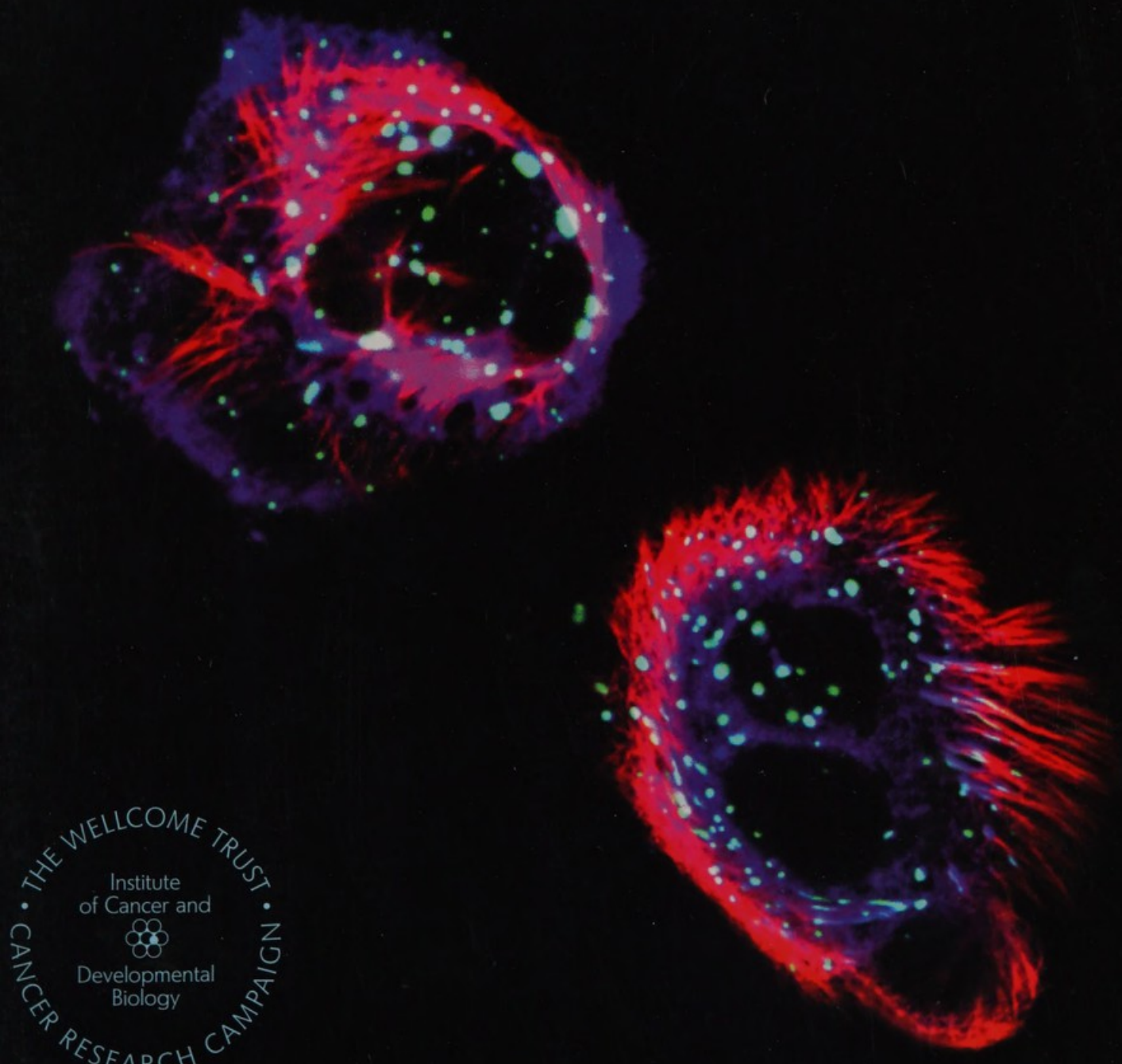
Annual report : 1999/2000 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

