Annual report : 2001/2002 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

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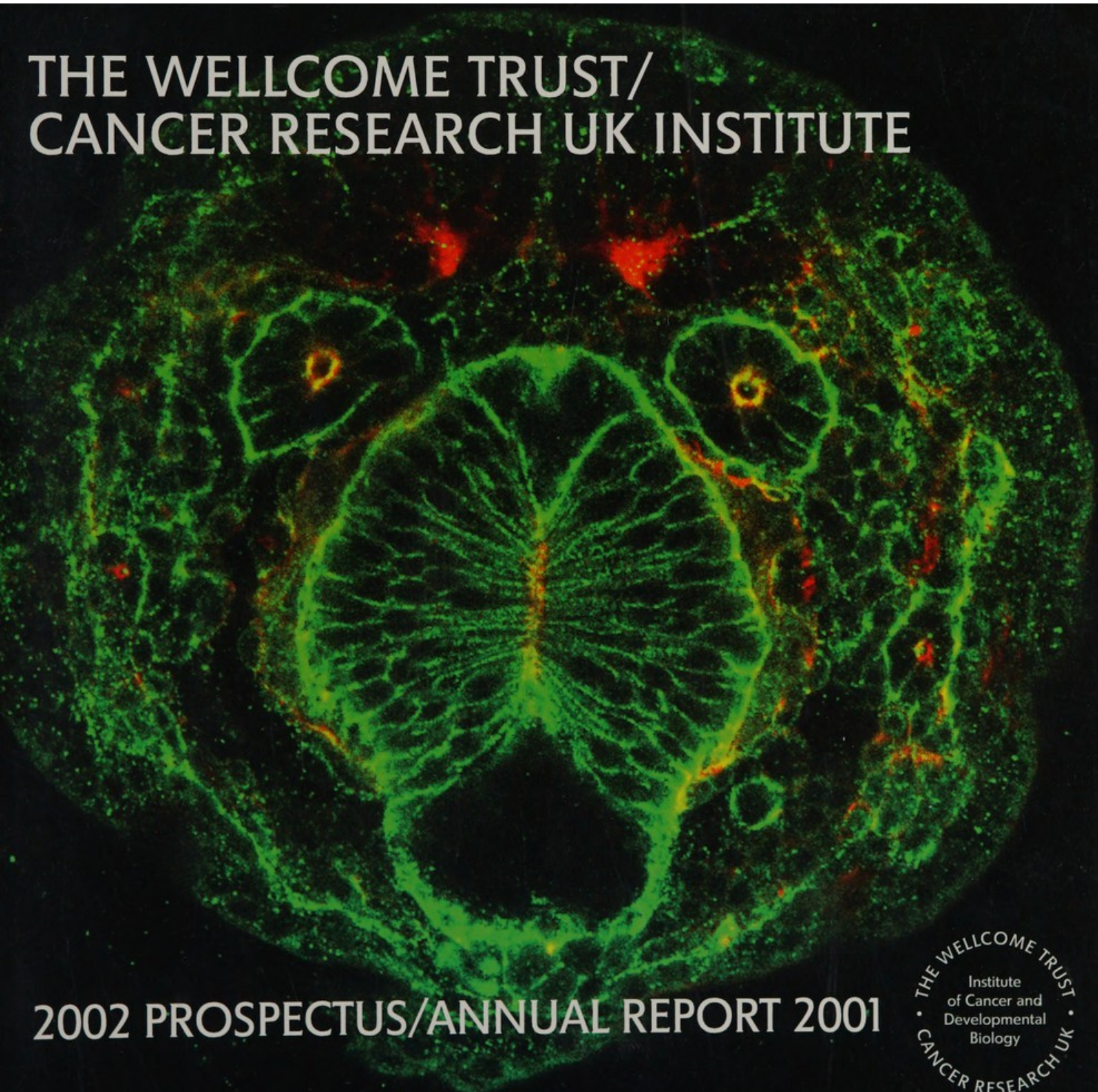

2002 PROSPECTUS/ANNUAL REPORT 2001

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Institute of Cancer and Developmental Biology

PROSPECTUS 2002

ANNUAL REPORT 2001

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CHAIRMAN'S INTRODUCTION

I write my first Introduction to this Prospectus two months after taking over the Chairmanship of the Institute from Professor Sir John Gurdon. We pay tribute to John's magnificent work in chairing the Institute and bringing it to its present level of success below. All I should say here is how pleased we are that John will remain in the Institute as a Wellcome Trust-funded Group Leader, and how conscious I am of what a hard act he will be to follow!

This is an exciting time to work at the Wellcome Trust/Cancer Research UK Institute. As described below, we have a new building on the way, we have recently been awarded funds to establish a microarray facility, and we have been joined by two new Group Leaders. We are also enthusiastic participants in a new Wellcome Trust Four-Year PhD programme, of which Daniel St Johnston is a co-organiser.

We are delighted that several present and former members of the Institute have received national and international recognition of their work this year. Martin Evans, who left the Institute in 2000, was awarded the Lasker Prize for his pioneering work in developing embryonic stem cells; John Gurdon was awarded the Conklin Medal of the Society for Developmental Biology; Azim Surani was awarded the Royal Society's Gabor Medal; Anne McLaren received the Unesco/L'Oreal Women in Science Award (Europe) as well as the US Society for Developmental Biology Award for Lifetime Scientific Achievement; Tony Kouzarides was made the Royal Society Napier Research Professor, awarded the Tenovus Medal, and received the Wellcome Trust Award for Research in Biochemistry related to medicine; Steve Jackson received the Anthony Dipple Carcinogenesis Young Investigator Award; Magda Zernicka-Goetz was made an EMBO Young Investigator, and Andrea Brand was awarded the Hooke Medal of the British Society for Cell Biology. Azim Surani, Steve Jackson and Tony Kouzarides were elected as Fellows of the Academy of Medical Sciences. Our congratulations to all.

As John Gurdon wrote last year, Ron Laskey has moved to become Director of the new MRC Cancer Cell Unit in the Cambridge Medical School. John had worked alongside Ron for one third of a century; I overlapped with Ron at the Wellcome/CRC Institute for only a year. Nevertheless, I quickly learned to value Ron's sage advice on many matters as much as I admired his science. Like everyone I'll miss him, and we wish him well.

New Group Leaders include Rick Livesey, who joins us from Harvard Medical School and brings expertise in microarray analysis to complement his work on the specification of neural cell types, and Magdalena Zernicka-Goetz who is studying early events in mouse development and was previously a Lister Fellow in the Institute. We are pleased that Jon Pines has been made a Senior Group Leader.

Readers of this prospectus will have noticed that the Institute has changed its name. This reflects the merger, on the 4th of February 2002, of the Cancer Research Campaign and the Imperial Cancer Research Fund. The fusion of the two charities makes Cancer Research UK the largest volunteer-supported cancer research organisation in the world and the largest funder of cancer research in the United Kingdom. We look forward to playing a full and active part in the success of this exciting new enterprise.

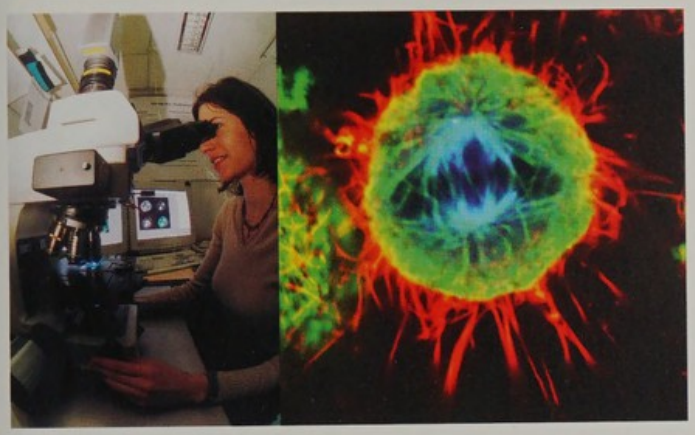
Finally, I should like to thank all the members of the Institute for making me so welcome; I look forward to working with everyone to ensure that the Institute's second decade is as successful as its first.

Jim Smith, Chairman

HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance from the centre of the historic city. 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 single 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.

The major sponsors of our Institute are the Wellcome Trust and Cancer Research UK, and Group Leaders are normally funded in large part by one or the other organisation. The Institute is an integrated part of Cambridge University, and all Group Leaders are affiliated to a University Department and contribute to teaching and graduate student supervision.

PROFESSOR SIR JOHN GURDON

John Gurdon, who has now retired from his position as Chairman of the Wellcome/CRC Institute, has been and continues to be one of the most influential developmental biologists of our time. John has made seminal contributions to at least three areas of developmental biology, namely nuclear transplantation and cloning, the use of *Xenopus* eggs and oocytes for mRNA microinjection, and intercellular signalling during embryonic development. As a result of this work, John has received honorary degrees and awards too many to mention, but including, as we all know, a Knighthood for services to developmental biology.

As outlined in a recent interview in the International Journal of Developmental Biology, we are fortunate that John entered science at all, for at school he was regarded as being not only unsuited for science but also the worst pupil the Biology master had ever taught in his whole career! However, he received encouragement from other teachers and his parents, and went to Oxford to read Zoology. After a PhD with Michael Fischberg and postdoctoral work at CalTech, he returned to Oxford as an Assistant Lecturer in Zoology in 1962. John then moved to the

On top of Mount Harvard, Colorado.
John Gurdon at 14,500 feet.

MRC Laboratory for Molecular Biology in Cambridge in 1971, where he became head of the Cell Biology Division before moving to the Department of Zoology and then setting up, with Ron Laskey, the CRC Unit of Molecular Embryology. In 1989 John, Ron and others founded the Wellcome/CRC Institute.

One of John's most remarkable characteristics is that, unlike most of his peers, he continues to do experiments. He has managed to do this while being Master of Magdalene, a Governor of the Wellcome Trust and Chairman of the Wellcome/CRC Institute, with all the work and responsibilities that those positions entail, and he is an example to all of us with lesser commitments who only rarely wield the test tube!

All members of the Institute owe John a debt of gratitude for making the Institute such a success, from its establishment in 1989, to the continuing support we have received from the Wellcome Trust and the Cancer Research Campaign, and most recently for his efforts in obtaining a grant from the Wellcome Trust and the UK Government to fund our new building.

Members also appreciate John's inclusive and democratic style of management, which has served the Institute so well in the past, and which I hope will continue to do so in the future.

John has recently become Chairman of the Board of Directors of the Company of Biologists, but we are delighted that he will stay at the Institute to continue his pioneering work on early amphibian development, and we look forward to many more years of his company, his experiments and his insightful comments.

CENTRAL SUPPORT SERVICES

Core staff provide administrative, technical and computing support to the scientists, in order to ensure the smooth running of the Institute. These vital tasks have been performed efficiently and well in 2001.

Desmond Schmidt, Computer Systems Manager, left us to return to his native Australia in August 2001. We miss both his professional skills and his dry sense of humour. His replacement, Alastair Downie, will join the Institute in January 2002.

FUNDING

During this year we learnt that our application to the Cancer Research Campaign for a further five years of core support (January 2001 to December 2005) was successful. This will therefore run alongside the core funding from the Wellcome Trust reported in last year's Prospectus/Annual Report. Both the Wellcome Trust and the CRC (now Cancer Research UK) continue to support the Institute in the form of Fellowships, individual project grants and equipment grants.

Other sources of funding, both direct and indirect, include the European Union, BBSRC, the Royal Society, the Lister Institute of Preventative Medicine, the Elmore Trust, the Isaac Newton Trust, the Leverhulme Trust, the Association for International Cancer Research and the European Molecular Biology Organization.

Applications to HEFCE and SRIF for funding for additional vital scientific equipment for the new building have been successful.

We are extremely grateful to all these organisations for their continuing support.

INSTITUTE FACILITIES

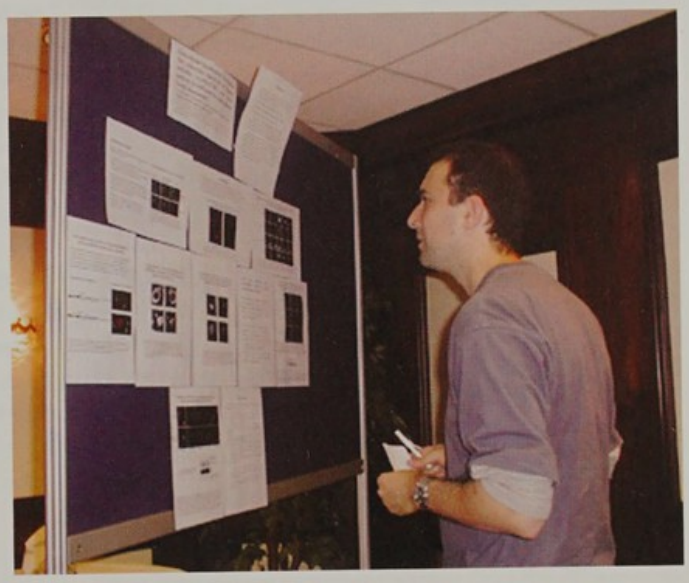
The Institute has excellent facilities and these are to be supplemented, thanks to generous contributions from the Wellcome Trust and the Cancer Research Campaign, by state-of-the-art microarray facilities and by expertise in bioinformatics. These will be of great use to all the members of the Institute, and will further encourage scientific interactions between different groups.

NEW BUILDING

Work on our new building has now begun, and we expect it to be completed by the autumn of 2003. The building will provide enhanced laboratory and communal facilities and more core equipment space. In particular, we will be able to accommodate our improved imaging, bioinformatics, proteomic and microarray facilities. The work has caused some inevitable disruption to the lives of our neighbours in the Biochemistry Department, and we thank them for their forbearance.

INSTITUTE RETREAT

This year marked the tenth Institute retreat, and we celebrated the occasion by going to Amsterdam. As usual the attendance was excellent and the Retreat was a great success, both scientifically and socially.



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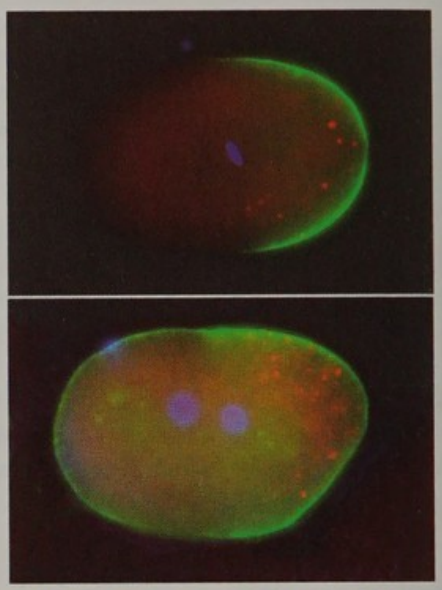
We are studying how patterns of cell divisions and cell fates are controlled, using *C. elegans* as a model system. One aim is to understand how polarity is established in the embryo and how this information is transduced to downstream events such as spindle positioning. Control of spindle position is widespread in animal development, but little is known about the mechanisms used. We have shown that one key to this process is heterotrimeric G protein signalling. We are currently studying how the G protein is activated and how it signals to the spindle.

One approach we are taking to identifying new genes involved is genome-wide RNA interference screening. We have constructed a bacterial library for RNAi by feeding that can individually target 87% of all *C. elegans* genes. Besides being quick and easy, RNAi has the major advantage that the sequence of the gene is known for which a phenotype is found. We are studying a number of new genes involved in polarity, spindle position, and spindle orientation identified using this approach.

