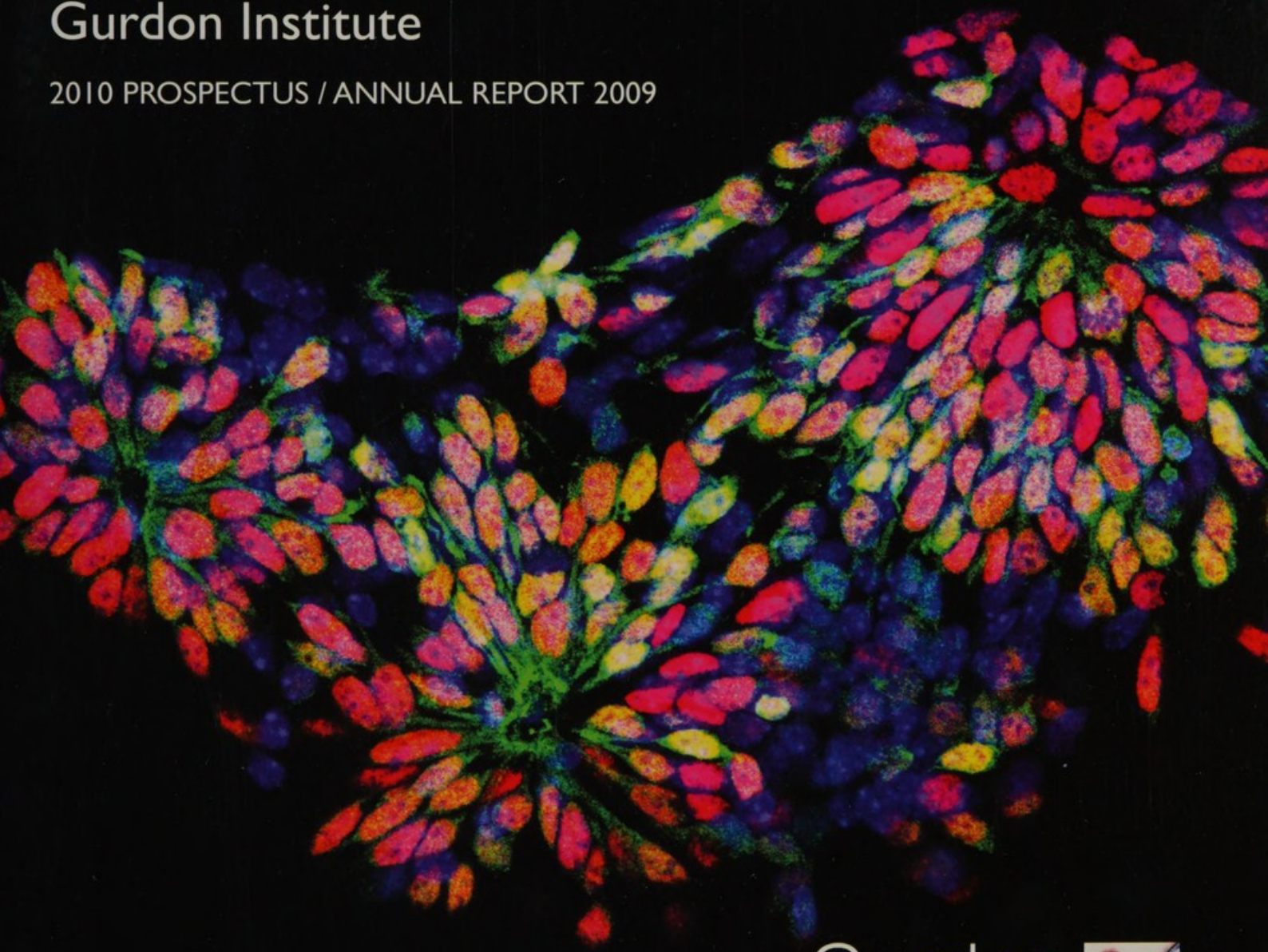
Annual report : 2009/2010 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

The Wellcome Trust/Cancer Research UK Gurdon Institute

2010 PROSPECTUS / ANNUAL REPORT 2009



Gurdon INSTITUTE

PROSPECTUS 2010

ANNUAL REPORT 2009

Gurdon INSTITUTE

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INTRODUCTION

This year has seen a number of changes to the Institute, not the least of which has been the departure of our chairman, Jim Smith, to become Director of the National Institute of Medical Research in London. Since taking over as Jim's successor in January, I have come to appreciate what a fantastic job Jim did in running the Gurdon Institute and what a tough act he will be to follow. We are very grateful to Jim for all his hard work during his eight successful years here, and particularly for his heroic efforts in managing the move to our new building. We shall all miss him (and his group), and wish him every success in his exciting new job running a much larger institute and organising a possible move to an even bigger new building.

The other notable departure was that of Jordan Raff to take up the César Milstein Chair at the Sir William Dunn School of Pathology in Oxford. As well as being an exceptional scientist , Jordan has been a wonderful colleague and friend during his fourteen years in the Institute. He did more than anyone to make this a happy and exciting place to work, and none of us will forget his impersonation of our chief media technician, Juanita, at the Christmas party. Finally, we also said good-bye to our bioinformatician, Mike Gilchrist, who has taken up a group leader position at the National Institute of Medical Research. Mike helped many groups during his seven years in the institute and was a co-author on papers from six different labs. We are very grateful for all Mike's help over the years, and are delighted that his time in the Institute has provided him with a springboard to establish his independent research career.



Farewell to Jim Smith, Jordan Raff and Mike Gilchrist

Although it is sad to see Jim, Jordan and Mike leave, it is a sign of a healthy institute when our group leaders and staff are recruited to top positions elsewhere. It also gives us the opportunity to renew the

The Gurdon Institute (Photograph by A Downie)

scientific environment of the Institute by recruiting new groups leaders, and we are delighted to welcome Phil Zegerman and Emma Rawlins who both started their research groups in the Institute this year. Phil works on the control of DNA replication in yeast (and more recently worms) and came to us after a successful postdoc in John Diffley's group at Clare Hall. Emma is focussing on the role of stem cells in the development and maintenance of the lung in the mouse, and joins us from Brigid Hogan's laboratory at Duke University. We will also shortly be joined by two more group leaders. Eugenia Piddini comes to us from Jean-Paul Vincent's lab at the National Institute of Medical Research and studies cell competition in *Drosophila* wing discs and in fly and mouse stem cells. Rafael is moving to us from a group leader position at ETH in Zurich and is taking a systems biology approach to understand microtubule organisation in fission yeast, funded by a European Research Council Starting Grant. Rafael will be a visiting group leader in the institute before moving to a joint appointment between the Cambridge Systems Biology Centre and the Department of Genetics.

Despite all of the comings and goings, the research in the Institute has continued to flourish, as illustrated by the accompanying group reports. Another mark of our success is the prizes awarded to institute members. Most notably, John Gurdon won the Albert Lasker Basic Medical Research Award with Professor Shinya Yamanaka from Kyoto University for "discoveries concerning nuclear reprogramming", a topic that John started working on as a graduate student and is still actively investigating to this day. Many congratulations as well to John for sharing the Lewis S Rosenstiel award for distinguished work in basic

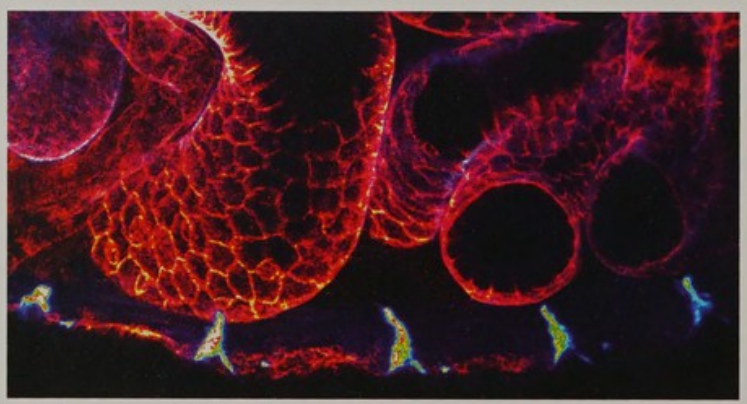
biomedical sciences with Shinya Yamanaka and Irvine Weissman. We are also delighted that Steve Jackson has been named the inaugural BBSRC Innovator of the Year "for his work to turn research on DNA damage and repair into cancer therapies that are now saving the lives of breast and ovarian cancer sufferers."

Our International Scientific Advisory Board made its annual visit to the Gurdon Institute in November. As always, the members of the Board gave us an enormous amount of valuable scientific and strategic advice, and I should like to thank them for all their hard work and support.

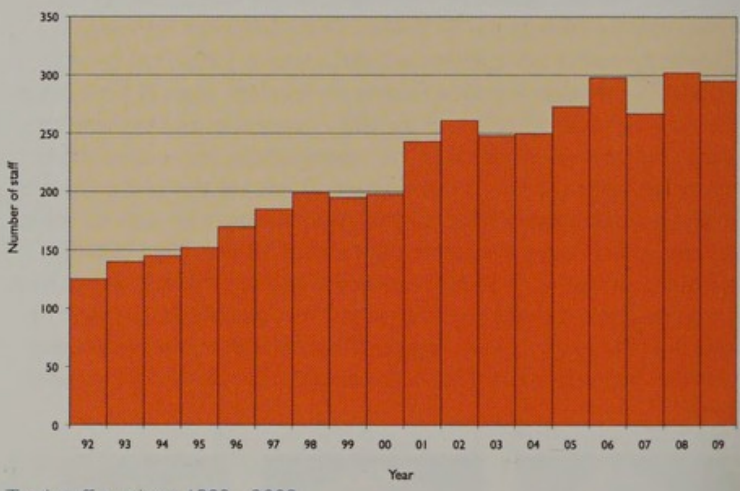
HISTORICAL BACKGROUND

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.



Alpha-integrin subunits in the muscle-epidermal layer and the gut of a *Drosophila* embryo (Jutta Wellman, Brown lab, 2009).



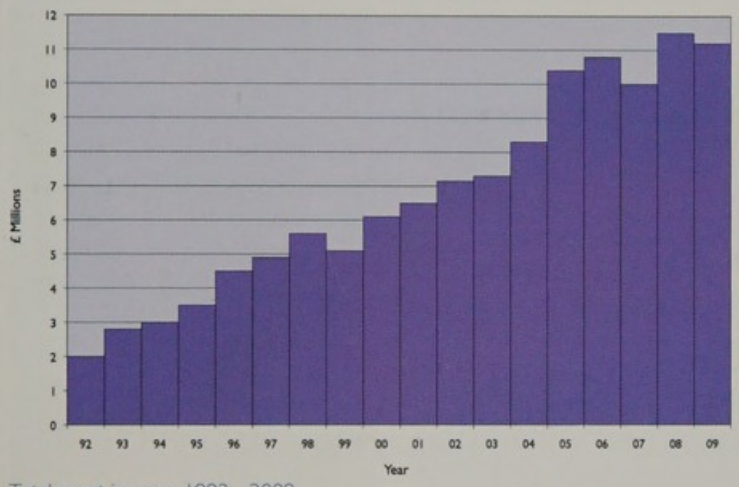
Total staff numbers 1992 - 2009

CENTRAL SUPPORT SERVICES

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

FUNDING

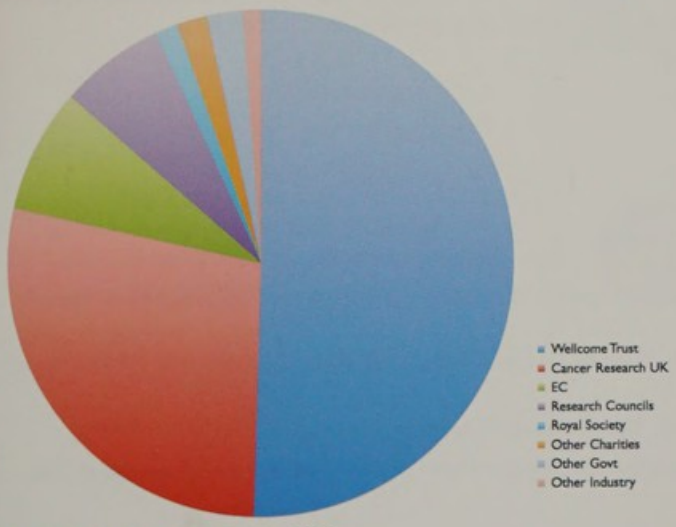
Our two major funding bodies, the Wellcome Trust and Cancer Research UK continue to offer the Institute vital backing in the form of Fellowships, individual programme, project and equipment grants, in addition to our invaluable core funding.



Total grant income 1992 - 2009

Other sources of funding, both direct and indirect, include The European Union, BBSRC, MRC, the Royal Society, the British Council, NIH, the Department of Trade and Industry, the European Molecular Biology Organisation, HFSP, NIH, JDRF, the Isaac Newton Trust, the Association for International Cancer Research, the March of Dimes, the Myrovlytis Trust, Life Technologies Corporation, Astra Zeneca, the Newton Trust, and Volkswagen Stiflung.

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



Grant sources (August 2007 - July 2009)

RETREAT

Our Annual Retreat this year was held at the Barcelo Hinckley Island Hotel on 1st and 2nd October 2009. The event was highly successful. Many Institute members attended and all gained from the experience both scientifically and socially.

The Institute on retreat in Leicestershire, October 2009. (John Overton, Brown group)

David St Johnston

Julie Ahringer

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

Co-workers: Anne Canonge, Ron Chen, Mike Chesney, Nicole Cheung, Yan Dong, Bruno Fievet, Moritz Hermann, Paulina Kolasinska-Zwierz, Sonja Kroschwald, Isabel Latorre, David Rivers, Josana Rodriguez, Christine Turner, Eva Zeiser

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

Cell polarity is important for many of the functions of animal cells, such as migration, axis formation, and asymmetric cell division. Many of the known molecules involved in cell polarity are conserved across animals, however, the mechanisms by which these function are not well understood. We use the one-celled *C elegans* embryo to investigate the polarity cue, its reception, and how polarisation leads to downstream events such as asymmetric spindle positioning. One current area of work is investigating the roles of phosphoinositides in spindle positioning. We are also undertaking a large number of genetic interaction RNAi screens to identify new cell polarity genes and build models. We study functions of these genes using a range of techniques, including live cell imaging, genetics, and biochemistry.

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

Panbianco C, Weinkove D, Zanin E, Jones D, Divecha N, Gotta M and Ahringer J (2008) A Casein Kinase 1 and PAR proteins regulate asymmetry of a PIP2 synthesis enzyme for asymmetric spindle positioning. **Developmental Cell** 15, 198-208

Boutros M and Ahringer J (2008) The art and design of genetic screens: RNA interference. **Nature Reviews Genetics** 9, 554-66

Rivers DM, Moreno S, Abraham M and Ahringer J (2008) PAR proteins direct asymmetry of the cell cycle regulators Polo-like kinase and Cdc25. **Journal of Cell Biology** 180, 877-885

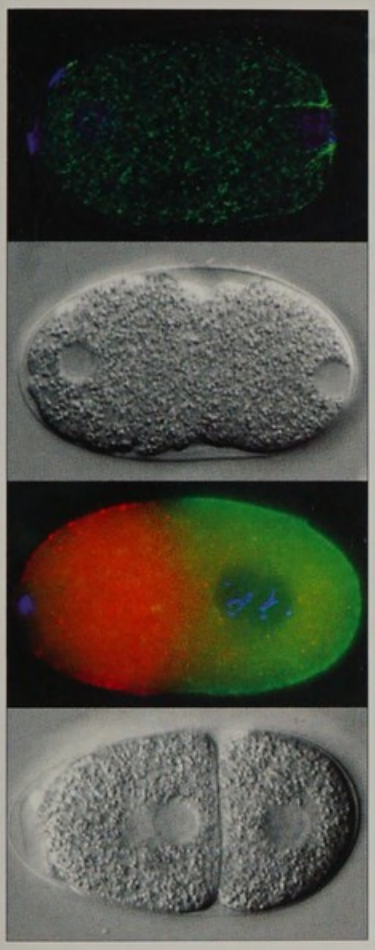


Fig. 1 Polarity is induced by an unknown signal requiring centrosomes and microtubules (top panel; microtubules in green, DNA in blue), leading to PAR protein asymmetry (third panel; red PAR-3, green PAR-2, blue DNA), which directs an asymmetric first cell division (bottom panel; anterior cell is larger than posterior cell).

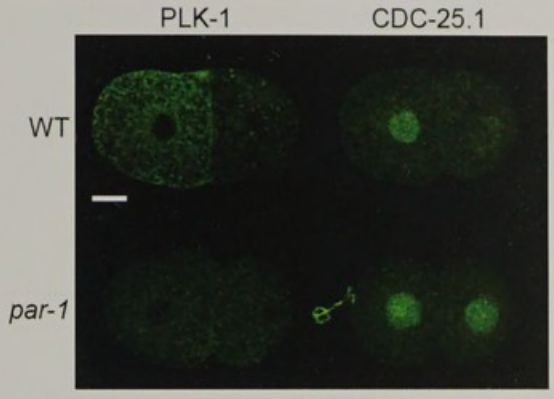


Fig. 2 PAR proteins control cell cycle timing through generating asymmetry of the key cell cycle regulators Polo-like kinase PLK-1 and the CDK phosphatase CDC-25.1

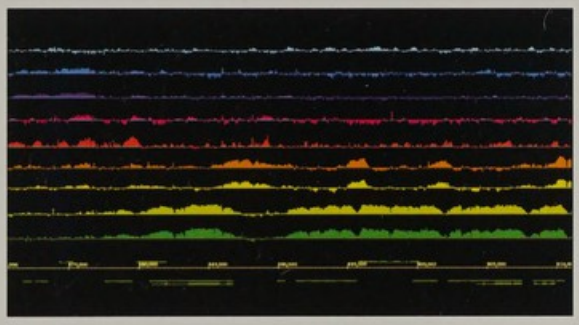


Fig. 3 Genome-wide identification of binding sites for chromatin regulators and modifications using chromatin immunoprecipitation

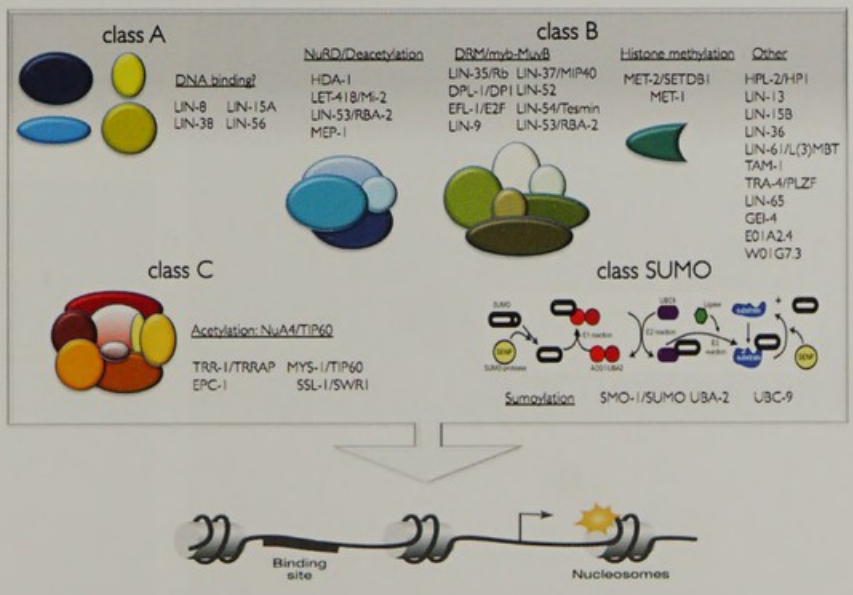
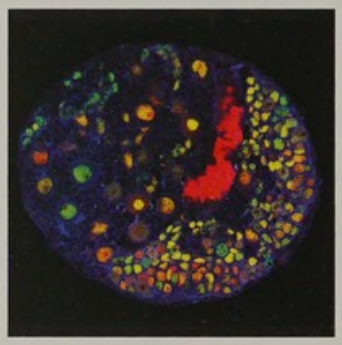


Fig. 4 Many synMuv proteins are homologs of chromatin regulators with histone modification or nucleosome remodelling activity and implicated in human disease.

Andrea Brand

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

Co-workers: Elizabeth Caygill, James Chell, Melanie Cranston, Catherine Davidson, James Dods, Boris Egger, Katrina Gold, Anne Pelissier, Tony Southall, Pauline Spéder, Alyson Thompson, Christine Turner, Jakob von Trotha, Pao-Shu (Paul) Wu



Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is a key step in the therapeutic use of stem cells to repair tissues after damage or disease. We are investigating the genetic networks that regulate stem cells in the *Drosophila* nervous system. Stem cells can divide symmetrically to expand the stem cell pool, or asymmetrically to self-renew and generate a daughter cell destined for differentiation. During asymmetric division, cell fate determinants are partitioned from the neural stem cell to its daughter. We showed that one determinant, the transcription factor Prospero, is a binary switch between self-renewal and differentiation. We identified Prospero's targets throughout the genome and showed that Prospero represses genes required 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.