THE WELLCOME/CRC INSTITUTE 2000

ANNUAL REPORT 1999/PROSPECTUS



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PROSPECTUS 2000

ANNUAL REPORT 1999

University of Cambridge

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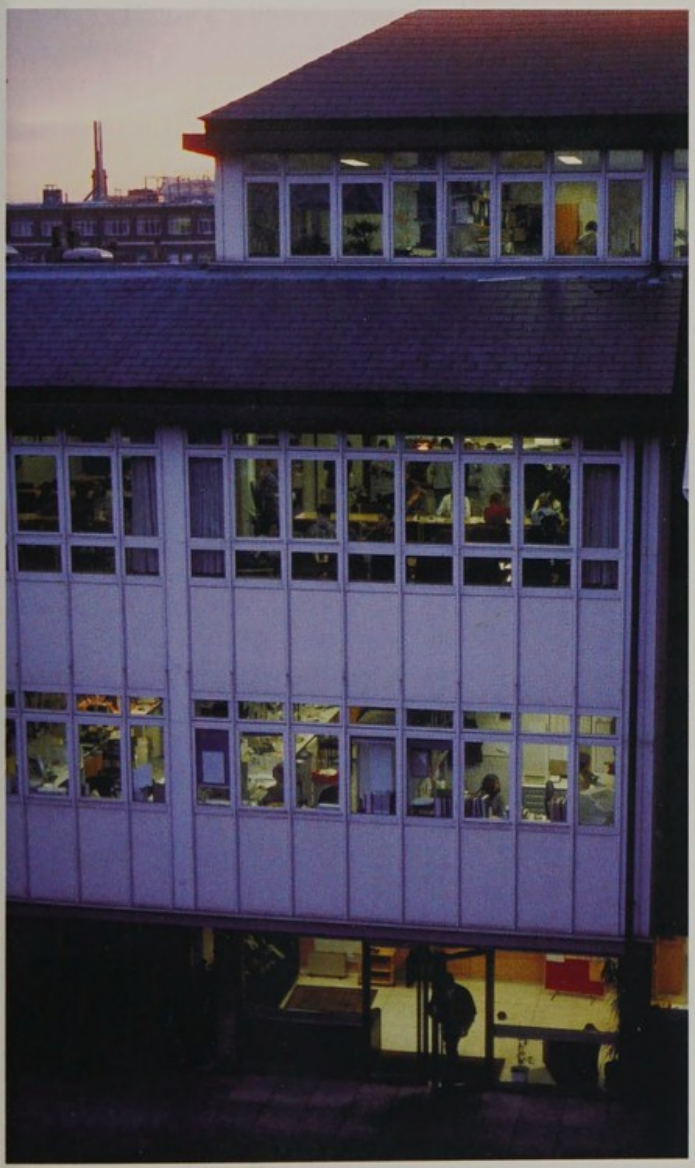


CHAIRMAN'S INTRODUCTION

During this year, two important decisions have taken place that positively affect the future of this Institute. One is that we have been awarded a major grant to relocate and upgrade our whole Institute to a new site adjacent to the new Biochemistry Department in Tennis Court Road. We will be physically attached to this Department which has a major strength in structural biology, and as such will complement our own expertise in cell, developmental and cancer biology. This grant has been made by the Wellcome Trust, who, in partnership with the UK Government, have provided a large sum for the refurbishment and upgrading of science laboratories in this country.

The other major decision affecting the future of this Institute is the appointment of Dr J C Smith FRS of the Medical Research Council's National Institute of Medical Research at Mill Hill, London as my successor. He will become the John Humphrey Plummer Professor of Cell Biology in Cambridge University and Chairman of this Institute with effect from October 2001. Jim Smith has a distinguished career as a Developmental Biologist. He was the first to identify a mesoderm-inducing factor, and to analyse its concentration-related effects on early development. We much look forward to him joining our Institute during next year.