We are also applying genome-wide RNAi screening to understanding the role of chromatin remodelling in later patterning events. In particular, we are studying functions of the NURD chromatin remodelling complex, which regulates many patterning decisions, including those involving Ras and Wnt signalling.



Posterior localisation of PAR-2::GFP (green) in wild-type *C. elegans* (above) is abolished in a new polarity mutant identified by RNAi screening (below). P granules (red) are localised to the posterior; DNA, blue.

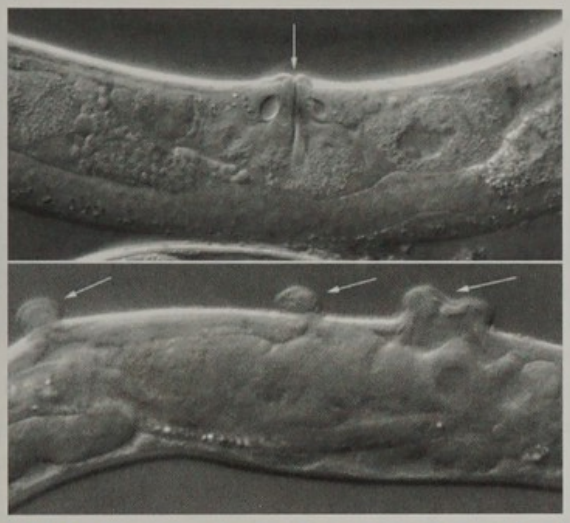
Gotta, M. and Ahringer, J. (2001) Axis determination in *C. elegans:* initiating and transducing polarity. **Curr. Opin. Genet. Dev.** *11,* 367–373.

Zipperlen, P., Fraser, A., Kamath, R., Martinez-Campos, M. and Ahringer, J. (2001) Roles for 147 embryonic lethal genes on *C. elegans* chromosome I identified by RNA interference and video-microscopy. **EMBO J.** *20,* 3984–3992.

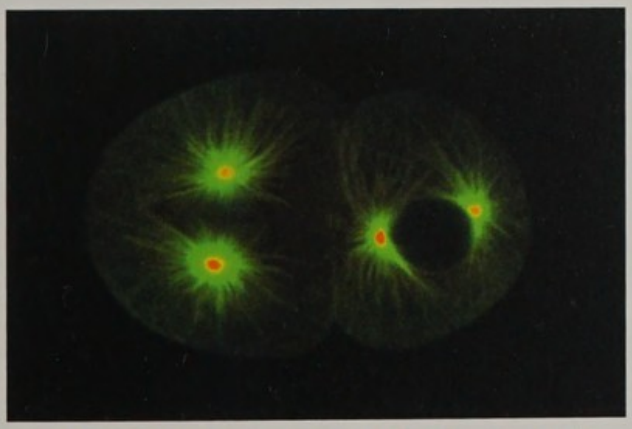
Fraser, A., Kamath, R.K., Zipperlen, P., Martinez-Campos M., Sohrmann, M. and Ahringer, J. (2000) Functional genomic analysis of *C. elegans* chromosome I by systematic RNA interference. **Nature** *408,* 325–330.

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

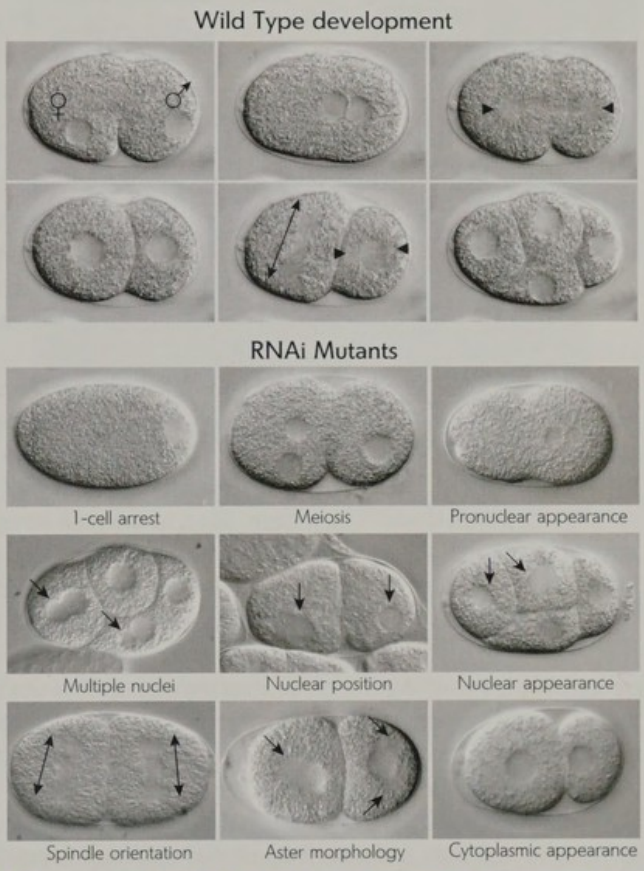
For further publications, see numbers 32, 37 and 39 on pages 54 and 55.



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).

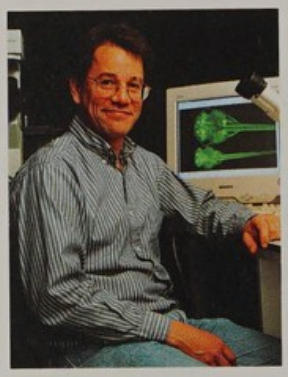


A two-cell embryo with microtubules in green and centrosomes in red. The anterior cell (left) and the posterior cell (right) will divide in different orientations, specified by the positions of the centrosomes.



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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SHOKO ISHIBASHI
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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. 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 of the nervous system and morphogenesis of the heart. We are generating transgenic embryos that aberrantly express genes that upregulate or downregulate growth factor signalling molecules specifically in these tissues. For these studies we have recently begun to use the binary Gal4-UAS mis-expression system.

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.

Tadpole overexpressing *Xsprouty2* fails to undergo proper morphogenesis resulting in a shortened phenotype.

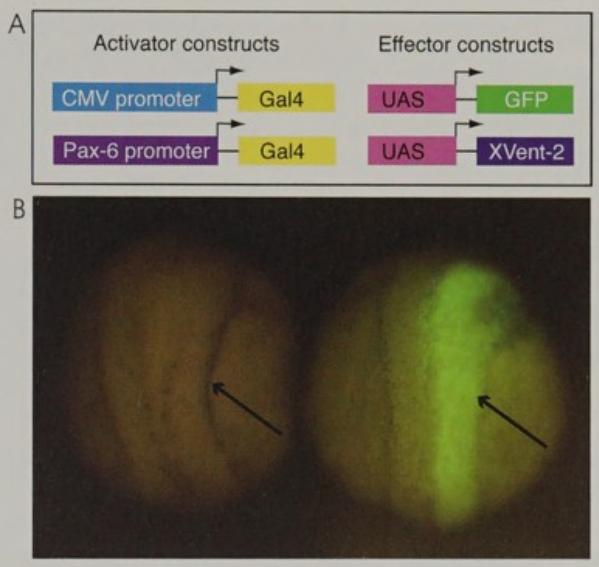
Nutt, S.L., Dingwell, K.S., Holt, C.E. and Amaya, E. (2001) *Xenopus* Sprouty2 inhibits FGF-mediated gastrulation movements but does not affect mesoderm induction and patterning. **Genes Dev.** *15,* 1152–1166.

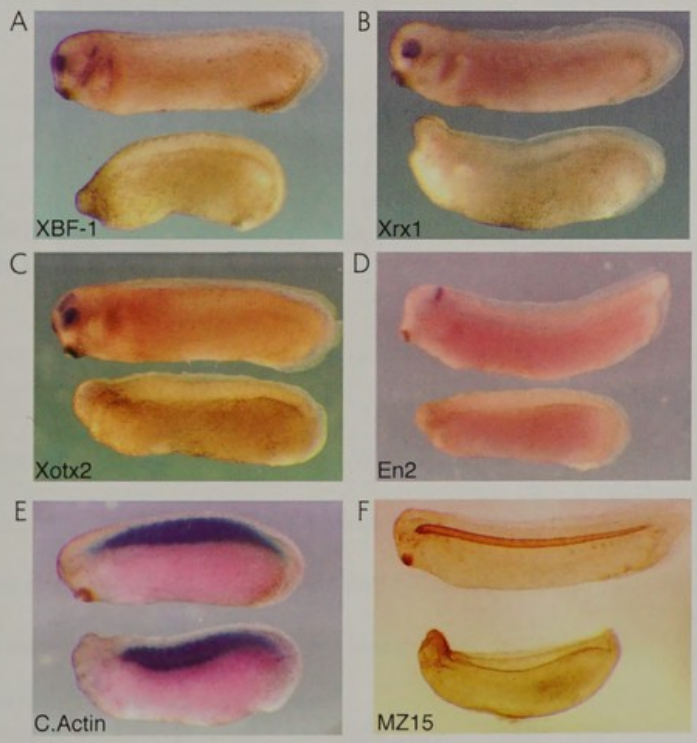
Hartley, K.O., Hardcastle, Z., Friday, R.V., Amaya, E. and Papalopulu. N. (2001) Transgenic *Xenopus* embryos reveal that anterior neural development requires continued suppression of BMP signalling after gastrulation. **Dev. Biol.** *238,* 168–184.

Hartley, K.O., Nutt, S.L. and Amaya E. (2002) Targeted gene expression in transgenic *Xenopus* using the binary Gal4-UAS system. **Proc. Natl. Acad. Sci. (USA)** *99,* 1377–1382.

For further publications, see numbers 14 and 72 on pages 53 and 57.

A. Schematic diagram showing GAL4 activator and UAS effector constructs.
B. F1 progeny from a UASGFP effector line were injected into one cell at the two-cell stage with 100pg of Gal4 mRNA. The embryo on the right inherited the UASGFP transgene and is fluorescent due to transactivation by Gal4 (arrow). The embryo on the left failed to inherit the UASGFP transgene and therefore is not fluorescent even though it was injected with Gal4 mRNA (arrow).





Mating between a CMVGal4 line and a UASXvent-2 line results in a headless phenotype at stage 30. Xvent-2 is a transcription factor which is a direct target of BMP4 signalling. *In situ* hybridisation to anterior neural markers (A, B, C, D) show that the microcephalic embryos lack brain structures. They also fail to develop a notochord (F), but are able to develop muscle (E). Each panel shows a normal (upper) and microcephalic (lower) embryo.

ANDREA BRAND

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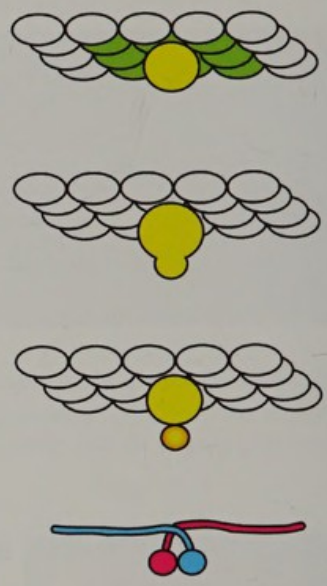
My group is interested in how cellular diversity is generated in the nervous system, and in the signalling pathways that direct axon pathfinding. In the *Drosophila* central nervous system, neurons and glia arise from neural progenitors called neuroblasts. As they divide, neuroblasts renew themselves in a stem cell fashion and generate a series of daughter cells called GMCs. GMCs divide only once to produce two post-mitotic neurons. Neuroblasts and GMCs differ with respect to size, mitotic potential and developmental fate. A simple way to generate these two different cell types is through the asymmetric segregation of cell fate determinants. At each division the cell fate determinants Prospero and Numb are segregated from the neuroblast to its daughter.

We are studying the molecular mechanisms that direct asymmetric cell division in the nervous system, and the role of microtubules and the actin cytoskeleton in this process. We have shown that the adapter protein, Miranda, is required to segregate not only Prospero protein, but also its 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. We use time lapse confocal microscopy to follow asymmetric cell division in living embryos, and have fused different spectral variants of GFP to Miranda, Prospero, Myosin, actin and microtubules for double labelling *in vivo*.

We are also characterising the role in axon pathfinding of the *Drosophila* Ephrin and Fer homologues, using classical and reverse genetic approaches such as ectopic expression and targeted RNAi to eliminate expression in specific cells.



Neuroblasts (yellow) delaminate from a layer of ectodermal cells (white and green) and undergo a series of stem cell divisions to produce daughter cells called GMCs (orange). GMCs divide only once to generate two post-mitotic neurons (red and blue).

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.

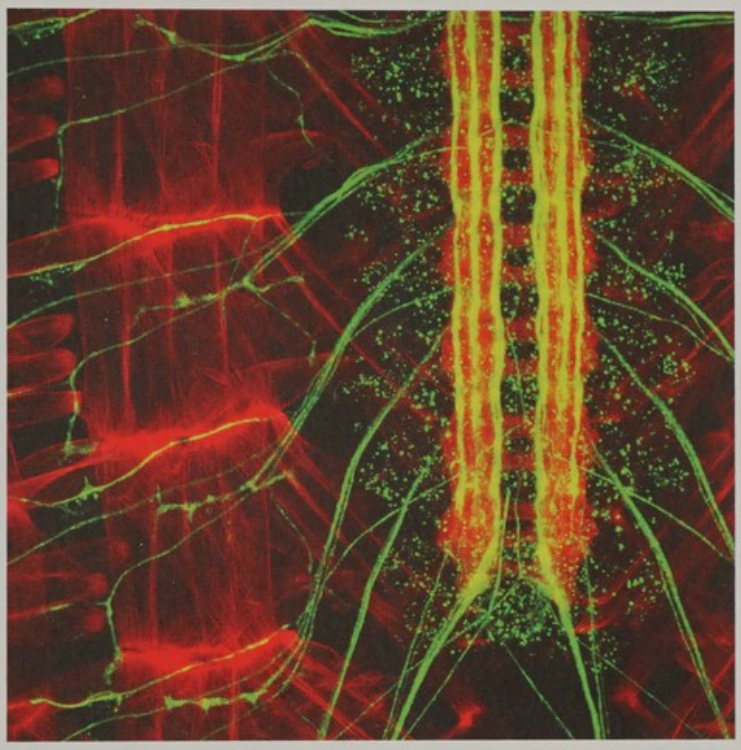
Kaltschmidt, J.A., Davidson, C.M., Brown, N.H. and Brand, A.H. (2000) Rotation and asymmetry of the mitotic spindle direct asymmetric cell division in the developing central nervous system. **Nat. Cell Biol.** *2*, 7–12.

Bellaiche, Y., Gho, M., Kaltschmidt, J.A, Brand, A.H. and Schweisguth, F. (2001) Frizzled regulates the localization of cell-fate determinants and mitotic spindle rotation during asymmetric cell division. **Nat. Cell Biol.** *3*, 50–57.

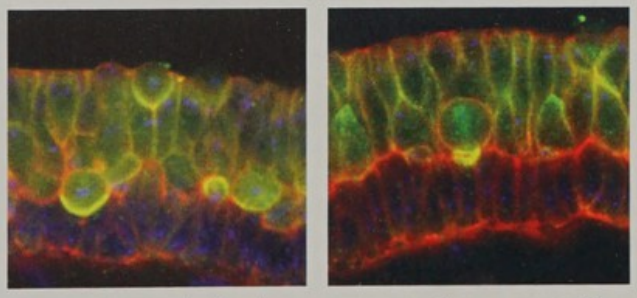
van Roessel, P. and Brand, A.H. (2002) Imaging into the future: visualizing gene expression and protein interactions with fluorescent proteins. **Nat. Cell Biol.** *4*, E15–20.

