Annual report : 2000/2001 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

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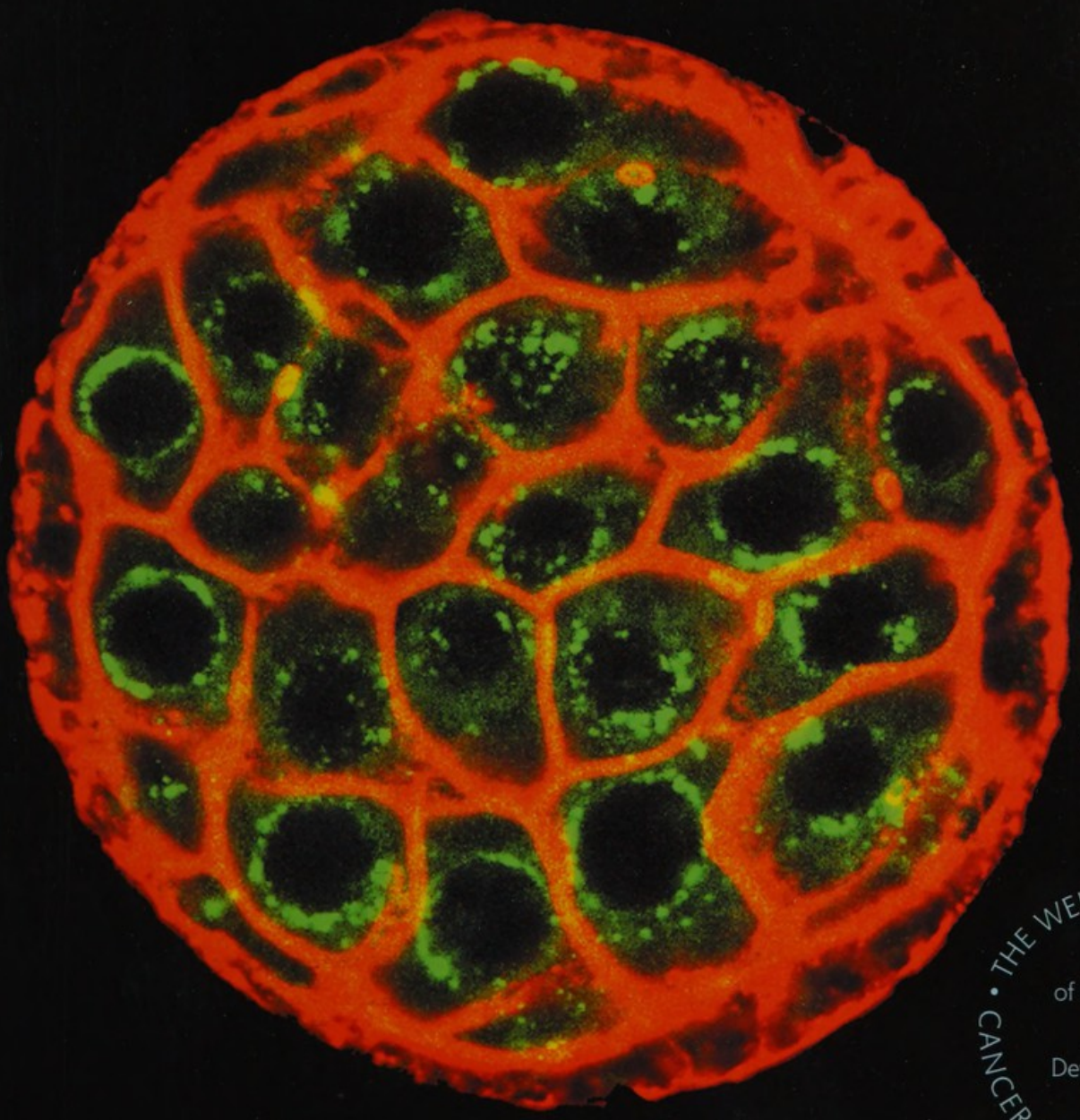
THE WELLCOME/CRC INSTITUTE

2001 PROSPECTUS/ANNUAL REPORT 2000



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PROSPECTUS 2001

ANNUAL REPORT 2000

University of Cambridge

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CHAIRMAN'S INTRODUCTION

This is my last year as Chairman of this Institute. As noted in last year's Prospectus, I will hand over the Chairmanship, on 1 October 2001, to Professor J.C. Smith who happily has already moved into this Institute with his group. Jim Smith will also succeed me as John Humphrey Plummer Professor of Cell Biology, a post that I inherited from Sir Alan Hodgkin in 1983.

It is now ten years since our Institute was formally opened by the Duke of Edinburgh and we moved into our newly constructed building, which we share with another part of the University. During this decade, we have increased our numbers threefold to our present size of well over 200 persons. We now have fifteen independent Group Leaders, who collectively attract about £6.5 million per year from 165 different research grants. We have become excessively crowded and in need of our own facilities. Through a large grant from the Wellcome Trust and the Government's Office of Science and Technology, we will be provided in 2003 with our own new building adjacent to the University's Biochemistry Department. We will have a high standard of laboratory provision with much improved equipment. The overall direction of research will continue to be the analysis of normal cell development (Wellcome Trust as major sponsor), and of abnormal cell function, especially cancer (Cancer Research Campaign as major sponsor). We will continue to be an integrated part of Cambridge University and to contribute teaching and graduate student supervision.

During 2001 we will see the departure of Ron Laskey who will enhance the cancer screening aspect of his research by directing a new MRC Cancer Cell Unit in the Cambridge Medical School. Having had the privilege of close scientific association with Ron Laskey for one third of a century, it is a special pleasure for me to congratulate him on the extraordinary success of his work. We all wish him well in his next appointment.

THE INSTITUTE IN 2000

Although not in accord with some current ideas of business organisation, I believe that our democratic style of management which we have developed over the last ten years has worked well and I feel it will continue to do so as the Institute embarks on its second decade.

John Gurdon.

John Gurdon, Chairman

HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and a short distance from the centre of the historic city. It was founded in 1989 to promote research in the areas of developmental biology and cancer biology, and 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 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 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 a 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 one person can master, such as gene cloning, antibody preparation, cell culture 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.

CENTRAL SUPPORT SERVICES

David Dunbar, Administrator from the inception of the Institute, left in September 2000. He has moved to Edinburgh to study for an MBA. His wide-ranging knowledge of the Institute, and of the University as a whole, will be sorely missed. To commemorate David's departure, the David Dunbar Trophy will be awarded annually to the winning football team at the Institute's Annual Retreat. David's replacement, Ann Cartwright, joined us in December from the Isaac Newton Institute.

This year has seen the introduction of a new University-wide commitment accounting system, CAPSA. The system has not been entirely problem-free during the implementation period but it is hoped that, once fully operational, it will enhance the service provided by our Accounts team.

During the year we learnt that our application to the Wellcome Trust for a further five years of core support (October 2000 to September 2005) was successful. The application included funding for several new support posts, made necessary by the continuing expansion of the Institute and its work. These include two new part-time staff, an Administrative Assistant and a Purchasing Assistant to assist the Secretary/Personnel Assistant (Linda Millett) and the Accounts Assistant (Jane Cooper).

Administration has been re-organised. The Laboratory Administrator is now supported by a Laboratory Manager/ Principal Technician (Diane Foster) and there is a further new post of Chief Technician to which Kathy Hilton has been appointed.

Computing facilities have also been enhanced. There is now one full-time Computer Associate (Alex Sossick) who specialises in the imaging equipment, and two further full-time Computer Associates (Desmond Schmidt and Nigel Smith) who deal with all other computing issues. A further part-time person will also be recruited.

Central media and glass-washing workers provide a comprehensive and vital service under the expert guidance of the Senior Media Technician, Juanita Peacock.

NEW BUILDING

Plans for the new building are now at an advanced stage. Work on the site will begin in March 2001 and it is expected to be completed by the summer of 2003. The building will provide enhanced facilities and additional laboratory space, both of which are now essential if the Institute is to continue its meteoric progress.

WELLCOME TRUST CENTRE

The Wellcome Trust has now designated the Institute as a Wellcome Trust Centre. It shares this status with a number of centres of excellence throughout the UK, although it is unique in being the only one which is jointly funded by the CRC.

OTHER FUNDING

The CRC continues to support the Institute, both by means of a grant for its core activities and further grants for individual groups within the Institute.

Other sources of funding have included the European Union, HFSP, SmithKline Beecham, Kay Kendal Fund, AICR, Leukaemia Fund, The Royal Society, the Isaac Newton Trust and Abcam Ltd.

INSTITUTE RETREAT

The Institute Retreat took place in September 2000 in Cirencester. There was an excellent attendance and the whole occasion was both scientifically profitable and enjoyable.

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ANDREW FRASER
MONICA GOTTA
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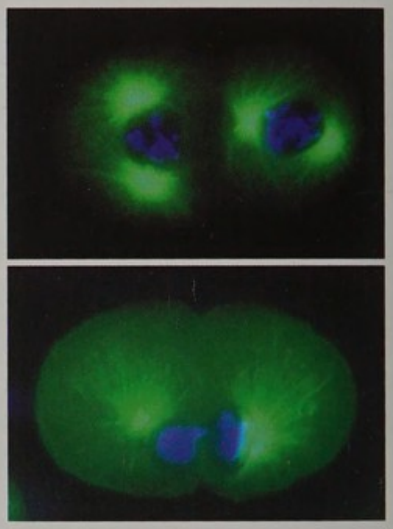
CARA NEADES
FLORENCE SOLARI
CHRISTINE TURNER
PEDER ZIPPERLEN

We are studying how patterns of cell divisions and cell fates are controlled during embryogenesis, using *C. elegans* as a model system. One of the first indications of pattern in the *C. elegans* embryo is the orientation of the mitotic spindle. Although the control of spindle orientation is a widespread phenomenon in animal development, little is known about how correct axes are chosen. We have shown that heterotrimeric G proteins are required for the correct orientation and position of mitotic spindles during early embryonic cleavages. We are screening for other genes involved to identify targets and understand what polarity cues are used, using a wide range of approaches.

One approach we are taking is a genome wide RNA interference screen, which has the major advantage of knowing the sequence of the gene for which a phenotype is found. After screening a chromosome I RNAi library, we found new genes involved in many early processes including spindle orientation, cell cycle timing, cytokinesis, and chromosome segregation. Construction and screening of libraries for other chromosomes is underway.

A second area of research in the lab is on later patterning events. In a screen for genes involved in embryonic patterning, we identified *egl-27*, which encodes a component of the NURD chromatin regulatory complex. Further analyses of the NURD complex indicate that it has a role in regulating many patterning decisions, including those involving Ras and Wnt signalling. Future work is aimed at understanding the connection between patterning and chromatin remodelling by the NURD complex and to identify its targets.



Heterotrimeric G proteins regulate microtubule distribution (green) in the embryo. In embryos lacking Gα subunits, centrosomes fail to separate (bottom) and microtubule arrays are disorganised compared to wild type (upper panel). DNA is blue.

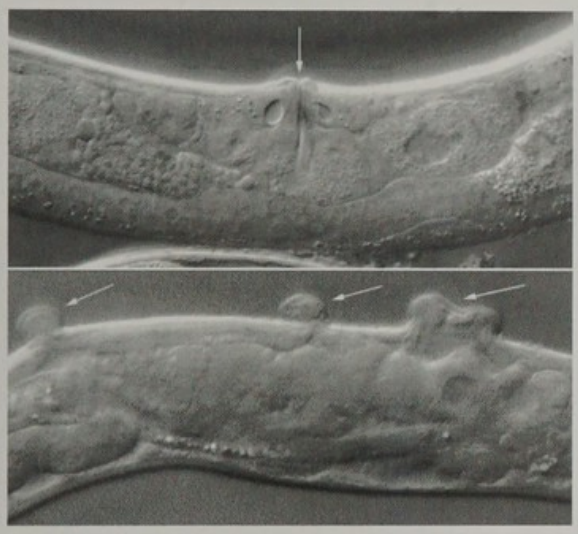
Ahringer, J. (2000) Developmental roles of NuRD and SIN3 histone deacetylase complex proteins. **Trends Genet.** *16,* 351–356.

Fraser, A., Kamath, R.K., Zipperlen, P., Martinez-Campos M., Sohrmann, M. and Ahringer, J. (2000) Functional genomic analysis of *C. elegans* Chromosome I by systematic RNA interference. **Nature** *408,* 325–330.

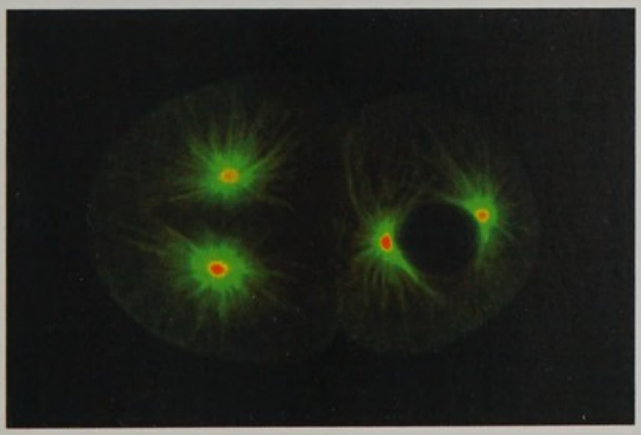
Gotta, M., and Ahringer, J. (2001) Distinct roles for Gα and Gβγ in regulating spindle position and orientation in early *C. elegans* embryos. **Nat. Cell Biol.,** *in press.*

Solari, F. and Ahringer, J. (2000) NURD complex genes antagonise Ras induced vulval development in *C. elegans.* **Curr. Biol.** *10,* 223–226.

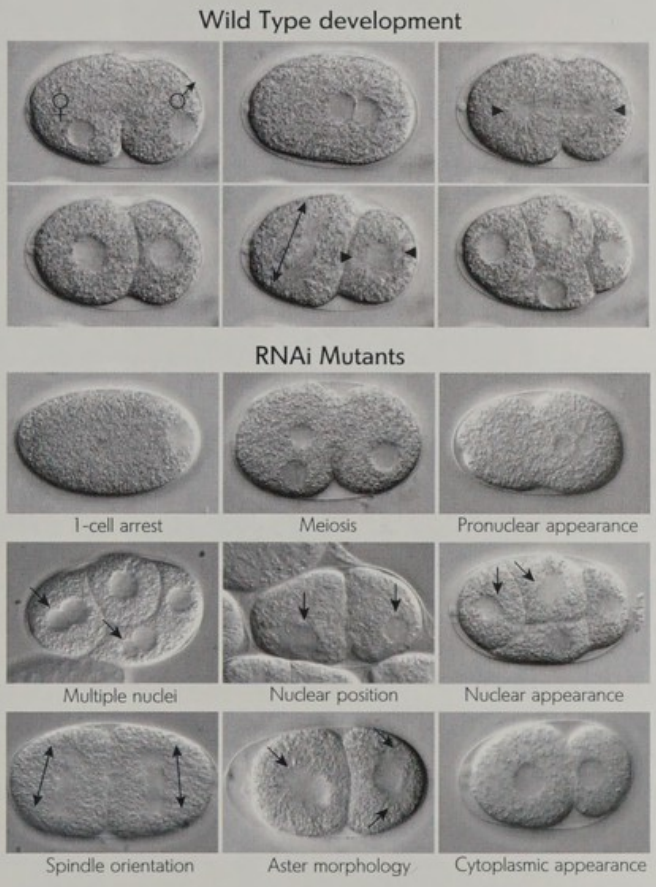
For further publications, see number 49 on page 51.



