Annual report : 2004/2005 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

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Publication/Creation

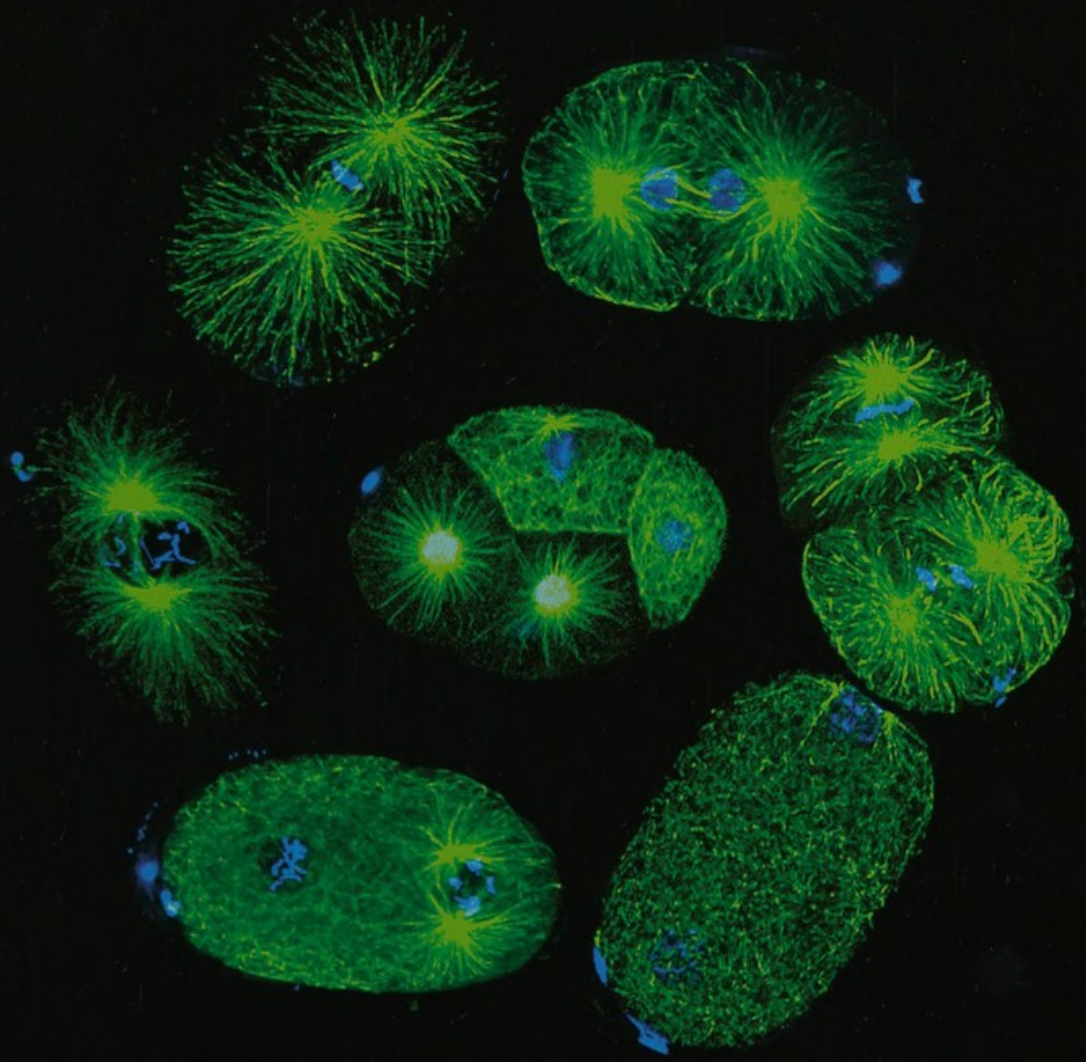
Cambridge : Wellcome Trust / Cancer Research UK Gurdon Institute, 2005

Persistent URL

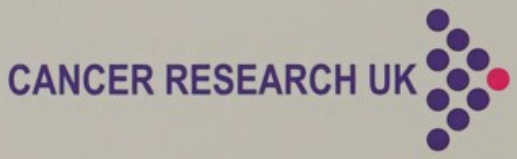
https://wellcomecollection.org/works/hcvjmv6n

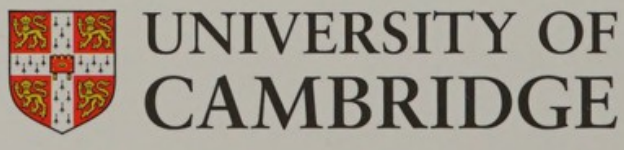
THE WELLCOME TRUST/ CANCER RESEARCH UK GURDON INSTITUTE

2005 PROSPECTUS/ANNUAL REPORT 2004



Gurdon INSTITUTE





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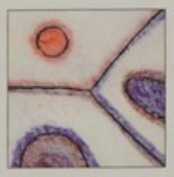

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CHAIRMAN'S INTRODUCTION

As I write, members of the Gurdon Institute are moving out of the original Wellcome Trust/Cancer Research UK building, which we first occupied in 1991, and into our new accommodation just a hundred yards away along Tennis Court Road. The move is proceeding smoothly and the inevitable hiccups that occur on such occasions, and the necessary items of 'snagging' (fixing minor defects in the building), are being dealt with by our administrative team efficiently and well. Members of the Institute appreciate the modern laboratory design, the improved core and meeting space and the dedicated areas for confocal microscopy and microarray analyses. We are very grateful to the Wellcome Trust for funding this initiative.

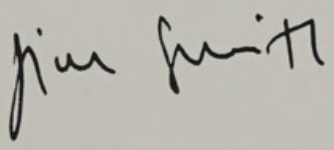
The Wellcome Trust/Cancer Research UK Gurdon Institute, December 2004

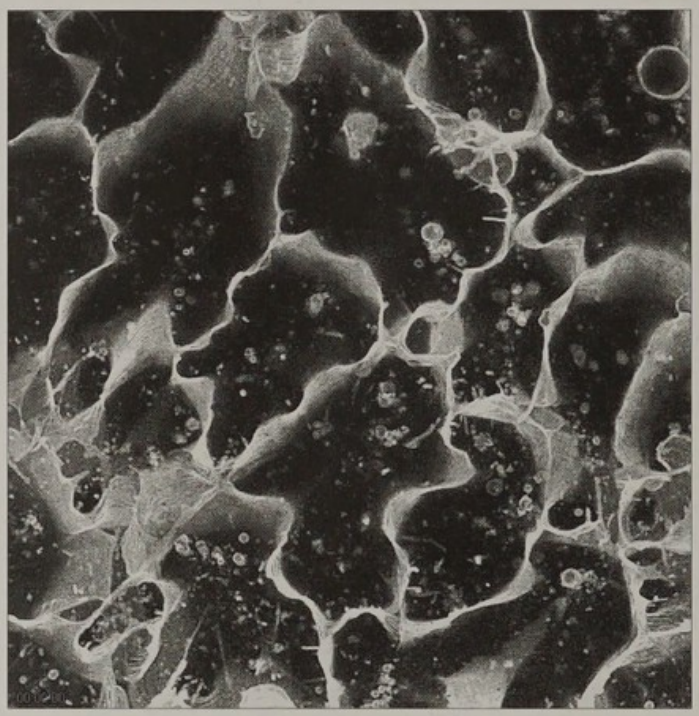
To mark the opening of our new building, and to honour our eponymous founding Chairman, the Gurdon Institute is organising a symposium to be held in June 2005. The meeting will include lectures by world leaders in cell, molecular and developmental biology, and we are greatly looking forward to the event. We are hoping that many former members of the Institute will be able to attend, so that everyone involved in the Institute's success will be able to join in the celebration.

The opening symposium will be preceded at the end of March 2005 by a visit from our International Advisory Board, and we look forward to their usual insightful and helpful comments. Members of the IAB are listed at the back of this Prospectus. We are very grateful to them for giving up their valuable time to help us.

I am delighted that Eric Miska has now joined us as a Group Leader, and I hope to be able to report additional newcomers in next year's Introduction. Meanwhile, I am very pleased that current members of the Gurdon Institute continue to receive international awards and recognition. These include Julie Ahringer, who was selected to deliver the Royal Society's Francis Crick Lecture for 2004, and Daniel St Johnston who was elected a Fellow of the Academy of Medical Sciences. We congratulate Andy Chalmers (Nancy Papalopulu's group) and Cath Lindon (Jonathon Pines's group), who were awarded MRC Career Development Awards, and Renata Basto (Jordan Raff's group) and Ugo Mayor (Andrea Brand's group), both of whom were awarded Royal Society Dorothy Hodgkin Fellowships.

We have also had a highly successful group of students this year, including Miao-Chih Tsai (Julie Ahringer's group), who won the poster prize at the recent Harden Conference on The Ubiquitin-26S Proteasome Pathway, and Bernhard Strauss (Nancy Papalopulu's group), who won the poster prize of the British Society for Cell Biology.



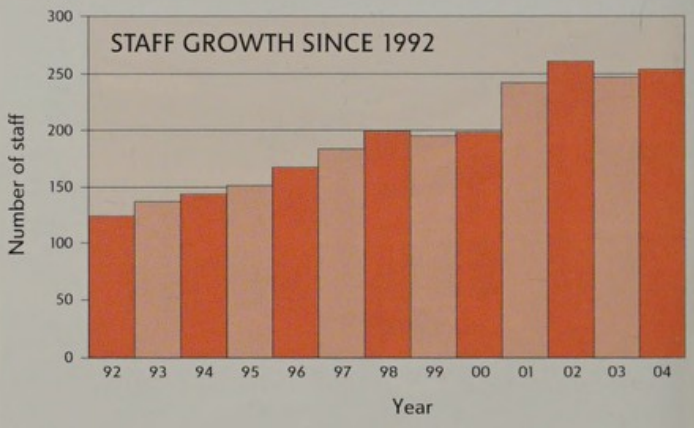


Radiance confocal image of *Xenopus laevis* blastula tissue expressing GFP-GAP43, a membrane marker. Anja Hagemann (Smith Group), 2004

HISTORICAL BACKGROUND

The Institute continues to be situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance of 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, such as gene cloning, antibody preparation, cell culture, microarray technology, imaging and embryonic manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

The Institute is an integrated part of Cambridge University, and all Group Leaders are members of a University Department and contribute to teaching and graduate student supervision.

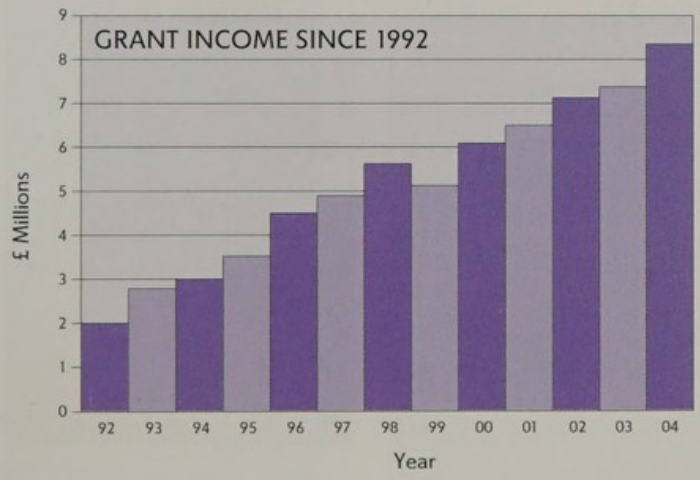


CENTRAL SUPPORT SERVICES

The Institute's 'core staff' provides administrative, technical and computing support to scientists, in order to ensure the smooth running of the Institute. During 2004 this has involved an enormous amount of work in preparing for our move to the new building, in helping coordinate the move, and then in getting the new building up and running, all the while ensuring that the 'old' building continued to function effectively. This juggling act has been performed with typical grace and good humour, and the Institute is grateful to every member of the Core team.

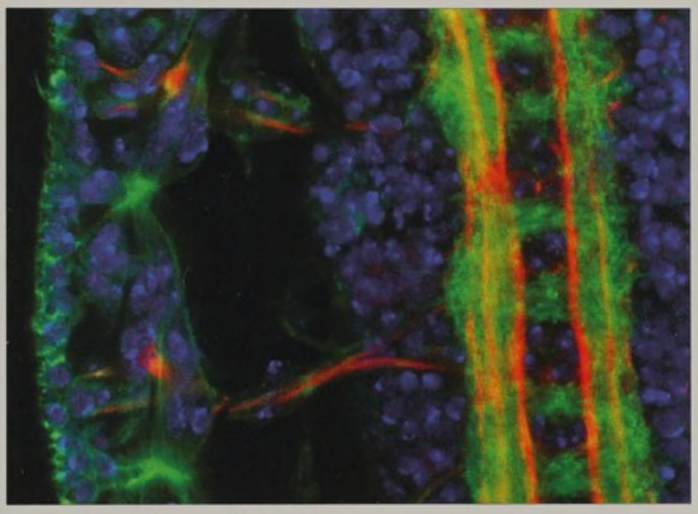
FUNDING

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. During 2004 we submitted applications for renewed funding from 2005 onwards.

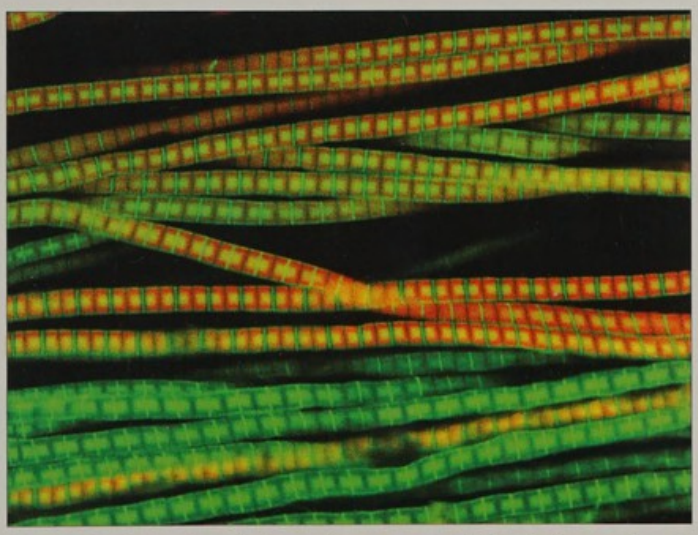


Other sources of financial support, both direct and indirect, include the European Community, BBSRC, the MRC, EPSRC, the Royal Society, the Lister Institute, the Elmore Trust, the Isaac Newton Trust, the Leverhulme Trust, Beit Memorial Fellowships, the Association for International Cancer Research, NIH, and the European Molecular Biology Organisation. 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.



A section of the *Drosophila* CNS. Green: overexpressed actin, Red: Fasciclin II, Blue: DNA. Motor neurons (red) exit the CNS (Green) and synapse on specific target muscles on the body wall of the embryo (also in green). Mike Hewett (Brand Group), 2004



Drosophila adult indirect flight muscles expressing GFP-actin (in green) and labelled with phalloidin (in red). Katja Röper (Brown Group), 2004

JULIE AHRINGER

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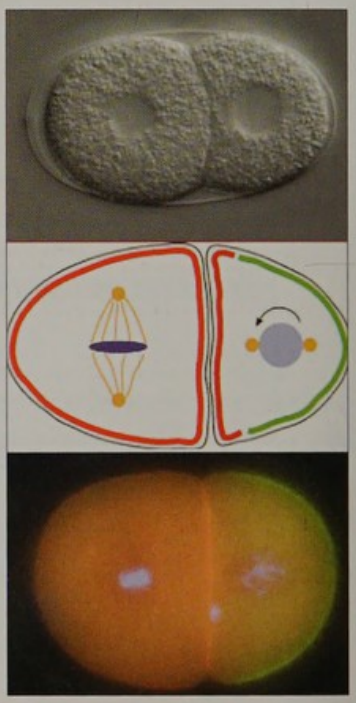
Shane Woods

We study how patterns of cell divisions and cell fates are controlled, using *C. elegans* as a model system. We have focused on two major questions. First, how is cell polarity established in the embryo and then how is this information transduced within the cell? Second, how is chromatin regulated to effect cell fate decisions? For these studies, we are taking advantage of a genome-wide RNAi library we have constructed.

Cell polarity is an essential feature of most animal cells. For example, it is critical for epithelial formation and function and for correct partitioning of fate-determining molecules. We use the large, transparent one-celled *C. elegans* embryo as a simple yet powerful model system for studying cell polarity. Using genome-wide RNAi screening coupled with videomicroscopy of live embryos, we identified many new conserved cell polarity genes, which we study using genetics, biochemistry, and real-time fluorescent cell imaging.

Transcription repression is often mediated through histone deacetylase (HDAC) complexes. However, little is known about the developmental roles and regulation of histone deacetylation. In *C. elegans*, HDAC complexes are involved in a range of different cell fate decisions, including inhibition of Ras signalling during vulval development. Through genome-wide RNAi screening, we have identified many new chromatin factors that cooperate with histone deacetylation. We are studying the function of these proteins in transcriptional control and their relationships to each other using chromatin immunoprecipitation and other techniques.



C. elegans embryos are highly polarised. At the 2-cell stage, the anterior cell is larger than the posterior one (top), and the two cells have different cortical proteins (PAR-3, red; PAR-2 green), different spindle orientations, and different cell cycle times.

Poulin G, Nandakumar R and Ahringer J (2004) Genome-wide RNAi screens in *C. elegans*: Impact on cancer research, **Oncogene** 23, 8340-8345

Lettre G, Kritikou EA, Jaeggi M, Calixto A, Fraser AG, Kamath RS, Ahringer J and Hengartner MO (2004) Genome-wide RNAi identifies p53-dependent and -independent regulators of germ cell apoptosis in *C. elegans*. **Cell Death & Differentiation** 11, 1198-203

Kemp CA, Kopish KR, Zipperlen P, Ahringer J and O'Connell KF (2004) The *C. elegans* spd-2 gene encodes a coiled-coil domain protein required for centrosome maturation and duplication. **Developmental Cell** 6, 511-523

Kamath RS, Fraser AG, Dong Y, Poulin G, Durbin R, Gotta M, Kanapin A, Le Bot N, Moreno S, Sohrmann M, Welchman D, Zipperlen P and Ahringer J (2003) Systematic Functional Analysis of the *C. elegans* Genome using RNAi. **Nature** 421, 231-237

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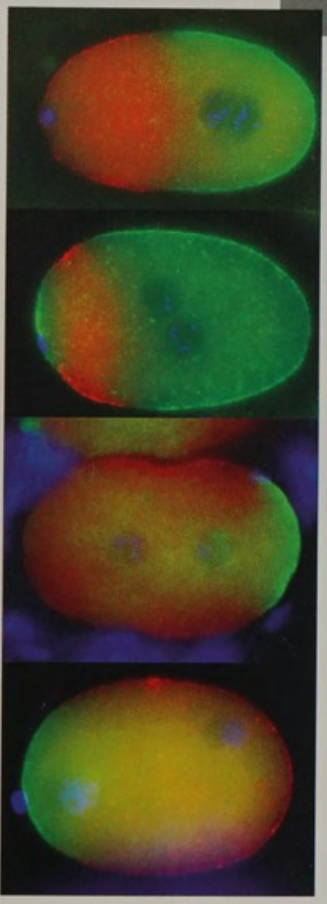
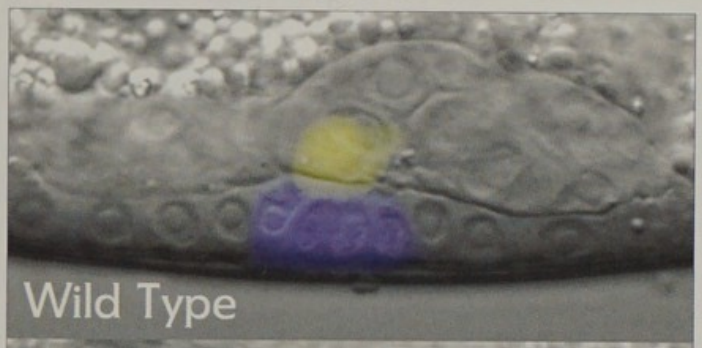
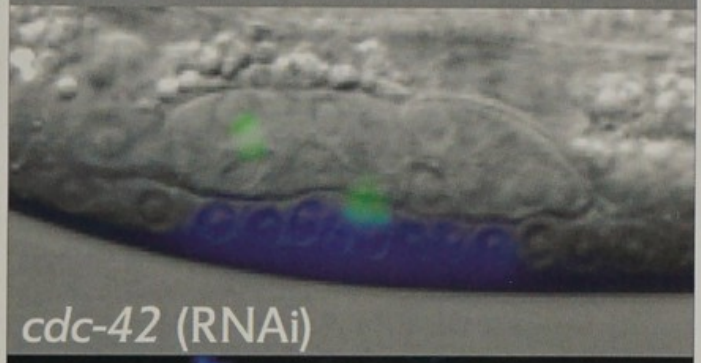
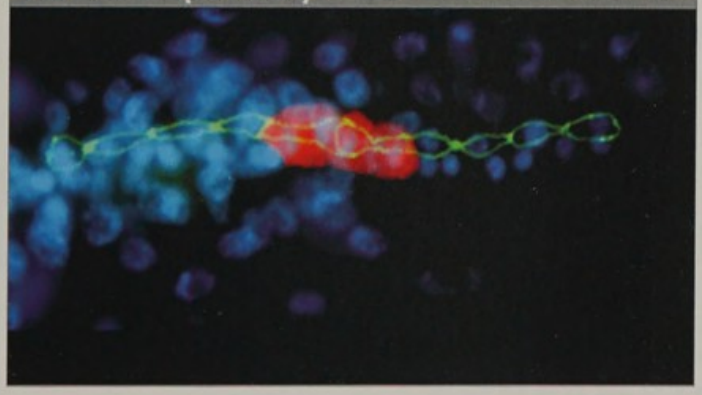
Relative cell sizes of live 2-cell stage embryos is an assay of correct asymmetric cell division. Top, wild-type asymmetric first division results in larger anterior cell and smaller posterior cell. Other three embryos are RNAi-induced phenotypes: no asymmetry, exaggerated asymmetry, or failure to move the spindle to the cell centre.



