem cell model of early Alzheimer's disease pathology in Down syndrome. **Sci Transl Med** 4, 124ra29
- Shi Y, Kirwan P, Smith J, Robinson HP and **Livesey FJ** (2012) Human cerebral cortex development from pluripotent stem cells to functional excitatory synapses. **Nat Neurosci** 15, 477-486



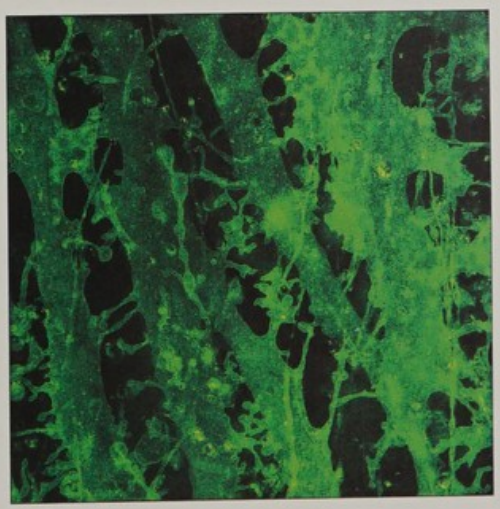
Extracellular aggregates (green) of the Alzheimer's disease pathogenic peptide Aβ42 in cultures of human cortical neurons generated from Down syndrome iPS cells.



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

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

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



Eric Miska

Small regulatory RNA

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

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

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

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

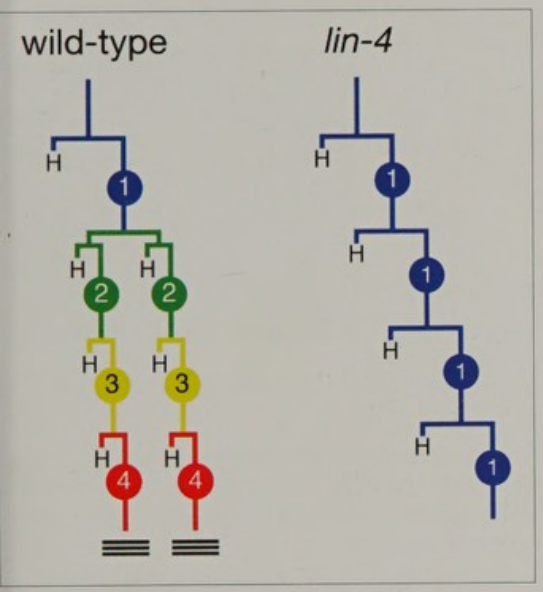
Selected publications:

• 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

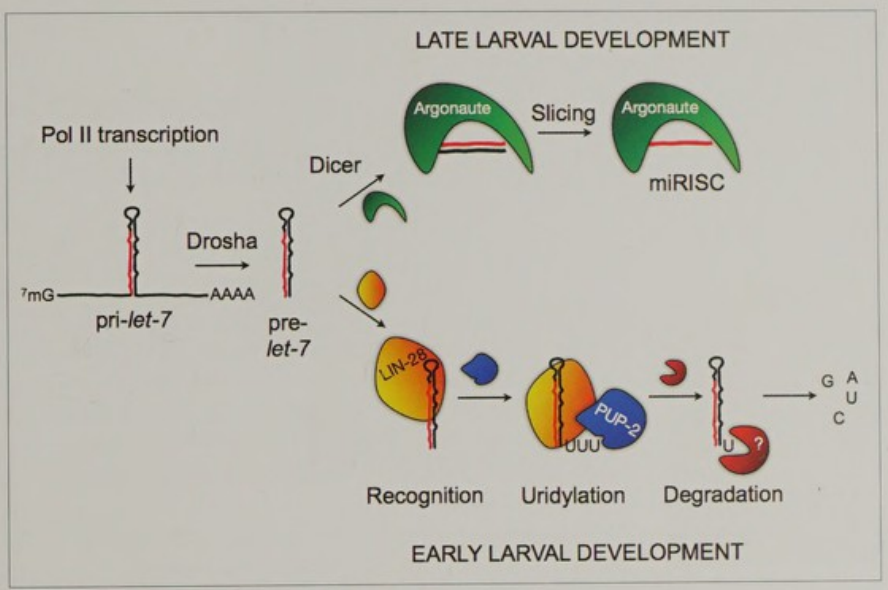
• Lehrbach NJ, Castro C, Murfitt KJ, Abreu-Goodger C, Griffin JL and **Miska EA** (2012) Post-developmental microRNA expression is required for normal physiology, and regulates aging in parallel to insulin/IGF-1 signaling in *C. elegans*. RNA 18, 2220 - 2235

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

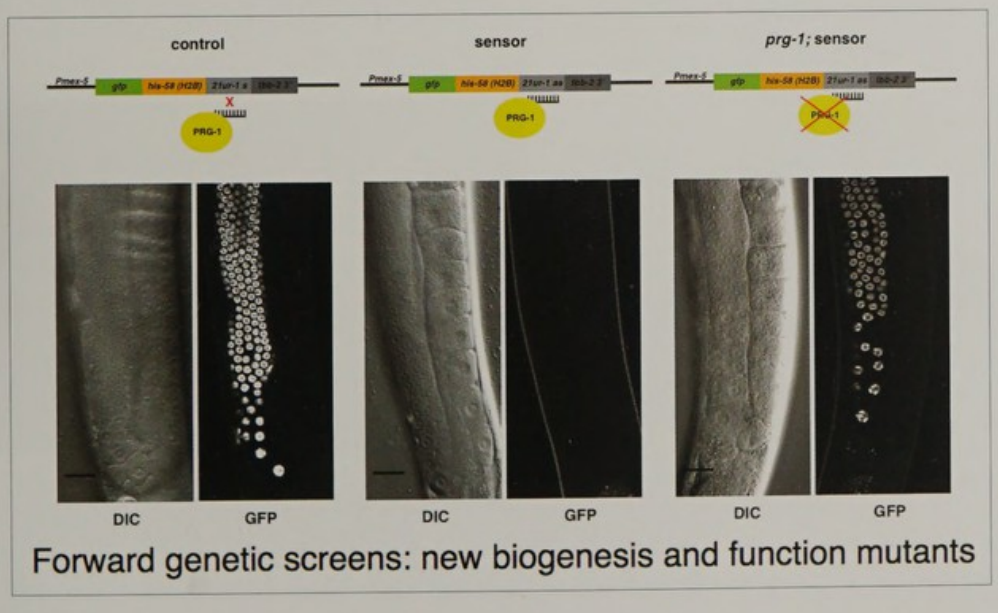
• Bagijn MP, Goldstein LD, Sapetschnig A, Weick EM, Bouasker S, Lehrbach NJ, Simard MJ and **Miska EA** (2012) Function, targets, and evolution of *Caenorhabditis elegans* piRNAs. Science 337, 574 - 578



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



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



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

Eugenia Piddini

Competitive cell interactions in normal physiology and cancer

Co-workers: Maja Goschorska, Golnar Kolahgar, Iwo Kucinski, Kathy Oswald, Saskia Suijkerbuijk, Silvia Vivarelli, Laura Wagstaff

The elimination of suboptimal cells from tissues is an important process that helps preserve tissue integrity and function. Cells within tissues compare relative fitness and, when viable but suboptimal cells are present, they are eliminated by fitter neighbouring cells through competitive cell interactions. Much of the work in our lab focuses on investigating the mechanisms and the physiological role of competitive cell interactions.

Cell competition has been studied mostly in developing tissues and currently it is not clear to what extent this phenomenon is relevant to adult tissues. We are investigating whether adult tissues monitor and respond to the presence of cells with compromised fitness. This would have important implications, as selection of fitter cells during adult tissue maintenance could lead to improved tissue fitness and play a role in slowing down tissue ageing. Our model system for these studies is the adult *Drosophila* gut, a simple epithelial layer with high cellular turnover, maintained by a pool of stem cells. Our recent data show that in adult tissues weaker cells are detected and eliminated through apoptosis and that this is accompanied by an increase in stem cell numbers and tissue colonisation properties in the fitter cell population.

Competitive cell interactions could play a role in cancer. Indeed it has been suggested that precancerous cells could act as supercompetitors and kill surrounding normal cells, to make more space for themselves. However, it has also been observed that cells carrying some tumour promoting mutations can be eliminated by wild-type cells, suggesting that cell competition could in some instances aid cancer prevention. Our lab is establishing *in vitro* assays to study these complex interactions between tumour cells and normal cells.

Selected publications:

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

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

• 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

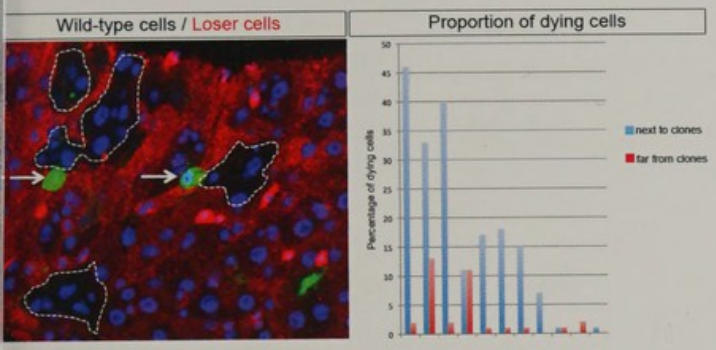


Figure 1: Minute mutant cells are outcompeted by fitter wild-type cells in the adult fly intestine. Left: Minute cells (labeled in red) display increased frequency of apoptosis (marked in green), if they are in proximity of fitter wild type clones. Right: quantification of apoptosis frequency in Minute cells next to or far away from wild-type clones.

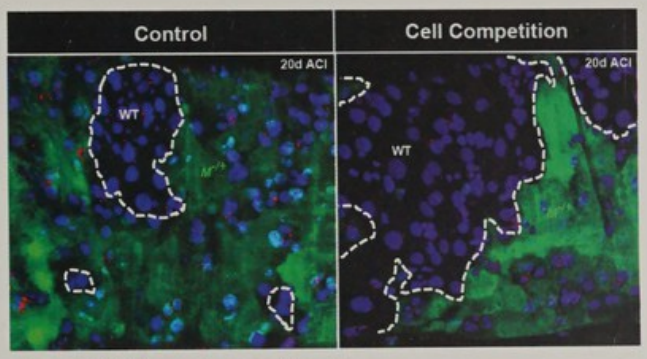
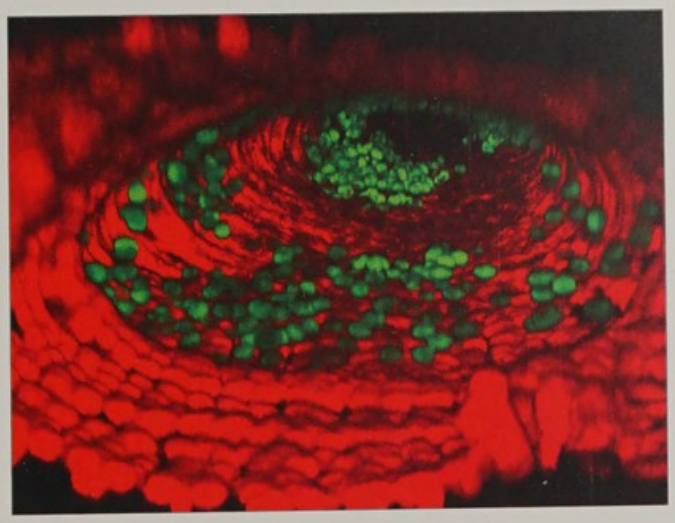


Figure 2: Wild-type cells expand into bigger clones when they are surrounded by loser Minute cells (right), than when they are surrounded by other wild-type cells (left).

Figure 3: 3D reconstruction of the lumen of an adult fly posterior midgut. APC mutant cells (green) have formed intestinal adenomas.



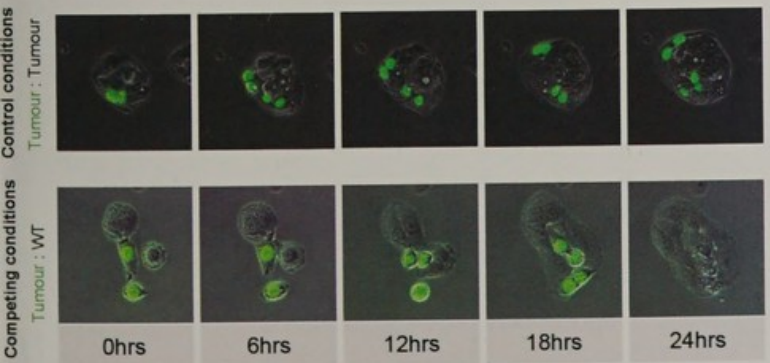


Figure 4: positive HepG2 tumor cells grow well in control cultures with other unlabelled HepG2 cells (top), but die at increased frequency when co-cultured with normal hepatocytes (bottom).

Jonathon Pines

How do cells control mitosis?

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

How do cells regulate entry to mitosis? And, once in mitosis, how do cells coordinate chromosome segregation with cell separation to ensure that the two daughter cells receive an equal and identical copy of the genome? The answers to both questions are provided by the interplay between protein kinases, protein phosphatases, and APC/C-mediated proteolysis, and this is the focus of our research. Since mitosis is a highly dynamic process we study living cells by time-lapse fluorescence microscopy, but complement this with biochemical analyses on cells in which we have knocked-out or mutated specific mitotic regulators using somatic cell recombination.