During this year, two group leaders have left us to move to senior appointments in this country. Martin Evans was one of the original scientists who initiated the founding of our Institute. He has moved to become Director of Biosciences at the University of Wales in Cardiff, where he will continue his work on insertional mutagenesis in the mouse.

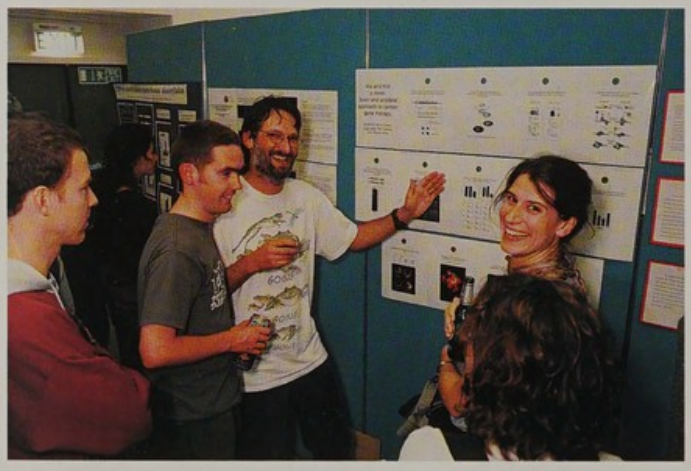
Charles ffrench-Constant has been elected to the Professorship of Neurological Genetics in the Cambridge University Medical School's Department of Medical Genetics; he has moved his laboratory to the Centre for Brain Repair on the Addenbrooke's Hospital site. He will continue his work on neural development and repair.

John Gurdon.

John Gurdon, Chairman

HISTORICAL BACKGROUND

The institute is situated in the middle of the area containing the science departments of the University of Cambridge and 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

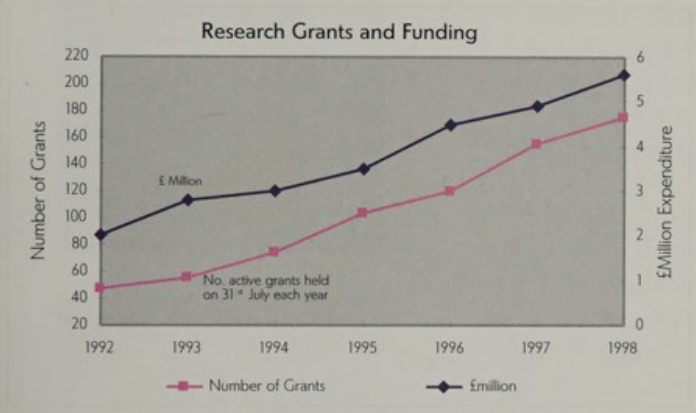


technical levels. To understand what goes wrong when a cell becomes cancerous requires a knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no one person can master, such as gene cloning, antibody preparation, cell culture, and embryonic manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

INSTITUTE FACILITIES

The Institute has a range of central facilities and services contributing to the research effort. Consolidating facilities has proved an efficient use of resources including space, consumables and staff. These facilities offer distinct areas of support, which release research staff from much administration and the more routine laboratory tasks. Providing communal areas equipped with instruments used by all groups is an efficient use of space and equipment, avoiding duplication. A relatively small number of multi-skilled staff perform these duties and liaise regularly with the research staff to ensure these central areas run smoothly and develop according to the needs of the Institute.

We have a single, centralised administration office which deals with grant processing, staff appointments and accounts. Information channelled through this office is disseminated appropriately to research staff, the University and sponsors, thus providing continuity and efficient use of research time and funds.

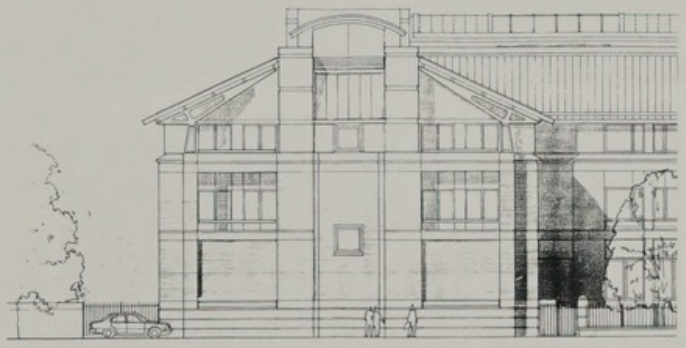


The number of grants awarded and the associated income has increased significantly since the Institute opened.