Abnormal distributions of polarity proteins PAR-3 (red) and PAR-2 (green) after RNAi of genes involved in establishing embryonic polarity. Top, wild-type, mutants below.

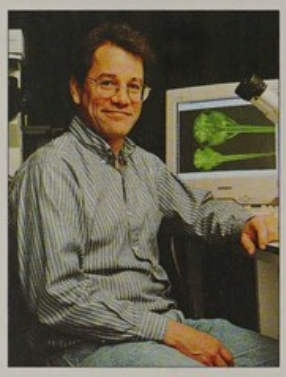






Fluorescent reporters for vulval and gonadal cells can be used to assay cell fates in live animals (top two panels; primary vulval cells are blue, gonadal anchor cells are green/yellow). Bottom, indirect immunofluorescence of a fixed animal outlines vulval cell junctions (green), primary vulval cells (red) and nuclei (blue).

ENRIQUE AMAYA



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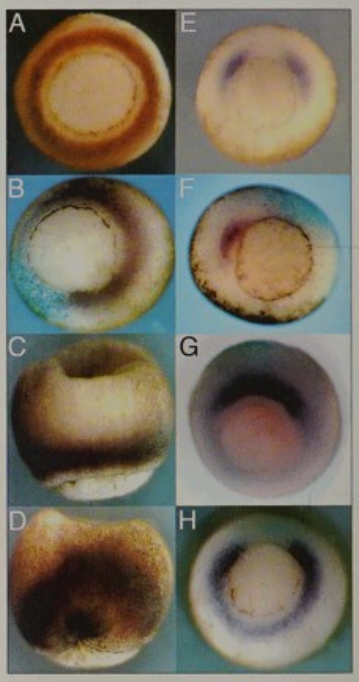
Ricardo Costa
Rosalind Friday
Kathy Hartley
Jeffrey Huang
Shoko Ishibashi
Lars Petersen
Jeremy Sivak

One of the main interests of our group is understanding the molecular events responsible for mesoderm formation and patterning. In particular we are investigating the role of fibroblast growth factor (FGF) signalling during mesoderm formation in the frog, *Xenopus*. We have shown that inhibiting FGF signalling during gastrulation disrupts mesoderm specification and morphogenesis. In order to better understand these processes, we have begun to isolate downstream targets of FGF signalling. We have identified Xsprouty2 as an important target gene. This protein and the related proteins, Xsprouty1, Xspred1 and Xspred2 are both targets and modulators of FGF signalling. We have recently shown that the Sprouty and Spred proteins play an important role in FGF signal interpretation, allowing mesoderm specification and morphogenesis to occur in a coordinate fashion.

In order to identify additional genes involved in mesoderm specification and morphogenesis, we are using bioinformatics tools in combination with functional screens to identify additional genes involved in these processes. As part of this project we have identified around 7000 full-length clones from *Xenopus tropicalis* and have screened nearly 2000 of these clones for genes affecting mesoderm formation and/or morphogenesis. Of those tested, we have isolated 82 genes, which alter or inhibit mesoderm formation and/or gastrulation movements (see figures).

In addition we are investigating the role of growth factor signalling in patterning of the nervous system. In particular we are examining the role for *Xenopus* Dachshund in the development of the nervous system and the role of neurotrophic factors in the pathfinding of the trigeminal nerve.



Gilchrist M, Zorn AM, Smith JC, Voigt J, Papalopulu N and Amaya E (2004) Defining a large set of full length clones from a *Xenopus tropicalis* EST project. **Dev Biol** 271, 498-516

Sivak JM and Amaya E (2004) FGF signaling during gastrulation. **Gastrulation** (Edited by Claudio Stern. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY) pp 463-473

Chen J-A, Voigt J, Gilchrist M, Papalopulu N and Amaya E. Identification of novel genes affecting mesoderm formation and morphogenesis through an enhanced large scale functional screen in *Xenopus*. **Mech Dev** [in press]

Voigt J, Chen J-A, Gilchrist M, Amaya E and Papalopulu N. Expression cloning screening of a unique and full-length set of cDNA clones is an efficient method for identifying genes involved in *Xenopus* neurogenesis. **Mech Dev** [in press]

For further publications, see numbers 8, 12 and 30 on pp 53–58

Facing page: A large-scale gain of function screen revealed many genes that are able to alter the expression pattern of the pan-mesodermal marker, *Xbra*, (panels A-D) and/or the dorso-lateral mesodermal marker, *Xmyf-5* (panels E-H). Panels A and C show the wild-type expression of *Xbra*, viewed from the vegetal pole and from the side in gastrula embryos, respectively. Panels B and D show embryos with either downregulated or shifted expression of *Xbra*, respectively. The gastrula embryos in panels E-H are viewed from the vegetal pole and dorsal at the top. Panel E shows the wild-type expression of *Xmyf-5*. Panels F-H show embryos with altered expression of *Xmyf-5* over the region where the injected mRNA is misexpressed (visualised by the blue nuclear stain). In panel F, the expression is downregulated; in panel G, the expression is expanded dorsally; and in panel H, the expression is expanded ventrally.

A montage of embryos showing the expression pattern of a select group of genes isolated in a large-scale gain of function screen aimed at identifying genes able to alter the specification and/or morphogenesis of the mesoderm. The top row shows embryos at the gastrula stages, the next two rows show embryos at the neurula stages and the bottom four rows show embryos at the tailbud stages.

ANDREA BRAND

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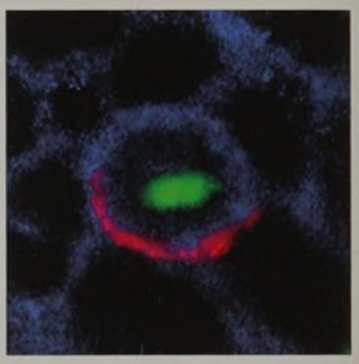
In the *Drosophila* nervous system, neural precursors (neuroblasts) divide in a stem-cell-like fashion, renewing themselves at each division and giving rise to smaller daughter cells (GMCs) that divide only once before differentiating. Cell fate determinants, such as the transcription factor Prospero, are partitioned from neuroblasts to GMCs where they act to distinguish GMCs from their mothers. We are comparing the transcriptional networks of neuroblasts and GMCs to highlight the genes that regulate regenerative versus differentiative cell division. By identifying neural stem-cell-specific genes and genes specific for differentiating daughters we can begin to assess the potential for redirecting GMC-like cells to divide in a regenerative manner.

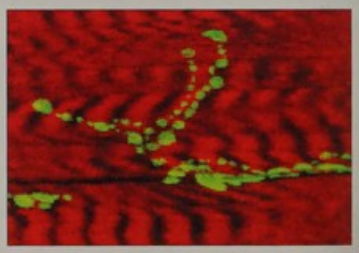
In vertebrates, adult neural stem cells can proliferate in response to injury. We have discovered that *Drosophila* ventral midline cells, which normally divide only once, can undergo an extra cell division if a sibling midline cell is destroyed. Remarkably, the regenerated midline cell differentiates appropriately to replace the damaged cell. Given its similarity to the vertebrate floorplate, the ventral midline may serve as a model system to study cellular regeneration in the vertebrate CNS.

We are also investigating the regulation of synaptic plasticity by localised protein degradation at synapses. One mechanism to control protein abundance is the ubiquitin-proteasome degradation system. Ubiquitin-mediated protein degradation is a central regulator of the eukaryotic cell cycle. A critical mediator of cell-cycle transitions is the anaphase-promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase. We have shown that the APC/C plays a novel role in post-mitotic cells: it regulates synaptic growth and synaptic transmission at neuromuscular synapses.

Please see Brand lab home page: http://www.gurdon.cam.ac.uk/~brandlab/



Miranda (red) forms a basal crescent prior to neuroblast cell division, whence it is partitioned asymmetrically to the daughter cell (the GMC; Lgl is in blue).



The APC/C localizes to neuromuscular synapses. The number of synaptic boutons (green) and the size of the synapse increase significantly when APC/C levels are reduced specifically in motor neurons (muscle actin, red).

Barros CS, Phelps CB and Brand AH (2003) *Drosophila* non-muscle myosin II promotes the asymmetric segregation of cell fate determinants by cortical exclusion rather than active transport. **Developmental Cell** 5, 829-840

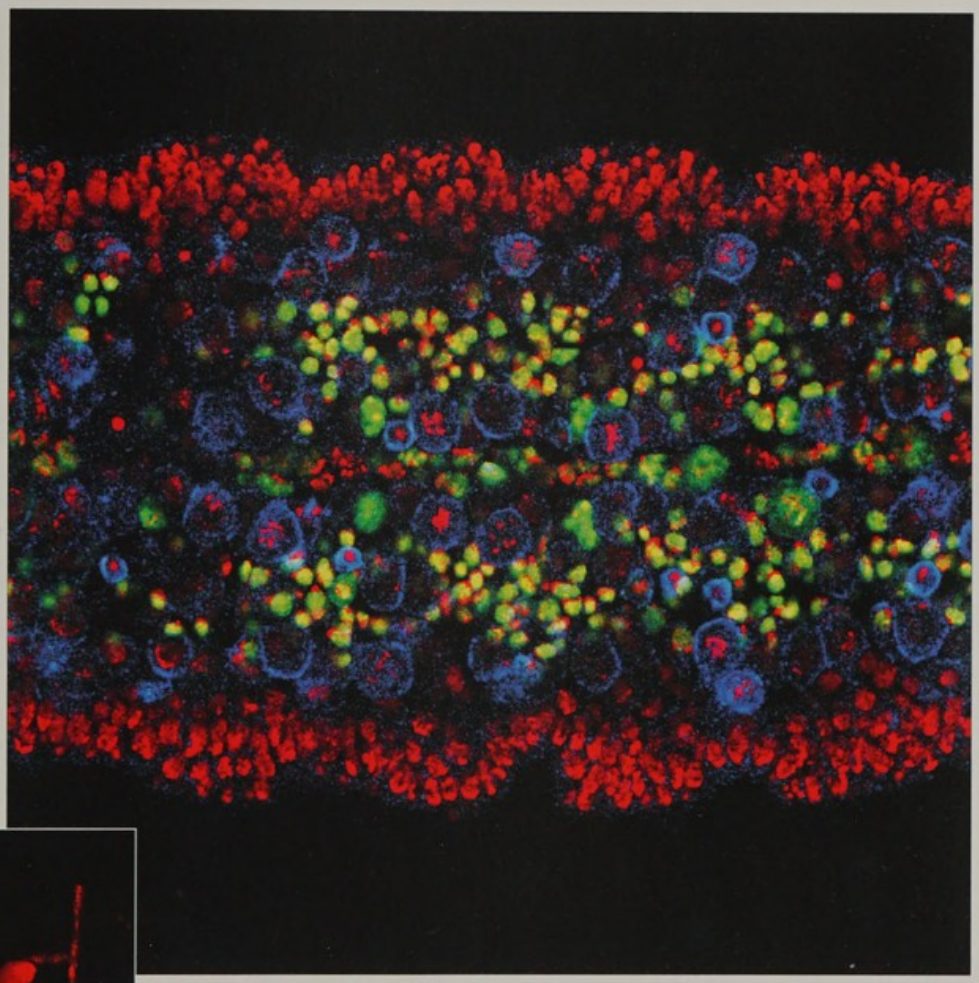
Brand AH and van Roessel PJ (2003) Region-specific apoptosis limits neural stem cell proliferation. **Neuron** 37, 185-187

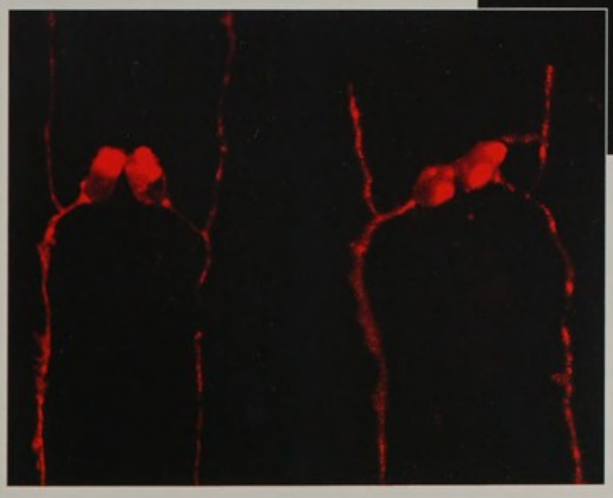
Carr A, Choksi SP and Brand AH (2004) Turning back the clock on neural progenitors. **BioEssays** 26, 711-714

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 further publications, see number 67 on pp 53–58

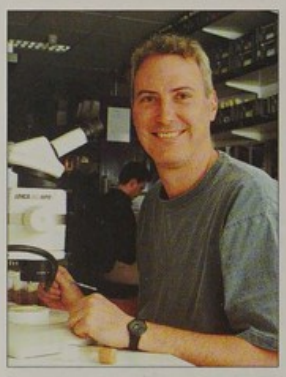
Dividing neuroblasts in the ventral nerve cord of the embryonic CNS (Miranda in blue, Prospero in green, DNA in red).





In the CNS, ventral midline cells can, uniquely, regenerate their damaged sisters. Remarkably, the regenerated cell differentiates appropriately. The left panel shows wildtype MP1 neurons; the right panel shows a regenerated MP1 neuron (regenerated neuron on the right).

NICK BROWN



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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. By mutating the gene encoding the second of the two β integrin subunits encoded in the fly genome, we have assayed the consequences of the complete absence of integrin function on fly development for the first time (Fig.1). Analysis of integrin function in dorsal closure has revealed unexpected roles in cell-cell adhesion within the epithelia surrounding the embryo (Fig. 2). The majority of our work focuses on the intracellular proteins required for integrin function, many identified by a genetic screen we performed. While some fit easily into an integrin pathway, others like the ubiquitous nuclear protein Cassowary (Fig. 3) have proven more challenging. Surpisingly, some well known integrin-associated proteins only affect integrin function when overexpressed (Fig. 4), and not when genetically removed.

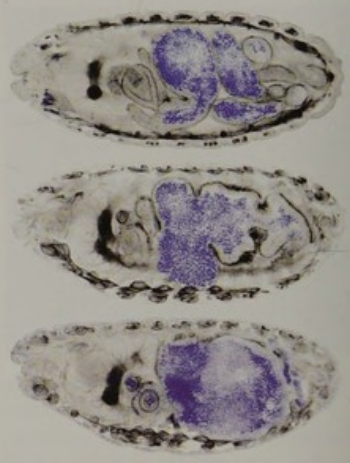


Fig 1: Increase in morphogenetic defects in the absence of all integrins. A normal embryo is shown at the top, one lacking the well-characterised integrin bPS subunit in the middle, and one lacking all integrins (βPS and βv) at the botttom. The yolk granules (blue) highlight the defects in the development of the gut.

Fig 3 (opposite): A protein required for integrin-mediated adhesion encodes a ubiquitous nuclear protein (green), which colocalises with the nuclear DNA (blue). Cell outlines are in red.

Bökel C and Brown NH (2002) Integrins in development: moving on, responding to, and sticking to the extracellular matrix. **Dev Cell** 3, 311-321

Torgler CN, Narasimha M, Knox AL, Zervas CG, Vernon MCH and Brown NH (2004) Tensin stabilises integrin adhesive contacts in *Drosophila*. **Dev Cell** 6, 357-369

Narasimha M and Brown NH (2004) Novel roles for integrins in epithelial morphogenesis. **Curr Biol** 14, 381-385

Devenport D and Brown NH (2004) Morphogenesis in the absence of integrins: mutation of both *Drosophila* β subunits prevents midgut migration. **Development** 131, 5405-5415

Grabbe C, Zervas CG, Hunter T, Brown NH and Palmer RH (2004) Focal adhesion kinase is not required for integrin function or viability in *Drosophila*. **Development** 131, 5795-5805

Bökel C, Prokop A and Brown NH. Papillote and Piopio, *Drosophila* ZP-domain proteins required for cell adhesion to the apical extracellular matrix and microtubule organization. **J Cell Sci** [in press]

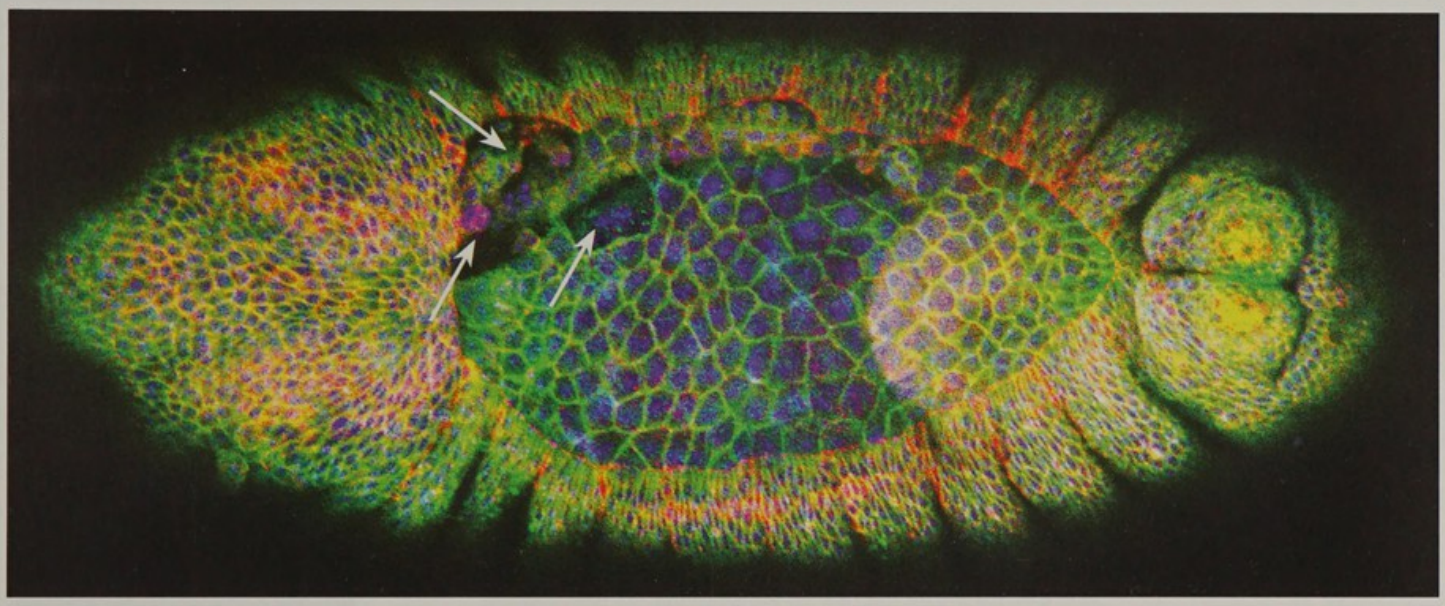


Fig 2: Lack of integrins produces a loss of cell-cell adhesion in the amnioserosa, an extraembryonic epithelial cell layer, which results in rips between the cells (arrows).