The NURD chromatin remodelling complex is involved in many cell fate decisions. Lack of NURD function results in ectopic vulval tissue (arrows, bottom) due to inappropriate activation of the Ras pathway. Wild type (top).

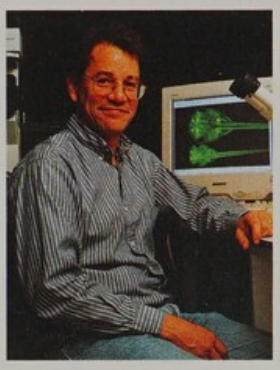


A two-cell embryo with microtubules in green and centrosomes in red. The anterior cell (left) and the posterior cell (right) will divide in different orientations, specified by the positions of the centrosomes.



Many genes involved in early processes were discovered in an RNA interference screen of chromosome I. Top: series of first two cleavages in wild-type embryos. Bottom: examples of RNAi mutant phenotypes.

ENRIQUE AMAYA



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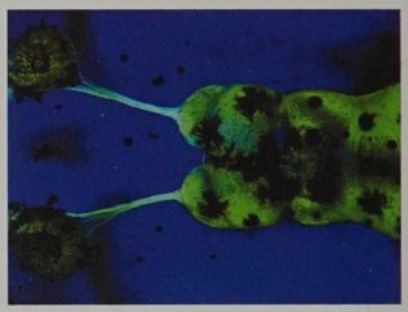
STEPHEN NUTT
MATTHEW POLLI
MARGARET TYCE-BUTCHER

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 laevis*. We have shown that inhibiting FGF signalling during gastrulation disrupts mesoderm formation and morphogenesis. In order to better understand this process, we have begun to isolate downstream targets of FGF signalling. One target we have identified is the gene *Xsprouty2*. This gene has the interesting property that it is both a target of FGF signalling and a modulator of FGF signalling. Our work suggests that, by having these two properties, *Xsprouty2* co-ordinates the cell movements of gastrulation.

We are also studying how mesoderm pattern is established in the amphibian embryo by investigating the transcriptional regulation of two early mesodermal genes in transgenic embryos. One of these genes, *Xnot*, is expressed in dorsal mesoderm fated to become notochord and the other gene, *XMyf-5*, is a myogenic gene expressed in dorso-lateral mesoderm fated to become muscle.

Another focus in our group is the role of growth factor signalling in patterning and morphogenesis of the heart and eye. We are generating transgenic embryos that aberrantly express genes that upregulate or downregulate growth factor signalling molecules specifically in these organs.

Finally, we are initiating an insertional mutagenesis screen using a gene trap approach in *Xenopus tropicalis*, a diploid frog related to *Xenopus laevis*, with a view to identifying novel genes involved during development.



Confocal image of the anterior brain of a living transgenic tadpole expressing a tau-GFP fusion construct under the control of the neural specific β-tubulin promoter.

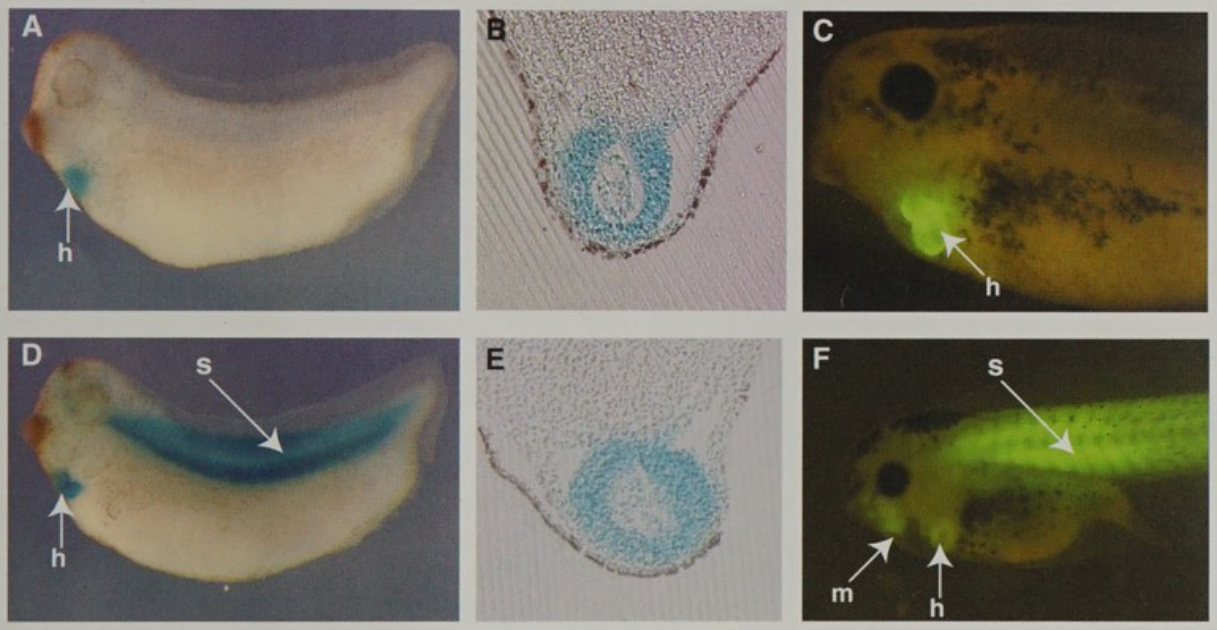
Please see Amaya Lab home page: http://www.welc.cam.ac.uk/~ea3

Breckenridge, R.A., Mohun, T.J. and Amaya, E. (2001) A role for BMP signalling in heart looping morphogenesis in *Xenopus*. **Dev. Biol.**, *in press*.

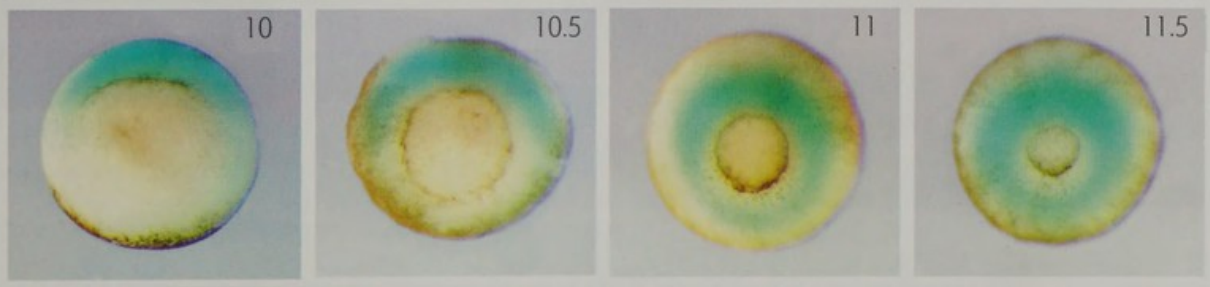
Bronchain, O.J., Hartley, K.O. and Amaya, E. (1999) A gene trap approach in *Xenopus*. **Curr. Biol.** *9*, 1195–1198.

Nutt, S.L., Dingwell, K.S., Holt, C.E. and Amaya, E. (2001) *Xenopus* Sprouty2 inhibits FGF mediated gastrulation movements but does not affect mesoderm induction and patterning. **Genes Dev.**, *in press*.

For further publications, see numbers 15, 39 and 52 between pages 49 and 52.



Transgenic embryos expressing the green fluorescent protein (GFP) under the control of promoters that are expressed in heart muscle (panels A, B, C) or skeletal and heart muscle (panels D, E, F). In panels A, B, D, E GFP mRNA is visualised following whole-mount in situ hybridisation and panels C and F are living embryos visualised under fluorescence. Panels B and E are sections through the heart of transgenic embryos stained for the presence of GFP RNA. (s) somites, (h) heart, (m) head muscle.



Expression of *Xsprouty2* during the gastrula stages.

ANDREA BRAND

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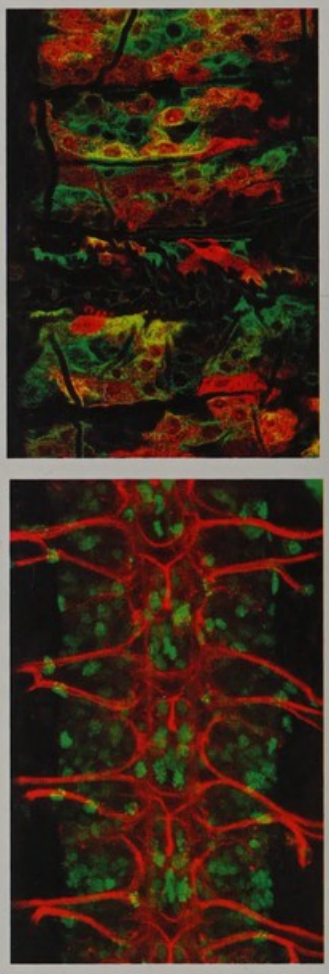
As the nervous system develops, thousands of neurons are born, each of which must assume a specific identity. Each neuron can then extend its axon towards, and synapse with, an appropriate target cell. We are interested in how cell diversity is generated in the nervous system, and how cell–cell interactions orchestrate axon pathfinding.

One way to generate diversity is to ensure that when a cell divides each of its daughters assumes a distinct identity. This can be simply achieved by segregating a cell fate determinant to only one of the two daughter cells at cell division. We are investigating the molecular mechanisms that direct the asymmetric segregation of cell fate determinants and their mRNAs, and the role of the cytoskeleton in asymmetric cell division. We have shown that the coiled-coil domain protein, Miranda, is essential for the segregation of the homeodomain protein, Prospero, and its mRNA. Miranda binds to Prospero and to the dsRNA binding protein, Staufen, which in turn binds the Prospero mRNA. Recently we have shown that myosins, motor proteins that interact with the actin cytoskeleton, play an integral role in asymmetric localisation of determinants in the nervous system. To follow cell fate determinants in living embryos, we have fused different spectral variants of GFP to cell fate determinants and cytoskeletal proteins. We can visualise several different proteins at once in living embryos by time lapse confocal microscopy.

We are also studying the cell–cell interactions that influence axon outgrowth and have identified several signalling molecules that direct axon pathfinding, including a *Drosophila* Ephrin. We are characterising their roles in nervous system development by ectopic gene expression and targeted RNAi, to eliminate their expression in specific cells.



The embryonic CNS
(axons red, nuclei green)

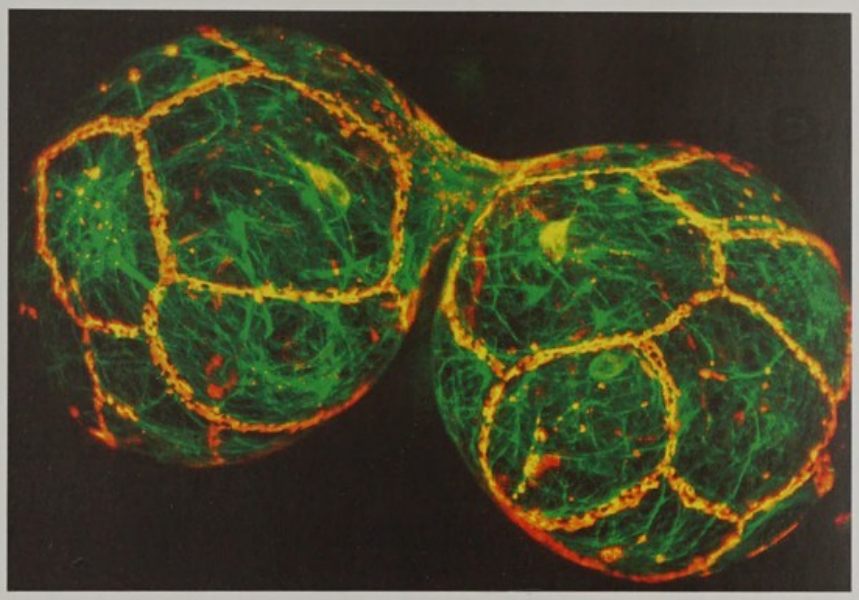
Kaltschmidt, J.A., Davidson, C.M., Brown, N.H. and Brand, A.H. (2000) Rotation and asymmetry of the mitotic spindle direct asymmetric cell division in the developing central nervous system. **Nat. Cell Biol.** *2*, 7–12.

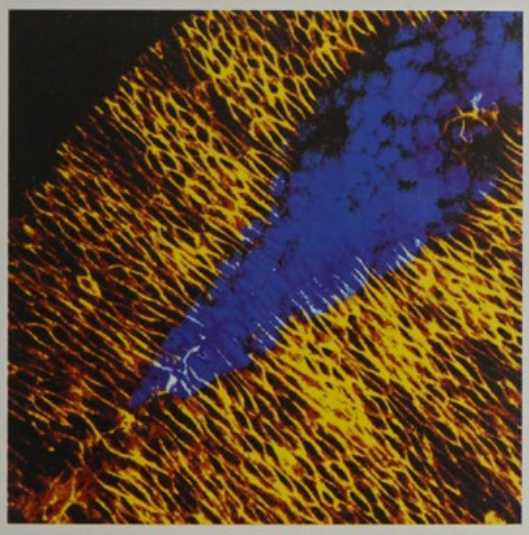
Schuldt, A.J. and Brand, A.H. (1999) Mastermind acts downstream of Notch to specify neuronal cell fates in the *Drosophila* CNS. **Dev. Biol.** *205* 287–295.

Schuldt, A.J., Adams, J.H.J., Davidson, C.M., Micklem, D.R., Haseloff, J., St Johnston, D. and Brand, A.H. (1998) Miranda mediates asymmetric protein and RNA localisation in the developing nervous system. **Genes Dev.** *12*, 1847–1857.

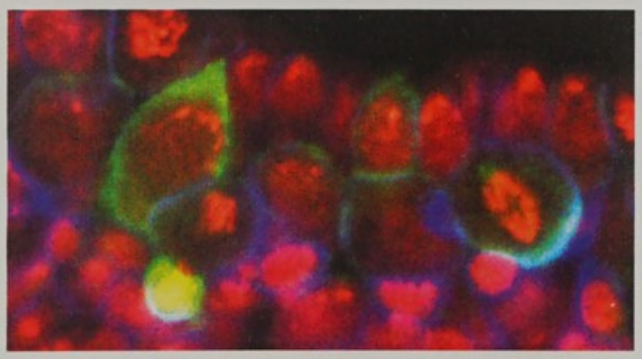
For further publications, see numbers 14 and 79 on pages 49 and 53.

In vivo labelling of the larval brain lobes (right) or epidermis (page 10, top) with two different spectral variants of green fluorescent protein (YFP in red, GFP in green, colocalisation in yellow).





Fluorescent antibody staining of a *Drosophila* embryo undergoing dorsal closure. The cells of the dorsal epidermis (gold) elongate and fuse at the dorsal midline enclosing the amnioserosal cells (blue) that overlay the yolk mass.



The cell fate determinant Miranda (green) is asymmetrically segregated when neuronal precursors divide. DNA is labelled in red and Neurotactin, which localises to the cell membrane, in blue.

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

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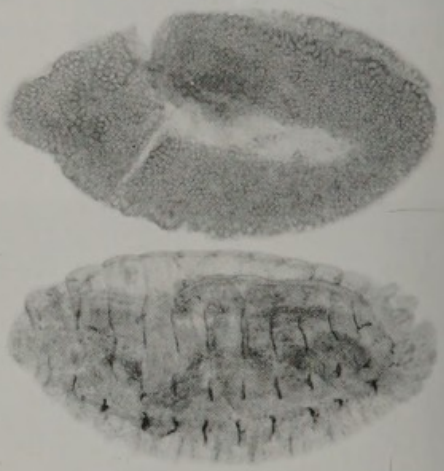
Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells that stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one family 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 the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers and cell differentiation.