Symmetrically dividing neuroepithelial stem cells are found in the optic lobe of the *Drosophila* brain, where they convert to asymmetrically dividing neuroblasts. We are identifying the molecular switches mediating this transition by isolating small groups of neuroepithelial cells and comparing their transcriptional profiles to neuroblasts. We find Notch is a key regulator of symmetric and asymmetric division, and that loss of Notch causes premature differentiation at the expense of neuroepithelial stem cells. 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.

For further information, please see Brand lab home page:

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

Inset left: Neural stem cells in a *Drosophila* larval brain lobe; on the left, the central brain neuroblasts, on the right, the precursors of the developing visual system (Deadpan in red, GFP in green and Discs large in blue).

Southall TD and Brand AH (2010) Multiple transcription factor binding identifies neural stem cell gene regulatory networks. **EMBO J** [in press]

Monier B, Pelissier A, Brand AH and Sanson B (2009) Asymmetric myosin II-dependent forces generate cell sorting at developmental boundaries. **Nature Cell Biology** [in press]

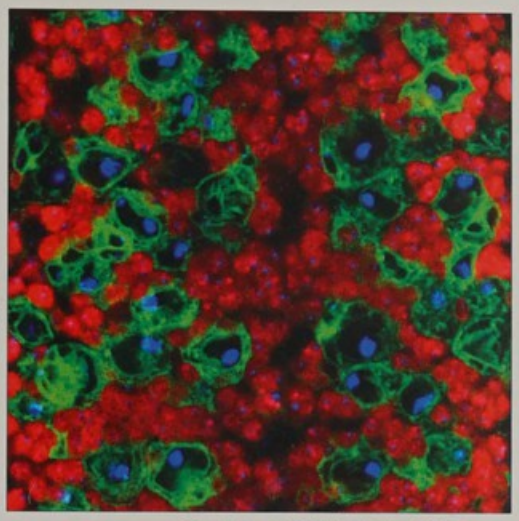
von Trotha JW, Egger B and Brand AH (2009) Cell proliferation in the *Drosophila* adult brain revealed by clonal analysis and BrdU labeling. **Neural Development** 4, 9

Southall TD, Egger B, Gold KS and Brand AH (2008) Regulation of self-renewal and differentiation in the *Drosophila* nervous system. **Cold Spring Harbor Symp Quant Biol** LXXIII, 523-528

Choksi SP, Southall T, Bossing T, Edoff K, de Wit E, van Steensel B, Micklem G and Brand AH (2006) Prospero acts as a binary switch between self-renewal and differentiation in *Drosophila* neural stem cells. **Developmental Cell** 11, 775-789

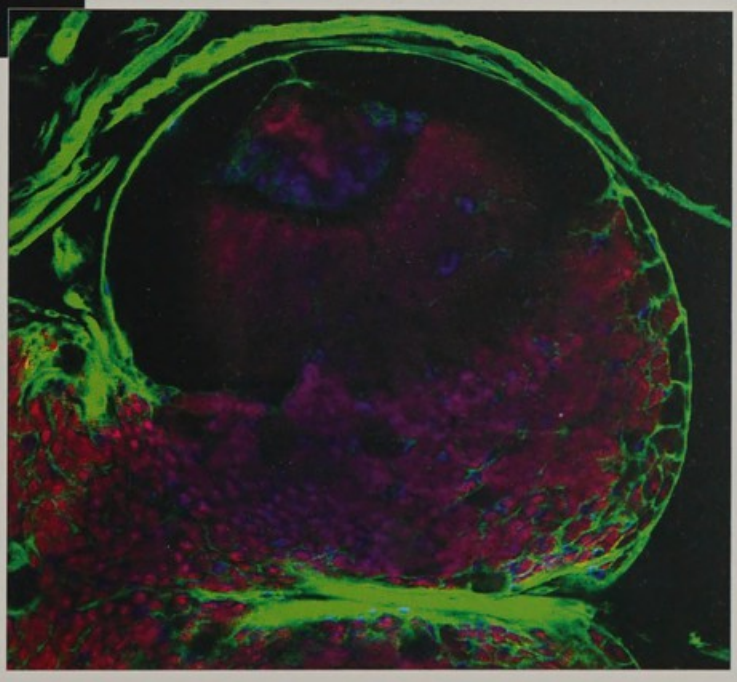
For complete list of this lab's publications since the last report, see numbers 9, 12, 30, 42, 50, 59, 60, 61, 62, 63, 73 and 76 on pp 50-53

Expression of the temporal transcription factor, Castor (green) in a late stage *Drosophila* embryo, neurons labeled in blue (Elav).

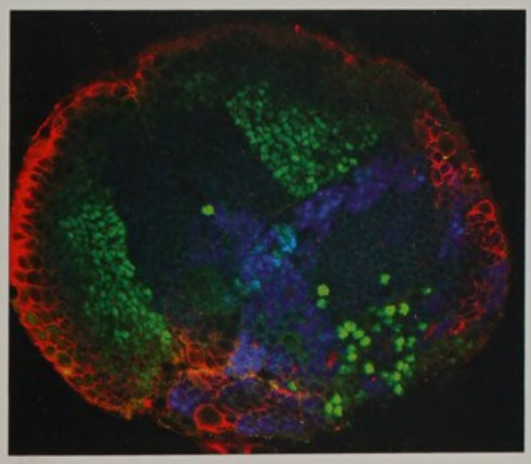


Grainyhead-GAL4 driving GFP in neural stem cells (green). Neuronal nuclei are labelled in red (ElaV), and nucleoli in blue (Fibrillarin).

Glia surrounding the optic lobe of the larval brain, labelled in green (membrane) and blue (nuclei), with neurons in magenta.



Ganglion mother cells in the larval brain labelled for Prospero (blue), Phalloidin (red) and GFP (green).



Nick Brown

Molecular analysis of morphogenesis

Co-workers: Natalia Bulgakova, Jonathan Friedlander, Qin Hu, Sven Huelsmann, Yoshiko Inoue, Benjamin Klapholz, Sushmita Maitra, John Overton, Jutta Wellmann

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

We use the genetics of the fruit fly *Drosophila* to elucidate integrin function within the developing animal, and to identify the proteins that work with integrins. In this way, we aim to discover how integrins perform such distinct roles at different times and places during development. For example, in the developing embryo a major role is linking muscles to epidermal tendon cells (Fig 1). In the epithelial cells that give rise to the adult body, integrins form tight clusters (Fig 2), which are bound to the basement membrane, which forms an insulating layer around this tissue. On the basal surface of another epithelial cell layer, integrins are essential for the organisation of the actin cytoskeleton into ordered parallel arrays (Fig 3). We are discovering that some integrin-associated proteins are just needed for specific developmental functions, and that the integrins used to mediate adhesion can change during the morphogenesis of a tissue.

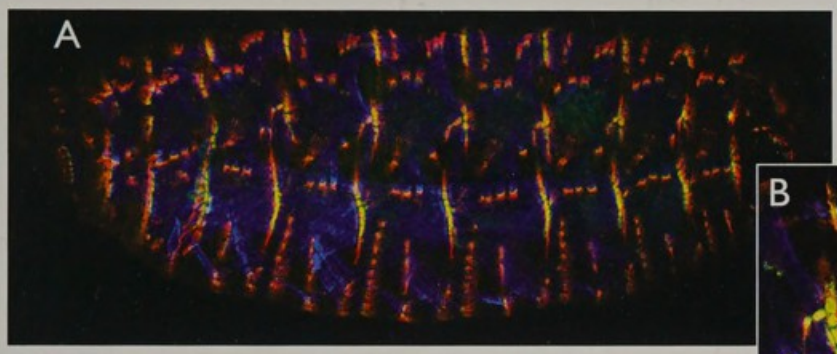
Delon I and Brown NH (2009) The integrin adhesion complex changes its composition and function during morphogenesis of an epithelium. **J Cell Sci** 122, 4363-4374

Urbano JM, Torgler CN, Molnar C, Tepass U, López-Varea A, Brown NH, de Celis JF and Martín-Bermudo MD (2009) *Drosophila* laminins act as key regulators of basement membrane assembly and morphogenesis. **Development** 136, 4165-4176

Brown NH (2008) Spectraplakins: the cytoskeleton's Swiss army knife. **Cell** 135, 16-18

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

For complete list of this lab's publications since the last report, see numbers 10, 16 and 71 on pp 50-53



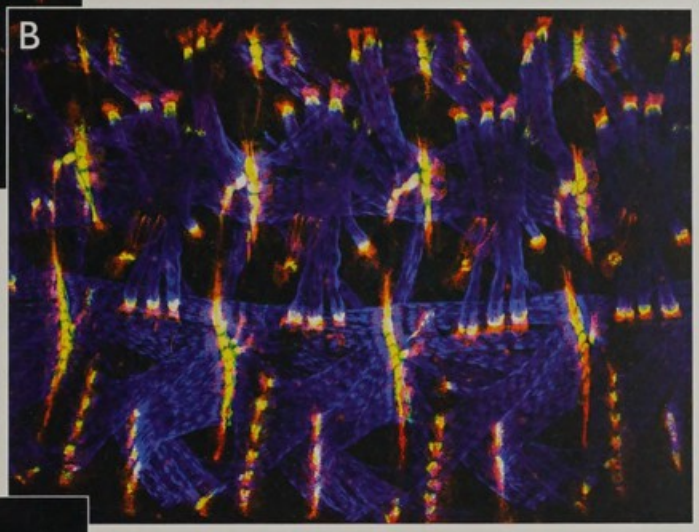


Fig 1A and B: A major site of integrin function within the developing embryo is the muscle attachment site. Muscle myosin (blue) shows the contractile apparatus within the muscles. Integrins and their associated intracellular proteins, such as talin (green), are concentrated at the muscle ends, where they attach to specialised epidermal cells, which express high levels of the cytoskeletal linker Shot (red). A shows the whole embryo, while B shows an enlargement.

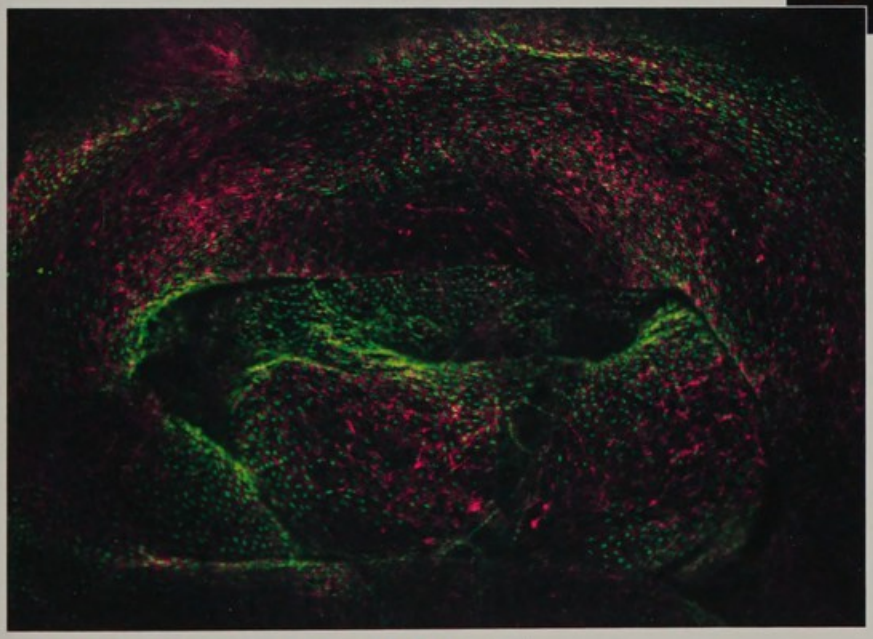


Fig 2: Integrin adhesive sites (green) and the associated actin cytoskeleton (purple) on the basal surface of an imaginal disc epithelia

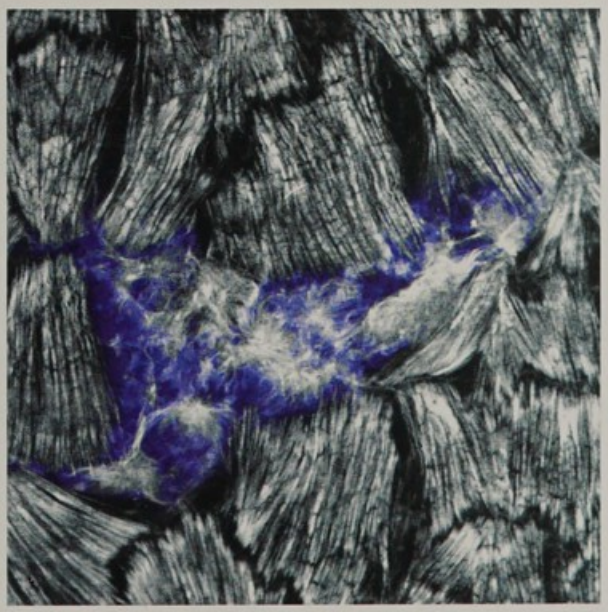
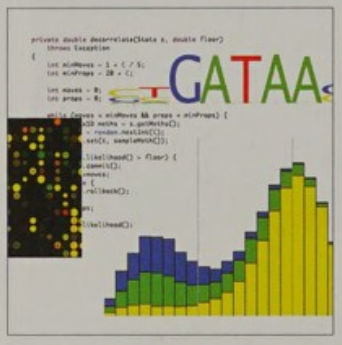


Fig 3: Integrin function is required to organise actin (white) into parallel arrays; cells lacking integrin (in blue) have disorganised actin.

Thomas Down

Transcription informatics

Co-workers: Siarhei Maslau



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 exploiting this technology 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.

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

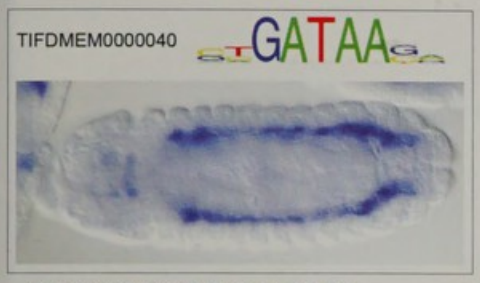
Down TA, Rakyan VK, Turner DJ, Flicek P, Li J, Kulesha E, Graf S, Johnson N, Herrero J, Tomazou EM, Thorne NP, Backdahl L, Herberth M, Howe KL, Jackson DK, Miretti MM, Marioni JC, Birney E, Hubbard TJP, Durbin R, Tavare S and Beck S (2008) A Bayesian deconvolution strategy for immunoprecipitation-based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

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

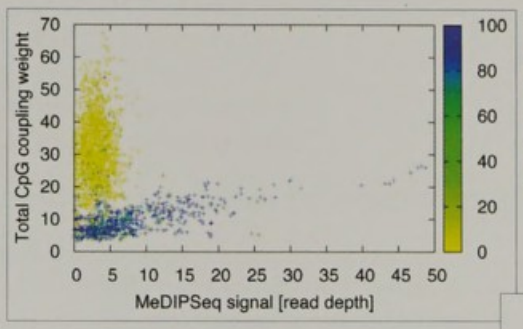
Eckhardt F, Lewin J, Cortese R, Rakyan VK, Attwood J, Burger M, Burton J, Cox TV, Davies R, Down TA, Haefliger C, Horton R, Howe K, Jackson DK, Kunde J, Koenig C, Liddle J, Niblett D, Otto T, Pettett R, Seemann S, Thompson C, West T, Rogers J, Olek A, Berlin K and Beck S (2006) DNA methylation profiling of human chromosomes 6, 20 and 22. **Nature Genetics** 38, 1378-1385

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

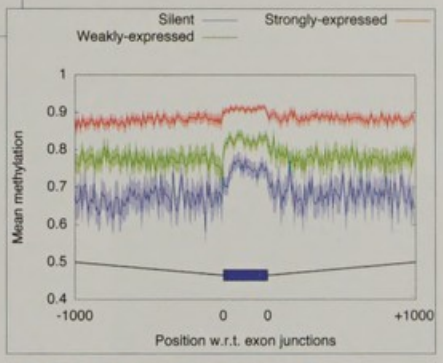
For complete list of this lab's publications since the last report, see numbers 11, 14, 31, 38 and 49 on pp 50-53



A regulatory motif discovered in the *Drosophila* genome, and the embryonic expression pattern of a gene regulated by this motif. (P Tomancak et al, Genome Biology 3:research0088)

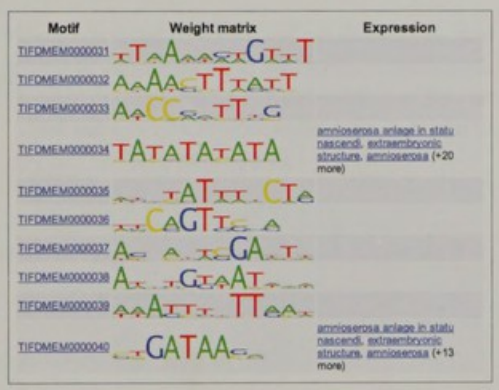


The Methyl DNA Immunoprecipitation (MeDIP) technique can be used to quantify the methylation state of genomic DNA on a large scale. In methylated regions (coloured blue), signal correlates with the density of CpG dinucleotides..



Multiple epigenetic marks "paint" exons in the genome. In the case of DNA methylation (shown here) the marking of exon boundaries is remarkably sharp, and appears to be independent of transcription. (single-base methylation data from Lister et al, **Nature** 462, 315-322).

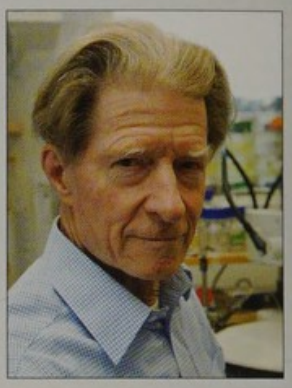
Visualisation of DNA methylation state using the Ensembl genome browser, with yellow indicating unmethylated sequences and blue indicating highly methylated regions.



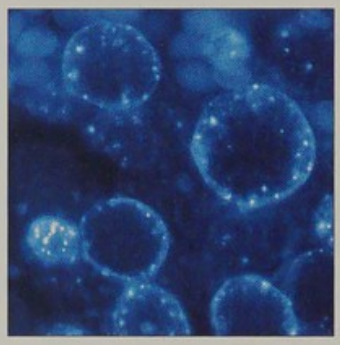
The BioTIFFIN interface for browsing regulatory sequence motifs.

John Gurdon

Reprogramming of gene expression by nuclear transfer



Co-workers: Carolina Åstrand, Dilly Bradford, Nigel Garrett, Richard Halley-Stott, Jo-Anne Johnson, Jerome Jullien, Kei Miyamoto, Patrick Narbonne, Vincent Pasque, Ilenia Simeoni



When the nucleus of a somatic cell is transplanted to an enucleated egg, the resulting embryos sometimes develop into entirely normal adults. More often, the embryos develop abnormally, but in many of these cases they contain a range of functional tissues wholly unrelated to that from which the transplanted nucleus was taken. In all these instances, a major change of gene expression has been induced by exposing the nucleus to egg cytoplasm. We aim to identify the molecules and mechanisms used by an egg to "reprogram" a somatic nucleus.

A second question that we address asks why the nucleus of a differentiated cell is much more resistant to the reprogramming activity of an egg than is the nucleus of an embryonic cell. What is the basis of the resistance, a property that is believed to be responsible for normal cells and their daughters remaining in their chosen pathway of differentiation during development and in adult life?

To analyse the basis of both the ability of eggs to reprogram nuclei and the resistance of the nuclei of specialised cells to this activity, we transplant nuclei from differentiated cells of both amphibia and mammals to the germinal vesicle of oocytes of *Xenopus*. Oocytes have the special property of directly switching the transcriptional profile of an adult somatic cell nucleus to that of an embryo or stem cell. They do this directly with no DNA synthesis or cell division and in the absence of protein synthesis; within a few hours, transcripts of Oct4, Sox2, and other stem cell marker genes increase by a factor of up to 100 times. We use antibodies to reduce the content of individual proteins of an oocyte to test the function of these proteins. We remove proteins from somatic nuclei before transplantation to identify gene repressors in somatic cells. We find that the oocyte can activate a wide range of genes in different lineages, and has a general gene derepressing activity likely to be characteristic of very early embryos. This identification of natural molecules and mechanisms that promote and inhibit gene reprogramming in somatic cells may eventually contribute to procedures for cell replacement in humans.