For further publications, see number 53 on page 56.

Live imaging of the RP2 motor neuron as it extends its axon out of the CNS towards its target muscle.



In the *Drosophila* embryonic CNS, interneuronal axons run along the longitudinal tracts (yellow; double labelled with anti Fasciclin II, green, and phalloidin, red) while the axons of motor neurons (green; anti Fasciclin II) exit the CNS to synapse on specific muscles (red; phalloidin).



Cell fate determinants (green/yellow) are asymmetrically segregated from neuroblasts to their daughters in the early embryonic CNS (DNA labelled in blue, actin in red).

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

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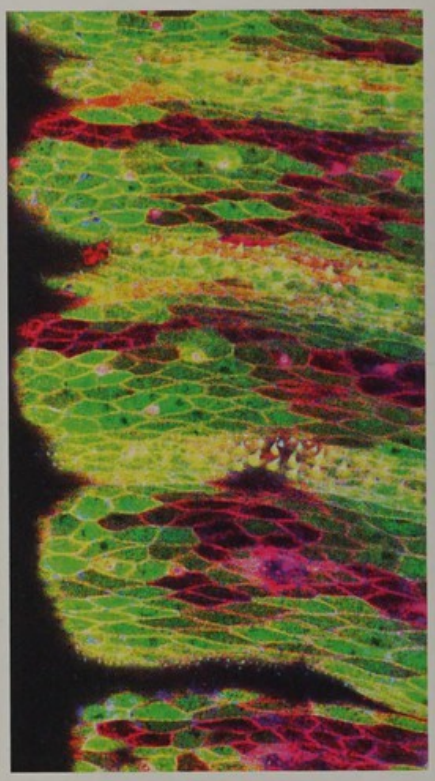
Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, which stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one 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 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 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. Recent work has shown that some of these components also contribute to the formation or regulation of cell–cell junctions formed by other types of receptor, thus connecting the different kinds of cell adhesion performed by the cell.



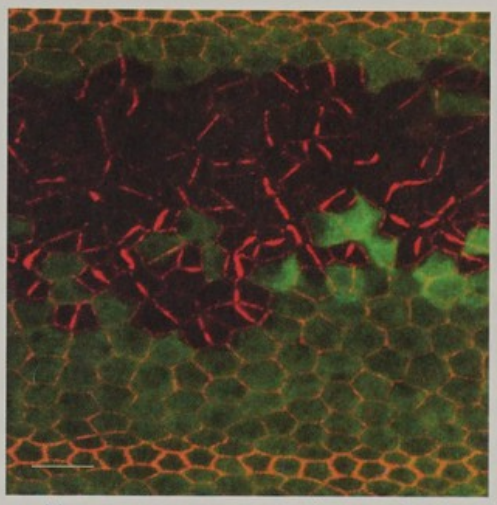
A short piece of the kakapo protein fused to green fluorescent protein (green) only partially localises to the periphery of the cell where the full length protein (magenta) resides.

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

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.** *152,* 1007–1018.

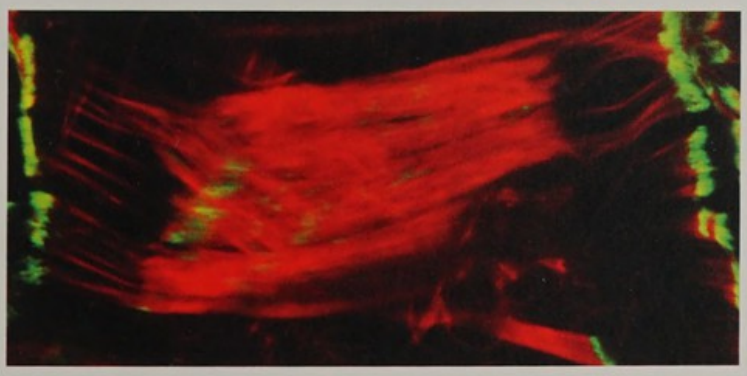
Knox, A.L. and Brown, N.H. (2002) Rap1 GTPase regulation of adherens junction positioning and cell adhesion. **Science** *295,* 1285–1288.

For further publications, see number 13 on page 53.



Maintaining an even distribution of cell–cell junctions (red) requires intracellular signalling (the cells that lack the green marker are defective in signalling).

Integrin based adhesion junctions (shown with tensin in orange) link together microtubule transalar arrays (blue) in the developing wing. The apical surface of each cell layer is visible from autofluorescence (darker orange).



Attachment of actin (red) to the ends of the muscles is reduced to a few strands when the sequence of integrin-linked kinase (green) is altered

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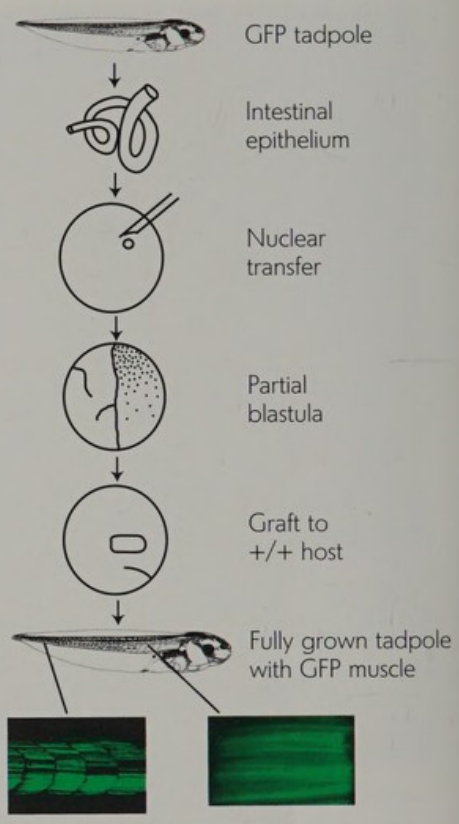
TIMOTHY ROBINSON
STINA SIMONSSON
CAROLINE WEBB
AARON ZORN

Our group is interested in nuclear reprogramming and cell fate determination by signal factors in amphibian development. The transplantation of a nucleus from specialised tissue such as the intestine to an enucleated egg generates embryos in which the expression of intestine-specific genes has been rapidly extinguished and that of early embryo genes activated. However, the expression of individual early zygotic genes in single nuclear transplant embryos (that is, in cells derived from the transplantation of a single intestine nucleus) is incorrectly and variably regulated. Nevertheless, cells from such embryos can differentiate into many tissue types, such as muscle, unrelated to the donor cell type (intestine).

Embryonic cells can be made to embark on diverse cell differentiation pathways by exposure to the appropriate concentration of a signal factor such as activin. Factors that work in this way are called morphogens, and are widely operative in development. We have determined the number of occupied receptors, the rapidity of intracellular Smad2 phosphorylation, and the real-time migration of GFP-Smad 2 to the nucleus. We conclude that, as a morphogen gradient changes with time, cells adjust the volume but not rate of intracellular transduction flow. Another concentration-dependent signal process is the community effect in which we find that cells signal to each other via FGF4 to collectively form a homogeneous tissue such as muscle.

Our aim is to understand the mechanisms of nuclear reprogramming, morphogen action, and the community effect, thereby elucidating basic processes of development and contributing to the eventual success of cell replacement therapies.



Nuclear reprogramming

Gurdon, J.B. and Bourillot, P-Y. (2001) Morphogen gradient interpretation. **Nature** *413,* 797–803.
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** *128,* 1347–1357.
Gurdon, J.B. and Colman, A. (2000) The future of cloning. **Nature** *402,* 743–746.

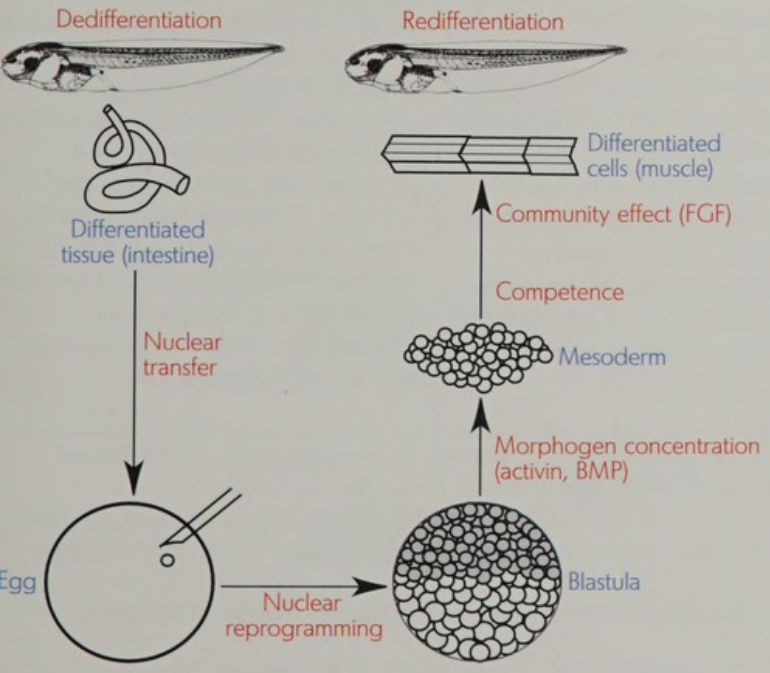
For further publications, see numbers 15, 16, 40, 63 and 87 on pages 53 and 55–57.

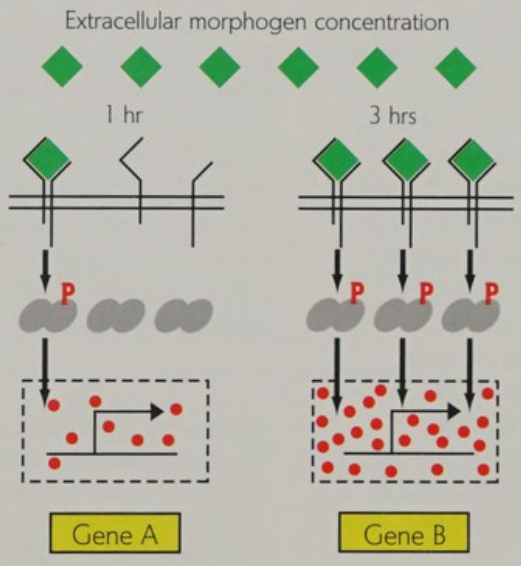
Graft of tissue from nuclear transplant embryo

GFP-Smad2 in the nucleus of a blastula cell

2 hours 4 hours

after a 10 min activin exposure





Receptor occupancy and volume, not rate of transduction flow, increases with time

STEVE JACKSON

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VERONIQUE SMITS
MANUEL STUCKI
SOO-HWANG TEO

To maintain genomic integrity, eukaryotic cells have developed elaborate, highly conserved pathways to detect, signal and repair DNA damage. One of our particular interests is DNA double-strand breaks and their repair by non-homologous end joining (NHEJ). In NHEJ, DNA damage is detected by the Ku heterodimer, part of DNA-dependent protein kinase (DNA-PK). Binding of Ku to DNA ends allows the efficient binding of DNA-PK's catalytic subunit to the break and the subsequent recruitment of other factors needed for efficient DNA damage repair, including a complex comprising two molecules of Xrcc4 and one DNA ligase IV molecule. In a recent collaboration, we determined the structure of this complex (Fig. 1).

We are also investigating the role that some components of the NHEJ apparatus play in telomere maintenance, another process essential for genome stability. Thus, we have found that inactivation of Ku in mice leads to telomere shortening and the appearance of dramatic chromosomal abnormalities (Fig. 2).

Finally, we are investigating DNA damage-induced checkpoints. These key responses to DNA damage, which are highly conserved between yeast and man, halt the cell cycle to allow time for DNA repair before genome replication and cell division occur. We have recently found that the yeast Xrs2p/Rad50p/Mre11p complex is important in checkpoint signalling (Fig. 3). This result provides insights into the mechanism of checkpoint activation in both yeast and human cells, where the orthologous NBS1/RAD50/MRE11 complex forms part of the medically important ATM DNA damage signalling pathway.

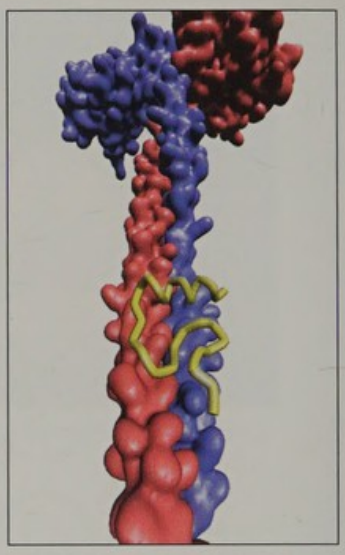


Fig. 1. The Xrcc4–DNA ligase IV complex is an essential NHEJ component, which is required for repairing ionising radiation-induced DNA damage and for V(D)J recombination. Here, we show a surface representation of two human Xrcc4 chains (blue and pink) bound to the DNA ligase IV peptide (yellow) that lies between DNA ligase IV's two BRCA1 C-terminal (BRCT) domains. Collaboration with T. Blundell, L. Pellegrini and B. Sibanda (Department of Biochemistry, University of Cambridge, UK).

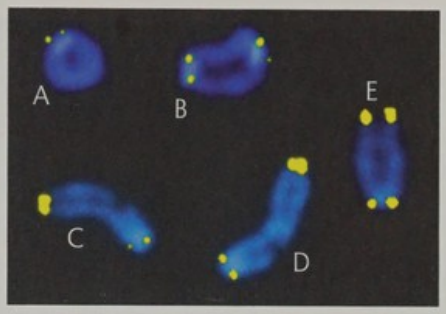
Sibanda, B.L., Critchlow, S.E., Begun, J., Pei, X.Y., Jackson, S.P., Blundell, T.L. and Pellegrini, L. (2001) Crystal structure of an Xrcc4–DNA ligase IV complex. **Nat. Struct. Biol.** *8*, 1015–1019.

d'Adda di Fagagna, F., Hande, M.P., Tong, W-M., Roth, D., Lansdorp, P.M., Wang, Z.Q. and Jackson, S.P. (2001) Effects of non-homologous end-joining factors on telomere length and chromosomal stability in mammalian cells. **Curr. Biol.** *11*, 1192–1196.

D'Amours, D. and Jackson, S.P. (2001) The yeast Xrs2 complex functions in S phase checkpoint regulation. **Genes Dev.** *15*, 2238–2249.

For further publications, see numbers 7–9, 22, 27, 28, 30, 34, 44, 50, 54 and 94 on pages 53–56 and 58.

Fig. 2. Telomeres are structures at chromosome ends that contribute to chromosomal stability. The figure shows examples of chromosomal abnormalities in mice lacking Ku. A shows a ring-like structure; B is a dicentric chromosome; C and D show chromosomes with gaps or chromatid breaks. For comparison, E shows a representative normal metaphase chromosome. The chromosomes have been hybridised to a telomeric probe (yellow) and the DNA stained with DAPI (blue). Collaboration with M. P. Hande (Columbia University, NY, USA).