To discover what other proteins are required to work with the integrins, we and others have used the genetics of the fruit fly *Drosophila* to identify genes required for integrin mediated adhesion. The molecular characterisation of these genes is providing a description of the proteins that make up the structure that links the integrins to the cytoskeleton. These proteins include the cytoskeletal linker proteins kakapo and talin, and the signalling adaptor proteins, integrin-linked kinase and tensin. By manipulating the structure of these proteins and assaying their function in the living animal we are elucidating how they contribute to integrin-mediated adhesion during development. A valuable new approach is to link the proteins to a fluorescent protein, green fluorescent protein, so that we can see where the protein is within the cells of a living embryo, and see how the integrin adhesive junctions are formed.



Talin (in black) becomes concentrated at sites of integrin function late in embryogenesis (bottom) compared with its general cytoplasmic distribution early in development (top).

Brown, N.H., Gregory, S.L. and Martin-Bermudo, M.D. (2000) Integrins as mediators of morphogenesis in *Drosophila*. **Dev. Biol.** *223*, 1–16.

Martin-Bermudo, M.D. and Brown, N.H. (2000) The localized assembly of extracellular matrix integrin ligands requires cell-cell contact. **J. Cell Sci.** *113*, 3715–3723.

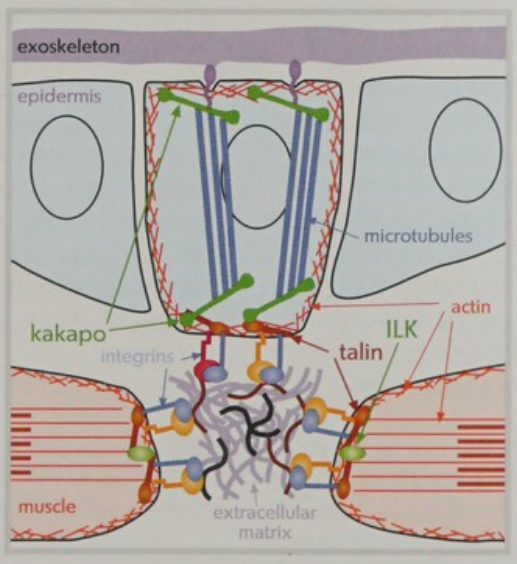
Zervas, C.G., Gregory, S. L. and Brown, N. H. (2001) *Drosophila* integrin linked kinase is required at sites of integrin adhesion to link the cytoskeleton to the plasma membrane. **J. Cell Biol.**, *in press.*

For further publications, see numbers 19 and 20 on page 50.

(Left) Integrin-linked kinase fused with green fluorescent protein (green) is in close proximity to integrins (red; the combination of the two appears yellow) in the developing embryo.

(Below) Building up a picture of the molecules involved in integrin-mediated adhesion

(Left) Examination of actin (red) and integrin-linked kinase (ILK; green) in the muscles of an embryo lacking one of the other intracellular components of integrin-mediated adhesion. Many of the detached muscles retain ILK at their ends, demonstrating that this component is not required for the positioning of ILK at the ends of the muscles.



JOHN GURDON

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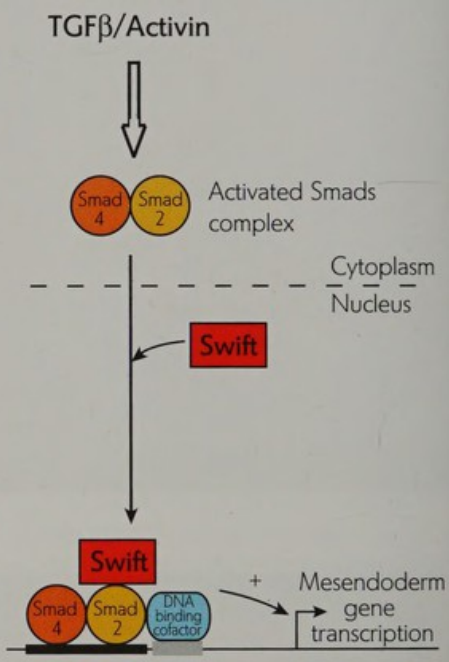
AARON ZORN

Our major interest is to analyse mechanisms of gene activation and cell fate determination in early vertebrate development. In several cases, cells activate different genes according to the concentration of a single signalling molecule, which is therefore described as a morphogen. We have concentrated on a detailed analysis of how activin, a member of the transforming growth factor β-family of signalling molecules and a candidate for a natural vertebrate inducer, can direct *Xenopus* blastula cells into many different cell fates. Three fold increases in the concentration of activin to which a *Xenopus* blastula cell is exposed lead to equivalent increases in the absolute number of ligand-bound receptors, and to completely different pathways of differentiation. We are now using real-time confocal imaging to analyse the quantitative transduction of activin signalling via GFP-Smad2, and the consequent promoter activity of the immediate T-box response genes *Antipodean* and *Eomesodermin*.

In parallel, we analyse how gene activation leads to a uniform and demarcated expression of genes, through the community effect. We find that eFGF can act as a community signalling factor, and that its mechanism of action is very different from that of activin, though both have concentration related effects.

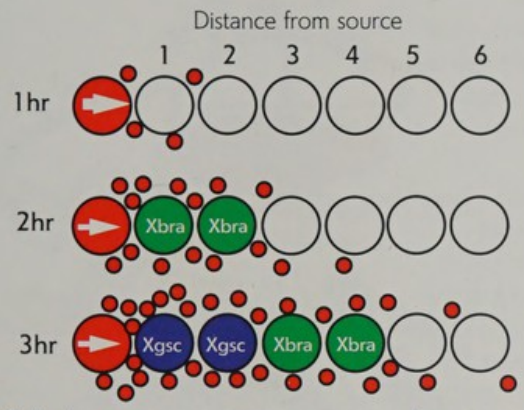
Complementary to the above work, we are using nuclear transplantation to reprogramme cell differentiation, thereby generating a wide range of gene expressions and cell-types from the nuclei of somatic cells. The combination of nuclear transfer and morphogen action may help to reprogramme cancer cells and to facilitate therapeutic cloning.



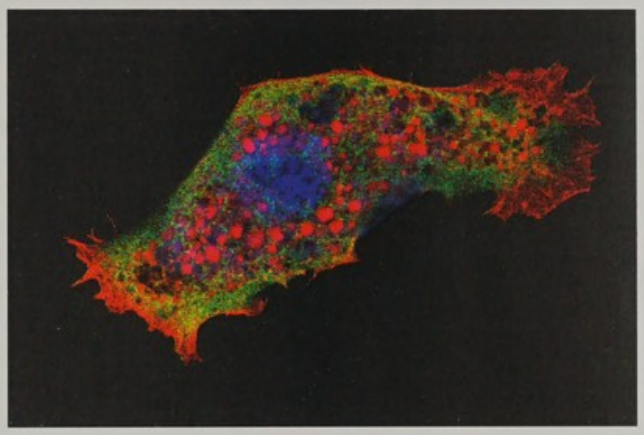
Swift is a new member of the TGFβ signalling pathway

Gurdon, J. B., Dyson, S. and St Johnston, D. (1998) Cells' perception of position in a concentration gradient. **Cell** *95*, 159–162.
Gurdon, J.B. and Colman, A. (2000) The future of cloning. **Nature** *402*, 743–746.
Standley, H.J., Zorn, A.M. and Gurdon, J.B. (2001) eFGF and its mode of action in the community effect during *Xenopus* myogenesis. **Development,** *in press.*

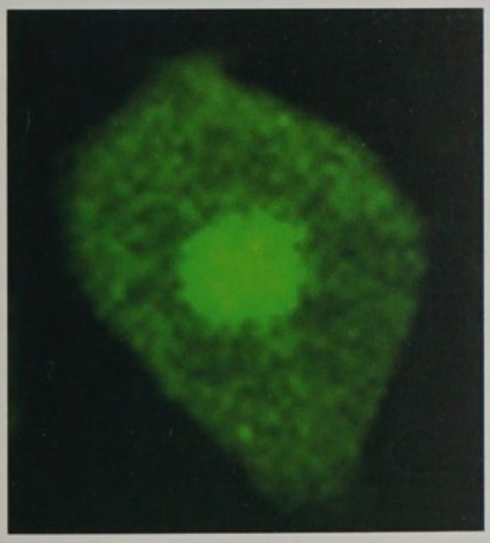
For further publications, please see numbers 22, 41–42, 47, 58, 84 and 86 between pages 50 and 54.



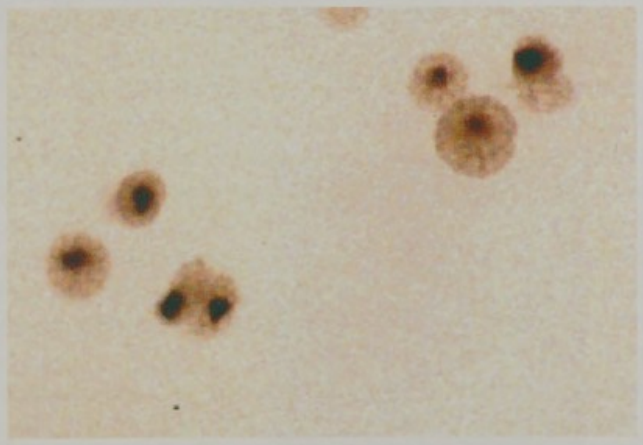
Cells change gene response as a morphogen gradient is formed.



A single cell can sense its position in a morphogen gradient.



Confocal view of GFP-Smad2 entering the nucleus of an activin induced cell.



eFGF behaves as a community factor to activate muscle genes in single cells.

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To maintain genomic integrity, eukaryotic cells have developed elaborate pathways to detect, signal and repair DNA damage. In our studies of the molecular basis of these important processes, we are using several approaches and exploiting the extensive similarities among the signalling pathways of different organisms.

One DNA damage signalling pathway that we have studied in depth is the *MEC1* pathway of *Saccharomyces cerevisiae*. We have recently found a new component of this pathway (Fig. 1) and have determined how components of the signalling pathway physically interact with each other (Fig. 2). In addition, we have investigated how *MEC1*-dependent phosphorylation of a core yeast histone in response to DNA damage may alter chromatin structure and facilitate DNA repair. We are using the information gained from these studies in our investigations of equivalent pathways in human cells.

This multi-organism approach has also been fruitful in the study of telomere maintenance. Work in yeast has indicated that several factors involved in DNA double-strand break repair are also involved in telomere maintenance. We have now found that the same is true in mammalian cells (Fig. 3).

A second interest within our group is the study of transcription in Archaea, a domain of life distinct from Bacteria and Eucarya. The archaeal basal transcription machinery corresponds to the core components of the eucaryal pol II apparatus. Notably, however, transcriptional regulators in Archaea are more closely related to those in bacteria. Thus, our studies are yielding insights into the fundamental mechanisms and evolution of transcriptional control.

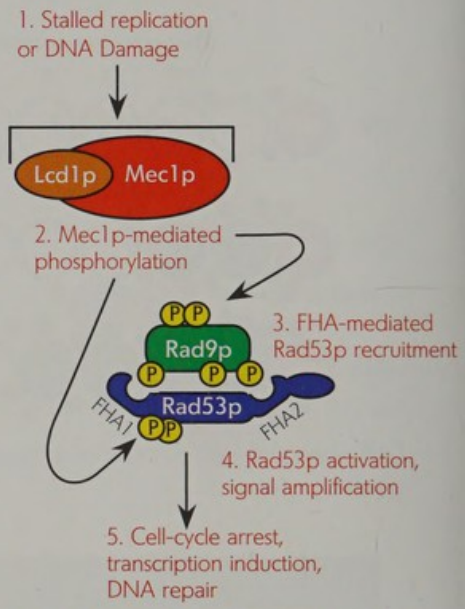


Fig. 1. When DNA is damaged or its replication blocked, the cell cycle must be halted to allow time for the cell to repair the damage or complete replication. In yeast, the *MEC1* pathway, a complex protein phosphorylation cascade, is activated in response to DNA damage or replication inhibition. We have recently discovered a novel protein, Lcd1p, which is an essential factor in the *MEC1* pathway and which functions at or very close to the DNA lesions.

Downs, J. A., Lowndes, N.F. and Jackson, S.P. (2000) A role for *Saccharomyces cerevisiae* histone H2A in DNA repair. **Nature** *408,* 1001–1004.

Durocher, D., Taylor, I.A., Sarbassova, D., Haire, L.F., Westcott, S.L., Jackson, S.P., Smerdon, S.J. and Yaffe, M.B. (2000) The molecular basis of FHA domain–phosphopeptide binding specificity and implications for phosphodependent signaling mechanisms. **Mol. Cell** *6,* 1169–1182.

Rouse, J. and Jackson, S.P. (2000) LCD1: an essential gene involved in checkpoint control and regulation of the *MEC1* signalling pathway in *Saccharomyces cerevisiae*. **EMBO J.** *19,* 5801–5812.

For further publications, see numbers 9–13, 23, 31, 50, 54, 70, 92 and 97 on pages 49–54.

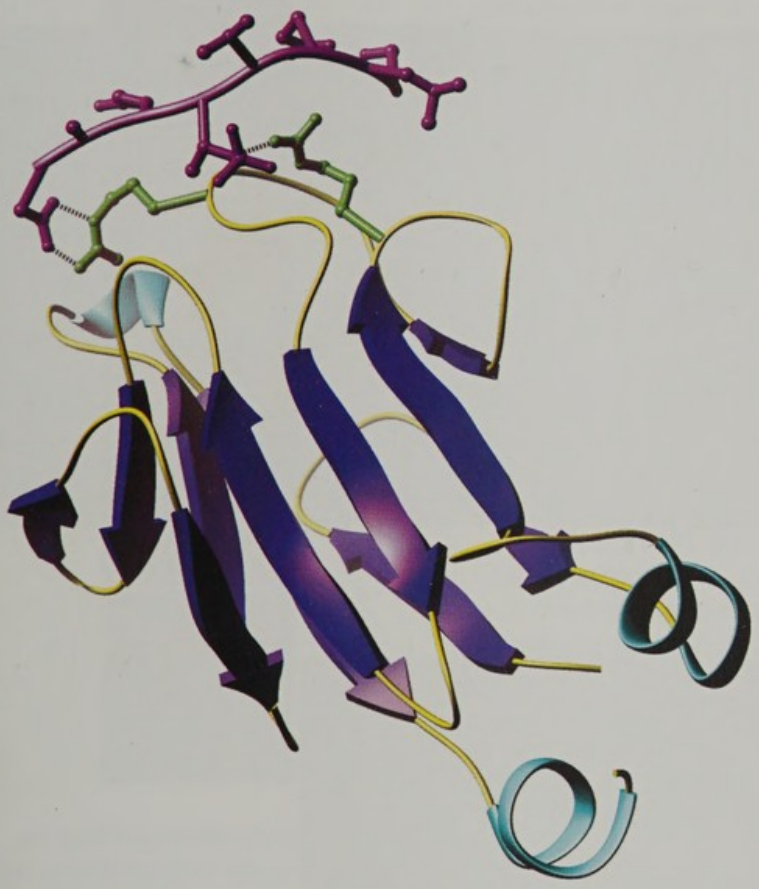
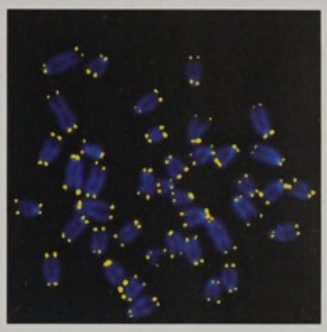


Fig. 2. Several proteins involved in DNA damage signalling contain a phospho-dependent protein–protein interaction module called the forkhead associated (FHA) domain. Yeast Rad53p contains two FHA domains that interact with phosphopeptides in Rad9p produced in response to DNA damage. Shown here is the structure of Rad53p-FHA1 and an optimal phosphopeptide derived from Rad9p (at the top of the figure). Collaboration with Stephen Smerdon (London, UK) and Michael Yaffe (Boston, MA, USA).