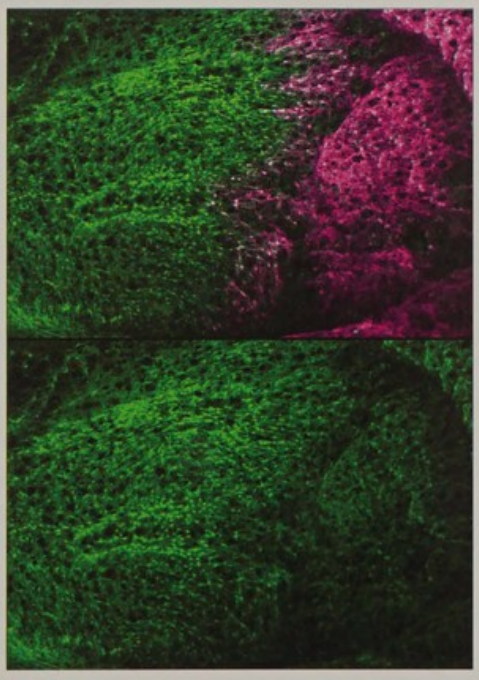
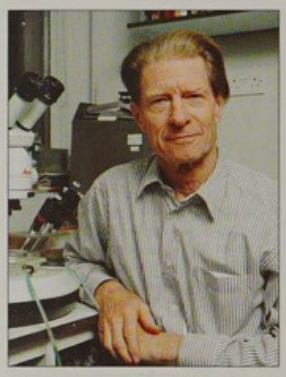


Fig 4 (right): Overexpression of focal adhesion kinase (magenta) suppresses the clustering of integrins (green) into adhesive complexes on the basal surface of the imaginal disc epithelium (in collaboration with C Grabbe and R Palmer, Umeå University).

JOHN GURDON



Co-workers:

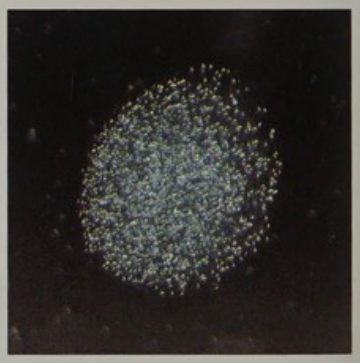
Adrian Biddle
Nigel Garrett
Jerome Jullien
Magdalena Koziol
Yen-Hsi Kuo
(Ray) Kit Ng
Ilenia Simeoni
Henrietta Standley
Caroline Webb

Our group is interested in nuclear reprogramming and cell fate determination by signal factors in amphibian development. We have the long-term aim of establishing a route for the production of replacement cells of the same genetic composition as the donor cells used. Many different cell-types can be generated by transplanting the nucleus of a specialised cell to an enucleated egg by which it is reprogrammed. We have recently found that mouse and human blood cell nuclei are induced to express the stem cell marker gene oct4 when they are injected into growing amphibian oocytes. Unlike eggs, oocytes do not induce DNA replication and therefore directly reprogram adult cell nuclei at the transcriptional level; they are large cells and are available in great abundance.

Amphibian oocytes are particularly well suited to our principal aim of understanding the mechanisms of nuclear reprogramming. We find that nuclear reprogramming entails both protein exchange between donor nuclei and recipient oocytes, and the demethylation of genomic DNA. Xenopus oocytes have a highly selective DNA demethylase activity that acts on the promoter but not enhancer regions of the stem cell marker gene oct4. This seems to constitute an essential part of the process by which somatic cell nuclei are reprogrammed.

We are also analysing the mechanisms by which secreted signal factors of the TGFbeta class can direct embryonic cells into divergent pathways of cell differentiation. These factors act as morphogens, and could be used to derive desired cell-types from the embryo cells resulting from somatic cell nuclear transfer.

Ovarian oocytes of *Xenopus*



The germinal vesicle of a *Xenopus* oocyte. The bright spots represent nucleoli and cajal bodies

Simonsson S and Gurdon JB (2004) DNA demethylation is necessary for the epigenetic reprogramming of somatic cell nuclei. **Nature Cell Biol** 6, 984-990

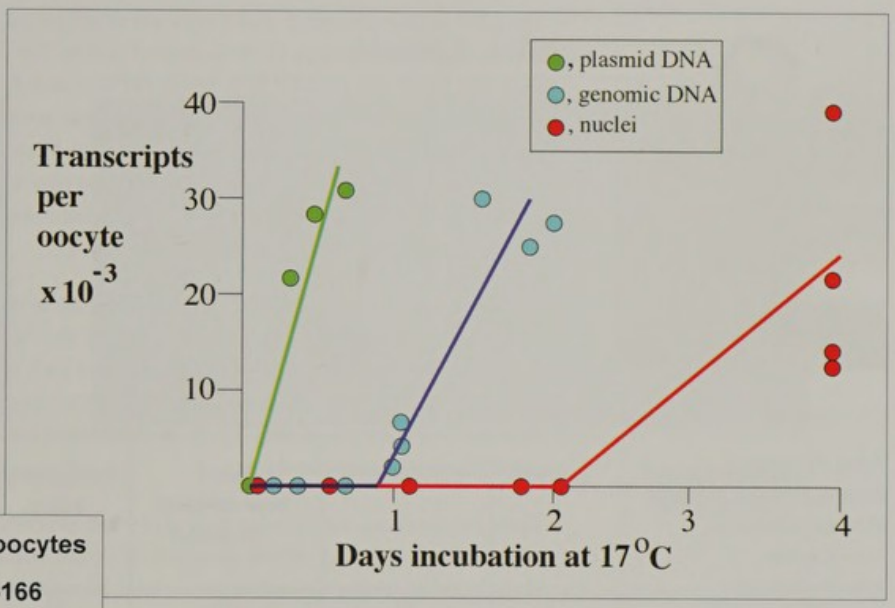
Gurdon JB, Bryne JA and Simonsson S (2003) Nuclear reprogramming and stem cell creation. **Proc Natl Acad Sci USA** 100, 11819-22

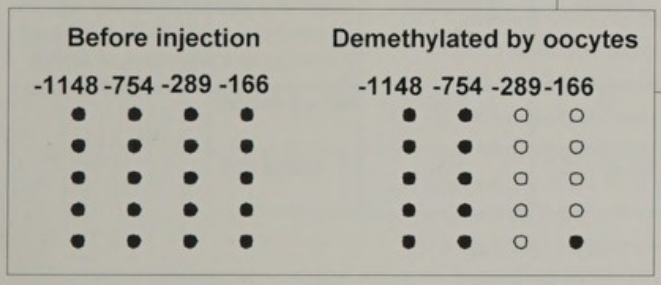
Byrne JA, Simonsson S, Western PS and Gurdon JB (2003) Nuclei of adult mammalian somatic cells are directly reprogrammed to oct-4 stem cell gene expression by amphibian oocytes. **Curr Biol** 13, 1206-1213

Standley HJ and Gurdon JB (2003) The community effect in *Xenopus* development. **The Vertebrate Organizer** pp 73-91. Ed H Grunz, Springer-Verlag, Heidelberg

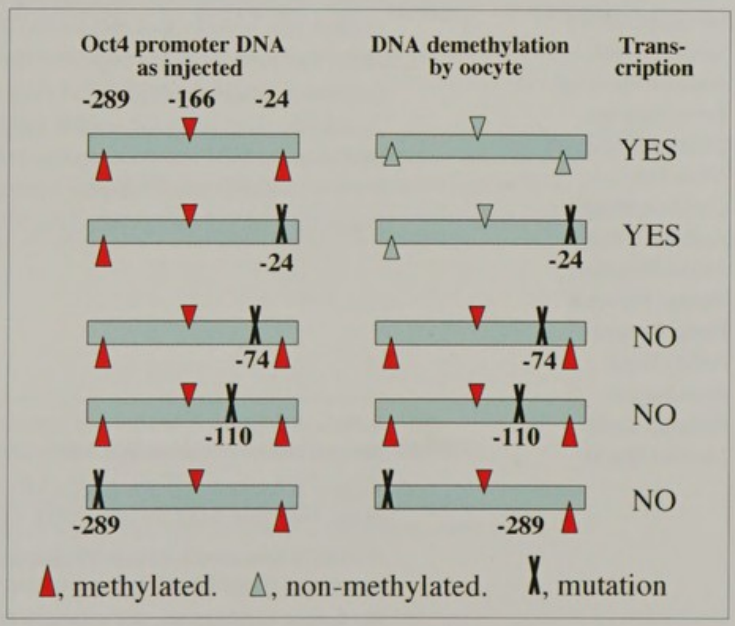
For further publications, see number 58 on pp 53–58

Deproteinisation and DNA demethylation accelerate nuclear reprogramming





Bisulphite analysis of oct4 promoter DNA demethylation



Mutational analysis of promoter demethylation

STEVE JACKSON

Co-workers:

Peter Ahnesorg
Rimma Belotserkovskya
Richard Chahwan
Julia Coates
Robert Driscoll
Kate Dry
Jacob Falck
Sabrina Giavara
Serge Gravel
Andrew Hammet
Pablo Huertas
Seyed Ali Jazayeri
Alicia Lee
Christine Magill
Andreas Meier
Abdel Moumen
Venkat Pisupati
Philip Reaper
Helen Reed
Alex Sartori
Philippa Smith
Manuel Stucki

The DNA within our cells is under constant attack by exogenously- and endogenously-arising DNA-damaging agents. The DNA-damage response (DDR) has evolved to optimise cell survival following DNA damage; it involves the recruitment of DNA repair proteins to sites of damage and the "checkpoint" events that slow down or arrest cell-cycle progression. Importantly, DDR proteins play key roles in preventing cancer, and their activities, in part, determine the outcome of cancer radiotherapy and chemotherapy.

Our work aims to decipher how – at the molecular level – cells detect DNA-damage then trigger the myriad events of the DDR. We also study how DDR proteins control other processes such as telomeric integrity. The DDR has been highly conserved throughout eukaryotic evolution, so we are analysing it both in mammalian cells and in the yeast *Saccharomyces cerevisiae*.

Over the past year, we have continued to make progress towards a better understanding of how chromatin structure influences chromosomal stability. For example, we have found that Sin3p and Rpd3p – two subunits of one of the main histone deacetylase complexes in yeast – are required for efficient repair by the pathway of DNA non-homologous end-joining (Figure 1). In addition, we have found that proteins of the High Mobility Group Box (HMGB) family promote genome stability both in yeast and mammalian cells (Figure 2). We have also provided insights into the functions of the human DDR protein, MDC, by showing that it facilitates the recruitment of the Mre11-Rad50-Nbs1 complex to sites of DNA-damage via its interactions with phosphorylated histone H2AX (Figure 3).

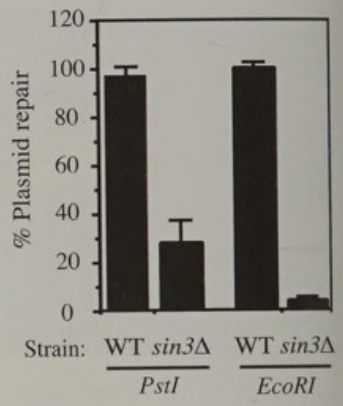


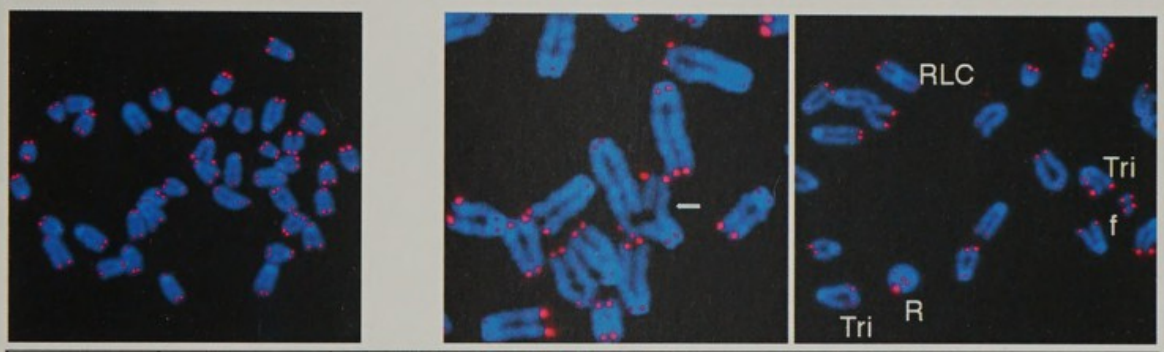
Figure 1: Deletion of SIN3 in S. cerevisiae causes a plasmid repair defect in a plasmid linearised with PstI (3' overhang) or EcoRI (5' overhang), indicating an involvement of Sin3 in DNA non-homologous end-joining.

d'Adda di Fagagna F, Teo SH and Jackson SP (2004) Functional links between telomeres and proteins of the DNA-damage response. **Genes Dev.** 18(15), 1781-99 (Review)

Jazayeri A, McAinsh AD and Jackson SP (2004) *Saccharomyces cerevisiae* Sin3p facilitates DNA double-strand break repair. **Proc Natl Acad Sci USA** 101(6), 1644-9

Giavara S, Kosmidou E, Hande MP, Bianchi ME, Morgan A, d'Adda di Fagagna F and Jackson SP. Yeast Nhp6A/B and mammalian Hmgb1 facilitate the maintenance of genome stability. **Current Biology** [In press]

For further publications, see numbers 17, 28, 31, 35, 37, 51, 60, 61 and 65 on pp 53–58



Sample	Metaphases analysed	Aneuploid cells	Total end-to-end fusions [a]	Fragments [b]	Breaks [c]	Tri-radial-like structures
Wild-type	25	0	0	0	0	0
Hmgb1 $^{-/-}$	25	15 (60%)	5 (20%)	3 (12%)	3 (12%)	4 (12%)

Figure 2: An increased level of chromosomal abnormalities and increased rates of aneuploidy are observed in mouse embryo fibroblasts (MEFs) derived from Hgmb1-/- knockout mouse embryos compared to wild-type MEFs, supporting a role for Hgmb1 in maintaining genome stability (photograph kindly provided by M. Prakash Hande).

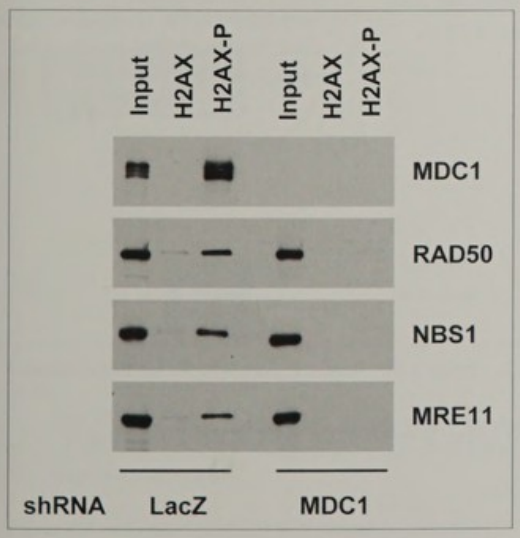


Figure 3: Nuclear extracts from HeLa cells stably expressing Mdc1-targeting (M) or a LacZ (Z) control shRNA were incubated with phosphorylated (H2AX-P) or nonphosphorylated (H2AX) peptides. Binding of Mre11, Rad50 and Nbs1 (together comprising the MRN complex) to phosphorylated H2AX requires MDC1.

TONY KOUZARIDES

Co-workers:

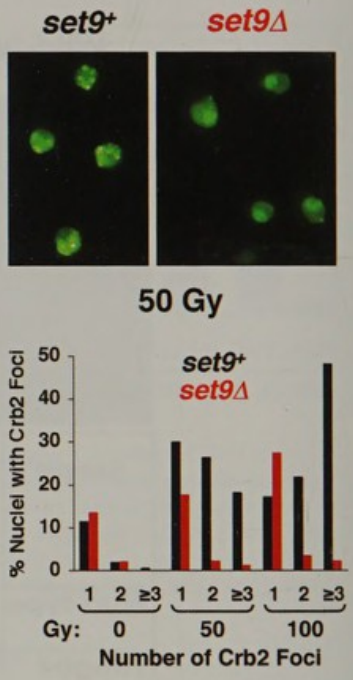
Andrew Bannister
Christine Blackwell
Alistair Cook
Graeme Cuthbert
Sophie Deltour
Karen Halls
Paul Hurd
Antonis Kirmizis
David Lando
Susana Lopes
Claudia Lopes
Chris Nelson
Claire Pike
Steven Sanders
Helena Santos Rosa
Bollivar Villacis

Many transcriptional regulators are de-regulated in cancer. Our group is interested in defining the mechanisms by which such transcription factors function during normal cell proliferation and in cancer.

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 mechanism by which histone modification affects chromatin function. In addition, a number of chromatin-modifying enzymes have been implicated in the genesis of cancer so we are interested in the pathways misregulated in cancer cells.

We have recently characterised a novel modification, namely histone deimination. We find that a specific enzyme PADI4, is able to deiminate histones by converting arginines or methyl-arginines to citrulline. The conversion to citrulline provides a mechanism to antagonise methylation of arginines and results in transcriptional repression.

We have also uncovered a lysine methylation site on histone H4 whose role is to regulate a DNA damage checkpoint. Analysis of H4 K20 methylation in the yeast, *S.pombe* demonstrates that this modification does not have any apparent role in gene expression but is necessary to deliver the checkpoint protein Crb2 to sites of DNA repair.