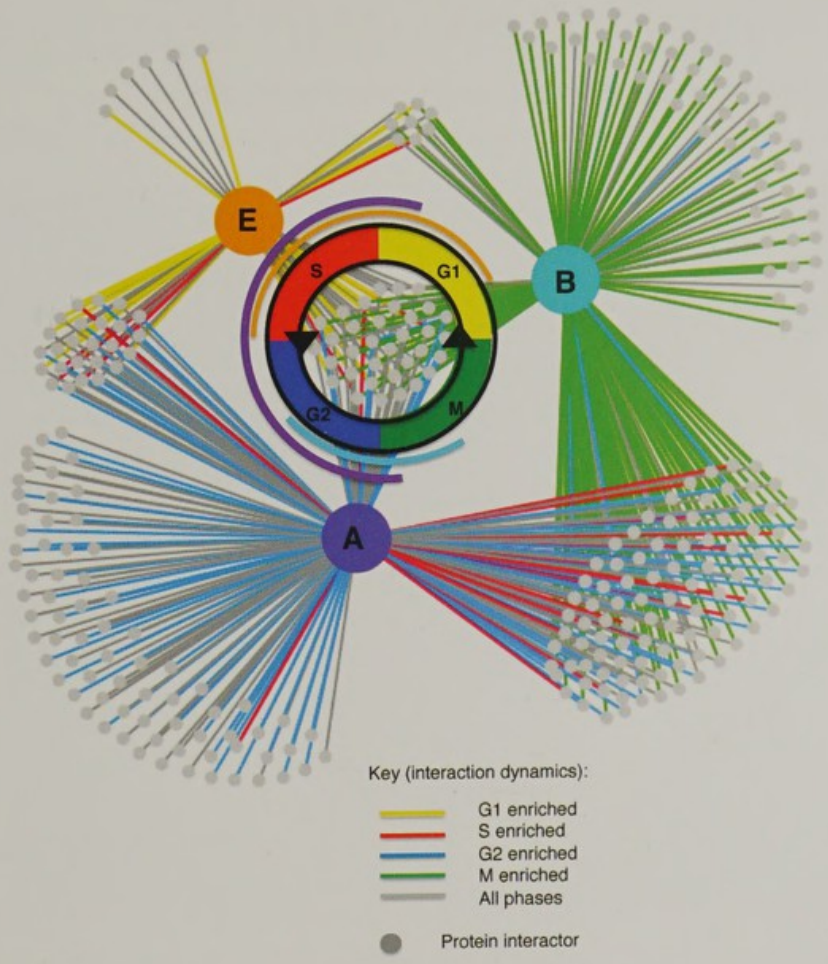
To understand how cells trigger mitosis we are analysing the behaviour of the key mitotic kinases, the Cyclin A- and B-dependent kinases, and their regulation by phosphorylation and dephosphorylation. We developed a FRET biosensor to assay Cyclin B1-Cdk1 activity *in vivo* and are using this to define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

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

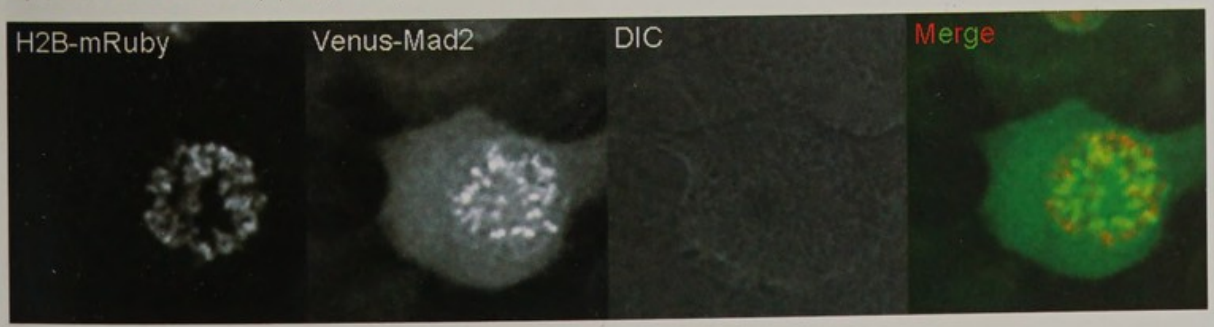
Selected publications:

- Izawa D and Pines J (2012) Mad2 and the APC/C compete for the same site on Cdc20 to ensure proper chromosome segregation. **J Cell Biol** 199, 27-37
- Mansfeld J, Collin P, Collins MO, Choudhary J and Pines J (2011) APC15 drives the turnover of MCC-Cdc20 to make the spindle assembly checkpoint responsive to kinetochore attachment. **Nat Cell Biol** 13, 1234-1244.
- Pagliuca F, Collins MO, Lichawska A, Zegerman P, Choudhary JS and Pines J (2011) Quantitative proteomics reveals the basis for the biochemical specificity of the cell cycle machinery. **Mol Cell** 43, 406-417.
- Gavet O and Pines J (2010) Progressive activation of Cyclin B1-Cdk1 coordinates entry to mitosis. **Dev Cell** 18, 533-543.
- Nilsson J, Yekezare M, Minshull J and Pines J (2008) The APC/C maintains the spindle assembly checkpoint by targeting Cdc20 for destruction. **Nat Cell Biol** 10, 1411-1420

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



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



Emma Rawlins

Stem and progenitor cells in the mammalian lung

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

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

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

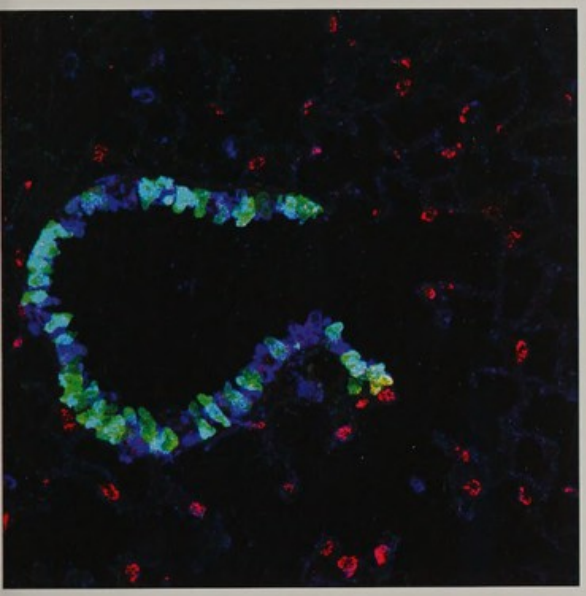
The identity of the epithelial stem and progenitor cells in the postnatal lung remains controversial. Our previous work has shown that each anatomical region (trachea, bronchioles, alveoli) has its own progenitor cell population and that the behaviour of these progenitors can change in response to local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

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

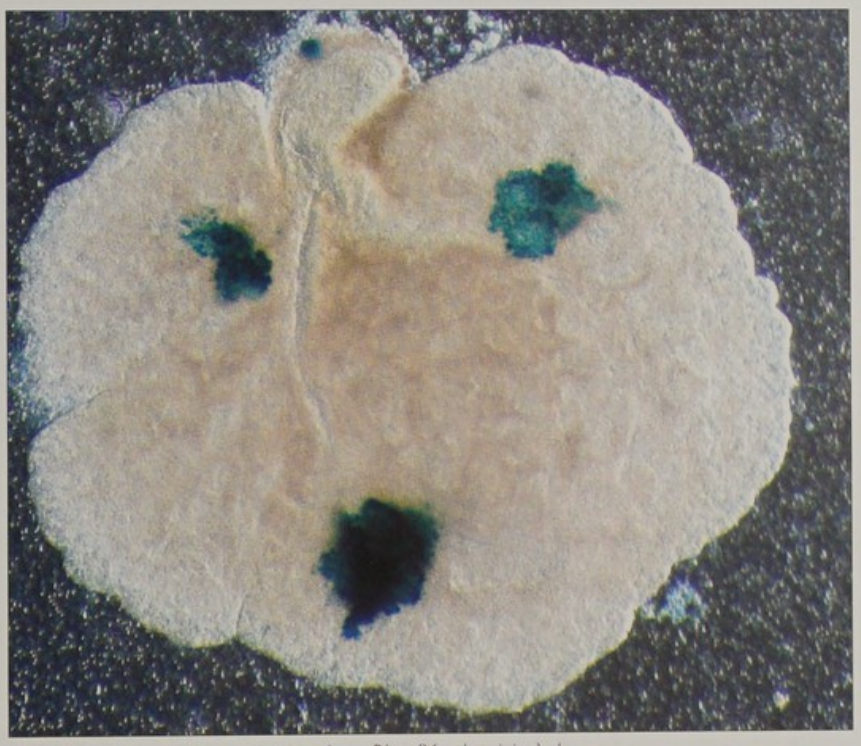
Our long-term vision is to combine the developmental and homeostatic aspects of our work to develop new approaches to ameliorate human pulmonary disease. In particular, we are working towards being able specifically to direct endogenous lung stem cells to generate any lung epithelial cell type.

Selected publications:

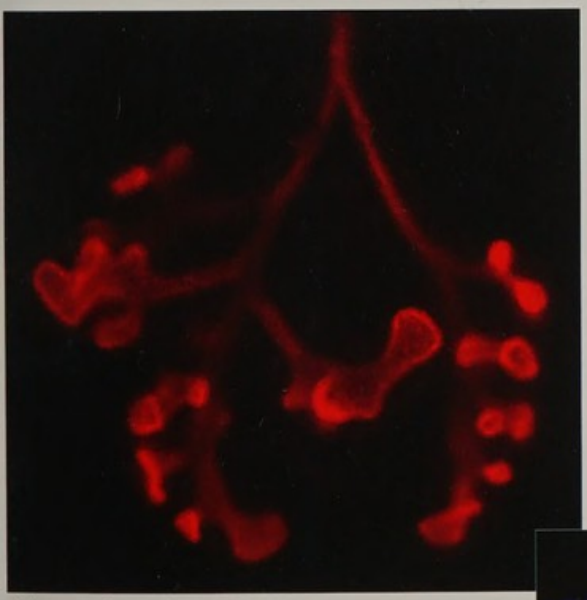
- Rawlins EL, Okubo T, Xue Y, Brass DM, Auten RL, Hasegawa H, Wang F and Hogan BLM (2009) The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. **Cell Stem Cell** 4 525-534
- Rawlins EL, Clark CP, Xue Y and Hogan BLM (2009) The Id2 distal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



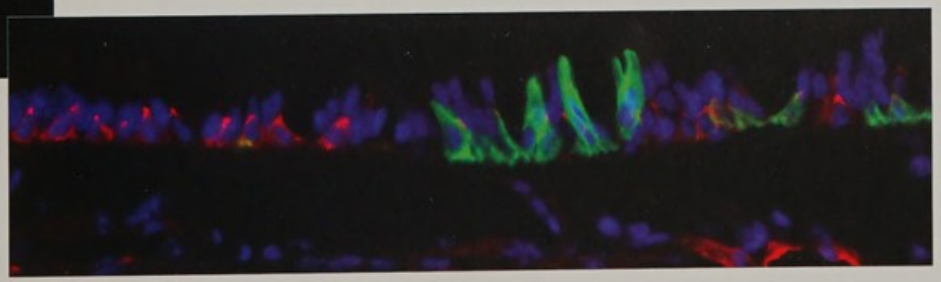
Adult mouse lung section showing lineage-labelled secretory cells (green) in the conducting airways.



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



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



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

Ben Simons

Patterns of stem cell fate in adult and developing tissues

Co-workers: Teresa Krieger

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

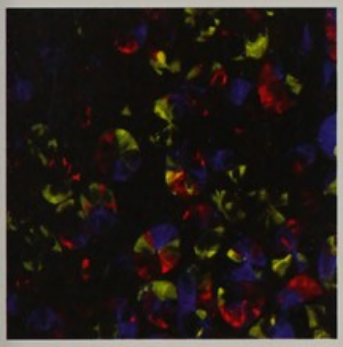
Theories of tissue maintenance place stem cells at the apex of proliferative hierarchies, possessing the lifetime property of self-renewal. In homeostasis the number of stem cells remains fixed imposing an absolute requirement for fate asymmetry in the daughters of dividing cells, such that only half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

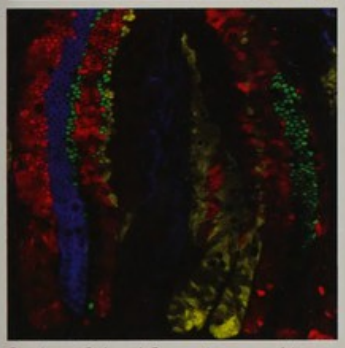
By drawing upon concepts from physics and mathematics, we have shown that strategies of stem cell self-renewal can be classified according to whether fate is specified by internal or extrinsic factors, and whether it leads to invariant asymmetric self-renewal or population asymmetry. As well as achieving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

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

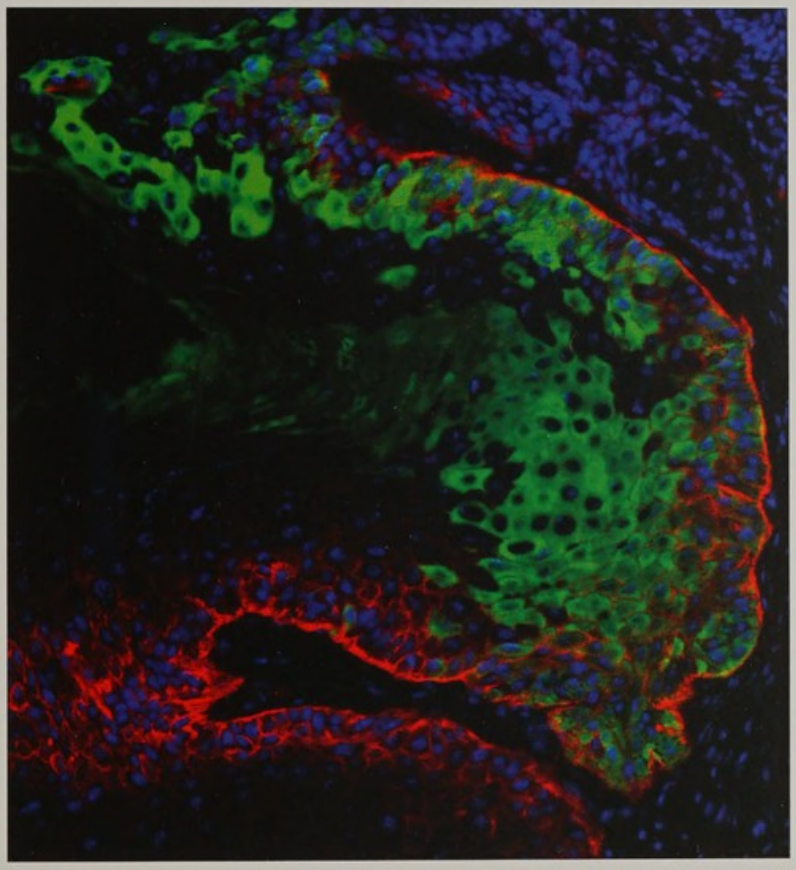
Selected publications:

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

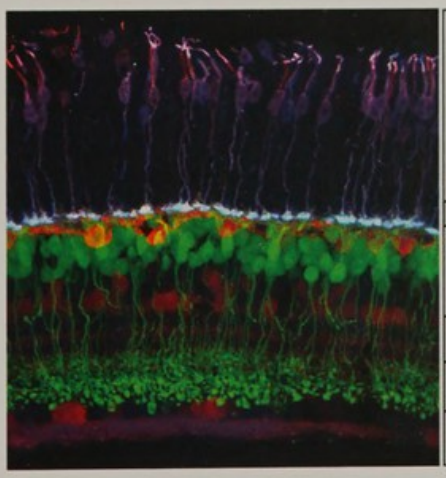


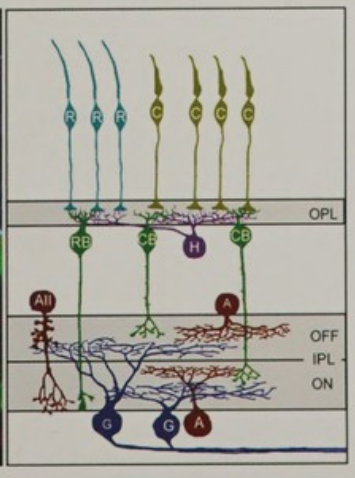


Studies of clonal fate using a multi-colour inducible genetic labelling system provide a vivid demonstration of neutral drift dynamics and the progession towards monoclonality in crypt. The top image shows a section through the base of the crypt showing the clonal progeny of the stem/paneth cell compartment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



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





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

Daniel St Johnston

Cell polarity, the cytoskeleton and mRNA localisation

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

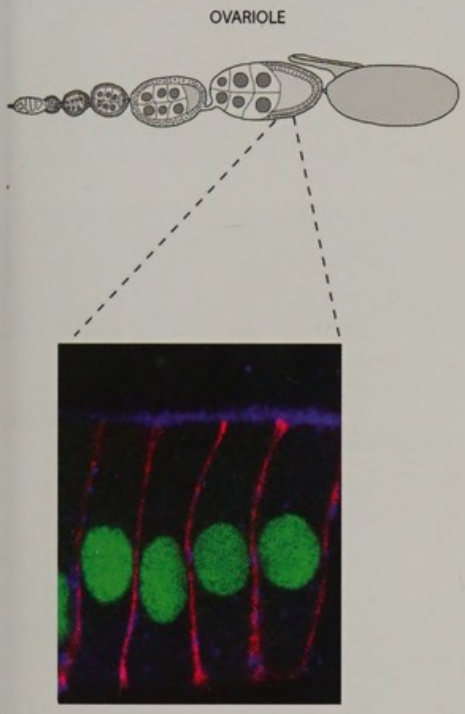
Cell polarity is essential for most cell functions and for several key developmental processes, such as cell migration, axis determination and asymmetric stem cell divisions, whereas loss of polarity is a critical step in the formation of tumours. We use *Drosophila* and mammalian tissue culture cells to analyse how cells become polarised and how this polarity controls the organisation of the cytoskeleton and intracellular trafficking.

Much of our work focuses on apical-basal polarity in epithelial cells, since these are the most common animal cell-type and must polarise to adhere to each other to form sheets of cells that act as barriers between compartments. As a model, we use the follicle cells that surround the developing egg chamber, as these form a typical secretory epithelium that is continuously generated from adult stem cells, making it easy to produce mutant clones. We are screening for novel polarity factors and investigating how cortical polarity controls spindle orientation, the organisation of the microtubule cytoskeleton and polarised secretion. We are also investigating polarity in the adult midgut, an absorptive epithelium, in which apical-basal arrangement of intercellular junctions is different.

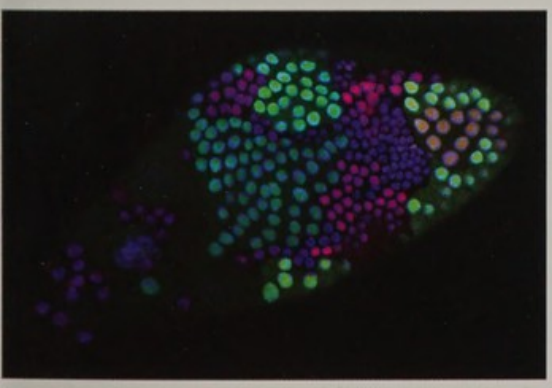
In parallel, we are examining how the *Drosophila* oocyte is polarised, since the localisation of bicoid and oskar mRNAs to opposite ends of this very large cell defines the anterior-posterior axis of the embryo. We use genetic, proteomic and biochemical approaches to elucidate how conserved polarity proteins regulate the organisation of the microtubule cytoskeleton in the oocyte, and analyse the mechanisms of mRNA transport and nuclear movement by making time-lapse films of moving mRNA particles and microtubule end markers in wildtype and mutant oocytes.

Selected publications:

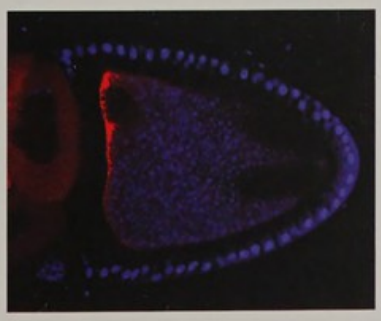
- Zhao T, Graham O, Raposo A and St Johnston D (2012) Growing microtubules push the oocyte nucleus to polarize the *Drosophila* dorsal-ventral axis. **Science** 336, 999-1003.
- St Johnston D (2012) Using mutants, knockdowns, and transgenesis to investigate gene function in *Drosophila*. **WiRES Developmental Biology** doi: 10.1002/wdev.101.
- Rees JS, Lowe N, Armean IM, Roote J, Johnson G, Drummond E, Spriggs H, Ryder E, Russell S, St Johnston D and Lilley KS (2011) In vivo analysis of proteomes and interactomes using Parallel Affinity Capture (iPAC) coupled to mass spectrometry. **Mol Cell Proteomics** 10, M110 002386.
- St Johnston D and Sanson B (2011) Epithelial polarity and morphogenesis. **Curr Opin Cell Biol** 23, 540–546.
- Chang CW, Nashchekin D, Wheatley L, Irion U, Dahlgaard K, Montague TG, Hall J and St Johnston D (2011) Anterior-posterior axis specification in *Drosophila* oocytes: identification of novel bicoid and oskar mRNA localisation factors. **Genetics** 188: 883-898



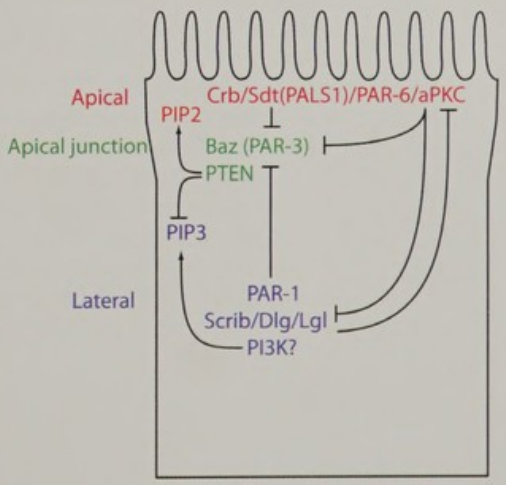
A diagram showing the epithelial organisation of the follicle cells of the ovary (left) and enterocytes of the adult midgut (right). The foillicle cells arise from adult stem cells in the germarium (left hand end of the ovariole) and migrate to surround the developing egg chamber. The enterocytes form the absorptive epithelium that lines the adult midgut, which is constantly replaced by basal stem cells.



An egg chamber containing two types of follicle cell clones homozygous for mutations that delay the switch between proliferation and differentiation, counterstained for DNA (blue).



A stage 10 egg chamber expressing a marker for the microtubule minus ends fused to Cherry fluorescent protein (red), counterstained for DNA (blue).



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

Azim Surani

Programming germ cells for totipotency and early mammalian development

Co-workers: Florencia Barrios, Delphine Cougot, Lynn Froggett, Nils Grabole, Ufük Günesdogan, Jamie Hackett, Naoko Irie, Shinseog Kim, Toshihiro Kobayashi, Caroline Lee, Harry Leitch, Kazuhiro Murakami, Roopsha Sengupta, Walfred Tang, Thor Theunissen, Julia Tischler, Mark Ziats, Jan Zylicz

We are interested in how the mammalian germ cell lineage is established, and how it is programmed towards generating the totipotent state (Fig 1). We are also interested in how the pluripotent state is established during early development, and the mechanisms that regulate initiation of cell fate decisions (Fig 2). In particular, we are investigating the molecular basis of PGC specification for which Prdm1, Prdm14 and Tcfap2c constitute a tripartite genetic network. These regulators initiate extensive epigenetic reprogramming, including global DNA demethylation. For these studies, we use *in vivo* approaches, and cell-based systems for generating PGC-like states using pluripotent stem cells

Epigenetic programming in PGCs is a key property, which includes extensive histone modifications and higher order changes in nuclear organisation. PGCs eventually reach the epigenetic ground state with unprecedented global DNA demethylation, during which Tet1 and Tet2 play an important but not an exclusive role (Fig 3).

We are also investigating the relationship between germ cells and pluripotent stem cells, in which some genes, (eg: Prdm14) play a pivotal role in inducing a ground state of pluripotency and promote transitions through epigenetic barriers during reprogramming. We are interested in exploring how mechanistic insights from studies on germ cells may be used for manipulating cell fates and for rejuvenation of somatic cells.

Selected publications:

- Gillich A, Bao S, Grabole N, Hayashi K, Trotter MW, Pasque V, Magnusdottir E and Surani MA (2012) Epiblast stem cell-based system reveals reprogramming synergy of germline factors. **Cell Stem Cell** 10, 425-439
- Bao S, Leitch H, Gillich A, Nichols J, Tang F, Kim S, Lee C, Zwaka T, Li X and Surani MA (2012) The germ cell determinant Blimp1 is not required for derivation of pluripotent stem cells. **Cell Stem Cell** 11, 110-117
- Hackett JA, Sengupta R, Zylicz JJ, Murakami K, Lee C, Down TA and Surani MA (2012) Germline DNA demethylation dynamics and imprint erasure through 5-hydoxymethylcytosine. **Science** [in press]

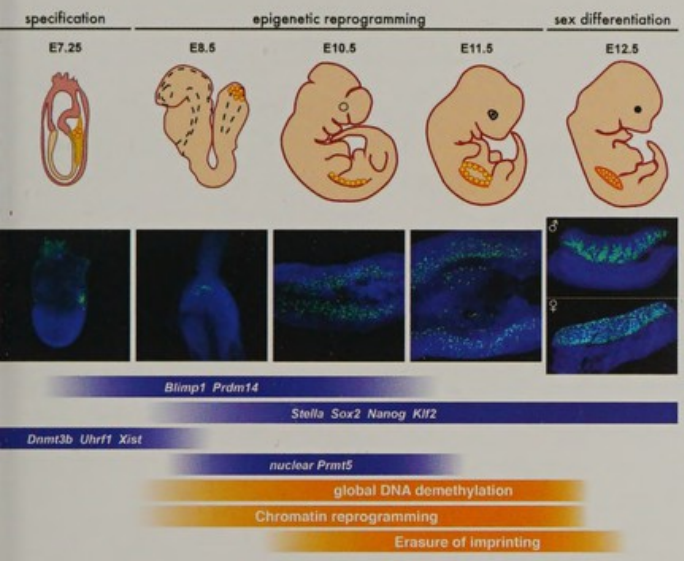


Fig 1. Primordial germ cell specification and epigenetic reprogramming.

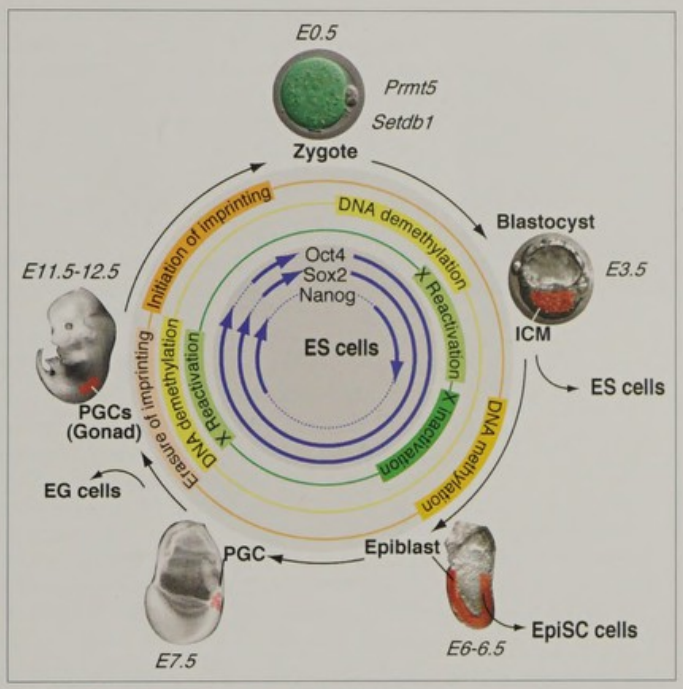


Fig2. Germline cycle depicting the origin of primordial germ cells and pluripotent stem cells, together with the key epigenetic reprogramming events

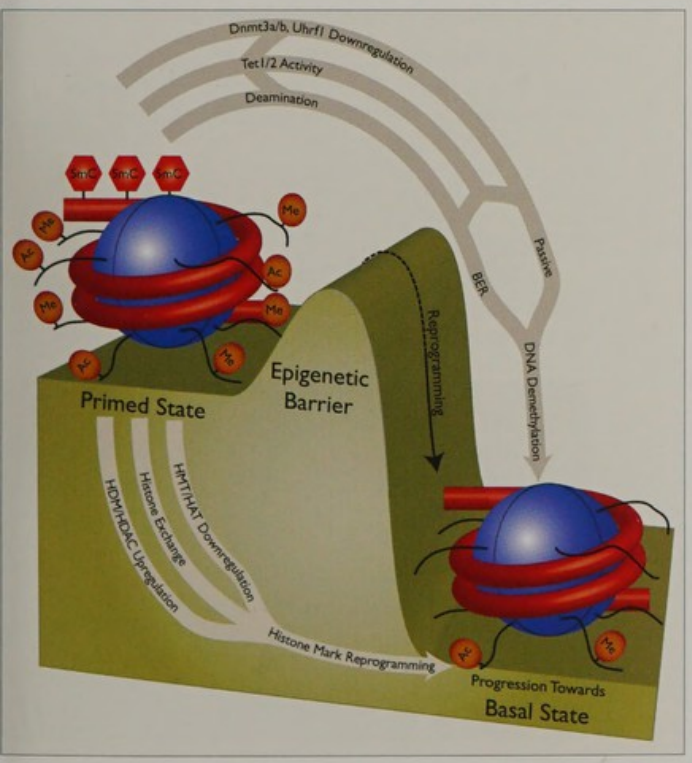


Fig 3. Parallel routes lead to reprogramming and the establishment of the basal epigenetic state in primordial germ cells

Philip Zegerman

The regulation of DNA replication initiation in eukaryotes

Co-workers: Jessica Black, Geylani Can, Vincent Gaggioli, Christine Hänni, Mark Johnson, Oleg Kovalevskiy, 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.