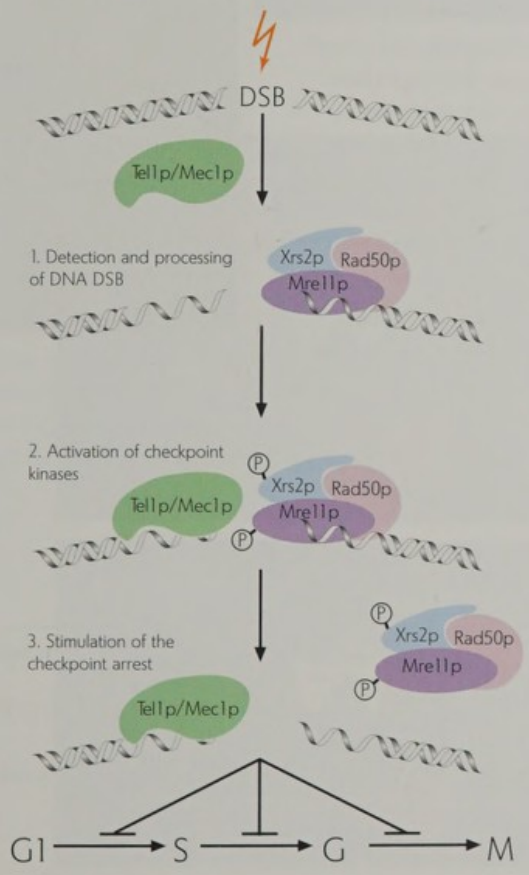


Fig. 3. This figure shows a working model for how the yeast Xrs2p/Rad50p/Mre11p complex might be involved in checkpoint signalling. In this model, production of a DNA double-strand break (DSB) by ionising radiation or radiomimetic agents is detected and processed by the nuclease activity of Mre11p. Next, the single-stranded DNA ends activate Tel1p and/or Mec1p, checkpoint kinases that are the yeast homologues of mammalian ATM and ATR, respectively. Finally, the activated kinases phosphorylate Xrs2p, Mre11p and other factors, and checkpoint arrest is stimulated.

TONY KOUZARIDES

Co-workers:

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ALISTAIR COOK
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PAUL HURD
EMMA LANGLEY
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HELENA SANTOS-ROSA
ROBERT SCHNEIDER
DANIEL WOLF
PHILIP ZEGERMAN

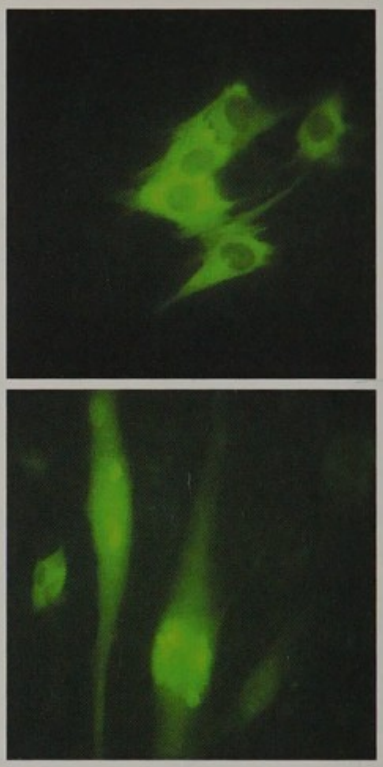
Many transcriptional regulators are de-regulated in cancer. Our group is interested in defining the mechanisms by which such transcription factors function during normal cell proliferation and in cancer.

Our attention is focused on a set of enzymes which modify histones and regulate transcription via chromatin remodelling. We would like to understand how, mechanistically, these modifications affect transcription, the biological role of histone modifying enzymes and their potential involvement in cancer.

Recently, we have focused on the process of histone methylation, which can occur on specific lysine or arginine residues. We have extensively studied the methylation of lysine 9 of histone H3. This methylation leads to the transcriptional silencing of genes found in heterochromatin and of cell cycle genes regulated by the retinoblastoma (RB) repressor. Lysine 9 methylation mediates silencing by recruiting the repressor protein HP1.

In contrast to methylation of lysine 9, methylation of lysine 4 on histone H3 is activatory for transcription. We have identified the enzymes in yeast that mediate methylation at lysine 4 and are now characterising their mammalian equivalents. We can show that lysine 4 methylation prevents the association of histones with deacetylases, a process which would otherwise lead to repression.

A distinct set of enzymes methylates arginines. We have characterised one such methylase, CARM1, which is a regulator of nuclear hormone receptors. Our data show that CARM1 methylates arginine 17 of histone H3 *in vivo* and that this modification is deposited on histones when estrogen receptor-regulated genes are active.



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

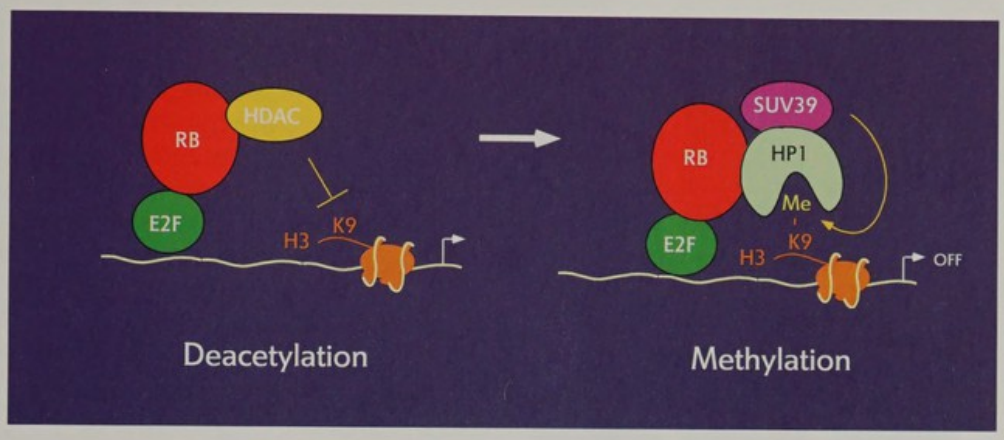
Bannister, A.J., Zegerman, P., Partridge, J.F., Miska, E.A., Thomas, J.O., Allshire, R.C. and Kouzarides, T. (2001) Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. **Nature** *410,* 120–124.

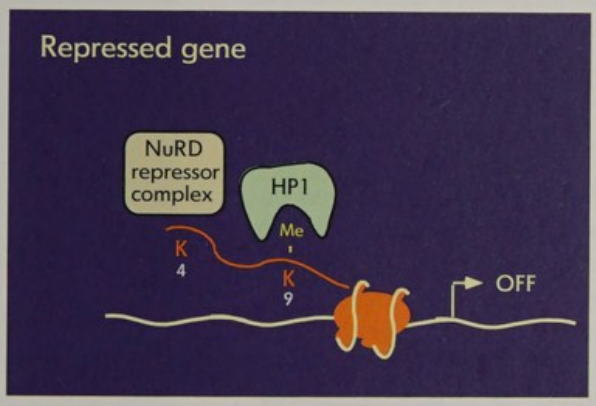
Nielsen, S., Schneider, R., Bauer, U-T., Morrison, A., O'Carroll, D., Cleary, M., Jenuwein, T., Herrera, R. and Kouzarides T. (2001) Rb targets histone H3 methylation and HP1 to promoters. **Nature** *412,* 561–565.

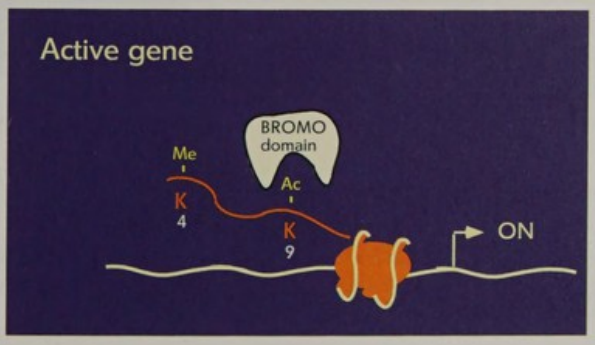
Bauer, U-M., Daujat, S., Nielsen, S.J, Nightingale, K. and Kouzarides, T. (2001) Methylation at arginine 17 of histone H3 is linked to gene activation. **EMBO Rep.** *3,* 39–44.

For further publications see numbers 21, 35, 56, 68, 93, 95 and 98 on pages 54–56 and 58.

Model of RB-mediated repression of the cyclin E gene. RB recruits methylase activity specific for lysine 9 of histone H3 to the promoter. This methylation is then recognised by the HP1 repressor protein.







The pattern of modifications on histone tails differs on active and repressed genes. The differentially modified histones are also associated with a distinct set of proteins.

RICK LIVESEY

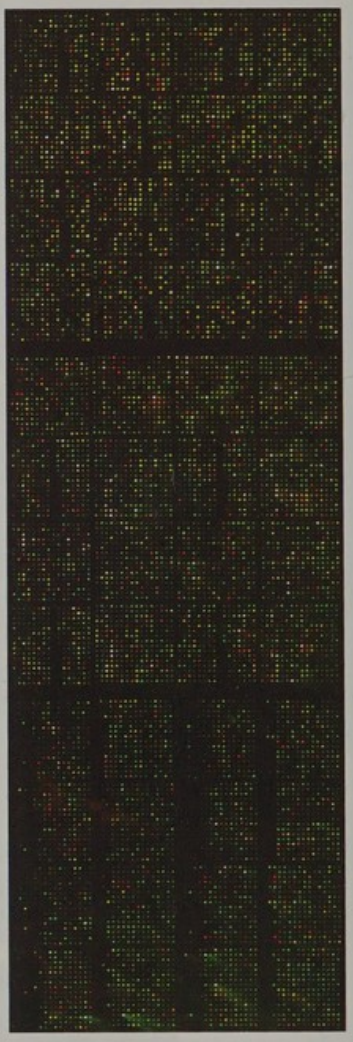
Co-worker:

JAMES SMITH

Mitotic neural stem and progenitor cells integrate extracellular and intracellular information in each cell cycle to decide the fates of their progeny. This is a fundamental cellular process, common to all tissues in the organism, and depends to a large extent on the dynamic use of the available genes in the genome. Our lab uses genomics technologies to understand how the genome is deployed during this decision-making process. The goal is to identify the genetic networks that control cell fate determination.

During development, different neurons are generated in a stereotyped order from the available pool of dividing stem and progenitor cells. One important mechanism that controls which cells are generated at a given time is the competence of stem and progenitor cells to generate particular cell types in response to extracellular signals. Progenitor competence changes over time, and this is a fundamental way in which the stereotyped order of genesis of cell types is achieved. However, little is known about the cellular mechanisms controlling progenitor competence, how they interact with the processes controlling cell cycle exit and cell fate determination, and how competence changes over time.

The lab investigates the intrinsic control of progenitor competence and neural cell fate determination using the mouse neocortex as a model system. The ordered genesis of the six cellular layers of the neocortex is achieved in part by temporal changes in the competence of cortical progenitors. We are using expression profiling of neural progenitors and their progeny to identify gene expression networks involved in regulating competence and laminar (cell layer) cell fate determination in the neocortex. Although composed of the same six layers in all areas, the neocortex has discrete areas primarily dedicated to, for example, motor control, the somatic senses, vision and hearing. Therefore, a second area of research is how the basic processes of cell fate determination in the neocortex are adapted and used to generate the different functional areas.



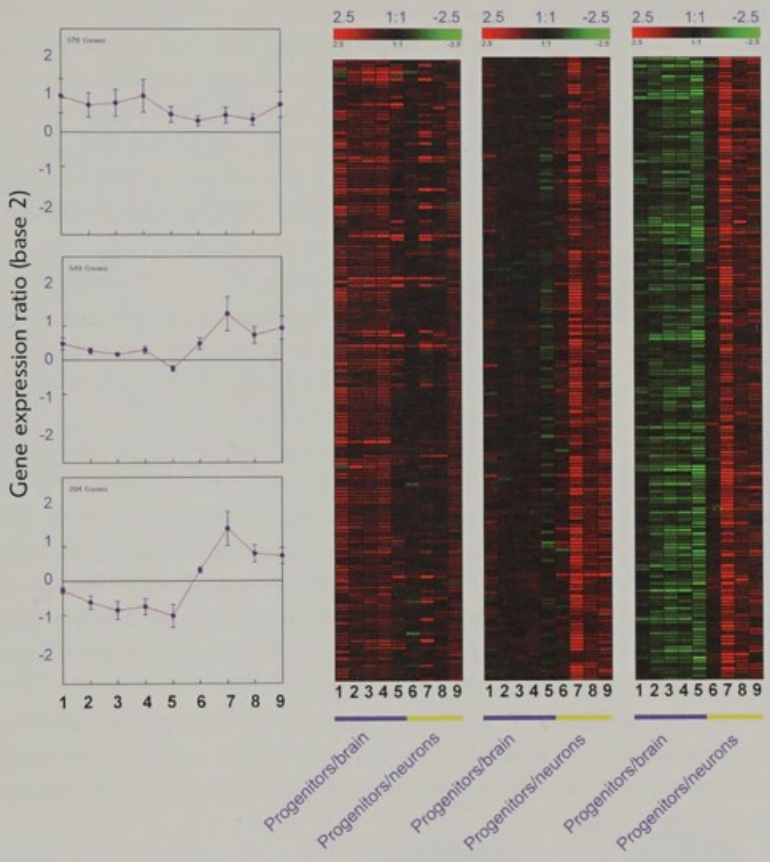
Blackshaw, S. and Livesey, F.J. (2002) Applying genomics technologies to neural development. **Curr. Opin. Neurobiol.** *12,* 110–114.

Livesey, R. and Cepko, C. (2001) Neurobiology: developing order. **Nature** *413,* 471–473.

Livesey, F.J. and Cepko, C.L. (2001) Vertebrate neural cell fate determination: lessons from the retina. **Nat. Rev. Neurosci.** *2,* 109–118.

Livesey, F.J., Furukawa, T., Steffen, M., Church, G.M. and Cepko, C.L. (2000) Microarray analysis of the transcriptional network controlled by the photoreceptor homeobox gene *crx.* **Curr. Biol.** *10,* 301–310.

Right: Characterising the gene expression program of mammalian neural progenitors and stem cells. Gene expression in purified populations of retinal progenitors was compared to that in total brain using cDNA microarrays of over 12,000 genes. The resulting data were analysed by several different forms of cluster analysis, a method of exploratory statistics, two of which are shown here. The graphs show part of the results of k-means clustering of the data, and the colour blocks the results of hierarchical clustering. In both cases, three classes of progenitor-enriched genes are shown, depending on their enrichment compared to total brain and retina. Overall, we have identified several hundred genes that are highly enriched in their expression in neural progenitors in all parts of the nervous system.



Facing page: Gene expression profiling of single neural progenitors using cDNA microarrays. cDNA amplified from a single progenitor cell (red) was compared with that of total brain (green) to identify progenitor-enriched transcripts on an array of over 12,000 mouse genes from the NIH Brain Molecular Anatomy Project (BMAP) – progenitor genes appear as bright red spots.

Examples of progenitor-enriched genes. *In situ* hybridisation showing expression of two progenitor-enriched genes in the developing neural retina.