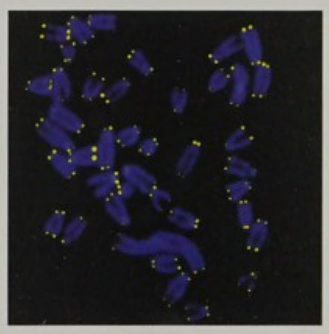


Fig. 3. Telomeres are structures at chromosome ends that contribute to chromosomal stability. At the top are normal metaphase mouse chromosomes (stained with DAPI) that have been hybridised to a telomeric probe (yellow). The figure below shows how the chromosomes taken from a mouse lacking Ku80, a protein involved in DNA double-strand break repair, exhibit telomeric shortening and chromosomal abnormalities. Collaboration with M. Prakash Hande (Columbia University, NY, USA).

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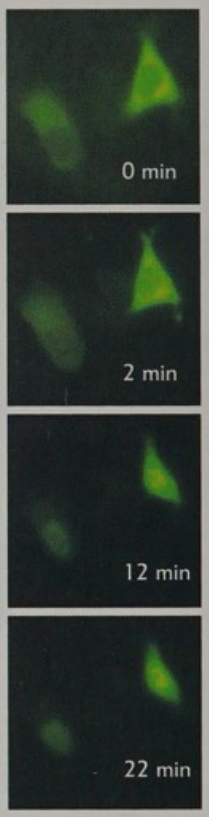
Many transcriptional regulators are found de-regulated in cancer. Our group is interested in defining the mechanisms by which such transcription factors function during normal cell proliferation and in cancer.

Our attention is focused on a set of enzymes which modify histones and regulate transcription via chromatin remodelling. Our analysis of acetylases, which stimulate transcription, has shown that one enzyme, p300, is found mutated in many different human cancers, and that this enzyme has several substrates other than histones. Dissection of histone deacetylases, which repress transcription, has shown that a specific enzyme, HDAC4, is involved in inducing the myogenic programme. In contrast, a distinct enzyme, HDAC1, acts as a co-repressor for the RB tumour suppresser protein and is therefore implicated in the G1/S cell cycle checkpoint. A role for HDAC1 in DNA methylation has also been highlighted by the finding that it forms a complex with DNA methylases.

Very recently our attention has turned to histone methylation, whose function is not well understood. We have identified a transcriptional repressor, HP1, which recognises and binds histone H3 when methylated at lysine 9. Methylation of histone H3 and the subsequent recruitment of HP1 leads to the formation of transcriptionally silent heterochromatin. We suspect that histone methylation is a widely used mechanism for the silencing of gene expression.



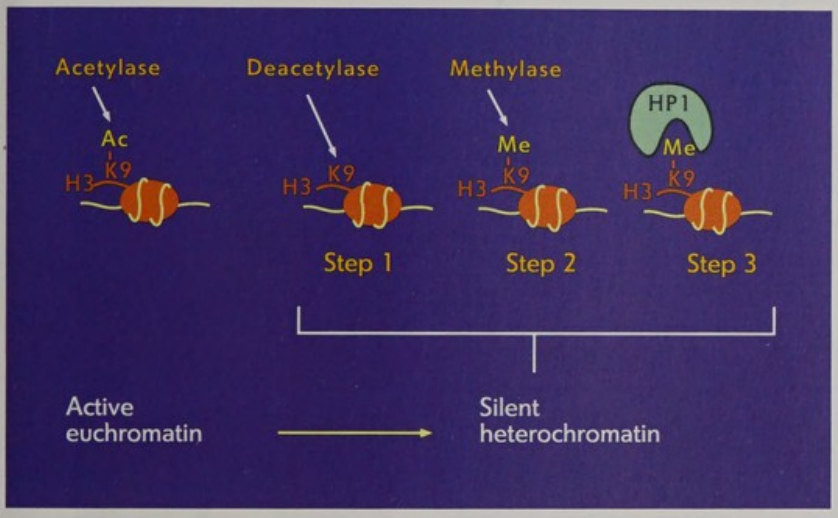
GFP-HDAC4 translocates from the cytoplasm to the nucleus following the inhibition of nuclear export by leptomycin B treatment.

Bannister, A.J., Zegerman, P., Partridge, J.F., Thomas, J., Miska, E.A., Allshirre, R.C. and Kouzarides, T. (2001) Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. **Nature,** *in press.*

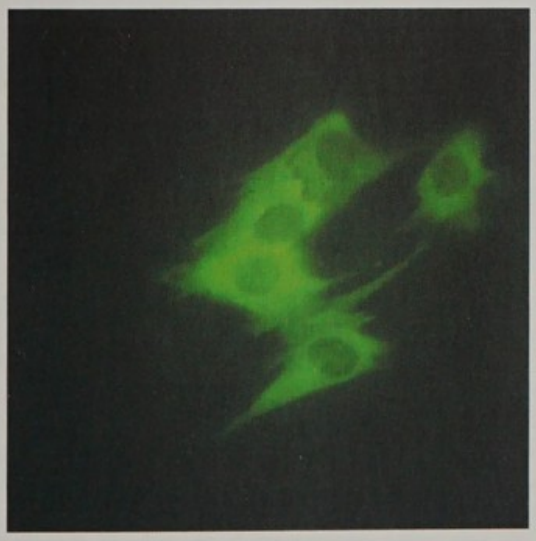
Fuks, F., Burgers, W.A., Brehm, A., Hughes-Davies, L. and Kouzarides, T. (2000) DNA methyltransferase Dnmt1 associates with histone deacetylase activity. **Nat. Genet.** *24,* 88–91.

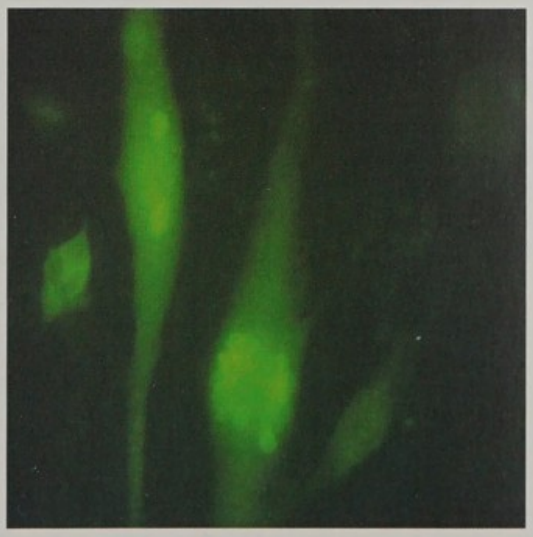
Martinez-Balbas, M.A., Bauer, U-M., Nielsen, S.J., Brehm, A. and Kouzarides, T. (2000) Regulation of E2F1 activity by acetylation. **EMBO J.** *19,* 662–671.

For further publications, see numbers 7–8, 16, 34, 45, 51, 56, 68–69, 90, 93 and 98 on pages 49–54.



Model for the steps necessary in the formation of transcriptionally repressed heterochromatin





Differentiation of myoblasts (left) into myotubes (right) induces translocation of GFP-HDAC4 from the cytoplasm to the nucleus.

RON LASKEY

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DAVID SZUTS
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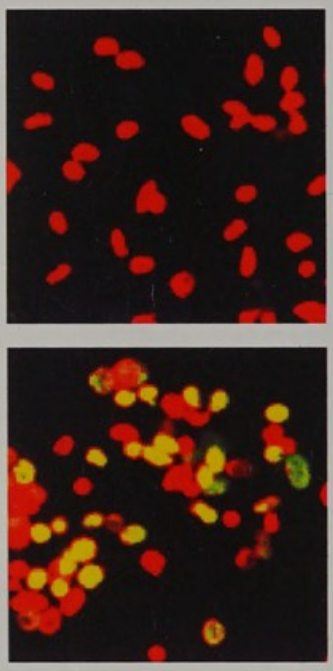
Our current research focuses on two topics, the control of eukaryotic chromosome replication and DNA replication proteins as diagnostic cancer markers. We have used cultured human cells to develop a family of cell-free systems that initiate DNA replication efficiently *in vitro*. We have focused our attention on proteins that regulate DNA replication by assembling a pre-replication complex on unreplicated DNA. These proteins are the origin recognition complex ORC, Cdc6 and proteins of the MCM family. The presence of MCM proteins distinguishes replicated DNA from unreplicated DNA, as MCMs are displaced during replication.

Using the human DNA replication cell-free systems, we have shown that competence of G1 nuclei to respond to S-phase factors depends on Cdc6 and specific combinations of cyclins with cyclin-dependent kinases (CDKs). We found CDKs determine the location and stability of Cdc6 helping to explain how DNA replication is coupled to the cell-cycle.

We have exploited MCM proteins as markers for proliferating cells, to develop an immuno-enhanced cervical smear test. We are able to combine immunostaining for Mcm5 with the conventional Papanicolaou stain, and we are testing the ability of this combination to decrease false negatives in cervical smear tests. We are extending this approach to other forms of cancer, including cancer of the colon, lung and bladder.

We have also developed a simple test to detect S-phase cells that were making DNA in tissue biopsies. We are testing its value in diagnostic pathology.



DNA replication (yellow) in 3T3 Cell nuclei in buffer (top) or in S-phase cytosol (bottom)

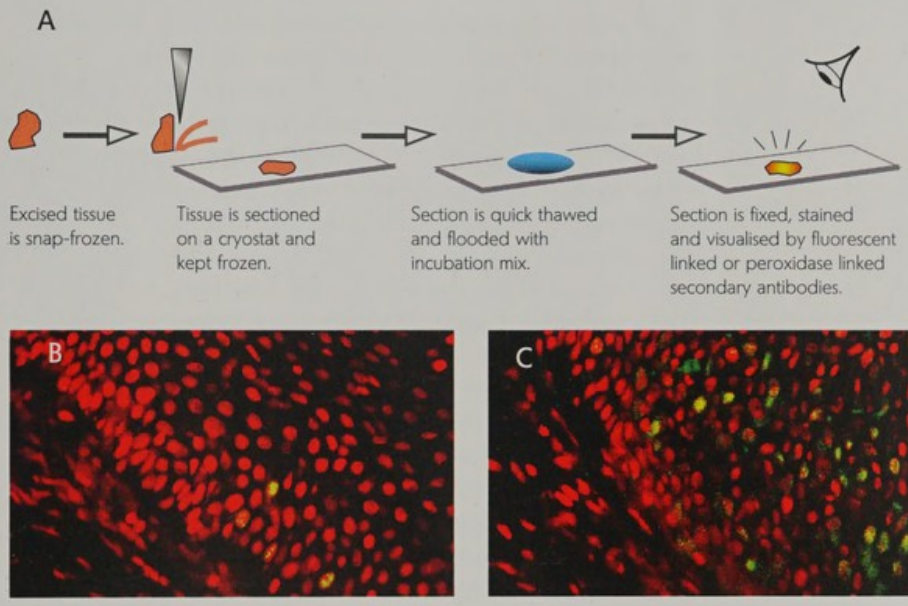
Mills, A.D., Coleman, N., Morris, L.S. and Laskey, R.A. (2000) Detection of S-phase cells in tissue sections by in situ DNA replication. **Nat. Cell Biol.** *2,* 244–245.

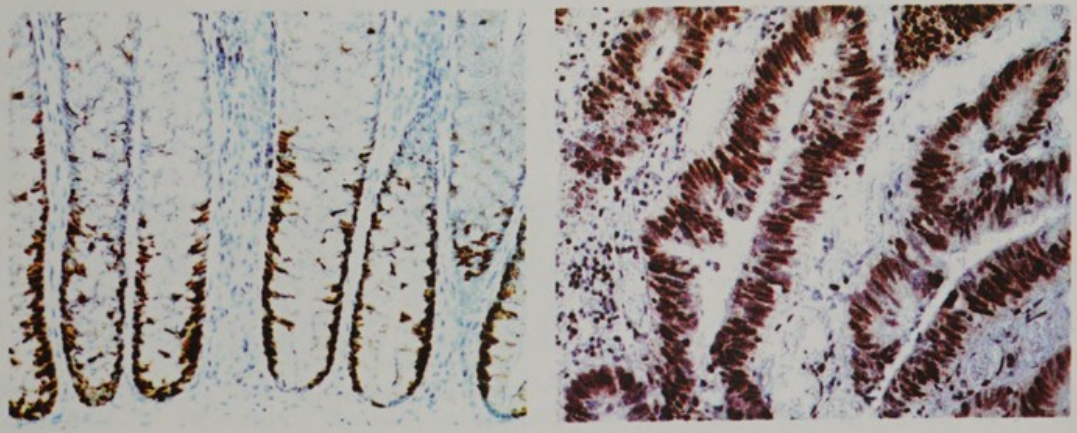
Pelizon, C., Madine, M.A., Romanowski, P. and Laskey, R.A. (2000) Unphosphorylatable mutants of Cdc6 disrupt its nuclear export but still support DNA replication once per cell cycle. **Genes Dev.** *14,* 2526–2533.

Williams, G.H., Romanowski, P., Morris, L., Madine, M., Mills, A.D., Stoeber, K., Marr, J., Laskey, R.A. and Coleman, N.C. (1998) Improved cervical smear assessment using antibodies against proteins that regulate DNA replication. **Proc. Natl. Acad. Sci. USA** *95,* 14932–14937.

For further publications, see numbers 25, 53, 64, 75, 80 and 96 between pages 50 and 54.

In situ DNA replication to detect S-phase cells in tissue biopsies. Frozen sections of normal (B) or CIN3 (C) cervix are incubated in a buffer containing a labelled DNA precursor (A). Incorporation of the precursor is detected by fluorescein-streptavidin (green) and nuclei are stained red with propidium iodide.





MCM staining of normal human colon (left), showing MCM proteins in nuclei only at the base of crypts, and of an adenocarcinoma of the colon (right).

ANNE McLAREN

Co-workers:

IAN ADAMS
GABRIELA DURCOVA-HILLS
MARGARET TYCE-BUTCHER

Our research focuses on the cellular and molecular basis of the various developmental pathways open to mouse primordial germ cells, both *in vivo* and *in vitro*. In the embryonic testes, the male germ cells undergo a period of mitotic arrest; but elsewhere (in the embryonic ovary, extra-gonadally, or in *ex vivo* tissue aggregates), we have established that entry into meiotic prophase appears to be the default state, irrespective of the germ cells' own sex chromosome constitution (XX or XY). We are investigating certain genes, isolated by subtractive hybridisation, that may play a role either in entry into meiosis or in cell cycle arrest.