Technical and laboratory support is provided in the form of Purchasing, Computing, Graphics and Network development, Media preparation, Glasswashing, Safety, Equipment maintenance and Stores sections. The aim is to provide prompt, cost effective and comprehensive research support.

Central Equipment areas accommodate large equipment (e.g. incubators, high-speed centrifuges, ultra low temperature freezers), and specialised instruments (e.g. for histology and microscopy). Graphics equipment and computers are available for image processing, time lapse analysis and 3D reconstruction. Core funding has allowed Institute members to plan new and replacement equipment purchases and Institute developments.

These supporting facilities ensure maximum interaction of neighbouring research activity. Centralised support for core activities has proved very successful within the Institute, benefiting the research groups working here. This is due not only to the convenience of the facilities, but also to the flexibility of all the staff responding promptly to changes or developments in the research requirements.



NEW BUILDING

Detailed planning for our new building is underway and it is hoped that structural work will start in the coming year. The larger premises will allow more space for core equipment, tissue culture and cold rooms; improved temperature control facilities will also be provided in these areas and the laboratories. Further improvements to Graphics, Library and Seminar/lecture rooms are also planned.

JULIE AHRINGER

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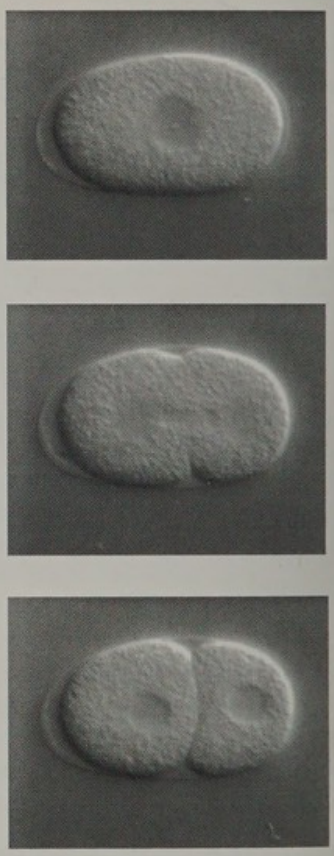
We are studying how patterns of cell divisions and cell fates are controlled during embryogenesis, using the nematode *C. elegans* as a model system. Work in the lab is focused on two embryonic patterning events: the correct choice of cell division axes in the early embryo and the control of body patterning later in embryogenesis.

One of the first indications of pattern in the *C. elegans* embryo is the orientation of the axis along which a cell divides. Although the control of spindle orientation is a widespread phenomenon in animal development, little is known about how correct axes are chosen. We have shown that heterotrimeric G proteins are required for the correct orientation of early embryonic cleavage axes. We are screening for other genes involved to identify targets and understand what polarity cues are used, using a wide range of approaches, including a genome wide RNA interference screen.

A second area of research in the lab is on patterning events that establish the body plan and the organisation of tissues. For example, we found that the gene *vab-7* encodes an *even-skipped* homologue required for patterning posterior mesodermal and epidermal tissues in the embryo. In addition, we found that T-box genes have a more widespread patterning role and are involved in regulating *vab-7* mesodermal expression. Using genetic and molecular methods, we are identifying and studying new genes involved in embryonic patterning. We identified the gene *egl-27* through genetic interactions with *vab-7* and found it is similar to MTA1, a component of the NURD chromatin regulatory complex. *egl-27* and a related gene *egr-1* are redundantly required globally for embryonic body patterning. We are now studying other functions for the NURD complex, including those involving Ras and *wnt* signalling.



