Annual report : 2008/2009 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

The Wellcome Trust/Cancer Research UK Gurdon Institute

2009 PROSPECTUS / ANNUAL REPORT 2008

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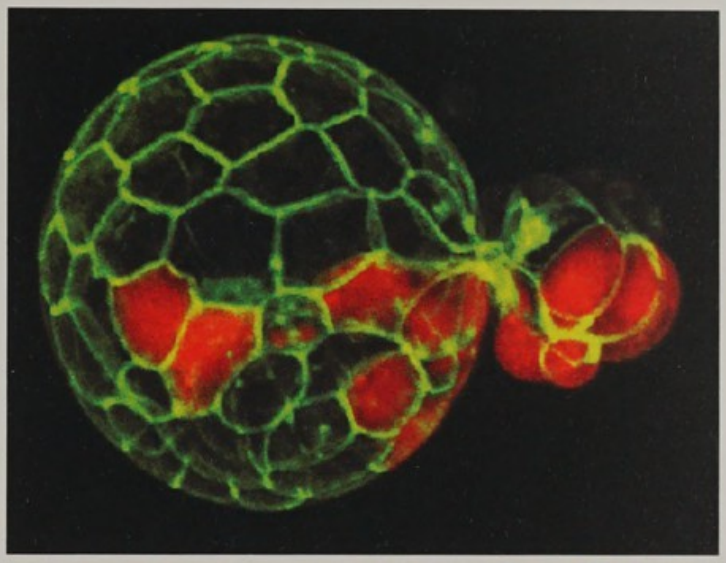
INTRODUCTION

It will be obvious from the Research Group pieces that make up a large of this Report that this has been another successful year of science for the Gurdon Institute, and as usual the work of our colleagues has been recognised by many awards and prizes. Most gratifyingly, Steve Jackson was elected to the Fellowship of the Royal Society, making him our second 'home-grown' FRS (the first being Daniel St Johnston). Steve's election is testament to the prescience of John Gurdon and Ron Laskey, who recruited him to the then Wellcome CRC Institute in 1991, and is just reward for Steve's pioneering work on the DNA damage response since then. We send Steve our warmest congratulations. Meanwhile we were delighted that Eric Miska became an EMBO Young Investigator and were also pleased to hear that Sir John Gurdon will receive the Rosenstiel Award for Distinguished Work in Basic Medical Science in 2009 (a distinction also received by Azim Surani, in 2007).

Last year's report announced the arrival of Thomas Down to the Institute as a Group Leader, and this year we look forward to welcoming Emma Rawlins and Philip Zegerman. Emma comes from Brigid Hogan's lab in the Department of Cell Biology at Duke University, and she will investigate epithelial stem and progenitor cells in the postnatal mouse lung. Philip comes from John Diffley's group at the Clare Hall laboratories of Cancer Research UK, where he studies DNA replication in budding yeast. We welcome both these scientists to the Gurdon Institute and look forward to working with them.

The Gurdon Institute (Photograph by A Downie)



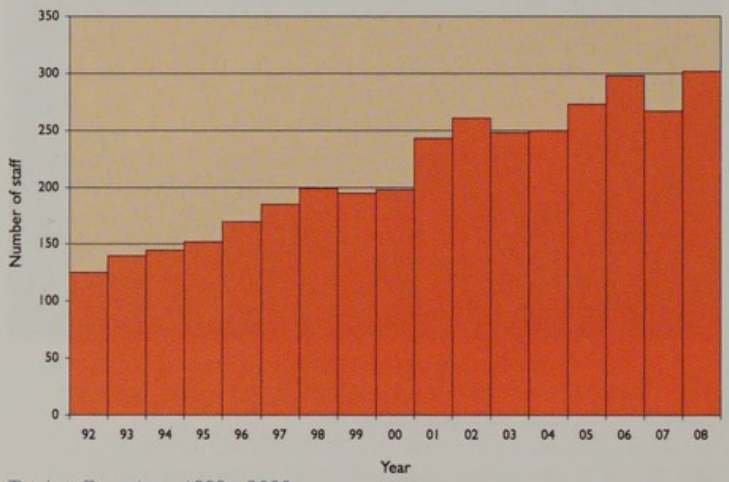
Hatching pre-implantation mouse embryo, injected with Tomato-RFP at 8 cell stage and stained with Oregon Green phalloidin to visualise the membrane. (Sam Morris, Zernicka Goetz Lab, 2008)

One marker of the success of an Institute is the departure of its senior members to influential positions elsewhere, and we therefore congratulate Jordan Raff on his election as the César Milstein Professor of Cancer Cell Biology at the Sir William Dunn School of Pathology in Oxford. We wish Jordan well, but of course we shall miss him and his lab enormously, not only for his great science (who would have thought that an animal could survive with no centrioles?) but also for his enthusiasm, his contributions to the social life of the Institute, and his wonderful 'outreach' work (for which he became life-long member of the Royal Institution). Jordan will want me to point out that he hasn't gone yet–he takes up his position in September 2009–but this is certainly the time to congratulate him on his achievement.

Our International Scientific Advisory Board visited the Gurdon Institute at the end of November 2008. As always the two-day meeting was extremely valuable both scientifically and strategically, and I should like to thank all members of the board (listed at the back of this report) for their hard work. It is greatly appreciated.

Finally, I should report that this is my last Introduction to the Gurdon Institute Annual Report and Prospectus, because from January 2009 I shall become Director of the Medical Research Council National

Institute for Medical Research. I have had a wonderful eight years at the Gurdon Institute, and I shall miss everyone who works here: group leaders, core staff, postdocs and students. I should like to thank everyone for making the Institute such a great place to work, and the University, the Wellcome Trust and Cancer Research UK for their support and encouragement over the years.



Total staff numbers 1992 - 2008

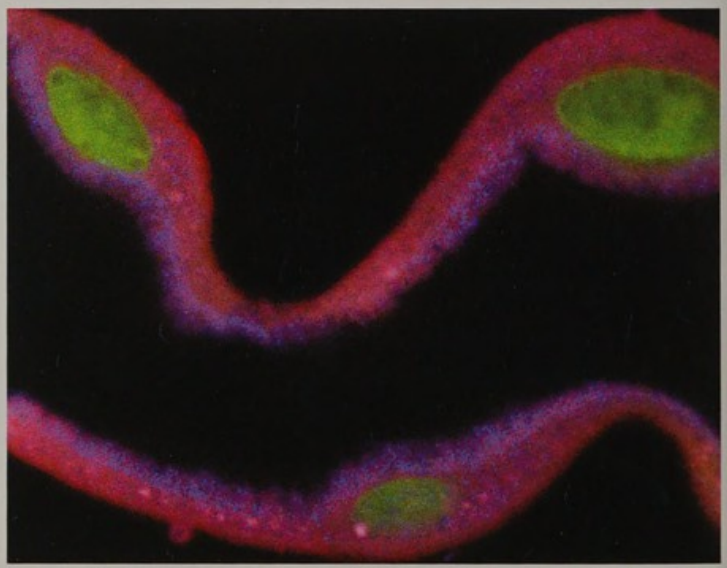
HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance from the centre of the historic city. Founded in 1989 to promote research in the areas of developmental biology and cancer biology, the Institute is an assemblage of independent research groups located in one 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 cellular and molecular levels. These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master, including molecular biology, biochemistry, microarray technology, bioinformatics, cell culture, imaging and embryonic manipulations. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another, as is the case in the Institute.

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

CENTRAL SUPPORT SERVICES

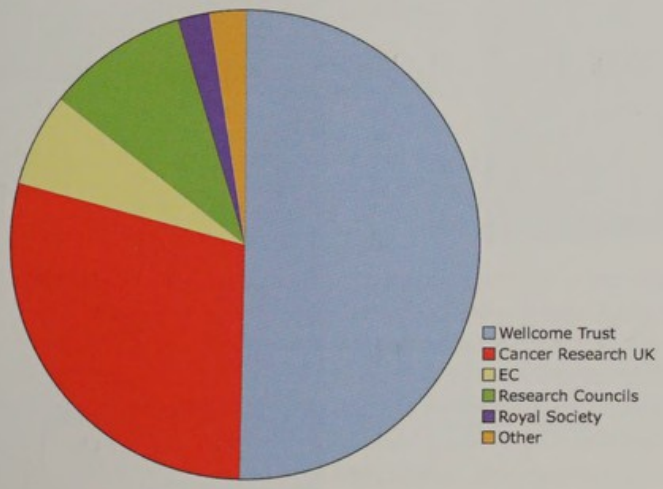
The Institute's 'core staff' provides essential administrative, technical and computing support to our scientists, so that the scientists can spend as much time as possible on their research. We thank these colleagues for their flexible, helpful and positive attitude to their work, which has contributed in no small part to the smooth running of the Institute.



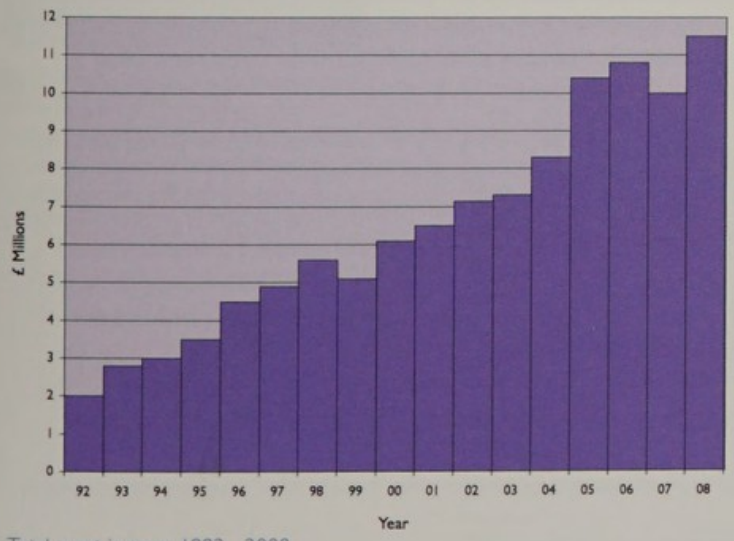
Nuclear GFP expression in *Drosophila* Malpighian tubules cells stained for aPKC (blue) and armadillo (red) (Eurico de Sa, St Johnston lab, 2008)

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 project grants, and programme and equipment grants, in addition to our invaluable core funding.



Grant sources (August 2007 - July 2008)



Total grant income 1992 - 2008

Other sources of financial support, both direct and indirect, include the European Union, the BBSRC, the MRC, the Royal Society, the Department of Trade and Industry, the Isaac Newton Trust, NIH, the European Molecular Biology Organisation, HFSP, the National Alliance for Autism Research, the Myrovlytis Trust, JDRF, Volkswagen Stiftung, Applera Corporation, Astra Zenica and the March of Dimes. We are extremely grateful to all these organisations for their continuing support.

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

RETREAT

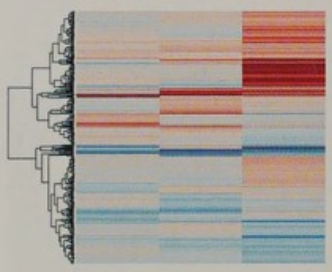
The Institute in Maldon, 2008. Photograph by John Overton (Brown group)

Our Annual Retreat this year was held for the first time at the Five Lakes Hotel near Maldon on 1st and 2nd October 2008; this provided an excellent venue, allowing members of the Institute every opportunity to interact both scientifically and socially. As always there was a strong attendance and we are grateful to the administrative team and to Jon Pines and Magdalena Zernicka-Goetz for organising it.

Julie Ahringer

Functions of chromatin regulatory complexes and the control of cell polarity

Co-workers: Anne Canonge, Ron Chen, Yan Dong, Bruno Fievet, Paulina Kolasinska-Zwierz, Isabel Latorre, David Rivers, Josana Rodriguez, Christine Turner, Shane Woods, Eva Zeiser



We study two separate research areas: the control of cell polarity and the regulation of chromatin remodelling during development. In both areas we use the genome-wide RNAi screening technology that we developed to identify new genes involved in these processes.

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, and additional cell polarity genes remain to be discovered. The one-celled *C elegans* embryo is one of the best-established systems for investigating cell polarity. It allows study of the polarity cue, its reception, and how polarisation leads to downstream events such as asymmetric spindle positioning. We are 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 real-time fluorescent cell imaging, genetics, and biochemistry.

Regulation of chromatin structure plays a central role in transcriptional control. A large number of chromatin regulating enzymes and complexes have been identified that induce changes in gene activity through alterations in local and/or higher order chromatin structure, however their mechanisms of action and relationships are poorly understood. The *C elegans* 'synMuv' genes function together in several developmental contexts and encode components of different chromatin regulatory complexes, including the histone deacetylase complex NuRD, the retinoblastoma complex Myb-MuvB, and a TIP60 histone acetyltransferase complex. We are studying the function of these proteins in transcriptional control and development using chromatin immunoprecipitation and other genetic and genomic methods.

(Inset left): Expression profiling of synMuv mutants using microarrays identifies gene expression changes compared to wild-type.

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 [in press]

Panbianco C, Weinkove D, Zanin E, Jones D, Divecha N, Gotta M, 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

Poulin G, Dong Y, Fraser AG, Hopper N and Ahringer J (2005) Chromatin regulation and sumoylation in the inhibition of Ras-induced vulval development in *C elegans*. **EMBO Journal** 24, 2613–2623

For complete list of this lab's publications since the last report, see numbers 8, 34, 47 & 49 on pp 49-53

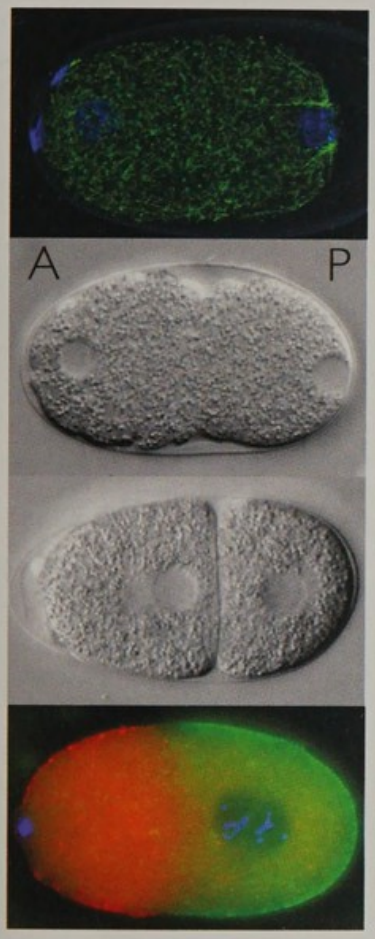
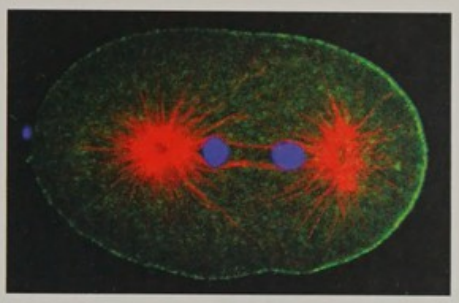


Fig. 1 Polarity is induced by an unknown signal requiring centrosomes and microtubules (green, top panel), leading to an asymmetric first cell division (middle panels) and asymmetrirc PAR protein distributions (lower panel).

Fig. 2. An asymmetrically distributed PIP2 synthesis enzyme (PPK-1, green) is required for spindle pulling forces that direct asymmetric spindle positioning.



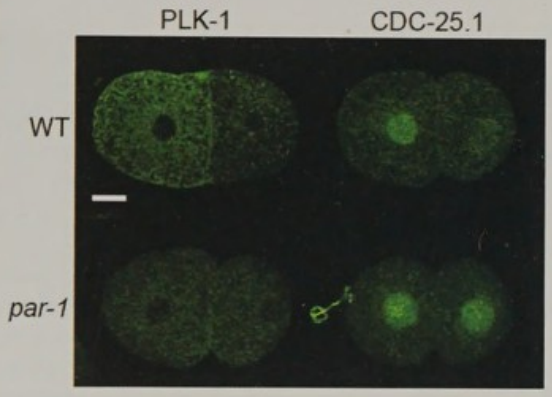
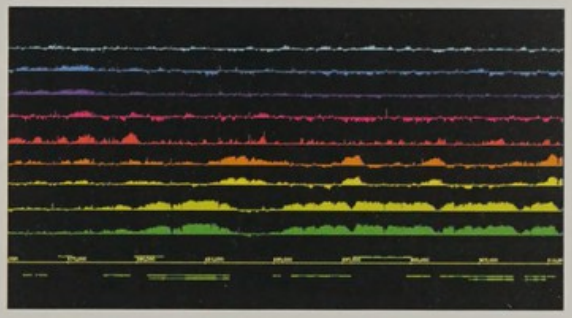


Fig. 3 PAR proteins control cell cycle timing through generating asymmetry of the key cell cycle regulators Polo-like kinase PLK-1 and the CDK phosphatase CDC-25.1.

Fig. 4 Genome-wide identification of binding sites for chromatin regulators and modifications using chromatin immunoprecipitation



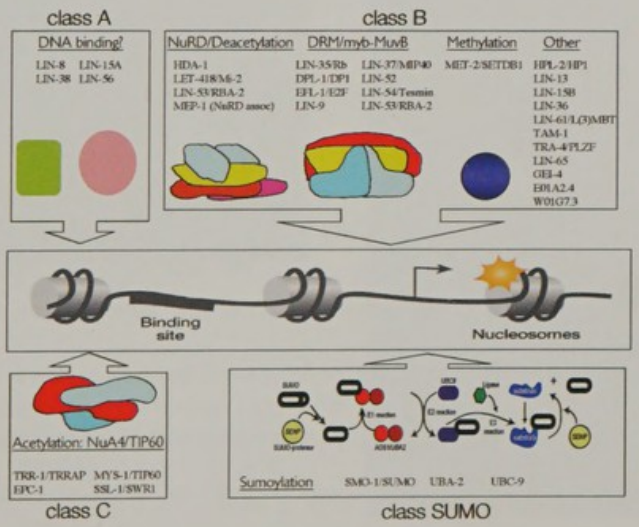
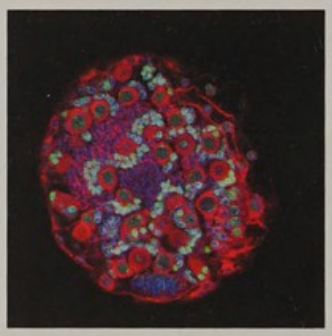


Fig. 5 synMuv proteins encode homologs of chromatin regulators found in complexes that modify histones or move nucleosomes.

Andrea Brand

Embryonic nervous system development: stem cells to synapses

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



Stem cells have the remarkable ability to self-renew and also produce differentiating daughter cells. Symmetric division expands the stem cell pool by generating similar daughter cells, while asymmetric division leads to self-renewal and differentiation. The proper balance between symmetric and asymmetric division is critical for the generation and subsequent repair of tissues, and unregulated stem cell division has been shown to result in tumourous overgrowth. We have shown that symmetrically dividing stem cells in the *Drosophila* optic lobe neuoroepithelium give rise to asymmetrically dividing cells (neuroblasts). To identify the molecular switches that mediate this transition, we isolate small groups of neuroepithelial cells or neuroblasts and compare their transcriptional profiles. The differentially expressed genes that we have identified highlight the Notch signal transduction pathway as key in regulating the switch from symmetric to asymmetric division.

Asymmetrically dividing stem cells segregate cell fate determinants at each division. We have shown that the determinant Prospero, a homeodomain transcription factor, acts as a binary switch between self-renewal and differentiation. We identified Prospero's targets throughout the genome and demonstrated that Prospero represses genes required for self-renewal, but is also required to activate genes for terminal differentiation. Without Prospero, differentiating daughters revert to a stem-cell-like fate: they express markers of self-renewal, proliferate, fail to differentiate and form small tumours.

By identifying neural stem-cell-specific genes, and genes specific for differentiating daughters, we can begin to assess the potential for redirecting post-mitotic cells to divide in a regenerative manner, or for inducing stem cells to differentiate.