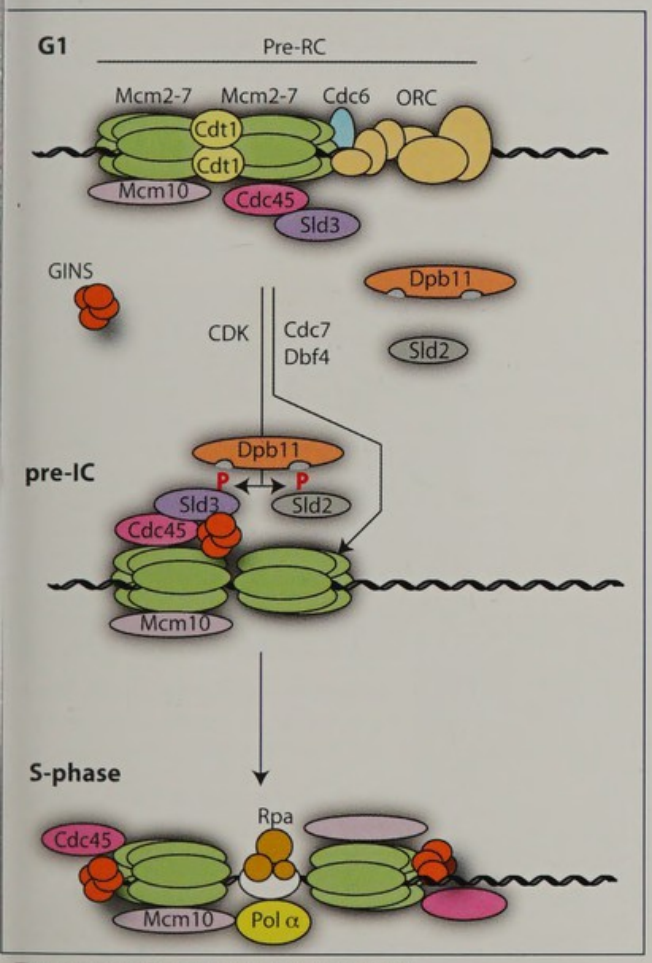
Selected publications:

• Mantiero D, Mackenzie A, Donaldson A and Zegerman P (2011) Limiting factors execute the temporal programme of origin firing in budding yeast. **EMBO J** 23, 4805-4814

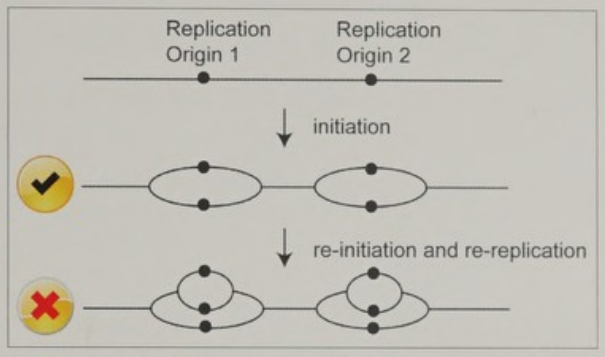
• Walton-Pagliuca F, Collins M, Zegerman P, Choudhary J and Pines J (2011) Quantitative proteomics reveals the basis for the biochemical specificity of the cell cycle machinery. **Mol Cell** 43, 406-417

• Zegerman P and Diffley JF (2010) Checkpoint dependent inhibition of DNA replication initiation via phosphorylation of Sld3 and Dbf4. **Nature** 467, 474-478

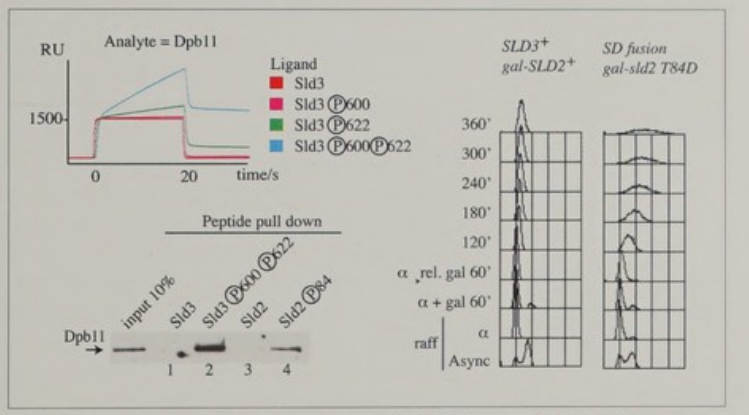
• Zegerman P and Diffley JF (2007) Phosphorylation of Sld2 and Sld3 by cyclin-dependent kinases promotes DNA replication in budding yeast. **Nature** 445, 281-285



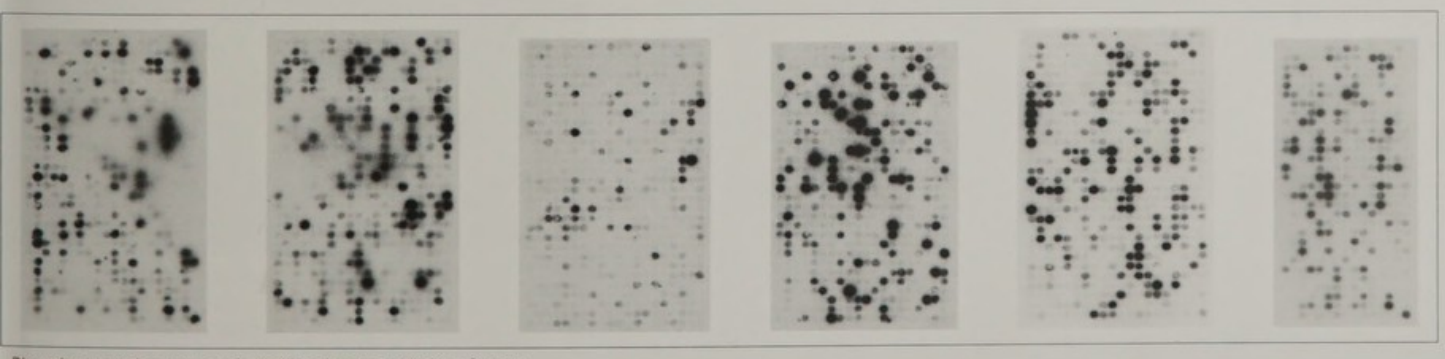
The sequence of eukaryotic replication initiation



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



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

Regulation and dynamics of cell fate transitions and morphogenesis during development of the early mouse embryo

Co-workers: Stoyana Alexandrova, Paula Almeia Coelho, Ivan Bedzhov, Monika Bialecka, Helen Bolton, Leah Bury, John Crang, Sarah Graham, Agnieszka Jedrusik, Chuen Yan Leung, Maryna Panamarova, Anoeska van de Moosdijk, Krzysztof Wicher

The mouse embryo provides an excellent model for studying mammalian development, including our own. It is also an excellent model to discover how to guide the differentiation of pluripotent cells towards specialised cell types. Initially mouse embryo cells are pluripotent and able to make any cell in the foetus or placenta but gradually this ability becomes restricted. The major focus of our group is to uncover the progressive cell fate transitions critical for generating pluripotent cells on one hand and cells that differentiate on the other, and how these transitions are coordinated with development of the embryo's unique form. We are particularly interested in a group of pluripotent cells, the epiblast, that is able to generate any cell type and indeed will form the entire body. We aim to understand how these cells are first set apart to prevent their differentiation while their neighbours enter differentiation pathways and, once this is achieved, how the distinct cell types interact and influence each other to build the foundation for the body. Until now it has been difficult to analyse these processes as they occur during the stages when the embryo is inaccessible, buried within the body of the mother. To gain insight into this developmental transition, we have established a culture system that, for the first time, permits manipulation and 4D-live imaging combined with computational analyses of embryos developing outside the mother continuously from fertilisation until future body plan emerges. This allows us to address how the pluripotent cells become endowed with the capability to develop into complex structures.

Selected publications:

• Morris S, Guo A and Zernicka-Goetz M (2012). Developmental plasticity is bound by pluripotency and the fgf and wnt signaling pathways. **Cell Reports**: S2211-1247(12)00269

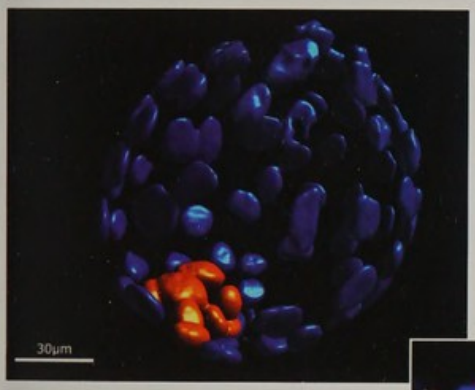
• Morris SA, Grewal S, Barrios F, Patankar SN, Strauss B, Buttery L, Alexander M, Shakesheff KM and Zernicka-Goetz M (2012) Dynamics of anterior-posterior axis formation in the developing mouse embryo. **Nature Commun**, 3:673.

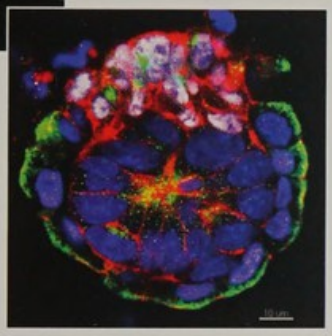
• Ajduk A, Ilozue T, Windsor S, Yu Y, Seres KB, Bomphrey RJ, Tom BD, Swann K, Thomas A, Graham C and Zernicka-Goetz M (2011) Rhythmic actomyosin-driven contractions induced by sperm entry predict mammalian embryo viability **Nature Commun** 2, 417 doi:10.1038/ncomms1424

• Zernicka-Goetz M, Morris S and Bruce A (2009) Making a firm decision: layers of regulation in early mouse embryo. **Nature Rev Genet** 10(7):467-77.

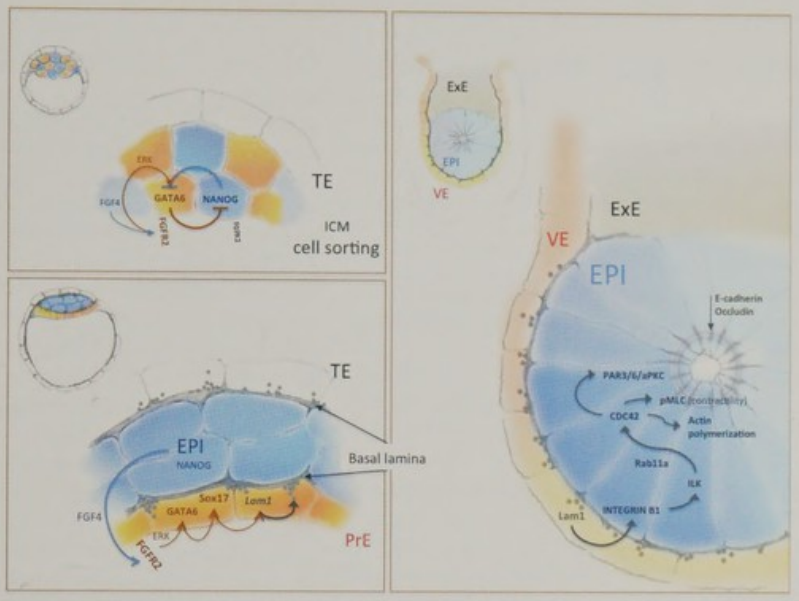
• Torres-Padilla ME, Parfitt DE, Kouzarides T and Zernicka-Goetz M (2007) Histone arginine methylation regulates pluripotency in the early mouse embryo. **Nature** 445, 214-218

Immunofluorescent staining of an E4.0 mouse blastocyst with trophectoderm nuclei in blue (Cdx2) and primitive endoderm nuclei in orange (Sox17). Captured with a Zeiss LSM 510 Meta Confocal Microscope with 1µm Z-stacks. Surface rendered with IMARIS.



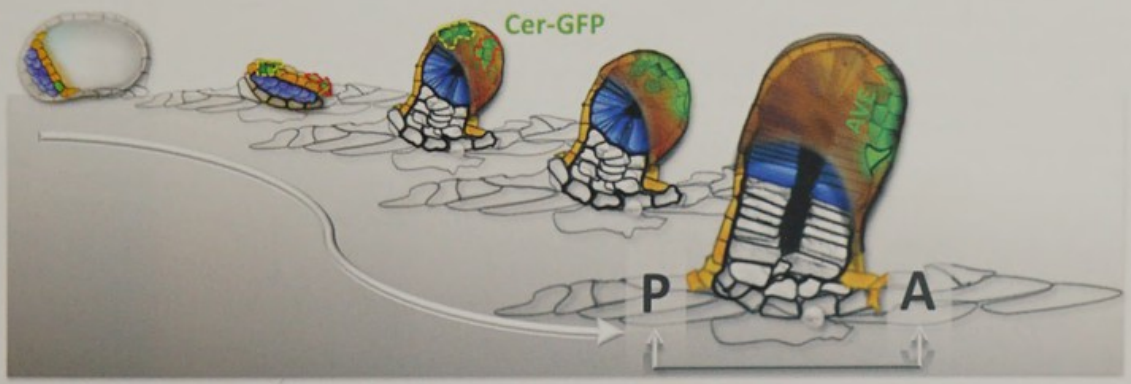


E5.0 mouse embryo stained for Rab11a (green), Phalloidin (red), Eomes (white) and DAPI (blue) at the onset of proamiotic cavity formation.