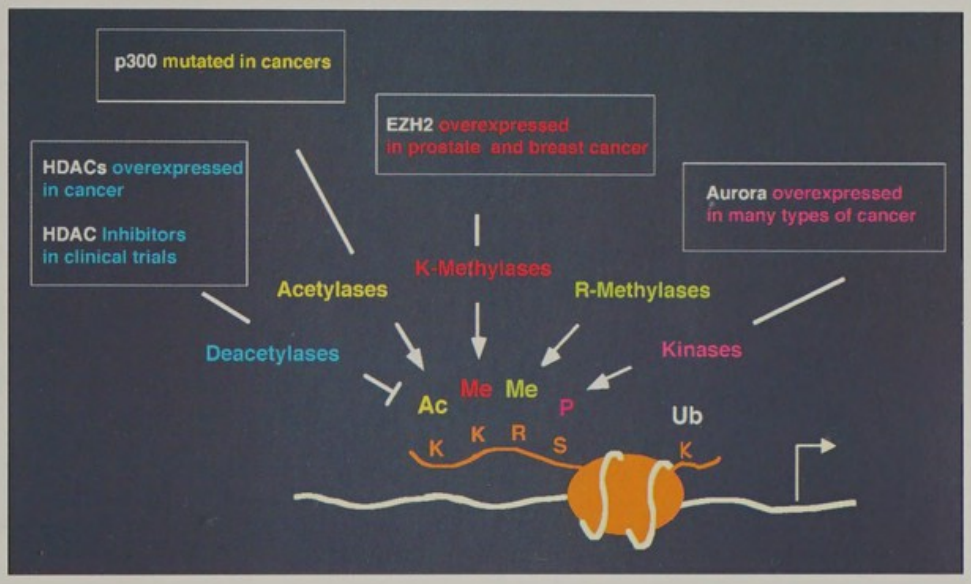
Methylation of H4 K20 by the Set9 enzyme is necessary for the correct recruitment of the checkpoint protein Crb2 to sites of DNA repair in the yeast S.pombe

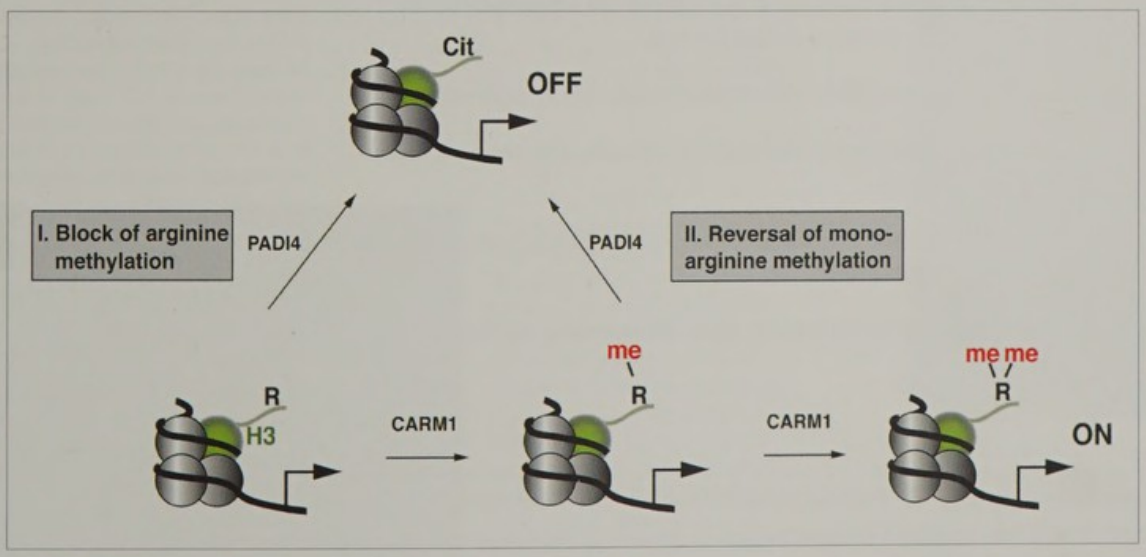
Cuthbert, GL, Daujat S, Snowden AW, Erdjument-Bromage H, Hagiwara T, Yamada M, Schneider R, Gregory PD, Tempst P, Bannister AJ and Kouzarides T (2004) Histone deimination antagonises arginine methylation. **Cell** 118, 545-553

Sanders SL, Portoso M, Mata J, Bahler J, Allshire R C. and Kouzarides T (2004) A role for histone H4 lysine 20 methylation in DNA damage response. **Cell** 119, 603-614

For further publications, see numbers 2, 3, 54 and 55 on pp 53–58

Chromatin modifying enzymes and their pathways are implicated in cancer.





The PADI4 histone deiminase converts arginines or mono-methyl arginines to citrulline and thus antagonises the positive transcriptional signal of arginine methylases.

RICK LIVESEY

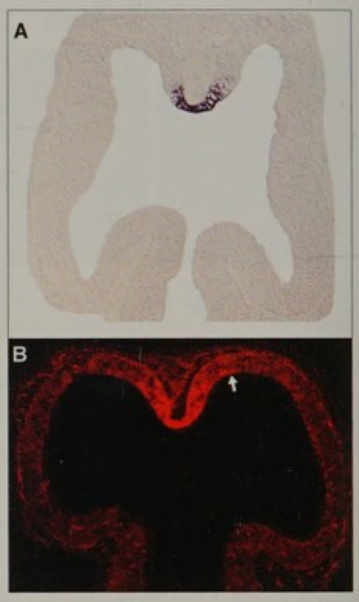
Co-workers:

Juliet Barrows
Dean Griffiths
Grace Nisbet
Sabhi Rahman
Stephen Sansom
James Smith
Tatiana Soubkhankoulova
Uruporn Thammongkol
Xiao-Yin Zhang

We wish to understand the molecular mechanisms that control how the correct types of neurons are generated in the appropriate places and times from progenitor cells in the developing mouse neocortex. The neocortex, the part of the brain that integrates sensations, executes decisions and is responsible for cognition and perception, is a region of the nervous system that is unique to mammals. The six layers of neurons that form the neocortex are generated from mitotic neural progenitor cells in a temporal sequence in which the inner layer neurons are generated before those destined for the outer layers. Neocortical progenitor cells are intrinsically different at different developmental stages in their ability or competence to generate neurons for each layer. There are also strict controls over which types of neurons can be produced in different parts of the neocortex.

Current areas of active research include:

- Using genomics and genetics to identify and study the functions of genes involved in the formation of neocortical areas;
- The transcriptional programs regulated by the extracellular signals that pattern neocortical progenitor cells;
- Transcriptional control of the temporal order of neurogenesis;
- The role of epigenetic mechanisms in controlling the temporal order of neurogenesis;
- Identifying the *in vivo* targets of transcription factors controlling cortical development;
- Classifying cortical neurons by single cell expression profiling



Expression of the secreted protein FGF8 in the commissural plate between the front of the two cerebral hemispheres (A). FGF8 acts several cell diameters away from its production, as shown by detection of activated downstream intracellular signalling pathways some distance away from the FGF8-expressing cells (B).

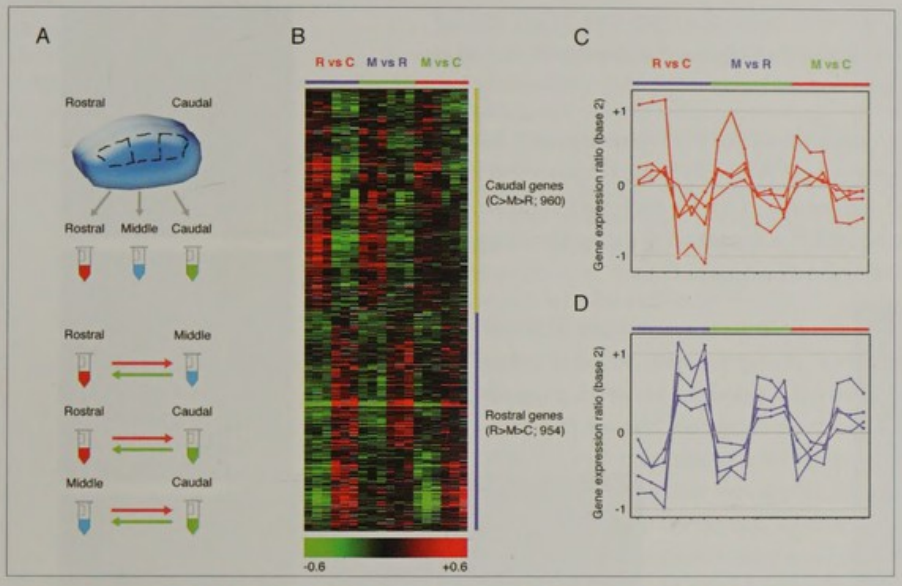
Kawasaki H, Crowley JC, Livesey FJ and Katz LC (2004) Molecular organization of the ferret visual thalamus. **J. Neurosci.** 24, 9962-9970

Livesey FJ, Young TL and Cepko CL (2004) An analysis of the gene expression program of mammalian neural progenitor cells. **PNAS**, 101, 1374-1379

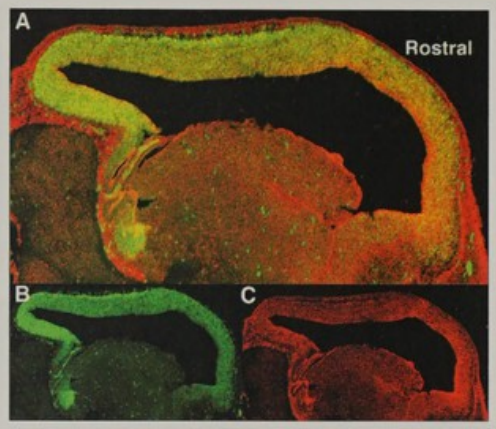
Livesey FJ (2003) Strategies for microarray analysis of limiting amounts of RNA. **Briefings in Functional Genomics and Proteomics** 12, 1-5

Dyer MA, Livesey FJ, Cepko CL and Oliver G (2003) Prox1 function controls progenitor cell proliferation and horizontal cell genesis in the mammalian retina. **Nature Genetics** 34, 53-58

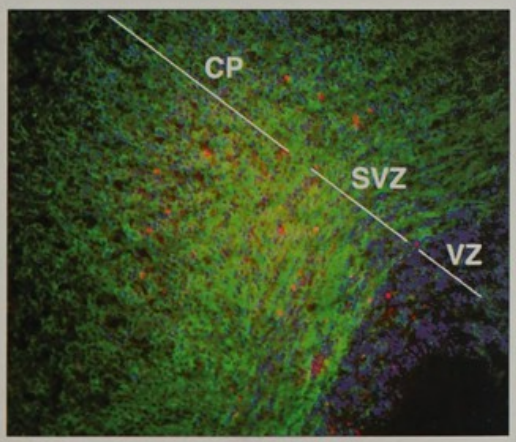
For further publications, see number 52 on pp 53–58



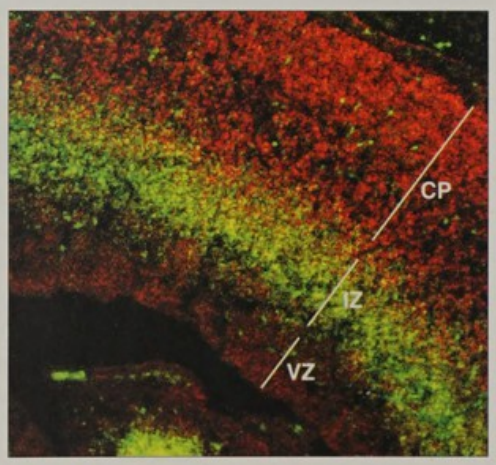
A genomics screen for genes showing spatial expression in neocortical progenitor cells. Embryonic cortex was divided into front, middle and back thirds (A) and cDNA prepared from each set of tissues compared in a set of 18 microarray hybridisations (B). Clusters of genes showing graded expression from front to back and vice versa were identified (C & D).



Front-to-back (red; B) and back-to-front (green; C)) gradients of expression across the developing neocortex, as shown by two-colour fluorescent in situ hybridisation (A).



A transcription factor (red) expressed in a subset of newly-born and differentiating neurons (green; Tuj1) in the developing neocortex. Newly-born neurons in the ventricular zone (VZ) express neuronal tubulin protein (Tuj1) that is also expressed by differentiating neurons in the subventicular zone (SVZ) and cortical plate (CP). A subset of Tuj1-positive newly-born and differentiating neurons express this transcription factor (red).



Parts of a hierarchy of transcription factors expressed in differentiating neocortical neurons. Two-colour fluorescent *in situ* hybridisation for two transcription factors expressed in differentiating neurons in the embryonic neocortex. One (green) is expressed in newly born neurons in the intermediate zone (IZ), whereas the other (red) is expressed in neurons later in their differentiation program with the cortical plate (CP). Neither is expressed by progenitor cells within the ventricular zone (VZ).

ANNE MCLAREN

Co-workers:

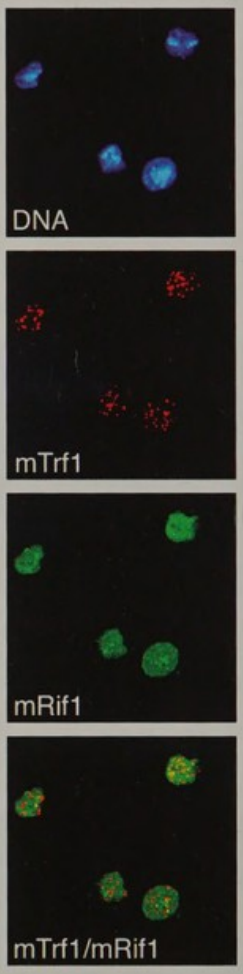
Dilly Bradford
Gabriela Durcova-Hills

Our research focuses on mouse primordial germ cells (PGCs) and the epigenetic changes undergone both by the PGCs themselves, and by the pluripotent stem cells derived from them.

The novel gene mRif1, derived from our PGC genetic screen, has a different expression pattern from other pluripotency genes that are expressed in the germ cell lineage. Oct-4 is expressed in the inner cell mass but mRif1 is not; mRif1 is expressed in the epiblast from 5.5 to 7.5 days post coitum, unlike Nanog and Stella.

The transition of PGCs to pluripotent embryonic germ (EG) cells requires the presence of FGFs during the initial period of culture. Addition of FGFs later does not support the transition, suggesting that FGF receptors may be down-regulated. We are therefore investigating the expression of FGF receptors and their isoforms. EG cell lines can be induced to differentiate into ectodermal, mesodermal and endodermal tissues: cartilage and bone are of particular interest to us, since skeletal defects have been detected in chimeras made with EG cells that have undergone erasure of genomic imprints.

We have shown that the differential erasure of site-specific methylation of imprinted genes in female EG cells is associated with the EG cell's own sex chromosome constitution, rather than the gender of the embryo from which the original PGCs were derived. Sex-reversed XX males resembled XX females in being hypomethylated; XY females, like XY males, were hypermethylated. We have extended this study to look at the imprinting of the paternally expressed gene Peg3 during oogenesis. We found that expression of Peg3 occurred not only in XX but also in XY females, so in this situation it was the gonadal environment rather than the germ cell's sex chromosome constitution that was the deciding factor.



Durcova-Hills G, Burgoyne P and McLaren A (2003) Analysis of a sex difference in EGC (embryonic germ cell) imprinting. **Dev Biol** 268, 105-110

Durcova-Hills G and McLaren A (2004) Isolation and maintenance of murine embryonic germ cell lines. **Handbook of Stem Cells,** ed Lanza et al, Vol.1, 451-457 Elsevier

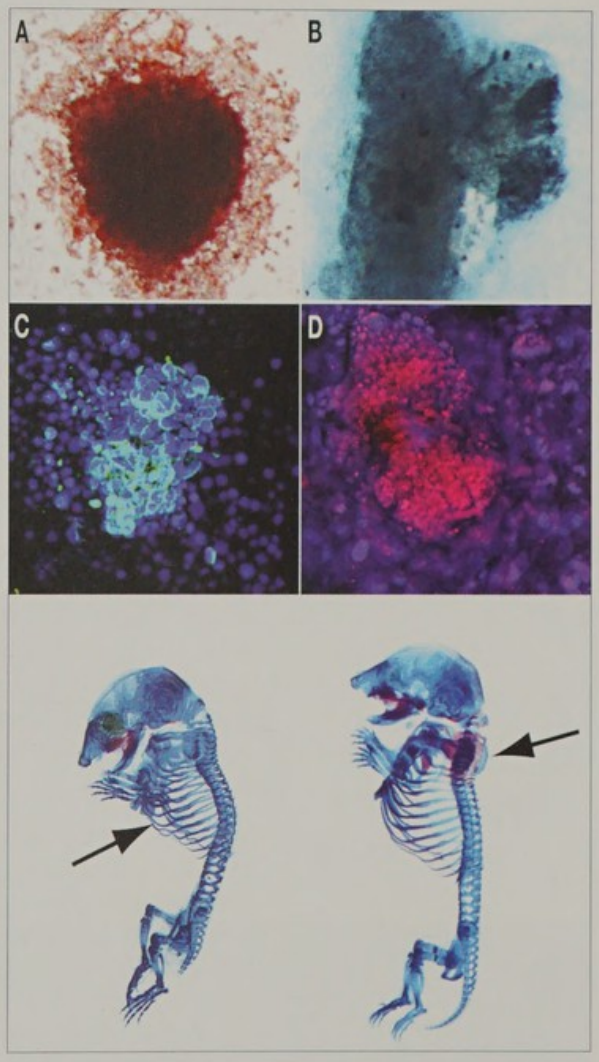
McLaren A (2004) Primordial germ cells in mouse and human. **Handbook of Stem Cells**, ed Lanza et al, Vol.1,187-192 Elsevier

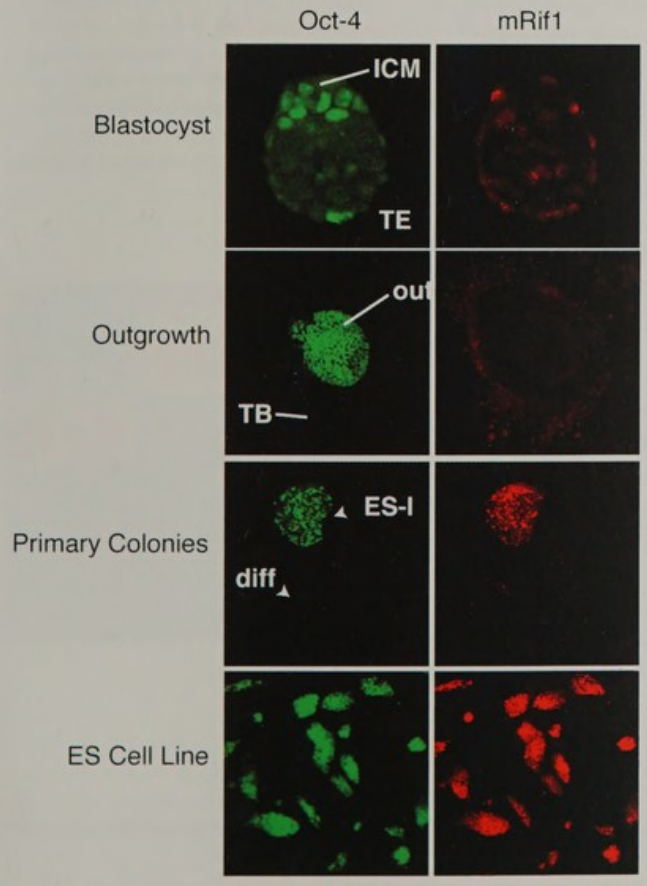
McLaren A (2003) Human Cloning. **Nature Encyclopedia of the human genome** 298-300. Macmillan Publishers Ltd

For further publications, see numbers 42 and 43 on pp 53–58

Facing page: In mouse ES cells, mRif1 (green) colocalises with the mouse telomeric protein mTrf1 (red) that binds to telomeric DNA repeats.

EG cells were induced to differentiate into bone nodules. Histochemical staining for Alizarin Red identifies mineralised nodules (A). Immunofluorescence staining of bone nodule demonstrates the localisation of osteocalcin (C) and collagen (D). EG cells were also induced to differentiate into cartilage. Histochemical staining for Alcian blue identifies cartilage (B). Mouse chimeras made with EG cells show some skeletal defects in ribs and spine. Skeletal preparations stained with Methylene Blue for cartilage, Alizarin Red for bone.





mRif1 and Oct-4 expression shown by immunofluorescence during ES cell derivation. mRif1 is expressed in ES cell lines and primary colonies (ES1) but not in differentiated cells (diff); at the blastocyst stage it is expressed in trophectoderm (TE) and trophoblast outgrowths (TB) but not in the inner cell mass (ICM) and its outgrowth (out), unlike Oct-4.

ERIC MISKA

Co-workers:

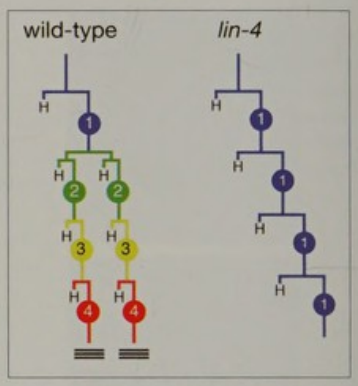
Eric's new lab will open in Jan 2005, and recruitment of co-workers is currently in progress.

The recent discovery of microRNAs has added a completely new dimension to the control of eukaryotic gene expression. MicroRNAs are a large class of 18-26 nucleotide short regulatory RNAs. Approximately 1% of all known human genes encode microRNAs, but very little is known about their biological roles. Our laboratory is interested in understanding how microRNAs contribute to the determination of cell fate, ie the decision to divide, die or differentiate, and how deregulation of microRNAs may contribute to disease, in particular to cancer.