Gurdon JB (2009) Nuclear reprogramming in eggs. **Nature Medicine** 15, 1141-1144

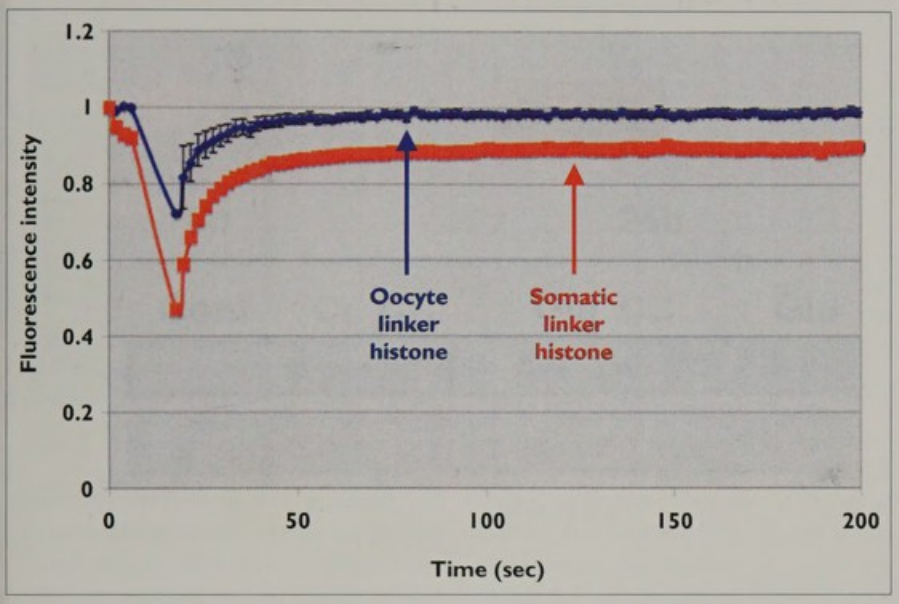
Biddle A, Simeoni I and Gurdon JB (2009) *Xenopus* oocytes reactivate muscle gene transcription in transplanted somatic nuclei independently of myogenic factors. **Development** 136, 2695-2703

Gurdon JB and Melton DA (2008) Nuclear reprogramming in cells. **Science** 322, 1811-1815

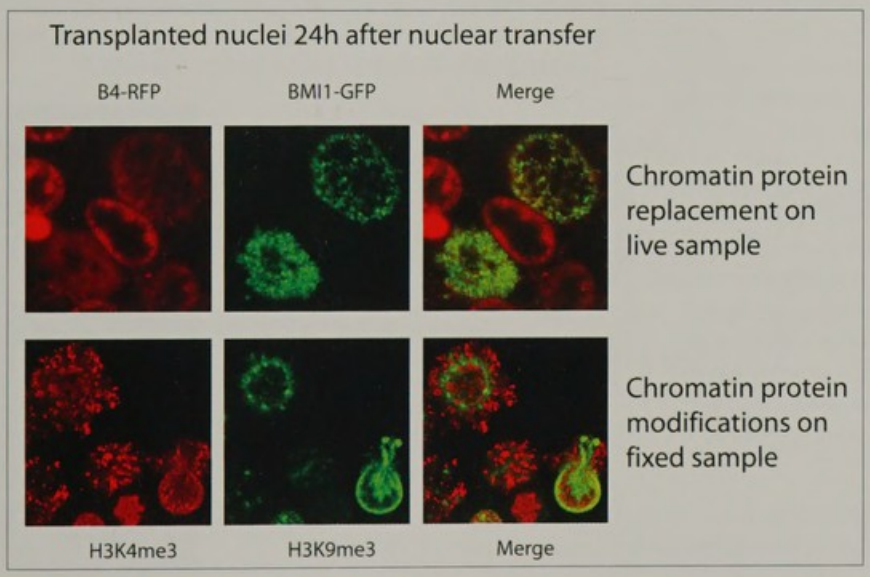
Ng RK and Gurdon JB (2008) Epigenetic inheritance of cell differentiation status. **Cell Cycle** 7:9, 1173-7

Gurdon J and Murdoch A (2008) Nuclear Transfer and iPS may work best together. Meeting Report, **Cell Stem Cell** 2, 135-138

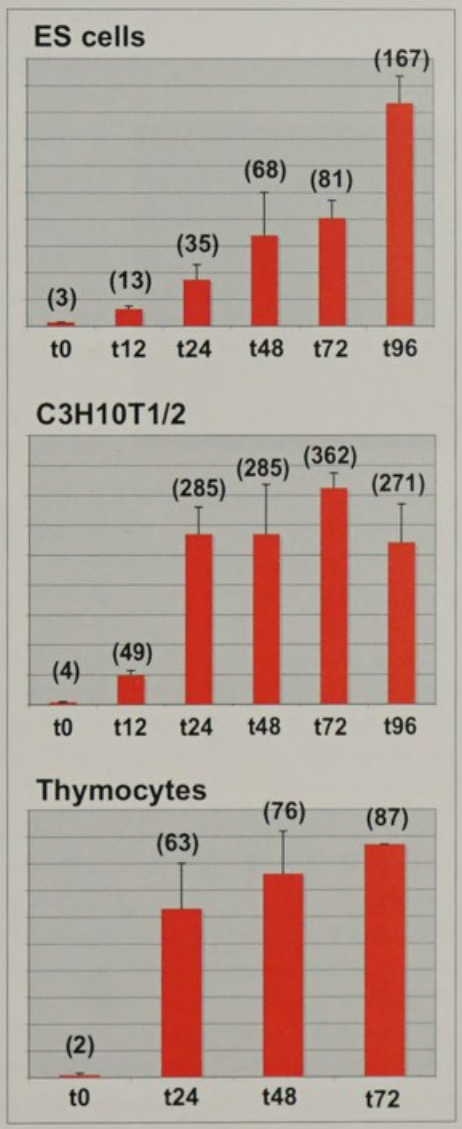
Gurdon JB (2008) Primate therapeutic cloning in practice. **Nature Biotechnology** 26(1), 64-65



FRAP (Fluorescence Recovery After Photobleaching). Oocyte-specific linker histones are fully mobile in transplanted nuclei.



Proteins are rapidly taken up by somatic nuclei transplanted to oocytes. The oocyte-specific linker histone is marked in red (B4-RFP). BMI 1-GFP is another oocyte protein marked in GFP.

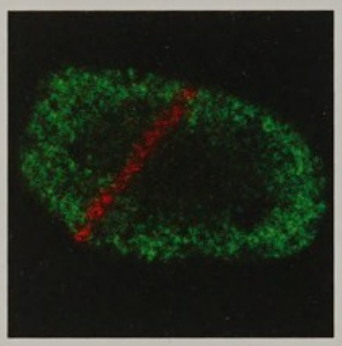


Accurate quantitation of induced MyoD transcripts per nucleus after nuclear transfer to oocytes.

Steve Jackson

Maintenance of genome stability

Co-workers: Linda Baskcomb, Rimma Belotserkovskaya, Melanie Blasius, Ross Chapman, Julia Coates, Kate Dry, Sonja Flott, Josep Forment, Yaron Galanty, Simona Giunta, Ilaria Guerini, Jeanine Harrigan, Pablo Huertas, Abderrahmane Kaidi, Natalia Lukashchuk, Kyle Miller, Tobias Oelschlägel, Sophie Polo, Helen Reed, Jorrit Tjeertes



Our work focuses on the DNA-damage response (DDR): the set of events that optimises cell survival and genomic integrity by detecting DNA damage, signalling its presence and mediating its repair. The importance of the DDR is underscored by defects in it being associated with neurodegenerative disease, immunodeficiency, premature ageing, infertility and cancer (1).

By working with both yeast and human cells, we are identifying new DDR factors, defining the functions of known DDR components, assessing how the DDR is affected by chromatin structure, and learning how DDR events are regulated. Much of this work is focussed on how the DDR is controlled by protein post-translational modifications. For example, by carrying out a large-scale screen in human cells, we recently found that acetylations on histone H3 lysine 9 (H3K9) and H3K56 are rapidly and reversibly reduced in response to DNA damage (2). Also, building on our previous work on the yeast Sae2 protein, we found that its human counterpart, CtIP, is phosphorylated by cyclin-dependent kinases to control DNA-double strand break (DSB) resection, thus promoting ATR signalling and DSB repair (3). Furthermore, with our colleagues, we recently defined the structure and biochemical properties of the N-terminus of the NBS1 protein, thus explaining how this region mediates phospho-dependent protein-protein interactions that control DSB repair and signalling in organisms ranging from yeast to man (4). Over the coming year, we will explore how the above post-translational modifications, together with others that we have very recently uncovered, control various aspects of the DDR.

1) Jackson SP and Bartek J (2009) The DNA-damage response in human biology and disease. **Nature** 461, 1071-1078

2) Tjeertes JV*, Miller KM* **, and Jackson SP** (2009) Screen for DNA-damage-responsive histone modifications identifies H3K9Ac and H3K56Ac in human cells. **EMBO Journal** 28, 1878-1889 (*authors contributed equally; **co-corresponding authors)

3) Huertas, P and Jackson, SP (2009) Human CtIP mediates cell cycle control of DNA end resection and double strand break repair. **Journal of Biological Chemistry** 284, 9558-9565

4) Lloyd J*, Chapman JR*, Clapperton JA, Haire LF, Hartsuiker E, Li J, Carr AM, Jackson SP** and Smerdon SJ** (2009) A supra-modular FHA/BRCT-repeat architecture mediates Nbs1 adaptor function in response to DNA-damage. **Cell** 139, 100-111 (*authors contributed equally; **co-corresponding authors).

For complete list of this lab's publications since the last report, see numbers 2, 18, 21, 32, 33, 44, 58 and 70 on pp 50-53

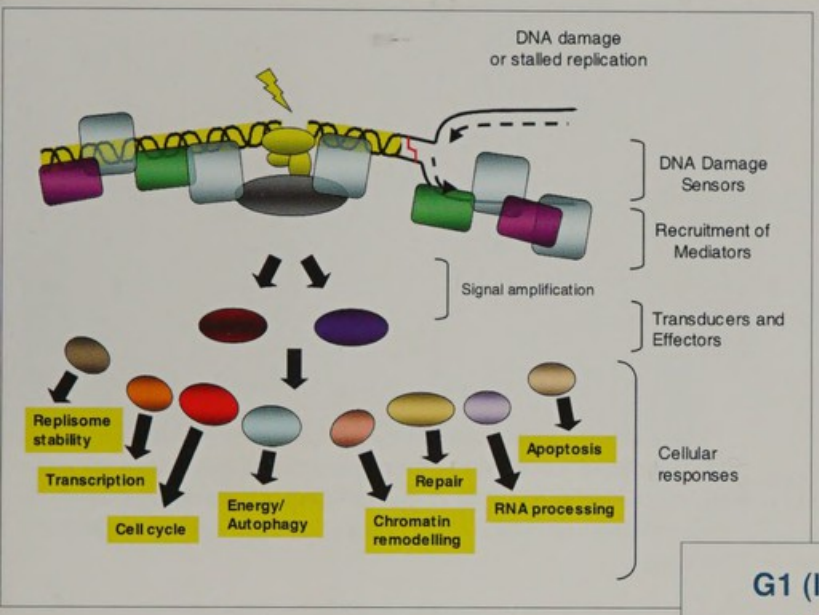


Fig 1: Model for the DNA damage response. Various sensor proteins recognise the presence of a lesion in the DNA, which can lead to replication stalling. These sensors initiate signalling pathways that have an impact on a wide variety of cellular processes.

Fig 3: Crystal structure of the N-terminus of the S pombe Nbs1 protein. The FHA, BRCT1, linker and BRCT2 domains are coloured red, green, magenta and blue, respectively. Image provided by our collaborator Professor Stephen Smerdon (NIMR, London).

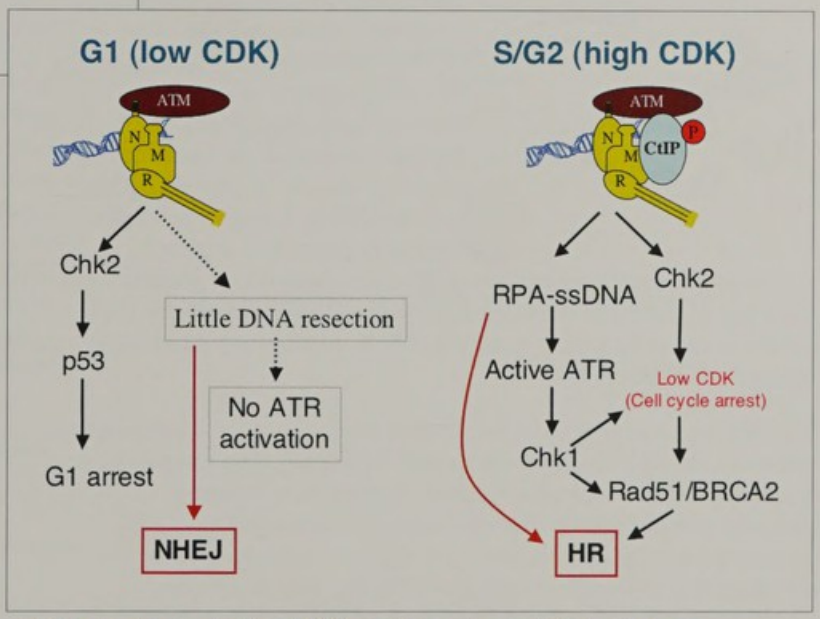
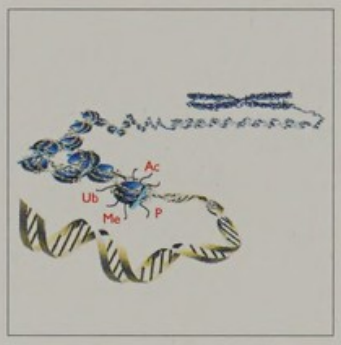


Fig 2: Cell-cycle coordination of DSB signalling and repair. In G1, cells carry out little DSB resection, leading to activation of ATM-dependent signalling and DSB repair by non-homologous end-joining (NHEJ). In S and G2 cells, ATM signalling also occurs but in these circumstances, CtIP – in conjunction with the MRE11-RAD50-NBS1 (MRN) complex – promotes DSB processing to generate single-stranded DNA (ssDNA) that triggers ATR activation and leads to repair by homologous recombination (HR). CtIP is phosphorylated on Thr847 by cyclin-dependent. kinases (CDKs)

Tony Kouzarides

Function of chromatin modifications and their role in cancer

Co-workers: Hatice Akarsu, Andrew Bannister, Till Bartke, Gonçalo Castelo-Branco, Maria Christophorou, Alistair Cook, Mark Dawson, Cynthia Hill, Antonis Kirmizis, Nikki Parsons, Helena Santos Rosa, Peter Tessarz, Emmanuelle Viré, Blerta Xhemalce



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

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

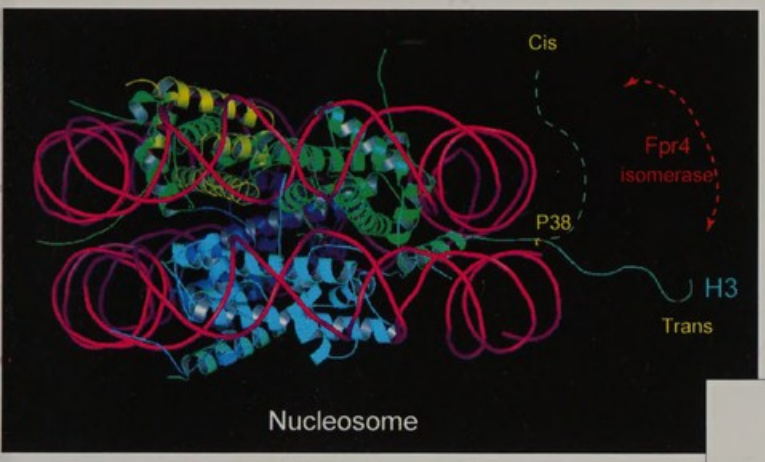
A major drive at the moment is to identify new histone modifications, as the pathways that control them may well be deregulated in cancer. In recent years, we have identified several novel pathways that modify chromatin such as arginine deimination, proline isomerisation, tyrosine phosphorylation and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

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

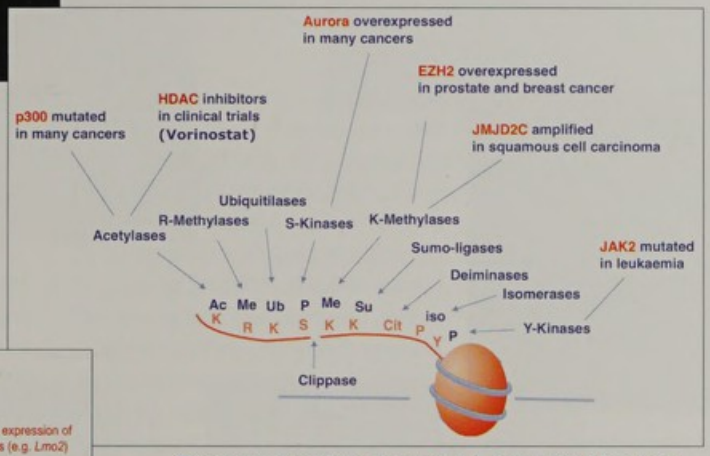
Kirmizis A, Santos-Rosa H, Penkett, CK, Singer MA, Green RD, Kouzarides T (2009) Distinct transcriptional outputs associated with mono- and di-methylated histone H3 arginine 2. **Nature Structural & Molecular Biology** 16, 449-51

Santos-Rosa H, Kirmizis A, Nelson CJ, Bartke T, Saksouk N, Cote J, Kouzarides T (2008) Histone H3 tail clipping regulates gene expression. **Nature Structural & Molecular Biology** 16, 17–22

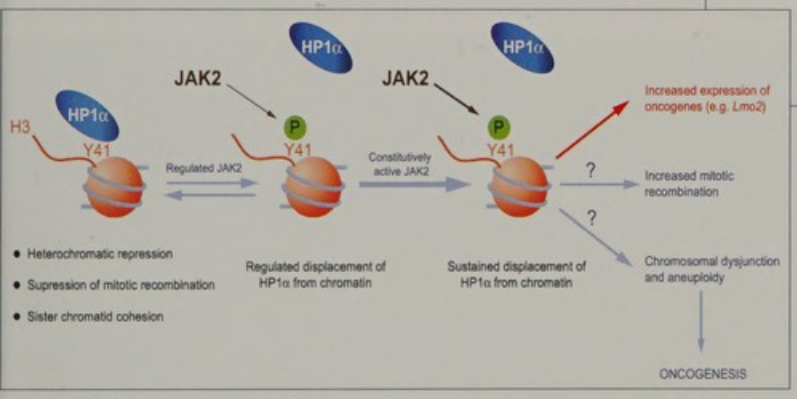
For complete list of this lab's publications since the last report, see numbers 7, 15, 34, 37 and 54 on pp 50-53



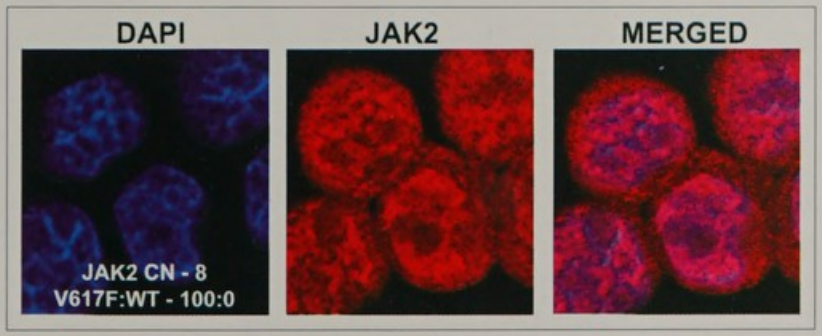
Isomerisation of proline 38 in the histone H3 tail has the potential to bend the tail and affect chromatin structure.



Chromatin-modifying enzymes are deregulated in cancer.



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

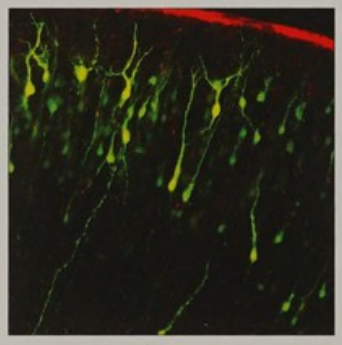


JAK2 goes nuclear: JAK2 is both cytoplasmic and nuclear in HEL cells containing mutant JAK2.

Rick Livesey

Development of the cerebral cortex: stem cells and circuits

Co-workers: Sarrita Adams, Jessica Alsio, Therese Andersson, Juliet Barrows, Chiba Ene, Joao Pereira, Stephen Sansom, Yichen Shi, James Smith, Uruporn Thammongkol



The cerebral cortex is the part of the mammalian brain that integrates sensations, executes decisions and is responsible for cognition and perception. Altered cortical development results in a range of human diseases, including epilepsy, autism, cerebral palsy and a range of learning disabilities. Understanding cortical development is essential for understanding the pathogenesis of human neurodevelopmental disorders and the rational design of neural repair strategies in adults. Research in the lab is focussed on understanding the molecular mechanisms controlling how this essential part of the brain assembles during embryonic development. We apply that understanding to studying how neurodevelopmental disorders arise in humans and also to developing methods to manipulate neural stem cells for therapeutic purposes.