In vitro we are making cell lines from germ cells during their migratory period, after entry into the gonad, and after birth, in order to study their differentiation under different conditions of culture and in different types of *ex vivo* tissue aggregate. The transition from germ cells to pluripotent embryonic germ (EG) cells involves changes in gene expression and cell behaviour, but little change in cell morphology. These immortalised cell lines will also be used to examine DNA methylation patterns, as an indication of the erasure of genomic imprinting in the germline.

Immunofluorescence of mouse embryonic oocytes showing assembly of the synaptonemal complex (green) during meiotic prophase.

Adams, I. and Kilmartin, J.V. (2000) Spindle pole body duplication: a model for centrosome duplication? **Trends Cell Biol.** *10,* 329–335.

Durcova-Hills, G., Tokunaga, T., Kurosaka, T., Yamaguchi, M., Takahashi, S. and Imai, H. (2000) Immunomagnetic isolation of primordial germ cells and the establishment of embryonic germ cell lines in the mouse. **Cloning** *1,* 217–224.

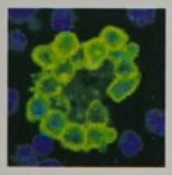
McLaren, A (2000) Germ and somatic cell lineages in the developing gonad. **Mol. Cell Endocrinol.** *163,* 3–9.

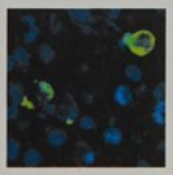
McLaren, A. (2000) Establishment of the germ cell lineage in mammals. **J. Cell Physiol.** *182,* 141–143.

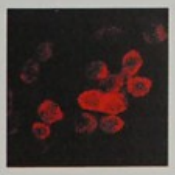
McLaren, A. (2000) Cloning: Pathways to a pluripotent future. **Science** *288,* 1775–1780.

For further publications see numbers 62–63 and 85 on pages 52 and 54.

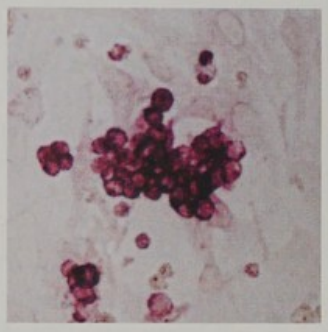
New EG cell lines carrying different transgenes have been established in our laboratory. An 11.5-day post coitum EG cell line expressing green fluorescent protein was used to follow the fate of EG cells in chimeric embryos. Our results showed that the EG cells (green) preferentially colonised the epiblast in the gastrulating embryo (left panel), but were also capable of colonising the primary endoderm. An EG cell line carrying a LacZ transgene was also established from migrating primordial germ cells of 9.5-day post coitum embryos. EG cells (blue) were injected into blastocysts and chimeric embryos were recovered on day 15 with high contribution of EG cells (right panel).

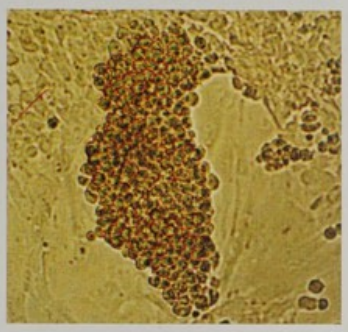




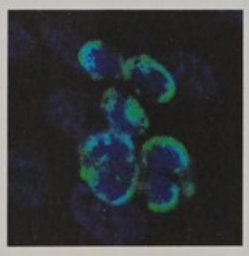


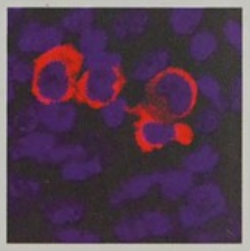
Cell suspension of primordial germ cells and somatic cells were immuno-stained for expression of the SSEA-1 antigen (left panel, green), for germ cell nuclear antigen (middle panel, green), mouse vasa homolog (right panel, red). Nuclei are counterstained blue in the left and centre panels.





Spermatogonial cells isolated from neonatal testes proliferate to form small colonies after 4 days in culture (left panel). Spermatogonial cells can be identified by their high alkaline phosphatase activity (red). After prolonged culture, spermatogonial cells form large multilayered colonies (right panel).





Spermatogonial cells after short-term culture stained for germ cell nuclear antigen (left panel, green) and mouse vasa homolog (right panel, red). Nuclei are counterstained blue.

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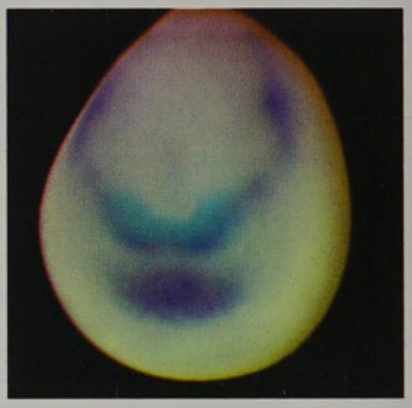
During embryonic development, neuroectodermal cells exit the cell cycle and differentiate in a stereotypical spatial and temporal pattern. The spatial and temporal control of neurogenesis is important for regulating cell type specification and the final number of differentiated cells. To understand how this control is achieved, we use the frogs *Xenopus laevis* and *Xenopus tropicalis* as a model system and a combination of molecular and classical embryology.

We have found that *XBF-1* is a winged helix transcription factor that acts as a suppressor or an activator of neuronal differentiation at a high and low concentration, respectively. Thus, when an ectodermal area expresses high levels of *XBF-1* and is surrounded by an area of lower expression, neurogenesis is induced at the borders of the high expression domain. We have suggested that the localised expression of dual function transcription factors such as *XBF-1* may represent one mechanism that the embryo uses to position neurogenesis. Recently, we have found that *XBF-1* also affects the proliferation of neuroectodermal cells by controlling the transcription of a cell cycle regulating factor, linking the control of differentiation with that of division.

With regards to the temporal order of neurogenesis, we have found that in early development it is controlled by an intrinsic difference in the competence of ectodermal cells to respond to neurogenesis inducing factors. Our data also suggest that this differential competence is likely to be established as a result of asymmetric cell divisions that take place at the blastula stage. We aim to exploit this aspect of early *Xenopus* development as a model system to understand the temporal control of neurogenesis in vertebrates.

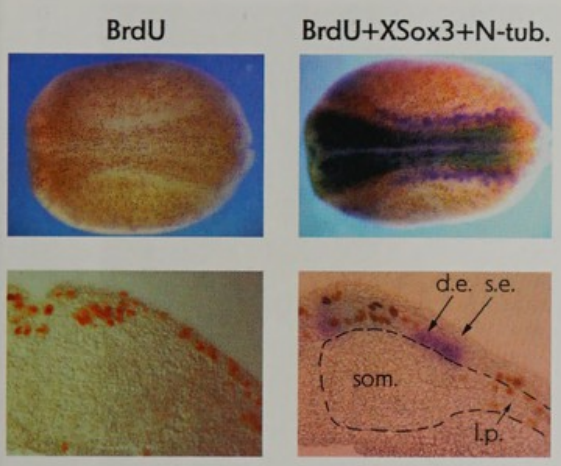


Localised gene expression in the anterior neural plate. *Xdll3* (purple) and *XBF-1* (light blue).

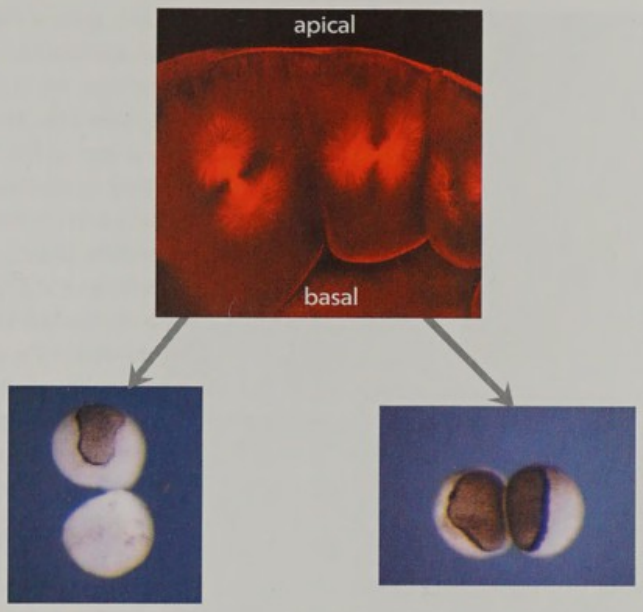
Bourguignon, C., Li, J. and Papalopulu, N. (1998) *XBF-1*, a winged helix transcription factor with dual activity, has a role in positioning neurogenesis in *Xenopus* competent ectoderm. **Development** *125,* 4889–4900.

Hardcastle, Z., Chalmers, A.D. and Papalopulu, N. (2000) FGF-8 stimulates neuronal differentiation through FGFR-4a and interferes with mesoderm induction in *Xenopus* embryos. **Curr. Biol.** *10,* 1511–1514.

Hardcastle, Z. and Papalopulu, N. (2000) Distinct effects of XBF–1 in regulating the cell cycle inhibitor p27XICI and imparting a neural fate. **Development** *127,* 1303–1314.

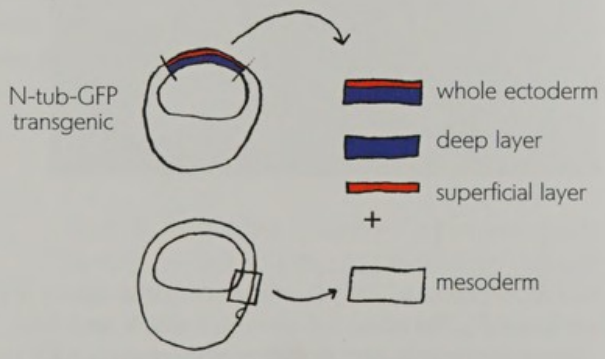


Neurogenesis is spatially and temporally controlled. Early differentiating neurons appear in defined domains (BrdU negative, *N-tubulin* positive: purple). Most cells on the neural plate do not differentiate at this stage but continue to divide (positive for BrdU, brown, and *XSox3*, light blue). Som., somites; d.e., deep ectoderm; s.e., superficial ectoderm; l.p., lateral plate mesoderm.



Oriented cell divisions at the blastula stage give rise to an inner (unpigmented) and outer (pigmented) population of ectodermal cells.

whole ectoderm + mesoderm | deep layer + mesoderm | superficial layer + mesoderm | N-tub-GFP transgenic



Inner and outer ectodermal cells differ in their ability to undergo early neuronal differentiation in response to signals from the mesoderm. Neurons express GFP driven by the N-tubulin promoter.

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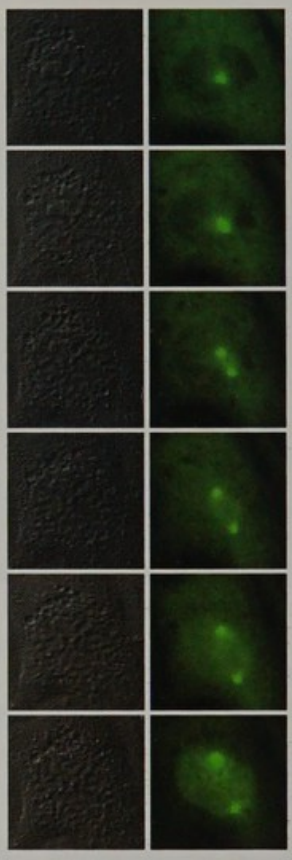
ROB WOLTHUIS

We are studying how cells control their division and are following two parallel approaches to this question. In one we are concentrating on how the proteins that trigger the entry into mitosis are regulated by their subcellular localisation. These proteins, such as the cyclins, the CDKs and the Cdc25 phosphatases, alter their localisation as cells progress through the cell cycle. Therefore, particular proteins can only interact with each other in specific places and at specific times. We are able to assay this behaviour in real time by time-lapse fluorescence and DIC video microscopy using GFP-fusion proteins. We use this assay to define the domains of the proteins that target them to specific subcellular structures, and to determine how their localisation is altered depending on the stage of the cell cycle. After defining these domains we use them to isolate the proteins that are responsible for targeting and controlling the subcellular location of mitotic regulators.

Our second avenue of research is directed towards understanding how proteolysis is used to regulate progress through mitosis. Again we are able to assay this in real time using GFP-fusion proteins, because fluorescence is directly related to the amount of a GFP-fusion protein. We are investigating the behaviour of key substrates at each stage of mitosis, including cyclin A, cyclin B1 and securin, and are using these to define the events and the mechanisms that trigger the destruction of specific proteins at specific times and in specific places.



Cyclin B1 translocates into the nucleus at the end of Prophase. Simultaneous fluorescence and DIC images of a cell expressing cyclin B1-GFP.

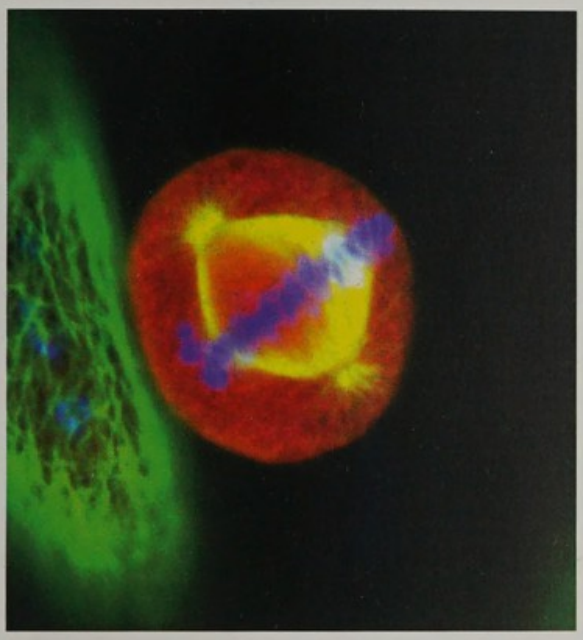
Clute, P. and Pines, J. (1999) Temporal and spatial control of cyclin B1 destruction in metaphase. **Nat. Cell Biol.** *1*, 82–85.

Draviam, V.M., Orrechia, S., Lowe, M., Pardi, R. and Pines, J. (2001) The localisation of human cyclins B1 and B2 determines their substrate specificity and neither enzyme requires MEK to disassemble the Golgi apparatus. **J. Cell Biol.**, *in press*.

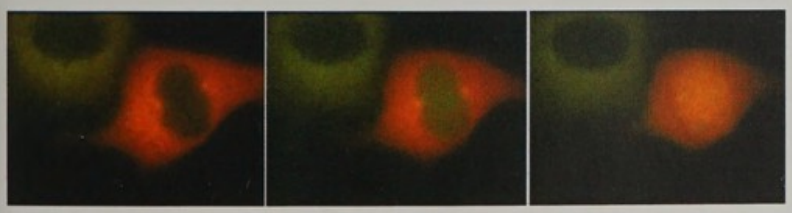
Furuno, N., den Elzen, N. and Pines, J. (1999) Human cyclin A is required for mitosis until late prophase. **J. Cell Biol.** *147*, 295–306.

Hagting, A., Jackman, M., Simpson, K. and Pines, J. (1999) The translocation of cyclin B1 to the nucleus at prophase requires a phosphorylation-dependent nuclear import signal. **Curr. Biol.** *9*, 680–689.