Further information is available on the Brand Lab website:
http://www.gurdon.cam.ac.uk/~brandlab

Inset left: A brain lobe from a *Drosophila* third instar larva labelled with Dlg (red), BrdU (green) and DAPI (blue).

Chell JM and Brand AH (2008) Forever young: death-defying neuroblasts. **Cell** 133, 769-771

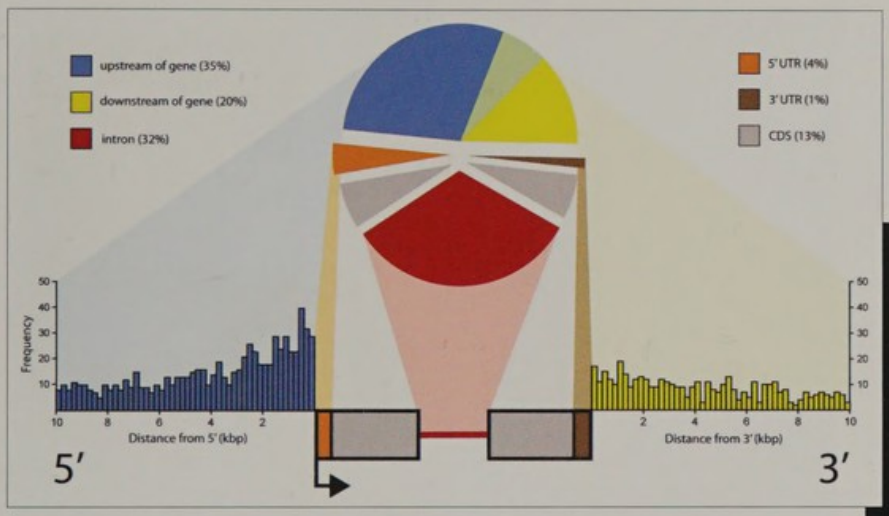
Egger B, Chell JM and Brand AH (2008) Insights into neural stem cell biology from flies. **Phil Trans Roy Soc B: Biological Sciences** 363, 39–56

Egger B, Boone JQ, Stevens NR, Brand AH and Doe CQ (2007) Regulation of spindle orientation and neural stem cell fate in the *Drosophila* optic lobe. **Neural Development** 2, 1

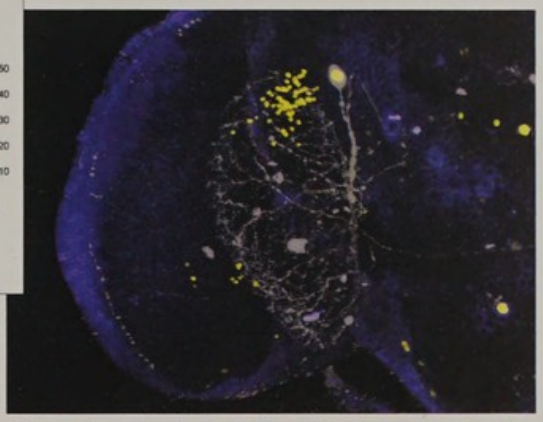
Choksi SP, Southall T, Bossing T, Edoff K, de Wit E, van Steensel B, Micklem G and Brand AH (2006) Prospero acts as a binary switch between self-renewal and differentiation in *Drosophila* neural stem cells. **Developmental Cell** 11, 775-789

van Roessel PJ, Elliott DA, Robinson IM, Prokop A and Brand AH (2004) Independent regulation of synaptic size and activity by the anaphase-promoting complex. **Cell** 119, 707-718

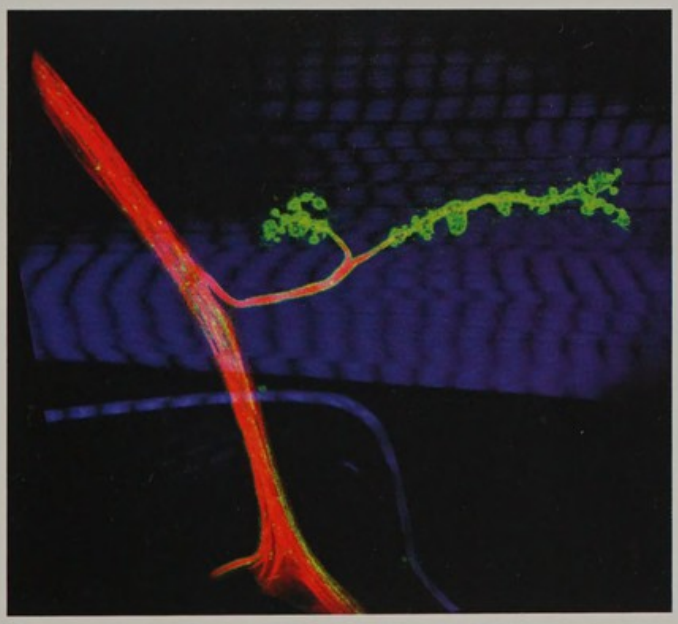
For complete list of this lab's publications since the last report, see number 22 on pp **49-53**



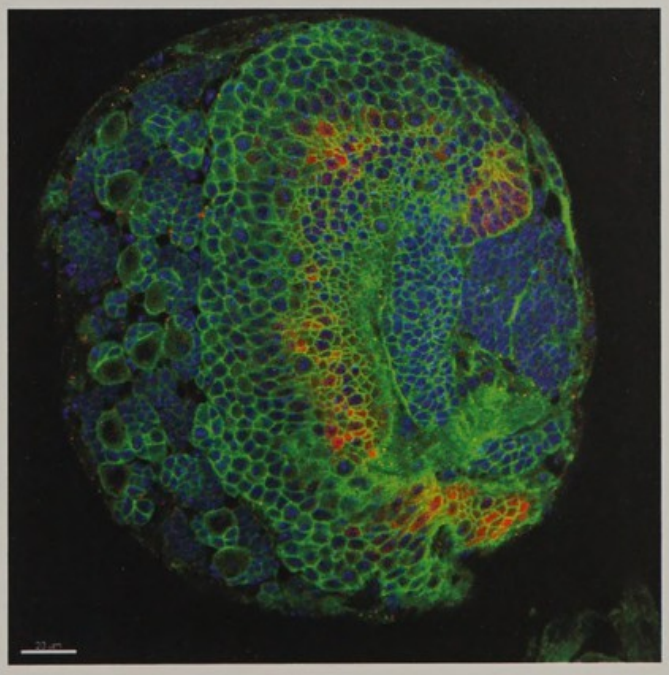
Genome-wide mapping of transcription factor binding sites using the DamID technique.



Three-dimensional visualisation of single cell clones in the adult brain. Dendritic and axonal projections are depicted in grey, cell nuclei in yellow, and cell outlines in blue.



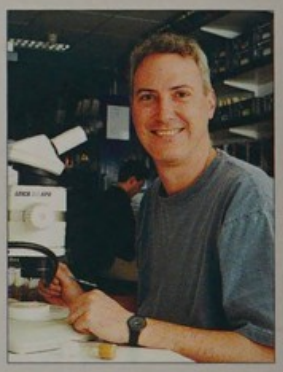
A neuromuscular synapse with synaptic boutons labelled in green, axon microtubules in red, and muscle actin in blue.



Neural stem cells in the larval brain: on the right can be seen the symmetrically dividing neuroepithelial cells and asymmetrically dividing neuroblasts of the optic lobe, on the left, the large neuroblasts of the central brain (Dlg, green; L'sc, red; DNA, blue).

Nick Brown

Molecular analysis of morphogenesis



Co-workers: Isabelle Delon, Jonathan Friedlander, 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 focused on determining how proteins inside and outside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers, and cell differentiation.

We use the genetics of the fruit fly *Drosophila* to elucidate integrin function within the developing animal, and to identify the proteins that work with integrins. The isolation of mutations in genes encoding proteins required for integrin function has been achieved using both forward genetics to identify genes that, like integrins, are required for adhesion between the two surfaces of the wing (inset picture), and using reverse-genetics to isolate mutations in genes encoding proteins that are associated with integrins in mammalian cells, such as paxillin (Fig1). While some of these proteins are required in all cells where integrins function, others such as Bloated are restricted to epidermal cells

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

Tanentzapf G, Devenport D, Godt D and Brown NH (2007) Integrin-dependent anchoring of a stem-cell niche. **Nature Cell Biol** 9, 1413-1418

Narasimha M, Uv A, Krejci A, Brown NH, Bray SJ (2008) Grainy head promotes expression of septate junction proteins and influences epithelial morphogenesis. **J Cell Sci** 121, 747-752

For complete list of this lab's publications since the last report, see numbers 15, 43 & 60 on pp 49-53

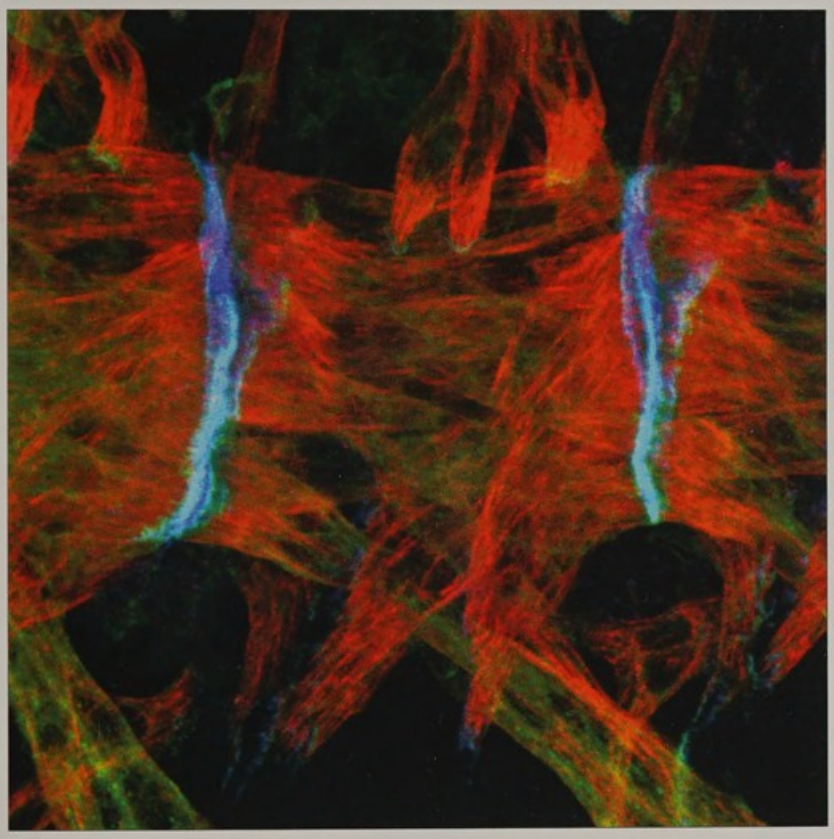


Fig 1: A major site of integrin function within the developing embryo is the muscle attachment site. Muscle myosin (red) shows the muscles, with integrins (blue) concentrated at the muscle ends, where they recruit a number of proteins that help link integrins to the cytoskeleton, such as paxillin (green).

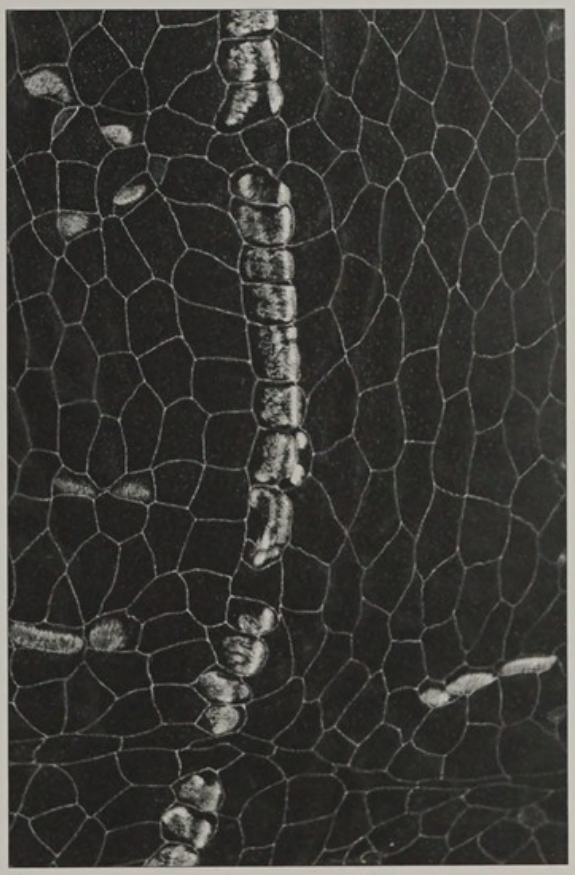


Fig 2: The novel integrin-associated protein Bloated is part of a cytoskeletal structure within specialised epidermal cells (called tendon cells), which transmits force from the muscles to the exoskeleton. The figure shows the epidermis of a larva containing two *Drosophila* proteins that have been fused to green fluorescent protein (GFP); the green fluorescence (in white) shows the distribution of these proteins. Cadherin-GFP is at the plasma membrane, and shows the outline of all epidermal cells. Bloated-GFP is found in bright dots in the middle of a subset of cells (the tendon cells) which corresponds to the position of the cytoskeletal structure.

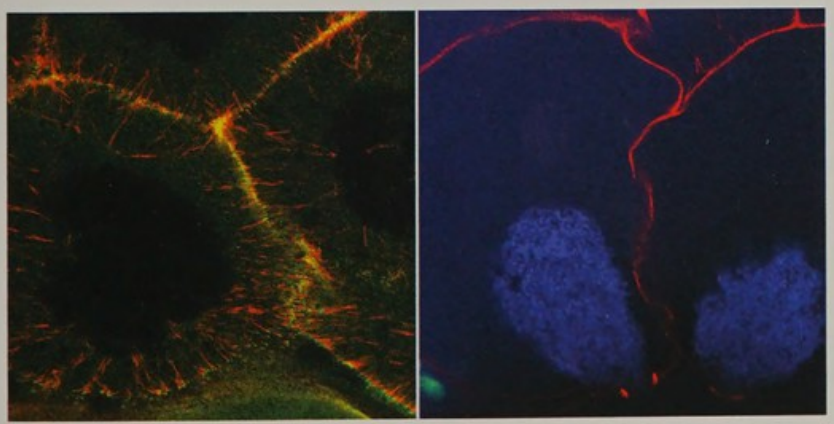
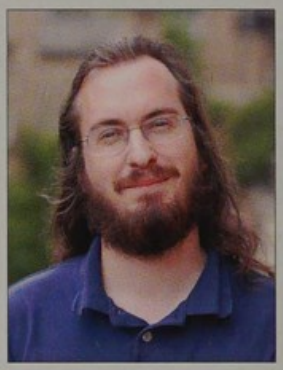


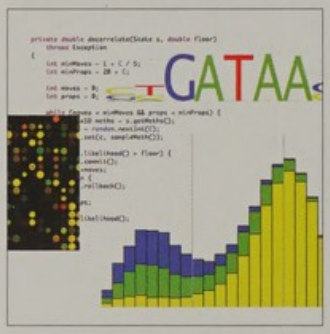
Fig 3: The integrin regulator Riam builds the actin struts that hold the nucleus in place. The left panel shows Riam-GFP (green) is positioned at one end of the actin struts (red) that extend from the plasma membrane to the nucleus (nuclei are unlabelled but visible as dark circles). Riam is required to form these actin struts, because in the absence of Riam (on the right), the struts are missing and the nuclei clog the ring canals (right).

Thomas Down

Transcription informatics



Co-workers: Siarhei Maslau, Jing Su



We study the mechanisms by which programs of gene expression are selected during the development of multicellular organisms. Regulatory sequences 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.

We would also like to understand how particular patterns of gene expression are stably maintained over time -- for instance, when a cell becomes committed to a particular developmental lineage. To this end, we are involved in studies of stable epigenetic modifications: particularly DNA cytosine methylation. High-throughput sequencing technologies allow epigenetic modifications to be studied on a genome-wide basis, and we have developed a new analytical technique, which we applied to deep sequencing data 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 mechanisms. We are also investigating how human DNA methylation changes are associated with ageing and complex diseases.

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, Beck S (2008) A Bayesian deconvolution strategy for immunoprecipitation-based DNA methylome analysis. Nature Biotech 26:779-785

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

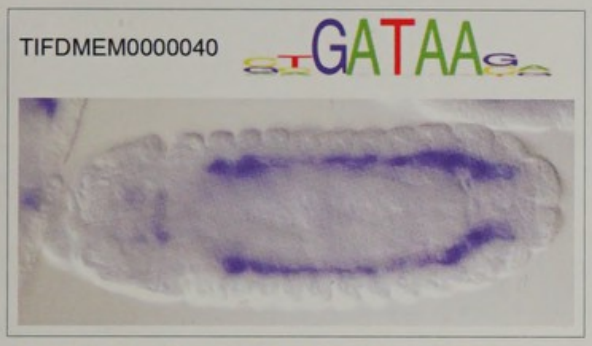
Eckhardt F, Lewin J, Cortese R, Rakyan VK, Attwood J, Burger M, Burton J, Cox TV, Davies R, Down TA, Haefliger C, Horton R, Howe K, Jackson DK, Kunde J, Koenig C, Liddle J, Niblett D, Otto T, Pettett R, Seemann S, Thompson C, West T, Rogers J, Olek A, Berlin K, Beck S (2006) DNA methylation profiling 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.

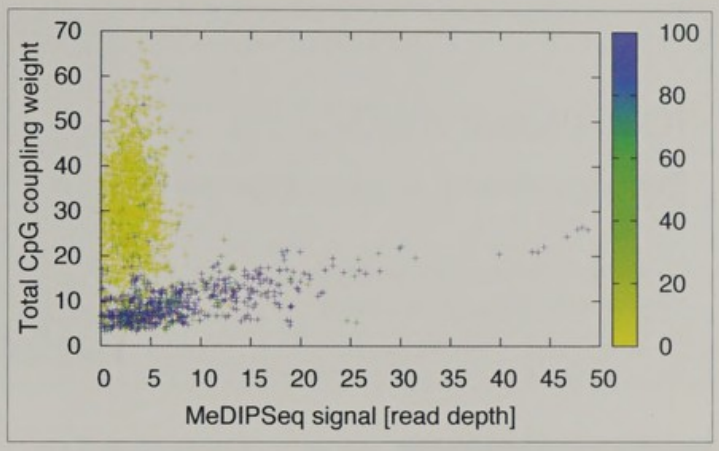
Down TA and Hubbard TJP (2002) Computational detection and location of transcription start sites in mammalian genomic DNA. **Genome Res** 12:458-461

Prlic A, Down TA, Kulesha E, Finn RD, Kahari A, Hubbard TJP (2007) Integrating sequence and structural biology with DAS. **BMC Bioinformatics** 8:333

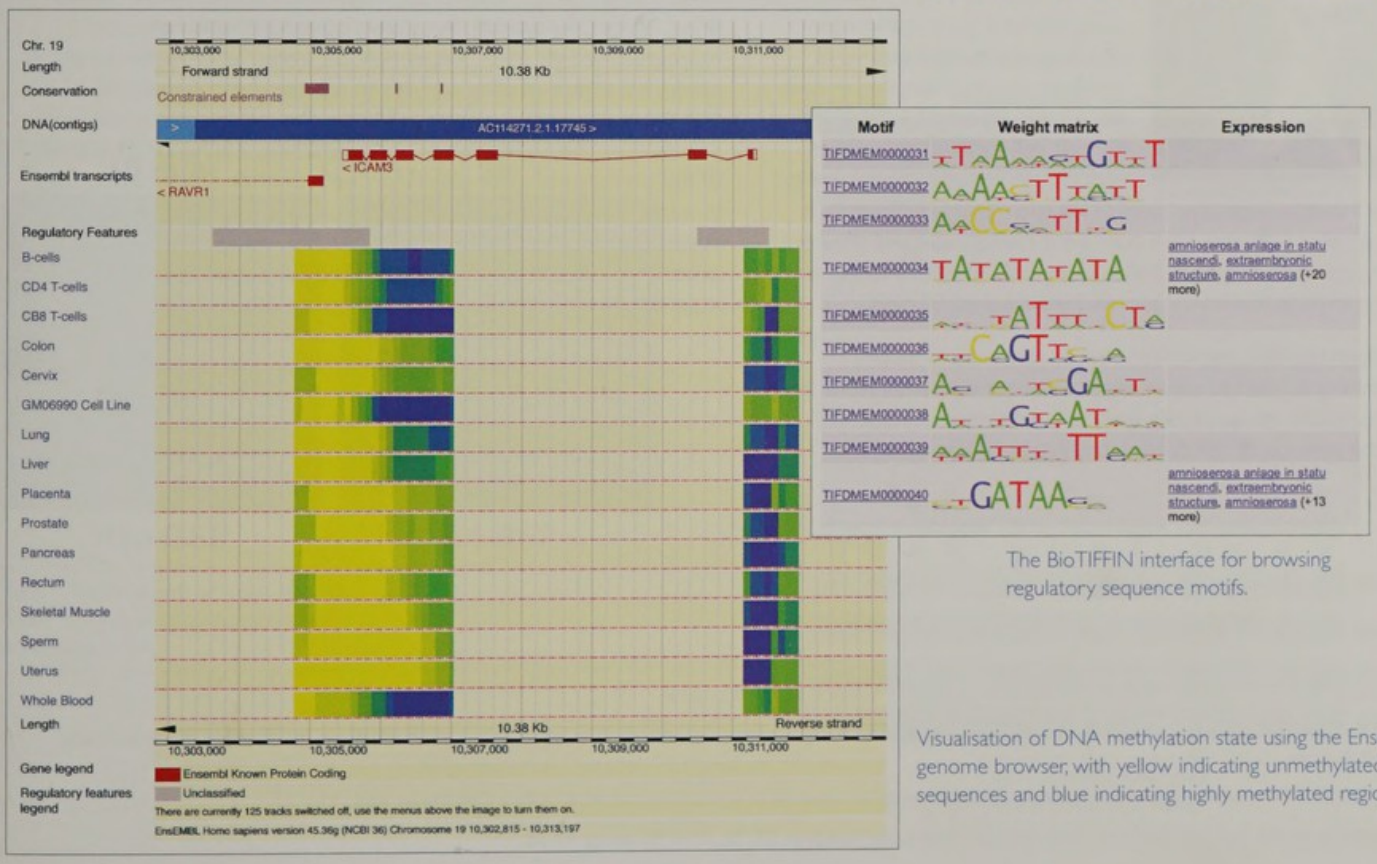
For complete list of this lab's publications since the last report, see numbers 17, 18, 33, 34, 46 & 48 on pp 49-53



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..