Our work has three main themes: cortical stem cell biology, cortical circuit formation and neurodevelopmental disorders. All of the neurons in the cortex are generated from a population of multipotent neocortical stem and progenitor cells. Much of the research in the lab centres on the biology of neocortical stem cells and in particular how neocortical stem cells produce layer-specific neurons in order (the timing problem) and for the correct area (the patterning problem). Having produced all of the neurons, they must assemble highly specific circuits so that the cortex functions correctly. How this happens is currently poorly understood and under active investigation in the lab. Problems with cortical development lead directly to neurodevelopmental disorders and we are currently studying the developmental pathology of neurodevelopmental conditions in both animal models and human stem cell culture systems, with particular interests in Down syndrome and autistic spectrum conditions.

Inset left: Cortical neurons (green, GFP) migrating and differentiating in cultured slices of developing cerebral cortex.

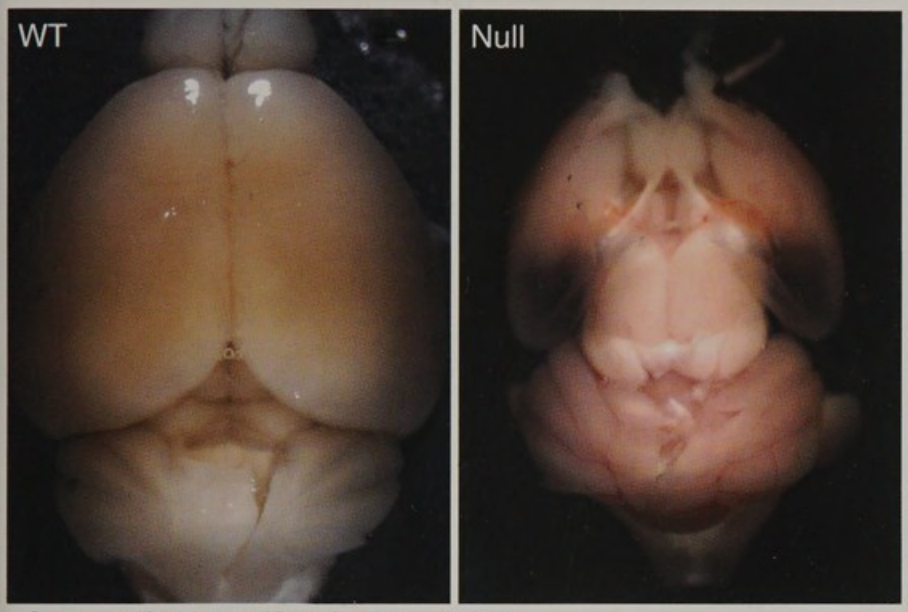
Sansom SN, Griffiths DS, Faedo A, Kleinjan DJ, Ruan Y, Smith J, van Heyningen V, Rubenstein JL and Livesey FJ (2009) The level of the transcription factor Pax6 is essential for controlling the balance between neural stem cell self-renewal and neurogenesis. **PLoS Genetics**, 5, e1000511

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

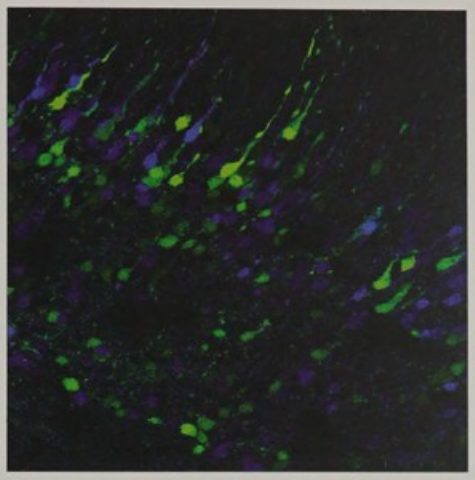
Yano K, Subkhankulova T, Livesey FJ, Robinson HP (2006) Electrophysiological and gene expression profiling of neuronal cell types in mammalian neocortex. **J. Physiol.**, 575:361-375

Sansom SN, Hebert JM, Thammongkol U, Smith J, Nisbet G, Surani MA, McConnell SK and Livesey FJ (2005) Genomic characterisation of a Fgf-regulated gradient-based neocortical protomap. **Development** 132: 3947-61

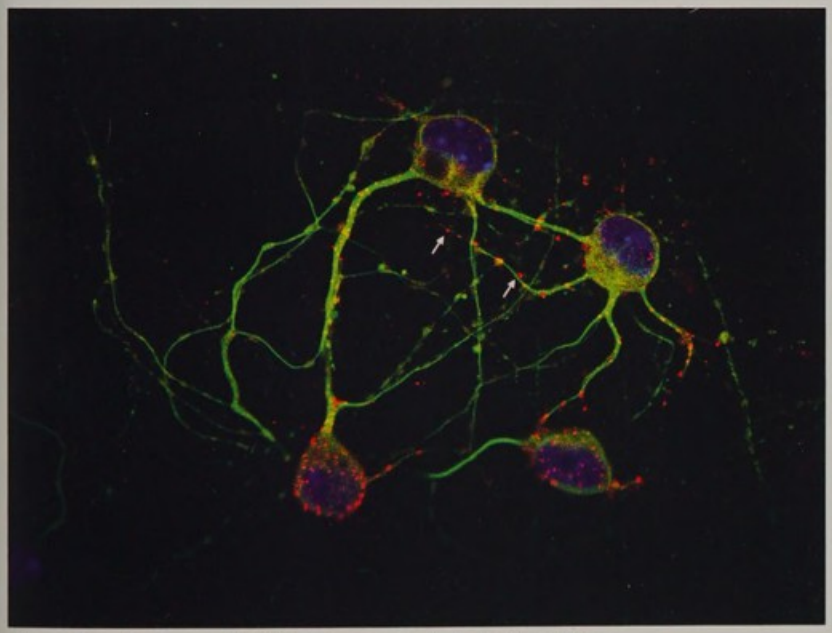
For a complete list of this lab's publications since the last report, see numbers 13, 52 and 53 on pp 50-53



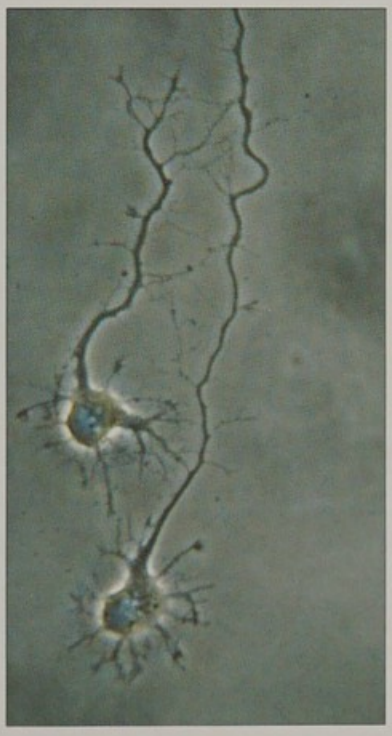
Cortex-specific deletion of Dicer function results in the formation of a smaller, thinner cerebral cortex in the null (Null) compared to the wildtype (WT) adult brain



GFP and CFP expressing cortical neurons in Brainbow/Emx1-Cre mice



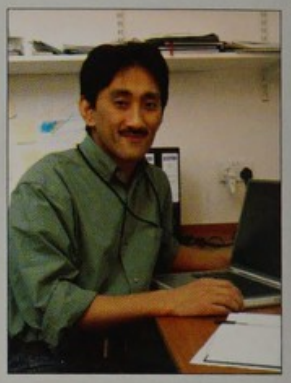
Formation of synapses (PSD95, red; examples indicated by white arrows) among neurons (Tuj1, green) generated in clonal density cultures of cortical stem cells.



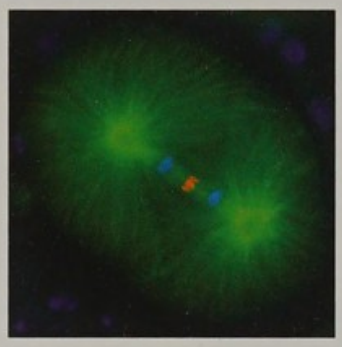
Phase contrast image of a pair of cortical neurons extending neurites in culture

Masanori Mishima

Molecular mechanism of cytokinesis



Co-workers: Tim Davies, Max Douglas, Andrea Hutterer, Nimesh Joseph, Kian-Yong Lee, Julia Mason, Eva Pablo-Hernando



Cytokinesis is essential for cell proliferation. Failure of cytokinesis leads to aneuploidy or chromosomal instability, which have been associated with human cancers. Successful cytokinesis relies on a dynamic interplay between microtubules, the actin cytoskeleton, and membrane compartments under the control of the cell cycle machinery. In spite of its importance, the molecular mechanism of cytokinesis in animal cells has not yet been fully clarified.

We would like to understand cytokinesis more fully, in terms of the dynamic assembly of molecular machinery. The central spindle is a microtubule-based molecular assembly that forms between the segregating chromosomes during anaphase. During telophase, it associates with the ingressing cleavage furrow and matures into the midbody. These microtubule-based structures have crucial roles through all the steps of cytokinesis from initiation to completion. We will address the following questions:

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

We have been focusing on centralspindlin, a stable protein complex of a mitotic kinesin-like protein and a Rho-family GTPase-activating protein (RhoGAP), which is crucial for assembly of the central spindle and the midbody. We use both *Caenorhabditis elegans*, a powerful model organism for genetic analysis, and mammalian cultured cells, which are more suitable for biochemical analyses of cell cycle events, to understand an evolutionary conserved fundamental mechanism of cytokinesis. Recently, we have introduced a total internal reflection fluorescence (TIRF) microscope to the lab, which allows us to visualise directly the motility of centralspindlin at the single molecule level. We have discovered that centralspindlin travels along microtubules of the central spindle as higher-order clusters and that clustering is essential for both microtubule-bundling and motility along microtubules *in vitro* and for midbody formation *in vivo*. Based on these findings, we have proposed a positive feedback loop model to explain the distinct localisation pattern of centralspindlin during cytokinesis.

Inset left: A *C elegans* one-cell-stage embryo about to undergo cytokinesis. Following segregation of chromosomes (blue), a bundle structure of microtubules (green) called the central spindle is formed between them. Centralspindlin (red), a critical factor for the formation of this structure, accumulates steeply to the center of the microtubule bundle.

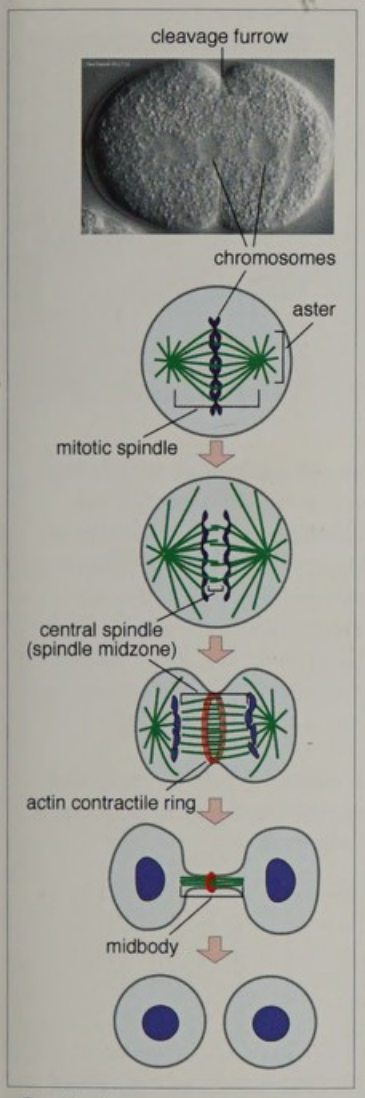
Hutterer A, Glotzer M, Mishima M (2009) Clustering of centralspindlin is essential for its accumulation to the central spindle and the midbody. **Curr Biol** [in press]

Guse A, Mishima M and Glotzer MA (2005) Conserved role for Aurora B phosphorylation of ZEN-4/MKLP1 in completion of cytokinesis. **Curr Biol** 15, 778-86

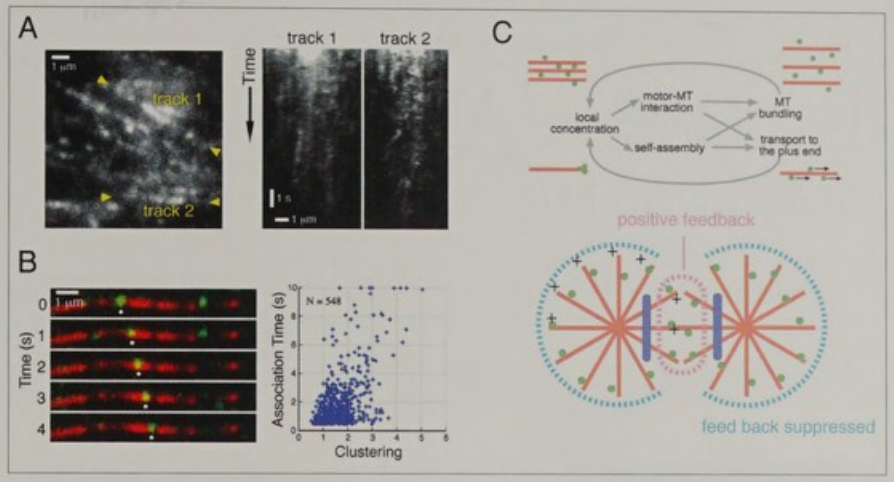
Mishima M, Pavicic V, Grüneberg U, Nigg EA, and Glotzer M (2004) Cell cycle regulation of central spindle assembly. **Nature** 430, 908-13

Mishima M, and Glotzer M (2004) Cytokinesis. In **Encyclopedia of Biological Chemistry** (WJ Lennarz & MD Lane eds), Elsevier, Oxford, vol 1, pp. 556-62

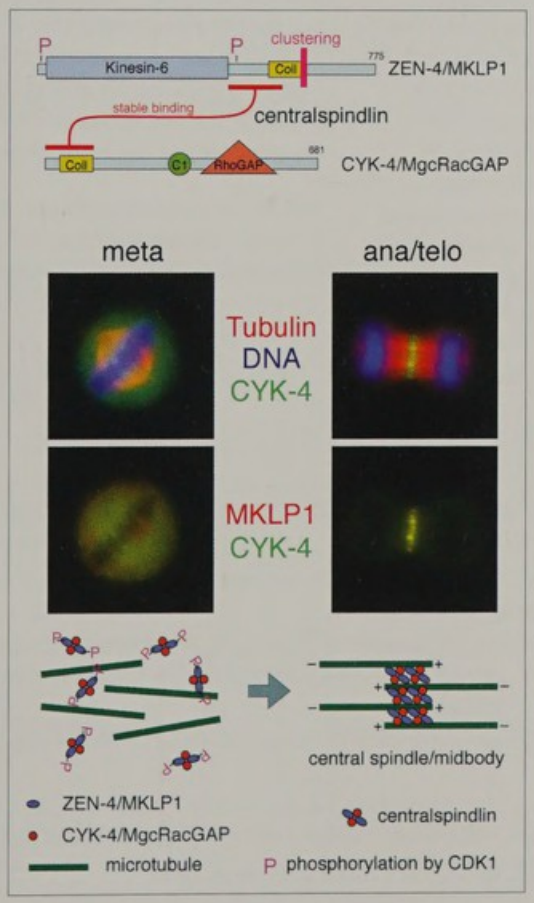
For an additional publication since the last report, see number 35 on pp 50-53



Cytokinesis



Centralspindlin is an evolutionarily conserved microtubule-bundling protein complex. Both Kinesin-6 and RhoGAP components are essential for *in vivo* formation of the central spindle and for *in vitro* microtubule-bundling activity. During cell division, it shows dynamic changes in subcellular localisation. Control of the affinity of the kinesin motor domain for microtubules by CDK1 kinase-mediated phosphorylation plays a major role in the temporal regulation of the activity of centralspindlin. However, the mechanism enabling its distinct localisation to the center of microtubule bundles has been unclear.

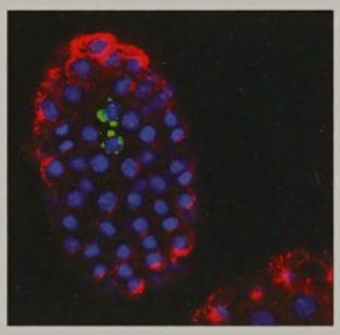


Using total internal reflection fluorescence (TIRF) microscopy, we have succeeded in directly observing the movement of particles of centralspindlin both *in vivo* (A) and *in vitro* (B). This data, in combination with genetic analyses with a specific separation-of-function mutant, has enabled us to conclude that clustering of centralspindlin is essential for cytokinesis. We have proposed a novel positive feedback mechanism to explain the distinct localisation pattern of centralspindlin, which is crucial for the proper recruitment of various downstream cytokinesis factors between the segregating chromosomes.

Eric Miska

Small regulatory RNA

Co-workers: Javier Armisen Garrido, Marloes Bagijn, Alejandra Clark, Ethan Kaufman, Nic Lehrbach, Helen Lightfoot, Alexandra Sapetschnig, Funda Sar, Robert Shaw, Eva-Maria Weick, Julie Woolford



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

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

We also have developed tools for the analysis of miRNA expression in human disease and have discovered miRNAs that have potential as molecular markers for diagnosis and prognosis.

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

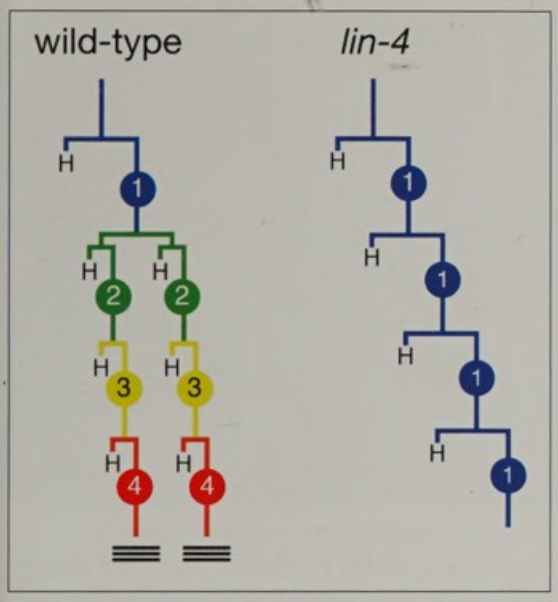
Armisen J, Gilchrist MJ, Wilczynska A, Standart N and Miska EA (2009) Abundant and dynamically expressed miRNAs, endo-siRNAs and piRNAs in the African clawed frog *Xenopus tropicalis*. **Genome Research** 19, 1766-1755

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

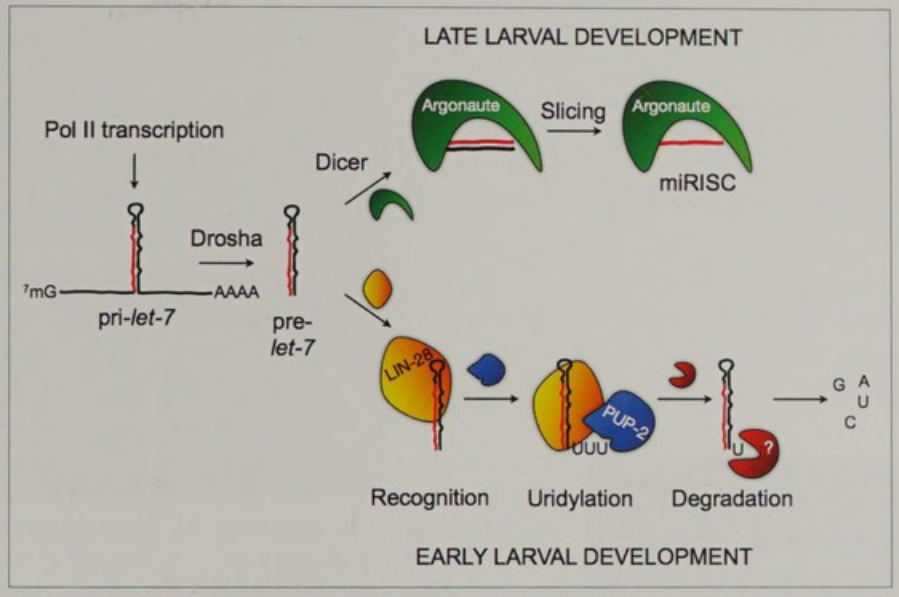
Miska EA, Alvarez-Saavedra E, Abbott AL, Lau NC, Hellman AB, Bartel DP, Ambros VR, Horvitz HR (2007) Most *Caenorhabditis elegans* microRNAs are individually not essential for development or viability. **PLoS Genet** 3, e215

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

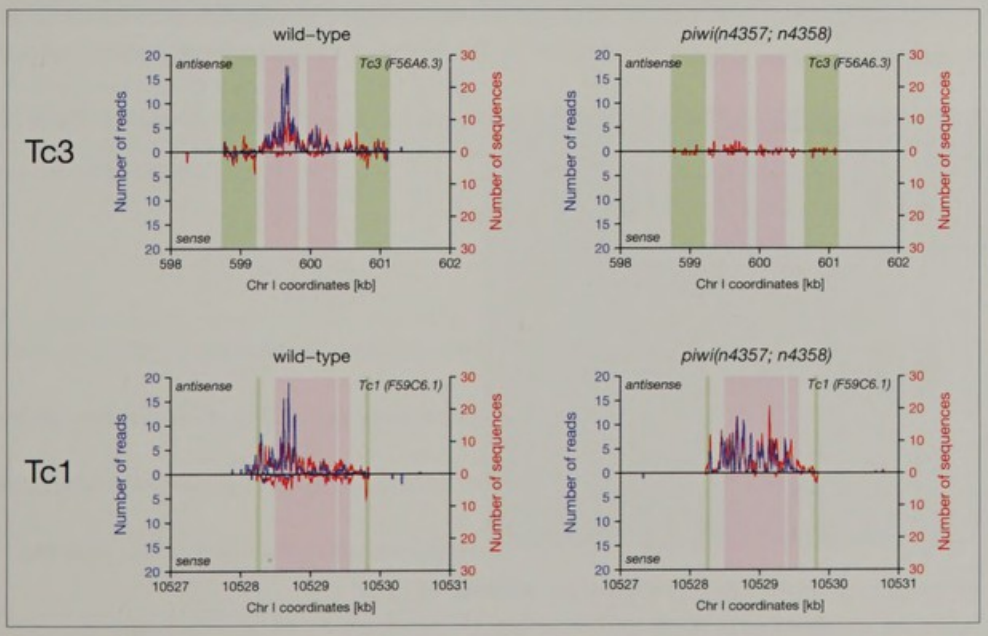
For complete list of this lab's publications since the last report, see numbers 5, 39 and 75 on pp 50-53



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



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

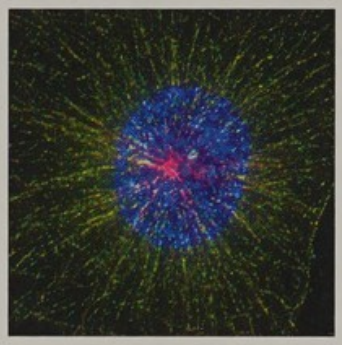


piRNAs and **Piwi** proteins are required to generate endogenous siRNAs that silence the Tc3 DNA transposon in the germline.