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

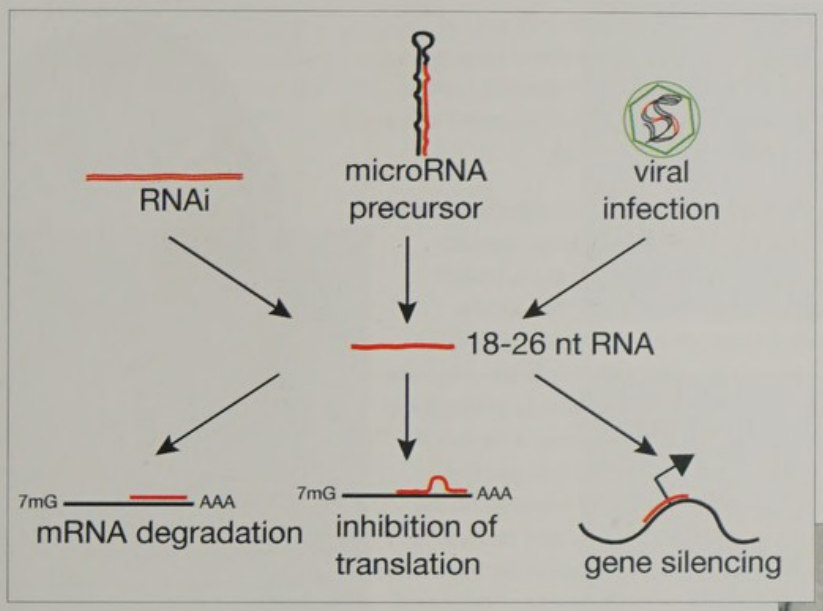
We are also interested in the mechanism of microRNA action. Currently we are focussing on the Argonaute family of RNA-binding proteins, which have been implicated in both the mechanism of RNAi and microRNA pathways. Of particular interest to us are the orthologues of two *Drosophila Argonaute* family members, Aubergine and Piwi that define germ line identity in the fly. We use a combination of biochemical and genetic approaches to understand their function.

In invertebrates microRNAs have been implicated as regulators of developmental timing (e.g. *lin-4*), neuronal differentiation, cell proliferation, programmed cell death and fat metabolism. In contrast, no in vivo function for any microRNA has been established in mammals. To help uncover the biological roles of microRNAs in mammals we first ask the question where and when microRNAs are expressed using microarray profiling. One focus is the analysis of microRNA expression in primary human tumours. This work is being carried out as a collaboration with the Cancer Genomics Group at the Broad Institute of MIT, and Harvard.

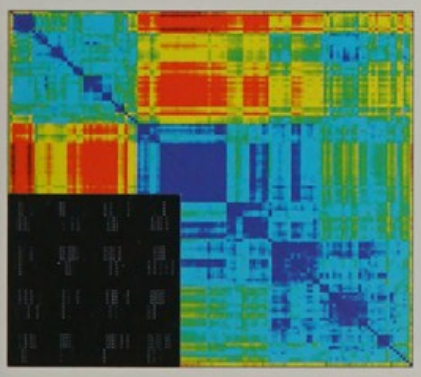


The first microRNA to be identified was the product of the *C. elegans* gene *lin-4*. Loss of function of *lin-4* leads to an over-proliferation defect of the seam cells, which are part of the outer epithelial covering of the worm. The cell divisions of the first larval stage (l) are reiterated in these mutants: l, l, l, l, ...

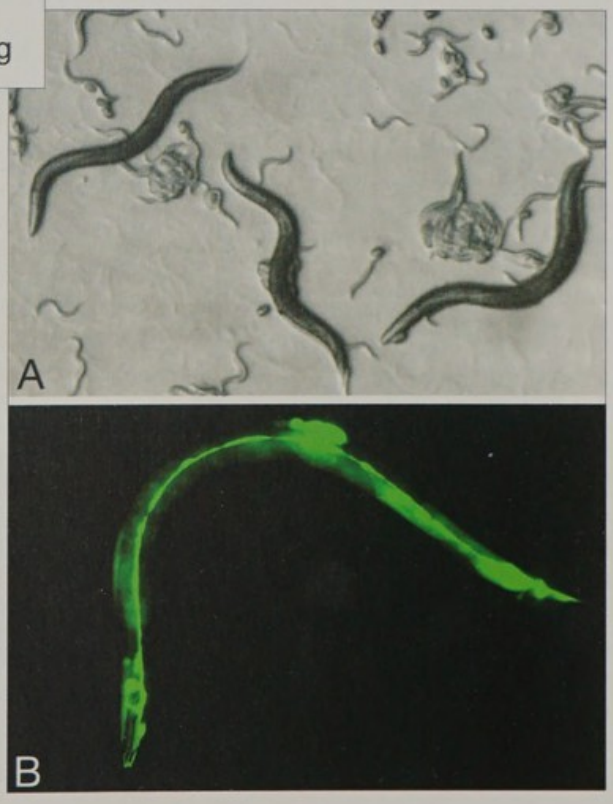
Miska EA, Alvarez-Saavedra A, Townsend M, Yoshii A, Sestan N, Rakic P, Constantine-Paton M, Horvitz HR (2004) Microarray analysis of microRNA expression in the developing mammalian brain. **Genome Biol.** 5, R68



Short RNAs as key players of gene regulation: Primary microRNA gene transcripts contain stem-loop structures that are processed by RNAse type III enzymes such as Dicer to give rise to the mature microRNA. Dicer is also required for the processing of double-stranded viral RNA and for generating siRNAs in RNAi. microRNAs can act through the inhibition of translation, mRNA degradation and possibly transcriptional gene silencing.



We have developed microRNA microarrays to profile microRNA expression in *C. elegans* and mammals (insert). We compare the expression of microRNAs in different tissues, at different stages during development and under a variety of physiological conditions to understand where microRNAs act and how their expression is regulated. Shown here is a correlation heat map.



A. We are using a functional genomics approach in *Caenorhabditis elegans* to study microRNA function. B. The microRNA *mir-84* is expressed in a number of cell types including the seam cells, as assayed by a GFP reporter in the living animal.

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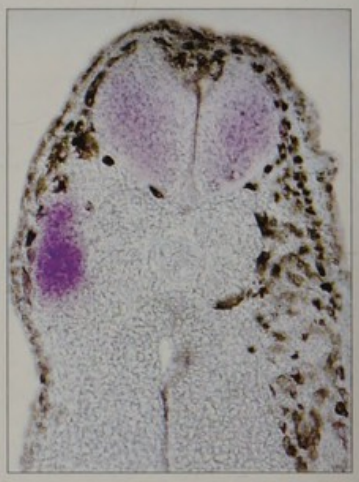
During embryonic development neuroectodermal cells exit the cell cycle and differentiate in a stereotypical spatial and temporal pattern. To understand how neurogenesis is controlled we use the frogs *Xenopus laevis* and *Xenopus tropicalis* as model systems and a combination of molecular and classical embryology.

We are studying the function and regulation of localised transcription factors, such as FoxG1, a master gene controlling neurogenesis and cell division in the forebrain. We are looking at the protein modifications that influence the activity of FoxG1 and we are using microarrays to identify target genes. We have found, that n addition to the localised expression of transcription factors, neuronal differentiation is controlled by the intrinsic competence of the cells to differentiate. An intrinsic difference in competence is the result of asymmetric cell divisions of polarised cells that take place at the blastula stage. In these polarised cells, aPKC is located on the apical membrane and Lgl-2 on the basal side. By gain and loss of function experiments we have shown that an antagonistic interaction between aPKC and Lgl-2 defines apical/basal polarity of these cells in early vertebrate development. We are now investigating whether membrane asymmetries influence the transcriptional program of these polarised cells. To this end, we have identified several inner and outer cell-specific genes whose function is being determined.

In parallel we are developing genomic resources for Xenopus and we have produced the first *X. tropicalis* oligo microarray. Gain and loss of function screens, based on a *X. tropicalis* EST project, have begun to uncover novel genes that affect neural development.



Increased number of neural crest derived pigmented cells (brown) at the expense of neuronal cells (purple) following unilateral spinal cord overexpression (left) of a clone identified in a functional screen. (Jana Voigt)

Voigt J, Chen JA, Gilchrist M, Amaya E and Papalopulu N. Expression cloning screening of a unique and full-length set of cDNA clones is an efficient method to identify gene function in *Xenopus* neurogenesis. ***Xenopus* Genetics and Genomics special issue-Mechanisms of Development** [in press]

Gilchrist M, Zorn AM, Voigt J, Smith JC, Papalopulu N and Amaya E (2004) Defining a large set of full length clones from a *Xenopus tropicalis* EST project. **Dev Biol** 271, 498-516

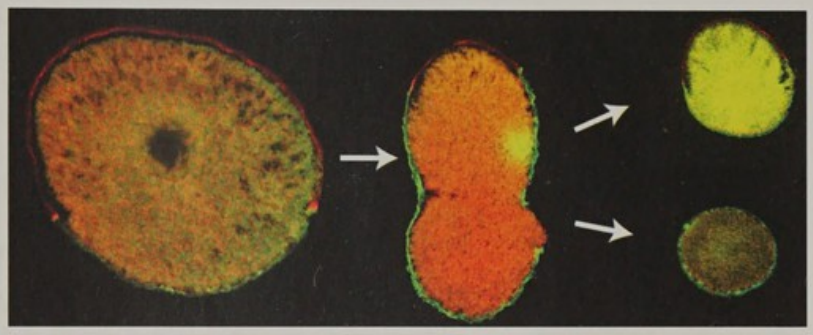
Kenwrick S, Amaya E and Papalopulu N (2003) A pilot morpholino screen in *Xenopus tropicalis* identifies a novel gene involved in head development. **Dev Dyn** 229, 289-299

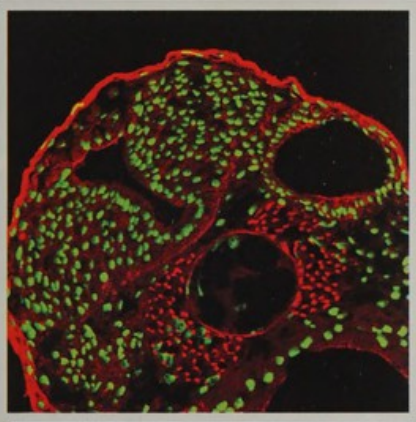
Chalmers AD, Strauss B and Papalopulu N (2003) Oriented cell divisions asymmetrically segregate aPKC and generate cell fate diversity in the early *Xenopus* embryo. **Development** 130, 2657-68

Chalmers A, Welchman D and Papalopulu N (2002). Intrinsic differences between the superficial and deep layers of the *Xenopus* ectoderm control primary neuronal differentiation. **Dev Cell** 2, 171-182

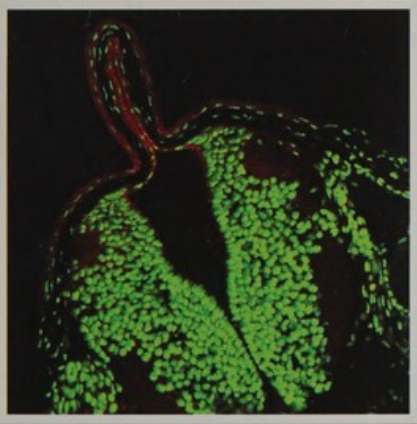
For further publications, see numbers 8, 9 and 10 on pp 53–58

A polarised, isolated, frog blastomere divides to generate a similarly polarised and and a non-polarised cell. red: aPKC, green: β-integrin. (Andrew Chalmers)





st. 35



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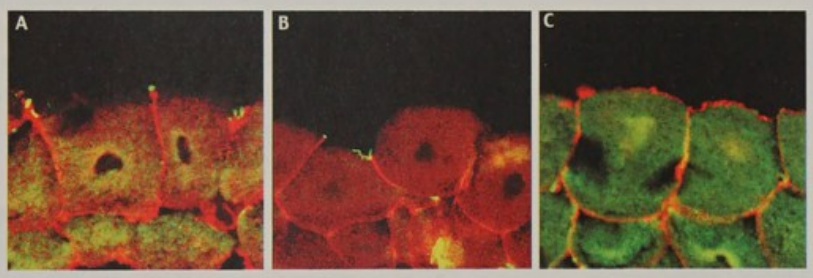
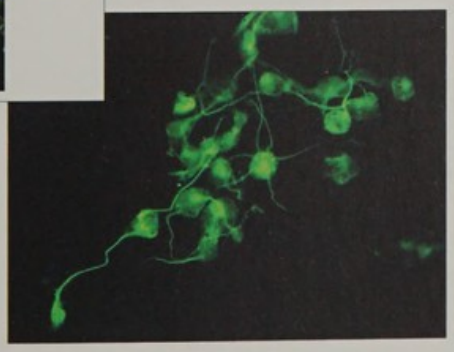
Section through the neural tube of a frog embryo showing the increase in cell numbers in 2 days of development. Cell nuclei are shown in green. (Eva Asscher)



A normal cell showing apical-basal polarity (A), a super-apical (B) and a super-basal cell (C), produced by overexpression of aPKC and Lgl-2 respectively. Red: β-integrin, green: cingulin. (Andrew Chalmers)



Isolated frog ectodermal cells form neurons in culture driven by the expression of a proneural gene. (Niki Panagiotaki)

Confocal image of an anaphase spindle visualised with α-tubulin antibody. (Bernhard Strauss)

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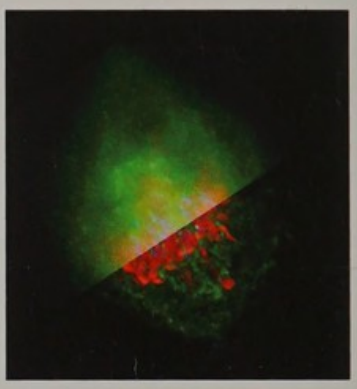
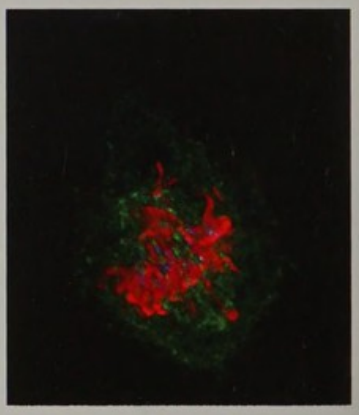
We are studying how cells divide, focusing on two main aspects: how the cell initiates mitosis, and how the cell co-ordinates mitosis by ubiquitin-mediated proteolysis. Because mitosis is a highly dynamic process we are studying these processes in real time by time-lapse fluorescence microscopy. We use FRAP and photo-activation to gain a better understanding of the kinetics of protein behaviour, deconvolution to improve the spatial resolution and FRET to assay protein-protein interaction and kinase activity *in vivo*.

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. Using GFP-fusion proteins to determine how their localisation changes through mitosis we are able to define the domains of the proteins that target them to specific subcellular structures. To identify the proteins responsible for targeting we are analysing protein complexes at different points in mitosis by mass spectrometry.

To understand how proteolysis is used to regulate progress through mitosis we assay the degradation of the GFP-fusion proteins in living cells. We are studying key APC/C substrates at each stage of mitosis to define the events and the mechanisms that trigger the destruction of specific proteins at specific times, and how this coordinates chromosome segregation and cytokinesis. We are focusing on whether the ubiquitination machinery is spatially regulated in mitosis; in particular whether this accounts for the exquisite control of protein degradation by the spindle assembly checkpoint.





Top: Montage of 'normal' and deconvolved image. HeLa cells stained for the APC/C (green), centromeres (blue) and DNA (red). Bottom: Fully deconvolved image.

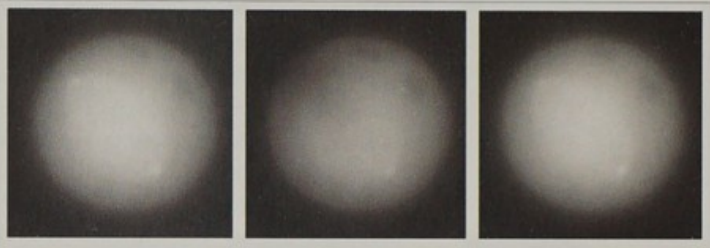
Acquaviva C, Herzog F, Kraft C and Pines J (2004) The Anaphase Promoting Complex/Cyclosome is recruited to centromeres by the spindle assembly checkpoint. **Nature Cell Biology** 6, 892-898

Matsusaka T, and Pines J (2004) Chfr acts with the p38 stress kinase to block entry to mitosis in mammalian cells. **J Cell Biol** 166, 507-516

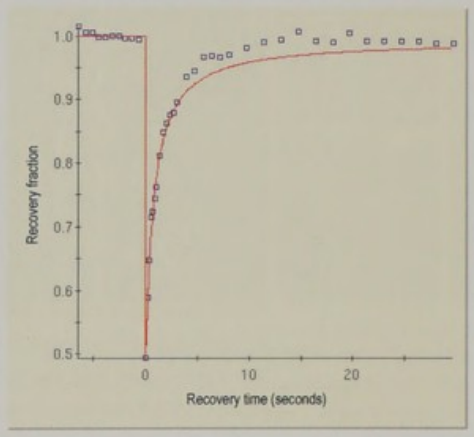
Lindon C and Pines J (2004) Ordered proteolysis in anaphase inactivates Plk1 to contribute to proper mitotic exit in human cells. **J Cell Biol** 164, 233-241

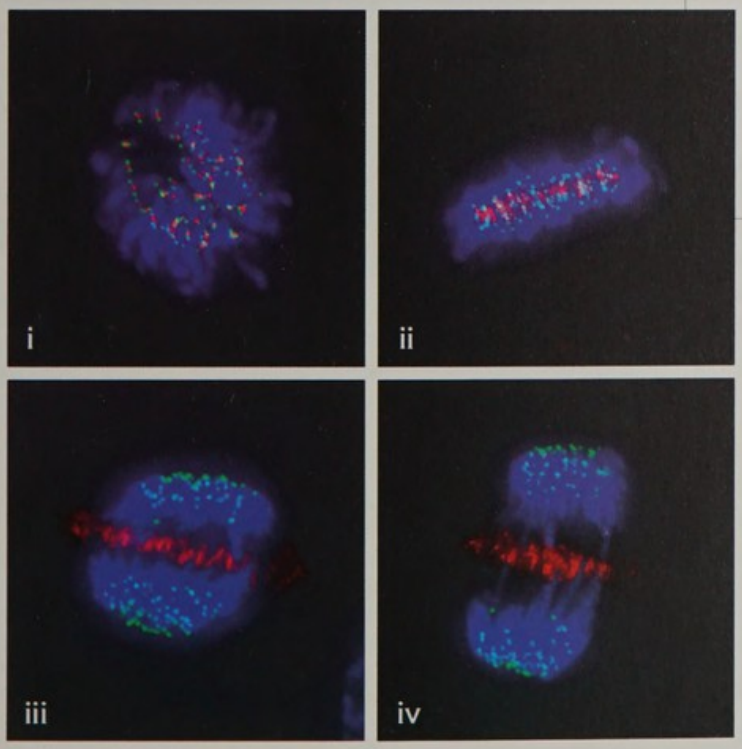
Jackman M, Lindon C, Nigg EA and Pines J (2003) Active cyclin B1-Cdk1 first appears on centrosomes in prophase **Nature Cell Biol** 5, 143-148

HeLa cells expressing cyclin B1 linked to GFP. One spindle pole was irradiated with 488 nm laser light (middle panel) and the cell imaged using a GFP filter set. Cyclin B1 fluorescence recovers at the spindle pole within 6 secs (right panel).



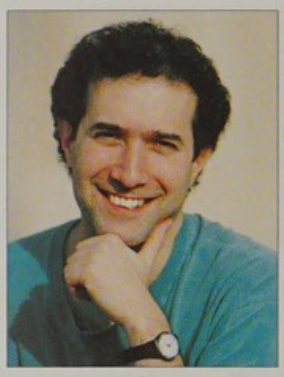
Recovery of Cyclin B1-GFP on Spindle Poles





HeLa cells stained for centromeres (green), DNA (blue) and Aurora B (red) in i) pro-metaphase ii) metaphase iii) anaphase A and iv) anaphase B. Aurora B appears to be important in both the spindle checkpoint and in setting up cytokinesis.