Model of epiblast (Epi) morphogenesis and proamniotic cavity formation. Cell sorting in the ICM establishes the Epi and the primitive endoderm (PrE). The transition from pre- to postimplantation Epi in vitro and in vivo is mediated by a dramatic change in cell shape during the time of implantation, with the cells forming a rosette-like structure. The cells acquire epithelial apical/basal polarity, where the apical sites in the centre face the expanding proamniotic cavity. The underlying signalling cascades that are currently investigated are indicated on the scheme. (Ivan Bedzhov)

The development of anterior–posterior (AP) polarity is a crucial developmental process that in the mouse has been very difficult to analyse, because it takes place as the embryo implants within the mother. To overcome this obstacle, we have established an in vitro culture system that allows us to follow the step-wise development of anterior visceral endoderm (AVE), critical for establishing AP polarity. (Ivan Bedzhov)



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SENIOR GROUP LEADER
Professor, Director of Research or Reader

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

CAREER DEVELOPMENT FELLOW
4-year grant-funded appointment

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

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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

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ITALICS: LEAVERS DURING THE LAST YEAR

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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, Director

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

REBECCA BASTOCK PhD
Wellcome Trust Research Associate

DAN BERGSTRALH PhD
Wellcome Trust Research Associate

JIA CHEN PhD
Wellcome Trust Research Associate

HÉLÈNE DOERFLINGER PhD
Wellcome Trust Research Associate

ARTUR FERNANDES MPhil
School of Biological Sciences PhD Student

WERONIKA FIC PhD
Wellcome Trust Research Associate

ALEJANDRA GARDIOL PhD
Wellcome Trust Research Associate

TIMM HAACK MPhil
Wellcome Trust PhD Student

JACKIE HALL MSc
Wellcome Trust Senior Research Technician

HOLLY LOVEGROVE MSc
Herchel Smith PhD Student

NICK LOWE PhD
Wellcome Trust Research Associate

AVIK MUKHERJEE MSc
CISS PhD Student

DMITRY NASHCHEKIN PhD
Wellcome Trust Research Associate

ROSS NIEUWBURG BSc
PhD Student

ARAM SAYADIAN MPhil
Wellcome Trust PhD Student

VANESSA STEFANAK PhD
Administration Manager for the Office of the Director

VITOR TROVISCO PhD
Marie Curie Intra-European Fellow/Wellcome Trust Research Associate

YU YE PhD
Henslow Research Fellow/Wellcome Trust Research Associate

ELODIE ZHANG BSc
Visiting Student from Pierre et Marie Curie University, Paris

TONGTONG ZHAO BSc
PhD Student

JULIE AHRINGER PhD FMedSci

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

ALEX APPERT PhD
Wellcome Trust Research Associate

DARYA AUSIANNIKAVA BSc
Darwin Trust PhD Student

FANÉLIE BAUER PhD
Wellcome Trust Research Associate

RON CHEN PhD
Wellcome Trust Research Associate

MIKE CHESNEY PhD
Wellcome Trust Reseach Associate

MARIANA DEL ROSARIO RUIZ VELASCO LEYVA
Visiting Student from UNAM, Mexico

YAN DONG MSc
Wellcome Trust Research Assistant

BRUNO FIEVET PhD
Wellcome Trust Research Associate

MORITZ HERRMANN BSc
BBSRC PhD Student

JÜRGEN JÄNES MSc
Wellcome Trust Mathematical Biology PhD Student

DJEM KISSIOV BA
Wellcome Trust Research Assistant

JOSANA RODRIGUEZ PhD
Herchel Smith Research Fellow/Wellcome Trust Research Associate

PRZEMYSLAW STEMPOR MSc
Wellcome Trust Research Associate

CHRISTINE TURNER
PA/Secretary

EVA ZEISER BSc
Wellcome Trust Research Assistant

ANDREA BRAND PhD FRS FMedSci

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

JANINA ANDER BSc
BBSRC PhD Student

ELIZABETH CAYGILL PhD
Herchel Smith Research Fellow

SETH CHEETHAM BSc
Herchel Smith PhD Student

ESTEBAN CONTRERAS SEPULVEDA MPhil
Wellcome Trust PhD Student

MELANIE CRANSTON BA
Wellcome Trust Research Assistant

ABHIJIT DAS PhD
Wellcome Trust Research Associate

CATHERINE DAVIDSON BSc
Wellcome Trust Research Associate

DAVID DOUPÉ PhD
Sidney Sussex College Junior Research Fellow

JACK ETHEREDGE BS
Janelia Farm/Cambridge University PhD Student

PAUL FOX PhD
EMBO Fellow

KATRINA GOLD PhD
Wellcome Trust Research Associate

JUN LIU BA
Dr Herchel Smith Graduate Fellow

OWEN MARSHALL PhD
EMBO Fellow

LEO OTSUKI MPhil
Wellcome Trust PhD Student

CHLOE SHARD BSc
CISS/Pointer PhD Student

TONY SOUTHALL PhD
Wellcome Trust Research Associate

PAULINE SPÉDER PhD
Sir Henry Wellcome Postdoctoral Fellow

CHRISTINE TURNER
PA/Secretary

JESSIE VAN BUGGENUM MSc
Erasmus 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/BBSRC Research Associate

JONATHAN FRIEDLANDER MA
Gates Scholarship and BBSRC PhD Student

ANNABEL GRIFFITHS BA
MRC PhD Student

SVEN HUELSMANN PhD
Wellcome Trust Research Associate/University of Jyväskulä Research Associate

YOSHIKO INOUE PhD
Wellcome Trust Research Associate

BENJAMIN KLAPHOLZ PhD
Wellcome Trust Research Associate

CÉZARY KUCEWICZ MA
PA

AIDAN MAARTENS PhD
Wellcome Trust Research Associate

KERRIE McNALLY
Amgen Scholar

JOHN OVERTON HNC
Wellcome Trust Chief Research Technician

PAULA RODRIGUEZ SANCHEZ MSc
Wellcome Trust Research Assistant

PEERAPAT THONGNUEK MRes in Regenerative Medicine
Thai Government PhD Student

JOHN GURDON Kt DPhil DSc FRS

Distinguished Group Leader
Nobel Laureate
Foreign Associate, US National Academy of Sciences
Foreign Associate, Institute of Medicine, USA
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
Honorary Fellow UK Academy of Medical Sciences
(Member of the Department of Zoology)

DILLY BRADFORD & SALLY FENN
PA/Secretary

CELIA DELAHAYE BSc
Visiting Student from ENSTBB, Bordeaux University

RICHARD HALLEY-STOTT PhD
MRC Research Associate

EVA HÖRMANSEDER PhD
Research Associate

JO-ANNE JOHNSON MB ChB MRCPCH
Wellcome Trust Clinical Research Fellow

JEROME JULLIEN PhD
Wellcome Trust Research Associate

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

PATRICK NARBONNE PhD
HSFP Research Fellow

VINCENT PASQUE MPhil
PhD Student

MARTA TEPEREK-TKACZ MSc
Wellcome Trust PhD Student

STAN WANG BS
NIH/Gates MD-PhD Student

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
Associate Faculty Member of the Wellcome Trust Sanger Institute
(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

ANDREW BLACKFORD PhD
Cancer Research UK Research Associate

MELANIE BLASIUS PhD
EU Research Associate

SEBASTIEN BRITTON PhD
EMBO Research Fellow/Cancer Research UK Research Associate

JESSICA BROWN MB BChir
Wellcome Trust Clinical Fellow/PhD Student

JULIA COATES MA
Cancer Research UK Research Assistant

MUKERREM DEMIR BSc
ERC Senior Research Technician

KATE DRY PhD
Cancer Research UK Information Specialist

JOSEP FORMENT PhD
Cancer Research UK Research Associate

ANNIKA FRAUENSTEIN
Erasmus Student from University of Regensburg, Germany

YARON GALANTY PhD
ERC Senior Research Associate

NICOLA GEISLER BSc
Cancer Research UK Senior Research Technician

ILARIA GUERINI PhD
EU Research Associate

ABDERRAHMANE KAIDI PhD
Herchel Smith Research Fellow/ERC Research Associate

DELPHINE LARRIEU PhD
EMBO Research Fellow

CARLOS LE SAGE PhD
EMBO Research Fellow

NATALIA LUKASHCHUK PhD
Cancer Research UK Research Associate

RYOTARO NISHI PhD
Sankyo Foundation of Life Science Research Fellow/Cancer Research UK Research Associate

TOBIAS OELSCHLÄGEL PhD
Cancer Research UK Research Associate

HELEN REED
PA/Secretary

CHRISTINE SCHMIDT PhD
FEBS Research Fellow

MATYLDA SCZANIECKA-CLIFT PhD
ERC Research Associate

HUIZHONG SU
CSSS Student

SASA SVIKOVIC
Amgen Scholar

JON TRAVERS PhD
Wellcome Trust Research Associate/EU Research Associate

PAUL WIJNHOVEN BSc
Cancer Research UK Research Assistant/MPhil Student

TONY KOUZARIDES PhD FMedSci

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

PAULO AMARAL PhD
Royal Society Newton International Fellow

ANDREW BANNISTER PhD
Cancer Research UK Senior Research Associate

ISAIA BARBIERI PhD
Cancer Research UK Research Associate

ESTER CANNIZZARO MSc
Visiting Research Assistant from CIMR

GONÇALO CASTELO-BRANCO PhD
Marie Curie Research Fellow

MARIA CHRISTOPHOROU PhD
Cancer Research UK Research Associate

ALISTAIR COOK GIBiol
ERC Chief Research Technician

MARK DAWSON MBBS (Hons) BMEDSci FRACP FRCPA PhD
Wellcome-Beit Intermediate Clinical Fellow

DENNIS GASCOIGNE BEng GDBA
Visiting PhD student from University of Queensland

SRI LESTARI MSc
Cancer Research UK Senior Research Laboratory Technician

VALENTINA MIGLIORI PhD
EU Research Associate

NIKKI PARSONS BA/MIRANDA LANDGRAF MA
PA/Secretary

SAM ROBSON PhD
ERC Research Associate (Bioinformatics)

HELENA SANTOS ROSA PhD
Cancer Research UK Senior Research Associate

MARC SCHNEIDER PhD
Leopoldina Research Fellow

PETER TESSARZ PhD
Cancer Research UK Research Associate

MARTA TOJO PhD
Visiting Researcher from Addenbrooke's Hospital, Cambridge

CHRISTOPHER TSUI
CSSS Visiting Student

EMMANUELLE VIRÉ PhD
ERC/Cancer Research UK Research Associate

MEIKE WIESE
Visiting Student from Heidelberg University

BEATA WYSPIANSKA MSc
BBSRC Case PhD Student

JONATHON PINES PhD FMedSci

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

PHILIPPE COLLIN PhD
BBSRC Research Associate

BARBARA DI FIORE PhD
Cancer Research UK Research Associate

ANJA HAGTING PhD
Cancer Research UK Research Associate

EMILIE HAINE BA
PA/Secretary

DAISUKE IZAWA PhD
Cancer Research UK Research Associate

MARK JACKMAN PhD
Cancer Research UK Research Associate

AGATA LICHAWSKA MSc
Herchel Smith PhD Student

JÖRG MANSFELD PhD
Cancer Research UK Research Associate

PAOLA MARCO PhD
MRC Research Associate

CHIARA MARCOZZI MSc
BBSRC PhD Student

TAKAHIRO MATSUSAKA PhD
Cancer Research UK Research Associate

OXANA NASHCHEKINA MSc
Cancer Research UK Chief Research Technician

BERNHARD STRAUSS PhD
MRC Research Associate

JILL TEMPLE MSc
MRC Research Assistant

NIKE WALTHER
Visiting Student from DKFZ, Heidelberg, Germany

SAMUEL WIESER MSc
Liechtenstein Government PhD Student

MAXIME WORINGER
Amgen Student

CLAUDIA WURZENBERGER PhD
MRC Research Associate

AZIM SURANI PhD CBE FRS FMedSci

Director of Germline and Epigenomics Research
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)

FLORENCIA BARRIOS PhD
Royal Society Newton International Fellow

DELPHINE COUGOT PhD
Wellcome Trust Research Associate

LYNN FROGGETT
PA/Secretary

ASTRID GILLICH MSc
Wellcome Trust PhD Student

NILS GRABOLE BSc
Wellcome Trust PhD Student

UFUK GÜNESDOGAN PhD
Wellcome Trust Research Associate

JAMIE HACKETT PhD
Wellcome Trust Research Associate

NAOKO IRIE PhD
JSPS/University of Keio Visiting Research Fellow

SHINSEOG KIM PhD
Wellcome Trust Research Associate

CAROLINE LEE ONC
Wellcome Trust Chief Research Technician

HARRY LEITCH MA (Cantab) PhD
MB/PhD Student

ERNA MAGNÚSDÓTTIR PhD
Marie Curie Research Fellow/Wellcome Trust Research Associate