Cell divisions are easily followed in live embryos

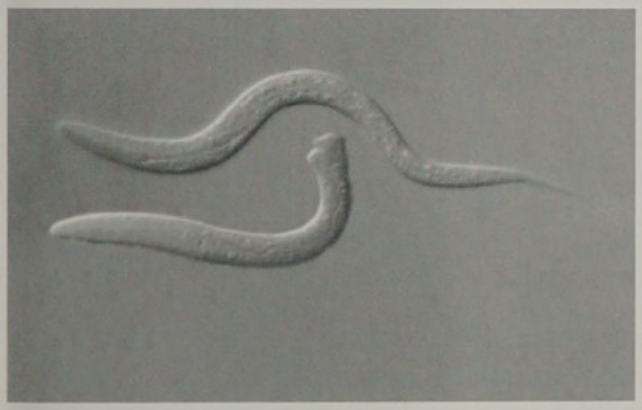
Solari, F., and Ahringer, J. (2000) NURD complex genes antagonise Ras induced vulval development in *C. elegans*. **Curr. Biol.,** in press.

Solari, F., Bateman, A, and Ahringer, J. (1999). The *Caenorhabditis elegans* genes *egl-27* and *egr-1* are similar to MTA1, a member of a chromatin regulatory complex, and are redundantly required for embryonic patterning. **Development, 126,** 2483–2494.

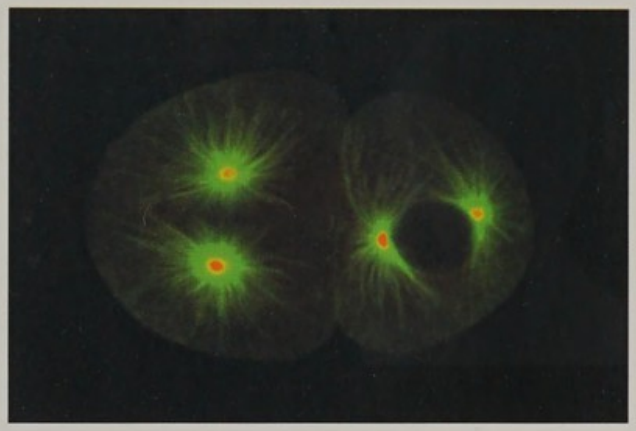
Ahringer, J. (1997) Maternal control of a zygotic patterning gene in *C. elegans*. **Development,** *124,* 3865–3869.

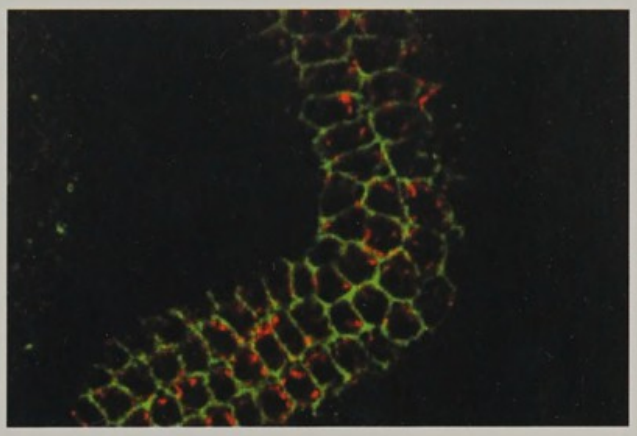
Zwaal, R., Ahringer, J., Rushforth, A., Anderson, P., and Plasterk, R. (1996). G proteins are required for spatial orientation of early cell cleavages in *C. elegans* embryos. **Cell,** *86,* 619–629

Ahringer, J. (1996) Posterior patterning by the *Caenorhabditis elegans even-skipped* homolog *vab-7*. **Genes Dev.,** 10, 1120–1130.



vab-7 mutant larva (bottom) has severe posterior defects





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.
Bottom: Localisation of GPB-1 (green), a heterotrimeric G protein subunit, to the membrane in the germ line. P granules (red).