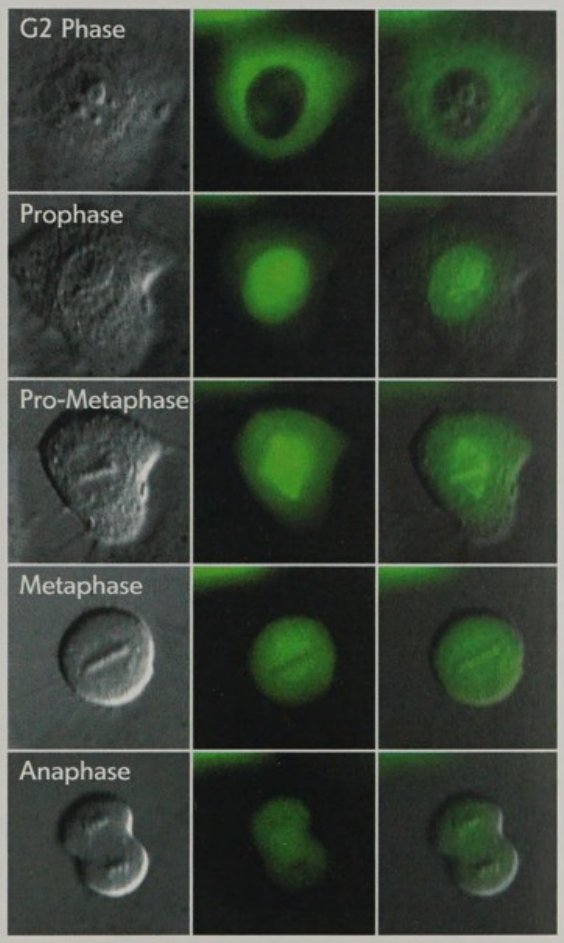
For further publications, see numbers 69 and 76 on page 53.



The Cks1 subunit has a markedly different localisation from cyclin B1 in mitosis. Mitotic HeLa cell stained with anti-Cks1 (red), anti-tubulin (green) and DAPI (blue).

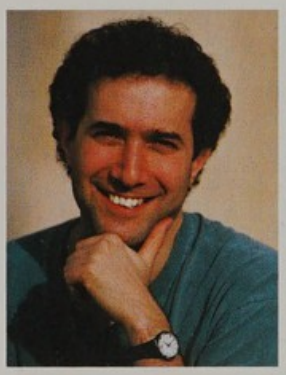


Cyclin B1 has to be phosphorylated to enter the nucleus. Wild type cyclin B1 was linked to GFP (green) and a non-phosphorylatable mutant linked to YFP (red). Only the wild type protein can enter the nucleus (middle panel) before nuclear envelope breakdown (right panel).



Cyclin B1–degradation visualised in real time. Cyclin B1–GFP purified from baculovirus-infected cells was injected into a HeLa cell and then imaged with a cooled slow-scan CCD camera. Left panels: DIC images; middle panels: fluorescence; right panels: merged images.

JORDAN RAFF

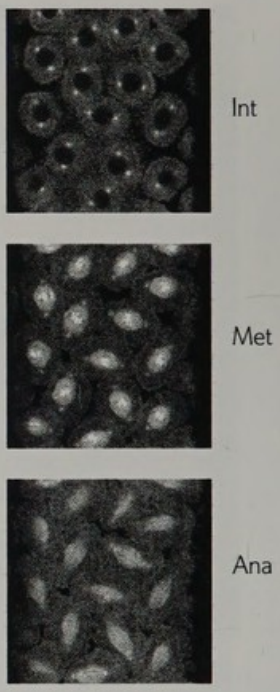


Co-workers:

FANNI GERGELY
JUNYONG HUANG
KIM JEFFERS
MICHAEL LEE
CHODAGAM SASIDHAR

The centrosome is the main microtubule organising centre in animal cells. Despite its central role in organising many cellular events, very little is known about how centrosomes function. We have taken a reductionist approach to this problem, using *Drosophila* as a model system to isolate proteins that bind to microtubules *in vitro* and associate with centrosomes *in vivo*. By studying these proteins we hope to gain a better understanding of how centrosomes function at the molecular level. One of these proteins, called D-TACC, is essential for mitotic spindle function in the early embryo. We have shown that D-TACC interacts with microtubules in association with minispindles, the *Drosophila* homologue of XMAP215, a well-characterised microtubule stabilising protein that is also strongly concentrated at centrosomes. This interaction strongly influences the stability of centrosomal microtubules: if D-TACC levels are reduced, Msps is no longer strongly concentrated at centrosomes and centrosomal microtubules are destabilised. If D-TACC levels are increased, extra Msps is recruited to centrosomes and centrosomal microtubules are stabilised.

Many cell cycle regulators are associated with centrosomes and we have started to analyse the potential role of the centrosome in regulating cell cycle events. We have made a cyclin B-GFP construct and shown that the degradation of cyclin B (an event that is crucial for the exit form mitosis) is spatially regulated within cells. Our observations suggest that centrosomes are required to initiate the destruction of cyclin B in *Drosophila* embryos, and we are currently investigating how this might be regulated at the molecular level. We have shown that the *Drosophila* anaphase promoting complex (APC) is not strongly concentrated at centrosomes, but that two regulators of the APC (fzy and fzr) are concentrated at centrosomes.

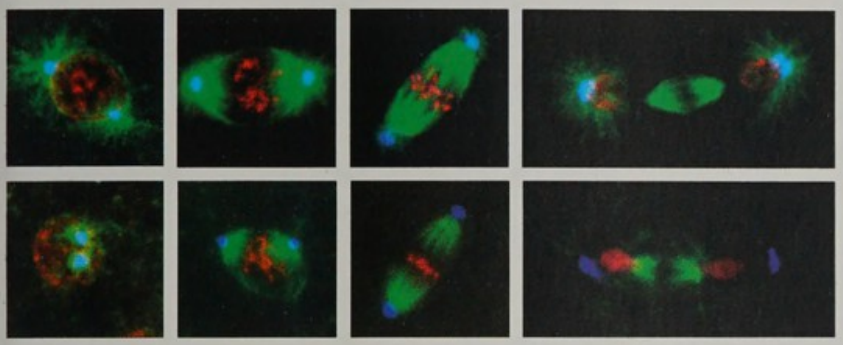


The distribution of GFP-fzy in a living embryo. GFP-fzy is concentrated at centrosomes in interphase and at centrosomes and kinetochores (the bright dots in the middle of the spindle) in metaphase. By anaphase, GFP-fzy has disappeared from the kinetochores and centrosomes.

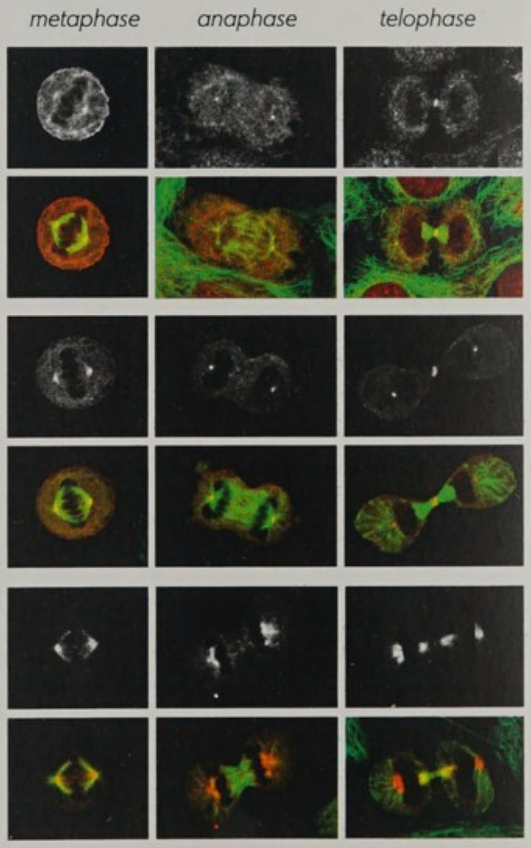
Gergely, F., Karlsson, C., Still, I., Cowell, J., Kilmartin, J. and Raff, J.W. (2000) The TACC domain identifies a new family of centrosomal proteins that can interact with microtubules. **Proc. Nat. Acad. Sci. USA** *97,* 14352–14357.

Wakefield, J.G., Huang, J-Y., and Raff, J.W. (2000) A role for centrosomes in regulating the destruction of cyclin B in early *Drosophila* embryos. **Curr. Biol.** *10,* 1367–1370.

Gergely, F., Kidd, D., Jeffers, K., Wakefield, J.G. and Raff, J.W. (2000) D-TACC: a novel centrosomal protein required for normal spindle function in the early *Drosophila* embryo. **EMBO J.** *19,* 241–252.



The distribution of DNA (red), microtubules (green) and centrosomes (blue) in normal (top panels) and *d-tacc* mutant (bottom panels) embryos. In the mutant embryos the microtubules associated with the centrosomes are too short at all stages of the cell cycle.



The distribution of the three known human TACC proteins (TACC1, TACC2 and TACC3) in human cells. The TACC proteins are shown in red and microtubules in green in the merged image.

DANIEL ST JOHNSTON

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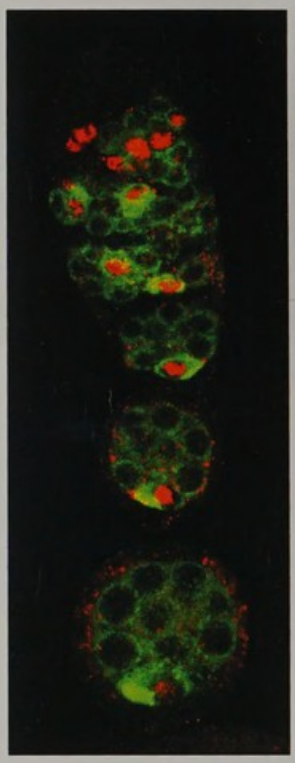
RUTH McCAFFREY
MARK SHEPPARD
JOSHUA SHULMAN
LUCIE WHITEHEAD
VITALY ZIMYANIN

The localisation of *bicoid, oskar* and *gurken* mRNAs to three distinct positions within the *Drosophila* oocyte defines the anterior–posterior and dorsal–ventral axes of the embryo, and provides an excellent model system for analysing the molecular mechanisms that underlie cell polarity and mRNA localisation. My group is taking a variety of approaches to address these questions:

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 to the basal side of dividing neuroblasts. We are currently characterising proteins that interact with Staufen to mediate mRNA transport along actin or microtubules. Since Staufen co-localises with each mRNA, we are also using GFP-Staufen to visualise mRNA transport *in vivo*.

2) The PAR-1 kinase is required for posterior localisation of *oskar* mRNA, and provides the first example of a protein that plays a conserved role in axis formation in *Drosophila* and *C. elegans*. We are now analysing the role of PAR-1 in polarising other cell types in *Drosophila* and are searching for its targets.

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



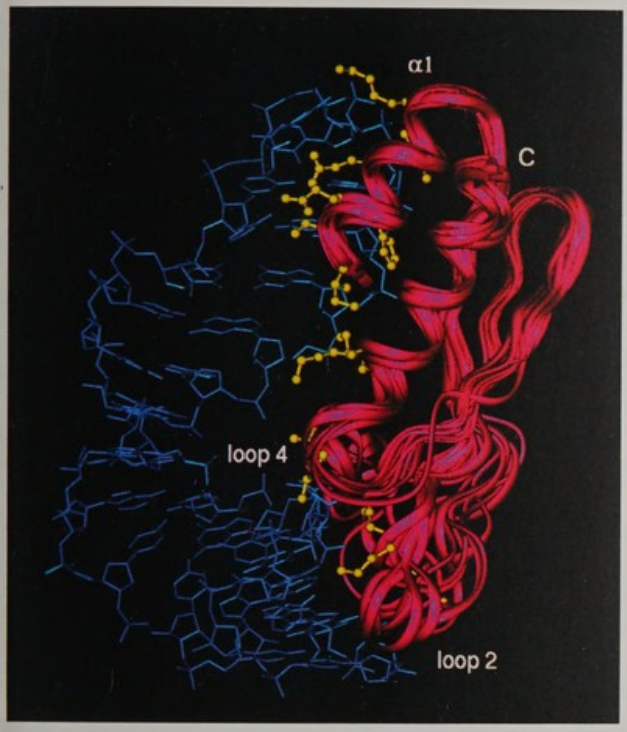
The selection of the oocyte as a *Drosophila* germline cyst moves through the germarium. Several cells per cyst initially enter meiosis and form synaptonemal complex (red) before one cell is selected to remain in meiosis and accumulates oocyte-specific proteins such as Orb (green).

Huynh, J-R., St Johnston, D. (2000) The role of BicD, Egl, Orb and the microtubules in the restriction of meiosis to the *Drosophila* oocyte. **Development** *127*, 2785–2794.

Micklem, D.R., Adams, J., Grünert, S. and St Johnston, D. (2000) Distinct roles of two conserved Staufen domains in *oskar* mRNA localization and translation. **EMBO J.** *19*, 1366–1377.

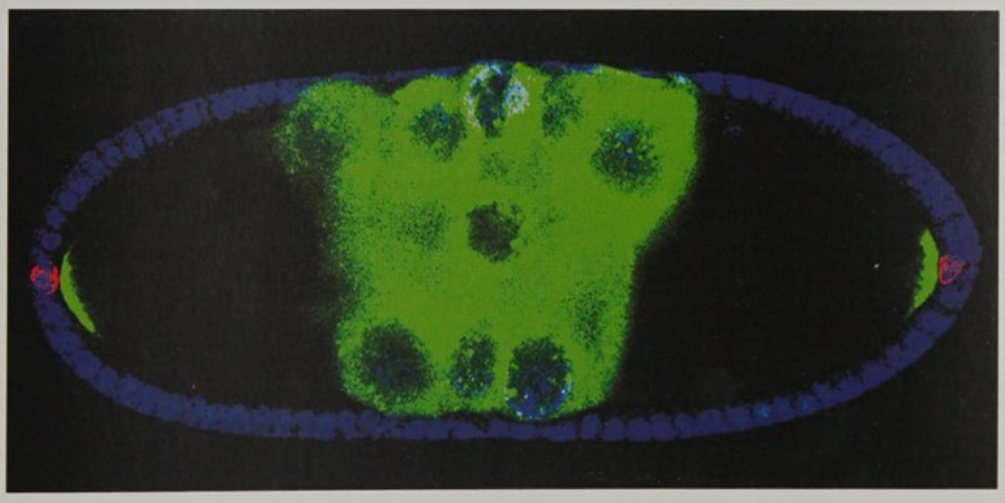
Shulman, J.M., Benton, R. and St Johnston, D. (2000) The *Drosophila* homolog of *C. elegans* PAR-1 organizes the oocyte cytoskeleton and directs *oskar* mRNA localization to the posterior pole. **Cell** *101*, 377–388.

For further publications, see number 78 on page 53.



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).

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



A fused egg chamber with two oocytes of opposite polarity, marked with GFP-Staufen (green), Fasciclin III (red) and a nuclear stain (blue). The fusion was caused by a follicle cell clone of *agro*, a novel component of the Notch pathway.

JIM SMITH

Co-workers:

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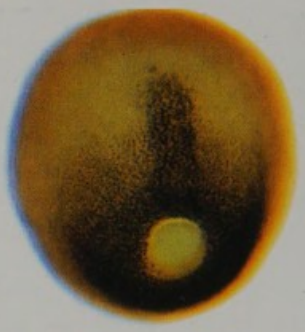
DUNJA KNAPP
SARA MERCURIO
NIGEL MESSENGER
OLAF PIEPENBURG
YASUSHI SAKA
SHANKAR SRINIVAS
RICHARD WHITE
HUW WILLIAMS

Our research addresses the mechanisms by which the mesoderm of the vertebrate embryo is formed. Most of the work involves use of the amphibian species *Xenopus laevis* and *Xenopus tropicalis*, but we also make use of zebrafish embryos when appropriate. We are interested in studying mesoderm-inducing signals such as the nodal-related genes and derrière, in the signal transduction pathways used by these factors (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 making extensive use of morpholino anti-sense oligonucleotides to block gene function, both in *Xenopus laevis* and in the diploid species *Xenopus tropicalis*.