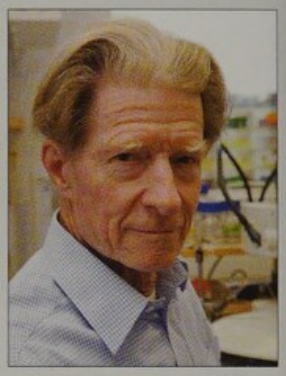


The BioTIFFIN interface for browsing regulatory sequence motifs.

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

John Gurdon

Reprogramming of gene expression by nuclear transfer



Co-workers: Carolina Åstrand, Dilly Bradford, Nigel Garrett, Richard Halley-Stott, Jerome Jullien, Kazutaka Murata, Vincent Pasque, Ilenia Simeoni

We aim to understand how nuclei of adult somatic cells can be experimentally reprogrammed to express embryo or stem cell genes. This has been achieved by others using retroviral gene transfection to induce pluripotent stem cells. However we are interested in how this can be achieved by transplanting somatic cell nuclei to unfertilised eggs. By this route, reprogramming uses natural components that operate on sperm after fertilisation; it works at a higher efficiency than does gene transfection, and does not impose any genetic changes in the resulting cells. We wish to identify the reprogramming molecules and mechanisms used by eggs.

We use amphibian oocytes in first meiotic prophase to induce reprogramming in injected mammalian nuclei, because embryo or stem gene transcription can be readily seen in transplanted somatic cell nuclei in the absence of cell division or protein synthesis.

We find that nuclear reprogramming requires the removal of differentiation marks from somatic cell nuclei. These include the demethylation of promoter DNA, and the substitution of certain modifications on core histones. Particularly important is the exchange of somatic H1 linker histones for the oocyte-specific variant named B4 or H1foo. Surprisingly the transcriptional activation of some reprogrammed genes is independent of transcription factor supply. A special advantage of using oocytes to reprogramme somatic nuclei is that the process can be observed under the microscope in real time. This permits the application of photobleaching, and hence an analysis of the exchange of gene-specific proteins on their DNA-binding sites. In some cases we use nuclei of mammalian cells in which multiple copies of the bacterial lac repressor binding site has been integrated, in order to follow the real-time binding and dissociation of the GFP-lac repressor, as an example of a gene-specific protein.

Gurdon JB and Melton DA (2009) Nuclear reprogramming in cells. **Science** 322, 1811-1815

Ng RK and Gurdon JB (2008) Epigenetic memory of an active gene state depends on histone H3.3 incorporation into chromatin in the absence of transcription. **Nature Cell Biology**, 10,102-109

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

For complete list of this lab's publications since the last report, see numbers 25, 26, 27 & 45 on pp 49-53

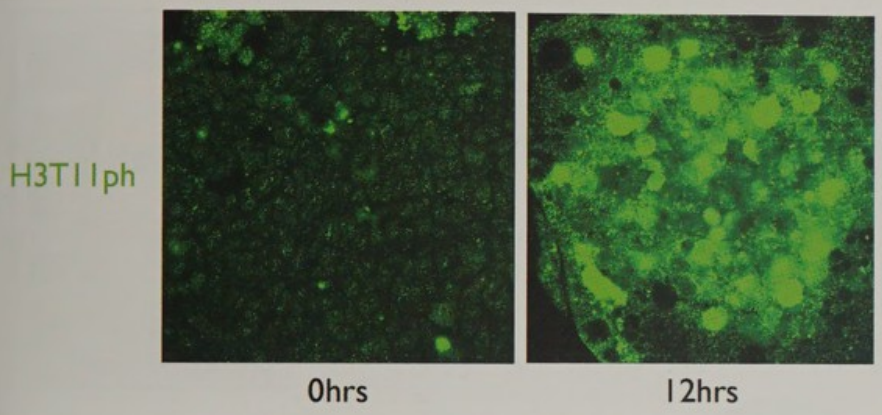


Fig.1. Modified histone H3T6Ph is increased in mammalian nuclei transplanted to *Xenopus* oocytes. (0 hours, left; 24 hours, right).

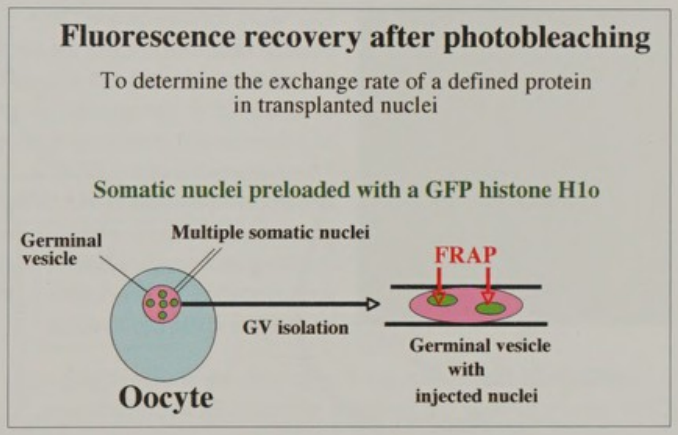


Fig.2. Design of a FRAP experiment on somatic nuclei injected into an oocyte germinal vesicle.

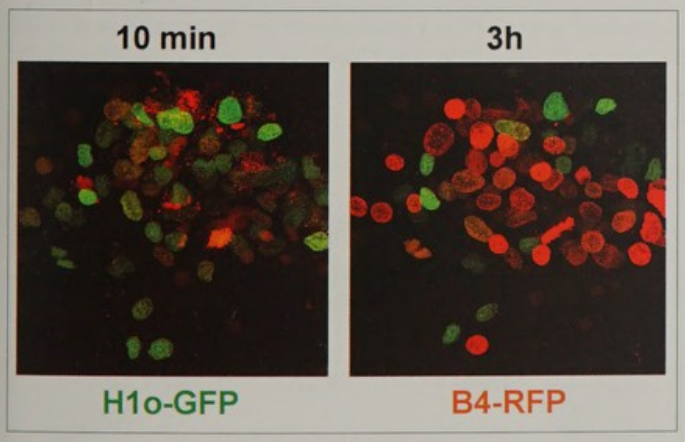


Fig.3. Replacement of adult somatic linker histone H1o by oocyte-specific linker histone B4.

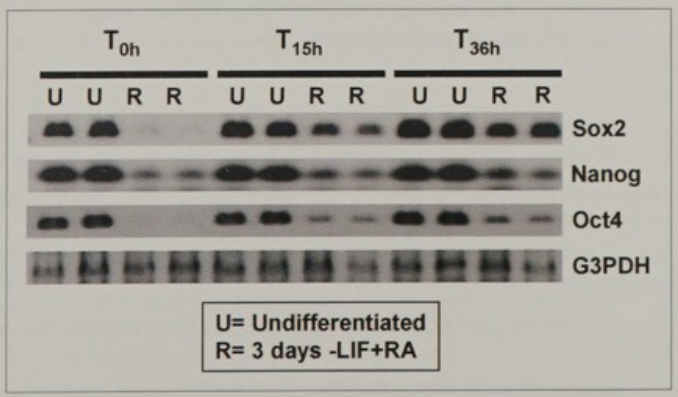
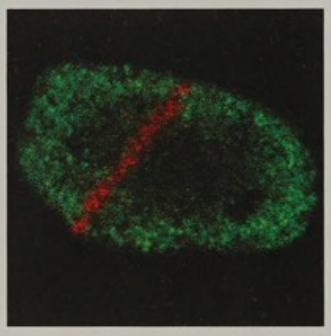


Fig.4. Reprogramming of nuclei from differentiated ES cells (T0,R) to an undifferentiated state (T15 or T36, U) as a result of injection into oocytes.

Steve Jackson

Maintenance of genome stability

Co-workers: Rimma Belotserkovskaya, Melanie Blasius, Ross Chapman, Julia Coates, Kate Dry, Sonja Flott, Josep Forment, Yaron Galanty, Simona Giunta, Jeanine Harrigan, Pablo Huertas, Abderrahmane Kaidi, 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 by detecting DNA damage, signalling its presence and mediating its repair. The importance of the DDR is underscored by defects in it being associated with various pathologies, including neurodegenerative disease, immunodeficiency, premature ageing, infertility and cancer.

By working with both yeast and human cells, we are identifying new DDR factors, defining the functions of known DDR components, assessing how the DDR is affected by chromatin structure, and learning how DDR events are regulated. For example, we recently discovered that – like the yeast Sae2 protein – the human CtIP protein functionally interacts with the MRN complex to promote processing (resection) of DNA double-strand breaks (DSBs) to generate single-stranded DNA that activates the DDR kinase ATR and triggers DNA repair by homologous recombination. Moreover, we found that CtIP and Sae2 share a highly conserved cyclin-dependent kinase (CDK) phosphorylation site, and discovered that its phosphorylation facilitates resection, thus promoting ATR signalling and HR in S/G2 but not G0/G1. Furthermore, we recently discovered that the yeast Sgs1 helicase and its human counterpart BLM (mutated in cancer-predisposed Bloom syndrome patients) promote resection, HR and ATR signalling by a pathway that is distinct from that mediated by MRN and Exonuclease 1. Another highlight over the past year has been our demonstration that phosphorylation-dependent interactions between MRN and the DDR-mediator protein MDC1 are required for the association of MRN with chromatin flanking DSB sites. Our current work is geared towards further defining the mechanisms and biological functions of these and other DDR events.

Sartori AA, Lukas C, Coates J, Mistrik M, Fu S, Bartek J, Baer R, Lukas J and Jackson SP (2007) Human CtIP promotes DNA end resection. **Nature** 450:509-14

Chapman JR and Jackson SP (2008) Phospho-dependent interactions between NBS1 and MDC1 mediate chromatin retention of the MRN complex at sites of DNA damage. **EMBO Reports** 9:795-801

Huertas P, Cortes-Ledesma F, Sartori AA, Aguilera A and Jackson SP (2008) CDK targets Sae2 to control DNA-end resection and homologous recombination. **Nature** 455:689-692

Gravel S, Chapman JR, Magill C and Jackson SP (2008) DNA helicases Sgs1 and BLM promote DNA double-strand break resection. **Genes and Development** 22:2767-2772

For complete list of this lab's publications since the last report, see numbers 9, 24, 31 & 68 on pp 49-53

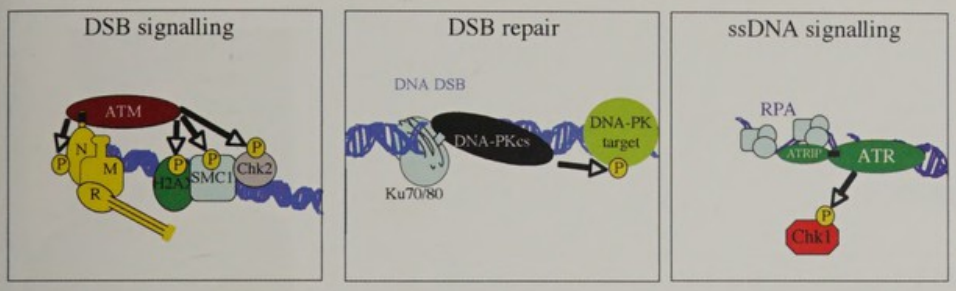
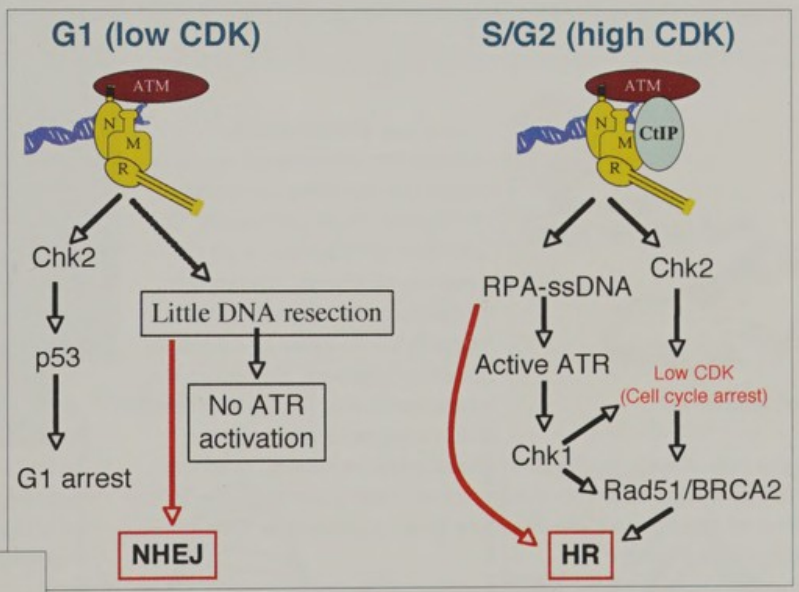


Fig 1: Common DNA-damage recruitment and activation mechanisms for ATM, DNA-PKcs and ATR. These proteins are recruited and activated at sites of damage through interactions with their partner proteins – NBS1 that is part of the MRE11-RAD50-NBS1 (MRN) complex, Ku80 and ATRIP – to bring about DDR signalling or repair, as indicated. Model derived from Falck J, Coates J, Jackson SP (2005). **Nature** 434:605-611.

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 that triggers ATR activation and leads to repair by homologous recombination (HR). Our recent work has shown that CDK phosphorylation of CtIP and its yeast homologue, Sae2, promotes ssDNA formation and HR.



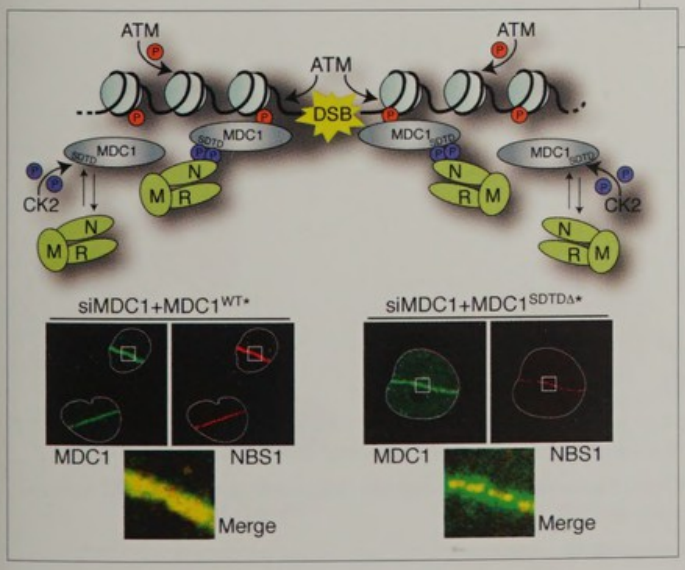
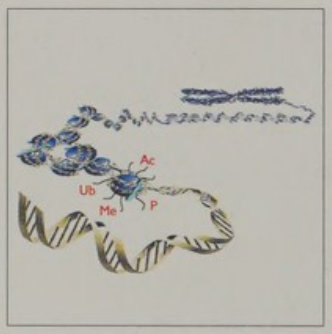


Fig 3: MDC1-dependent retention of the MRN complex on γH2AX-coupled chromatin spanning DSBs. The Casein Kinase 2 (CK2) phosphorylated SDTD repeat-motifs of MDC1 are bound by the FHA-domain of NBS1, allowing the MRN complex to be recruited to damaged chromatin when MDC1 binds ATM-phosphorylated histone H2AX (γH2AX). The resulting co-localisation of MDC1 and NBS1 can be visualised along tracts of laser-induced DNA DSBs (lower left panels), yet this co-localisation is compromised in human cells expressing an MDC1 mutant lacking the SDTD motifs, resulting in an impaired NBS1 recruitment (lower right panels).

Tony Kouzarides

Function of chromatin modifications

Co-workers: Hatice Akarsu, Andrew Bannister, Till Bartke, Maria Christophorou, Alistair Cook, Sophie Deltour, Cynthia Hill, Antonis Kirmizis, David Lando, Nikki Oliver, Claire Pike, Helena Santos Rosa, Emmanuelle Viré, Blerta Xhemalce



Our group is interested in defining the mechanisms by which chromatin modifications function to regulate cellular processes. Our attention is focused 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.

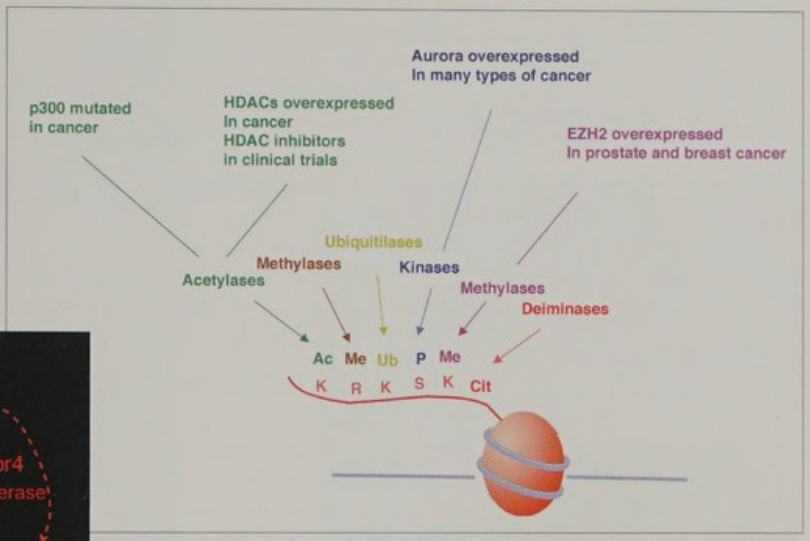
We are taking a number of complimentary approaches in both yeast and human cells to characterise chromatin modifications. We use yeast as a model system whenever possible, to investigate their mechanism of action. The recently developed Chromatin Immunoprecipiation-sequencing technology is used to map the global position of histone modifications in both yeast and human cells. Recombinant nucleosome arrays carrying specific modifications are being constructed, in order to understand how they affect compaction of chromatin.