ANNE McLAREN

Co-workers:

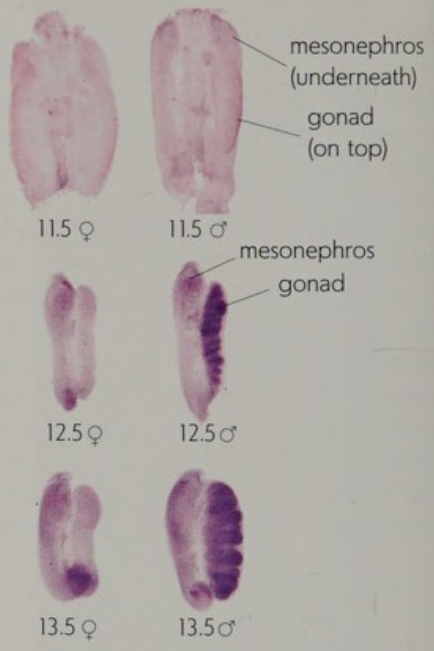
IAN ADAMS
GABRIELA DURCOVA-HILLS
MARGARET TYCE-BUTCHER

Our research focuses on mouse primordial germ cells and the pluripotent stem cells derived from them.

We have established that prenatal entry into meiosis, the prelude to oogenesis, occurs spontaneously in both XX and XY germ cells, but is inhibited in the male genital ridge. In a search for the molecular basis of this masculinising influence, one of the genes that we have identified is prostaglandin D synthase. Prostaglandin D_2, a signalling molecule, is expressed in both germ cells and supporting cells in the male genital ridge, possibly generating a masculinising feedback loop. We are now investigating some of the other genes that have come out of our screening programme. In a different series of experiments, we are exploring the genetic basis of entry into meiosis in the female genital ridge.

Using the embryonic germ (EG) cell lines that we have derived from primordial germ cells both during migration and after reaching the genital ridge, we are now comparing the methylation status of imprinted genes in EG cells with that of their progenitor cells, as a measure of imprint erasure. Some imprinted genes show sex differences in the degree of hypomethylation in EG cells: using sex-reversed embryos we are exploring whether these differences reflect genotypic or phenotypic sex.

We are also interested in the effect of culture conditions on cell differentiation, for example the duration of exposure to culture that is required to shift the germ-cell to the stem-cell phenotype, and the subsequent possibilities for directed differentiation of the pluripotent stem cells.



In situ hybridisation of prostaglandin D synthase shows that this gene is expressed in developing male but not female gonads from 12.5 dpc onwards.

Adams, I. and McLaren, A. (2002) Sexually dimorphic development of mouse primordial germ cells: switching from oogenesis to spermatogenesis. **Development** *129,* 1155–1164.

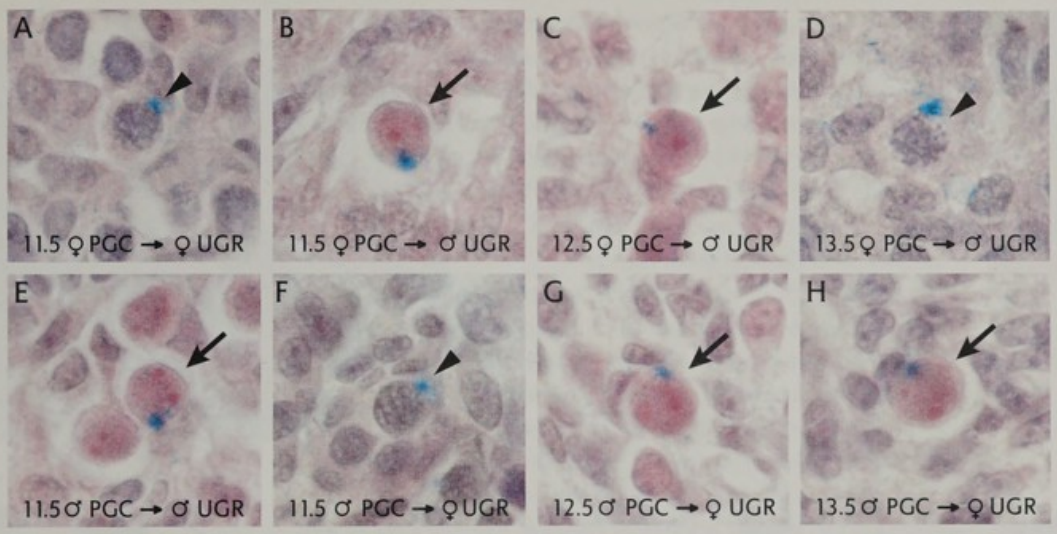
Durcova-Hills, G., Ainscough, J.E. and McLaren, A. (2001) Pluripotential stem cells derived from migrating primordial germ cells. **Differentiation** *68,* 220–226.

McLaren, A. (2001) Mammalian germ cells: birth, sex and immortality. **Cell Struct. Funct.** *26,* 119–122.

McLaren, A. (2001) Dolly mice. In: **The Cloning Sourcebook** (ed. A.J. Klotzko), Oxford University Press.

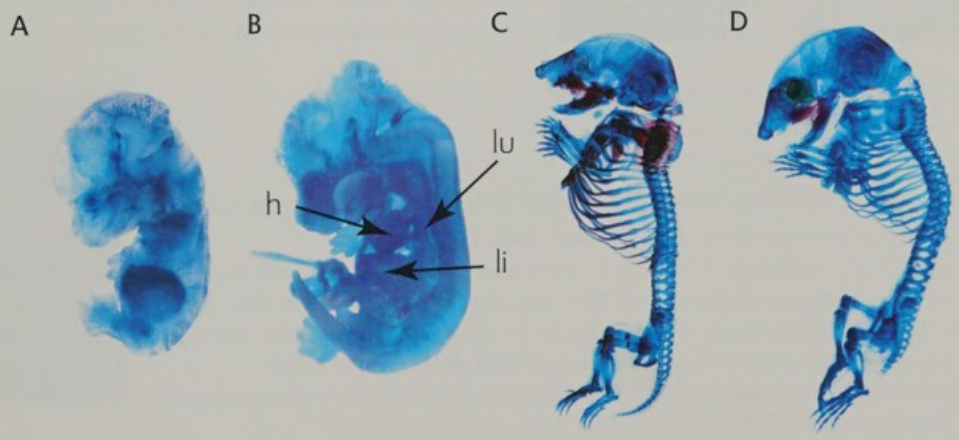
McLaren, A. and Durcova-Hills, G. (2001) Germ cells and pluripotent stem cells in the mouse. **Reprod. Fertil. Dev.** *13,* 661–664.

For further publications see numbers 66 and 70 on pages 56 and 57.



Primordial germ cells (PGCs) were isolated from male (♂) or female (♀) donor urogenital ridges (UGR), mixed with male or female 12.5 dpc recipient UGRs and cultured. Donor PGCs are marked with a cyan perinuclear dot (LacZ+). Meiotic oocytes (arrowheads) have condensed chromatin staining. Arrested prospermatogonia (arrows) have diffuse chromatin staining with prominent nucleoli. At 11.5 dpc PGCs are sexually bipotential and develop as male or female, depending on the sex of the surrounding cells. By 13.5 dpc PGCs have become committed to develop as either oocytes or prospermatogonia and continue to develop along that pathway, regardless of the sex of the surrounding cells.

Primordial germ cells carrying a LacZ transgene are converted, after short culture, into pluripotent stem cells. These cells showed low (A) and high (B) level of contribution to chimeras. Cells preferentially colonised the lungs (lu), heart (h), and liver (li). At later stages, skeletal abnormalities are evident in a few of these chimeras. A fetal chimera with a normal skeleton is shown in (C) and one with skeletal defects is shown in (D).



NANCY PAPALOPULU

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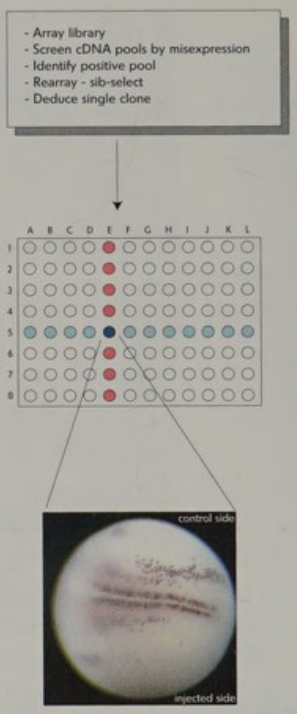
SAMANTHA CARRUTHERS
ANDREW CHALMERS
PENNY DAY
ELENA FINEBERG
SUE KENWRICK
BERNHARD STRAUSS
MARGARET TYCE-BUTCHER
JANA VOIGT

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 model systems and a combination of molecular and classical embryology.

At the onset of neuronal differentiation, the neural ectoderm expresses a number of highly localised transcription factors. We are aiming to understand how these transcription factors instruct subsets of cells to differentiate and others to continue dividing. Our recent work focused on the interaction of a telencephalic transcription factor, XBF-1, and components of the cell cycle. While research on this front is continuing, we are working to identify additional genes in this pathway as well as novel genes that affect neural development.

Recently, we have discovered that the early neural ectoderm is not a homogeneous population of progenitor cells. Instead it contains progenitor cells with intrinsically different capacities for differentiation. As a result, a subset of neuronal progenitor cells do not differentiate in response to the inducing signals present in the early embryo and continue to divide instead. This intrinsic difference is likely to result from asymmetric cell divisions that take place at the blastula stage. Nucleic acid and protein screening projects are under way to identify the determinants involved in this process.



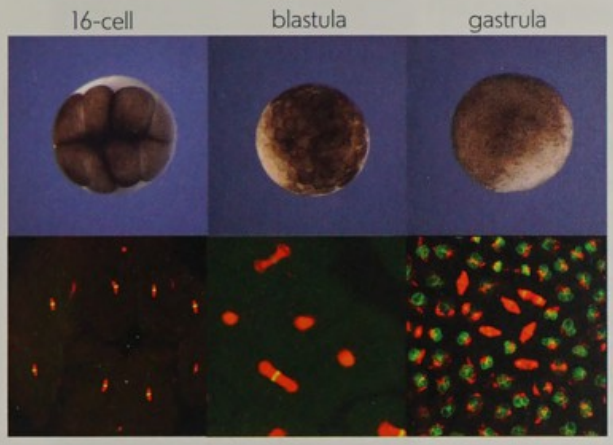
A pooled cDNA expression screen is used to identify molecules that affect neurogenesis. In this example, a single identified clone inhibited differentiation on the injected side (Jana Voigt).

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.

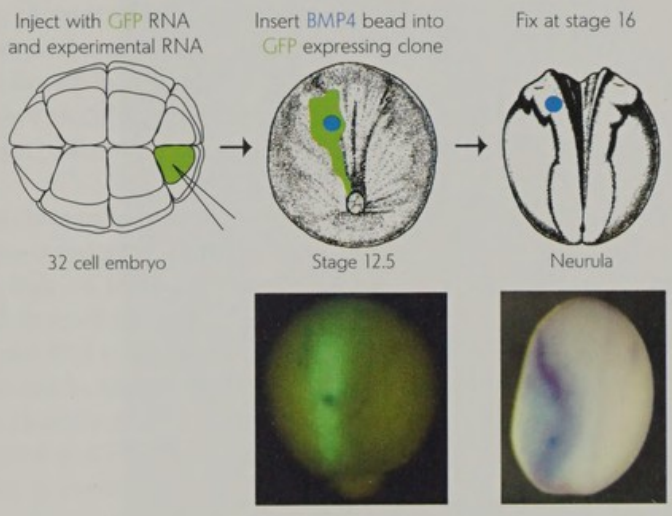
Hartley, K.O., Hardcastle, Z, Amaya, E. and Papalopulu, N. (2001) Transgenic *Xenopus* embryos reveal that anterior neural development requires continued suppression of BMP signalling after gastrulation. **Dev. Biol.** *238,* 168–184.

Hardcastle, Z., Chalmers A. and Papalopulu, N. (2000) FGF-8 stimulates neurogenesis through the FGF receptor 4 (FGFR4) 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 p27(Xic1) and imparting a neural fate. **Development** *127,* 1303–1314.



At the 16-cell stage, spindles are parallel to the surface of the embryo. At the late blastula stage, spindles are either parallel or perpendicular to the surface of the embryo, generating cells with different intrinsic properties. Just before gastrulation, all spindles are once again oriented parallel to the surface (Andrew Chalmers and Bernhard Strauss).



Implantation of BMP4 protein soaked beads (blue) into experimental + GFP RNA injected region (green) shows the co-operation of two signalling pathways in inducing a neural border marker gene (Penny Day).

Knocking out the cell cycle inhibitor p27 Xic by an antisense morpholino oligo inhibits neuronal differentiation (Samantha Carruthers).

JONATHON PINES

Co-workers:

CLAIRE ACQUAVIVA
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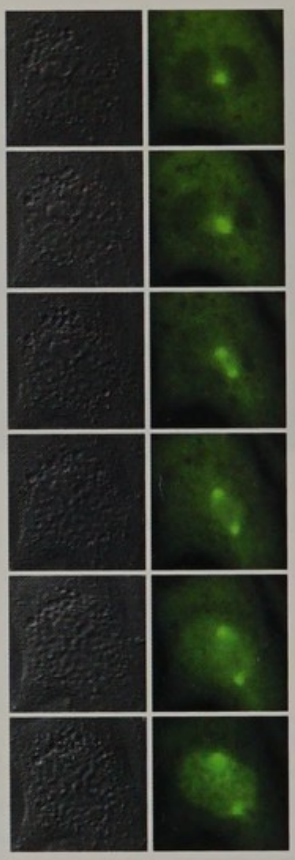
VIJI MYTHILY DRAVIAM
ANJA HAGTING
MARK JACKMAN
CATHERINE LINDON
TAKAHIRO MATSUSAKA
JO RICHARDSON
ROB WOLTHUIS

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.



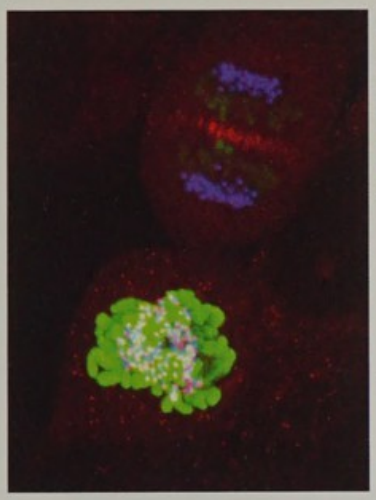
Cyclin B1 translocates into the nucleus at the end of prophase. Simultaneous fluorescence and DIC images of a cell expressing cyclin B1-GFP.

den Elzen, N. and Pines, J. (2001) Cyclin A is destroyed in prometaphase and can delay chromosome alignment and anaphase. **J. Cell Biol.** *153,* 121–135.