ENRIQUE AMAYA

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KATHY HARTLEY
LUCY HAYTER
STEPHEN NUTT
MATT POLLI

The vertebrate embryo is organised and patterned following a series of inductive events. As a long term goal we would like to understand the molecular basis of the inductions that organise the vertebrate embryo.

To facilitate our studies we recently developed an approach for generating transgenic frog embryos. We are using this technique to study the role of fibroblast growth factor (FGF) signalling during mesoderm formation in the frog, *Xenopus laevis*.

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

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

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

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

Figure 1. Transgenic embryos expressing the green fluorescent protein (GFP) using a promoter fragment isolated from the *Pax-6* gene. The different panels show embryos at the specified stages of development.

Amaya, E. and Kroll, K.L. (1999). A method for generating transgenic frog embryos. **Methods Mol. Biol.** *97*, 393–414.
Amaya, E., Offield, M. and Grainger, R.M. (1998). Frog genetics: *Xenopus tropicalis* jumps into the future. **Trends Genet.** *14*, 253–255.
Bronchain, O.J., Hartley, K.O. and Amaya, E. (1999). A gene trap approach in Xenopus. **Curr. Biol.** *9*, 1195–1198.
Kroll, K.L. and Amaya, E. (1999). Transgenesis in *Xenopus* Embryos. in Early Development of *Xenopus laevis*. Edited by H.L. Sive, R.M. Grainger and R.M. Harland, eds. (Cold Spring Harbor Laboratory Press: Cold Spring Harbor), Chapter 11, in press.

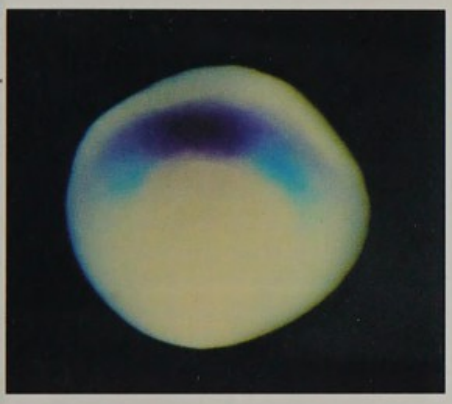

Figure 2 (left).
Early gastrula stage embryo stained for the expression of *Xnot* (dark purple) and *Xmyf-5* (light blue).

Figure 3 (right).
Transgenic frog expressing the green fluorescent protein (GFP) under the control of a lens specific promoter.

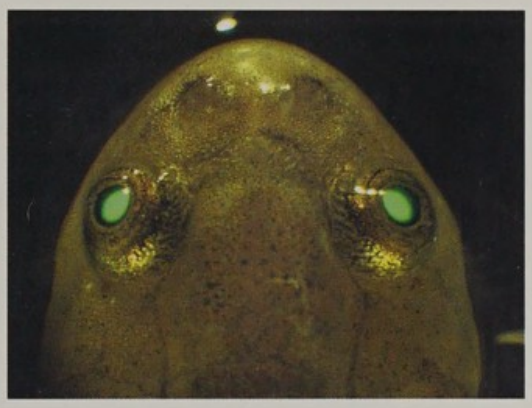

Figure 4 (left). Transgenic tadpole expressing a tau-GFP fusion construct under the control of the neural specific β-tubulin promoter (top panel). Similarly staged tadpole fixed and stained for neurofilament protein (bottom panel).