KAZUHIRO MURAKAMI PhD
Riken/JSPS Visiting Research Fellow

ROOPSHA SENGUPTA PhD
Wellcome Trust Research Associate

QIN SI PhD
Wellcome Trust Research Associate

WALFRED TANG MPhil
Croucher Cambridge International PhD Student

THOR THEUNISSEN PhD
Sir Henry Wellcome Postdoctoral Fellow

JULIA TISCHLER PhD
KAUST/APART Research Fellow

KATARZYNA WILCZYNSKA PhD
EMBO Research Fellow/Wellcome Trust Research Associate

JAN ZYLICZ MSc
Wellcome Trust PhD Student

RAFAEL CARAZO SALAS PhD

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

JUAN FRANCISCO ABENZA MARTINEZ PhD
Ramón Areces Foundation Research Fellow

ANATOLE CHESSEL PhD
HFSP/ERC Research Associate

JONATHAN D'GAMA
Visiting Undergraduate Student from Harvard

JAMES DODGSON PhD
HFSP/ERC Research Associate

TARA FINEGAN BA
Clare Hall MPhil Student

MARCO GEYMONAT PhD
ERC Research Associate

VERONIKA GRAML MSc
SystemsX.ch PhD Student

JONATHAN LAWSON MPhil
Wellcome Trust PhD Student

YUNG-CHIN OEI MSc
Cancer Research UK PhD Student

KATHY OSWALD MA
PA/Secretary

XENIA STUDERA MSc
ERC Research Assistant

THOMAS DOWN PhD

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

PAULINA CHILARSKA BSc
Wellcome Trust PhD Student

KENNETH EVANS PhD
Wellcome Trust Bioinformatics Research Associate

JENNIFER GALLOP PhD

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

GUILHERME CORREIA MSc
Visiting Student

LYNN FROGGETT
PA/Secretary

JULIA MASON BSc
Wellcome Trust Research Assistant

ASTRID WALRANT PhD
ERC Research Associate

RICK LIVESEY MB BChir PhD

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

JESSICA ALSIO BSc
MRC Research Associate

THERESE ANDERSSON PhD
Wenner-Gren Foundation Research Fellow

ROBERTA CAGNETTA
Erasmus Student

TATYANA DIAS PhD
ARUK Research Associate

CHIBAWANYE ENE BSc
NIH-Cambridge PhD Student

MACUSHLA HUGHES BA
PA

PETER KIRWAN BSc
Wellcome Trust/ARUK PhD Student

GROUP LEADERS

TERESA KRIEGER BA MSci
EPSRC PhD Student

NORAH LIANG
Vacation Student from Harvard

STEVEN MOORE PhD
ARUK Research Associate

JOAO PEREIRA BSc
Fundação para a Ciência e Tecnologia PhD Student

TOMOKI OTANI MPhil
Wellcome Trust PhD Student

NATHALIE SAURAT BSc
Woolf Fisher PhD Student

YICHEN SHI BSc
PhD Student

JAMES SMITH BSc
Wellcome Trust/MRC Research Assistant

ANTHONY WALSH PhD
ARUK Research Associate

SELINA WRAY PhD
Visiting Researcher from UCL

ERIC MISKA PhD

Cancer Research UK Group Leader
ERC Starting Independent Researcher
(Member of the Department of Biochemistry)

JAVIER ARMISEN GARRIDO PhD
Cancer Research UK Research Associate

ALPER AKAY PhD
Cancer Research UK Research Associate

ALYSON ASHE PhD
Herchel Smith Research Fellow

RAMSAY BOWDEN MA MB BChir
Visiting Academic Clinical Fellow/Wellcome Trust MPhil Student

ALEJANDRA CLARK PhD
Cancer Research UK Research Associate

AMY CORDING BSc
ERC/Cancer Research UK Research Assistant

CARL FRANZ BA MA
Visiting PhD Student from Washington University, St Louis

LEONARD GOLDSTEIN PhD
Cancer Research UK Research Associate

ETHAN KAUFMAN BSc
PhD Student

MIRANDA LANDGRAF MA
PA/Secretary

JÉREMIE LE PEN MPhil
Wellcome Trust PhD Student

NIC LEHRBACH PhD
ERC Research Associate

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

MILAN MALINSKY MPhil
Wellcome Trust Mathematical Biology PhD Student

KAYLA McKAVENEY
Visiting Undergraduate Student from University of Wisconsin-Madison, USA

MIKEL MCKIE
Vacation Student

SYLVIANE MOSS PhD
Cancer Research UK Research Associate/Lab Manager

KENNETH MURFITT MPhil
Wellcome Trust/Cancer Research UK PhD Student

JAMES PATTERSON
Vacation Student

GRETA PINTACUDA
Scuola Normale Superiore Pisa Visiting Graduate Student

AMIE REGAN
Visiting Student

ALEXANDRA SAPETSCHNIG PhD
Herchel Smith/HFSP Research Fellow

PETER SARKIES PhD
Gonville and Caius Research Fellow

MÉLANIE TANGUY PhD
Cancer Research UK Research Associate

EVA-MARIA WEICK BSc
Herchel Smith/BBSRC PhD Student

JULIE WOOLFORD MPhil
Cancer Research UK PhD Student

EUGENIA PIDDINI PhD

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

ALEXIS BRAUN MSc
PhD Student

MAJA GOSCHORSKA BSc
CCC PhD Student

GOLNAR KOLAHGAR PhD
Cancer Research UK Research Associate

IWO KUCINSKI MPhil
Wellcome Trust PhD Student

CAROLINA MENDOZA TOPAZ PhD
Cancer Research UK Research Assistant

KATHY OSWALD MA
PA/Secretary

ENZO POIRIER BSc
Visiting Graduate Student from Ecole Normale Supérieure, Paris

SASKIA SUIJKERBUIJK PhD
Cancer Research UK Research Associate

SILVIA VIVARELLI PhD
MRC/Cancer Research UK Research Associate

LAURA WAGSTAFF PhD
MRC/Cancer Research UK Research Associate

EMMA RAWLINS PhD

MRC Research Fellow
(Member of the Department of Pathology)

GAYAN BALASOORIYA BSc
MRC Research Technician/PhD Student

CHRISTOPH BUDJAN MPhil
Wellcome Trust PhD Student

SIMON GERBER PhD
SNF Research Fellow

MACUSHLA HUGHES BA
PA

WAJID JAWAID MB ChB, BSc Med Sci(Hons), MRCS(Ed), MRCS(Eng)
Visiting Clinical Fellow

JO-ANNE JOHNSON MB ChB MRCPCH
Wellcome Trust Clinical Research Fellow

USUA LARESGOITI GARAY PhD
Basque Government Visiting Research Fellow

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

DANIEL O'REILLY
Amgen Scholar

CHANDRIKA RAO MSc
March of Dimes Chief Research Technician

RACHEL SEEAR MPhil
Wellcome Trust Chief Research Laboratory Technician

PHILIP ZEGERMAN PhD

AICR Research Fellow
(Member of the Department of Zoology)

GEYLANI CAN MSc
Turkish Government PhD Student

VINCENT GAGGIOLI PhD
AICR Research Associate

BENJAMIN FOSTER
Vacation Student

CHRISTINE HÄNNI MSc
CCC PhD Student

MARK JOHNSON PhD
AICR Research Assistant

OLEG KOVALEVSKIY PhD
Cancer Research UK Research Associate

DAVIDE MANTIERO PhD
EMBO Research Fellow

NIKKI PARSONS BA/JESSICA BLACK
PA

BARBARA SCHÖPF PhD
EMBO Fellow

MAGDALENA ZERNICKA-GOETZ PhD

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

STOYANA ALEXANDROVA BA
MRC PhD Student

PAULA ALMEIDA COELHO PhD
Visiting Academic

ELNUR BABAYEV
Visiting Master's Student

FLORENCIA BARRIOS PhD
Royal Society Newton International Fellow

IVAN BEDZHOV PhD
Wellcome Trust Research Associate

MONIKA BIALECKA PhD
Wellcome Trust Research Associate

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

LEAH BURY Dipl Mol Med
CCC PhD Student

JOHN CRANG DPhil
PA

RICHARD FREIMAN PhD
Sabbatical Visitor from Brown University, Providence, USA

SARAH GRAHAM MSc
PhD Student

AGNIESZKA JEDRUSIK PhD
Wellcome Trust Research Associate

JOANNA KOSALKA
Amgen Scholar

CHUEN YAN LEUNG BSc
Graduate Student

CLARA SLADE OLIVEIRA MVB
Visiting Graduate Student from FAPESP, Brazil

SAMEER PATANKAR MRes
Visiting Student from the University of Nottingham

MARYNA PANAMAROVA BSc
Darwin Trust PhD Student

MARIA SKAMAGKI PhD
Wellcome Trust Research Associate

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

ANOESKA VAN DE MOOSDIJK
Erasmus Student from Utrecht University, Netherlands

KRZYSZTOF WICHER PhD
Wellcome Trust Research Associate

AFFILIATED GROUP LEADER

BEN SIMONS PhD
(Herchel Smith Professor of Physics of Medicine at the Cavendish Laboratory)

TERESA KRIEGER BA MSci
EPSRC PhD Student

SABBATICAL VISITORS

MARVIN WICKENS PhD
Sabbatical Visitor (Max Perutz Professor of Molecular Biology and Biochemistry, University of Wisconsin-Madison)

ADMINISTRATION

ANN CARTWRIGHT MPhil
Institute Administrator

JESSICA BLACK
Receptionist

GEORGE BROWN
Accounts Manager

SUZANNE CAMPBELL BSc
HR/Grants Manager

MAISIE CATTELL
Receptionist

JANE COURSE
Accounts/Admin Assistant

DIANE FOSTER
Deputy Administrator

EMILIE HAINE BA
Receptionist

KATHY HILTON DipMgm
CBSG Manager

LYNDA LOCKEY
Office Manager

ALICIA MAVONG MSc
Receptionist

NIKKI PARSONS BA
Receptionist

COMPUTING

ALASTAIR DOWNIE
Computer Systems Manager

RICHARD BUTLER PhD
Research Associate (Imaging)

NICOLA LAWRENCE PhD
Computer Imaging Associate

NIGEL SMITH
Computer Associate

ALEX SOSSICK BSc
Computer Imaging Associate

PETER WILLIAMSON BSc
Computer Associate

BIOINFORMATICS

CHARLES BRADSHAW PhD
Senior Bioinformatician

GEORGE ALLEN PhD
Bioinformatician

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
Senior Stores Technician

MICK WOODROOFE
Purchasing/Accounts Assistant

TECHNICAL SUPPORT

KEITH SAVILL
Senior Technical Officer

DIANE FOSTER
Administrative Officer

POLLY ATTLESEY
Unit Manager

RYAN ASBY
CAROLINE BLAKE
FARON BROWN
DANIEL DUDMAN
PAWEL FRATCZAK
MARK GILLILAND
GEMMA HORTON
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MARIA JUHL LARSEN
URSZULA KOKOT
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SOPHIE BROUGHTON
SARAH DRAKE
EMMA FILBY
GARY GARNER
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GILLIAN HYNES
SHANE JOHNSON
GRACE LUCAS
FALLON MILLER
DOMINIC OSBORNE
JASON RISEBOROUGH
HANNAH RULE
CLAIRE WALKER
JO WATSON

COMBINED BUILDING SERVICES GROUP (CBSG)

CLIVE BENNETT
MIGUEL GONÇALVES
STEPHEN SALT
PAUL TURRELL
KATHERINE BENNETT
ALAN RIX
STUART TURNER
SIMON WILSON

MEDIA/GLASS WASHING

JUANITA BAKER-HAY
Media/Glasswashing Manager

SUE HUBBARD
Deputy Media/Glasswashing Manager

JANIS ABBOTT
LISA BAKER
VINCE DAMS
MARK JOHNS
AGNES ASSELIN LE FOLL
KAZUKO COLLINS
SANDRA HUMAN
TRACY MITCHELL

ZEST CATERING

AMANDA HARRIS
MELISSA PLOWDEN ROBERTS
REECE WEISSFLOG

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

1 **Abenza JF**, Galindo A, Pinar M, Pantazopoulou A, de los RÍos V and Peñalva MA (2012) Endosomal maturation by Rab conversion in *Aspergillus nidulans* is coupled to dynein-mediated basipetal movement. Mol Biol Cell 23, 1889 - 1901 [**Carazo Salas** Group]

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INSTITUTE PUBLICATIONS

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JANUARY

JULIE AHRINGER: Keystone Meeting, Keystone resort, Colorado, USA
ANDREA BRAND: Symposium on Neural Development: Stem Cells, Tokyo, Japan
JOHN GURDON: University Andres Bello, Santiago, Chile
STEVE JACKSON: Sanger Institute, Hinxton
TONY KOUZARIDES: Research Institute of Molecular Pathology (I.M.P.), Vienna, Austria
ALEX SAPETSCHNIG: RNA UK, Lake District, UK
DANIEL ST JOHNSTON: Vanderbilt University, Nashville, CA, USA
AZIM SURANI: Wellcome Trust Stem Cell Institute
AZIM SURANI: Kranjska Gora Ski Resort, Slovenia

FEBRUARY

ANDREA BRAND: Genomics and Sysyems Biology, NYU, Abu Dhabi
ANDREA BRAND: Australian National University, Canberra, Australia
RAFAEL CARAZO SALAS: TEDx Pura Vida, San Jose, Costa Rica
YARON GALANTY: The Sixth International Conference SUMO, Ubiquitin, UBL Proteins: Implications for Human Diseases, Houston, USA
JOHN GURDON: Natural Sciences Club, Trinity Hall, Cambridge
JOHN GURDON: University of Manchester, UK
JOHN GURDON: Gordon Research Conference, Galveston, Texas, USA
STEVE JACKSON: London Cell Cycle Club Meeting, London, UK
JON PINES: CR UK London Research Institute, UK
DANIEL ST JOHNSTON: Yale University, Sears Memorial Lecture, USA
AZIM SURANI: Gordon Research Conferences, Galveston, Texas, US
EVA MARIA WEICK: Keystone Symposium, Vancouver, Canada

MARCH

DAN BERGSTRALH: Drosophila Research Council, Chicago, USA
RAFAEL CARAZO SALAS: Institute Curie, Paris, France
MARK DAWSON: American Association for Cancer Research Annual Meeting, Chicago, USA
MARK DAWSON: Epigenetic Drug Discovery Meeting, Freiburg, Germany
JENNY GALLOP: University of Warwick, UK
JOHN GURDON: Gulbenkian Institute, Lisbon, Portugal
JOHN GURDON: Institute of Molecular Biology Opening Symposium, Mainz, Germany
JOHN GURDON: Company of Biologists, Wiston House Steyning, West Sussex
STEVE JACKSON: British Association for Cancer Research and Gray Institute Meeting DNA Damage Repair, Oxford
STEVE JACKSON: Gordon Research Conference, Ventura, California
JEROME JULLIEN: UK Xenopus Meeting, Sanger Institute, Hinxton, Cambridge
TONY KOUZARIDES: Institute Curie, Paris, France
RICK LIVESEY: Alzheimer's Research UK Annual Conference, Birmingham
ERIC MISKA: Centre for Cancer Research & Cell Biology, Belfast
EUGENIA PIDDINI: Inserm, Paris, France
JON PINES: UK-Korea Mitosis workshop, Seoul, Korea
EMMA RAWLINS: Royal Society, Seventh John Vane Memorial Symposium on Prostaglandin Science, London
ALEX SOSSICK: EMBO Practical Course in Advanced Optical Microscopy The Marine Biological Association of the United Kingdom, Plymouth
DANIEL ST JOHNSTON: University of California, San Francisco, USA
AZIM SURANI: Keystone Symposia, Squaw Creek, Olympic Valley, CA, US