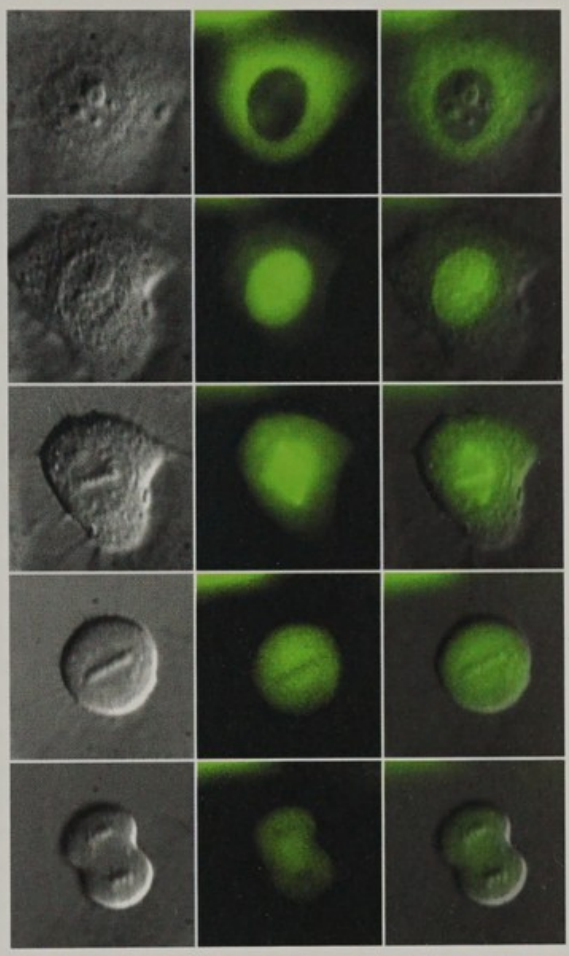
Draviam, V.M., Orrechia, S., Lowe, M., Pardi, R. and Pines, J. (2001) The localization of human cyclins B1 and B2 determines CDK1 substrate specificity and neither enzyme requires MEK to disassemble the golgi apparatus. **J. Cell Biol.** *152,* 945–958.

Jackman, M., Kubota, Y., den Elzen, N., Hagting, A. and Pines, J. (2002) Cyclin A- and cyclin E-CDK complexes shuttle between the nucleus and the cytoplasm. **Mol. Biol. Cell** *13,* 1030–1045.

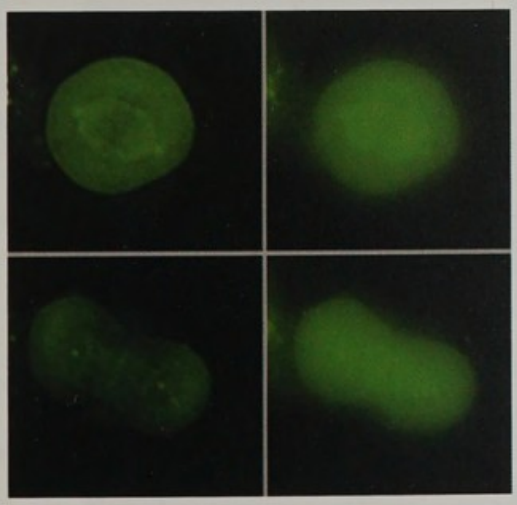
For further publications, see numbers 55, 68, 75, 78 and 100 on page 56–58.



HeLa cells in anaphase (top) and prometaphase (bottom) stained for anti-phospho-histone H3 (green), anti-CENP-E (red) and CREST anti-centromere antibodies (blue).

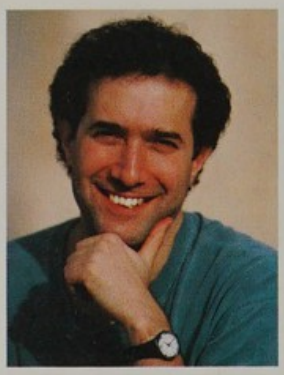


Cyclin B1-degradation visualised in real time. Cyclin B1–GFP purified from baculovirus-infected cells was injected into a HeLa cell and then imaged with a cooled slow-scan CCD camera. Left panels: DIC images; middle panels: fluorescence; right panels: merged images.



HeLa cells expressing Cdc20-GFP in metaphase (top) and anaphase (bottom). The images on the left are derived by deconvolution from those on the right.

JORDAN RAFF



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MARUXA MARTINEZ
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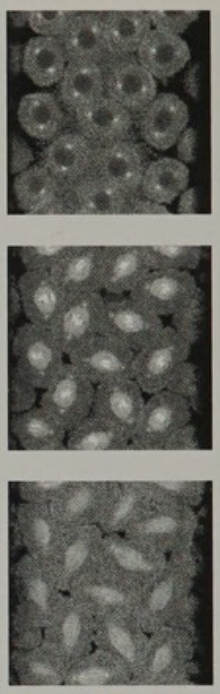
The centrosome is the main microtubule organising centre in animal cells. Despite their central role in organising many cellular events, very little is known about how centrosomes function. We have taken a reductionist approach to this problem, using *Drosophila* as a model system to isolate proteins that bind to microtubules *in vitro* and associate with centrosomes *in vivo*. One of these proteins, called D-TACC, interacts with microtubules in association with Minispindles, the *Drosophila* homologue of XMAP215, a well characterised microtubule stabilising protein that is also concentrated at centrosomes. The interaction between D-TACC and Msps appears to play a crucial role in regulating the stability of centrosomal microtubules in embryos. The interaction between D-TACC and Msps is conserved in evolution, and the human homologues of both D-TACC and Msps have previously been implicated in cancer. We are currently using double-stranded RNA-mediated interference (RNAi) to probe the function of these proteins in human cells.

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 shown that the degradation of cyclin B 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.

Lee, M.J., Gergely, F., Jeffers, K., Peak-Chew, S-Y. and Raff, J.W. (2001) Msps/XMAP215 interacts with the centrosomal protein D-TACC to regulate microtubule behaviour. **Nat. Cell Biol.** *3,* 643–649

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. Natl. Acad. Sci. USA** *97,* 14352–57.

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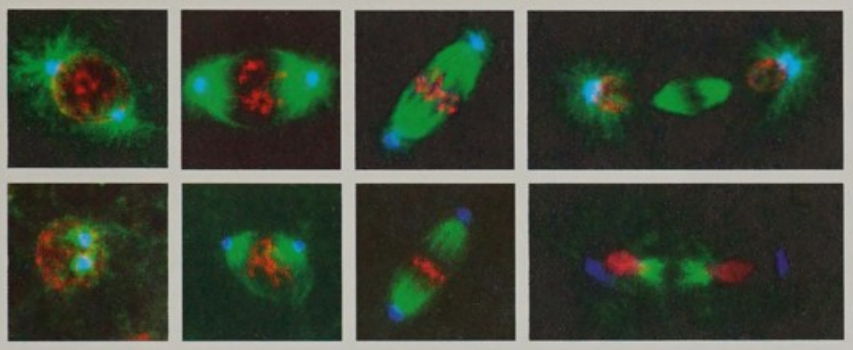
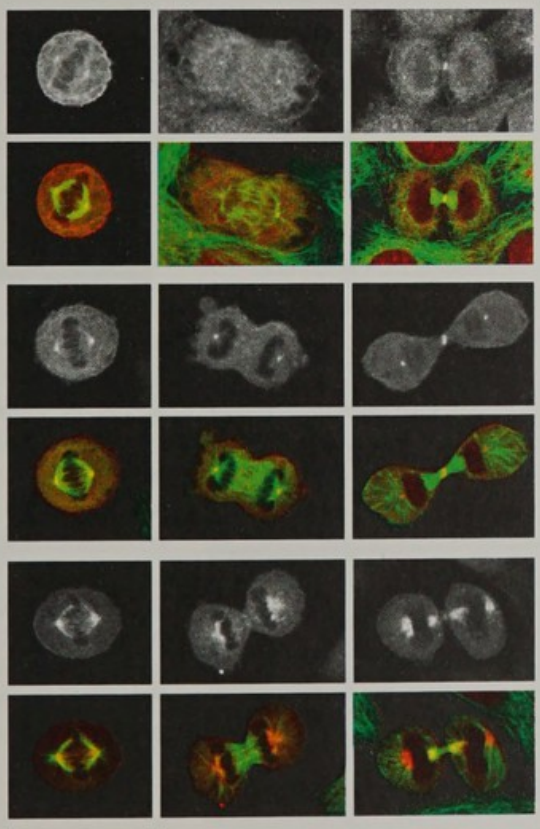
For further publications, see numbers 36 and 82 on pages 55 and 57.

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.

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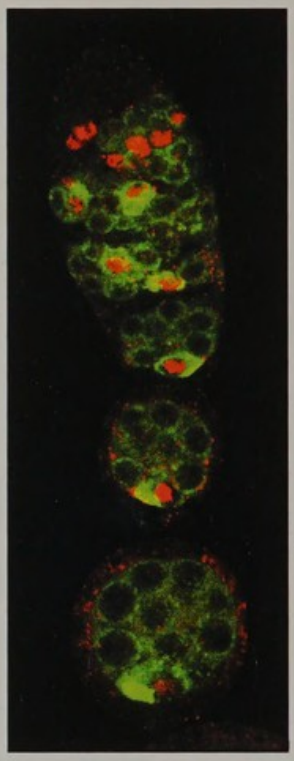
The localisation of *bicoid*, *oskar* and *gurken* mRNAs to three distinct positions within the *Drosophila* oocyte defines the anterior-posterior and dorsal-ventral axes of the embryo, and provides an excellent model system for analysing the molecular mechanisms that underlie cell polarity and mRNA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

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 that are required for the polarisation of the oocyte or for the localisation of *bicoid* or *oskar* mRNA, and are now analysing their functions.



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

Huynh, J-R., Petronczki, M., Knoblich, J.A. and St Johnston, D. (2001) Bazooka and PAR-6 are required with PAR-1 for the maintenance of oocyte fate in *Drosophila*. **Curr. Biol.** *11*, 901–906.

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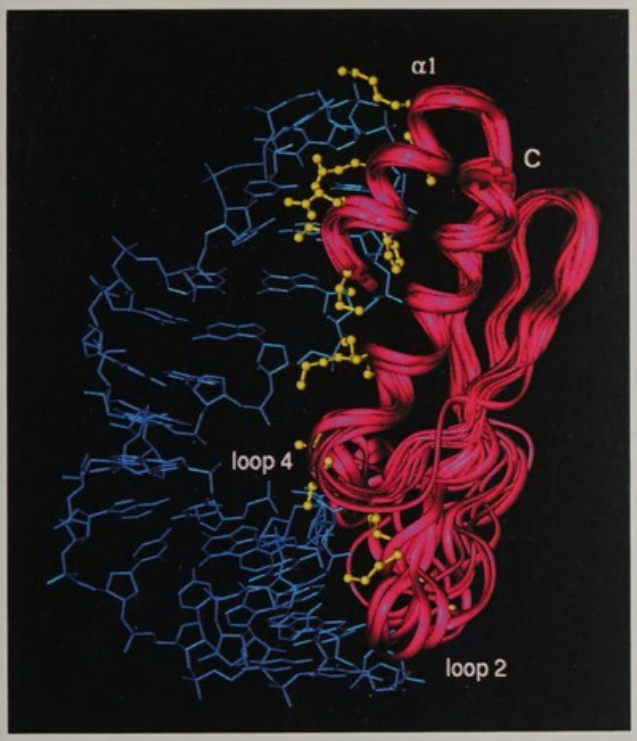
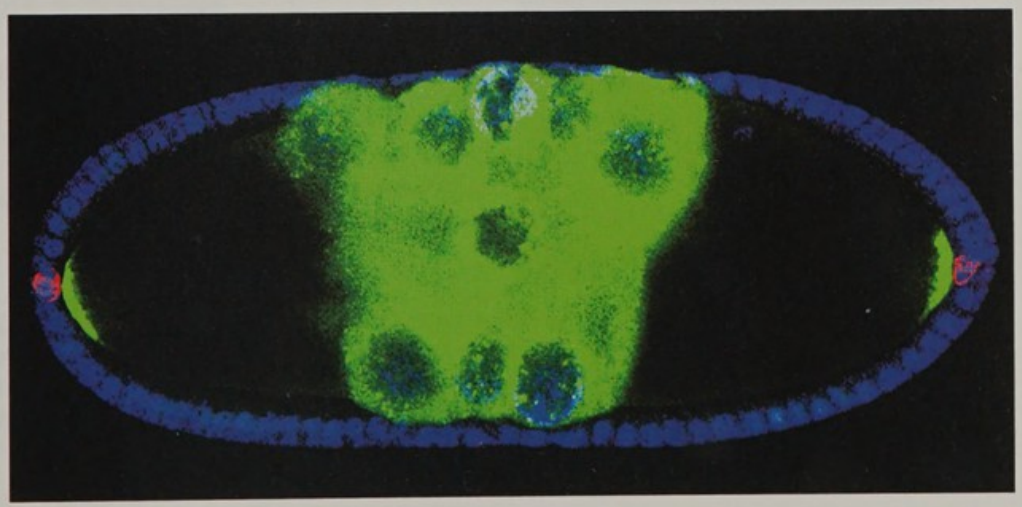
For further publications, see numbers 12, 29, 47, 62, 76, 85 and 96 on pages 53–58.



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), Fascilin 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.

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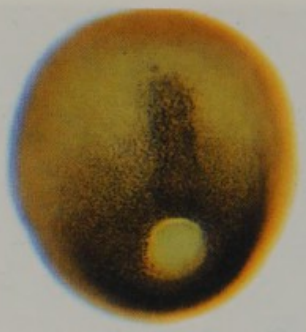
HUW WILLIAMS

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 also study the regulation of the cell cycle in the mesoderm and we make 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 T box gene family, and especially *Brachyury*, 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 identified *Wnt11* as a target of *Brachyury* that is required for gastrulation movements in both *Xenopus* and zebrafish. Wnt11 signals through the planar polarity pathway, and we are investigating the roles of Wnt11 and components of the planar polarity pathway in gastrulation using cell biological and imaging techniques. We are also investigating the functions of other T box targets such as members of the Bix family of homeodomain-containing proteins.



An anti-Brachyury antibody stains nuclei in the notochord and in the posterior mesoderm of the neurula-stage embryo.

Ectopic expression of SIP1, in the cells expressing a red lineage label, causes down-regulation of Xbra.

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.

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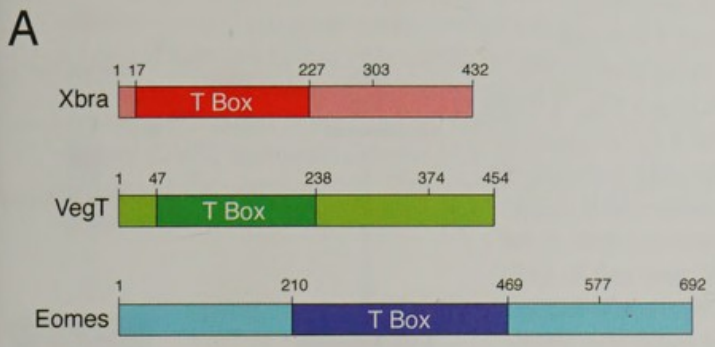
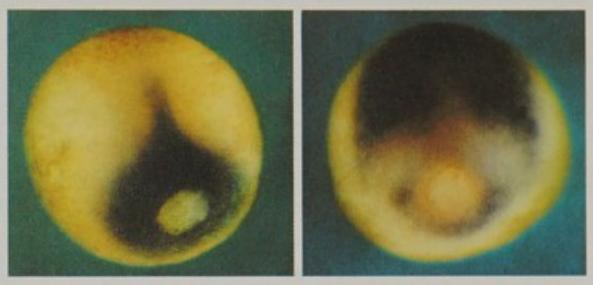
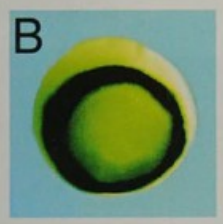
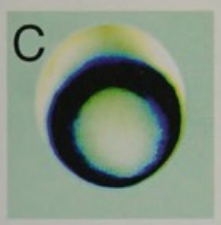
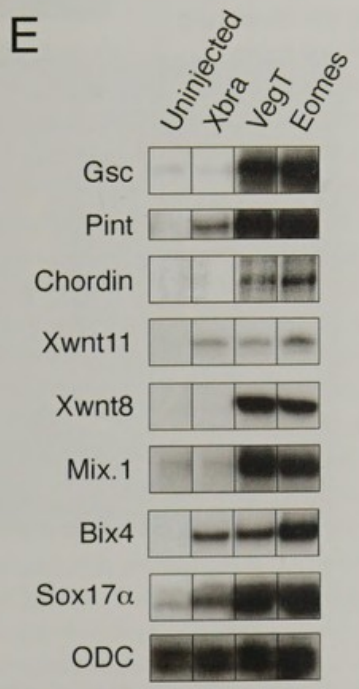




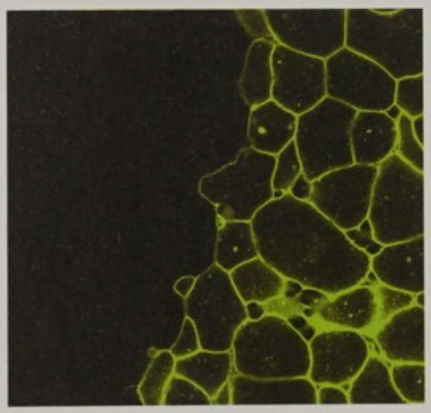
Expression of Xbra (left) and SIP1 (right) at the late gastrula stage.The two expression domains are mutually exclusive.