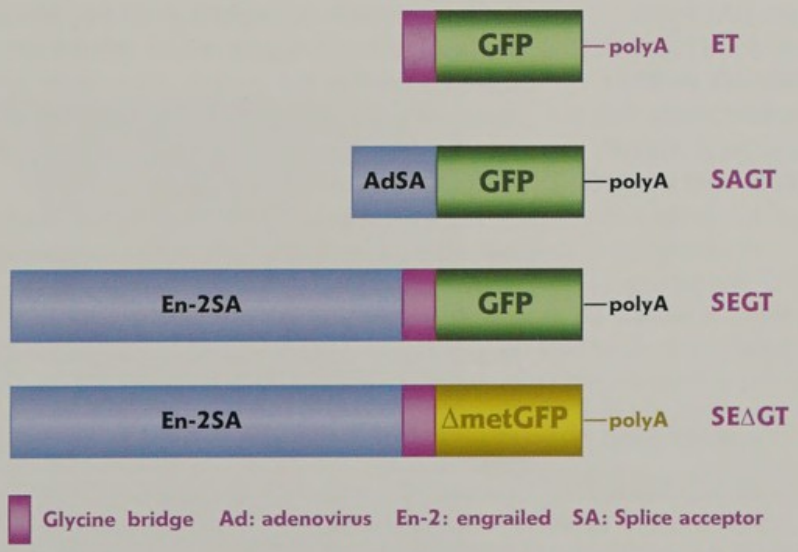

Figure 5. Diagram of the gene trap vectors used for insertional mutagenesis in *Xenopus*

ANDREA BRAND

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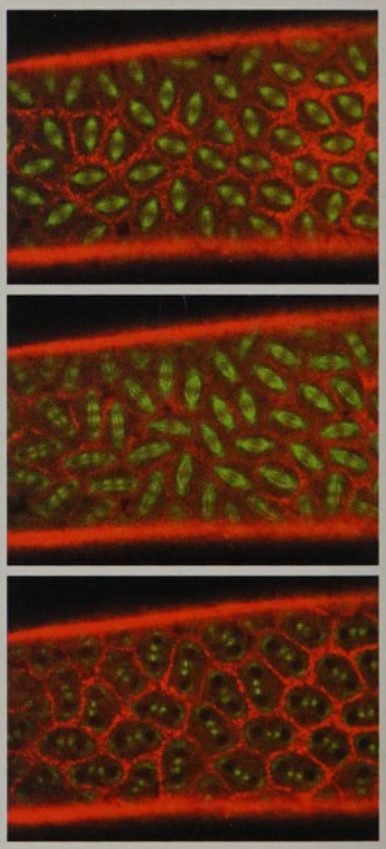
MICHAEL MURRAY
CHRISTOPHER PHELPS
ALISON SCHULDT
PETER VAN ROESSEL

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

One mechanism for generating cell diversity is to ensure that, upon cell division, each daughter cell adopts a different fate. This can be achieved by the asymmetric segregation of cell fate determinants. We are investigating the molecular mechanisms that control asymmetric segregation, and the role of the cytoskeleton in directing unequal cell division. To follow cell fate determinants in living embryos, we have fused green fluorescent protein (GFP) to the determinants Prospero, Staufen and Miranda. Using colour variants of GFP, we can follow several different proteins at once *in vivo* in both wild type and mutant embryos.

The asymmetric segregation of cell fate determinants and the generation of daughter cells of different size rely on the correct orientation and position of the mitotic spindle. To monitor the cytoskeleton during neuronal cell division, we label actin and microtubules *in vivo* and carry out time lapse analysis by confocal microscopy.

We are also studying the neuronal and glial interactions that influence axon outgrowth, and have identified several signalling molecules that direct axon pathfinding. We are characterising their roles in nervous system development by targeted gene expression, to ectopically express these molecules, and RNAi, to eliminate their expression.



Miranda (red) and microtubules (green), labelled with two different spectral variants of green fluorescent protein, can be followed simultaneously in a living embryo. Three time points shown.