APRIL

JULIE AHRINGER: CNRS, Roscoff, France
JOHN GURDON: IPSEN, Paris, France
JOHN GURDON: Yale Medical School, New Haven USA
JOHN GURDON: CSHL Symposium on Molecular Pathways in organ development & disease, Cold Spring Harbor, New York, USA
STEVE JACKSON: The Dutch Society for Radiobiology, Radiation Science Meeting, Noordwijkerhout, The Netherlands
TONY KOUZARIDES: Keystone Meetings, Snowbird, Utah, USA
EMMA RAWLINS: Biochemistry Department, University of Leicester, UK
DANIEL ST JOHNSTON: EMBO/ESF, Pultusk, Poland
AZIM SURANI: Cold Spring Harbor, Suzhou, China
PETER TESSARZ: London Chromatin Club, Abcam, London, UK
JULIE WATSON: Eurosystem Consortium Meeting, Prague
PHIL ZEGERMAN: British Yeast Group, Edinburgh
PHIL ZEGERMAN: BSCB Warwick, UK
MAGDA ZERNICKA-GOETZ: Institute of Zoology and Tsinghua University, Beijing, China
MAGDA ZERNICKA-GOETZ: University Hawaii at Manoa, Honolulu
MAGDA ZERNICKA-GOETZ: Vertebrate Organogenesis in Health and Disease, Cold Spring Harbor, New York, USA
MAGDA ZERNICKA-GOETZ: Alpha Reproductive Medicine Meeting, London

MAY

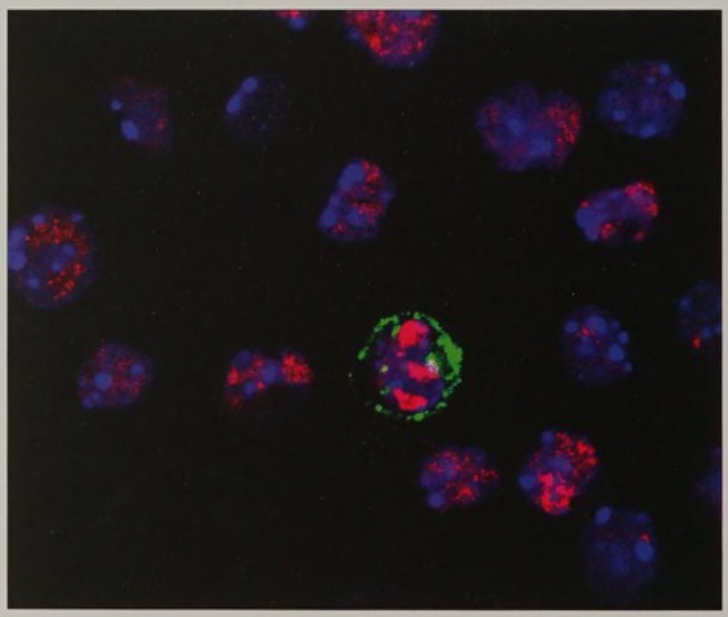
JULIE AHRINGER: ModENCODE Consortium, Cambridge MA, USA
JULIE AHRINGER: INSERM Meeting, Bordeaux, France
ANDREA BRAND: Columbia University Medical School, USA
JENNY GALLOP: University of Birmingham, UK
JOHN GURDON: Symposium to honour Sir Ian Wilmut + opening of new Scottish Centre for Regenerative Medicine, Edinburgh, Scotland
TONY KOUZARIDES: GRC, Lucca, Italy
RICK LIVESEY: Lunchtime Neuroscience/CNR Series, IOP, Kings College London

TALKS BY INSTITUTE RESEARCHERS

ERIC MISKA: EMBO YIP, Barcelona
JON PINES: Cold Spring Harbor Cell Cycle Meeting, New York, USA
JON PINES: UCL Cancer Centre, London
AZIM SURANI: Gordon Research Conferences, Lucca, Italy
SILVIA VIVARELLI: NIMR, London
LAURA WAGSTAFF: NIMR, London
MAGDA ZERNICKA-GOETZ: 11th International Conference on Preimplantation Genetics Diagnosis, Bregenz, Austria

JUNE

JULIE AHRINGER: University of Wisconsin, Madison, USA
ANDREA BRAND: EMBO International Workshop, Kolymbari, Crete
JENNY GALLOP: Engineering and Physical Sciences Research Council, Cambridge
JOHN GURDON: Cambridge University Post-Docs, Clare College, Cambridge
JOHN GURDON: ISSCR 10th Annual Meeting, Yokohama, Japan
JOHN GURDON: Japanese Soc.for Regen.Med, Yokohama, Japan
JOHN GURDON: CIG Symposium Transcription from development to nutrigenomics (to honour Prof Wahli), Lausanne, Switzerland



DNA methylation reprogramming by 5-hydroxymethylcytosine (5hmC) in primordial germ cells (PGC). Mouse PGCs (green) erase their global DNA methylation as part of their reprogramming towards totipotency. A significant proportion of DNA methylation erasure occurs via conversion to 5hmC (red), which is enriched only in PGCs. DAPI (blue) marks all DNA. (Jamie Hackett, Surani Group, 2012)

JOHN GURDON: Company of Biologists Royal Institution, Wilton Park, Steyning
TONY KOUZARIDES: Tenovus Symposium 30th Anniversary, University of Glasgow, UK
TONY KOUZARIDES: IGBMC, Chromatin: From Structure to Epigenetics Conference 2012, Illkirch, France
RICK LIVESEY: BBSRC, London
RICK LIVESEY: Fidelity Biomedical Research Initiative, Kronberg, Germany
RICK LIVESEY: A-T Society, Cambridge
PAOLA MARCO-CASANOVA: Dana Farber Cancer Institute, Center for LIfe Science, Boston, USA
ERIC MISKA: Institute Zurich, Switzerland
ERIC MISKA: EMBO Fellows Meeting, Heidelberg, Germany
KEI MIYAMOTO: Stem Cells & Bioprocessing Europe, London
JON PINES: Imaging the Cell, Toulouse, France
JON PINES: London Cell Cycle Meeting, UCL, London
CHRISTINE SCHMIDT: Institute of Integrated Nanosciences, IFW Dresden , Dresden, Germany
ALEX SOSSICK: CamBridgeSens, Murray Edwards College, Cambridge
AZIM SURANI: Iviomics, University of Valencia, Spain
AZIM SURANI: Abcam, Strasbourg, France
PETER TESSARZ: EMBO, Girona, Spain

JULY

ANDREA BRAND: Glia in Health and Disease, CSHL, NY, USA
MARK DAWSON: Translational Medicine and Therapeutics Meeting, Gonville & Caius College Cambridge
JENNY GALLOP: CIC Biomagune, San Sebastian, Spain
JOHN GURDON: InStem Bangalore + UCL Centre for Stem Cells & Regenerative Medicine, London
STEVE JACKSON: Ubiquiting drug discovery and diagnostics conference, Philadelphia, USA
RICK LIVESEY: Alzheimer's Association International Conference, Vancouver
JOERG MANSFELD: Leibniz Institute for Age Research - Fritz Lipmann Institute, Germany
JOERG MANSFELD: University of Dusseldorf, Germany
ERIC MISKA: Harden, University of Cambridge
JON PINES: Institute of Cancer Research , London
AZIM SURANI: Insem (Bangalore) & UCL centre for stem cells and regenerative medicine, London

AUGUST

JULIE AHRINGER: Beijing Genome Institute, Beijing, China
ANDREA BRAND: Gordon Research Conference, Newport, USA

MARK DAWSON: Anaplastic Lymphoma International Meeting, Kings College Cambridge
JOHN GURDON: Ralph Brinster Tribute Symposium, Philadelphia, USA
TONY KOUZARIDES: EMBL , Heidelberg, Germany
PAOLA MARCO- CASANOVA: Gulbenkian Institute, Oeiras, Portugal
ERIC MISKA: Les Trielles, Nice, France
ALEX SOSSICK: Confocal Microscopy Workshop, Department of Molecular Biology, University of South Bohemia, Czech Republic
AZIM SURANI: EMBL, Heidelberg, Germany

SEPTEMBER

ALYSON ASHE: Vardhman Raykan, London Epigenomics Club (Blizard Institute, Barst and London School of Medicine)
IVAN BEDZHOV: EMBO Workshop, Cell Biology of Early Mouse Development, Cambridge
ANDREA BRAND: EMBO, Heidelberg, Germany
MARIA CHRISTOPHOROU: London Chromatin Club, Abcam, UCL, London
JAMES DODGSON: Pombe Club, Cancer Research UK, London
MARK DAWSON: Epigenetics Europe Conference, Frankfurt, Germany
JOHN GURDON: 14th International Xenopus Conference, Marseille, France
JOHN GURDON: Institut Pasteur Seminar for Department of Developmental Biology, Paris, France
STEVE JACKSON: Amgen Symposium, Cambridge
GOLNAR KOLAHGAR: Beatson Institute, Glasgow
TONY KOUZARIDES: Cold Spring Harbor Labs, New York, USA
RICK LIVESEY: ELRIG Drug Discovery Conference,, Manchester
JOERG MANSFELD: FEBS Fellows Program, Costa Ballena, Spain
ERIC MISKA: UCL, London
ERIC MISKA: EEMS, Warsaw University
JON PINES: Jacques Monod Cell Cycle Meeting, Roscoff, France
JON PINES: EMBO Workshop on Cell Biology of the Early Mouse Embryo, Cambridge
CHRISTINE SCHMIDT: FEBS Fellowships Committee, Cadiz
DANIEL ST JOHSTON: 26th French Drosophila Meeting, Clermont-Ferrand, France
PETER TESSARZ: German Genetics Society, Essen, Germany

OCTOBER

ANDREA BRAND: Institut Curie, Paris, France
JOHN GURDON: EMBO/EMBL Symposium, Heidelberg, Germany
JOHN GURDON: UNIST, Busan, South Korea
JOHN GURDON: ISSCR Roddenberry Stem Cell Centre, Gladstone Institute Symposium, San Francisco, USA
ERIC MISKA: LRI, London
ERIC MISKA: Zurich Brain Institute, Zurich, Switzerland
EUGENIA PIDDINI: EMBL, Heidelberg, Germany
JON PINES: Genome Damage Centre, Sussex University, UK
JON PINES: Sheffield University, UK
JON PINES: Konstanz University, Germany
DANIEL ST JOHSTON: Institut Curie, Paris, France
AZIM SURANI: CSH conferences, Cold Spring Harbor, New York, US
AZIM SURANI: EMBO/EMBL, Heidelberg, Germany
AZIM SURANI: IMB, Mainz, Germany

NOVEMBER

PAULO AMARAL: Department of Cell Biology, University of Brasília, Brazil
ANDREA BRAND: Institute of Interdisciplinary Research Brussels, Belgium
RAFAEL CARAZO SALAS: University of Lausanne, Switzerland
RAFAEL CARAZO SALAS: Institut Curie, Paris, France
STEVE JACKSON: Babraham Insitute, Cambridge
STEVE JACKSON: The British Genetics Society , London
TONY KOUZARIDES: 4D CellFate, Mallorca, Spain
ERIC MISKA: Jacques Monod Conferences, Roscoff, France
EUGENIA PIDDINI: Institut Curie, Paris, France
JON PINES: IGBMC, Strasbourg, France
AZIM SURANI: Wellcome Trust, London
AZIM SURANI: Wellcome Trust, Hinxton, Cambridge
JULIA TISCHLER: Unilever Cell Market, Cambridge
PHIL ZEGERMAN: University of Sussex, UK
MAGDA ZERNICKA-GOETZ: International Society of Differentiation Meeting, Amsterdam, Holland

DECEMBER

ANDREA BRAND: Hubrecht Institute, Utrecht, Netherlands
RAFAEL CARAZO SALAS: Harvard, USA
JOHN GURDON: Nobel Prize Committee, Stockholm, Sweden
STEVE JACKSON: 2nd Copenhagen Bioscience Conference - PTMs in Cell Signalling , Denmark
TONY KOUZARIDES: World Epigenetics Summit, London, UK
TONY KOUZARIDES: University of Leeds, UK
EUGENIA PIDDINI: Yale, USA
AZIM SURANI: MBSJ Meeting, Fukuoka, Japan
JULIA TISCHLER: Helmholtz Zentrum (Center) , Munich, Germany
MAGDA ZERNICKA-GOETZ: 40th anniversary of the Committee on Cell Biology of the Polish Academy of Science, Warsaw, Poland

OTHER INFORMATION

STAFF AFFILIATIONS

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

ANDREA BRAND was Chair of the Royal Society Young People's Book Prize Judging Panel, is a member of the Royal Society/Wellcome Trust Sir Henry Dale Fellowship Committee, member of Royal Society Sectional Committee 7, member of the EMBO Young Investigator Committee, Founding Board Member of The Rosalind Franklin Society (USA). She is also a member of the steering group of the Cambridge Women in Science, Engineering and Technology Initiative, a Patron of the Cambridge Science Festival, and a member of Council, Jesus College.

JOHN GURDON is an honorary member of the Scientific Advisory Board of the Harvard Stem Cell Institute (USA) and the Rambam Medical Center (Israel), an honorary member of the British and American Anatomical Societies, Chairman of the Company of Biologists (until July 2012), a board member of Diagnostics for the Real World and a member of the Faculty of 1,000.

STEVE JACKSON is founding Scientist and Chief Scientific Officer of MISSION Therapeutics Ltd. He is Chairman of the Board of the Scottish Centre for Cell Signalling and is a member of the Scientific Advisory Boards for the MRC Protein Phosphorylation and Ubiquitylation Unit (Dundee), the Cancer Research UK (CRUK) London Research Institute, the Beatson Institute (Glasgow), the MRC Toxicology Unit (Leicester) and the Radiation Oncology and Biology Institute (Oxford). He is on the Steering Committee for the Cambridge Cancer Centre, and is a member of the CRUK Science Committee and its Drug Discovery Advisory Group.

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

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

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

AZIM SURANI is Chairman of the Scientific Advisory Board of the Centre for Trophoblast Research, University of Cambridge, a member of the Steering Committee of the Cambridge Stem Cell Institute and Leader of the Pluripotency Programme, a member of the Cambridge India Partnership Advisory Group, founder and Chief Scientific Advisor for CellCentric Ltd, a member of the Steering Committee for the UK Stem Cell Bank, and a member of the Royal Society Hooke Committee

MAGDALENA ZERNICKA-GOETZ is a Board Member of the International Society of Differentiation, an Associate Member of the MRC Stem Cell Centre in Cambridge, and a Member of Council of the Cambridge Philosophical Society.