Much of our work concentrates on the *Brachyury* gene, which responds to mesoderm-inducing factors in a strict dose-dependent fashion and which, when mis-expressed, can cause prospective ectodermal cells to form mesoderm. *Brachyury* is also required for the morphogenetic movements of gastrulation, and we have recently identified *Wnt11* as a target of Brachyury which is required for gastrulation movements in both *Xenopus* and zebrafish. Future work will investigate the role of *Wnt11* in gastrulation using cell biology and imaging techniques. We also plan to investigate the functions of other *Brachyury* targets such as members of the Bix family of homeodomain-containing proteins and genes that regulate the cell cycle.



Expression of *Xenopus* Brachyury protein in a mid-gastrula stage embryo.

381 nucleotides 5′ of the *Xbra* transcription start site are sufficient to drive expression of a reporter gene throughout the mesoderm of a transgenic embryo, with the exception of the prospective notochord.

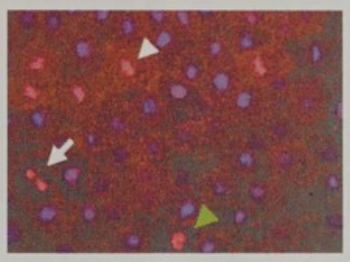
Tada, M. and Smith, J.C. (2000) Xwnt11, a target of *Xenopus Brachyury*, regulates gastrulation movements via Dishevelled, but not through the canonical *Wnt* pathway. **Development** *127*, 2227–2238.

Heisenberg, C-P., Tada, M., Saude, L., Concha, M.L., Rausch, G-J., Geisler, R.E., Stemple, D., Smith, J.C. and Wilson, S. (2000) *Silberblick/Wnt11* mediates convergent extension movements during zebrafish gastrulation. **Nature** *405*, 76–81.

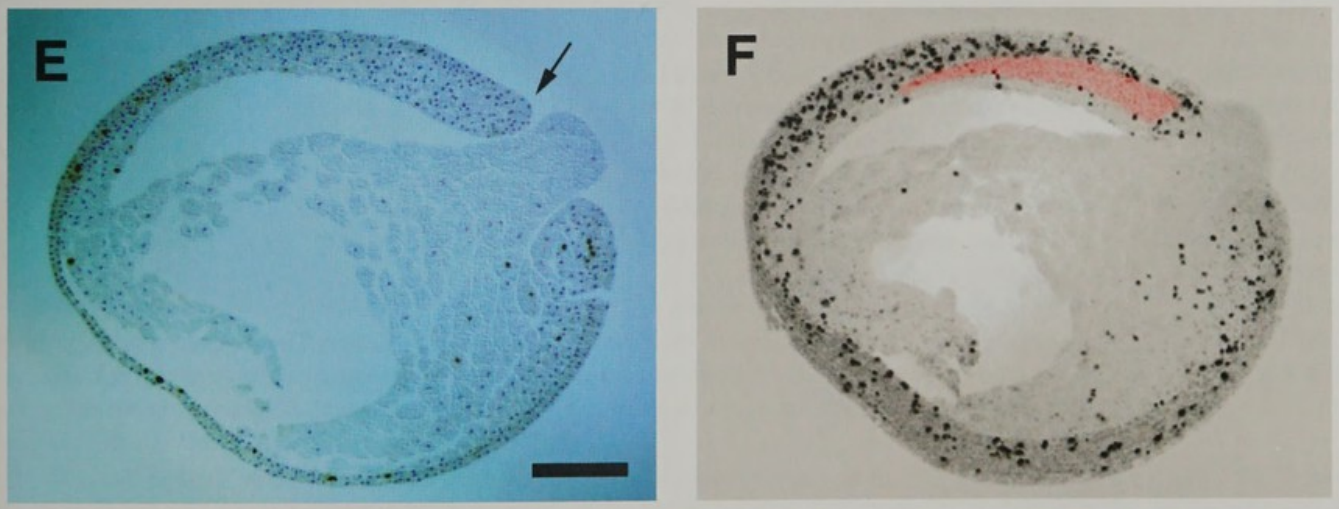
Lerchner, W., Latinkic, B.V., Remacles, J., Huylebroeck, D. and Smith, J.C. (2000) Two repressor modules in the *Xenopus Brachyury* promoter confine expression to the mesoderm during gastrulation: a study using transgenic frogs. **Development** *127*, 2729–2739.

For further publications, see number 88 on page 54.

Isolated ectodermal tissue from *Xenopus* embryos forms a sphere if cultured alone (A), but elongates in the presence of the mesoderm-inducing factor activin (B). Elongation is inhibited if Brachyury function is abolished (C).

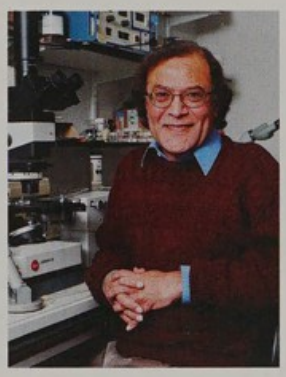


Mitotic nuclei in a *Xenopus* embryo are marked with an antibody recognising phosphorylated Histone H3 (arrows; nuclei are purple). Interphase nuclei are blue.



Left-hand panel shows a section of a gastrulating *Xenopus* embryo with interphase nuclei in purple and mitotic nuclei brown. Right-hand panel depicts a 'stack' of sections showing only mitotic nuclei. Note that the involuting dorsal mesoderm contains no mitotic cells (pink).

AZIM SURANI



Co-workers:

JUSTIN AINSCOUGH
TAKAHIRO ARIMA
KATHARINE ARNEY
SIQIN BAO
SHEILA BARTON
ROBERT DREWELL
SYLVIA ERHARDT
KATHY HILTON
ROSALIND JOHN
SANJEEV KHOSLA
JOANNA MALDONADO
MARY MALKIN
MITINORI SAITOU
IRENE SZETO
PATRICK WESTERN

We are investigating the origin of the mouse germ cell lineage, together with some of the epigenetic modifications that are unique to this lineage. Germ cells develop from the proximal epiblast cells in response to signalling molecules from the extraembryonic tissues (Fig. 1). These precursor cells are not lineage restricted as they can develop either into primordial germ cells or somatic cells. We have established single cell analysis to identify the critical events and genes, to resolve the decision-making process within individual cells towards either the somatic or germ cell fate. This should also uncover the basis for the retention or loss of totipotency in germ cells and somatic cells, respectively.

After the germ cells migrate into developing gonads, epigenetic modifications unique to this lineage follow. This includes reactivation of the X chromosome, erasure of genomic imprints and genome-wide demethylation (Fig. 2). At this time, members of the *Polycomb* (PcG) group genes may have a critical role in transcriptional regulation and for the maintenance of the germ cell lineage. Germ cells remain pluripotent until d12.5 p.c. as revealed by the derivation of embryonic germ (EG) cell lines *in vitro;* EG cells are similar to the pluripotent embryonic stem (ES) cells derived from the epiblast cells (Fig. 3). Further, we are exploring mechanisms by which epigenetic states can be reversed to confer pluripotency to differentiated somatic cells.

Following erasure of genomic imprints, new imprints are initiated during gametogenesis (Fig. 2). Imprinted genes serve diverse functions, including adult behaviour and complex physiological pathways that are unique to mammals.

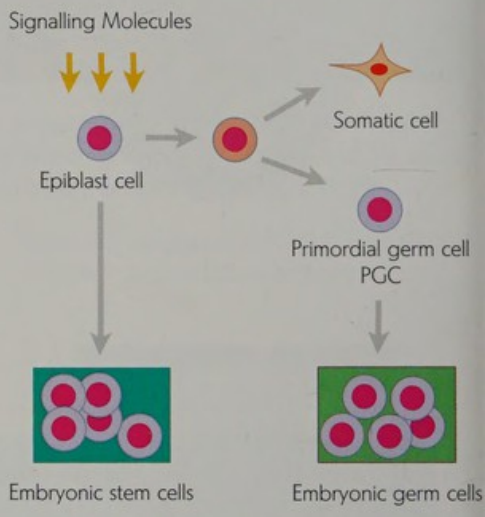


Fig. 3. The relationship between epiblast, primordial germ cells (PGCs) and pluripotent stem cells. A somatic nucleus when fused with a pluripotent EG or ES cell undergoes epigenetic modifications, including demethylation, so that it resembles pluripotent stem cells in most respects. This suggests that epigenetic states can be reversed to confer pluripotency on somatic cells.

Surani, M.A. (1999) Reprogramming a somatic nucleus by trans-modification activity in germ cells. **Seminars Cell Dev. Biol.** *10,* 273–277.

Kato, Y., Rideout III, W.M., Hilton, K., Barton, S.C., Tsunoda, Y. and Surani, M.A. (1999) Developmental potential of mouse primordial germ cells. **Development** *126,* 1823–1832.

Drewell, R.A., Brenton, J.D., Ainscough, J.F-X., Barton, S.C., Hilton, K.J., Arney, K. L., Dandolo, L. and Surani, M. A. (2000) Deletion of a silencer element disrupts H19 imprinting independently of a DNA methylation epigenetic switch. **Development** *127,* 3419–3428.

John, R.M. and Surani, M.A. (2000) Genomic imprinting, mammalian evolution, and the mystery of egg-laying mammals. **Cell** *101,* 585–588.

For further publications, see numbers 3–6, 55, 71, 73 and 83 between pages 49 and 54.

Fig.2 (right). A. Germ cells migrate into the fetal gonads by d 12.5 p.c, shown here as expressing Oct4-GFP, during which time major epigenetic modifications occur. Erasure of imprints is followed by the initiation of new imprints that are propagated after fertilisation. In the female germ line, imprinting is initiated in the growing oocytes. B. A *cis* control element (DMD) associated with the *H19* gene that confers silencing of the paternal allele. Complete or partial deletion (SIL) of the control region results in de-repression of the silent paternal allele.

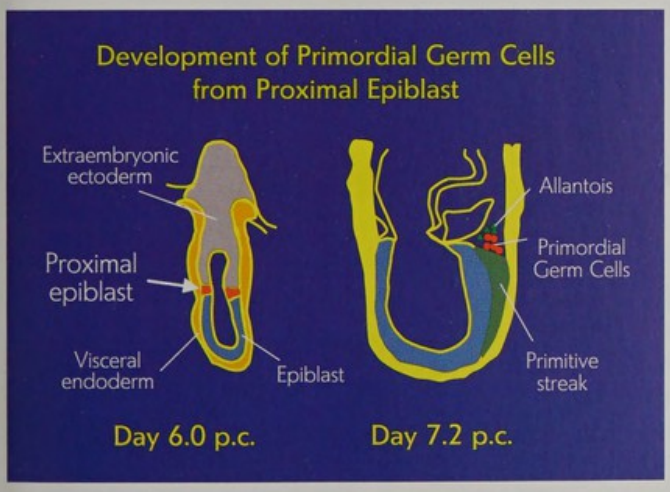
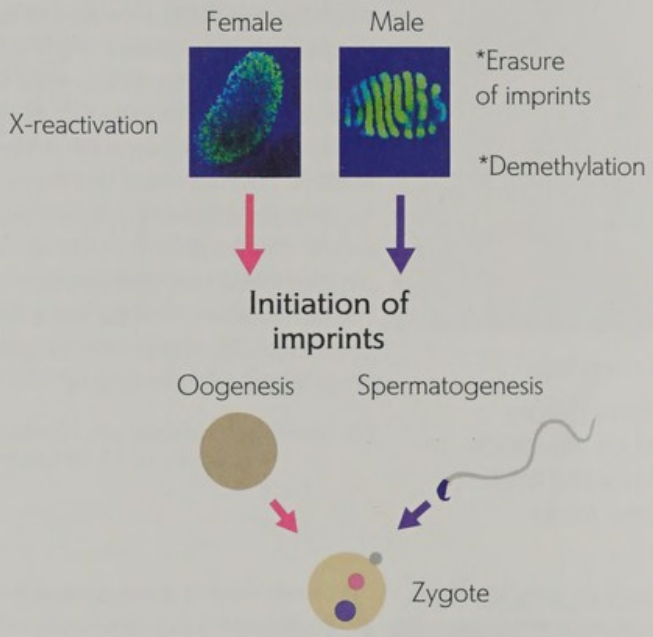


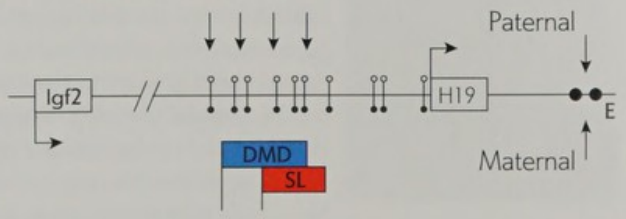
Fig. 1 (above). The proximal epiblast cells on d 6.0 p.c are the precursor cells for the germ cell lineage. They converge towards the posterior region where the primitive streak develops. These precursor cells develop either as germ cells or as somatic extraembryonic mesoderm. Approximately 40 founder primordial germ cells (PGCs) are detected at d7.2 p.c. Development of PGCs is dependent on signalling molecules from the extraembryonic ectoderm, and possibly on a second signal from the posterior region whose nature and origin is unknown.

2A Germ cells in fetal gonads at d12.5 p.c.



Pre-implantation development propagation of imprints

2B Imprinting *cis* control element



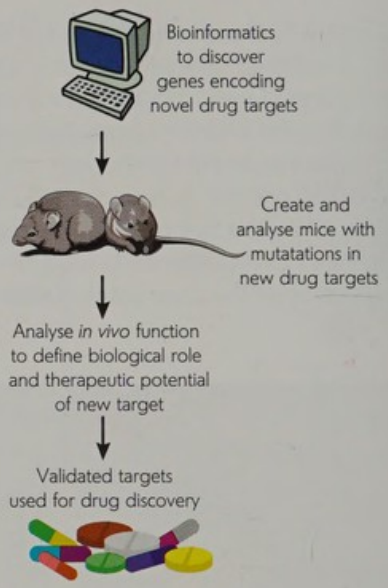
MARK CARLTON

Co-workers:

JOHN DIXON
ALAN HENDRICK
ANDREAS RUSS
DIRK ZAHN

G protein-coupled receptors (GPCRs) are a superfamily of proteins controlling a wide range of physiological pathways. GPCRs have proven to be excellent drug targets; roughly half of all modern drugs act on this class of receptor. Genome sequencing data suggest that in addition to the approximately 250 known GPCRs there is a similar number of structurally related receptors with unknown biological function. These so called orphan receptors hold great promise for drug development. In a joint project with Sam Aparicio we are using bioinformatics to identify novel orphan GPCRs which are then functionally characterised by gene disruption in mice. The identification of receptor function in development and physiology will be important to guide the development of drugs acting on these targets.

For recent publications, see numbers 82–83 on page 54.