JORDAN RAFF



Co-workers:

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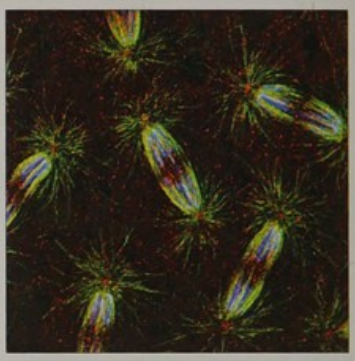
Renata Basto
Sue Croysdale
Carly Dix
Fanni Gergley
Joyce Lau
Eliana Lucas
Nina Peel

The centrosome is the main microtubule organising centre in animal cells. Using *Drosophila* as a model system, we are studying several centrosomal proteins in order to understand how centrosomes function at the molecular level. The *Drosophila* transforming acidic coiled-coil (D-TACC) protein is essential for stabilising centrosomal microtubules in embryos, and it functions by recruiting the microtubule stabilising protein Minispindles (Msps) to centrosomes. We have isolated mutations in D-TACC that affect its ability to interact with Msps and to target to the centrosome. These studies suggest that D-TACC not only recruits Msps to centrosomes, but also activates its microtubule stabilising activity. In collaboration with the Hyman lab in Dresden, we have shown that this activation appears to depend on the phosphorylation of the TACC protein by Aurora A at the centrosome. There are three TACC proteins in humans, and these have all been implicated in cancer. We are currently trying to dissect the function of the different proteins by creating chicken DT40 cell lines that are "knocked-out" for each protein individually and in combination.

As we now have many centrosomal proteins isolated, we are trying to understand how these proteins are assembled at the centrosome. We have shown that the *Drosophila* Pericentrin-like protein (D-PLP) is required for the efficient recruitment of many, if not all, components of the pericentriolar material (PCM). A live analysis in D-PLP mutant embryos, however, suggests that D-PLP does not recruit proteins to the centrosome, but rather prevents their dispersal along the centrosomal microtubules. These observations have important structural implications for our understanding of how the PCM is assembled.



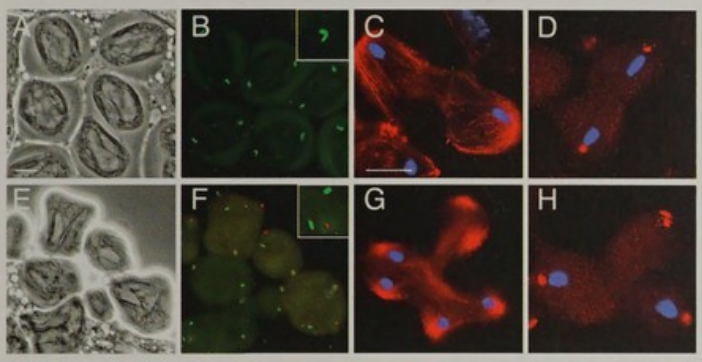
The D-TACC/Msps complex is concentrated at centrosomes, and also in punctate dots that decorate the spindle microtubules. The distribution of Msps (red), microtubules (green) and chromosomes (blue) is shown in embryos where the nuclei have entered anaphase.

Martinez-Campos M, Basto R, Baker J, Kernan M, and Raff JW (2004) The *Drosophila* pericentrin-like protein is essential for cilia/flagella function but appears to be dispensable for mitosis. **J Cell Biol** 165, 673-683

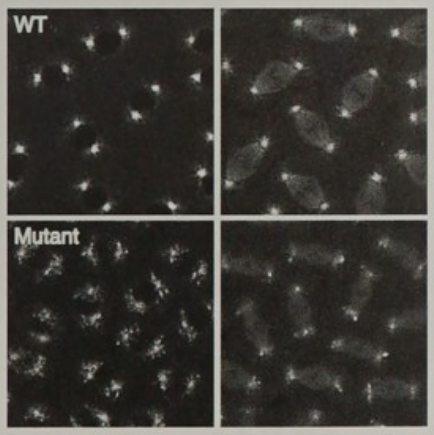
Butcher RDJ, Chodagam S, Basto R, Wakefield J, Henderson DS, Raff JW and Whitfield WGF (2004).The *Drosophila* centrosome-associated protein CP190 is essential for viability, but not for cell division **J Cell Sci** 117, 1191-1199

Raff JW (2003) Genome maintenance. **Nature** 423, 493-495

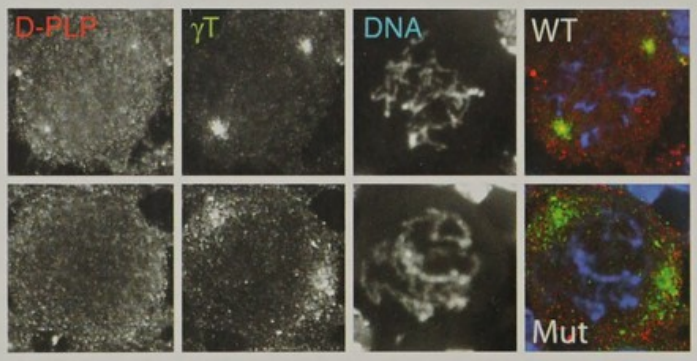
Gergely F, Mythily V, Lee M, and Raff JW (2003) The ch-Tog/XMAP215 protein is essential for spindle pole organisation in human somatic cells. **Genes and Dev** 17, 336-341



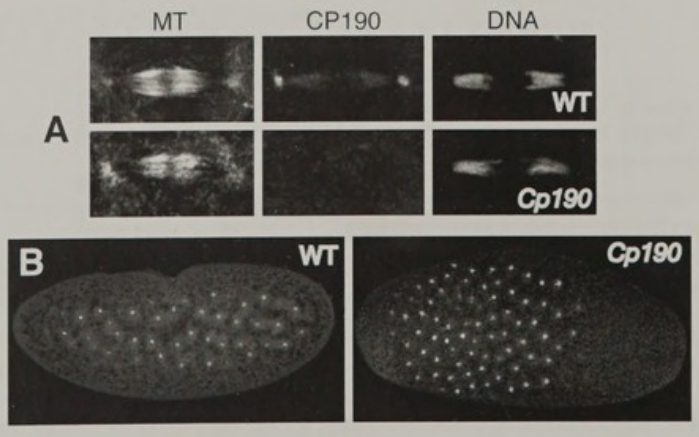
The *Drosophila* pericentin-like protein (D-PLP) is essential for maintaining the structural integrity of the centrioles during male meiosis. (A,E) shows a phase contrast image of meiotic spindles in WT (A) and D-PLP mutant (E) spermatocytes. In WT spermatocytes (top panels) a pair of very large centrioles (B) are found at the pole of each meiotic spindle, and a single centrosome is present at each spindle pole (C,D). In D-PLP mutants, the centrioles are fragmented (F), and the spindles are multipolar (G,H).



Above: In living D-PLP mutant embryos the PCM is abnormally dispersed along the centrosomal microtubules. In WT embryos, the PCM (here visualised with a GFP-D-TACC fusion protein) is tightly concentrated at the centrosomes in interphase (left panels) and in mitosis (right panels – a weak spindle staining is also apparent with this fusion protein). In D-PLP mutant embryos, the PCM is abnormally dispersed along the centrosomal microtubules in both interphase and mitosis, although the process of mitosis does not seem to be dramatically perturbed.



D-PLP is present in the centrioles, and is required to recruit proteins efficiently to the pericentriolar material (PCM). In WT larval brain cells, D-D-PLP (red in merged image) is concentrated in centrioles, and, as cell enter mitosis, g-tubulin (green in merged image) is recruited to the PCM. In D-PLP mutant brain cells, D-PLP is no longer detectable in the centrioles, and the recruitment of g-tubulin to centrosomes is inefficient.



Right: The centrosomal protein CP190 is dispensable for mitosis, but is essential for proper actin/myosin function in the early embryo. (A) In Cp190 mutant embryos, CP190 is no longer detectable at centrosomes, but mitosis appears to be unaffected. The mutant embryos, however, have a defect in "axial expansion", an actin/myosin dependent process that normally spreads the nuclei evenly along the anterior/posterior axis (B). Thus, CP190 appears to form an important link between the centrosome and the actin/myosin cytoskeleton.

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Nigel Messenger
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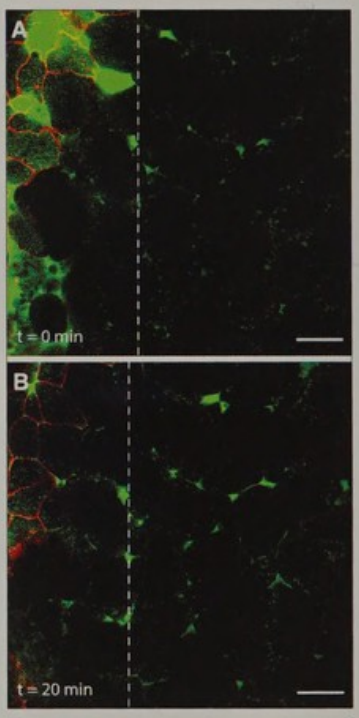
Amer Rana
Yasushi Saka
Fiona Wardle

Our research uses the amphibian species *Xenopus laevis* and *Xenopus tropicalis* to investigate mesoderm formation during vertebrate development. We are interested in mesoderm-inducing signals such as activin, the nodal-related proteins and derrière, in the range over which these factors can act, in their signal transduction pathways (especially the Smad proteins), and in the genes that are activated as immediate-early responses to induction. Transgenic *Xenopus* embryos are used to study how these immediate-early genes are regulated and to identify their targets. We are also analysing the regulation of the cell cycle in the mesoderm, and are making extensive use of over-expression screens and anti-sense morpholino oligonucleotides to investigate gene function.

Much of our work concentrates on the T box gene family, and especially Brachyury, which responds to mesoderm-inducing factors in a dose-dependent fashion and which, when mis-expressed, can cause prospective ectodermal cells to form mesoderm. One issue concerns the specificity of T box gene action, and to investigate this question we are characterising proteins that interact with Brachyury and the related protein VegT. Brachyury is also required for the morphogenetic movements of gastrulation, and we previously identified Wnt11 as a target of Brachyury that is required for normal gastrulation in both Xenopus and zebrafish. Wnt11 signals through the planar cell polarity pathway, and we are analysing how components of this pathway control gastrulation and other aspects of early development, using cell biology and imaging techniques. We are also investigating the functions of other Brachyury and VegT targets such as members of the Bix family of homeodomain-containing proteins.



Mercurio S, Latinkic B, Itasaki N, Krumlauf R and Smith JC (2004) Connective-tissue growth factor (CTGF) modulates cell signalling by Wnt family members. **Development** 131, 2137-2147

Piepenburg O, Grimmer D, Williams PH and Smith JC (2004) Activin redux: specification of mesodermal pattern in *Xenopus* by graded concentrations of endogenous activin B. **Development** 131, 4977-4986

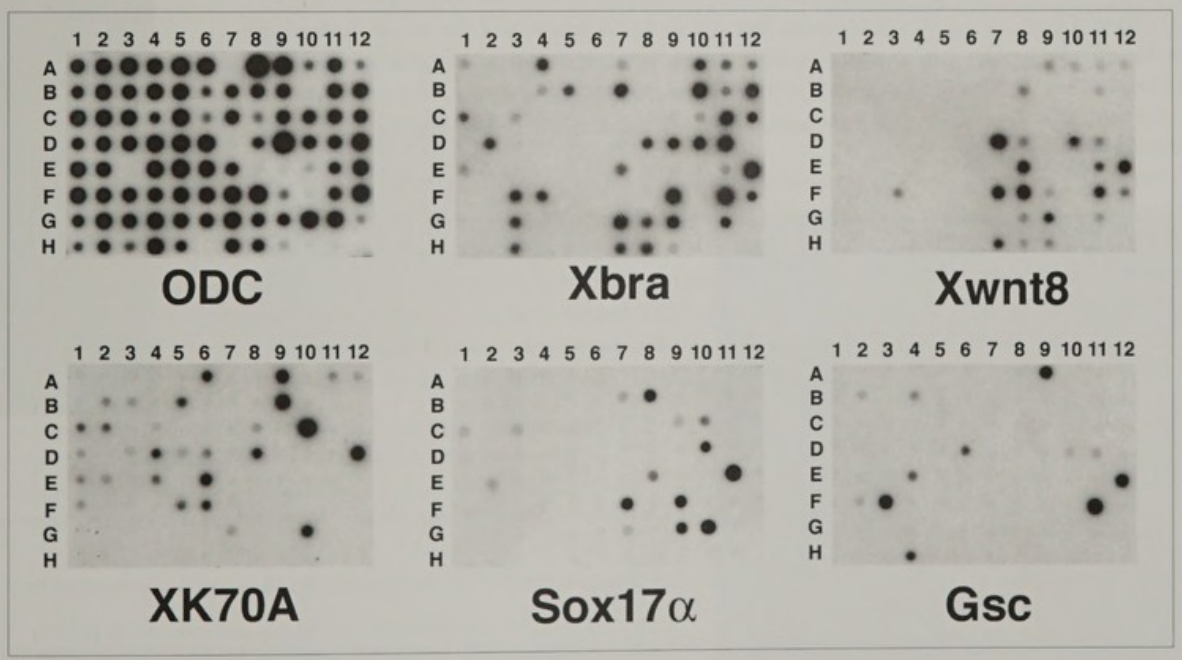
Williams PH, Hagemann A, González-Gaitán M and Smith JC (2004) Visualizing long-range movement of the morphogen Xnr2 in the *Xenopus* embryo. **Current Biology** 14, 1916-1923

Saka Y and Smith JC (2004) A *Xenopus* tribbles orthologue is required for the progression of mitosis and for development of the nervous system. **Dev Biol** 273, 210-225

For further publications, see numbers 8, 21, 27, 34, 50, 58, 59 and 69 on pp 53–58

Facing page: Xnr2 exerts long-range effects by diffusion. Two animal pole regions, one expressing EGFP-tagged Xnr2 (green) and a cell membrance marker (red) were juxtaposed at the late blastula stage. They were photographed shortly after the two tissues had healed (t=0 min) and then 20 minutes later (t=20 min). Tagged Xnr2 in the responding tissue, to the right of the dotted line, is almost exclusively extracellular, and has traversed 2-3 cell diameters over the course of the experiment.

The laboratory is carrying out an extensive screen to investiage gene function in *Xenopus tropicalis*. The left-hand panel shows normal *X. tropicalis* tadpoles; the right hand panel shows embryos in which the function of a previously-unstudied gene has been inhibited. The embryos are stunted and axial structures are disrupted.



Dot blots showing gene expression in individual cells of a *Xenopus* gastrula embryo. Each 'dot' corresponds to a single cell.

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Nick Lowe
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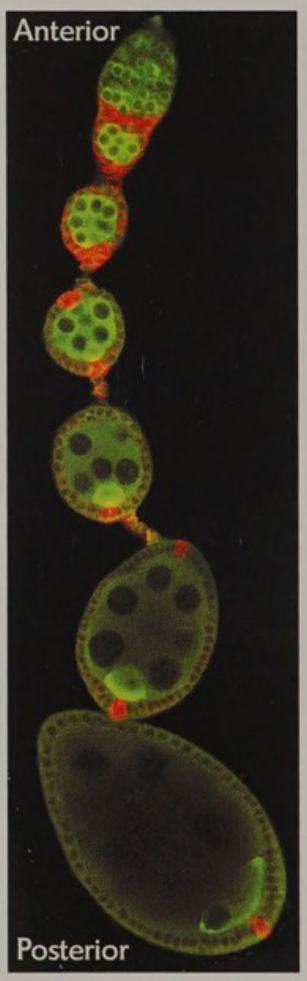
Isabel Torres
Vitaly Zimyanin

The localisation of *bicoid* and *oskar* mRNAs to the anterior and posterior poles of the *Drosophila* oocyte defines the AP axis of the embryo, and provides an excellent model for analysing the molecular mechanisms that underlie cell polarity and mRNA localisation. We are taking a combination of cell-biological, genetic and molecular approaches to investigate these mechanisms:

1) The dsRNA-binding protein, Staufen, is required for the microtubule-dependent localisation of *bicoid* and *oskar* mRNAs, and for the actin-dependent localisation of *prospero* mRNA in neuroblasts. We are investigating how Staufen mediates mRNA transport along both actin and microtubules, and are analysing other proteins required for these processes. Since Staufen co-localises with these mRNAs, we are also using GFP-Staufen to visualise mRNA transport *in vivo*.

2) We have shown that the homologues of three genes required for AP axis formation in *C. elegans* (PAR-1, LKB1 (PAR-4), and 14-3-3 (PAR-5)) are required for the polarisation of the oocyte. Furthermore, mutants in these genes disrupt epithelial polarity. We are now screening for other components of this conserved polarity pathway, and are analysing how it regulates the cytoskeleton.

3) Since many proteins involved in mRNA transport or cell polarity are required throughout development, they were not identified in the classical screens for mutations that disrupt axis formation. To overcome this problem, we are performing screens in germline clones for mutants that affect GFP-Staufen localisation. We have identified many novel genes required for the polarisation of the oocyte or for the localisation of *bicoid* or *oskar* mRNA, and are now analysing their functions.



Palacios I, Gatfield D, St Johnston D and Izaurralde I (2004) An eIF4AIII-containing complex required for mRNA localization and nonsense-mediated mRNA decay. **Nature** 427, 753-757

Huynh JR, Munro T, Smith Litière K and St Johnston D (2004) The *Drosophila* hnRNPA/B homologue, Hrp48, is specifically required for a distinct step in osk mRNA localisation. **Dev Cell** 6, 625-635

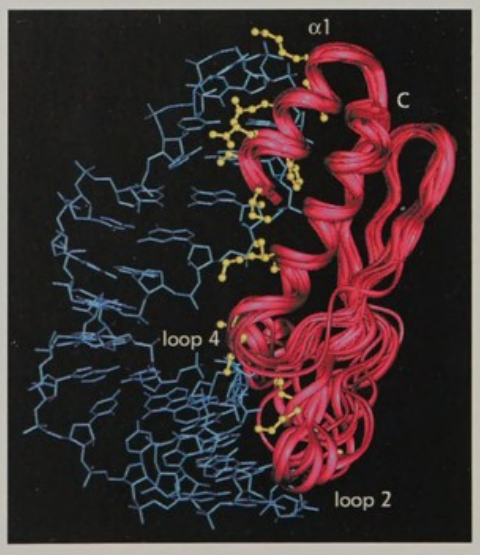
Benton R and St Johnston D (2003) *Drosophila* PAR-1 and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells. **Cell** 115, 691-704

For further publications, see numbers 4, 11, 18 and 38 on pp 53–58

Facing page:
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.

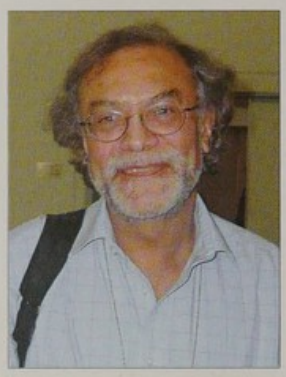
Mutants in LKB1 disrupt *oskar* mRNA localisation and the polarity of the microtubule cytoskeleton. The localisation of GFP-Staufen (green; left), *oskar* mRNA (centre) and microtubules (right) in wildtype oocytes (top), and in *lkb1* mutant germline clones (bottom).

The localisation of *bicoid* mRNA (black) and *oskar* mRNA (red) to the anterior and posterior poles of the stage 10 oocyte.



NMR structure of one double-stranded RNA binding domain from Staufen protein (red) bound to a 12bp RNA stem-loop (blue). The amino acid side chains that contact the RNA are shown in yellow. Collaboration with Andres Ramos and Gabrielle Varani (LMB-MRC).