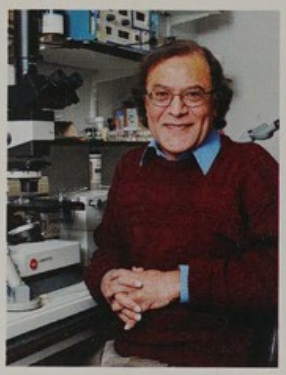


Specificity of T box genes in the early *Xenopus* embryo. Xbra, VegT and Eomesodermin are expressed in similar domains, but they activate the expression of different genes.



Xenopus animal pole regions adhere strongly to fibronectin, allowing clear visualisation of cells in the confocal microscope. In this image, two animal caps, one of which is labelled with a membrane marker, are juxtaposed.

AZIM SURANI



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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 the signalling molecules from extraembryonic tissues (Fig. 1). These precursor cells are not lineage restricted as they can develop either into primordial germ cells or somatic cells, including the allantois. We have established a genetic screen using single cell cDNAs, which has identified novel genes involved in the specification of the 45 founder primordial germ cells in E7.5 embryos. Some of the novel genes may also have a role in pluripotent embryonic stem cells (ES) and embryonic germ (EG) cells (Fig. 2).

After the germ cells begin to migrate into the developing gonads at E10.5, epigenetic modifications unique to this lineage follow, perhaps in response to signal(s) from somatic cells. Reprogramming and erasure of epigenetic modifications within germ cells includes reactivation of the X chromosome, erasure of genomic imprints and genome-wide demethylation (Fig. 3). We are investigating the identity of the intrinsic factors involved in this reprogramming event. We are also exploring the mechanisms by which epigenetic states can be reversed to confer pluripotency to differentiated somatic cells.

New imprints are initiated during gametogenesis that require *cis* control elements associated with imprinted genes (Fig. 3). Mature oocytes contain factors, including HP1 and Ezh(2), that regulate, enhance and maintain the epigenetic asymmetry between parental genomes in early embryos. The imprints are heritable from the zygote into adulthood where they regulate expression of imprinted genes serving diverse functions, including growth, differentiation and behaviour.

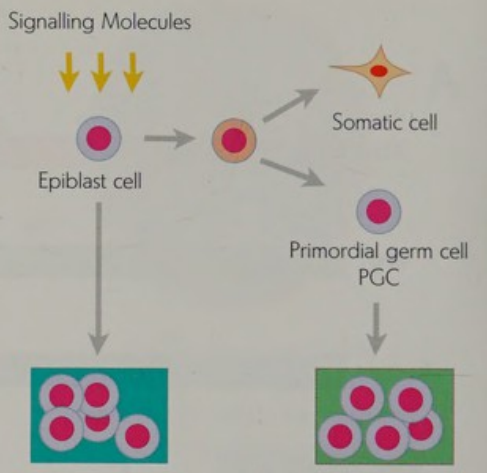


Fig. 2. The relationship between the epiblast, primordial germ cells (PGCs) and pluripotent stem cells. A somatic nucleus when fused with a pluripotent EG or ES cell undergoes epigenetic modifications, including demethylation, so that it resembles pluripotent stem cell in most respects. This suggests that epigenetic states can be reversed to confer pluripotency on somatic cells.

Surani, M.A. (2001) Reprogramming of genome function through epigenetic inheritance. **Nature** *414,* 122–128.
Ferguson-Smith, A.C. and Surani, M.A. (2001) Imprinting and the epigenetic asymmetry between parental genomes. **Science** *293,* 1086–1089.
Arney, K.L., Erhardt, S., Drewell, R.A. and Surani, M.A. (2001) Epigenetic reprogramming of the genome – from the germ line to the embryo and back again. **Int. J. Dev. Biol.** *45,* 509–516.

For further publications, see numbers 2, 5, 25, 45, 50–52, 69 and 74 on pages 53–57.

Fig. 3 (right). A. Germ cells migrate into the fetal gonads by day 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. Deletion of SL also results in de-repression of the silent paternal allele.

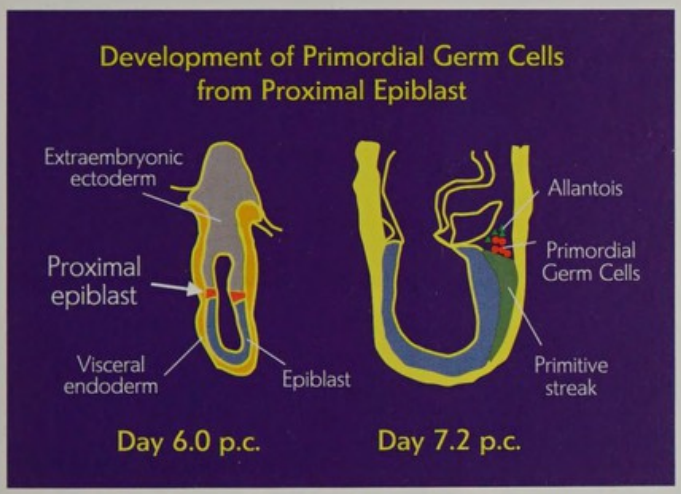
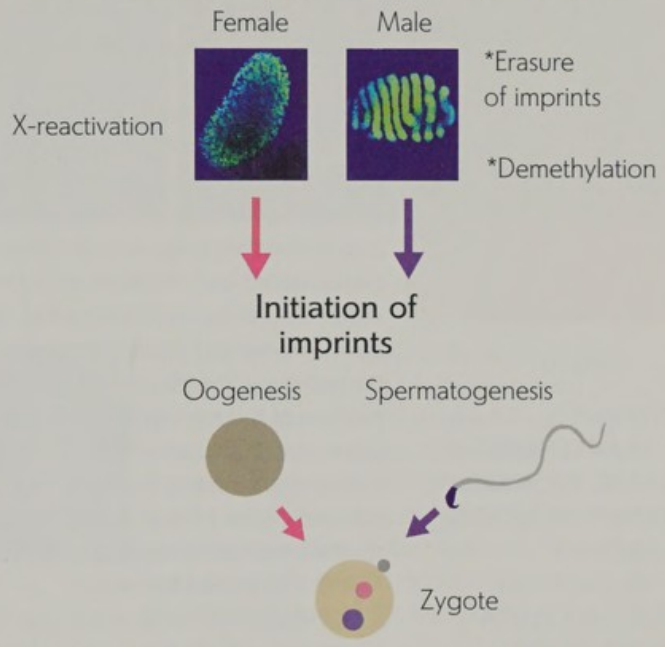


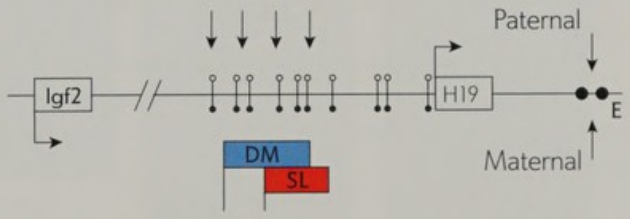
Fig. 1 (above). The proximal epiblast cells on day 6.0 p.c are the precursor cells for the germ cell lineage. They converge towards the posterior region where the primitive streak develops. These precursor cells develop either as germ cells or as somatic extraembryonic mesoderm. Approximately 40 founder primordial germ cells (PGCs) are detected at day 7.2 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.

3A Germ cells in fetal gonads at day 12.5 p.c.



Pre-implantation development propagation of imprints

3B Imprinting *cis* control element



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FLORENCE WIANNY

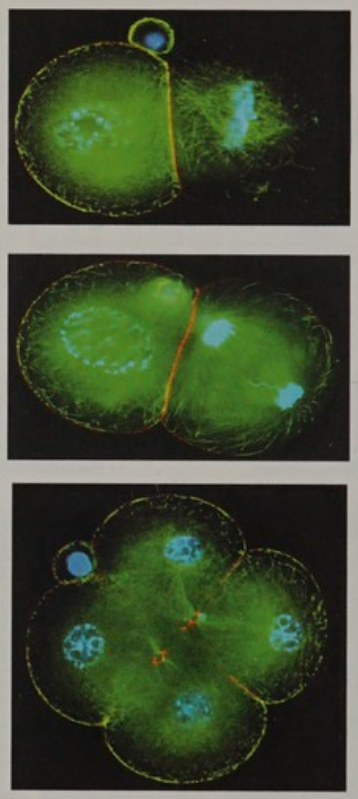
We are studying how polarity and patterning becomes established during early mouse development. Whereas in most species the polarity of the embryo is laid down in the egg, mammalian embryos were thought to be exceptional, their polarity apparently developing only after implantation. However, our recent cell fate studies showed that mouse embryo polarity is anticipated before implantation and relates to spatial patterning of the egg. This was unexpected because preimplantation embryos can withstand experimental perturbations and still develop normally. Now we wish to understand those mechanisms that establish polarity in normal development and those that compensate for developmental perturbation. Specification of polarity appears to stem from the position of the meiotic divisions in the egg and the site of sperm entry. The pattern of cell division is influenced by these cues and can dictate the basic features of blastocyst organisation and hence of later stages. These surprising findings open several questions about the origin of polarity in mammals.

We address the following:

1) How do developmental cues lead to asymmetry? We are combining experimental and molecular embryology to disturb egg polarity and examine its role in early patterning.

2) How does polarity of the preimplantation embryo lead to organised signalling activity at later developmental stages? We are using lineage and transplantation studies to examine the normal fate of cells and their impact in novel combinations.

3) What are the mechanisms that establish polarity? We are applying microarray analysis to discover genes that mediate the development of polarity and then perturbing spatial and temporal patterns of expression of such genes through mis-expression and RNAi.

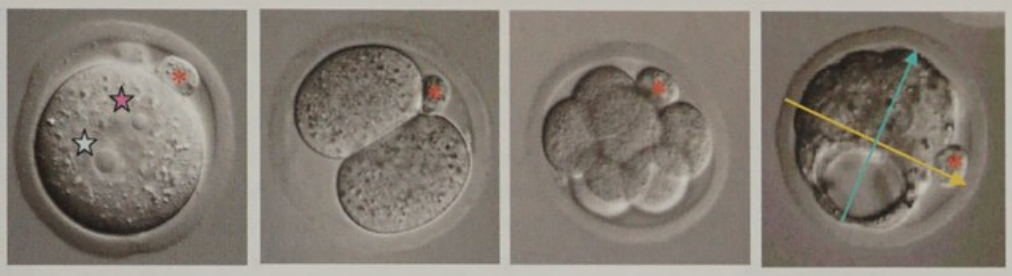


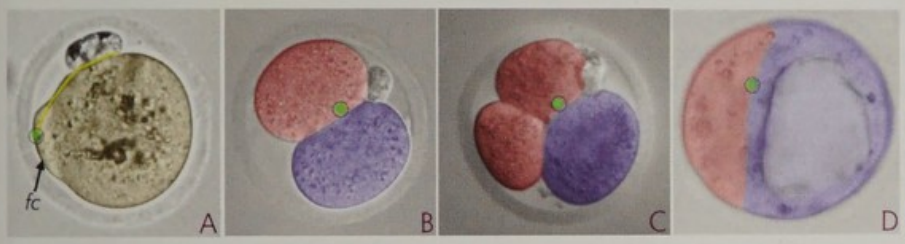
Mouse embryo undergoing second cleavage division. Orientation of the cleavage plane relates to the animal pole. Microtubules (green), actin (red) and chromatin (blue).

Zernicka-Goetz, M. (2002) Patterning of the embryo – the first spatial decisions in the life of a mouse. **Development** *129*, 815–829.
Piotrowska, K. and Zernicka-Goetz, M. (2001) Role for sperm in spatial patterning of the early mouse embryo. **Nature** *409*, 517–521.
Wianny, F. and Zernicka-Goetz, M. (2000) Specific interference with gene function by double stranded RNA in mouse. **Nat. Cell Biol.** *2*, 70–75.

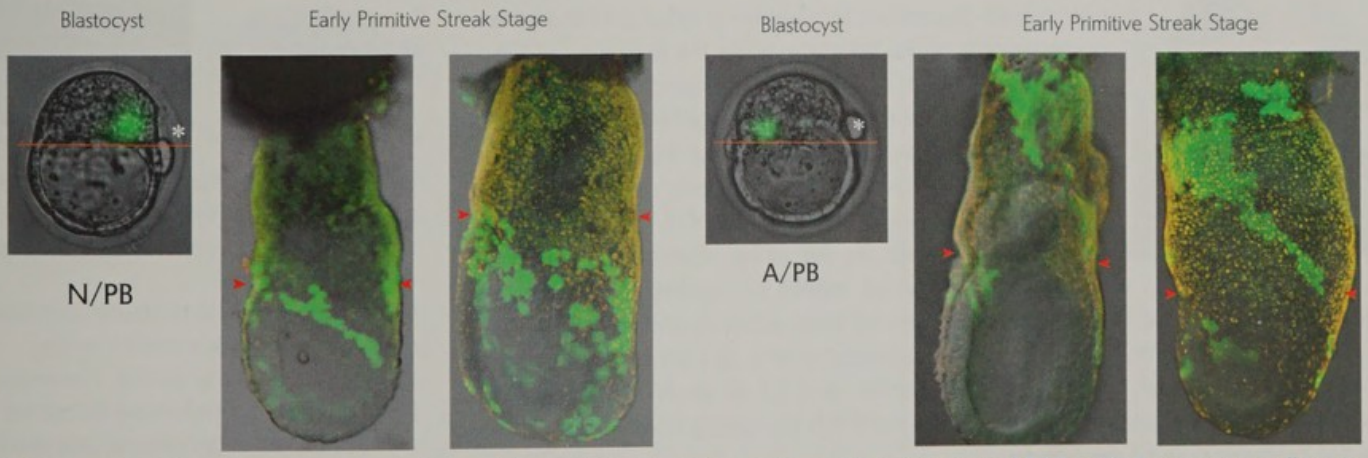
For further publications, see numbers 80, 81, and 100 on pages 57 and 58.

Preimplantatation development of the mouse embryo. Fertilised egg with female and male pronuclei (pink and blue stars, respectively) and polar body marking the animal pole (red asterisk). Blastocyst with its animal-vegetal (yellow) and embryonic-abembryonic (blue) axes.