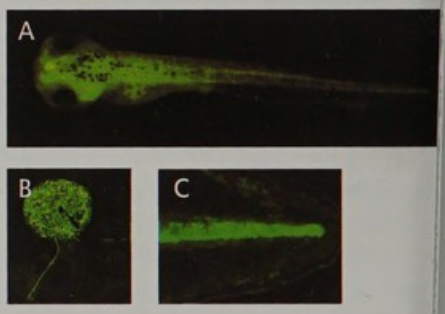
MIRANDA GOMPERTS

Co-worker:

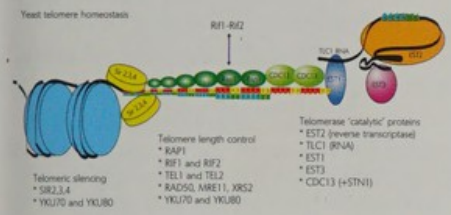
KIM GOLDSTONE

A major issue in developmental biology is how the embryo subdivides into progressively smaller regions, each with a unique identity. This project concerns the mechanism by which two such regions are specified, the notochord and the pineal gland. The earliest known transcription factor expressed by these tissues is encoded by the *not/flh* gene. Zebrafish harbouring mutations in this gene fail to form either tissue indicating that the gene functions at or near the top of a hierarchy specifying their development. In order to identify the direct regulators of the *not/flh* gene we are using transgenesis in *Xenopus*. We have also prepared a transgenic line of animals expressing GFP under the control of the *flh* regulatory elements. These animals are being used to study the development and neural networking of the pineal gland, which in *Xenopus* functions as a light sensor mediating early behavioural responses to environmental stimuli.

For recent publications, see number 15 on page 49.



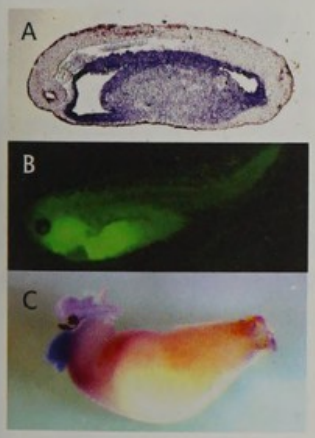
Xenopus embryos expressing GFP unde the control of *flh* regulatory sequences.
A. whole embryo
B. pineal gland
C. notochord



Inaccurately repaired DNA often features in the development of cancer. Cells have therefore evolved very efficient mechanisms for the repair of DNA that is damaged by sunlight, chemical mutagens and other agents. My research has focused on the repair of DNA double-strand breaks and, in particular, on the final step of DNA end-joining – a reaction catalysed by DNA ligase 4 (Lig4p) and regulated by its partner protein, Lif1p. In addition, more recent work has focused on how some double-strand break repair components, notably Ku, are involved in the maintenance of telomeres, the normal chromosome ends. Current investigations use a combination of yeast genetics and biochemistry to analyse how DNA repair components normally regulate telomere length and homeostasis, and how these are integrated with cell cycle checkpoints.

For recent publications, see number 92 on page 54.

SOO-HWANG TEO



(A) *XSox17b* (blue) in the naïve endoderm. (B) Transgenic *Xenopus* embryos expressing GFP in the developing foregut. (C) Homeobox genes *Hex* in the liver bud (blue) and *Pdx* in the pancreatic region (brown) of the embryonic gut.

Our research focuses on the molecular mechanisms underlying the formation of organs such as the liver, pancreas and lungs. In vertebrate embryos, naïve endoderm is patterned by a complex and poorly understood series of tissue interactions. As a result some endodermal cells are induced to form the liver while others give rise to the pancreas or lungs. Using the frog embryo as a model, we are applying a combination of molecular and embryological techniques, including micro-array technology and transgenics, to uncover the molecular and cellular events responsible for early liver development. Current investigations examine how transcription factors integrate signals from different growth factors to specify endoderm and embryonic liver. We are also conducting a number of screens to find novel genes involved in liver organogenesis.

For recent publications, see numbers 22, 47, 86 and 91 between pages 50 and 54.

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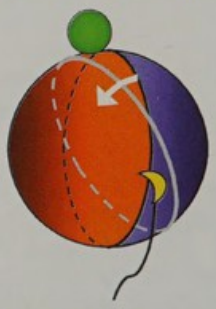
The aim of our research is to determine how the body plan of mammals is established. Until recently we had believed that the polarity of the mammalian embryo was only established after implantation. However, when we followed cell fate in mouse embryos we found that polarity is anticipated before implantation and is related to the spatial organisation of the egg. This is an unexpected finding, because the preimplantation embryo can withstand severe experimental perturbations and still develop normally. Now, we wish to discover the earliest stage in development at which differential gene expression could mediate the establishment of polarity, and to learn mechanisms used by the embryo to compensate for developmental perturbations. Specification of polarity seems to stem from the relationship between the position of the meiotic divisions in the egg and the site of sperm entry. Our recent work has shown that the pattern of cleavage divisions is influenced by these developmental cues and can dictate the basic features of the organisation of the blastocyst and hence later stages.

For recent publications see numbers 24, 40, 77, 95 and 99–100 between pages 50 and 54.

Image of fertilised mouse egg, showing the fertilisation cone (upper left) and polar body (upper right). Bead marking sperm entry position is shown in green, and sperm tail in orange.



A model showing the consequences of the first cleavage division that is defined by sperm entry position (sperm head in yellow) and the polar body (green).

CATEGORIES OF APPOINTMENT

Senior Group Leader
Professor, Reader or Lecturer Level

Junior 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, within individual groups, appointed by group leader

Graduate Student
3 year studentship within individual groups, mainly grant-funded

Research Assistant
Postgraduate, within individual groups, mainly grant-funded

Research Technician
Within individual groups, mainly grant-funded

Laboratory Assistant
Within individual groups or part of core support, grant-funded

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are supported mainly by the Wellcome Trust or the Cancer Research Campaign 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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CATERING

CHRISTINE CORNWELL

The following is a list of works by the Institute that were either published or accepted for publication in 2000.

1. Adams, I.R. and Kilmartin, J.V. (2000) Spindle pole body duplication: a model for centrosome duplication? **Trends Cell Biol.** *10,* 329–335.
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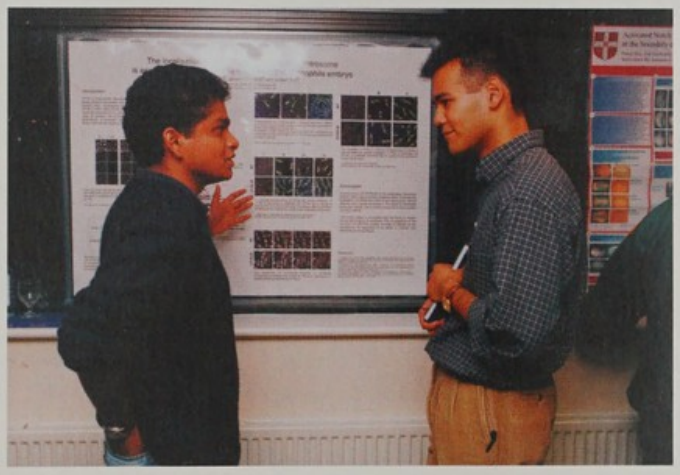

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STAFF AFFILIATIONS

JULIE AHRINGER is a Board Member of the British Society of Developmental Biology.

ANDREA BRAND is on the Scientific Advisory Board of the Promega Corporation, and is a Research Fellow at King's College.

JOHN GURDON is Master of Magdalene College, Cambridge, Member, Conseil Scientifique of the Institut Curie, France, and a member of the Royal Society Working Group on Stem Cells.

STEVE JACKSON is a member of the Biochemical Society Nucleic Acids and Molecular Biology Group Committee, the Biochemical Society Council, and Chief Scientific Officer, KuDOS Pharmaceuticals Ltd.

TONY KOUZARIDES is a member of the Cancer Research Campaign Grants Committee and a non-executive director of AbCam Ltd.

RON LASKEY is on the Scientific Advisory Committee of the European Molecular Biology Laboratory, a member of the Cancer Research Campaign Scientific Committee, and a Trustee of Strangeways Research Laboratories. He is Honorary Director of the MRC Cancer Cell Unit, opening in 2001, and a member of the Council of the ICRF.

ANNE McLAREN is a member of the Human Fertilisation and Embryology Authority, the European Group on Ethics (an advisory group to the European Commission) and is also a Trustee of the National History Museum.

JON PINES is a committee member of the British Society for Cell Biology.

JORDAN RAFF is a member of the Academy of Medical Sciences' working group on the Careers of Basic Scientists, and judge of the Aventis Junior Prize for Science Book of the Year.

DANIEL ST JOHNSTON is a non-executive Director of the Company of Biologists.

JIM SMITH is a Member of Council of the Academy of Medical Sciences and co-Chair of the Academy's Working group on Careers for non-clinical Scientists, a non-executive Director of the Company of Biologists, a member of the HFSPO Review Committee on 'Molecular Approaches' and a Member of the Wellcome Trust Basic Science Interest Group.

AZIM SURANI is a member of the Royal Society International Exchange Panel, and a member of the Royal Society Working Group on Stem Cells.

HONOURS AND AWARDS

JOHN GURDON, Jean Brachet Prize and Memorial Lecture, International Society of Differentiation, Australia, 2000. Doctor of Science, *Honoris Causa,* University of Glasgow.

TONY KOUZARIDES, Tenovus Medal award 2001.

RON LASKEY, Special Lecture: 2001 Croonian Lecture of the Royal Society. His group won the BBC Tomorrow's World Award for Health Innovation.

ANNE McLAREN in November 2000 visited Michigan State University as McPherson Professor for the Understanding of Science.

JIM SMITH, Feldberg Foundation Award, 2000; Member, Academia Europaea, 2000.

DANIEL ST JOHNSTON European Molecular Biology Organisation Gold Medal, 2000.

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CHAIRMAN OF THE MANAGEMENT COMMITTEE

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

OTHER INFORMATION

LEAVERS DURING 2000

JAN ADAMS, Böhringer Ingelheim Graduate Student, is doing postdoctoral research in Granada, Spain.

SAM APARICIO has moved to the Department of Oncology.

SUSAN BEGG, secretary of the St Johnston Group, has moved to the Department of Chemistry.

JOE BOUTELL, CRC Research Associate, is working at Babraham Hall, Cambridge.

ROSS BRECKENRIDGE, British Heart Foundation Clinical Research Fellow, has returned to clinical work at UCL London.

ODILE BRONCHAIN, EC TMR Graduate Student, is doing postdoctoral research at the University of Geneva.

AIDAN BUDD, Amersham Research Assistant, has gone to Heidelberg as a PhD student at EMBL.

DR SUSAN CRITCHLOW, AICR Research Associate, is now at the ICRF Clare Hall Laboratories, Potters Bar.

GUILLERMO DE LA CUEVA MENDEZ, CRC Research Assistant, has moved temporarily to Centro Nacional de Biotechnologia, Madrid.

CHARLOTTE DUBERN, BBSRC Graduate Student, is working at the DTI in London.

DAVID DUNBAR, former Laboratory Administrator, is doing an MBA at Edinburgh University.

DR DAVID GELL, CRC Research Associate, has gone to Australia.

KELVIN HAWKER, Wellcome Research Assistant, has moved to the Department of Oncology.

LUCY HAYTER, NIH Research Technician, is in Wales tagging grouse for a research project.

NEIL HAYWARD, MRC Graduate Student, is now working for the Cambridge biotechnology company AbCam Ltd.

TUNKIAT KO, CRC Graduate Student left in June for postdoctoral research at NYU after obtaining his PhD.

TANIA LANGON, EC Research Associate has returned to France.

FIONA LAVIN, CRC Chief Research Technician, is studying osteopathy in London.

DR RICHARD MAY, CRC Research Associate, is now a research analyst at Cambridge Antibody Technology, Royston.

RUTH McCAFFREY, EC TMR Student, is in the USA.

NATASHA McDOWELL, Magdalene College Manifold Research Fellow, is now working as a scientific journalist.

ERIC MISKA, CRC Graduate Student, is doing *C. Elegans* research at MIT, Harvard.

CARA NEADES, Wellcome Research Assistant, is studying accountancy with RSM Robson Rhodes.

DR SØREN NIELSON, CRC Research Associate, is scientific officer for a biotechnology company in Copenhagen.

CHRISTOPHER PHELPS, Wellcome Prize Student, is working in London for Inpharmatica, a biotech company.

MATTHEW POLLI, Wellcome Graduate Student, is working for Barings (Guernsey) Ltd.

DR ANDREAS RUSS, Wellcome Senior Research Associate, is doing postdoctoral research in Germany.

ALISON SCHULDT, Wellcome Research Associate, is working for the journal *Nature* in London.

JOSHUA SHULMAN, graduate student, completed his PhD and is now studying for an MD at Harvard Medical School.

DR FLORENCE SOLARI, EC TMR Fellow, is doing postdoctoral research at the Laboratoire de Genetique, Faculté de Medicine, Lyon, France.

FIONA STENNARD, Royal Society Howard Florey Fellow, is now working at the Victor Chang Cardiac Research Institute in Sydney, Australia.

GORDON STOTT, Wellcome Prize Student, has gone to Heidelberg.

DR GARETH WILLIAMS, CRC Senior Clinical Research Fellow, has moved to the Department of Pathology to set up his own laboratory.

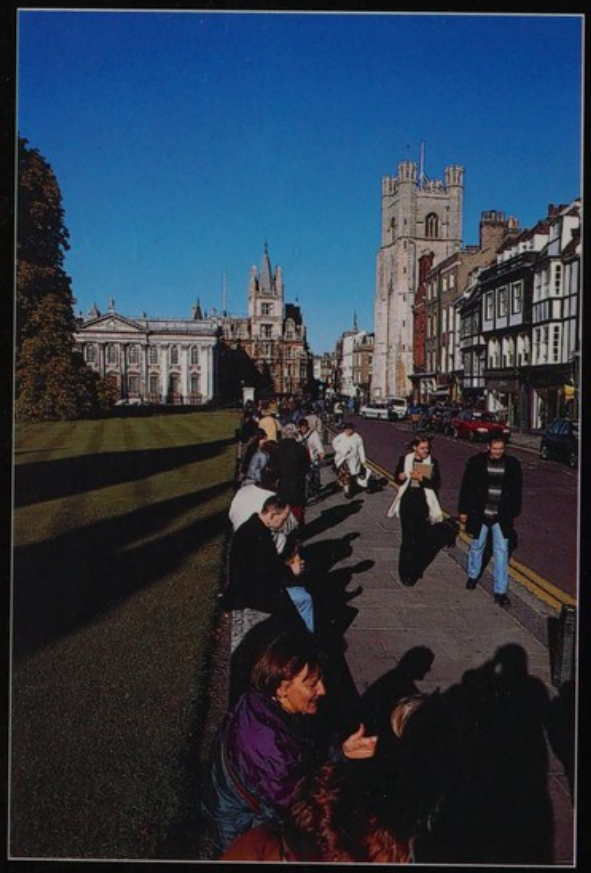
MARY ZENGENI, secretary to Anne McLaren, has retired.

ACKNOWLEDGEMENTS

Prospectus produced in the Wellcome/CRC Institute by Desmond Schmidt. Photography: Chris Green (Biochemistry) and John Overton. Printed by Cambridge University Press.

Front cover image by Katia Litière, St Johnston Group: Expression of GFP-Staufen (green) in an eggchamber of a *Drosophila* mutant isolated in a genetic screen. The nurse cells and follicle cells are indicated by staining of the actin (red). Back cover: Kings Parade, Cambridge.

Annual Retreat, Cirencester 2000



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