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 metabolism and function. 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 two novel pathways that modify chromatin, arginine deimination and proline isomerisation. Both of these modifications appear to have a negative effect on transcription. Most recently we have defined a new arginine methylation pathway that modifies histone H3R2. Di-methylation acts to inhibit the enzyme which tri-methylates H3K4 and therefore is a gatekeeper for transcriptional activation. In contrast, mono-methylation of H3R2 tracks with active transcription and does not prevent H3K4 methylation.

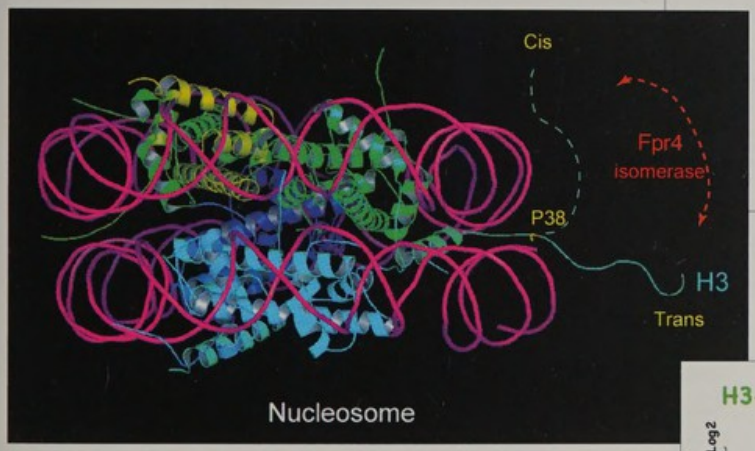
Nelson CJ, Santos-Rosa H and Kouzarides T (2006) Proline isomerisation of histone H3 regulates lysine methylation and gene expression. **Cell** 126, 905-916.

Kirmizis A, Santos-Rosa H, Penkett CJ, Singer MA, Vermeulen M, Mann M, Bahler J, Green RD and Kouzarides T (2007) Arginine methylation at histone H3R2 controls deposition of H3K4 trimethylation. **Nature** 449, 928-932

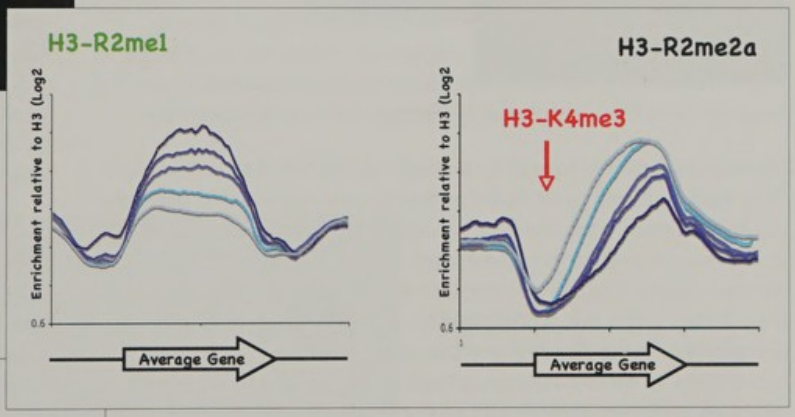
For complete list of this lab's publications since the last report, see numbers 2, 35 & 54 on pp 49-53



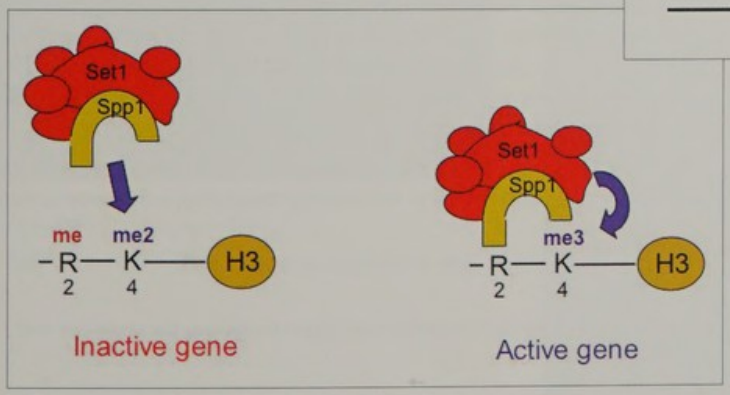
Chromatin-modifying enzymes are deregulated in cancer.



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



Genome-wide pattern of methylation for mono-and-di-methyl H3R2 on genes in yeast (light blue = least active and dark blue = most active genes).

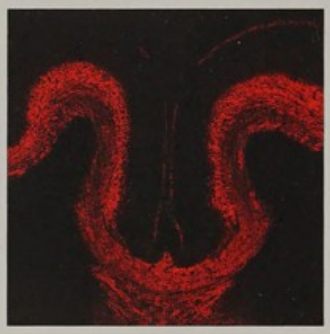


Methylation of H3R2 prevents the binding of the SPP1 component of the Set1 methylase complex and in doing so controls the deposition of H3K4 tri-methylation and subsequent gene activity.

Rick Livesey

Neocortical development – neural stem cell biology

Co-workers: Jessica Alsio, Therese Andersson, Juliet Barrows, Astrid Erber, Joao Pereira, Stephen Sansom, Yichen Shi, James Smith, Uruporn Thammongkol



Understanding brain development is essential for understanding the pathogenesis of human neurodevelopmental disorders and the rational design of neural repair strategies. The neocortex is the part of the mammalian brain that integrates sensations, executes decisions and is responsible for cognition and perception. Altered neocortical development results in a range of human diseases, including epilepsy and learning disabilities.

Neocortical neurons have two identities that dictate their connections. They belong to one of six layers of neurons, each of which is generated in a stereotyped order, and each of which has characteristic connectivity to other layers and parts in the cortex and to subcortical parts of the nervous system. Cortical neurons also belong to a discrete piece or area of the cortex that is dedicated to a single function, such as visual processing or motor control, and this also dictates the long-range connectivity of cortical neurons so that those areas communicate effectively with one another and subcortical structures.

All of the neurons in the cortex are generated from a population of multipotent neocortical stem and progenitor cells. The majority of the research in the lab centers 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). Our current work on the patterning problem is focused on how a transcription factor-based map that controls spatial identity is set up in neocortical stem cells and subsequently used to produce spatially discrete populations of neurons. Current projects include characterisation of how the transcription factor map is generated and how the gradient-based map is used to generate spatially discrete populations of neurons. For example, we are identifying the target genes of each transcription factor by combining *in vivo* location analysis by chromatin-IP (ChIP-on-chip and ChIP-seq) with gene expression profiling.

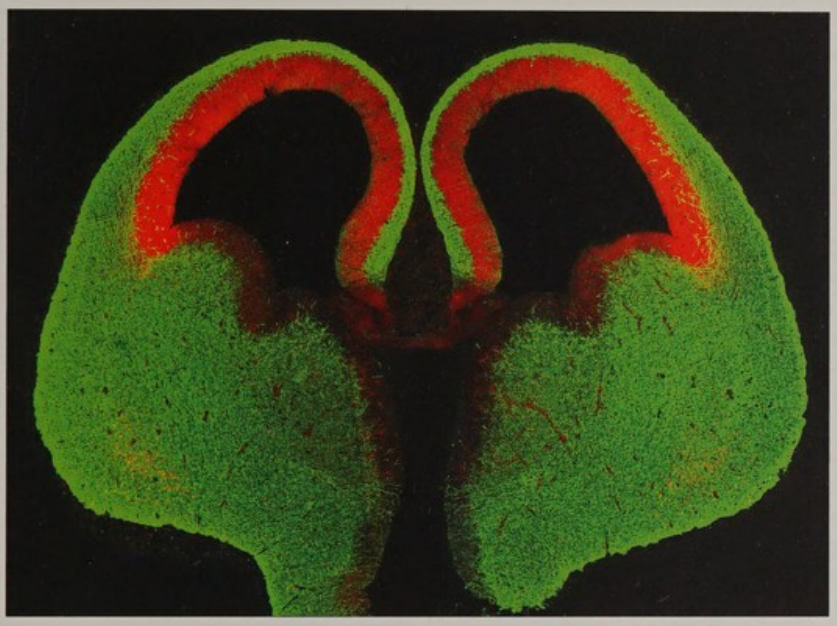
How neurons for specific layers are generated in order is a timing problem, in that it is controlled by a cellular mechanism intrinsic to neocortical stem cells. Our work in this area concentrates on testing candidate genes and mechanisms for controlling developmental timing in neocortical stem cells *in vivo*. Examples of projects in this area include generating mice mutant for key transcription factors regulating timing in the cortex, and studies of the roles of epigenetic processes, such as microRNAs and chromatin modifiers, in controlling self-renewal, neurogenesis and cell fate determination.

Subkhankulova T, Gilchrist MJ and Livesey FJ (2008) Modelling and measuring single cell RNA expression levels find considerable transcriptional differences among phenotypically identical cells. **BMC Genomics** 9: 268

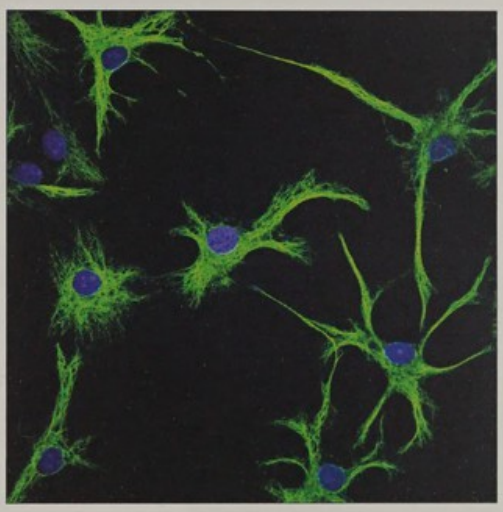
Yano K, Subkhankulova T, Livesey FJ and Robinson HP (2006) Electrophysiological and gene expression profiling of neuronal cell types in mammalian neocortex. **J Physiol** 575(Pt 2): 361-365

Subkhankulova T and Livesey FJ (2006) Comparative evaluation of linear and exponential amplification techniques for expression profiling at the single-cell level. **Genome Biol** 7(3): R18.1

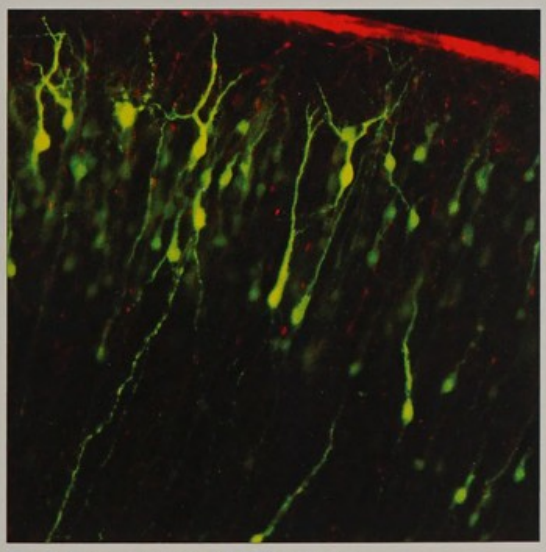
For an additional publication since the last report, see number 57 on pp 49-53



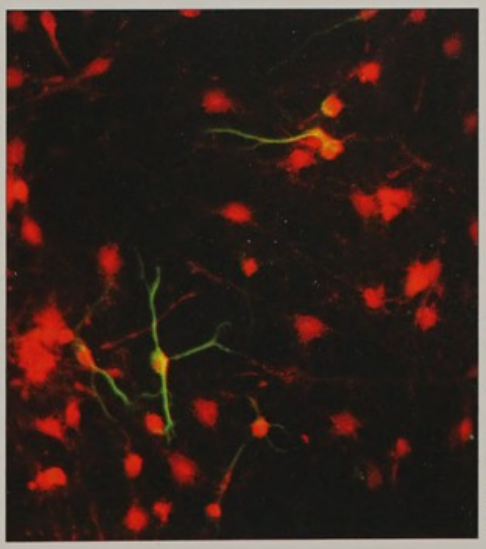
The embryonic mouse forebrain, showing the position of neocortical stem cells (red) and post-mitotic neurons (green).



Astrocytes, the most abundant non-neuronal cell in the brain, differentiating in cell culture.



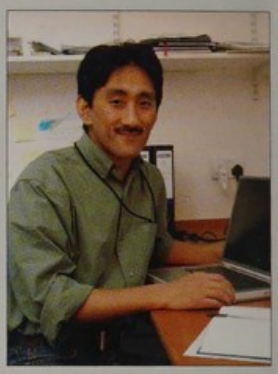
Cortical neurons (green, GFP) migrating and differentiating in cultured slices of developing cerebral cortex.



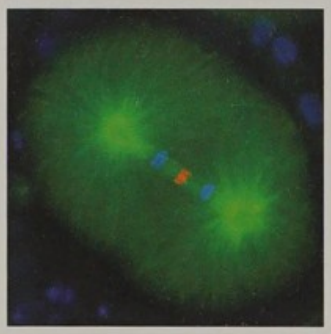
Cortical neurons (green) differentiating from cultures of cortical stem cells (red).

Masanori Mishima

Molecular mechanism of cytokinesis



Co-workers: Sue Croysdale, Tim Davies, Max Douglas, Andrea Hutterer, Nimesh Joseph, Kian-Yong Lee, Julia Mason



Cytokinesis is essential for cell proliferation. Failure of cytokinesis leads to aneuploidy or chromosomal instability, which has 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 will focus 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 will characterise the dynamic behaviour of centralspindlin and investigate centralspindlin-interacting proteins by using mammalian cultured cells and *Caenorhabditis elegans* embryos as model systems. In addition to biochemical and genetical analyses, live imaging both at single molecule level *in vitro* and at subcellular level *in vivo* will be performed. We will also develop experimental strategies to (in)activate molecules of interest *in vivo* in a reasonable time resolution to dissect the molecular mechanism of 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, steeply accumulates to the center of the microtubule bundle.

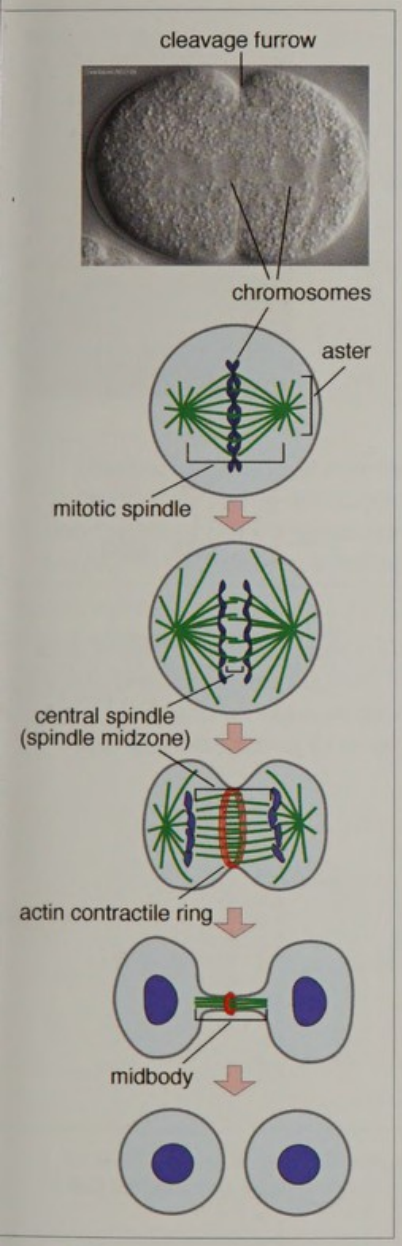
Guse A, Mishima M and Glotzer MA (2005) Conserved role for Aurora B phosphorylation of ZEN-4/MKLP1 in completion of cytokinesis. **Curr Biol** 15, 778-86

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

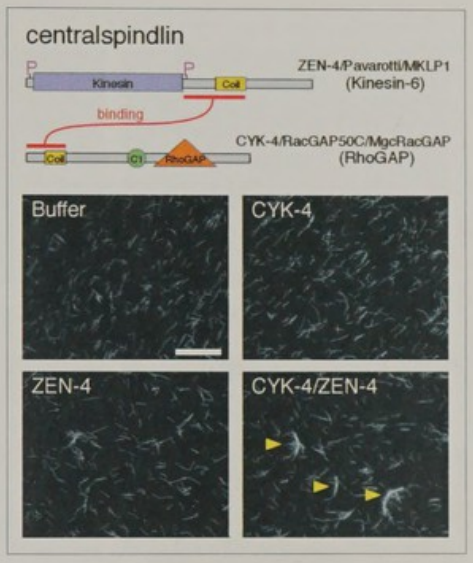
Mishima M and Glotzer M (2003) Cytokinesis: a logical GAP. **Curr Biol** 13, R589-91

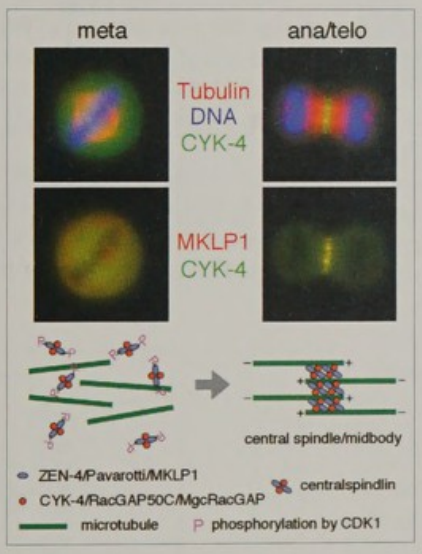
Mishima M, Kaitna S and Glotzer M (2002) Central spindle assembly and cytokinesis require a kinesin-like protein/RhoGAP complex with microtubule bundling activity. **Dev Cell** 2, 41-54



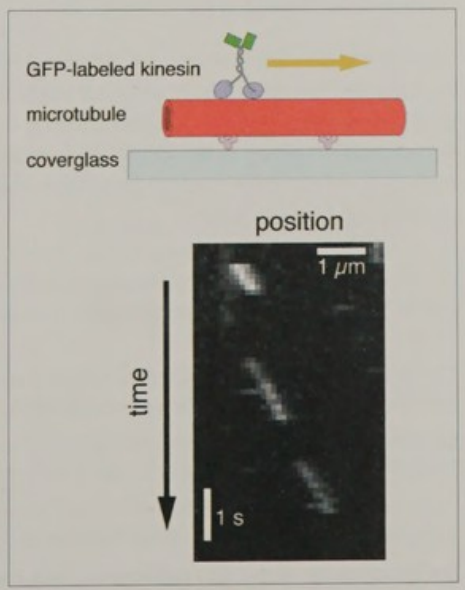
Cytokinesis

Centralspindlin is an evolutionarily conserved protein complex of a mitotic kinesin and a RhoGAP critical for the assembly of the central spindle. Being in a complex is essential both for the formation of the central spindle and for the *in vitro* microtubule-bundling activity. When incubated with microtubules, the complex causes the strong bundling of microtubules (arrowheads), while neither the kinesin subunit alone nor the RhoGAP subunit alone does.





Centralspindlin dramatically changes its localisation at metaphase/anaphase transition under the control of a master cell-cycle regulating protein kinase, CDK1. The kinesin subunit is phosphorylated by CDK1 at the sites flanking its catalytic core (P). This phosphorylation reduces the affinity for microtubules and contributes to the prevention of premature formation of the central spindle before anaphase onset, ensuring proper segregation of genetic materials.

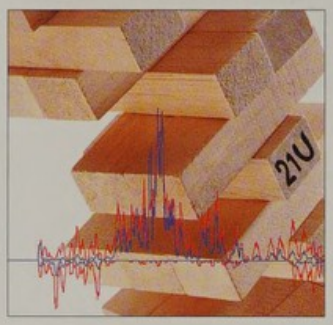


Total internal reflection fluorescent microscopy (TIRFM) allows us to directly visualise single molecules of conventional kinesin labeled with green fluorescent protein (GFP) moving along a microtubule immobilised on a coverglass surface. A similar analysis of centralspindlin is underway.