Jonathon Pines

How do cells control mitosis?

Co-workers: Philippe Collin, Barbara Di Fiore, Anja Hagting, Daisuke Izawa, Mark Jackman, Agata Lichawska, Jörg Mansfeld, Paola Marco, Takahiro Matsusaka, Oxana Nashchekina, Bernhard Strauss, Felicia Walton, Mona Yekezare



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

To understand how cells initiate mitosis we are analysing the behaviour of the key mitotic kinases, the Cyclin A- and B-dependent kinases, and their regulation by phosphorylation and dephosphorylation. We have developed a biosensor to assay Cyclin B1-Cdk1 activity *in vivo* that for the first time reveals the kinetics with which it is activated, and are using this to define the events that link the completion of DNA replication with the initiation of mitosis. To identify the proteins responsible for regulating the Cyclin-Cdks, and provide insights into their substrates, we are analysing protein complexes through the cell cycle by SILAC mass spectrometry.

To understand how proteolysis regulates progress through mitosis we complement the analysis of APC/C-dependent degradation in living cells with biochemical analyses of protein complexes and ubiquitination activity. These studies are revealing how the APC/C is activated, how it is able to select a particular protein for destruction at a specific time, and how its activity is regulated by the spindle assembly checkpoint that is essential to the control of chromosome segregation and cytokinesis.

Inset left: A prophase cell stained for MCAK (green), microtubules (red) and DNA (blue) (Catherine Lindon)

Garnett MJ, Mansfeld J, Godwin C, Matsusaka M, Wu J, Russell P, Pines J and Venkitaraman A (2009) UBE2S elongates ubiquitin chains on APC/C substrates to promote mitotic exit **Nat Cell Biol** 11, 1363-1369

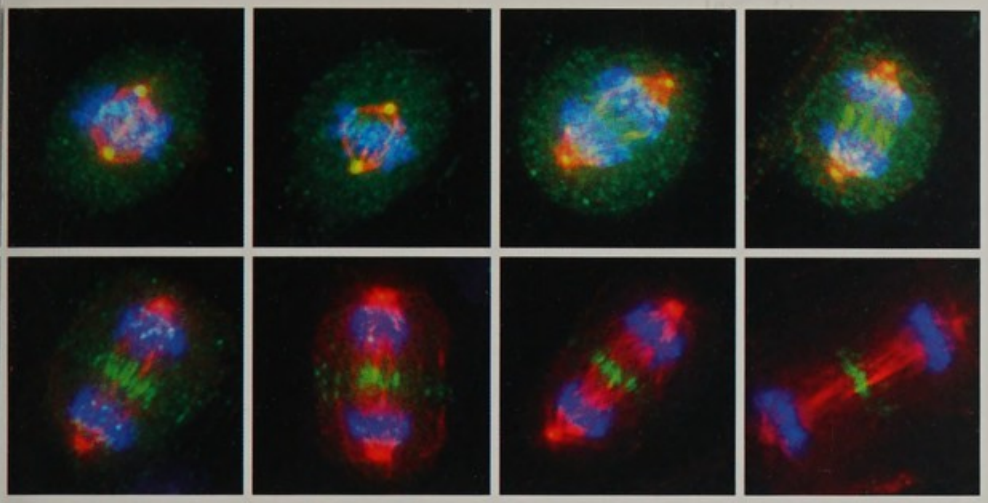
Nilsson J, Yekezare M, Minshull J and Pines J (2008) The APC/C maintains the spindle assembly checkpoint by targeting Cdc20 for destruction. **Nat Cell Biol** 10, 1411-1420

Wolthuis R, Clay-Farrace L, van Zon W, Yekezare M, Ogink J, Medema R and Pines J (2008) Cdc20 and Cks direct the spindle checkpoint-independent destruction of cyclin A. **Mol Cell** 30, 290-302

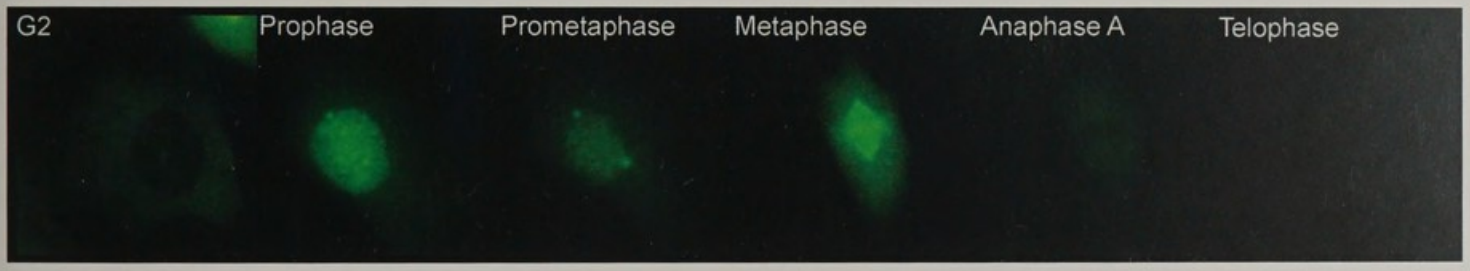
Di Fiore B and Pines J (2007) Emi1 is needed to couple DNA replication with mitosis but does not regulate activation of the mitotic APC/C. **J Cell Biol** 177, 425-437

Pines J (2006) Mitosis: a matter of getting rid of the right protein at the right time. **Trends in Cell Biology** 16, 55-63

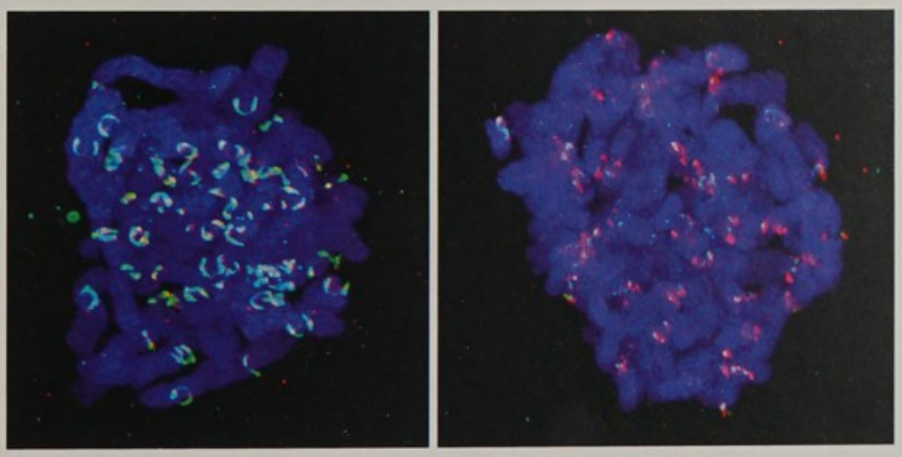
For an additional publication since the last report, see number 48 on pp 50-53



Plk: Deconvolved images of Hela cells progressing through mitosis stained for Polo-like kinase 1 (green), tubulin (red) and DNA (blue) (Catherine Lindon).



One allele of the cyclin B1 gene tagged with the Venus fluorescent protein allows us to visualise the behaviour of the endogenous protein through the cell cycle. (Oxana Nashchekina and Philippe Collin).

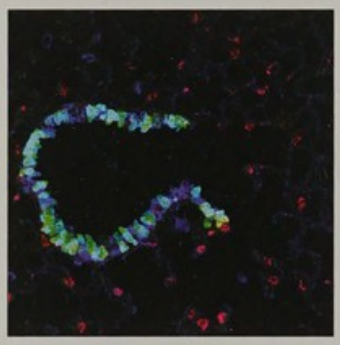


Cyclin B1 targeting to kinetochores. Cyclin B1 at a wild type (left) and mutant (right) kinetchore. Cyclin B1 in green, CREST serum in red and DNA in blue (Mark Jackman).

Emma Rawlins

Stem and progenitor cells in the mammalian lung

Recruitment to the Rawlins Group will commence in 2010



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

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

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

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

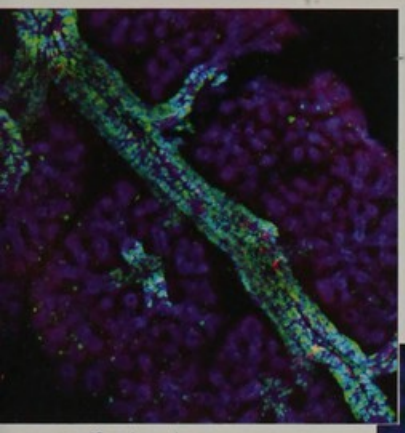
Inset left: Lineage-labelled bronchiolar cells (green) in the adult mouse lung. These cells are descended from progenitor cells which both self-renew and make new ciliated cells throughout the lifespan of the animal.

Rawlins EL, Clark CP, Xue Y and Hogan BLM (2009) The Id2 distal tip lung epithelium contains individual multipotent embryonic progenitor cells. **Development** 136 3741-3745

Rawlins EL, Okubo T, Xue Y, Brass DM, Auten RL, Hasegawa H, Wang F and Hogan BLM (2009) The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. **Cell Stem Cell** 4 525-534

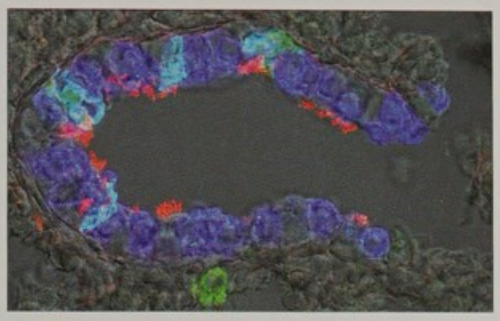
Rawlins EL and Hogan BLM (2008) Ciliated epithelial cell lifespan in the mouse trachea and lung. **American Journal of Physiology: Lung Cell Molecular Physiology** 295 L231-234

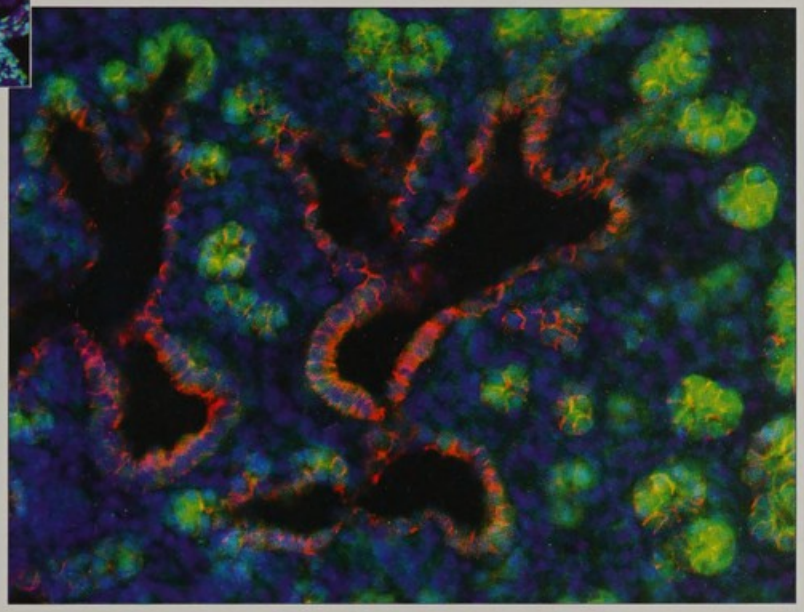
Rawlins EL, Ostrowski LE, Randell SH and Hogan BLM (2007) Lung development and repair: contribution of the ciliated lineage. **Proc Natl Acad Sci USA** 104 410-417



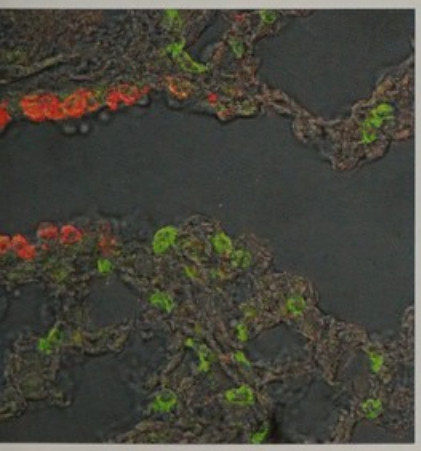
Low magnification view of the embryonic mouse lung showing the branching airways (blue) and differentiating bronchiolar cells (red and green).

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





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



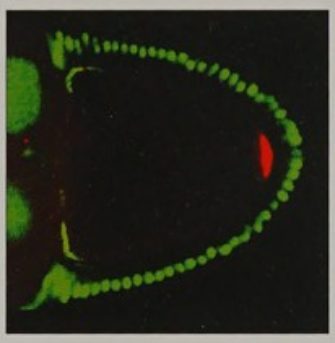
Lineage-labelled bronchiolar cells (green) in the growing mouse lung. These cells are descended from an embryonic-specific progenitor cell population.

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

Daniel St Johnston

Cell polarity and mRNA localisation in *Drosophila*

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



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

Much of our work uses the oocyte as a model, 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 are using proteomic and biochemical approaches to elucidate how conserved polarity proteins regulate the organisation of the cytoskeleton, and we are investigating the mechanisms of mRNA transport by making time-lapse movies of mRNA particles in wildtype and mutant oocytes. We are also performing large scale screens for mutants that affect the localisations of *bicoid* and *oskar* mRNAs, and are analysing novel polarity and mRNA localisation factors that these identify.

In parallel, we are examining how the apical-basal polarity of epithelial cells is established using the follicle cells and the adult gut as models. We have recently discovered that the tumour suppressor, LKB1, and the energy sensor, AMPK, are specifically required for epithelial polarity under conditions of energetic stress, revealing the existence of a distinct low energy polarity pathway. We have now identified several other components of this pathway, all of which have also been implicated in cancer. We are therefore performing RNAi screens for new genes that are required for polarity under either high or low energy conditions.

Inset left: The localisation of *bicoid* mRNA (green) and *oskar* mRNA (red) in a stage 10A *Drosophila* oocyte. Bicoid mRNA has been labelled with MS2-GFP and *oskar* mRNA with RFP-Staufen

Mirouse V, Christoforou CP, Fritsch C, St Johnston D and Ray R (2009) Dystroglycan and Perlecan provide a basal cue that is required for epithelial polarity during energetic stress. **Dev Cell** 16, 83-92

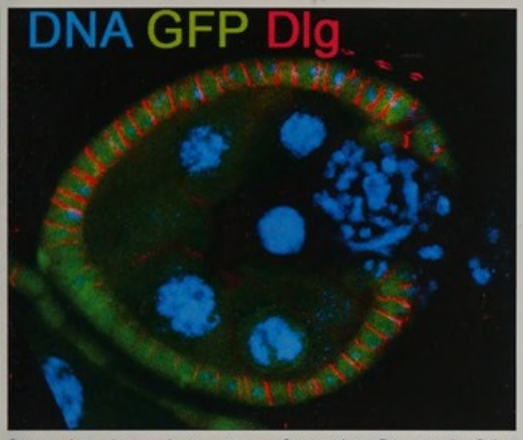
Zimaynin VL, Belaya K, Pecreaux J, Gilchrist MJ, Clark A, Davis I and St Johnston D (2008) *In vivo* imaging of *oskar* mRNA transport reveals the mechanism of posterior localization. **Cell** 134. 843-853

Bastock R and St Johnston D (2008) *Drosophila* oogenesis. **Curr Biol**, 18, R1082-7

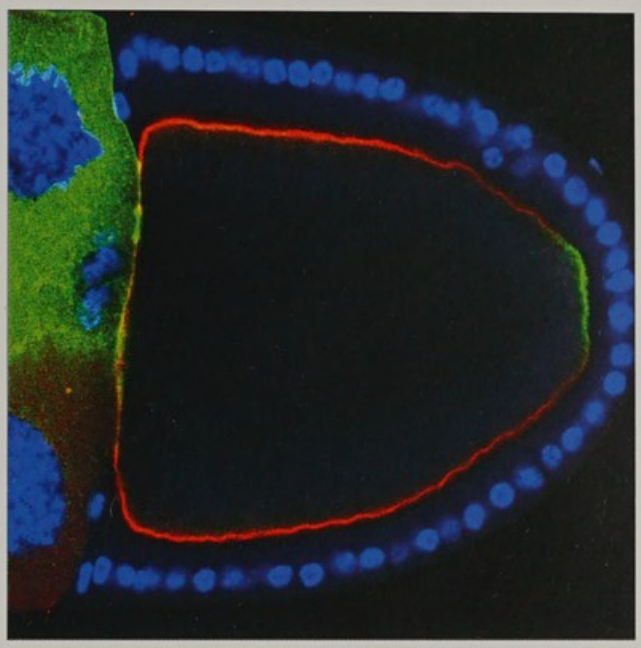
Mirouse V, Swick LS, Kazgan N, St Johnston D and Brenman JE (2007) LKB1 and AMPK maintain epithelial cell polarity under energetic stress. **J Cell Biol** 77, 387-392

Irion U and St Johnston D (2007) Localisation of the *Drosophila* anterior determinant, bicoid RNA, requires an endosomal sorting complex. **Nature** 445, 554-557

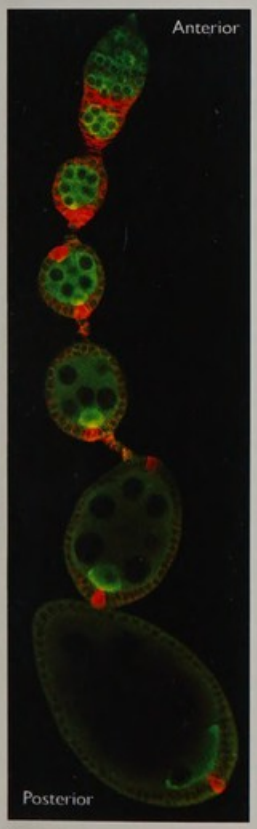
For complete list of this lab's publications since the last report, see numbers 3, 6, 19, 41, 45, 51 and 65 on pp 50-53

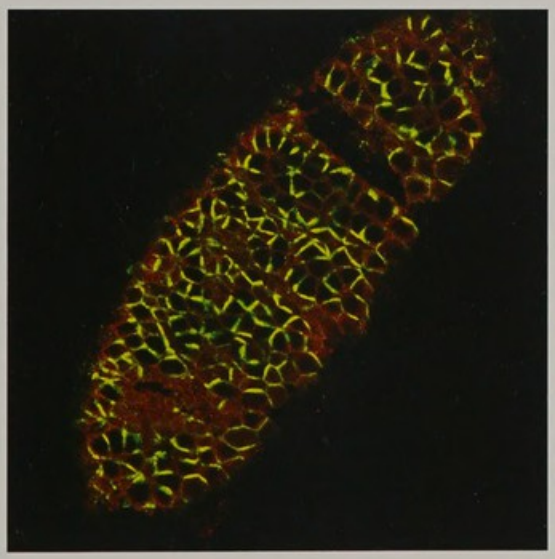


Starvation-dependent tumour formation. Removal of the AMP-dependent protein kinase from clones of follicle cells (marked by the absence of GFP; green) causes the cells to lose their polarity and over-proliferate, resulting in small tumours. This phenotype is only observed under starvation conditions.