HONOURS AND AWARDS

JOHN GURDON – Nobel Prize in Physiology or Medicine; Honorary Degree from Universidad Andres Bello in Chile

TONY KOUZARIDES – Fellow of the Royal Society

ERIC MISKA – BSCB Hooke Medal; Member of the European Molecular Biology Organization

VINCENT PASQUE – Wellcome Trust Image Award

EDITORIAL BOARDS OF JOURNALS

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

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

JOHN GURDON – Current Biology; Development; Growth and Differentiation; International Journal of Developmental Biology; Proceedings of the National Academy of Sciences of the USA

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

RICK LIVESEY – BMC Developmental Biology; Molecular Autism

EMMA RAWLINS – Pediatric Research

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

DANIEL ST JOHNSTON – Development; Faculty of 1,000

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

MAGDALENA ZERNICKA-GOETZ – Development; Developmental Dynamics; Faculty of 1,000; Reproduction; BMC Dev Biol; Differentiation

INTERNATIONAL SCIENTIFIC ADVISORY BOARD

DR GENEVIEVE ALMOUZNI, Institut Curie, Paris, France

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

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

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

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

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

DR MATTHIAS PETER, ETH Zurich

CHAIRMAN OF THE MANAGEMENT COMMITTEE

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

SABBATICAL VISITORS

MARVIN WICKENS: Max Perutz Professor of Molecular Biology and Biochemistry, University of Wisconsin-Madison

POSTDOCTORAL RESEARCHERS

JAVIER ARMISEN GARRIDO: Researcher, EASIH, Medical Genetics Dept, University of Cambridge (Miska Group)

REBECCA BASTOCK: Trainee position, Clinical Diagnostic Genetics Department, Sheffield Children's Hospital (St Johnston Group)

MELANIE BLASIUS: Researcher, Danish Cancer Society Research Centre, Copenhagen, Denmark (Jackson Group)

ALEJANDRA CLARK: Editor at EMBO Reports, Heidelberg, Germany (Miska Group)

GONCALO CASTELO-BRANCO: Assistant Professor, Dept of Medical Biochemistry and Biophysics Karolinska Institute, Stockholm (Kouzarides Group)

RICHARD FREIMAN: Associate Professor of Medical Science, Brown University, Providence, Rhode Island USA (Zernicka-Goetz Group)

SIMON GERBER: Postdoctoral Researcher, University of Freiburg, Germany (Rawlins Group)

ILARIA GUERINI: Scientific Officer, Peer Review, AICR, Milan, Italy (Jackson Group)

ERNA MAGNÚSDÓTTIR: Research Scientist, Dept of Biochemistry & Molecular Biology, University of Iceland, Reykjavik, Iceland (Surani Group)

DAVIDE MANTIERO: Business Development Associate, Abcam, Cambridge (Zegerman Group)

JÖRG MANSFELD: Group Leader, Biotec Institute, TU Dresden, Germany (Pines Group)

PATRICK NARBONNE: Postdoctoral Researcher, Paul Maddox lab, University of Montreal, Canada (Gurdon Group)

TOBIAS OELSCHLÄGEL: Senior Scientist, Roche Diagnostics, GmbH, Penzberg, Germany (Jackson Group)

MARC SCHNEIDER: Consultant, Bayer Business Consulting, Leverkusen, Germany (Kouzarides Group)

QIN SI: Returned to Inner Mongolia, applying for research positions (Surani Group)

ANTHONY WALSH: Postdoctoral Researcher, Wilson Wong's lab, Biomedical Engineering Dept, Boston University, Boston, USA (Livesey Group)

KATARZYNA WILCZYNSKA: Research Scientist, Neurobiology, Pfizer Neusentis, Cambridge (Surani Group)

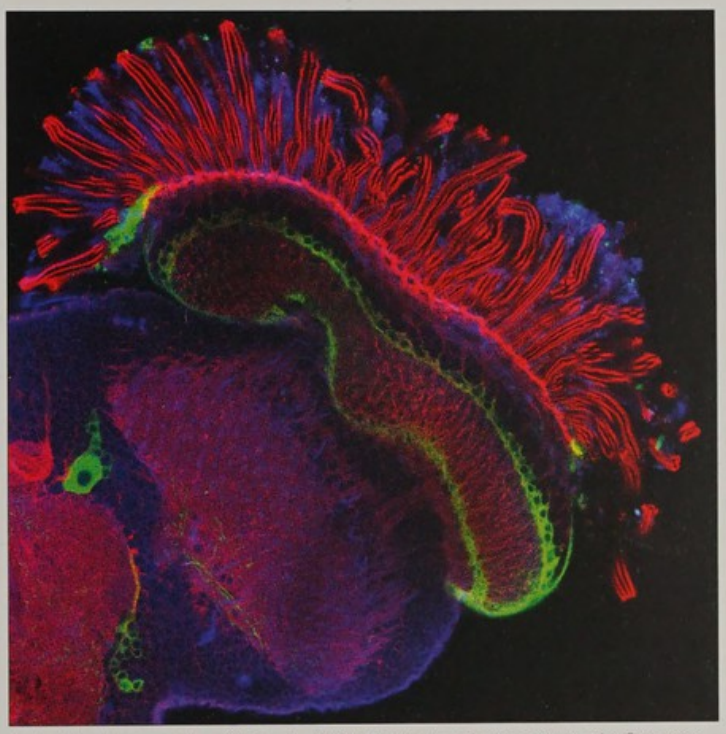
RESEARCH ASSISTANTS/TECHNICIANS

CAROLINA MENDOZA TOPAZ: Maternity Leave (Piddini Group)

RACHEL SEEAR: Technician, Department of Pathology, University of Cambridge (Rawlins Group)

PHD STUDENTS

JESSICA ALSIO: Applying for Postdoctoral positions in Basel, Switzerland (Livesey Group)



Actin-rich photoreceptors (stained with Phalloidin in red) transmit visual information from the eye to the brain, where visual cues are processed and interpreted by neurons in the optic lobe (marked with GFP in green) (Kat Gold, Brand Group, 2012)

ALEXIS BRAUN: PhD Student, Dept of Zoology, University of Cambridge (Piddini Group)

CHIBAWANYE ENE: Medical Student, USA (Livesey Group)

JACK ETHEREDGE: PhD Student, Janelia Farm, Howard Hughes Medical Institute, Chevy Chase, MD, USA (Brand Group)

JONATHAN FRIEDLANDER: Research Scientist, Novogy Inc, Boston USA (Brown Group)

ASTRID GILLICH: Postdoctoral Researcher, Mark Krasnow's group, Stanford University, Palo Alto, CA, USA (Surani Group)

LEONARD GOLDSTEIN: Postdoctoral Research Fellow, Robert Gentleman's group at Genentech, South San Francisco, California (Miska Group)

ETHAN KAUFMAN: Sabbatical year (Miska Group)

HELEN LIGHTFOOT: Postdoctoral Research Fellow at ETH, Zurich (Miska Group)

ROSS NIEUWBURG: Central Database Administrator, RBC, Jersey (St Johnston Group)

VINCENT PASQUE: Postdoctoral Researcher, Dept of Biological Chemistry, University of California, Los Angeles, USA (Gurdon Group)

JOAO PEREIRA: Postdoctoral Researcher, Instituto de Medicina Molecular, Lisbon, Portugal (Livesey Group)

DESTINATIONS OF LEAVERS DURING 2012

MARIA SKAMAGKI: Research Fellow, Sloan Kettering Institute for Cancer Research, New York (Zernicka-Goetz Group)

JULIE WOOLFORD: Sabbatical Year (Miska Group)

TONGTONG ZHAO: Postdoctoral Researcher, Joshua Kaplan's lab, Harvard Medical School, Massachusetts General Hospital, USA (St Johnston Group)

VISITING/VACATION STUDENTS/VISITING RESEARCHERS/VOLUNTEER RESEARCHERS

ELNUR BABAYEV: (Visiting Student) Master's Student, Oxford (Zernicka-Goetz Group)

RAMSAY BOWDEN: (Visiting Clinical Fellow) Academic Clinical Fellow, Addenbrooke's Hospital, Cambridge/Wellcome Trust MPhil Student in Translational Medicine and Therapeutics (Miska Group)

MARIANA DEL ROSARIO RUIZ VELASCO LEYVA: (Visiting Student) Master's Student, UNAM, Mexico (Ahringer Group)

JONATHAN D'GAMA: (Visiting Student) Undergraduate Student, Harvard University, Cambridge, USA (Carazo Salas Group)

BENJAMIN FOSTER: (Vacation Student) Part III Student, Dept Biochemistry, University of Cambridge (Zegerman Group)

CARL FRANZ: PhD Student, Washington University, St Louis, USA (Miska Group)

ANNIKA FRAUENSTEIN: (Erasmus Student) Undergraduate Student, University of Regensburg, Germany (Jackson Group)

DENNIS GASCOIGNE: (Visiting Student) PhD Student, University of Queensland, Australia (Kouzarides Group)

WAJID JAWAID: (Visiting Clinical Researcher) Paediatric Surgical Registrar at Alder Hey Children's Hospital, Liverpool (Rawlins Group)

JOANNA KOSALKA: (Amgen Scholar) Undergraduate Student, University of Nottingham (Zernicka-Goetz Group)

NORAH LIANG: (Vacation Student) Undergraduate Student, Harvard University, Cambridge USA (Livesey Group)

KAYLA McKAVENEY: (Visiting Student) Undergraduate Student, University of Wisconsin-Madison, United States (Miska Group)

MIKEL MCKIE: (Vacation Student) Undergraduate Student, University of Cambridge (Miska Group)

KERRIE MCNALLY: (Amgen Scholar) Undergraduate Student, Sheffield University (Brown Group)

DANIEL O'REILLY: (Amgen Scholar) Undergraduate Student, Trinity College, Dublin (Rawlins Group)

SAMEER PATANKAR: PhD Student, University of Nottingham (Zernicka-Goetz Group)

JAMES PATTERSON: (Vacation Student) Undergraduate Student, University of Cambridge (Miska Group)

GRETA PINTACUDA: (Visiting Student) Graduate Student, Scuola Normale Superiore Pisa, Italy

ENZO POIRIER: (Visiting Student) Master's Student, Ecole Normale Supérieure, Paris (Piddini Group)

AMIE REGAN: (Visiting Student) PhD Student, Department of Medicine, University of Cambridge (Miska Group)

CLARA SLADE OLIVEIRA: (Visiting Student) Research Analyst, Brazilian Enterprise for Agricultural Research, Brazil (Zernicka-Goetz Group)

HUIZHONG SU: (CSSS Visiting Student) Returned to China to complete undergraduate degree (Jackson Group)

SASA SVIKOVIC: (Amgen Scholar) Undergraduate Student, University of Belgrade (Jackson Group)

MARTA TOJO: (Visiting Researcher) Histopathology Department, Addenbrooke's Hospital, Cambridge (Kouzarides Group)

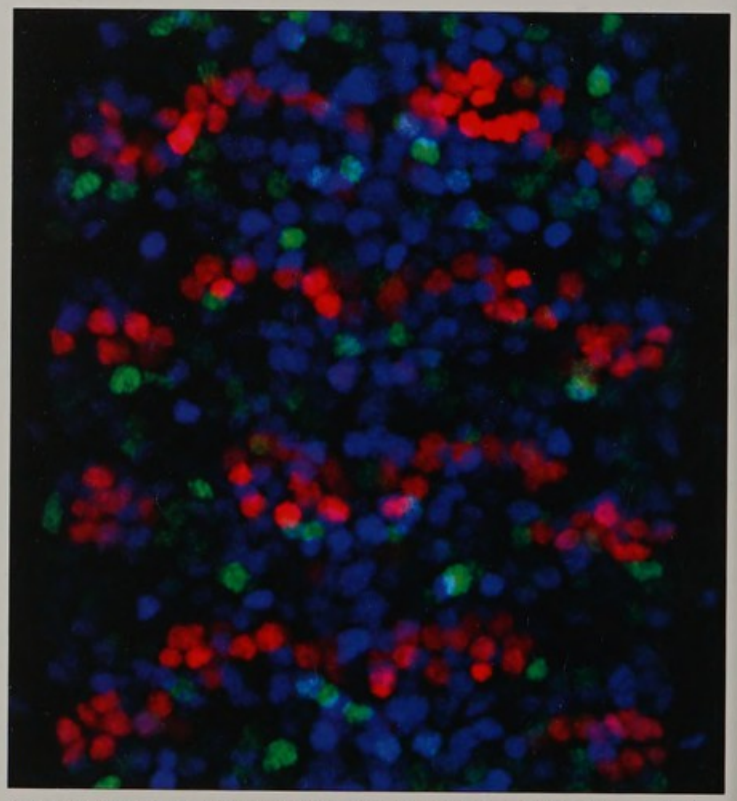
CHRISTOPHER TSUI: (CSSS Student) Undergraduate Student, China (Kouzarides Group)

JESSIE VAN BUGGENUM: (Erasmus Student) Master's Student, Radboud University, Netherlands (Brand Group)

NIKE WALTHER: (Visiting Student) Master's Student, DKFZ, Heidelberg, Germany (Pines Group)

MAXIME WORINGER: (Amgen Scholar) Undergraduate Student, Pierre & Marie Curie University, Paris (Pines Group)

ELODIE ZHANG: (Visiting Student) Master's Student, Pierre & Marie Curie University, Paris (St Johnston Group)



A ventral view projection of 4 segments of a Stage 16 Drosophila embryo ventral nerve cord stained for even skipped (red) cut (blue) and kruppel (green). (David Doupé, Brand Group, 2012)

Here's to the next 21 years! The Gurdon Institute 21st Anniversary Symposium. (photos by James Smith and John Overton)

ACKNOWLEDGEMENTS

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Front cover: Human iPS-derived cerebral cortex neurons (146 days) infected by GFP-expressing lentivirus, DAPI blue; GFP green; Tujl purple. 20x multi-area picture by Leica SP5 confocal. (Roberta Cagnetta, Livesey Group, 2012)

Back cover: Young frogs cloned from albino adult donor tissue, using pigmented recipient eggs (from the pigmented female frog pictured). This work established the principles of genome conservation and demonstrated for the first time that adult cells could be reversed to form 'pluripotent' stem cells. (John Gurdon, circa 1975)

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