Eric Miska

Small regulatory RNA

Co-workers: Javier Armisen Garrido, Marloes Bagijn, Katsiaryna Bichel, Cherie Blenkiron, Alejandra Clark, Partha Das, Ethan Kaufman, Nic Lehrbach, Helen Lightfoot, Alexandra Sapetschnig, Funda Sar, Robert Shaw, Julie Woolford



The recent discovery of microRNAs (miRNAs) has added a completely new dimension to the control of eukaryotic gene expression. miRNAs are a large class of approximately 22 nucleotide short regulatory RNAs. Approximately 3% of all known human genes encode miRNAs, but very little is known about their biological roles. Our laboratory is interested in understanding how miRNAs contribute to the determination of cell fate, ie the decision to divide, die or differentiate, and how deregulation of miRNAs may contribute to disease, in particular to cancer.

We use the powerful genetics of the nematode *Caenorhabditis elegans* to study the function of miRNAs. Our starting point is a collection of over one hundred miRNA knockout strains covering the majority of all known miRNA genes in this organism. To place miRNAs into biological networks we combine phenotypic analysis, expression studies, genetic screens and bioinformatics.

We are also interested in the mechanisms by which small RNAs regulate gene expression. We currently use genetic screens, high-throughput sequencing and computational analyses to define how small RNAs mediate post-transcriptional gene silencing (PTGS) and transcriptional gene silencing (TGS).

We recently discovered piRNAs in *C elegans*, a distinct class of small RNAs that are required for germ stem cell proliferation and germline development. Current work focuses on understanding the biogenesis of these RNAs and how they contribute to germline development.

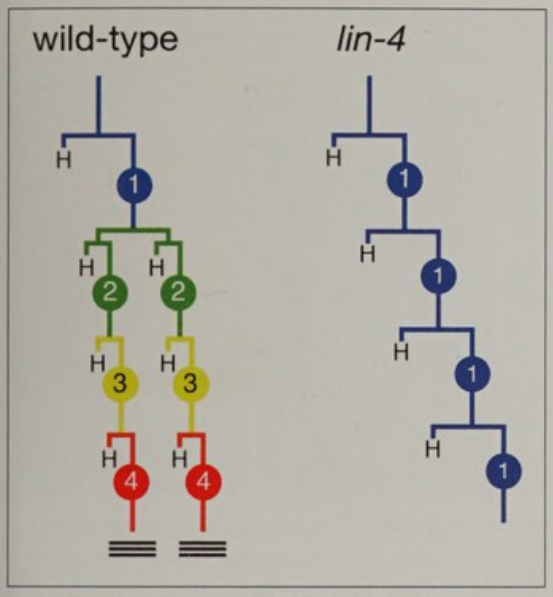
Das PP, Bagijn MP, Goldstein LD, Woolford JR, Lehrbach NJ, Sapetschnig A, Buhecha HR, Gilchrist MJ, Howe KJ, Stark R, Berezikov E, Ketting RF, Tavaré S, Miska EA (2008) Piwi and piRNAs act upstream of an endogenous siRNA pathway to suppress Tc3 transposon mobility in the *Caenorhabditis elegans* germline.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

Choi PS, Zakhary L, Choi WY, Caron S, Alvarez-Saavedra E, Miska EA, McManus M, Harfe B, Giraldez AJ, Horvitz RH, Schier AF, Dulac C. (2008) Members of the miRNA-200 family regulate olfactory neurogenesis. **Neuron** 57, 41-55.

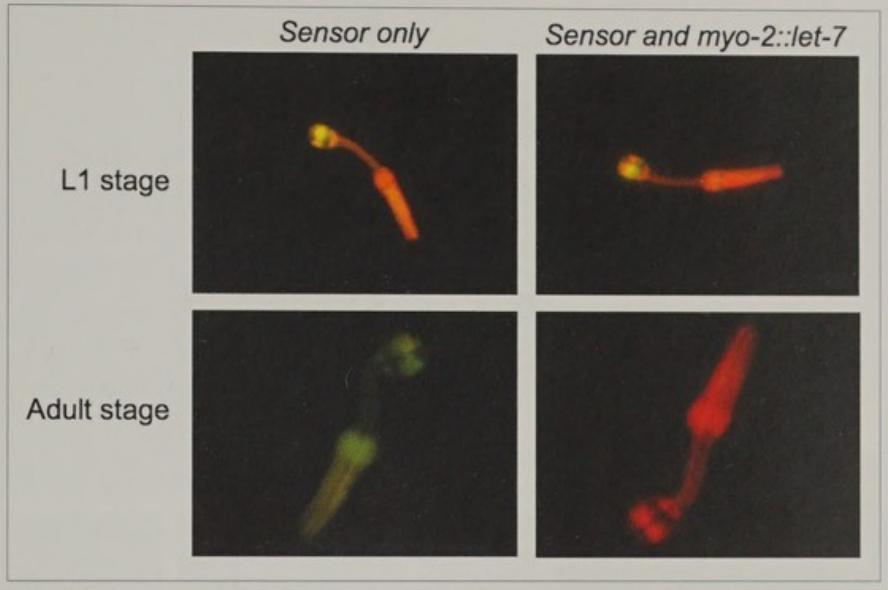
Blenkiron C, Goldstein LD, Thorne NP, Spiteri I, Chin SF, Dunning M, Barbosa-Morais NL, Teschendorff A, Green AR, Ellis IO, Tavaré S, Caldas C, Miska EA (2007) MicroRNA expression profiling of human breast cancer identifies new markers of tumour subtype. **Genome Biology** 8, R214

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.

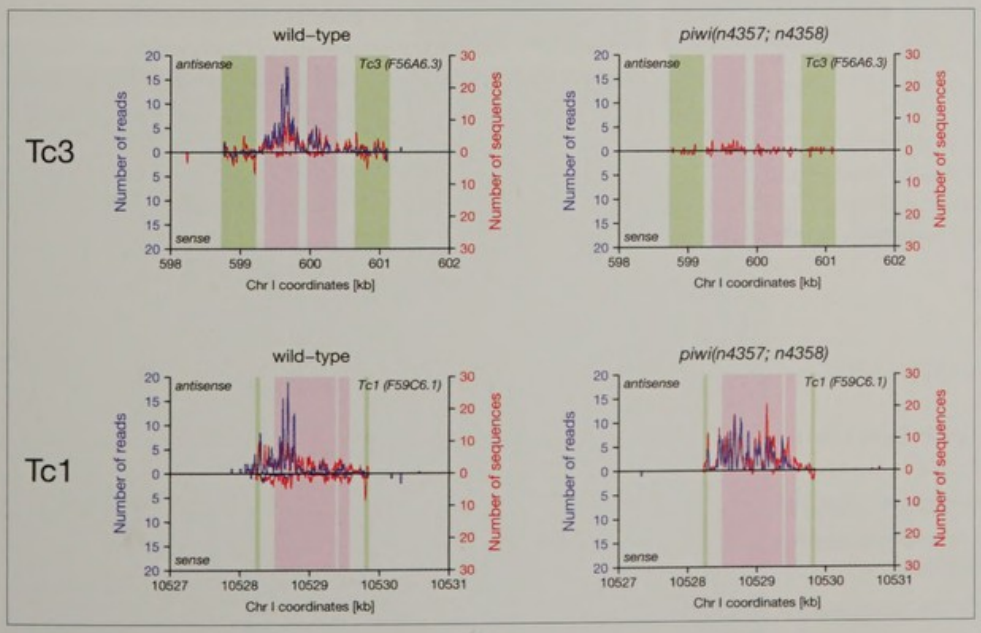
For complete list of this lab's publications since the last report, see numbers 3, 7, 10, 14, 37, 38, 40, 41, 42, 51, 63 & 66 on pp 49-53



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



We have developed an *in vivo* assay to study miRNA function. Expression of the let-7 miRNA turns a green pharynx red. We use this assay to discover new genes required for miRNA function.

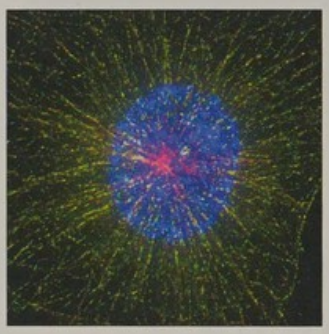


piRNAs and Piwi proteins are required to generate endogenous siRNAs to specifically regulate the Tc3 DNA transposon.

Jonathon Pines

How do cells control mitosis?

Co-workers: Emmanuel Boucrot, Philippe Collin, Barbara di Fiore, Olivier Gavet, Anja Hagting, Daisuke Izawa, Mark Jackman, 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 alignment and 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 and phosphatases, and ubiquitin-mediated proteolysis - in particular ubiquitination by the Anaphase Promoting Complex/Cyclosome (APC/C) - and this is the focus of our research. Because mitosis is a highly dynamic process we study living cells by time-lapse fluorescence microscopy and complement this with biochemical analyses.

To understand how cells initiate mitosis we are analysing the behaviour of the mitotic cyclin-CDKs, cyclins A and B1, and their regulation by phosphorylation and subcellular localisation. We use GFP-fusion proteins to reveal the dynamics of protein localisation through the cell cycle, and to define how proteins are targeted to specific subcellular structures. To identify the proteins responsible for targeting the cyclins, and to provide insights into Cdk substrates, we analyse protein complexes by mass spectrometry. Recently, we have developed a biosensor to assay Cyclin B1-Cdk1 activity *in vivo*.

To understand how proteolysis regulates progress through mitosis we measure the degradation of GFP-fusion proteins in living cells and complement this 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 in mitosis and, most importantly, how its activity is regulated by the spindle assembly checkpoint that is essential to the control of chromosome segregation and cytokinesis. We hope that these studies will increase our understanding of how cells prevent improper chromosome segregation (aneuploidy) that is the hallmark of many cancers.

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

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

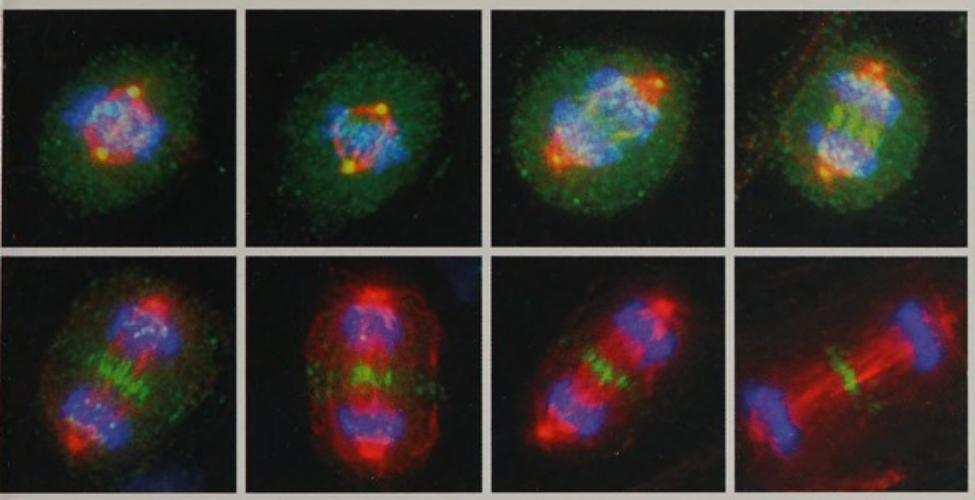
Wolthuis R, Clay-Farrace L, van Zon W, Yekezare M, Ogink J, Medema R and Pines J (2008) Cdc20 and Cks direct the spindle checkpoint-independent destruction of Cyclin A. **Mol. Cell** 30, 290-302

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

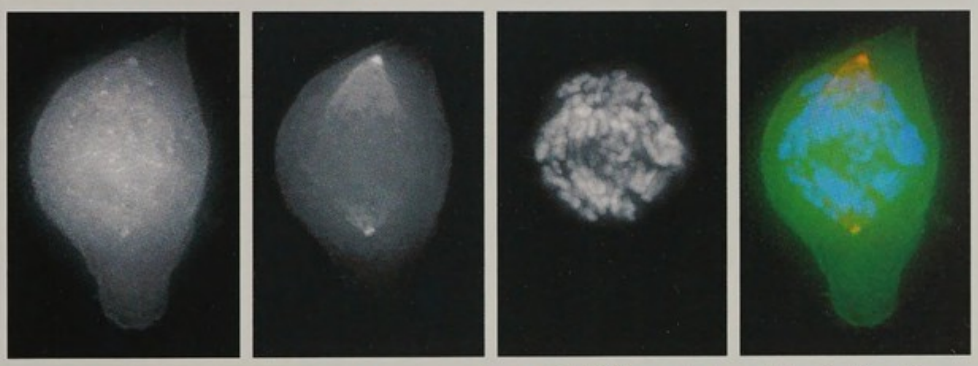
Walker A, Acquaviva C, Matsusaka M, Koop L and Pines J (2008) UbcH10 has a rate-limiting role in G1 phase but may not act in the spindle checkpoint or as part of an autonomous oscillator. **J Cell Sci** 121 2319-2326

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

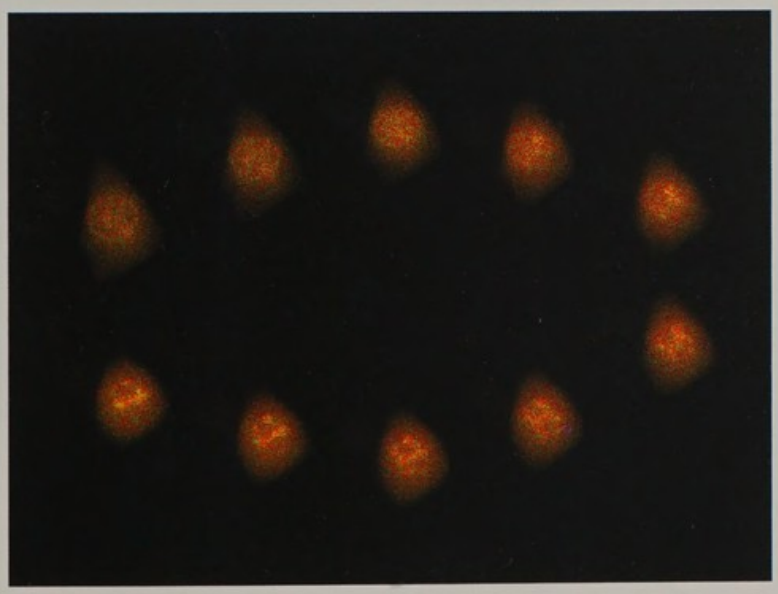
For complete list of this lab's publications since the last report, see numbers 4, 21, 23, 44, 64 & 67 on pp 49-53



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



Aurora_Cdc20: Pro-metaphase Hela cell stained for Cdc20 (left and green), Aurora A (middle and red), DNA (right and blue) (Lorena Clay).

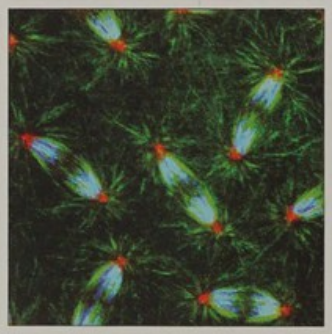


Montage of cyclin B1-Cdk1 kinase activity detected in mitosis using a novel FRET biosensor. (Red, high activity, green, low activity) (Olivier Gavet)

Jordan Raff

Molecular analysis of the centrosome

Co-workers: Juliet Barrows, Kathrin Brunk, Paul Conduit, Jeroen Dobbelaere, Anna Franz, Richard Reschen, Jenny Richens, Naomi Stevens



The centrosome is the main microtubule organising centre in animal cells, and it comprises a pair of centrioles surrounded by an amorphous pericentriolar material (PCM). We have recently performed a genome-wide RNAi screen in *Drosophila* cells to identify all of the components required for centrosome duplication and PCM recruitment. Encouragingly, we identified all of the known proteins required for these processes as well as several new ones, some of which have human homologues. We have used GFP-tagging to show that many of these proteins are localised to centrosomes and we are now investigating how these proteins cooperate to ensure proper centriole/centrosome function.

Many different types of cancer exhibit a phenomenon of genetic instability, where the genome of the population of cancer cells is in constant flux. It has long been postulated that centrosome amplification could drive genetic instability, as cells with extra centrosomes form multipolar spindles and so segregate their chromosomes abnormally.

We have generated flies that constitutively have too many centrosome in ~60% of their somatic cells. Surprisingly, this does not lead to a large-scale genetic instability as these cells invariably divide in a bipolar fashion due to clustering and/or inactivation of the extra centrosomes during mitosis. In abdominal injection assays, however, cells with extra centrosomes can form tumours. We are currently investigating how centrosome amplification initiates tumourigenesis in this system.

Finally, we have recently discovered that all centrosome divisions are intrinsically asymmetric in *Drosophila* embryos. This may have important implications for the mechanisms of asymmetric stem cell division.

Inset left: Anaphase in a *Drosophila* embryo. D-TACC (red), microtubules (green) and DNA (blue).

Dobbelaere J, Josué F, Suijkerbuijk S, Baum B, Tapon N, Raff J (2008) A genome-wide RNAi screen to dissect centriole duplication and centrosome maturation in *Drosophila*. **PloS Biol**. 6, e224

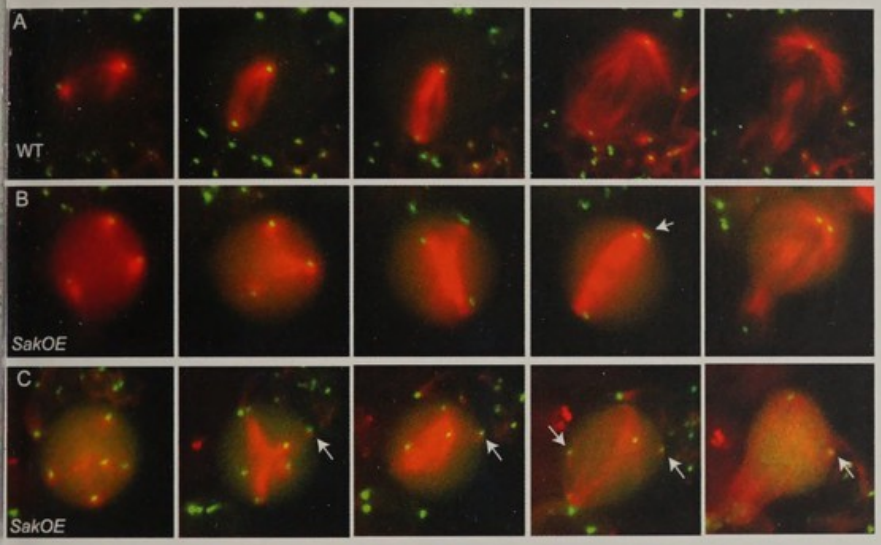
Basto R, Brunk K, Vinadogrova T, Peel N, Franz A, Khodjakov A and Raff JW (2008) Centrosome amplification can initiate tumourigenesis in flies. **Cell** 133, 1032-1042

Stevens NR, Raposo ASF, Basto R, St Johnston D and Raff JW (2007) From stem cell to embryo without centrioles. **Curr Biol** 21, 1498-1503

Lucas E and Raff JW (2007) Maintaining the proper connection between the centrioles and the PCM requires *Drosophila* Centrosomin. **J Cell Biol** 178, 725-732

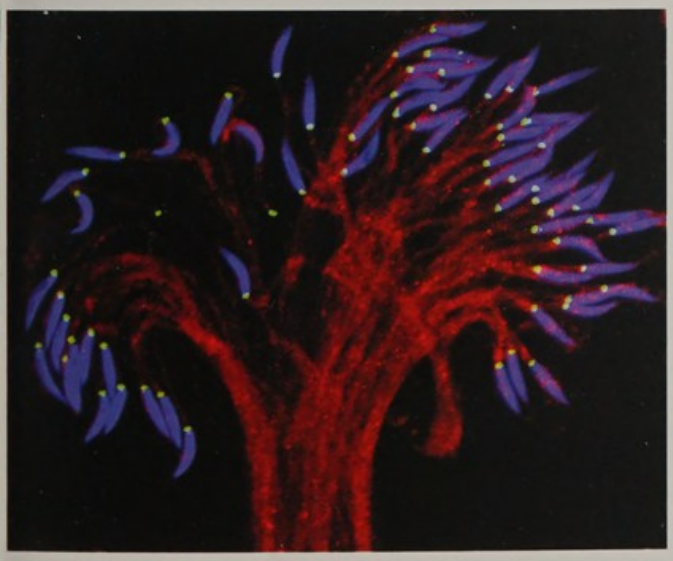
Basto R, Lau J, Vinogradova T, Gardiol A, Wood G, Khodhjakov A and Raff JW (2006) Flies without centrioles. **Cell** 125, 1375-1386

For complete list of this lab's publications since the last report, see numbers 4, 5 & 16 on pp 49-53



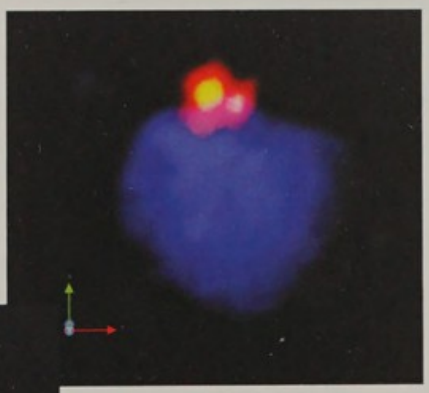
Drosophila neuroblasts always divide in a bipolar fashion, even if they contain extra centrosomes. Stills from movies of a WT neuroblast (A) or two neuroblasts that overexpress the centriole duplication protein SAK (B and C). These latter cells have too many centrosomes and transiently form multipolar spindles; eventually, however, these cells always divide in a bipolar fashion. microtubules (red) centrioles (green).