Drosophila anterior-posterior axis formation. A stage 10A egg chamber showing the localisation of PAR-6 (red) and PAR-1 (green) to complementary cortical domains in the oocyte. The nuclei are stained in blue. These PAR proteins control the polarity of the microtubule cytoskeleton to define where *bicoid* and *oskar* mRNAs are localised



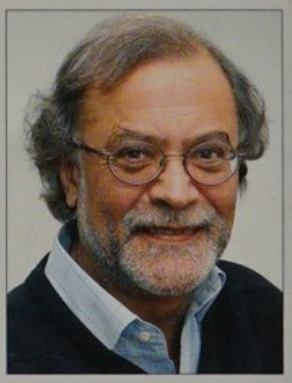


Mislocalisation of adherens junctions in an embryo expressing Bazooka S980A. Bazooka (PAR-3) is normally excluded from the apical domain of epithelial cells by its phosphorylation on serine 980 by atypical protein kinase C (aPKC). A mutant form of Bazooka (green) that cannot be phosphorylated by aPKC causes the aggregation of the adherens junctions (stained with Armadillo in red) along one side of the cell leading to a loss of epithelial organisation.

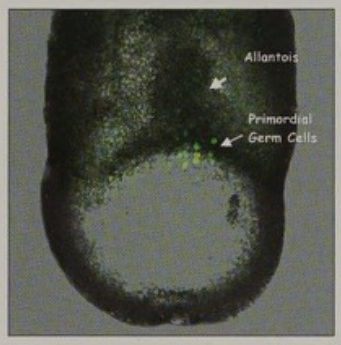
Drosophila oogenesis. A *Drosophila* ovariole, containing a series of germline cysts (green, BicD) that progress through oogenesis as they move posteriorly. The cysts are born at the anterior of the ovariole, and become surrounded by somatic follicle cells (red, FasIII) as they exit the germarium. Each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

Azim Surani

Genetic and epigenetic regulators of the germ line and pluripotency



Co-workers: Suzan Ber, Delphine Cougot, Lynn Froggett, Astrid Gillich, Nils Grabole, Sophie Hanina, Shinseog Kim, Caroline Lee, Harry Leitch, Erna Magnúsdóttir, William Mifsud, Qin Si, Fuchou Tang, Wee Wei Tee, Katarzyna Wilczynska



We aim to elucidate the genetic programme that regulates specification of mouse primordial germ cells (PGCs), which includes active repression of the somatic programme adopted by the neighbouring cells. We discovered that the transcriptional repressor, Blimp1/Prdm1, is the key regulator of PGC specification. We are exploring the role of this and other key genes involved in PGC specification. Furthermore, Blimp1 forms a novel complex with Prmt5 arginine methylase that is apparently critical for the specification and maintenance of early PGCs, while PRMT5 itself is independently implicated in regulating pluripotency in stem cells, which underlines the relationship between germ cells and pluripotent stem cells.

Following PGC specification, extensive epigenetic reprogramming of the genome follows, which is an essential first step towards the eventual generation of totipotency. In particular, when PGCs migrate into developing gonads at E11.5, they undergo extensive epigenetic modifications, including genome-wide DNA demethylation, erasure of imprints and reactivation of the X chromosome. Dedifferentiation of PGCs into pluripotent EG cells also results in a similar epigenetic reprogramming event following the loss of Blimp1 (Fig 4). We are investigating the mechanism, including the identity of intrinsic factors involved in the epigenetic reprogramming of PGCs, together with the nature of the external signals that trigger it.

Our broader objectives are to develop model systems that will attempt to mimic the key aspects of PGC specification and epigenetic reprogramming *in vitro*. The key factors and mechanisms that govern erasure of epigenetic information in PGCs could be relevant for investigations of genomic reprogramming of somatic cells towards pluripotency *in vitro*. This knowledge could also contribute to advances in human medicine, including the causes of cancers, as well as for the repair and rejuvenation of somatic tissues.

Inset left: Expression of Stella-GFP at E 7.8. PGCs are detected at the base of the allantois. Stella is located within a cluster of pluripotency genes, including nanog and Gdf3 that are expressed in ES and EG cells.

Surani MA, Durcova-Hills G, Hajkova P, Hayashi K and Tee WW (2009) Germ line, stem cells and epigenetic reprogramming. **Cold Spring Harb Symp Quant Biol** doi:10.1101/sqb.2008.73.015

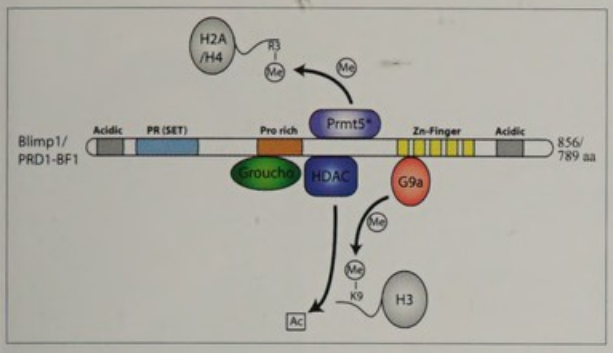
Bao S, Tang F, Li X, Hayashi K, Gillich A, Lao K, Surani MA (2009) Epigenetic reversion of postimplantation epiblast to pluripotent embryonic stem cells. **Nature** 29;461(7268):1292:1295

Hayashi K, Surani MA (2009) Resetting the epigenome beyond pluripotency in the germline. **Cell Stem Cell** 5;4(6):493-498

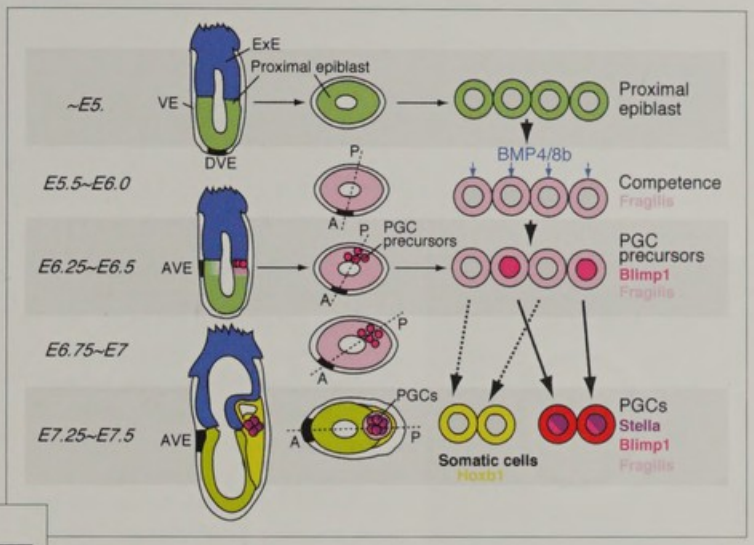
Hajkova P, Ancelin K, Waldman T, Lacoste N, Lange UC, Cesari F, Lee C, Almouzni G, Schneider R and Surani MA (2008) Chromatin dynamics during epigenetic reprogramming in the mouse germ line. **Nature** 452, 877-881

Hayashi K, de Sousa Lopes SM, Surani MA (2007) Germ cell specification in mice. **Science** 316, 394-396

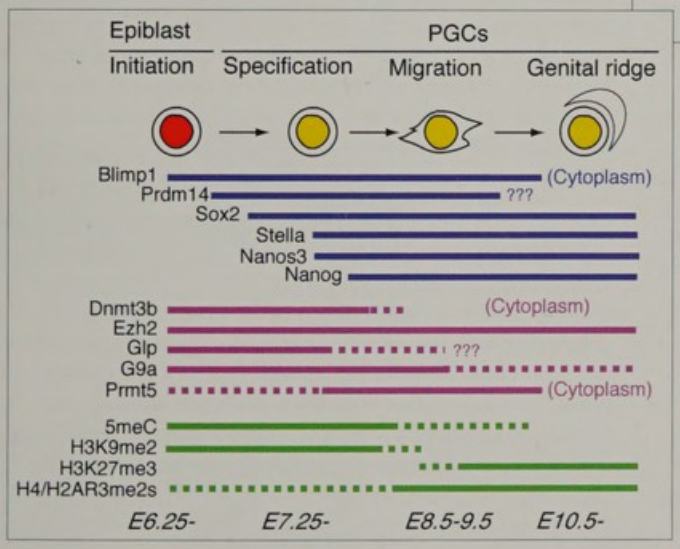
For complete list of this lab's publications since the last report, see numbers 17, 20, 25, 29, 36, 64, 67, 68, 69 and 74 on pp 50-53



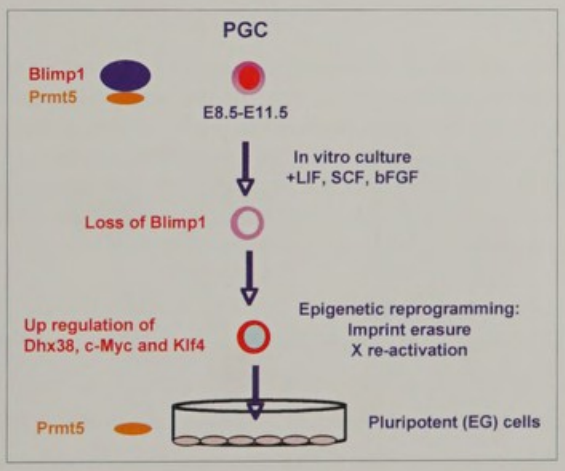
Blimp1, the key determinant of germ cell specification in mice, with a SET/PR domain and five Krueppel-like zinc fingers, which bind to DNA. BLIMP1 can potentially interact with several co-repressors to repress target genes. In germ cells, BLIMP1 forms a novel complex with an arginine methylase, PRMT5.



Role of Blimp1 in PGC specification. Shown are early embryos from E5.0 to E7.5 depicting the formation of PGCs. The proximal epiblast respond to signals from extraembryonic tissues that induce expression of fragilis in the epiblast, and of Blimp1 in the lineage restricted PGC precursors, which develop as founder PGCs and show expression of Stella.



Genetic regulators, expression of pluripotency genes and epigenetic modifications in nascent PGCs

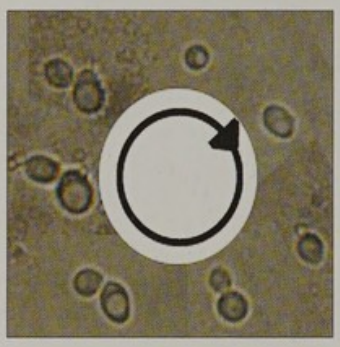


During dedifferentiation of PGCs into pluripotent embryonic germ cells (EG), Blimp1 is down-regulated resulting in the expression of the repressed targets of BLIMP1, and epigenetic reprogramming in EG as observed in gonadal PGCs *in vivo*. Prmt5 expression is maintained and may have an independent role in pluripotency.

Philip Zegerman

The regulation of DNA replication initiation in eukaryotes

Co-workers: Davide Mantiero



To successfully pass on its genetic information, every organism must make a perfect duplicate of its 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.

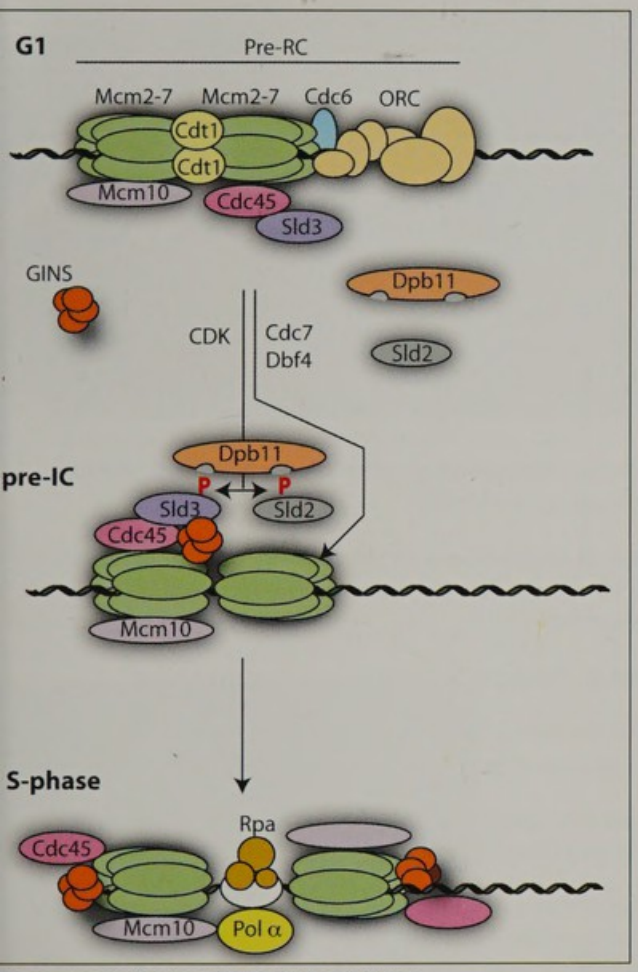
Our research is focused on the pre-initiation complex step in the replication reaction. This step is the key CDK regulatory step, but the function of this intermediate is not known. Furthermore, the pre-IC may also integrate information from other kinases, such as the DNA damage checkpoint and may be 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.

Zegerman P and Diffley JF (2010) Checkpoint dependent inhibition of DNA replication initiation via phosphorylation of Sld3 and Dbf4. **Nature** [Under revision]

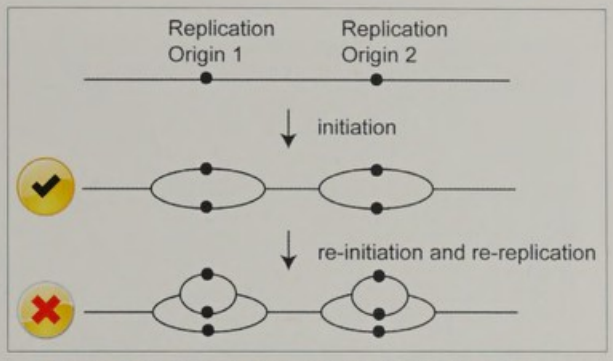
Zegerman P and Diffley JF (2009) DNA replication as a target of the DNA damage checkpoint. **DNA repair** 8,1077-88

Zegerman P and Diffley JF (2007) Phosphorylation of Sld2 and Sld3 by cyclin-dependent kinases promotes DNA replication in budding yeast. **Nature** 445, 281-5

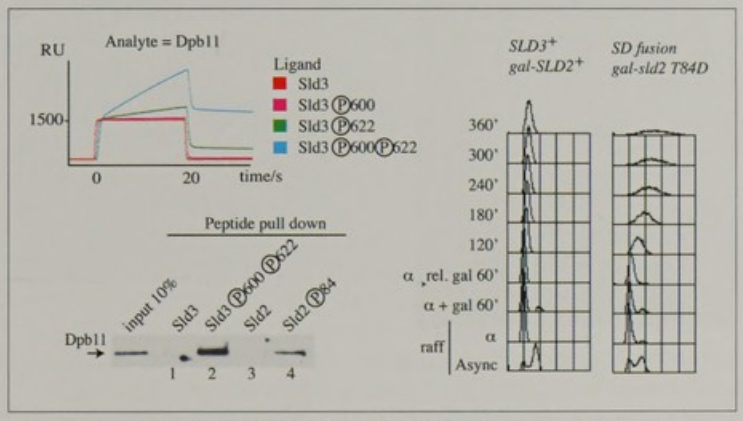
Zegerman P and Diffley JF (2003) Lessons in how to hold a fork. **Nature Struct Biol** 10, 778-9



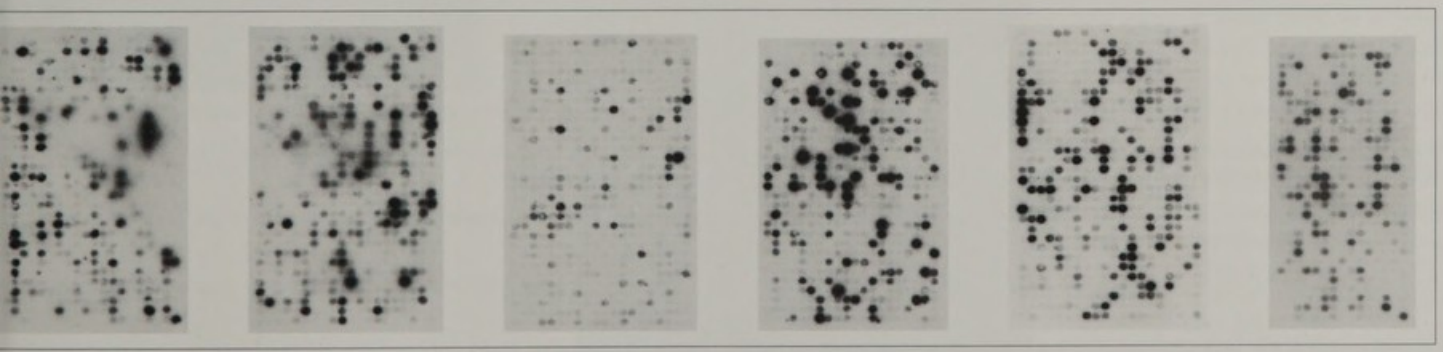
The sequence of eukaryotic replication initiation



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



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



hospho-peptide array analysis of replication initiation factors.