Blastomeres of the 2-cell mouse embryo have distinguishable fates. The fertilisation cone (fc) with sperm tail (yellow) and fluorescent bead (green) marks the sperm entry point (SEP) in the zygote. The 2-cell blastomere that inherits the SEP (red) tends to divide first to produce cells that populate the embryonic part of the blastocyst. The other blastomere (blue) tends to populate the abembryonic part of the blastocyst.



Polarity of the blastocyst anticipates polarity of the post-implantation embryo. Microinjection of GFP mRNA into inner cell mass cells either near (N/PB) or away (A/PB) from the polar body demonstrates differential fate in the post-implantation egg cylinder.

FOUR-YEAR RESEARCH GRANT HOLDERS

MIRANDA GOMPERTS

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.

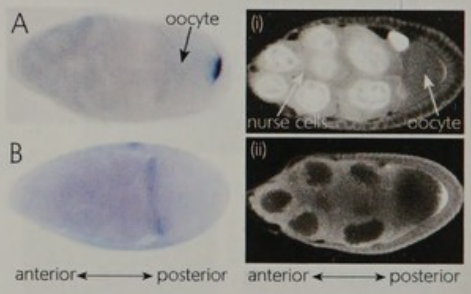
Xenopus embryos expressing GFP under the control of *flh* regulatory sequences.
A. whole embryo
B. pineal gland
C. notochord

Co-worker:

KIM GOLDSTONE

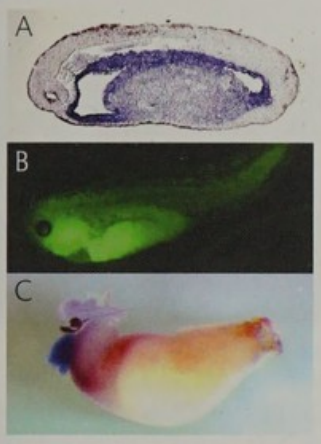
ISABEL PALACIOS

Intracellular localisation of messenger RNA (mRNA) is a common way of targeting proteins to the regions where they are required. One of the best characterised examples of localised mRNA is found in the *Drosophila* oocyte, where the microtubule-dependent localisation of *oskar* mRNA to the posterior pole of the oocyte specifies the formation of the pole plasm. Genetic screens have identified genes that are required for the localisation of *oskar* mRNA. These genes can be compiled into two categories: Those that are required for cell polarity and those that are specifically required for the transport of *oskar* mRNA, such as *staufen, mago nashi, barentsz* and *kinesin*. The aim of my research is to understand the mechanism of *oskar* mRNA localisation by analysing the precise function of those factors. I am taking several approaches to address this question: 1) I am using GFP-Staufen to visualise mRNA transport *in vivo;* 2) I am searching for new proteins that interact with Mago nashi and Barentsz; and 3) I am studying how Kinesin, a microtubule motor protein, recognises the *oskar* mRNA-containing complex and localises it to the posterior pole of the oocyte.



Left: Localisation of *oskar* mRNA at the posterior (A) or at the anterior pole (B) in wild type or *barentsz* mutant oocytes, respectively.
Right: Mago nashi and Staufen proteins co-localise with *oskar* mRNA to the posterior pole of the oocyte. However, (i) Mago nashi is predominantly nuclear and (ii) Staufen is cytoplasmic (apparent in the nurse cells).

For recent publications, see numbers 29, 76 and 96 on pages 54, 57 and 58.



A. *XSox17b* (blue) in the naïve endoderm. B. A transgenic *Xenopus* embryo 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 microarray 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 15, 87, 91 and 103 on pages 53, 57 and 58.

AARON ZORN

Co-workers:

JULIA MASON
RICARDO COSTA

CATEGORIES OF APPOINTMENT

Senior Group Leader
Professor, Reader or Lecturer Level

Group Leader
Five-year grant-funded appointment (maximum 10 years)

Career Development Fellow
Four-year grant-funded appointment, within individual groups

Independent Senior Research Associate
Three-year grant-funded appointment, within individual groups

Research Associate/Fellow
Postdoctoral, within individual groups, appointed by group leader

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

POSTGRADUATE OPPORTUNITIES

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

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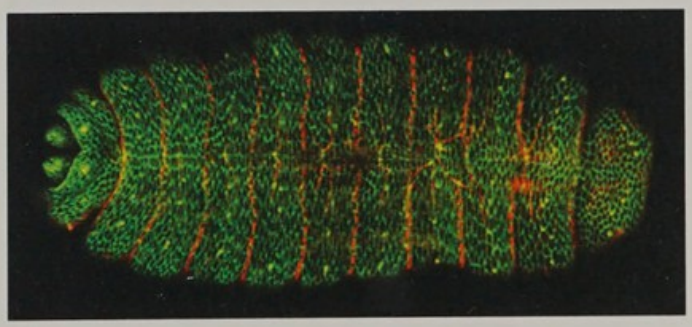

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The following is a list of works by the Institute that were either published or accepted for publication in 2001.

1 Adams, I. and McLaren, A. (2002) Sexually dimorphic development of mouse primordial germ cells: switching from oogenesis to spermatogenesis. **Development** *129,* 115–1164.

2 Arima, T., Drewell, R.A., Arney, K.L., Inoue, J., Makita, Y., Hata, A., Oshimura, A., Wake, N. and Surani, A. (2001) A conserved imprinting control region at the *HYMAI/ZAC* domain is implicated in transient neonatal diabetes mellitus. **Hum. Mol. Genet.** *10,* 1475–1483.

3 Arney, K.L., Erhardt, S., Drewell, R.A. and Surani, M.A. (2001) Epigenetic reprogramming of the genome—from the germ line to the embryo and back again. **Int. J. Dev. Biol.** *45,* 509–516.

4 Bannister, A.J., Zegerman, P., Partridge, J.F., Miska, E.A., Thomas, J.O., Allshire, R.C. and Kouzarides, T. (2001) Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. **Nature** *410,* 120–124.

5 Barton, S.C., Arney, K.L., Shi, W., Niveleau, A., Fundele, R., Surani, M.A. and Haaf, T. (2001) Genome-wide methylation patterns in normal and uniparental early mouse embryos. **Hum. Mol. Genet.** *10,* 2983–2987.

6 Bauer, U-M., Daujat, S., Nielsen, S.J, Nightingale, K. and Kouzarides, T. (2001) Methylation at arginine 17 of histone H3 is linked to gene activation. **EMBO Rep.** *3,* 39–44.

7 Bell, S.D. and Jackson, S.P. (2001) Mechanism and regulation of transcription in archaea. **Curr. Opin. Microbiol.** *4,* 208–213.

8 Bell, S.D., Magill, C.P. and Jackson, S.P. (2001) Basal and regulated transcription in Archaea. **Biochem. Soc. Trans.** *29,* 292–395.

9 Bell, S.D., Brinkman, A.B., van der Oost, J. and Jackson, S.P. (2001) The archaeal TFIIEα homologue facilitates transcription initiation by enhancing TATA box regulation. **EMBO Rep.** *2,* 133–138.

10 Bellaiche, Y., Gho, M., Kaltschmidt, J.A., Brand, A.H. and Schweisguth, F. (2001) Frizzled regulates the localization of cell-fate determinants and mitotic spindle rotation during asymmetric cell division. **Nat. Cell Biol.** *3,* 50–57.

11 Blackshaw, S. and Livesey, F.J. (2002) Applying genomics technologies to neural development. **Curr. Opin. Neurobiol.** *12,* 110–114.

12 Bolivar, J., Huynh, J-R., López-Schier, H., González, C., St Johnston, D. and González-Reyes, A. (2001) Centrosome migration into the *Drosophila* oocyte is independent of *BicD* and *egl,* and of the organisation of the microtubule cytoskeleton. **Development** *128,* 1889–1909.

13 Boube, M., Martin-Bermudo, M.D., Brown, N.H. and Casanova, J. (2001) Specific tracheal migration is mediated by complementary expression of cell surface proteins. **Genes Dev.** *15,* 1554–1562.

14 Breckenridge, R.A., Mohun, T.J. and Amaya, E. (2001) A role for BMP signalling in heart looping morphogenesis in *Xenopus*. **Dev. Biol.** *232,* 191–203.

15 Butler, K., Zorn, A.M. and Gurdon, J.B. (2001) Nonradioactive *in situ* hybridization to *Xenopus* tissue sections. **Methods** *23,* 303–312.

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STAFF AFFILIATIONS

JULIE AHRINGER is a Board Member of the British Society for 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, Paris, France; Member, 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 Biochemical Society Nucleic Acids and Molecular Biology Group Committee and Chief Scientific Officer, KuDOS Pharmaceuticals Ltd.
TONY KOUZARIDES is a member of the Cancer Research UK Grants Committee, 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 Human Fertilisation and Embryology Authority, the European Group on Ethics (an advisory group to the European Commission) and is also a Trustee of the Natural History Museum.
NANCY PAPALOPULU is a Board Member of the British Society for Developmental Biology.
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 was made 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 was co-Chair of the Academy of Medical Sciences working group on the Careers of Non-clinical Scientists and Chair of the Royal Society's working group on Genetically Modified Plants for Food Use. He was a member of the Royal Society Working Group on the Use of Genetically Modified Animals. He is a non-executive Director of the Company of Biologists 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.
MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Research Fellow at Sidney Sussex College and EMBO Young Investigator.

HONOURS AND AWARDS

ANDREA BRAND, Hooke Medal of the British Society for Cell Biology, 2002. Dietrich Bodenstein Lecturer, University of Virginia, 2002. Invited Professor, Ecole Normale Superieure, Paris, France, 2002.
JOHN GURDON, Conklin Medal of the American Society for Developmental Biology.
STEVE JACKSON, Anthony Dipple Carcinogenesis Young Investigator Award, elected Fellow of the Academy of Medical Sciences.
TONY KOUZARIDES, awarded the Tenovus Medal 2001 and the Wellcome Trust Medal for Biochemical Research Related to Medicine, a Royal Society Napier Research Professorship, and made a Fellow of the Royal Academy of Medical Sciences.
ANNE McLAREN received the L'Oreal/UNESCO Women in Science 2001 Award for Europe and the US Society for Developmental Biology Award for Lifetime Scientific Achievement.
JONATHON PINES, elected Member of the European Molecular Biology Organization.
DANIEL ST JOHNSTON European Molecular Biology Organization Gold Medal, 2000.
AZIM SURANI Elected Fellow of the Academy of Medical Sciences, recipient of The Royal Society Gabor Medal.

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CHAIRMAN OF THE MANAGEMENT COMMITTEE

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

LEAVERS DURING 2001

JUSTIN AINSCOUGH is now working at the Institute for Cardiovascular Research in Leeds as a British Heart Foundation Fellow.

INES ALVAREZ-GARCIA has taken up a post-doctoral position at Harvard University, USA.

REBECCA APPELHOFF is continuing her studies at the University of Oxford.

TAKAHIRO ARIMA has returned to Japan to work as a clinician and Research Fellow at the Department of Reproduction Physiology and Endocrinology, Kyushu University.

TIM BRADBEER died suddenly on 8 August 2001.

CAROLYN BULLMAN has retired.

WENDY BURGERS is working as a post-doctoral fellow in Cape Town, South Africa.

KAREN BUTLER has left to run a public house in Royston with her husband.

ROSEMARY COULSON is now working as an insurance claim assessor.

DAMIEN D'AMOURS has taken up a postdoctoral position in Dr Angelika Amon's Laboratory at the Center for Cancer Research, Howard Hughes Medical Institute, MIT, USA.

NICOLE DEN ELZEN has returned to Australia to a post-doctoral position at the Peter MacCallum Institute, Melbourne.

BEHROOZ ESMAEILI got his PhD in May and has taken up a post-doctoral position at the University of Oxford.

ROBERT DREWELL has taken up a post doctoral position at the Department of Molecular and Cell Biology, Berkley, University of California, USA.

DANIEL DUROCHER is working at the Samuel Lunenfeld Research Institute in Toronto, Canada.

CHRISTINE FOX has transferred to the MRC Cancer Cell Unit, Cambridge.

FRANCOIS FUKS is working at the Faculty of Medicine, Laboratory of Molecular Virology, Brussels, Belgium.

STEPHEN GREGORY has returned to Australia to take up a post doctoral position at the University of Adelaide.

ZOË HARDCASTLE is working as a Clinical Trial Assistant at Quintiles in London.

KIM JEFFERS has returned to Australia with her husband.

ROSALIND JOHN has moved to London to look after her young baby.

JULIA KALTSCHMIDT is a post-doctoral fellow at the Howard Hughes Medical Institute, Columbia University, New York, USA.

ANDREA KNOX has taken up a position at the Royal Society in New Zealand.

TORSTEN KRUDE has moved to the Department of Zoology, Cambridge.

NICHOLAS LAKIN has taken up a post doctoral post at the Department of Biochemistry, University of Oxford.

PROFESSOR RON LASKEY and the following members of his group have moved to the MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Cambridge: **MAGDALENA ASSENBERG, STEVE BELL, DAWN COVERLEY, GUILLERMO de la CUEVA MENDEZ, LORENA FARRACE, JACKIE MARR, TONY MILLS, CHRISTINA PELIZON, DAVID SANTAMARIA, DAVID SZUTS** and **YOSHINORI TAKEI.**

VINCENT LECLERC is now working as a Maitre de Conference at the IBMC, Strasbourg, France.

YVONNE LEWIS is now working at Clinical Pharmacology, Cambridge.

KATIA LITIÈRE is now working for PA Consulting in Melbourn.

HERNÁN LÓPEZ-SCHIER is working at the Howard Hughes Medical Institute in New York, USA.

LESLIE MANACE is a medical student at Mount Sinai School of Medicine, New York, USA.

ANDREW MCAINSH is now working at the Department of Biology, MIT, USA.

STEPHEN NUTT is a Group Leader at the Walter & Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Australia.

CATHY PAPIN has returned to France, to work in Montpellier.

PAULA PEACHEY is now working at the Department of Education, University of Cambridge.

DESMOND SCHMIDT has returned to Australia with his family.

KAZUYA SHIMIZU has returned to a post-doctoral position at Osaka University, Japan.

DONNA SMITH is continuing her PhD studies in law.

HENRIETTA STANDLEY has taken up a post-doctoral position with Dr Janet Heasman in Cincinnati, USA.

CHRISTINE STEWART left to take up a post as an Administrative Officer at the University of Cambridge Clinical School.

VERONICA SYMONDS has moved to the Department of Archaeology and Anthropology, University of Cambridge.

JEAN-YVES THURET has gone to CEA-SACLAY, France.

ELIZABETH TWEED has retired.

BRANDI WILLIAMS is now working for Myriad Genetics in Utah, USA.

LUCIE WHITEHEAD has moved to the Department of Anatomy, University of Cambridge.

JOOST WOOLTERING returned to Holland to finish his degree.

Annual Retreat, Amsterdam 2001

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Prospectus produced in the Wellcome Trust/Cancer Research UK Institute, edited by Jane Bradbury and Ann Cartwright. Photography by Chris Green (Biochemistry) and Alex Sossick. Printed by University Printing Services, University Press, Cambridge.

Front cover image by Maithreyi Narasimha, Brown Group: A section through the *Drosophila* embryo stained for integrin (green) and actin (red).

Back cover: The Institute's new building progresses.

Our new building under construction

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