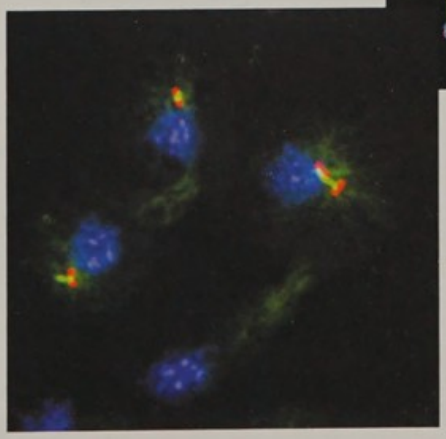
Centrioles in love. 3D reconstruction of two centriole pairs in *Drosophila* spermatocytes.



The Tree of life. A cluster of *Drosophila* sperm. DNA (blue), basal bodies (green) and microtubules (red).

Centriole and centrosome asymmetry in a *Drosophila* neural stem cell. Note how the dividing centrioles (green) and PCM (red) are asymmetric in size in this cell.

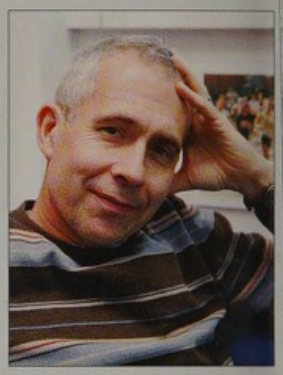




The ties that bind. *Drosophila* spermatocytes in telophase. A link (green) between the centrioles (red) has failed to break in one of these dividing meiosis II telophase cells, so both centrioles are segregated to one pole, while the other pole has none.

Jim Smith

Molecular basis of mesoderm formation



Co-workers: Liz Callery, John Cannon, Nicole Chan, Mike Chesney, Clara Collart, Kevin Dingwell, Amanda Evans, George Gentsch, Anja Hagemann, Steve Harvey, Kim Lachani, Amer Rana, Xin Xu

We study the basis of mesoderm formation in the vertebrate embryo. As well as shedding light on fundamental developmental mechanisms, our work should assist efforts to direct stem cells down particular developmental pathways, and it might even allow us to make differentiated cells move backwards in developmental time, so that they can then be re-programmed as the experimenter desires.

We use *Xenopus* species and the zebrafish, and have recently started work with mouse and human ES cells. In the embryo, one interest concerns the mechanism by which inducing factors exert long-range effects, and we are studying this by means of tagged forms of inducing factors such as activin and by using novel approaches to identify, in real time, the cells that respond to such signals. Like other members of the transforming growth factor type β family, activin exerts its effects by causing Smad proteins to form heteromeric complexes, and another aspect of our work has been to identify and characterise Smad-interacting proteins such as SmicI.

A second line of work involves elucidating the genetic regulatory networks that underlie mesoderm formation, and to this end we are carrying out ChIP-on-Chip and ChIP-Seq experiments, focussing on members of the T box family of proteins. The founder member of this family, Brachyury, is both necessary and sufficient for mesoderm formation. We shall go on to study gene function by use of antisense morpholino oligonucleotides, and we are also asking to what extent our results apply to ES cells and mammalian embryos.

Inset left: Dissociated animal pole cells expressing nuclear cyan fluorescent protein (blue) and Rab5 tagged with green fluorescent protein

Saka Y, Hagemann A, Piepenburg O and Smith JC (2007) Nuclear accumulation of Smad complexes occurs only after the midblastula transition in *Xenopus*. **Development** 134, 4209-4218

Eisen JS and Smith JC (2008) Controlling morpholino experiments: don't stop making antisense. **Development** 135, 1735-1743.

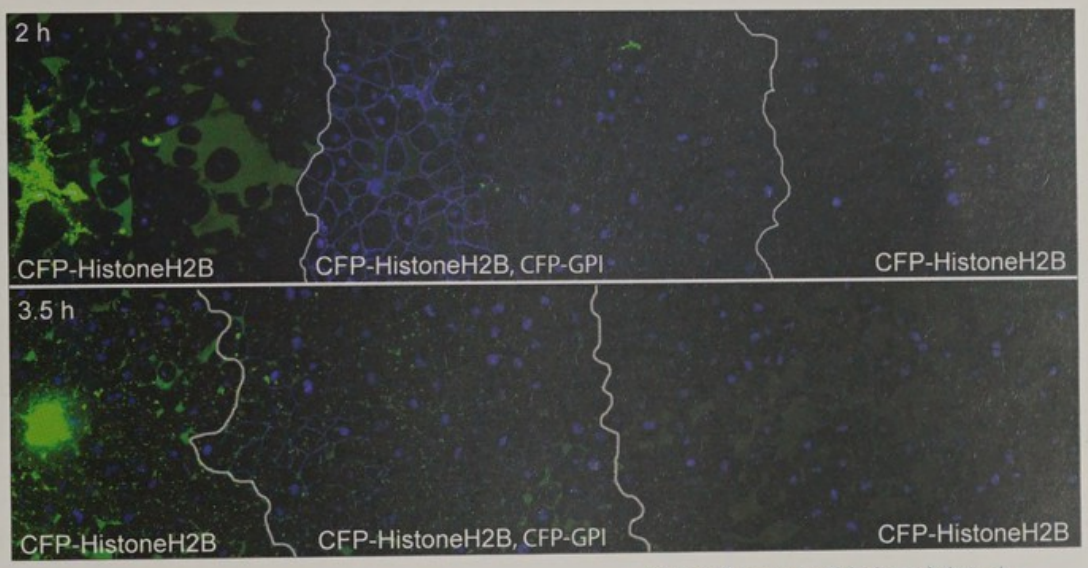
Sevilla LM, Rana AA, Watt FM, Smith JC (2008) KazrinA is required for axial elongation and epidermal integrity in *Xenopus tropicalis*. **Dev Dyn** 237, 1718-1725

von Hofsten J, Elworthy S, Gilchrist M, Smith JC, Wardle FC and Ingham PW (2008) Prdm1- and Sox6-mediated transcriptional repression specifies muscle fibre type in the zebrafish embryo. **EMBO Reports** 9, 683-689

Colas A, Cartry J, Buisson I, Umbhauer M, Smith JC and Riou JC (2008) Mix.1/2-dependent control of FGF availability during gastrulation is essential for pronephros development in *Xenopus*. **Dev Biol** 320, 351-365

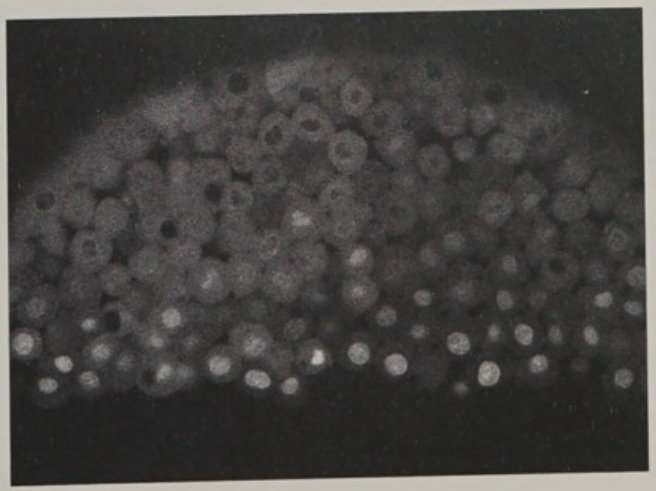
For complete list of this lab's publications since the last report, see numbers 1, 13, 20, 50, 52 & 55 on pp 49-53

Expression of Brachyury (blue stain) in a 9-day mouse embryo.



Spread of labelled activin (green) through a responding tissue. The source of activin is to the left. At 2 hours (top) activin is predominantly extracellular; at 3.5 hours (bottom) much has become internalised.

Development of a new method of transgenesis should allow insertion of DNA sequences into defined insertion points in the genomes of *Xenopus* (above) as well as zebrafish and mouse embryos.



Use of bimolecular fluorescence complementation reveals that signalling by nodal family members is strong near the margin of the embryo (bottom of image) and weak near the animal pole (top).

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, 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 the *Drosophila* ovary 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.

We are also examining the establishment of apical-basal polarity in epithelial cells 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.

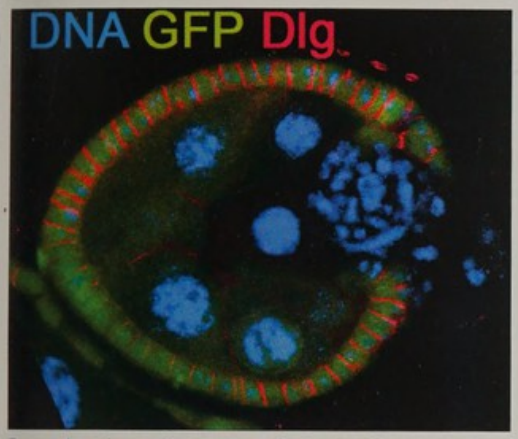
Inset left: The localisation of *bicoid* mRNA (green) and *oskar* mRNA (red) in a stage 10A *Drosophila* oocyte. Bicoid mRNA has been labelled with MS2-GFP and *oskar* mRNA with RFP-Staufen

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

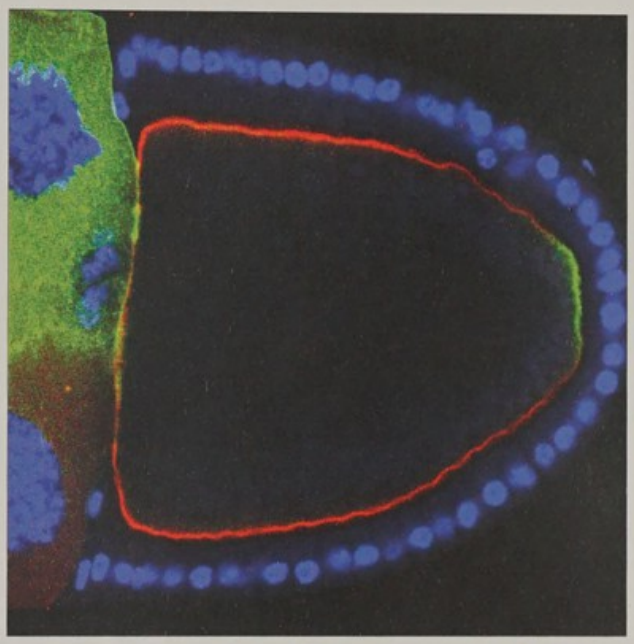
Mirouse V, Christoforou CP, Fritsch C, St Johnston D and Ray R (2009) Dystroglycan and Perlecan provide a basal cue that is required for epithelial polarity during energetic stress. **Dev Cell** [in press]

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

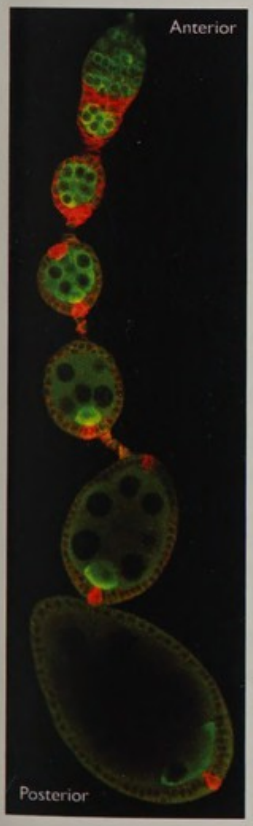
For complete list of this lab's publications since the last report, see numbers 39, 59 & 69 on pp 49-53

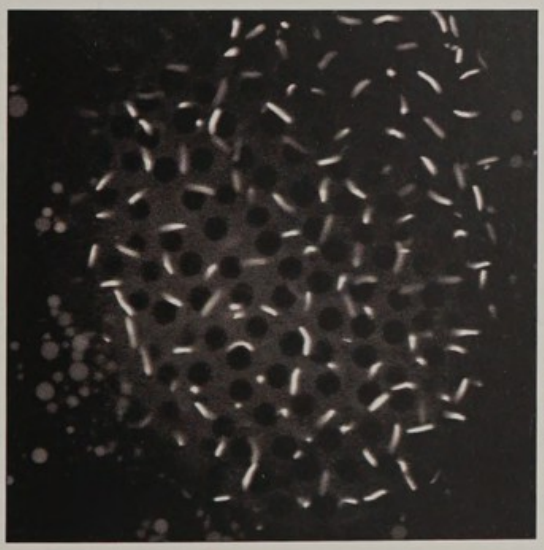


Starvation-dependent tumour formation. Removal of the AMP-dependent protein kinase from clones of follicle cells (marked by the absence of GFP; green) causes the cells to lose their polarity and over-proliferate, resulting in small tumours. This phenotype is only observed under starvation conditions.



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





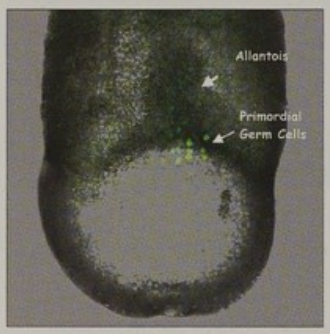
Novel rod-like structures in the epithelial follicle cells. We have performed a large-scale protein trap screen, in which a transposon containing an artificial exon encoding GFP and two protein affinity tags is jumped around the genome. When this inserts in the right frame between protein coding exons of a gene, the endogenous protein is tagged with GFP. The image shows the GFP-tagged protein produced by one these lines, which labels a novel structure in each follicle cell.

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, Lynn Froggett, Astrid Gillich, Sam Gossage, Petra Hajkova, Sophie Hanina, Katsuhiko Hayashi, Sean Jeffries, Shinseog Kim, Caroline Lee, Harry Leitch, Erna Magnúsdóttir, William Mifsud, Qin Si, Fuchou Tang, Wee Wei Tee, Leng Siew Yeap



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 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** [in press]

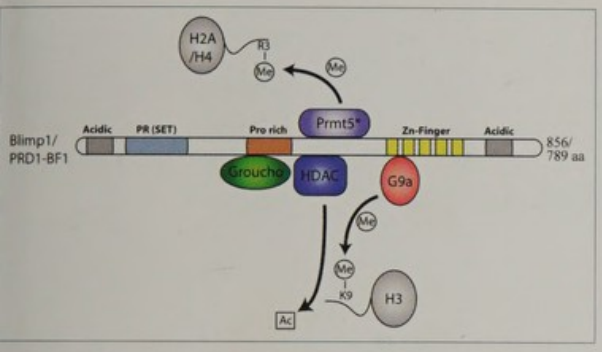
Hayashi K, Lopes SM, Tang F and Surani MA (2008) Dynamic equilibrium and heterogeneity of mouse pluripotent stem cells with distinct functional and epigenetic states. **Cell Stem Cell** 3, 391-401

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

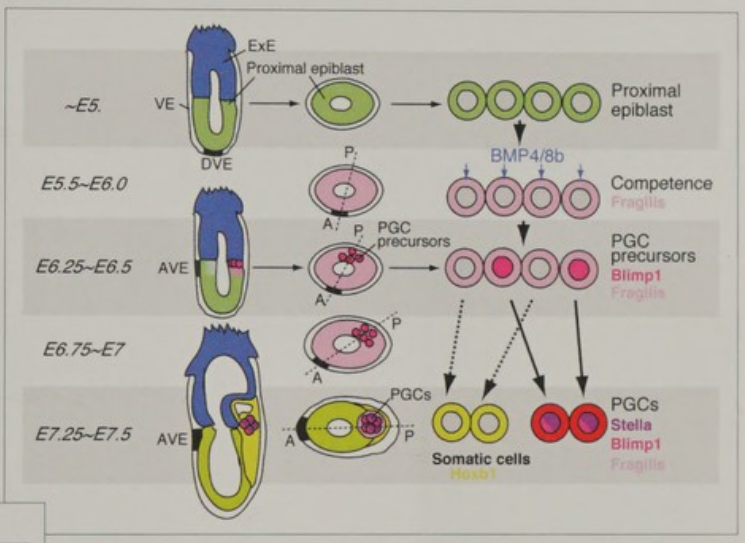
Surani MA, Hayashi K, and Hajkova P (2007) Genetic and epigenetic regulators of pluripotency. **Cell** 128, 747-762

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

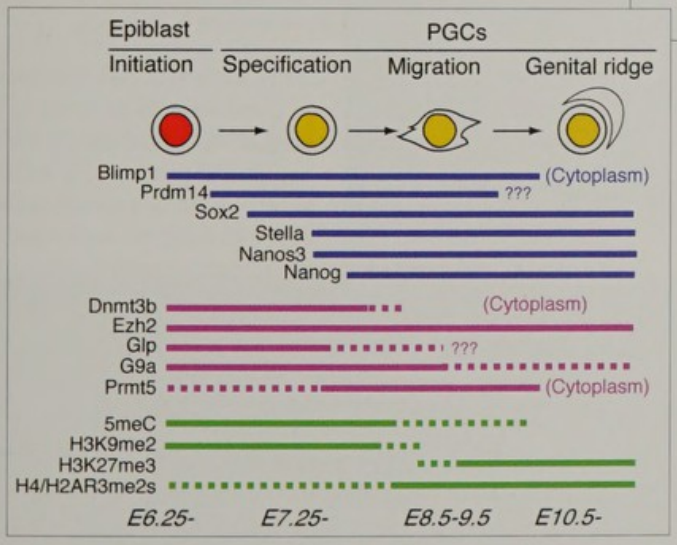
For complete list of this lab's publications since the last report, see numbers 11, 12, 19, 28, 29, 30, 36, 53, 58, 61, 62 & 65 on pp 49-53



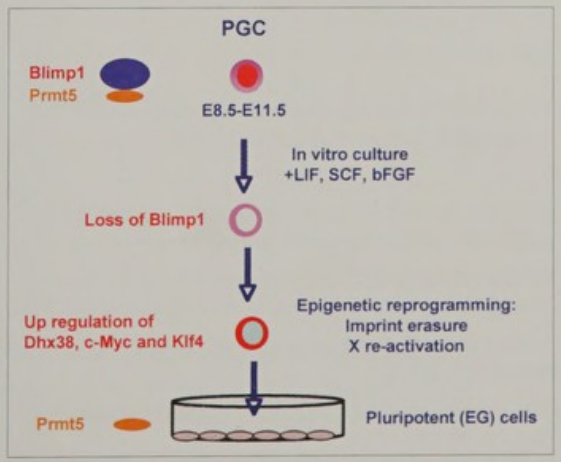
Blimp1, the key determinant of germ cell specification in mice, with a SET/PR domain and five Krueppel-like zinc fingers, which bind to DNA. BLIMP1 can potentially interact with several co-repressors to repress target genes. In germ cells, BLIMP1 forms a novel complex with an arginine methylase, PRMT5.