Magdalena Zernicka-Goetz

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

Co-workers: Anna Ajduk, Helen Bolton, Alex Bruce, Seema Grewal, Agnieszka Jedrusik, Samantha Morris, Bedra Sharif, Jackie Simcox, Maria Skamagki, Bernhard Strauss, Roy (Tang Yi) Teo, Krzysztof Wicher

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

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

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

Inset left: 3D reconstruction of mouse blastocyst. Yellow: pluripotent cells of the inner cell mass; blue and green: outside cells of trophectoderm. (Image from Emlyn Parfitt)

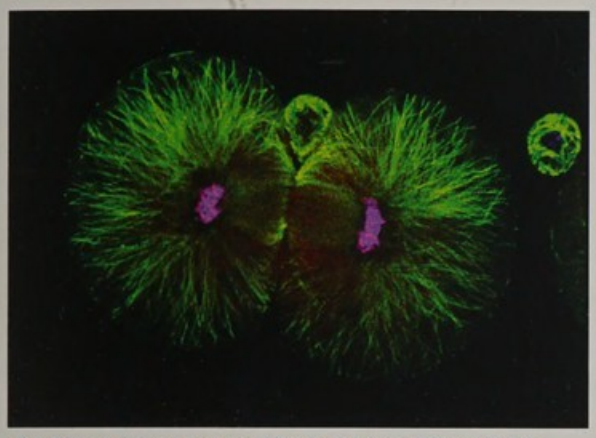
Zernicka-Goetz M, Morris S and Bruce A (2009) Making a firm decision: layers of regulation in early mouse embryo. **Nature Rev Genet** 10, 467-77

Jedrusik A, Parfitt DE, Guo G, Skamagki M, Grabarek JB, Johnson MH, Robson P and Zernicka-Goetz M (2008) Role of Cdx2 and cell polarity in cell allocation and specification of trophectoderm and inner cell mass in the mouse embryo. **Genes Dev** 22, 2692-706

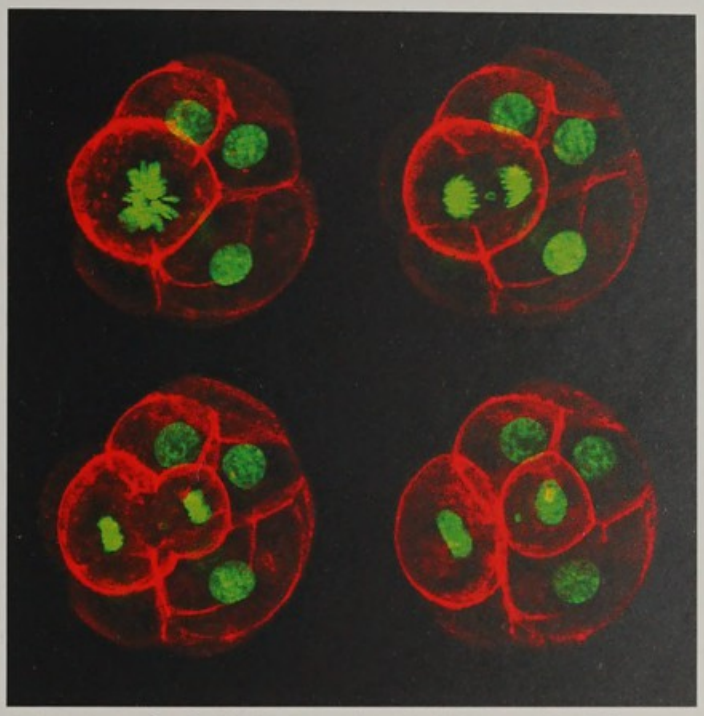
Bischoff M, Parfitt DE, Zernicka-Goetz M (2008) Formation of the embryonic-abembryonic axis of the mouse blastocyst: relationships between orientation of early cleavage divisions and pattern of symmetric/asymmetric divisions. **Development** 135, 953-62

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

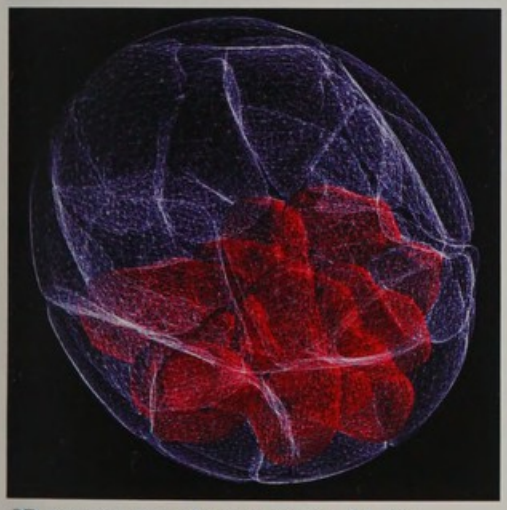
For complete list of this lab's publications since the last report, see numbers 1, 11, 40, 77 and 79 on pp 50-53



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



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



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

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

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Professor, Reader, Director of Research, Assistant Director of Research or equivalent

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

CAREER DEVELOPMENT FELLOW
4-year grant-funded appointment

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

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Postdoctoral Fellow within individual groups, appointed by group leader

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Postgraduate within individual groups, mainly grant-funded

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

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LABORATORY ASSISTANT / TECHNICIAN
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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, Chairman

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

REBECCA BASTOCK PhD
Wellcome Trust Research Associate

KATSIARYNA BELAYA PhD
Wellcome Trust Research Associate

DAN BERGSTRALH PhD
Marie Curie Research Fellow

EURICO de SA
Portuguese Foundation of Science and Technology Graduate Student

HÉLÈNE DOERFLINGER PhD
Wellcome Trust Research Associate

CELIA FARIA BSc
Wellcome Trust Graduate Student

ALEJANDRA GARDIOL PhD
Wellcome Trust Research Associate

JACKIE HALL MSc
Wellcome Trust Senior Research Technician

NICK LOWE PhD
Wellcome Trust Research Associate

SOLÈNE MOLLE
Visiting Student

DMITRY NASHCHEKIN PhD
Wellcome Trust Research Associate

ROSS NIEUWBURG BSc
Graduate Student

JENNY PESTEL
Visiting Student from Heidelberg

HANNA REUTER
Erasmus Student

ARAM SAYADIAN BSc
Wellcome Trust Graduate Student

VANESSA STEFANAK BA
PA

VITOR TROVISCO GRADISSIMO PhD
BBSRC Research Associate

ANTONIO VEGA RIOJA PhD
FEBS Fellow

LUCY WHEATLEY BSc
Wellcome Trust Research Assistant

TONGTONG ZHAO BSc
Graduate Student

JULIE AHRINGER PhD FMedSci

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

FREDERIC ANTIGNY
Visiting Student

ANNE CANONGE MSc
NIH Research Assistant

RON CHEN PhD
Wellcome Trust Research Associate

MIKE CHESNEY PhD
Wellcome Trust Research Associate

NICOLE CHEUNG PhD
Wellcome Trust/NIH Research Associate

YAN DONG MSc
Wellcome Trust Research Assistant

BRUNO FIEVET PhD
HFSP Research Fellow

MORITZ HERMANN BSc
BBSRC Graduate Student

VOLKAN KARABACAK
Visiting Student

PAULINA KOLASINSKA-ZWIERZ MSc
Gates Scholarship Graduate Student

SONJA KROSCHWALD
Visiting Student from Max Planck Institute in Dresden

ISABEL LATORRE PhD
NIH/Isaac Newton Trust Research Associate

ANDREA MAFFIOLETTI
Visiting Student

DAVID RIVERS PhD
Wellcome Trust Research Associate

JOSANA RODRIGUEZ PhD
Herchel Smith Research Fellow

CHRISTINE TURNER
Secretary

SHANE WOODS
Graduate Student

EVA ZEISER MSc
Wellcome Trust Research Assistant

ANDREA BRAND PhD FMedSci

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

ELIZABETH CAYGILL PhD
Research Associate

JAMES CHELL MPhil
Wellcome Trust Graduate Student

SENIOR GROUP LEADERS

MELANIE CRANSTON BA
Wellcome Trust Research Assistant

CATHERINE DAVIDSON BSc
Wellcome Trust Research Associate

JAMES DODS BSc
Wellcome Trust Graduate Student/Research Associate

KARIN EDOFF PhD
MRC Stem Cell Career Development Fellow

BORIS EGGER PhD
Swiss National Science Foundation Fellow

KATRINA GOLD MPhil
Wellcome Trust Graduate Student

ANNE PELISSIER PhD
EMBO Fellow/Research Associate

TONY SOUTHALL PhD
Herchel Smith Fellow

PAULINE SPÉDER PhD
Sir Henry Wellcome Postdoctoral Fellow

ALYSON THOMPSON BSc
MRC Graduate Student

CHRISTINE TURNER
Secretary

JAKOB von TROTHA BSc
DAAD Graduate Student

PAO-SHU (PAUL) WU BSc
Cambridge Overseas Trust Graduate Student

NICK BROWN PhD

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

NATALIA BULGAKOVA PhD
HFSP Research Associate

ISABELLE DELON PhD
BBSRC Research Associate

JONATHAN FRIEDLANDER MA
Gates Scholarship and BBSRC Graduate Student

SANDRA GEHRKE
Visiting Student from Hanover

QIN HU PhD
Visiting Academic

SVEN HUELSMANN PhD
Wellcome Trust Research Associate

YOSHIKO INOUE PhD
Wellcome Trust Research Associate

BENJAMIN KLAPHOLZ PhD
Wellcome Trust Research Associate

SUSHMITA MAITRA PhD
Wellcome Trust Research Associate/Visiting Academic

JOHN OVERTON HNC
Wellcome Trust Chief Research Technician

JUTTA WELLMANN MPhil
Herschel Smith and BBSRC Graduate Student

JOHN GURDON Kt DPhil DSc FRS

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

CAROLINA ÅSTRAND PhD
Swedish Research Council Fellow/Visiting Academic

DILLY BRADFORD
Secretary

NIGEL GARRETT MIBiol
Wellcome Trust Research Associate

RICHARD HALLEY-STOTT BSc
Graduate Student

JO-ANNE JOHNSON MB ChB MRCPCH
BRC Clinical Research Fellow

JEROME JULLIEN PhD
Wellcome Trust Research Associate

KEI MIYAMOTO PhD
Wellcome Trust Research Associate

KAZUTAKA MURATA BSc
Graduate Student

PATRICK NARBONNE PhD
NSERC/EMBO Research Fellow

VINCENT PASQUE BSc
Wellcome Trust Graduate Student

ILENIA SIMEONI PhD
EU Research Associate/Visiting Academic

STEVE JACKSON PhD FRS FMedSci

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

LINDA BASKCOMB MSc
Cancer Research UK Chief Research Laboratory Technician

RIMMA BELOTSERKOVSKAYA PhD
Cancer Research UK Research Associate

MELANIE BLASIUS PhD
Swiss National Foundation Research Fellow

ROSS CHAPMAN BSc
Cancer Research UK Research Assistant

JULIE COATES MA
Cancer Research UK Research Assistant

KATE DRY PhD
Cancer Research UK Senior Research Associate

SONJA FLOTT PhD
Ernst Schering Foundation Fellow

JOSEP FORMENT PhD
Cancer Research UK Research Associate

SENIOR GROUP LEADERS

YARON GALANTY PhD
Cancer Research UK Research Associate

SIMONA GIUNTA BSc
BBSRC CASE Graduate Student

ILARIA GUERINI PhD
EU Research Associate

JEANINE HARRIGAN PhD
Cancer Research UK Research Associate

PABLO HUERTAS PhD
BBSRC Research Associate

KAMILA JOZWIK
Amgen Student visiting from Warsaw University

ABDERRAHMANE KAIDI PhD
Herchel Smith Research Fellow

AMANDA KINGSNORTH BSc PGCE
Cancer Research UK Senior Research Laboratory Technician

HELEN KIRKMAN BSc
Cancer Research UK Senior Research Laboratory Technician

NATALIA LUKASHCHUK PhD
Cancer Research UK Research Associate

KYLE MILLER PhD
Wellcome Trust Research Associate

TOBIAS OELSCHLÄGEL PhD
EMBO Fellow

SOPHIE POLO PhD
HFSP Research Fellow

HELEN REED
Secretary

JORRIT TJEERTES
BBSRC CASE Graduate Student

TONY KOUZARIDES PhD FMedSci

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

HATICE AKARSU PhD
EU Research Associate

SOPHIE BALERDI-DELTOUR PhD
Cancer Research UK Research Associate

ANDREW BANNISTER PhD
Cancer Research UK Senior Research Associate

TILL BARTKE PhD
Cancer Research UK Research Associate

GONÇALO CASTELO-BRANCO PhD
EMBO Research Fellow

MARIA CHRISTOPHOROU PhD
HFSP Research Fellow

ALISTAIR COOK GIBiol
Cancer Research UK Chief Research Technician

MARK DAWSON MBBS(Hons) BMedSci FRACP FRCPA
Graduate Student

CYNTHIA HILL MS
NIH Senior Research Technician

ANTONIS KIRMIZIS PhD
EU Research Associate

DAVID LANDO PhD
Cancer Research UK Research Associate

NIKKI PARSONS BA
Secretary

CLAIRE PIKE BSc
Cancer Research UK Graduate Student

HELENA SANTOS ROSA PhD
Cancer Research UK Senior Research Associate

PETER TESSARZ PhD
Cancer Research UK Research Associate

EMMANUELLE VIRÉ PhD
Wiener-Anspach Foundation Research Fellow

BLERTA XHEMALCE PhD
EU Research Associate

JONATHON PINES PhD FMedSci

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

EMMANUEL BOUCROT PhD
HFSP Research Fellow

PHILIPPE COLLIN PhD
Isaac Newton Trust/BBSRC Research Associate

BARBARA DI FIORE PhD
Cancer Research UK Research Associate

OLIVIER GAVET PhD
MRC Research Associate

ANJA HAGTING PhD
Cancer Research UK Research Associate

DAISUKE IZAWA PhD
AICR Research Associate

MARK JACKMAN PhD
Cancer Research UK Research Associate

AGATA LICHAWSKA BSc
Herchel Smith Graduate Student

JÖRG MANSFELD PhD
FEBS Research Fellow

PAOLA MARCO BSc
BBSRC CASE Graduate Student

TAKAHIRO MATSUSAKA PhD
Cancer Research UK Research Associate

OXANA NASHCHEKINA MSc
Cancer Research UK Chief Research Technician

JAKOB NILSSON PhD
BBSRC Research Associate

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

FELICIA WALTON
Marshall Scholar

MONA YEKEZARE
Yousef Jameel Graduate Student

JORDAN RAFF PhD

Director of Research in Cancer Cell Biology
Cancer Research UK Senior Research Fellow
(Member of the Department of Genetics)

JULIET BARROWS BA
Secretary

KATHRIN BRUNK PhD
Cancer Research UK Research Associate

PAUL CONDUIT BSc
Cancer Research UK Graduate Student

JEROEN DOBBELAERE PhD
Cancer Research UK Research Associate

ANNA FRANZ BSc
Wellcome Trust Graduate Student

RICHARD RESCHEN BSc
MRC Graduate Student

JENNY RICHENS PhD
Cancer Research UK Senior Research Technician

NAOMI STEVENS MPhil
Wellcome Trust Graduate Student

JIM SMITH PhD FRS FMedSci

John Humphrey Plummer Professor of Developmental Biology
Member, European Molecular Biology Organization
Member, Academia Europaea
(Member of the Department of Zoology)

LIZ CALLERY PhD
Wellcome Trust Research Associate

JOHN CANNON BSc MBBS
National Institute of Health Research (NIHR) Cambridge Biomedical Centre Graduate Student

NICOLE CHAN PhD
Wellcome Trust Research Associate

MIKE CHESNEY PhD (Transferred to Ahringer Group)
EU Research Associate

SENIOR GROUP LEADERS

CLARA COLLART PhD
EU Research Associate

KEVIN DINGWELL PhD
Wellcome Trust Research Associate

AMANDA EVANS HNC
Wellcome Trust Research Assistant

GEORGE GENTSCH MPhil
Wellcome Trust Graduate Student

STEVE HARVEY PhD
Wellcome Trust Research Associate

KIM LACHANI
EU Chief Research Technician

AMER RANA PhD
Wellcome Trust Senior Research Associate

XIN XU
EU Graduate Student

AZIM SURANI PhD FRS FMedSci

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

SUZAN BER PhD
Wellcome Trust Research Associate

DELPHINE COUGOT PhD
Wellcome Trust Research Associate

LYNN FROGGETT
Secretary

ASTRID GILLICH
Wellcome Trust Graduate Student

SAM GOSSAGE MSc
Wellcome Trust Research Assistant

NILS GRABOLE BSc
Wellcome Trust Graduate Student

PETRA HAJKOVA PhD
Wellcome Trust Research Associate

SOPHIE HANINA
Graduate Student

KATSUHIKO HAYASHI PhD
Wellcome Trust Research Associate

SEAN JEFFRIES
NIH Graduate Student

SHINSEOG KIM PhD
Wellcome Trust Research Associate

CAROLINE LEE ONC
Wellcome Trust Chief Research Technician

HARRY LEITCH
Graduate Student

ERNA MAGNÚSDÓTTIR PhD
Marie Curie Research Fellow

WILLIAM MIFSUD
Graduate Student

QIN SI PhD
Wellcome Trust Research Associate

FUCHOU TANG PhD
Wellcome Trust Research Associate

WEE WEI TEE
Graduate Student

KATARZYNA WILCZYNSKA PhD
Wellcome Trust Research Associate

LENG SIEW YEAP
Graduate Student

THOMAS DOWN PhD

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

RAYMOND LIM
Visiting Student from Canada

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

RICK LIVESEY MB BChir PhD

Wellcome Trust Group Leader
(University Senior Lecturer in Biochemistry)

SARRITA ADAMS BSc
Graduate Student

JESSICA ALSIO BSc
Wellcome Trust Graduate Student

THERESE ANDERSSON PhD
Wenner-Gren Foundation Research Fellow

JULIET BARROWS BA
Secretary

CHIBA ENE
NIH-Cambridge Graduate Student

JOAO PEREIRA BSc
Graduate Student

STEPHEN SANSOM PhD
Wellcome Trust Research Associate

YICHEN SHI
Graduate Student

JAMES SMITH BSc
Wellcome Trust Research Assistant

URUPORN THAMMONGKOL BSc
Graduate Student

MASANORI MISHIMA PhD

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

SUE CROYSDALE
Secretary

TIM DAVIES BSc
BBSRC Graduate Student

MAX DOUGLAS MBiochem
BBSRC Graduate Student

GROUP LEADERS

ANDREA HUTTERER PhD
HFSP Research Fellow

NIMESH JOSEPH PhD
Cancer Research UK Research Associate

KIAN-YONG LEE BSc
Cancer Research UK Graduate Student

JULIA MASON BSc
Cancer Research UK Research Assistant

EVA PABLO-HERNANDO PhD
Cancer Research UK Research Associate

ERIC MISKA PhD

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

JAVIER ARMISEN GARRIDO PhD
BBSRC Research Associate

MARLOES BAGIJN MSc
Graduate Student

KATSIARYNA BICHEL BSc
Cancer Research UK Research Assistant

CHERIE BLENKIRON PhD
EU Research Associate

ALEJANDRA CLARK PhD
Cancer Research UK Research Associate

PARTHA DAS MSc
Cancer Research UK Chief Research Technician

ETHAN KAUFMAN BSc
Gates Graduate Student

NIC LEHRBACH MPhil
Graduate Student

HELEN LIGHTFOOT BSc
Graduate Student

ALEXANDRA SAPETSCHNIG PhD
Herchel Smith Research Fellow

FUNDA SAR PhD
Cancer Research UK Research Associate

ROBERT SHAW BA MPhil
Graduate Student/Myrovlytis Trust Research Assistant

EVA-MARIA WEICK BSc
Herchel Smith Graduate Student

JULIE WOOLFORD MPhil
Cancer Research UK Graduate Student

EMMA RAWLINS PhD

MRC Research Fellow

JULIET BARROWS
Secretary

PHILIP ZEGERMAN PhD

AICR Research Fellow
(Member of the Department of Zoology)

SUE CROYSDALE
Secretary

Davide Mantiero PhD
AICF Research Associate

MAGDALENA ZERNICKA-GOETZ PhD

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

ANNA AJDUK PhD
Foundation for Polish Science Research Fellow

HELEN BOLTON
Wellcome Trust MD Graduate Student

ALEX BRUCE PhD
Wellcome Trust Research Associate

SUE CROYSDALE
Secretary

DAN FILIPESCO
Visiting Student

SEEMA GREWAL PhD
Wellcome Trust Research Associate

AGNIESZKA JEDRUSIK
Graduate Student

RUI MARTINS PhD
EMBO Research Fellow

SAMANTHA MORRIS PhD
Wellcome Trust Research Associate

EMLYN PARFITT
MRC Graduate Student

BEDRA SHARIF
Gates Graduate Student

JACKIE SIMCOX
Secretary

MARIA SKAMAGKI
Greek State Scholarship Graduate Student

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

ROY (TANG YI) TEO
A* Graduate Student

KRZYSZTOF WICHER PhD
Wellcome Trust Research Associate

PIRAYE YURTTAS PhD
Wellcome Trust Research Associate

ADMINISTRATION

ANN CARTWRIGHT MPhil
Institute Administrator

SUZANNE CAMPBELL BSc
HR / Grants Manager

DIANE FOSTER
Deputy Administrator

LYNDA LOCKEY
Office Manager

JACKIE SIMCOX
Receptionist

GEORGE BROWN
Accounts Manager

JANE COURSE
Accounts/Admin Assistant

KATHY HILTON DipMgm
CBSG Manager

NIKKI PARSONS BA
Receptionist

SUPPORT STAFF

COMPUTING

ALASTAIR DOWNIE
Computer Associate

NICOLA LAWRENCE PhD
Computer Associate

ALEX SOSSICK BSc
Computer Imaging Associate

CLIONA HANN BSc BA ACMA
Computer Associate

NIGEL SMITH
Computer Associate

PETER WILLIAMSON BSc
Computer Associate

BIOINFORMATICS

MIKE GILCHRIST PhD
Computer Associate (Bioinformatics)

SAM TAYLOR PhD
Computer Associate (Bioinformatics)

MIKKEL CHRISTENSEN PhD
Computer Associate (Bioinformatics)

ACCOUNTS/PURCHASING/STORES

IAN FLEMING
Stores/Purchasing Manager

DAVID COOPER
Stores Technician

ANDY VINCENT
Stores Technician

SIMON ALDIS
Purchasing/Accounts Assistant

RICHARD ETTERIDGE MA
Purchasing/Accounts Assistant

MICK WOODROOFE
Purchasing/Accounts Assistant

TECHNICAL SUPPORT

KEITH SAVILL
Senior Technical Officer

POLLY ATTLESEY
ROBERT BRETT
GARY GARNER
RICHARD HARPER
WEN JIN
URSZULA KOKOT
FALLON MILLER
JASON RISEBOROUGH
RACHEL SMITH-MILLER
KATIE WOODHOUSE

NIGEL BARNETT
ANNABELLE CURRY
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JAMES SMITH (JT)

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JUANITA BAKER-HAY
Media/Glass Washing Manager

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AGNES ASSELIN-LE-FOLL
BETTINA CASHIN
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LINDA ADAMS
LISA BAKER
BEVERLEY CORNELL
SANDRA HUMAN
TRACY MITCHELL

CATERING

AMANDA HARRIS
DARIA SKRODZKA
MELISSA PLOWDEN ROBERTS

Embryonic muscles stained for beta3-tubulin (purple) and the integrin alphaPS2 (green). (Isabel Delon, Brown Lab, 2009)

INSTITUTE PUBLICATIONS

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

* Indicates equal priority.