AZIM SURANI



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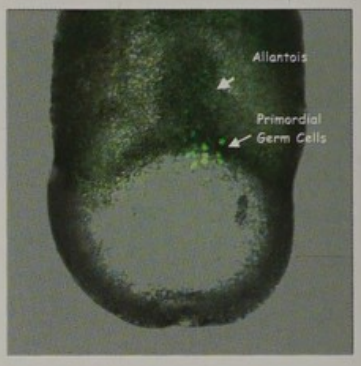
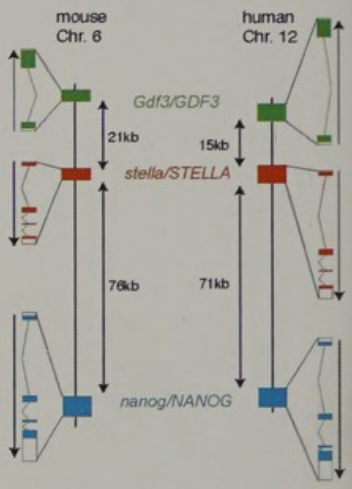
We are investigating the origin and properties of the mouse germ line. As transmitters of genetic and epigenetic information to subsequent generations, germ cells undergo extensive epigenetic reprogramming of the genome during the germ line cycle (Fig.1). Germ cells are also the source of the totipotent state, which is sustained, in part, by the maternal inheritance of factors associated with totipotency.

To elucidate the genetic basis of the mouse germ cell lineage, we are using molecular analysis of single germ cells and their nearest somatic neighbours. These studies are beginning to reveal the mechanism of PGC specification, which includes active repression of the somatic programme represented by region-specific Hox genes, as well as the up regulation of pluripotency associated genes (Fig 2).

As PGCs proliferate and migrate into developing gonads at E11.5, they undergo extensive epigenetic modifications, including genome-wide DNA demethylation and reactivation of the X chromosome. We are investigating the identity of the intrinsic factors involved in this reprogramming event, together with the nature of the external signals that trigger this event (Fig 3).

Our studies have broader implications concerning how cell fate decisions may be regulated by epigenetic mechanisms, for example, during differentiation of pluripotent stem cells. These studies will also elucidate the mechanisms that govern erasure of epigenetic information associated with genomic reprogramming and dedifferentiation of somatic cells.





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.

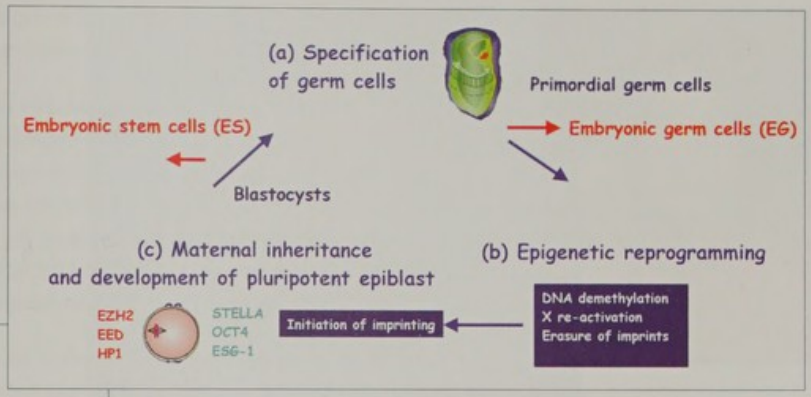
Surani MA Reprogramming of genome function through epigenetic inheritance (2001) **Nature** 414, 122-128

Payer B, Saitou M, Barton SC, Thresher R, Dixon JP, Zahn D, Colledge WH, Carlton MB, Nakano T and Surani MA (2003) *stella* Is a maternal effect gene required for normal early development in mice. **Curr Biol** 13, 2110-2117

Surani MA, Ancelin K, Hajkova P, Lange, UC, Payer B, Western P and Saitou M. Mechanism of germ cell specification: A genetic programme regulating epigenetic reprogramming. Cold Spring Harbor Symposium 69. **Epigenetics**. [in press]

For further publications, see numbers 13, 26, 62, 63 and 66 on pp 53–58

Fig 1 Mouse germ line cycle. (a) Founder population of primordial germ cells are detected at E7.5 consisting of about 45 cells. (b) They proliferate and migrate into the developing gonads at E10.5, when a major epigenetic reprogramming event commences, and continues during gametogenesis. (c) There is also maternal inheritance of key epigenetic and totipotency factors in oocytes, which are essential for early development.



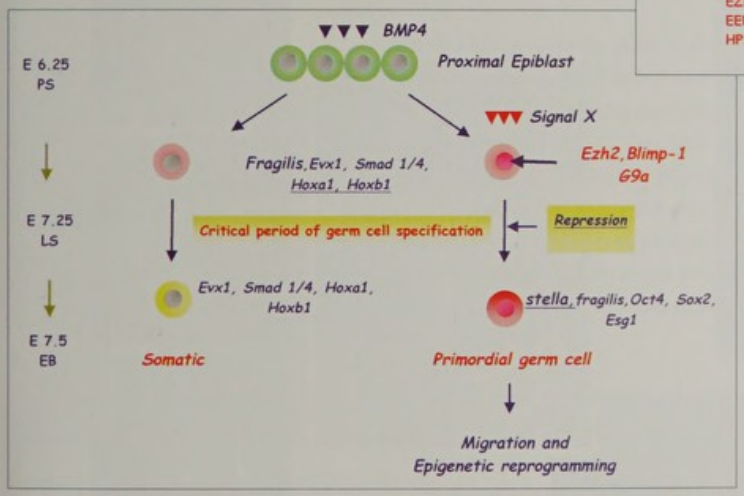
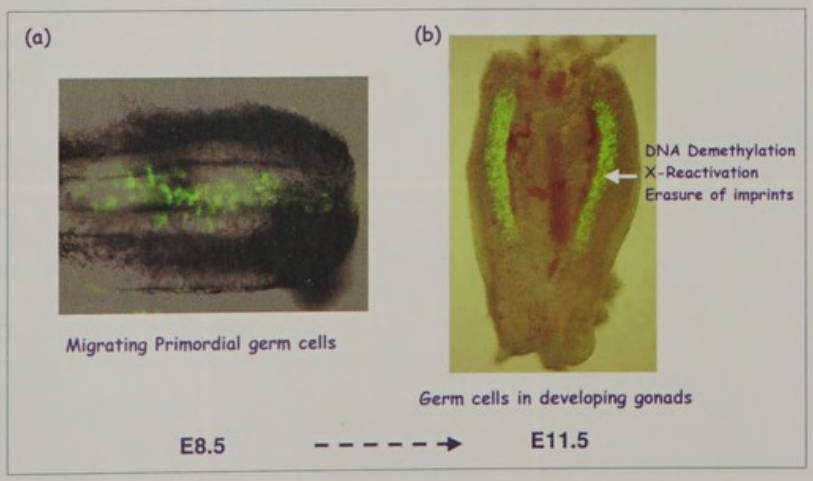


Fig 2 Mechanism of PGC specification. The proximal epiblast cells acquire germ cell competence in response to signalling molecules, including BMP4. Some of these cells acquire PGC fate subsequently, which is associated with transcriptional repression of genes that are expressed in the neighbouring cells, including Hox genes. Several epigenetic modifiers including Ezh2, G9a and Blimp-1 probably have a critical role in this process. PGCs continue to express pluripotent-specific genes such as Oct4, and the germ cell specific gene, stella, which is the definitive marker of nascent PGCs.

Fig 3 Epigenetic reprogramming in PGCs. (a) PGCs expressing Stella-GFP are seen migrating into the developing gonads. (b) When PGCs enter into the developing gonads, they undergo extensive epigenetic reprogramming of the genome that includes genome-wide DNA demethylation and reactivation of the inactive X-chromosome.



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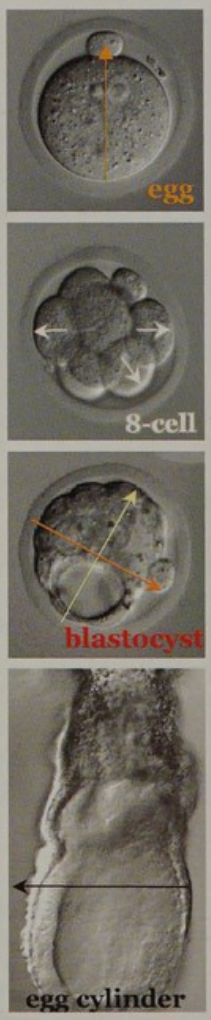
We are interested in origins of spatial patterning and cell fate determination in the mouse embryo focussing on three major questions.

First, how is the polarity of the egg first established to permit the drastically asymmetric, meiotic divisions and then re-organised following fertilisation to allow apparently symmetric, embryonic divisions? We are addressing this question by a combination of experimental embryology and molecular techniques to disturb egg polarity. Time-lapse fluorescent imaging allows us to follow dynamics of these processes and the ectopic expression of GFP-fusion proteins enables us to perturb these processes.

Second, how are the decisions made to allow early embryonic cells to shift their division patterns from being initially symmetric to asymmetric in order to establish inside and outside cells with different potency and thereby a different fate? We have recently found that we can change these cell fate decisions by down-regulating the function of cellular polarity proteins such as Par3 and aPKC. This leads us to study the role of these proteins and their partners in establishing cellular polarity and cell fate in the early mouse embryo. One of our ways to achieve this is by microinjecting dsRNA into individual blastomeres in order to follow the consequences in a clonal population of cells.

Third, we would like to understand further the influence of these asymmetric events in the preimplantation embryo on the development of first signalling centres important for establishing the anterior-posterior axis. To address when and how are such signalling centers established, we are taking a variety of approaches such as expression profiling and lineage tracing combined with RNAi and overexpression of signalling genes. To determine when and where signalling centres first become active our approach is to transplant them to ectopic sites. Our understanding of these events could be broadened by better knowledge of the spatial and temporal pattern of gene expression when the signalling centres emerge. Thus we have carried out screens that identified novel genes asymmetrically expressed at these early stages and are currently characterising their function.



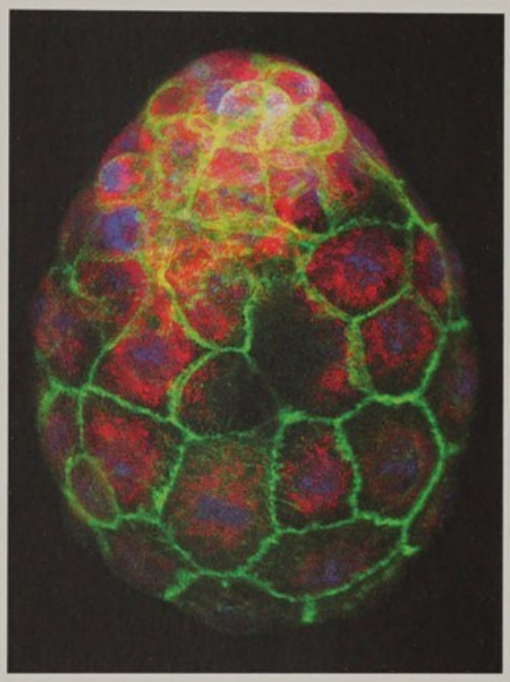
Wang QT, Piotrowska K, Ciemerych MA, Milenkovic L, Scott MP, Davis RW, and Zernicka-Goetz M (2004) A genome-wide study of gene activity reveals developmental signalling pathways active in mammalian oocytes and pre-implantation embryos. **Dev Cell** 6, 133-144

Mesnard D, Filipe M, Belo JA and Zernicka-Goetz M (2004) Emergence of the anterior-posterior axis after implantation relates to the re-orienting symmetry of the mouse embryo rather than the uterine axis. **Curr Biol** 14, 184-196

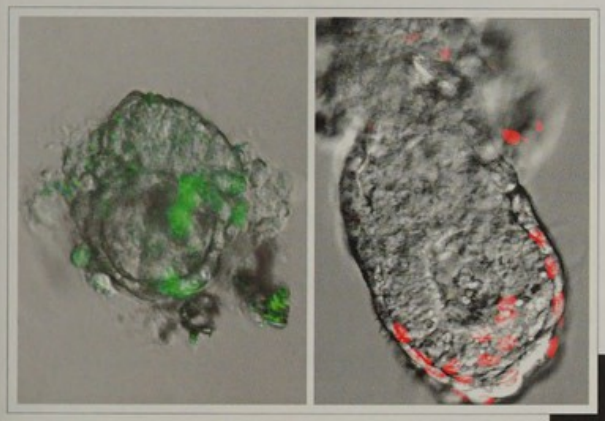
Zernicka-Goetz M (2004) First cell fate decisions and spatial patterning in the early mouse embryo. **Semin Cell Dev Biol** 5, 563-72

For further publications, see numbers 6, 19, 22, 23, 25, 71 and 72 on pp 53–58

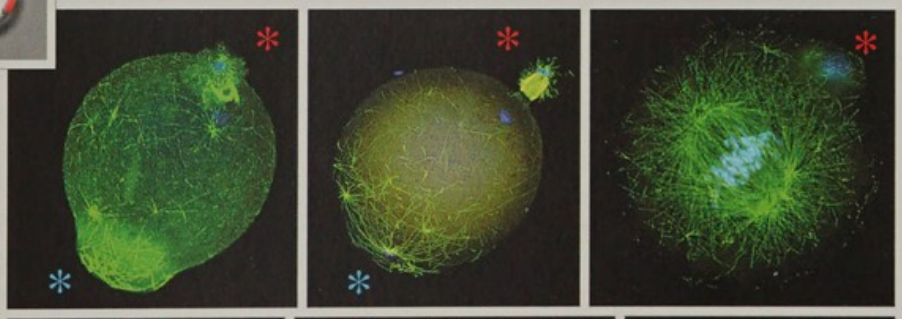
Facing page: Development of the early mouse embryo from fertilisation, through cleavage to the blastocyst stage and until shortly after implantation when the anterior-posterior axis emerges. It is still largely unknown how a mouse embryo and its individual cells become polarised throughout these stages. Animal-vegetal axis of the egg (orange); polarisation of the blastomeres at the 8-cell stage (white) to generate inside and outside cells upon asymmetric divisions, embryonic-abembryonic axis of the blastocyst (yellow) and its axis of bilateral symmetry (orange); the anterior –posterior axis of the egg cylinder (black).

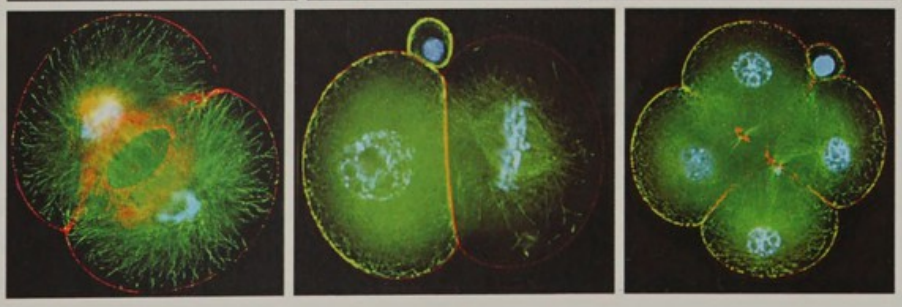


The localisation of dishevelled proteins (red) and b-catenin (green) are enriched in the ICM cells (nuclei in blue) of E4.25 blastocyst, indicating that embryos are primed for Wnt signalling before implantation.



Progeny of a single cell from the inner cell mass of the blastocyst, which colonises the visceral endoderm at implantation (E4.75, left) and postimplantation (E5.5, right) stages.





Cytoskeletal dynamics from fertilisation to the 4-cell stage. Microtubules (green), actin (red), chromatin (blue). Blue star-sperm entry position. Red star-extrusion of the second polar body.

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-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

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

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LISA BAKER
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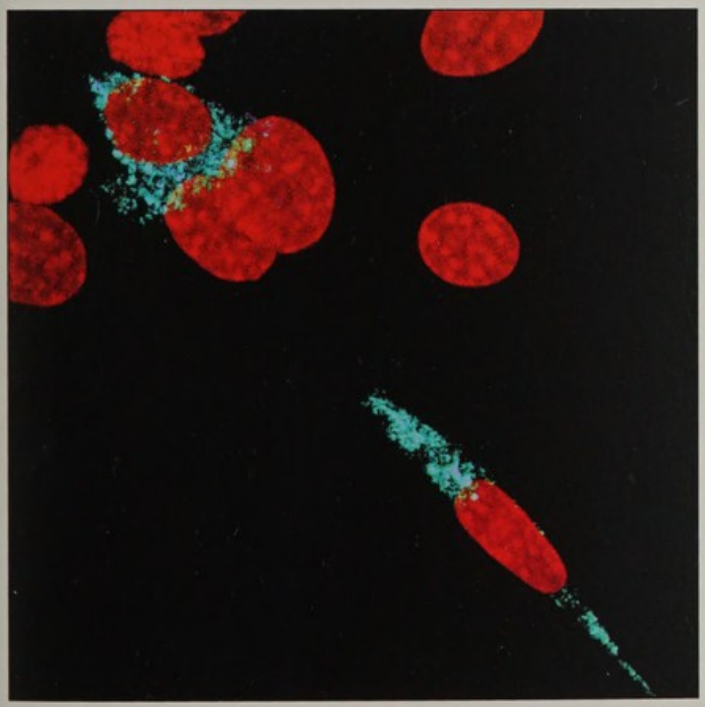
MARGARET HILL
SANDRA HUMAN
JOAN MENDHAM
CLAIRE PEARCE

The following is a list of articles by members of the Institute that were either published or accepted for publication since the date of our last annual report.

1 Acquaviva C, Herzog F, Kraft C and Pines J (2004) The Anaphase Promoting Complex/Cyclosome is recruited to centromeres by the spindle assembly checkpoint. **Nature Cell Biology** 6, 892-898

2 Bannister AJ, Kouzarides T (2004) Histone methylation: recognising the methyl mark. **Methods Enzymol** 376, 269-288

3 Bell SD and Bannister AJ (2004) Molecular transactions governing genome maintenance and expression. **Curr Opin Genet Devel** 14, 103-105



Part of a study to determine the topology of a transmembrane protein. 3T3 cells were transiently transfected with a tagged protein and subsequently stained with two antibodies recognising the tagged part (blue) and another part of the protein (blue); nuclei are counterstained with TOTO3 (red). Ulrike Lange (Surani Group), 2004

4 Benton R and St Johnston D (2003) A conserved oligomerisation domain in *Drosophila* Bazooka/PAR-3 is important for apical localisation and epithelial polarity. **Current Biology** 13, 1330-1334

5 Bökel C, Prokop A and Brown NH. Papillote and Piopio, *Drosophila* ZP-domain proteins required for cell adhesion to the apical extracellular matrix and microtubule organization. **J Cell Sci** [in press]

6 Carpenter L, Zernicka-Goetz M (2004) Directing pluripotent cell differentiation using diced RNA in transient transfection. **Genesis** 40, 3, 157-163

7 Carr A, Choksi SP and Brand AH (2004) Turning back the clock on neural progenitors. **BioEssays** 26, 711-714.

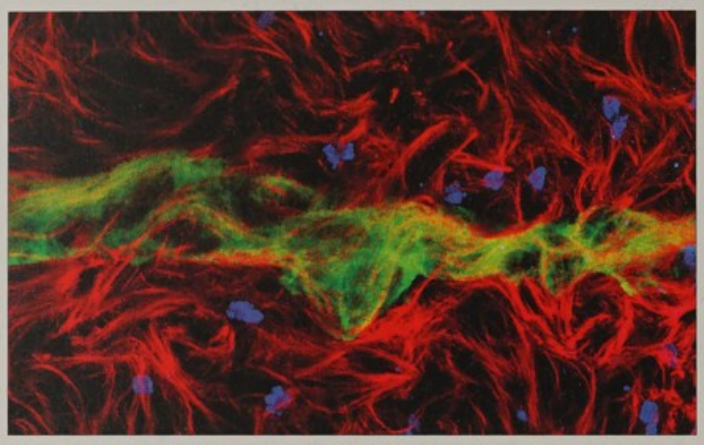
8 Chalmers AD, Goldstone K, Smith JC, Gilchrist M, Amaya E and Papalopulu N. A *Xenopus tropicalis* oligonucleotide microarray works across species using RNA from *Xenopus laevis*. **Mech Dev Xenopus Genetics and Genomics**: special issue [in press]

9 Chalmers A, Pambos M, Lang S, Wylie C and Papalopulu N. aPKC, crumbs3 and Lgl -2 control apical/basal polarity in early vertebrate development. **Development** [in press]

10 Chen J-A, Voigt J, Gilchrist M, Papalopulu N and Amaya E (2004) Identification of novel genes affecting mesoderm formation and morphogenesis through an enhanced large scale functional screen in *Xenopus*. **Mech Dev Xenopus Genetics and Genomics**: special issue [in press]

11 Cinnamon E, Gur-Wahnon D, Helman A, St Johnston D, Jiménez G and Paroush Z (2004) Capicua integrates input from two maternal systems in *Drosophila* terminal patterning. **EMBO J** 23, 4571-4582.