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.

Magdalena Zernicka-Goetz

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

Co-workers: Anna Ajduk, Helen Bolton, Alex Bruce, Debbie Gingell, Agnieszka Jedrusik, Rui Martins, Samantha Morris, Emlyn Parfitt, Bedra Sharif, Maria Skamagki, Bernhard Strauss, Roy (Tang Yi) Teo, Piraye Yurttas

We are investigating the cellular and molecular mechanisms underlying cell fate decisions in the early mouse embryo.

How is the polarity of the egg established to permit the asymmetric, meiotic divisions and then re-organised following fertilisation to allow symmetric embryonic divisions? We address this by combining experimental embryology with molecular techniques to reveal the spatial organisation of the embryo and time-lapse imaging of spindle positioning and cell division in live embryos. Together with modulation of gene expression in a clonal manner, we are gaining insight into the role played by key regulatory proteins in cell polarisation and cell fate, revealing that mouse embryo cells are heterogeneous before acquiring specific inside versus outside positions and that this biases their division orientation and, hence, cell fate.

What is the interplay between cell polarity, position, potency and chromatin structure in specifying cell fate? During the first cell fate specification, this relationship appears instrumental in generating pluripotent, inside cells that give rise to the ICM, future foetus, and outside cells that differentiate into extra-embryonic tissue, trophectoderm. We found that this partitioning can be influenced by polarity factors such as Par3 and aPKC, and transcription and co-factors such as Cdx2 and Carm1. This, in turn, led to our discovery that cell fate can be modulated by specific chromatin modifications. We now explore the mechanism behind this relationship and probe the role of chromatin remodelling factors in embryo polarisation.

In the second cell fate specification, some ICM cells differentiate into another extra-embryonic tissue, primitive endoderm. We found that both position dependent signalling as well as cell sorting are key for this cell fate decision. Moreover, cells that give rise to a major cluster-forming primitive endoderm are generated by a specific wave of asymmetric divisions. Finally we are studying the morphogenetic events leading to the genesis of the signalling centres within these extra-embryonic tissues and how their signalling affects embryo patterning.

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)

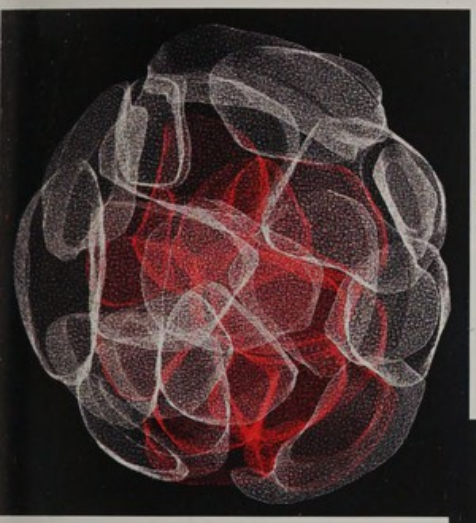
Jedrusik A, Parfitt DE, Guo G, Skamagki M, Grabarek JB, Johnson MH, Robson P, Zernicka-Goetz M (2008) Role of Cdx2 and cell polarity in cell allocation and specification of trophectoderm and inner cell mass in the mouse embryo. **Genes Dev** 22(19), 2692-706

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(5), 953-62

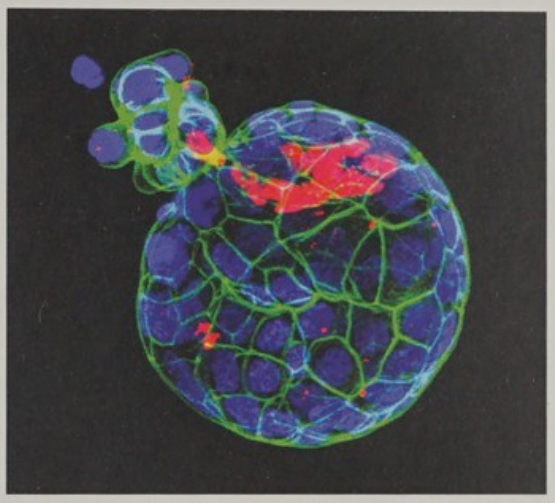
Torres-Padilla ME, Parfitt DE, Kouzarides T, and Zernicka-Goetz M (2007) Histone arginine methylation directs cells to pluripotency in the early mouse embryo. **Nature** 445, 214-8

Na J and Zernicka-Goetz M (2006) Asymmetric positioning and organisation of the meiotic spindle of mouse oocytes requires CDC42 function. **Curr Biol** 16(12),1249-54

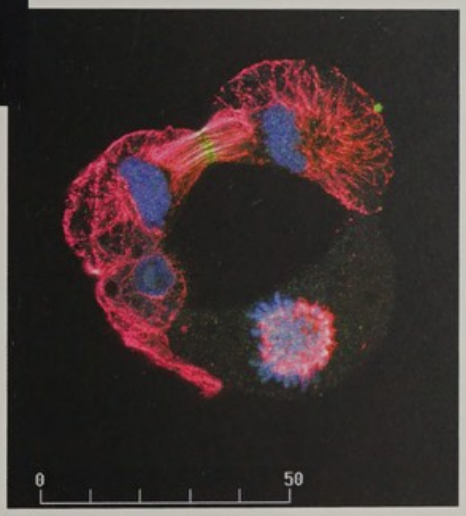
For complete list of this lab's publications since the last report, see numbers 6, 32, 38 & 56 on pp 49-53



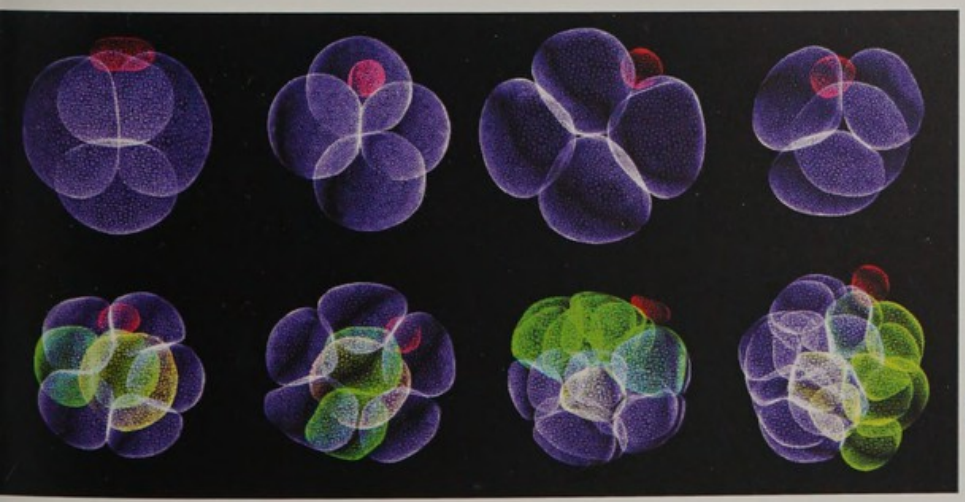
Mouse blastocysts after Carm1 overexpression in one 2-cell stage blastomere. Carm1 overexpression leads progeny of the blastomere to develop into the inner cell mass (red) while non-injected cells give rise to trophectoderm (white). (Image by Emlyn Parfitt)



The second cell fate decision: immunostaining for Gata4 (red) demonstrates the differentiation of primitive endoderm in the ICM of the late blastocyst. Cells are outlined by phalloidin staining (green) and nuclei visualised by Dapi staining (blue). (Image by Sam Morris)



Early blastocyst stage mouse embryo stained for tubulin (red), Aurora C-GFP (green) and DNA (blue), showing localisation of Aurora C-GFP on the spindle midzone of a dividing blastomere. (Image by Bedra Sharif)



3D reconstruction of mouse embryos at preimplantation stages of development. (Images from Maria Skamagki)

CATEGORIES OF APPOINTMENT

SENIOR GROUP LEADER
Professor, Reader or equivalent

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

CAREER DEVELOPMENT FELLOW
4-year grant-funded appointment, within individual groups

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

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

RESEARCH ASSISTANT
Postgraduate, within individual groups, mainly grant-funded

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

RESEARCH TECHNICIAN
Within individual groups, mainly grant-funded

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

POSTGRADUATE OPPORTUNITIES

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

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MEDIA/GLASS WASHING

JUANITA BAKER-HAY
Media/Glass Washing Manager

JANIS ABBOTT
LISA BAKER
BEVERLEY CORNELL
SANDRA HUMAN
LINDA ADAMS
BETTINA CASHIN
BETTY HUDSON
TRACY MITCHELL

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.

Drosophila eye disc - stained for Scribble in blue to outline cells, Eyes absent transcription factor in green. (Katrina Gold, Brand lab, 2008)

1) Alfred J and Smith J (2008) Pointing a digit at digitized JEEM. **Development** 135, 2339

2) Allis CD, Berger SL, Cote J, Dent S, Jenuwien T, Kouzarides T, Pillus L, Reinberg D, Shi Y, Shiekhattar R, Shilatifard A, Workman J, Zhang Y (2007) New nomenclature for chromatin-modifying enzymes. **Cell** 131(4), 633-636

3) Atherton HJ, Jones OA, Malik S, Miska EA, Griffin JL (2008) A comparative metabolomic study of NHR-49 in *Caenorhabditis elegans* and PPAR-alpha in the mouse. **FEBS Lett** 582, 1661-6

4) Basto R and Pines J (2007) The centrosome opens the way to mitosis, **Developmental Cell**. 12, 475-477

5) Basto R, Brunk K, Vinadogrova T, Peel N, Franz A, Khodjakov A and Raff JW (2008) Centrosome amplification can initiate tumorigenesis in flies. **Cell**, 133, 1032-1042

6) 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(5) 953-62

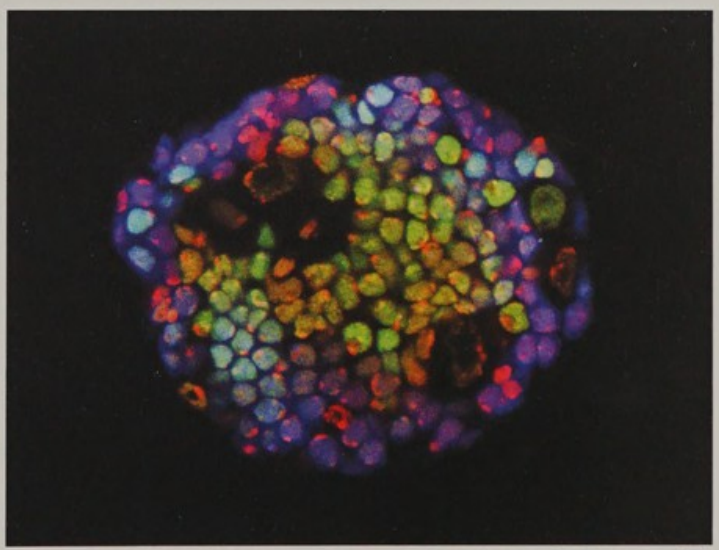
7) Blenkiron C*, Goldstein LD*, Thorne NP, Spiteri I, Chin SF, Dunning M, Barbosa-Morais NL, Teschendorff A, Green AR, Ellis IO, Tavaré S, Caldas C, Miska EA (2007) MicroRNA expression profiling of human breast cancer identifies new markers of tumour subtype. **Genome Biology** 8, R214

8) Boutros M and Ahringer J (2008) The art and design of genetic screens: RNA Interference. **Nature Review Genetics** 9, 554-566

9) Chapman JR and Jackson SP (2008) Phospho-dependent interactions between NBS1 and MDC1 mediate chromatin retention of the MRN complex at sites of DNA damage. **EMBO Reports** 9, 795-801

10) Choi PS, Zakhary L, Choi WY, Caron S, Alvarez-Saavedra E, Miska EA, McManus M, Harfe B, Giraldez AJ, Horvitz RH, Schier AF, Dulac C (2008) Members of the miRNA-200 family regulate olfactory neurogenesis. **Neuron** 57, 41-55

11) Chuva de Sousa Lopes SM, Hayashi K, Shovlin TC, Mifsud W, Surani MA, McLaren A (2007) X chromosome activity in mouse XX primordial germ cells. **PloS Genetics** 4:(2) e30



First instar larval neuroblasts and neurons stained with/against DAPI, histone-RFP and elaV. (Karin Edoff, Brand lab, 2008)

12) Chuva de Sousa Lopes SM, Hayashi K, Surani MA (2007) Proximal visceral endoderm and extraembryonic ectoderm regulate the formation of primordial germ cell precursors. **BMC Dev Biol** 1:140

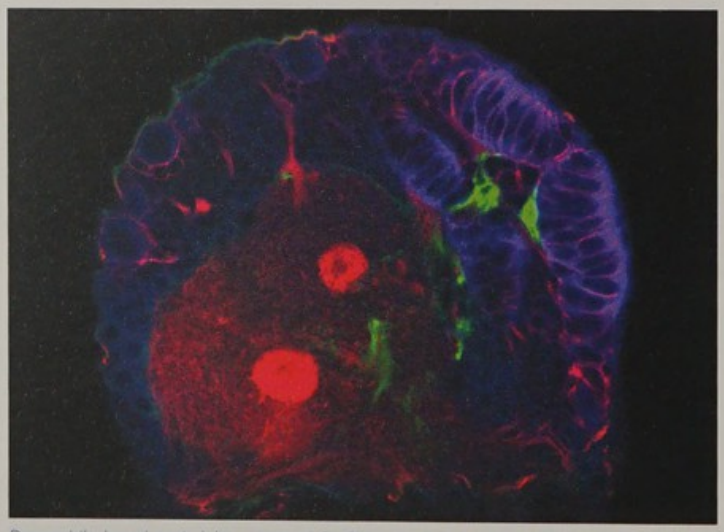
13) Colas A, Cartry J, Buisson I, Umbhauer M, Smith JC and Riou JC (2008) Mix1/2-dependent control of FGF availability during gastrulation is essential for pronephros development in *Xenopus*. **Dev Biol** 320, 351-365.

14) 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.

15) Delon I and Brown N (2008) Cell-matrix adhesion: the Wech connection. **Curr Biol** 18, R389-391.

16) Dobbelaere J, Josué F, Suijkerbuijk S, Baum B, Tapon N, Raff, J (2008) A genome-wide RNAi screen to dissect centriole duplication and centrosome maturation in *Drosophila*. **PLoS Biol** 6(9):e224 doi:10.1371/journal.pbio.0060224

17) Dogruel M, Down TA and Hubbard TJP (2008) NestedMICA as an ab initio protein motif discovery tool. **BMC Bioinformatics** 9: 19 doi:10.1186/1471-2105-9-19



Drosophila larval optic lobe - stained for Discs large in red to outline cells, Delta in blue and glia are marked in green (Katrina Gold, Brand lab, 2008)

18) Down TA, Rakyan VK, Turner DJ, Flicek P, Li H, 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 TJ, Durbin R, Tavare S, Beck S (2008) A Bayesian deconvolution strategy for immunoprecipitation-based DNA methylome analysis. **Nat Biotech** 26, 779 – 785

19) Durcova-Hills G and Surani A (2008) Reprogramming Primordial Germ Cells (PGC) to Embryonic Germ (EG) Cells. In: **Current Protocols in Stem Cell Biology**. (Wiley Interscience). 5:1A.31-1A.3.20

20) Eisen JS and Smith JC (2008) Controlling morpholino experiments: don't stop making antisense. **Development** 135, 1735-1743.

21) Elder AD, Domin A, Kaminski Schierle, GS, Lindon C, Pines J, Esposito A and Kaminski CF (2008) A quantitative protocol for dynamic measurements of protein interactions by Förster resonance energy transfer-sensitized fluorescence emission **J R Soc Interface** 6, 559-581

22) Elliott DA and Brand AH (2008) The GAL4 system : a versatile system for the expression of genes. **Methods Mol Biol**. 420:79-95.

23) Floyd S, Pines J, and Lindon C (2008) APC/CCdh1 targets Aurora kinase to control reorganization of the mitotic spindle at anaphase. **Curr Biol** 18, 1649-1658.

24) Gravel S, Chapman JR, Magill C, Jackson SP (2008) DNA helicases Sgs1 and BLM promote DNA double-strand break resection. **Genes Dev** 22, 2767-2772.

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

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

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

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

29) Hayashi K, Chuva de Sousa Lopes SM, Kaneda M, Tang F, Hajkova P, Lao K, O'Carroll D, Das PP, Tarakhovsky A, Miska EA, Surani MA (2008) MicroRNA Biogenesis is required for mouse primordial germ cell development and Spermatogenesis. **Plos One** 3(3):e1738

30) Hayashi K, Chuva de Sousa Lopes SM, Tang F, Surani MA (2008) Dynamic equilibrium and heterogeneity of mouse pluripotent stem cells with distinct functional and epigenetic states. **Cell Stem Cell** 3, 391-401.

31) Huertas P, Cortés-Ledesma F, Sartori AA, Aguilera A, Jackson SP (2008) CDK targets Sae2 to control DNA-end resection and homologous recombination. **Nature**. 455(7213):689-92

32) Jedrusik A, Parfitt DE, Guo G, Skamagki M, Grabarek JB, Johnson MH, Robson P, 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(19):2692-706.

33) Jenkinson AM, Albrecht M, Birney E, Blankenburg H, Down T, Finn RD, Hermjakob H, Hubbard TJ, Jimenez RC, Jones P, Kahari A, Kulesha E, Macías JR, Reeves GA and Prli A (2008) Integrating biological data – the Distributed Annotation System. **BMC Bioinformatics** 9, (Suppl 8):S3 doi:10.1186/1471-2105-9-S8-S3

34) 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**, in press.

35) Kouzarides T (2007) Snapshot: histone-modifying enzymes. **Cell** 131(4), 822

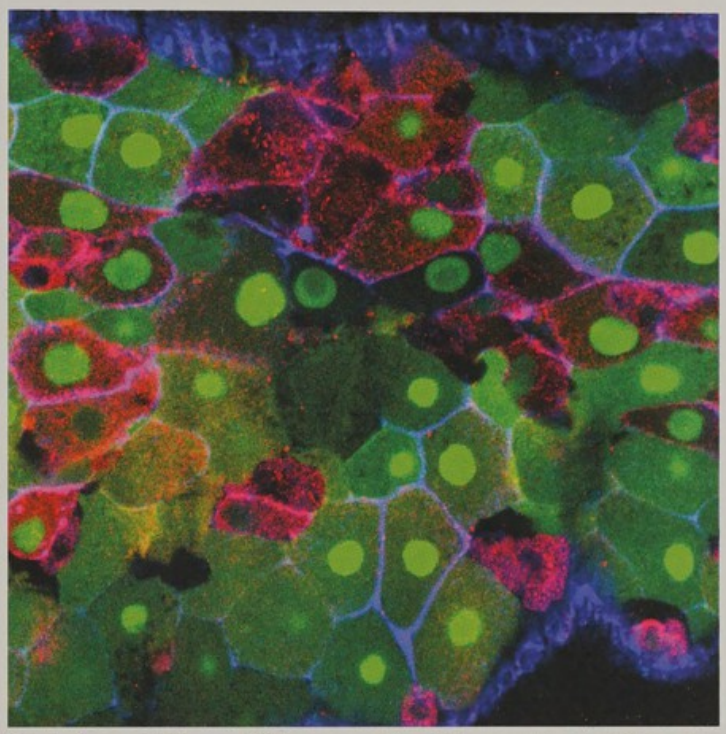
36) Lange UC, Adams DJ, Lee C, Barton S, Schneider R, Bradley A, Surani MA (2008) Normal germline establishment in mice carrying a deletion of the Ifitm/Fragilis gene Family cluster. **Mol Cell Biol** 28(15) 4688-4696.