1 Adjaye JA, Byskov AG, Cibelli JB, De Maria R, Minger S, Sampaolesi M, Testa G, Verfaillie C, Zernicka-Goetz M, Schöler H, Boiani M, Crosetto N, Redi CA (2008). Pluripotency and differentiation in embryos and stem cells. **Int J Dev Biol** 52(7), 801-9

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

3 Amin N, Khan A, St. Johnston D, Tomlinson I, Martin S, Brenman J and McNeill, H (2009) LKB1 regulates polarity remodeling and adherens junction formation in the *Drosophila* eye. **PNAS** 106, 8941– 8946

4 Argasinska J, Rana AA, Gilchrist MJ, Lachani K, Young A and Smith JC (2009) Loss of REEP4 causes paralysis of the *Xenopus* embryo. **Int J Dev Biol** 53, 37-43

5 Armisen J, Gilchrist MJ, Wilczynska A, Standart N and Miska EA (2009) Abundant and dynamically expressed miRNAs, piRNAs and other small RNAs in the African clawed frog *Xenopus tropicalis*. **Genome Res** doi:10.1101/gr.093054.109

6 Bastock R and St Johnston D (2008) *Drosophila* oogenesis. **Current Biology** 18, R1082

7 Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A (2009) An operational definition of epigenetics. **Genes Dev** 23(7),781-783

8 Biddle A, Simeoni I and Gurdon JB (2009) *Xenopus* oocytes reactivate muscle gene transcription in transplanted somatic nuclei independently of myogenic factors. **Development** 136, 2695-2703

9 Brand AH (2008) A new dawn for Aurora? **Nature Cell Biology** 10, 1253-1254

10 Brown NH (2008) Spectraplakins: the cytoskeleton's Swiss army knife. **Cell** 135, 16-18

11 Bruce AW, Lopez-Contreras AJ, Flicek P, Down TA, Dhami P, Dillon SC, Koch CM, Langford CF, Dunham I, Andrews RM & Vetrie D (2009) Functional diversity for REST (NRSF) is defined by *in vivo* binding affinity hierarchies at the DNA sequence level. **Genome Res** 19, 994-1005

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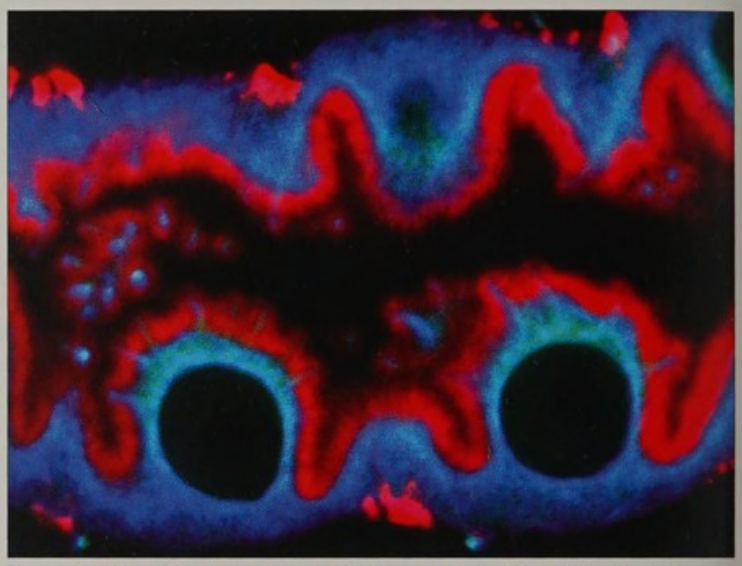

Drosophila Malpighian tubule. Red: actin, Green: tubulin, Blue: Shot. (Dmitri Nashchekin, St Johnston lab, 2009)

13 Codega P, Santina LD, Gargini C, Bedolla DE, Subkhankulova T, Livesey FJ, Cervetto L and Torre V (2009) Prolonged illumination up-regulates arrestin and two guanylate cyclase activating proteins: a novel mechanism for light adaptation. **J Physiol** 587, 2457-2472.

14 Collart C, Ramis JM, Down TA and Smith JC (2009) Smicl is required for phosphorylation of RNA polymerase II and affects 3'-end processing of RNA at the midblastula transition in *Xenopus*. **Development** 136, 3451-3461

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

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0 Gabory A, Ripoche MA, Le Digarcher A, Watrin F, Ziyyat A, Forné T, Jammes H, Ainscough JFX, Surani MA, Journot L and Dandolo L (2009) H19 acts as a trans regulator of the imprinted gene network controlling growth in mice. **Development** 136, 3413-3421

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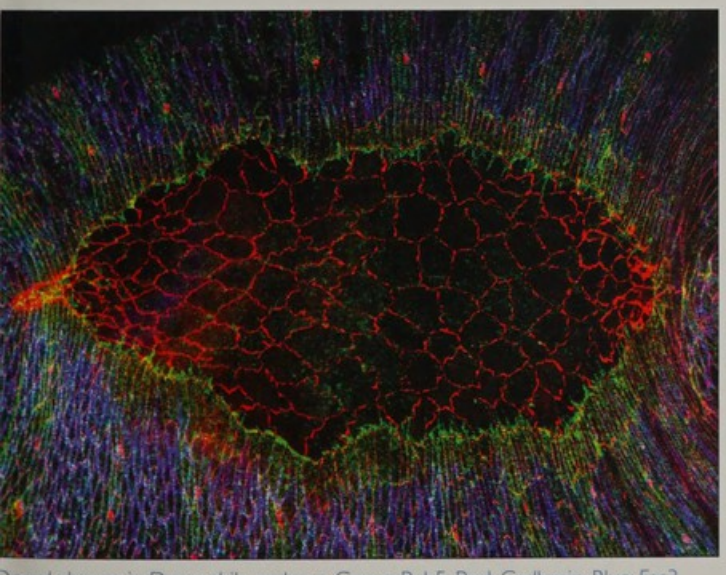
3 Garnett AT, Han TM, Gilchrist MJ, Smith JC, Eisen MB, Wardle FC and Amacher SL (2009) Identification of direct T-box target genes in the developing zebrafish mesoderm. **Development** 136, 749-760

4 Gilchrist MJ, Christensen MB, Harland R, Pollet N, Smith JC, Ueno N, Papalopulu N (2008) Evading the annotation bottleneck: using sequence similarity to search non-sequence gene data. **BMC Bioinformatics** 9, 442

5 Gu Y, Runyan C, Shoemaker A, Surani MA, Wylie C (2009) Steel factor controls primordial germ cell survival and motility from the time of their specification in the allantois, and provides a continuous niche throughout their migration. **Development** 136(8),1295-303

6 Gurdon JB (2009) Nuclear reprogramming in eggs. **Nature Medicine** 15, 1141-1144



Dorsal closure in Drosophila embryo. Green: Rab5, Red: Cadherin, Blue: Fas3 (Jonathan Friedlander, Brown lab, 2009).

27 Hagemann AI, Xu X, Nentwich O, Hyvonen M and Smith JC (2009) Long-range signalling and gene activation in the *Xenopus* embryo do not require Rab5-mediated endocytosis. **Development** 136, 2803-2813

28 Harvey SA and Smith JC (2009) Visualisation and quantification of morphogen gradient formation in the zebrafish. **PLoS Biology** 7: e1000101

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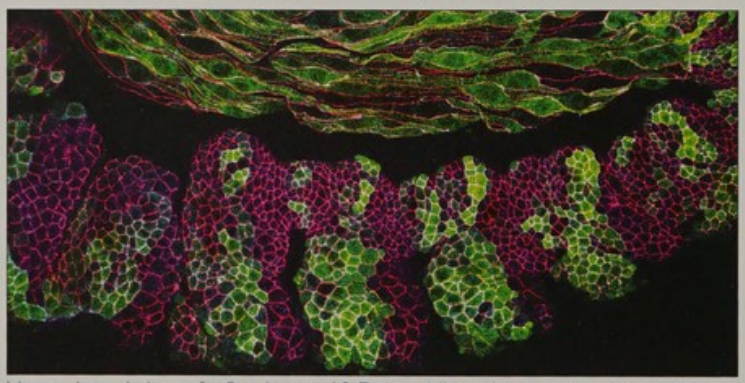

Ventro-lateral view of a fixed stage 10 Drosophila embryo expressing a UAS-GFP (green) construct driven by a patched-gal4 driver; co-staining is against E-Cadherin (red) and Enabled (blue). On top of the picture are amnioserosa cells and on the bottom the anterior parts of the germband; anterior is to the left, ventral is is to the bottom (Sven Huelsmann, Brown lab, 2009).

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57 Smith JC (2009) Forming and interpreting gradients in the early *Xenopus* embryo. **Cold Spring Harb Perspect Biol** [in press]

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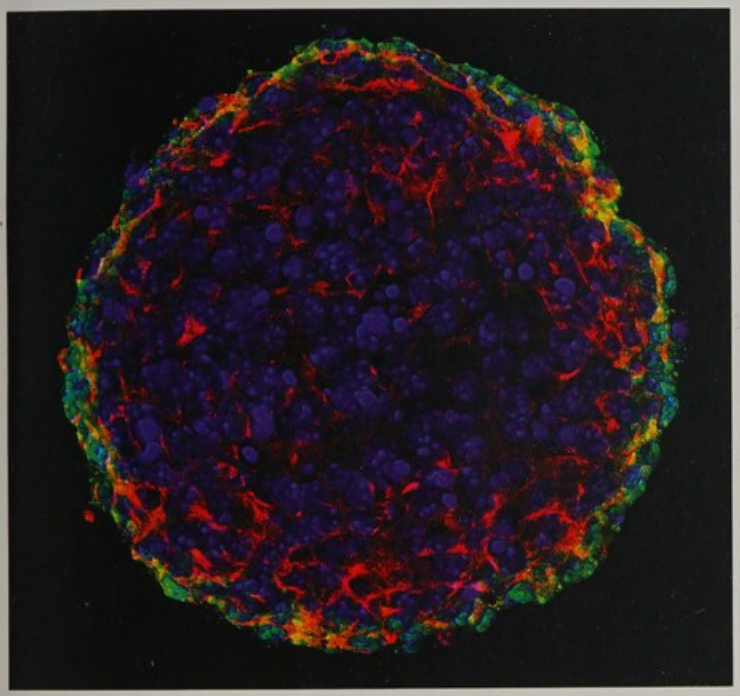
60 Southall TD, Egger B, Gold KS and Brand AH (2009) Regulation of self-renewal and differentiation in the *Drosophila* nervous system. **Cold Spring Harbor Symposia on Quantitative Biology** LXXIII, (Epub, doi: 10.1101/sqb.2008.73.051).



Immuno staining of a neurosphere formed by cultured mouse neural stem cells. Green: GFAP positive cells (astrocytes); Red: Nestin (Neural progenitors); Blue: DAPI. (James Smith, Livesey Lab, 2009)

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63 Southall TD and Brand AH (2009) Multiple transcription factor binding identifies neural stem cell gene regulatory networks. **EMBO J** [in press]

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79 Zernicka-Goetz M, Morris SA and Bruce AW (2009) Making a firm decision: multifaceted regulation of cell fate in the early mouse embryo. **Nat Rev Genet** 10, 467-77

STAFF AFFILIATIONS

JULIE AHRINGER is a member of the MRC Career Development Panel, of the European Research Council Starting Grant Panel, and on the Scientific Advisory Board of Reactome.

ANDREA BRAND is a Founding Board Member of The Rosalind Franklin Society, USA, member of the Sectional Committee of the Academy of Medical Sciences, member of the EMBO Young Investigator Committee, Vice Chair of the Neuroscience Review Panel of the Swedish Research Council and member of the Scientific Advisory Board for the MRC Centre for Developmental Neurobiology, King's College London. She is also a member of the University of Cambridge Neuroscience Committee, member of the steering group of the Cambridge Women in Science, Engineering and Technology Initiative, and a Patron of the Cambridge Science Festival.

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

STEVE JACKSON is a member of the Radiation Oncology and Biology External Advisory Board, Scientific Advisory Board for the Beatson Institute, University of Oxford Steering Committee for the UK Research Network on the Biomedical Applications of High Energy Ion Beams, University of Cambridge Advisory Group on Translation of Research, and is consultant for KuDOS Pharmaceuticals Ltd.

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 director of Abcam Plc.

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

JORDAN RAFF is a member of the Academy of Medical Sciences' working group on the Careers of Basic Scientists, a Non-Executive Director of the Company of Biologists, a life-long member of the Royal Institution, and a Committee Member and Honor Fell Travel Award Secretary of British Society for Cell Biology.

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

JIM SMITH is a member of the Board of Directors of the Babraham Institute and a member of the Cancer Research UK Assessment Panel for Senior University Salaries. He is also Chairman of the Royal Society Research Appointment Panel (Bi), Chairman of the Wellcome Trust Sir Henry Wellcome Postdoctoral Fellowship Committee and a member of the Wellcome Trust Molecular and Physiological Sciences Strategy Committee. He is Chairman of the Scientific Advisory Board of The Max-Planck-Institut für Immunbiologie and Institute for Toxicology and Genetics, Karlsruhe.

AZIM SURANI is Chairman of the Scientific Advisory Board of the Centre for Trophoblast Research, University of Cambridge, Member of the International Scientific Advisory Board of the Wellcome Trust Centre for Stem Cell Research, University of Cambridge, Member of the Cambridge India Partnership Advisory Group, Founder and Chief Scientific Advisor for CellCentric Ltd., Member of the Steering Committee for the UK Stem Cell Bank and Use of Human Stem Cell Lines, Sir Dorabji Tata Visiting Professor, Tata Institute for Fundamental Research, NCBS, Bangalore, India, Distinguished Fellow Jawaharlal Nehru Centre for Advanced Scientific Research, Member of the Royal Society International Grants Panel, and Visiting Professor, University of Kyoto, Japan.

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

HONOURS AND AWARDS

STEVE JACKSON - 2009 BBSRC Innovator of the Year

JOHN GURDON - 2009 Rosenstiel Award for Distinguished Work in Basic Medical Science (jointly with Irving L. Weissman and Shinya Yamanaka)

2009 Lasker Basic Medical Research Award (jointly with Shinya Yamanaka)

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ANDREA BRAND – Neural Development, Fly, Biology Image Library

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RICK LIVESEY – BMC Developmental Biology, Molecular Autism

JON PINES – EMBO Journal, EMBO Reports.

DANIEL ST JOHNSTON – Development, EMBO Journal, EMBO Reports.

JIM SMITH – Development (Editor-in-Chief), Trends in Genetics, EMBO Reports.

AZIM SURANI – Cell, Differentiation, Cell Stem Cell, BMC Epigenetics and Chromatin, Epigenome, Epigenetics, Regenerative Medicine, Faculty of 1,000.

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PROF ERICH NIGG, Max Planck Institute for Biochemistry, Martinsried, Germany

CHAIRMEN OF THE MANAGEMENT COMMITTEE

PROFESSOR SIR TOM BLUNDELL, Head of Department of Biochemistry and Chair of the School of Biological Sciences, University of Cambridge, UK (to September 2009)

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

LEAVERS DURING 2009

FREDERIC ANTIGNY completed placement and returned to full-time studies

SOPHIE BALERDI-DELTOUR grant funding ceased and project completed

KATSIARYNA BICHEL started a PhD at LMB, Cambridge

CHERIE BLENKIRON moved to New Zealand and took up a position at Auckland University

EMMANUEL BOUCROT is a Staff Scientist at MRC LMB

LIZ CALLERY transferred to Roger Pedersen's lab at Addenbrooke's, Cambridge

JOHN CANNON transferred to Addenbrooke's, Cambridge

NICOLECHAN moved with Smith Group to NIMR, London

MIKKEL CHRISTENSEN transferred to CIMR, Medical Genetics

CLARA COLLART moved to NIMR with Smith group

PAUL CONDUIT moved to Oxford with Raff group

PARTHADAS took up a postdoctoral position at Harvard Medical School

ISABELLE DELON Trainee Clinical Scientist in Molecular Genetics at Addenbrooke's hospital

KEVIN DINGWELL moved to NIMR with Smith group

JEROEN DOBBELAERE moved with Raff lab to Oxford

KARIN EDOFF Postdoctoral Research Associate in the Department of Zoology

AMANDA EVANS moved with Smith Group to NIMR, London

DAN FILIPESCU completed placement and returned to full-time studies at École Normale Supérieure, Paris

ANNA FRANZ moved with Raff lab to Oxford

OLIVIER GAVET is a Lecturer at University of Paris VI

SANDRA GEHRKE completed placement and returned to full-time studies

GEORGE GENTSCH moved with Smith Group to NIMR, London

MIKE GILCHRIST transferred to NIMR to become a Group Leader

SAM GOSSAGE moved to UCL to take up a new position

PETRA HAJKOVA Group Leader at MRC Unit, Hammersmith hospital

CLIONA HANN left to complete her PhD

STEVE HARVEY Postdoctoral position at Babraham Institute, Cambridge

KATSUHIKO HAYASHI Lecturer at Graduate School of Medicine, Kyoto University

SEAN JEFFRIES Studentship completed

KAMILA JOZWIK completed placement and returned to full-time studies

VOLKAN KARABACAK completed placement and returned to full-time studies

AMANDA KINGSNORTH has taken a Technician post in education sector

HELEN KIRKMAN took up a Technician position with Illumina

KIM LACHANI moved with Smith Group to NIMR, London

DAVID LANDO moved to Ernest Laue's lab, Biochemistry Department, University of Cambridge

RAYMOND LIM completed placement and returned to full-time studies

ANDREA MAFIOLETTI completed placement and returned to full-time studies

SUSHMITA MAITRA completed project and is an Academic Visitor in the Brown group

RUI MARTINS took up a postdoctoral position at Queen Mary University of London

SOLÈNE MOLLE completed placement and returned to full-time studies at École Normale Supérieure, Paris

KAZUTAKA MURATA Post Doc position at Stanford, USA

JAKOB NILSSON Group Leader at Biotech Research and Innovation Centre, Copenhagen

EMLYN PARFITT Post Doctoral position at Columbia University in New York

CLAIRE PIKE Research Associate in Paul Edward's lab at MRC/Hutchison Research Centre, Cambridge

JENNY PESTEL completed placement and returned to full-time studies

JORDAN RAFF Cesar Milstein Professor of Molecular Cancer Biology, University of Oxford

AMER RANA British Heart Foundation Lecturer in Vascular Biology, Department of Medicine, University of Cambridge

RICHARD RESCHEN moved with Raff lab to Oxford

HANNA REUTER completed placement and returned to full-time studies

JENNIFER RICHENS moved with Raff lab to Oxford, taking up Post Doctoral position

ILENIA SIMEONI completed project

NAOMI STEVENS Post Doctoral position at Sloan Kettering Institute, New York

SAM TAYLOR left to take up Bioinformatics post in Manchester

SHANE WOODS Studentship completed

PIRAYE YURTTAS setting up Biotechnology Company in US

LENG SIEW YEAP Studentship completed

Crick and Watson would have done it this way, if they'd thought of it. Fun and games at the Institute Retreat, Leicestershire, October 2009. (John Overton)

ACKNOWLEDGEMENTS

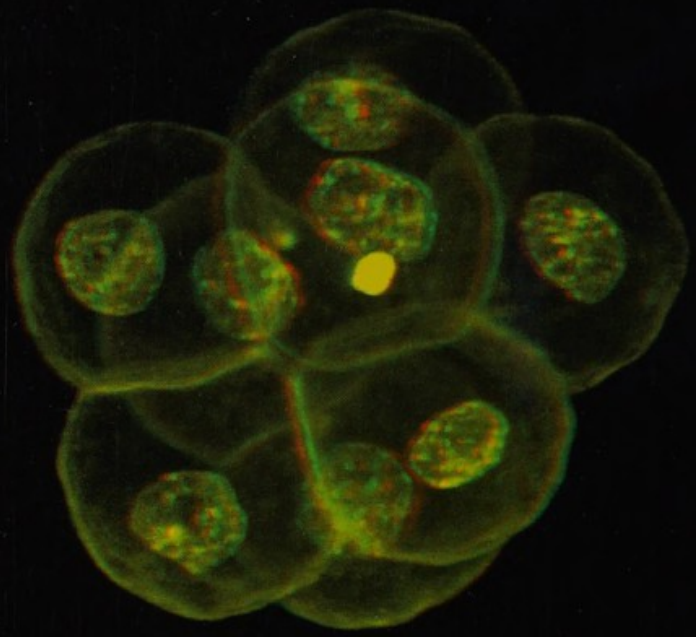
Prospectus produced in the Wellcome Trust/Cancer Research UK Gurdon Institute. Edited by Ann Cartwright, production by Alastair Downie

Group photographs by James Smith, Livesey Group.

Print management by H2 Associates, Cambridge

Front cover: Mouse embryonic stem cell-derived neural progenitors form rosette structures in culture. Pax6 (Red) and OTX1 (Green) are both homeodomain transcription factors expressed in developing dorsal forebrain neural progenitor cells. DAPI-Blue (Yichen Shi, Livesey lab, 2009)

Back cover: 3D projection of an 8-cell mouse embryo with DAPI and phalloidin staining. (Alex Bruce and Dan Filipescu, Zernicka-Goetz lab, 2009)



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