12 Concha ML, Russell C, Regan JC, Tawkl M, Sidi S, Gilmour DT, Kapsimali M, Sumoy L, Goldstone K, Amaya E, Kimelman D, Nicolson T, Gründer S, Gomperts M, Clarke JDW and Wilson SW (2003) Local tissue interactions across the dorsal midline of the forebrain establish CNS laterality. **Neuron** 39, 423-438



Microtubules (red) in the embryonic CNS after depolymerisation of actin (ventral midline: green; anti-phosphoHistone H3: blue) Torsten Bossing (Brand Group), 2004

13 Curly JP, Barton S, Surani MA and Keverne EB (2004) Coadaptation in mother and infant regulated by a paternally expressed imprinted gene. **Proc R Soc Lond B Biol Sci** 271, 1303-1309

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20 Giavara S, Kosmidou E, Hande MP, Bianchi ME, Morgan A, d'Adda di Fagagna F and Jackson SP. Yeast Nhp6A/B and mammalian Hmgb1 facilitate the maintenance of genome stability. **Current Biology** [in press]

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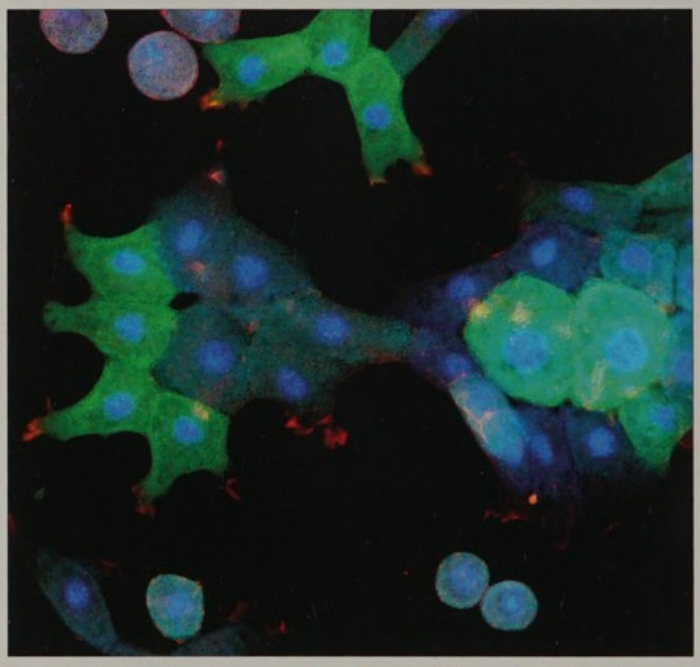

Dissociated animal cap cells expressing Xtes-eGFP (green), red: phalloidin, blue: nuclei. Kevin Dingwell (Smith Group), 2004

23 Grabarek JB and Zernicka-Goetz M (2003) RNA interference in mammalian systems – a practical approach. **Adv Exp Med Biol** 544, 205-216

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Xenopus animal caps, injected with a T-box gene, fused to form a spontaneous soccer sculpture. Liz Callery (Smith Group), 2004

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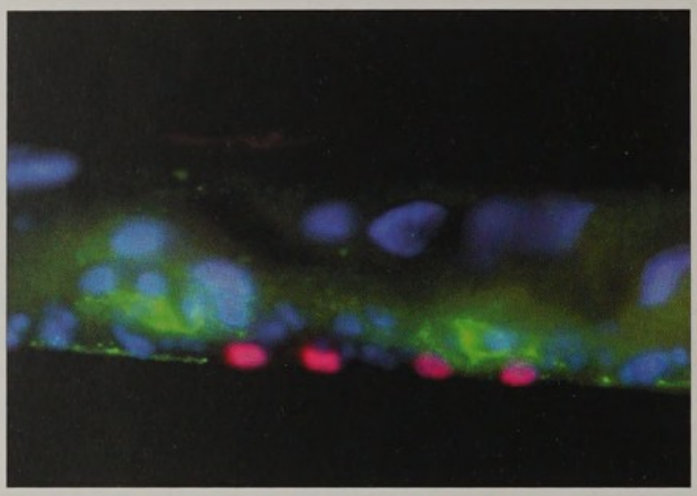

In *C. elegans*, RNAi of cdc-42 causes adjacent pairs of vulval cells to adopt the primary fate, expressing EGL-17 (red) and downregulating LIN-12 (green). Nuclei are stained with DAPI (blue).
David Welchman (Ahringer Group), 2004

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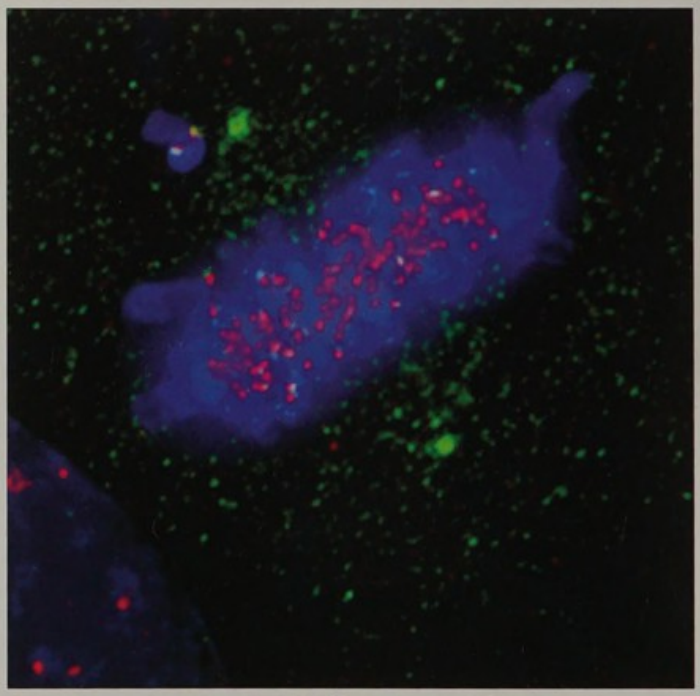
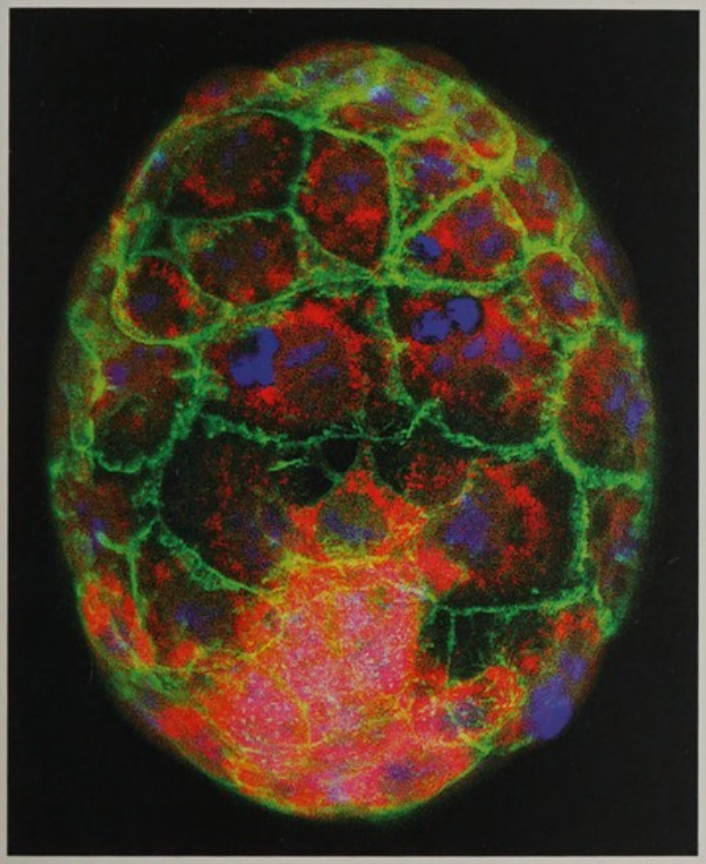


HeLa cell stained to show the APC/C (α-phosphoAPC1, green), the centromeres (CREST antiserum, red) and the chromosomes (Hoechst 33342, blue). The APC/C stains spindle poles and the kinetochores of the chromosome that has not attached to the spindle. Claire Acquaviva (Pines Group), 2004



Mouse blastocyst. Green, β-catenin; Red, protein highly expressed in the inner cell mass; Blue-purple, DNA. Jie Na (Zernicka-Goetz Group), 2004

44 Miska EA, Alvarez-Saavedra A, Townsend M, Yoshii A, Sestan N, Rakic P, Constantine-Paton M, Horvitz HR (2004) Microarray analysis of microRNA expression in the developing mammalian brain. **Genome Biol** 5, R68

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INSTITUTE PUBLICATIONS

56 Simonsson S and Gurdon J (2004) DNA demethylation is necessary for the epigenetic reprogramming of somatic cell nuclei. **Nature Cell Biology** published online 26/09/04

57 Sivak JM and Amaya E (2004) FGF signaling during gastrulation. In: **Gastrulation** 463-473 Ed. Claudio Stern, Cold Spring Harbor Laboratory Press

58 Smith JC and Gurdon JB (2004) Many ways to make a gradient. **BioEssays** 26, 705-706

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65 Surralles J, Jackson SP, Jasin M, Kastan MB, West SC and Joenje H (2004) Molecular cross-talk among chromosome fragility syndromes. **Genes and Development** 18, 1359-1370

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73 Zernicka-Goetz M (2004) First cell fate decisions and spatial patterning in the early mouse embryo. **Seminars in Cell Dev Biol** 15, 563-572

STAFF AFFILIATIONS

JULIE AHRINGER is a member of the Scientific Advisory Board of Genome Knowledgebase.

ENRIQUE AMAYA is a member of the Molecular and Cell Biology Panel for the Ramón y Cajal Fellowship Programme.

ANDREA BRAND is on the Scientific Advisory Board of the Promega Corporation, a Research Fellow at King's College, Cambridge, an Invited Professor at the Ecole Normale Superieure, Paris, a member of the Academy of Medical Sciences Academic Careers Committee, a member of the Editorial Board of BioEssays, and is the Institute representative to the Cambridge University Women in Science, Engineering and Technology Initiative (WiSETI).

JOHN GURDON is a member of the Conseil Scientifique of the Institut Curie, Paris, a member of the Scientific Advisory Board of the Max-Planck-Institut für Biophysikalische Chemie, Göttingen, and Chairman of the Company of Biologists.

STEVE JACKSON is a member of the Cancer Research UK Development Committee, and Chief Scientific Officer, KuDOS Pharmaceuticals Ltd..

TONY KOUZARIDES is a member of the Cancer Research UK Scientific Executive Board, a member of the Marie Curie Institute Scientific Committee, and non-executive director of AbCam Ltd and Chroma Therapeutics.

ANNE McLAREN is a member of the European Life Sciences Group, the European Group on Ethics (advisory groups to the European Commission) and a Member of the Archbishop of Canterbury's Ethics Group.

NANCY PAPALOPULU is a Board Member and an Officer of the British Society for Developmental Biology, and Managing Editor of Mechanisms of Development.

JONATHON PINES is a committee member of the British Society for Cell Biology, and a member of the HFSP Fellowship 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, and is a life-long member of the Royal Institution.

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, Editor-in-Chief of *Development*, a member of the University of Cambridge Sub-Committee for Biological Sciences and Clinical Medicine (Senior Academic Promotions), and a member of the Cancer Research UK Scientific Promotions and Salaries Assessment Panel.

AZIM SURANI is a member of the Royal Society Working Group on Stem Cells, a member of the German Stem Cells Initiative, Director of the Programme in Stem Cell Genetics, member of the Cambridge Stem Cell Institute Advisory Committee, Founder and Consultant for CellCentric Ltd, and a member of the Scientific Advisory Board of Paradigm Therapeutics Ltd.

MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Research Fellow at Sidney Sussex College and EMBO Young Investigator.

HONOURS AND AWARDS

JULIE AHRINGER - The Royal Society's Francis Crick Lecture Prize

DANIEL ST JOHNSTON - Elected Fellow of the Academy of Medical Sciences

JOHN GURDON - Elected Foreign Associate by the Institute of Medicine of the National Academy of Sciences USA

AZIM SURANI - Appointed Sir Dorabji Tata Professor, Tata Institute for Fundamental Research, NCBS, Bangalore, India. Elected Distinuished Fellow, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India.

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JULIE AHRINGER – Public Library of Science Biology

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ANDREA BRAND – BioEssays

JOHN GURDON – Current Biology, Development, Growth and Differentiation, International Journal of Developmental Biology

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

ANNE McLAREN – Gene Therapy, Current Opinion in Genetics and Development

NANCY PAPALOPULU – Developmental Dynamics, Mechanisms of Development.

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

JIM SMITH – Trends in Genetics, EMBO Journal, EMBO Reports.

AZIM SURANI – Transgenic Research, Molecular Human Reproduction, Faculty of 1,000, Biological Reviews.

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CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR SIR TOM BLUNDELL, Head, Department of Biochemistry, University of Cambridge, UK.

OTHER INFORMATION

LEAVERS DURING 2004

IAN ADAMS moved to Edinburgh to set up a Research Group at the Department of Oncology and MRC Human Genetics Unit

SIQIN BAO left to take up a new position at the Sanger Centre

LYNN BIDERMAN Part II Student – continuing full-time degree studies

SHARAI CORRELL returned to the full-time medical degree course at South Carolina Medical University

ANNABELLE CURRY transferred to the Department of Anatomy

SYLVAIN DAUJAT returned to France to take up a new position

STEPHEN FRANKENBERG moved to France to take up a new research position

TEO FRIGERIO is now working for the Dept of Biotechnology

MICHAL GOLDBERG is now a Lecturer at the Department of Genetics, Hebrew University, Institute of Life Sciences, Givat Ram, Jerusalem

DIONNE GRAY has transferred to the Department of Anatomy

MURIEL GRENON left to take up a new position with Dr Noel Lowndes at the National University of Ireland in Galway

DONNA GRIMMER is now working for Helena Bioscience

HUILI GUO returned to full-time degree studies after completing a Vacation Studentship at the Institute

DON HAYNES retired

JANET HENSBY transferred to the Staff Development Office

LUKE HUGHES-DAVIES transferred to Department of Oncology at Addenbrookes

MARGARET HILL left following maternity leave

SAM JAMESON left to start a Zoology degree course

CHRISTIN KABITSCHKE returned to Germany to take up a research position

SANTWANA KAR is now working as a Pharmaceutical Analyst at Data Monitor

TSUTOMU KINOSHITA returned to his position as Professor at Kwansei Gakuin University, Japan

FREDERIC LANGEVIN returned to France to complete his degree course following a spell of several months gaining experience at the Institute

JOANNA MALDONADO SALDIVIA completed her PhD Studentship

MARY MALKIN retired

MARUXA MARTINEZ CAMPOS completed her PhD Studentship

CATHERINE MOORE completed her PhD Studentship and is moving to the Department of Biomedical Science at the University of Sheffield

ISABEL PALACIOS transferred to the Department of Zoology to take up a Royal Society Fellowship

ELIZABETH PALMER returned to full-time degree studies after completing a Vacation Studentship at the Institute

MICHAEL PAMBOS Part II Student in Papalopulu group – is continuing full-time degree studies

SARAH PAYNE is now a Post-Graduate Student at the California Institute of Technology, USA

KAROLINA PIOTROWSKA moved to Atlanta, USA

VARUNI PRABHAKAR returned to full-time degree studies at Columbia University after completing a Vacation Studentship at the Institute

ROB SCHNEIDER is now a Group Leader at the Max-Planck-Institute of Immunobiology in Freiburg, Germany

RUTH SEAGER Part II Student in Papalopulu group – is continuing full-time degree studies

STINA SIMONSSON returned to Sweden to establish her own Research Group

VERONIQUE SMITS moved to Erasmus MC, Department of Cell Biology and Genetics, Rotterdam

NICOLA TAVERNER completed PhD Studentship

BETH THOMPSON Part III Student in Pines lab – left to start a PhD with Andrew Travers at the MRC-LMB

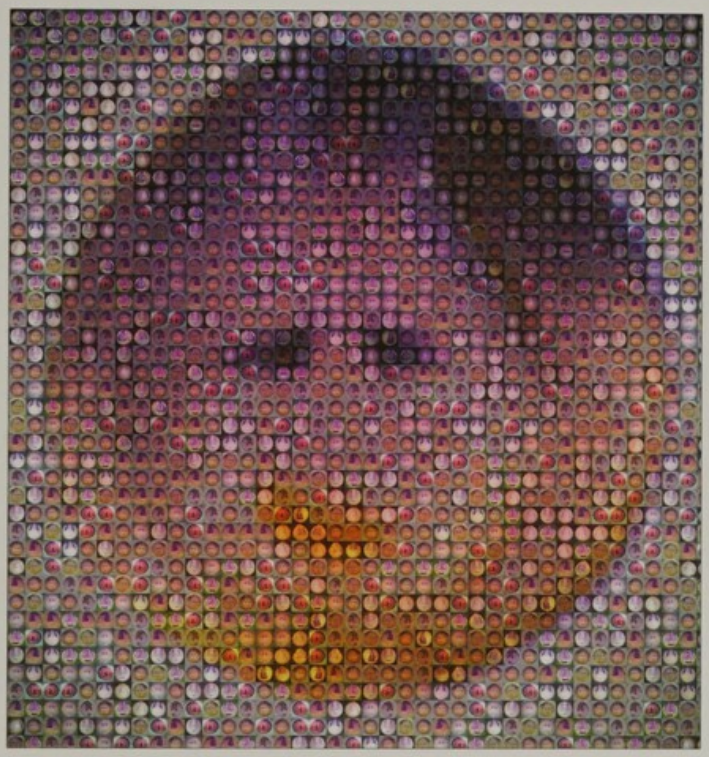
CATHY TORGLER moved to Vienna to take up a new research position

LUCY WHEATLEY returned to full-time degree studies after completing a Vacation Studentship at the Institute

HUW WILLIAMS took up a research position at the Sanger Centre

VIKKI WILLIAMS left to travel the world

CHRISTOS ZERVAS is now an Assistant Professor at the Institute of Foundation of Biomedical Research, Academy of Athens



Montage of *in situ* pictures from a large scale functional screen in *Xenopus*, reflecting a novel cyclin (cyclinDx) expression pattern at neurula. Jun-An Chen (Amaya Group), 2004

ACKNOWLEDGEMENTS

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

Group photographs by Chris Green (Dept of Biochemistry), John Overton (Brown Group) and Chris Down (Brand Group)

Printed by Cambridge University Press.

Front cover: Seven early stages of *C. elegans* embryogenesis. Fixed embryos stained with an anti-tubulin antibody (green), and with DAPI to show the DNA (blue). Nathalie Le Bot (Ahringer Group) 2004, with thanks to Alex Sossick (Imaging) for assistance with deconvolution.

Back cover: *C.elegans* hermaphrodite gonad showing syncitial meiotic region with DAPI stained nuclei (pink) and cellularisation of oocytes with membranes marked by nmy-2 (blue). Costanza Panbianco (Ahringer Group), 2004

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