37) Lehrbach NJ, Miska EA (2008) Functional genomic, computational and proteomic analysis of *C elegans* microRNAs. **Brief Funct Genomic Proteomic** 7, 228-35.

38) Lykke-Andersen K, Gilchrist MJ, Grabarek JB, Das P, Miska EA, Zernicka-Goetz M (2008) Maternal Argonaute 2 is essential for early mouse development at the Maternal-Zygotic Transition. **Mol Biol Cell** 10, 4383-92.

39) 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** [in press]

40) Miska EA*, Alvarez-Saavedra A*, Abbott AL*, Lau NC, Hellman A, McGonagle SM, Bartel DP, Ambros VR, Horvitz HR (2007) The biological roles of microRNAs in *Caenorhabditis elegans*. **PLoS Genetics** 12, e215



Mosaic *Drosophila* tissue - GFP is expressed in wild type cells but not in bazooka mutant cells, the apical marker aPKC is shown in blue, while Armadillo is red. (Eurico de Sa, St Johnston lab, 2008)

41) Miska EA (2007) The expanding world of small RNA: from germ cells to cancer. **European Pharmaceutical Review** 5, 34-37

42) Miska EA (2008) MicroRNAs–keeping cells in formation. **Nat Cell Biol** 10, 501-502.

43) Narasimha M, Uv A, Krejci A, Brown NH and Bray SJ (2008) Grainy head promotes expression of septate junction proteins and influences epithelial morphogenesis. **J Cell Sci** 121, 747-752.

44) 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

45) Ng RK and Gurdon JB (2008) Epigenetic inheritance of cell differentiation status. **Cell Cycle** 7(9), 1-5.

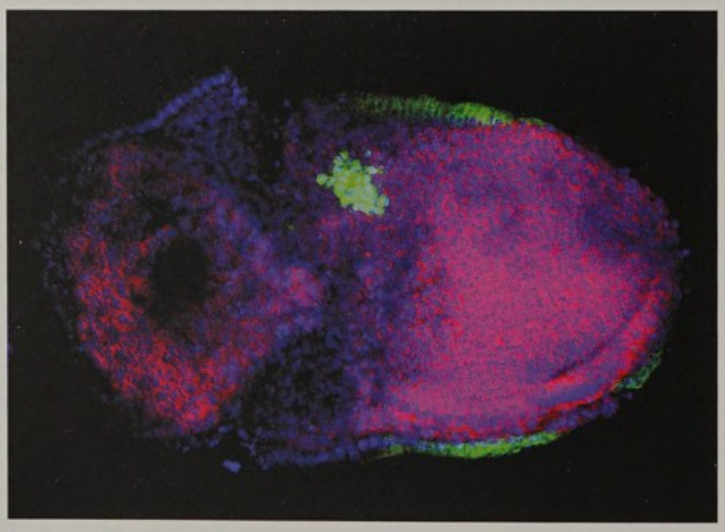
46) Novakovic B, Rakyan V, Ng HK, Manuelpillai U, Dewi C, Wong NC, Morley R, Down T, Beck S, Craig JM and Saffery R (2008) Specific tumour-associated methylation in normal human term placenta and first-trimester cytotrophoblasts. **Molecular Human Reproduction** 14(9):547-554.

47) Panbianco C, Weinkove D, Zanin E, Jones D, Divecha N, Gotta M, 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.

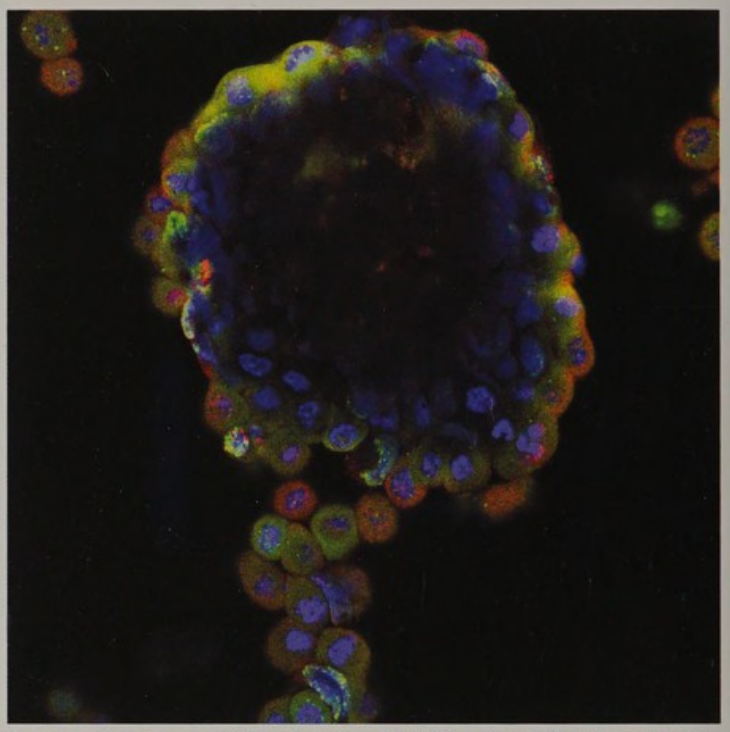
48) Rakyan VK, Down TA, Thorne NP, Flicek P, Kulesha E, Graf S, Tomazou EM, Backdahl L, Johnson N, Herberth M, Howe KL, Jackson DK, Miretti MM, Fiegler H, Marioni JC, Birney E, Hubbard TJ, Carter, N, Tavare S, Beck S (2008) An integrated resource for genome-wide identification and analysis of human tissue-specific differentially methylated regions (tDMRs). **Genome Research**, DOI: 10.1101/gr.077479.108

49) 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

50) Saka Y, Hagemann AI and Smith JC (2008) Visualizing protein interactions by Bimolecular Fluorescence Complementation in *Xenopus*. **Methods** 45, 192-195.



Embryonic Day 7.5 mouse embryo with primordial germ cells (cluster of cells in green on posterior side). Embryo couterstained with DNA marker DAPI (blue) and a cytoplasmic protein (red). (Wee Wei Tee, Surani lab, 2008)



Human osteosarcoma U2OS cells stained for MDC1 (red), 53BP1 (green) and DNA (blue), synchronised in the cell cycle phase of mitosis. (Simona Giunta, Jackson lab, 2008)

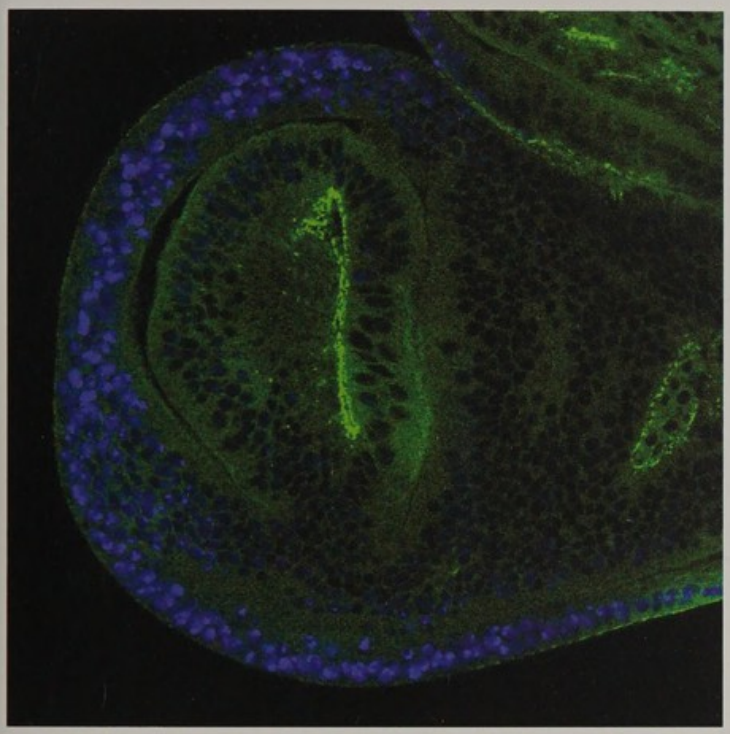
51) Sassen S, Miska EA, Caldas C (2008) MicroRNA - implications for cancer. **Virchows Arch** 452, 1-10

52) Sevilla LM, Rana AA, Watt FM, Smith, JC (2008) KaznrinA is required for axial elongation and epidermal integrity in *Xenopus tropicalis*. **Dev Dyn** 237, 1718-1725.

53) Shovlin TC, Durcova-Hills G, Surani MA, McLaren A (2007) Heterogeneity in imprinted methylation patterns of pluripotent embryonic germ cells derived from pre-migratory mouse germ cells. **Dev Biol** 313, 674-68

54) Smith AE, Hurd PJ, Bannister AJ, Kouzarides T, Ford KG (2008) Heritable gene repression through the action of a directed DNA methyltransferase at a chromosomal locus. **J Biol Chem** 283(15), 9878-9885.

55) Smith J and Alfred A (2008) Whither Development and developmental biology? **Development** 135, 1



PaxillinGFP localised to the basal surface of the imaginal disc cells (Isabelle Delon, Brown lab, 2007)

56) Soares ML, Torres-Padilla ME, Zernicka-Goetz M (2008) Bone morphogenetic protein 4 signaling regulates development of the anterior visceral endoderm in the mouse embryo. **Dev Growth Differ** 50(7):615-21

57) Subkhankulova T, Gilchrist MJ and Livesey FJ (2008) Modelling and measuring single cell RNA expression levels find considerable transcriptional differences among phenotypically identical cells. **BMC Genomics**, 9,268 doi:10.1186/1471-2164-9-268

58) Surani MA, and Reik W (2007) Germ line and pluripotent stem cells. In **Epigenetics** (Ed Allis, CD, Jenuwein T, Reinberg D. and Caparros M-L) pp 377-395, Cold Spring Harbor, NY

59) St Johnston D (2008) Counting motors by force. **Cell** 135, 6, 1000-1001

60) Tanentzapf G, Devenport D, Godt D and Brown NH (2007) Integrin-dependent anchoring of a stem-cell niche. **Nature Cell Biol**. 9, 1413-1418.

61) Tang F, Hajkova P, O'Carroll D, Lee C, Tarakhovsky A, Lao K, Surani MA (2008) MicroRNAs are tightly associated with RNA-induced gene silencing complexes *in vivo*. **Biochem Biophys Res Commun** 372, 24-29

62) Tang F, Hayashi K, Kaneda M, Lao K, Surani MA (2008) A sensitive multiplex assay for PiRNA expression **Biochem Biophs Res Commun** 369, 1190-1194

63) Vigorito E, Perks KL, Abreu-Goodger C, Bunting S, Xiang Z, Kohlhaas S, Das PP, Miska EA, Rodriguez A, Bradley A, Smith KG, Rada C, Enright AJ, Toellner KM, Maclennan IC, Turner M (2007) microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. **Immunity** 27, 847-59

64) Walker A, Acquaviva C, Matsusaka T, Koop L and Pines J (2008) UbcH10 has a rate-limiting role in G1 phase but might not act in the spindle checkpoint or as part of an autonomous oscillator. **Journal of Cell Science** 121, 2319-2326

65) Watanabe T, Totoki Y, Toyoda A, Kaneda M, Kuramochi-Miyagawa S, Obata Y, Chiba H, Kohara Y, Kono T, Nakano T, Surani M.A, Sakaki Y, Sasaki H (2008) Endogenous SiRNAs from naturally formed dsRNAs regulate transcripts in mouse Oocytes. **Nature** 453, 539-543

66) Wilczynska A, Armisen J, Miska EA, Standart N (2009) Two Piwi proteins, Xiwi and Xili, are expressed in the *Xenopus* female germline. **RNA** 15 (2) 337-345

67) 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.

68) Xie A, Hartlerode A, Stucki M, Odate S, Puget N, Kwok A, Nagaraju G, Yan C, Alt FW, Chen J, Jackson SP and Scully R (2007) Distinct roles of chromatin associated proteins MDC1 and 53BP1 in mammalian double-strand break repair. **Mol Cell** 28(6), 1045-57.

69) Zimyanin 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, 834-853

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, a member of the Scientific Advisory Board of the MRC Centre for Developmental Neurobiology, King's College London, a member of the University of Cambridge Neuroscience Committee, a member of the steering committee of the University of Cambridge Women in Science, Engineering and Technology Initiative.

JOHN GURDON is a member of the British and American Anatomical Societies, Chairman of the Company of Biologists and a member of the Board for Diagnostics of the Real World. He also sits on the Advisory Board of the new Harvard Stem Cell Institute, and is a member of the Israel Rambam Medical Health Care Campus Scientific Advisory Board.

STEVE JACKSON is a member of the Radiation Oncology and Biology External Advisory Board, 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 Chief Scientific Officer, KuDOS Pharmaceuticals Ltd.

TONY KOUZARIDES is non-executive director of Abcam Plc, a member of the Cancer Research UK Science and Strategy Advisory Group and part of the Scientific Advisory Board for the Marie Curie Institute (UK), the Centre for Genomic Research (Spain), the Institute of Molecular Biology (Crete) and the Centre for Epigenetics and Biology (Spain).

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. His University commitments include being a member of the University of Cambridge Sub-Committee for Biological Sciences and Clinical Medicine (Senior Academic Promotions), the School of Biological Sciences External Relations & Collaborations Group, and the Consultative Committee for Safety. He is also Chairman of the Darwin at Christ's 2009 College Committee.

AZIM SURANI is Chairman of 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, and Member of the Royal Society International Grants Panel.

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

HONOURS AND AWARDS

STEVE JACKSON - elected Fellow of the Royal Society

ERIC MISKA - elected to the EMBO Young Investigator Program

EDITORIAL BOARDS OF JOURNALS

JULIE AHRINGER – Public Library of Science Biology, Molecular Systems Biology, Phil. Transactions of the Royal Society B.

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

STEVE JACKSON – Carcinogenesis, EMBO Journal, EMBO Reports, Nature Reviews, DNA Repair, Faculty of 1,000, Science, Genes and Development, Current Biology, The Scientist.

RICK LIVESEY – BMC Developmental Biology.

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.

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

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CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR SIR TOM BLUNDELL, Head, Department of Biochemistry and Chair of the School of Biological Sciences, University of Cambridge, UK

LEAVERS DURING 2008

JOANNA ARGASINSKA took up a new position at Cytocell Ltd in Cambridge

RENATA BASTO moved to Paris to set up a research group at the Marie Curie Institute

JULIA BATE left to take up a new position at Abcam, Cambridge

CAROLINE BROAD left to take up new position at CIMR, Cambridge

ADRIAN CARR is now a Postdoctoral Researcher at the Cambridge Systems Biology Centre, University of Cambridge

CARLY DIX took up a Postdoctoral position in Simon Bullock's group at the LMB in Cambridge

ROBERT DRISCOLL is now a Postdoctoral Researcher in Karlene Cimprich's lab, Stanford University, California, USA

GABRIELA DURCOVA-HILLS is now a consultant for Albion Innovations, Cambridge

CRISTINA EGUIZABAL left to become a Postdoctoral Researcher at the Center of Regenerative Medicine, Barcelona

ASTRID ERBER returned to the University of Vienna to complete her full-time studies

KATARZYNA FILIMONOW returned to Poland to complete her full-time degree at the University of Warsaw

SERGE GRAVEL moved to Canada to take up a Postdoctoral position in Raymund Wellinger's lab, Sherbrooke University, Quebec.

TAN HAIHAN completed his Vacation Studentship and returned to his full-time degree studies

SAMANTHA HERBERT moved to the Center for Brain Research, Vienna Medical University to take up a PhD Studentship

MORGANE HILPERT returned to Paris to complete her full-time degree

GILLIAN HOWARD is now a Research Assistant at the LMB in Cambridge

CAN HUANG completed vacation studentship and returned to full-time studies at Cambridge University

PAUL HURD took up a lecturer position in Molecular Biology & Biochemistry at the School of Biological & Chemical Sciences, Queen Mary, University of London

TAGBO ILOZUE completed his PhD and returned to his medical studies

CHRISTINE LEE returned to the University of British Columbia to complete her undergraduate studies

DAMIEN LEFER returned to the Ecole Normale Supérieure in Lyon to complete his Masters degree

EUNICE LIN completed her degree and is applying to commence a PhD in Singapore

JULIA LINDROOS has been accepted to start a medical degree in Sweden

ANNE LORENZ completed her student placement and returned to full-time studies at Philipps University, Marburg, Germany

CHRISTINE MAGILL retired

UGO MAYOR will take up a Group Leader position at the CIC BioGUNE, Bizkaia, Spain

MICHAEL MENDES completed his Erasmus placement and returned to full-time studies at the University of Diderot, Paris

CHRISTOPHER NELSON is now an Assistant Professor at the Department of Biochemistry and Microbiology, University of Victoria, Canada

OLIVER NENTWICH took up a new position at TwistDx in Cambridge

JAKOB NILSSON moved to Denmark to take up a Group Leader position at BRIC-Biotech Research & Innovation Centre, University of Copenhagen

GRACE NISBET returned to medical studies after completing her PhD

COSTANZA PANBIANCO moved to Geneva to take up a Postdoctoral position

STEFANIA RAGONE took up another position in Cambridge

ALEXANDRE RAPOSO completed his PhD and took up a postdoctoral position with Michael Kiebler, Medical University of Vienna

DORA SABINO left to take up a postdoctoral position at the Marie Curie Institute in Paris

TANYA SHOVLIN moved to Belfast City Hospital to take up a Clinical Scientist position

JIM SMITH left to become Director of NIMR in London

PHILIPPA SMITH left to become a User Requirement Co-ordinator at the MRC Laboratory of Molecular Biology, Cambridge

MARTIN TAYLOR completed his vacation studentship and returned to full-time studies

STEFAN TÜMPEL returned to Germany

QIANG WU left to take up an Assistant Professor position in the Department of Biochemistry, National University of Singapore

KATHLEEN XIE completed her student placement and returned to MIT to complete her full-time degree studies

Santa Claus came down the Institute chimney again this year, to the delight of all the boys and girls who attended the Institute Children's Party. Thanks to Hélène Doerflinger and Anja Hagting for organising the party, and to Santa for finding time to drop in. (Anja Hagting, 2008)

ACKNOWLEDGEMENTS

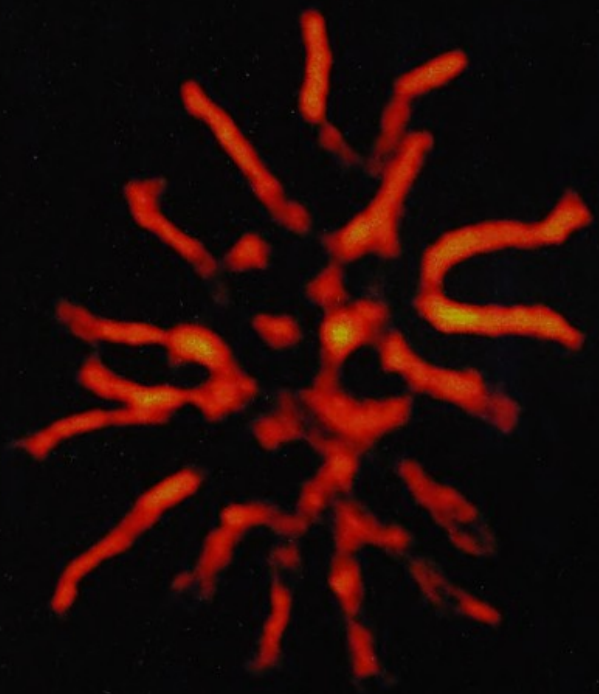
Prospectus produced in the Wellcome Trust/Cancer Research UK Gurdon Institute. Edited by Ann Cartwright, production by Alastair Downie

Group photographs by The Anatomy Visual Media Group

Printed by Cambridge University Press

Front cover: Third instar neuromuscular junction stained with/against phalliodin, HRP and bruchpilot (Karin Edoff, Brand lab, 2008)

Back cover: DNA in a *Drosophila* neuroblast stained with DAPI (Paul Conduit, Raff lab, 2008)



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