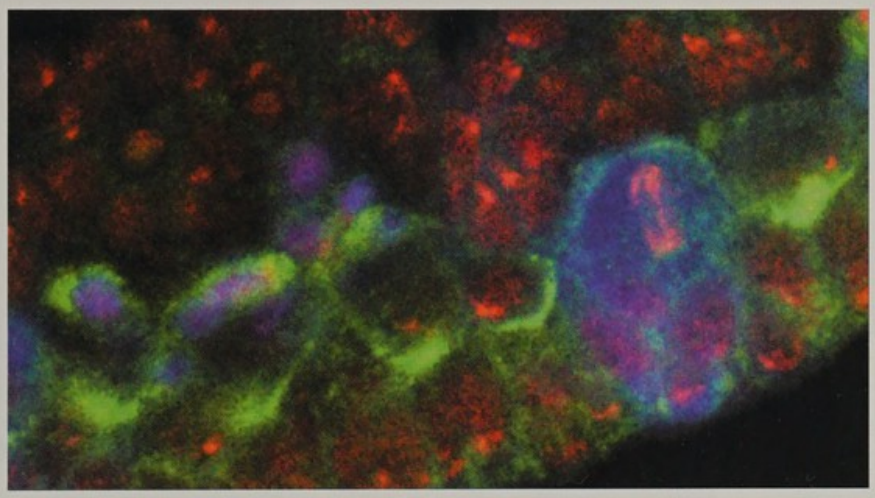
Please see Brand lab home page: http://www.welc.cam.ac.uk/~brandlab

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.

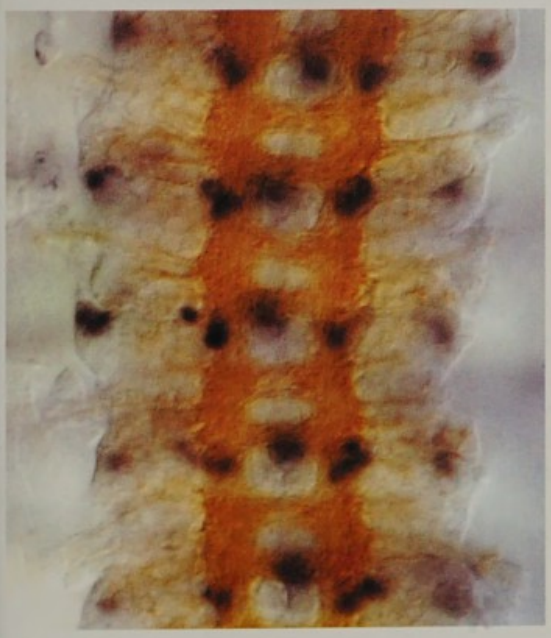
Schuldt, A.J. and Brand, A.H. (1999). Mastermind acts downstream of Notch to specify neuronal cell fates in the *Drosophila* CNS. **Dev. Biol.,** *205,* 287–295.

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.

For further publications, see numbers 11–12 and 114 on pages 48–54.



The cell fate determinant Miranda (green) is asymmetrically segregated when neuronal precursors divide. DNA is labelled in red and β-galactosidase in blue.



Axons in the CNS of a wild type embryo normally form a ladder-like scaffold (left; CNS axons are labelled in brown and the nuclei of Engrailed-expressing neurons in black). Axons misroute across the midline when a signalling molecule is removed by RNAi (right).

NICK BROWN

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CHRISTOS ZERVAS

Cellular adhesion and communication are vital during the development of multicellular organisms. These processes are initiated by proteins on the surface of cells, which can stick cells together or transmit signals across the plasma membrane. Members of one family of cell surface receptors, called integrins, are able to perform both of these functions, and thus provide a molecular link between cell adhesion and signalling. Our research is focused on determining how proteins inside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers and cell differentiation.

To discover what other proteins are required to work with the integrins, we and others have used the genetics of the fruit fly *Drosophila* to identify genes required for integrin mediated adhesion. We found that one encodes a cytoskeletal linker protein that is similar to plectin, which when defective in humans causes a skin blistering disease, emphasising the conservation of integrin adhesion mechanisms. Other wing blister loci we are characterising encode novel yet conserved proteins. The *Drosophila* genome sequencing progress has revealed many homologues of vertebrate proteins implicated in integrin function, and we are analysing their function in the fly.

We have identified genes in *Drosophila* that require integrin function for their normal pattern of expression, and demonstrated that these genes are regulated by a pathway initiated by integrin intracellular domains; this pathway is currently being dissected. In addition we have recently found that migration of cells within the embryo requires diverse inputs from the different integrins.

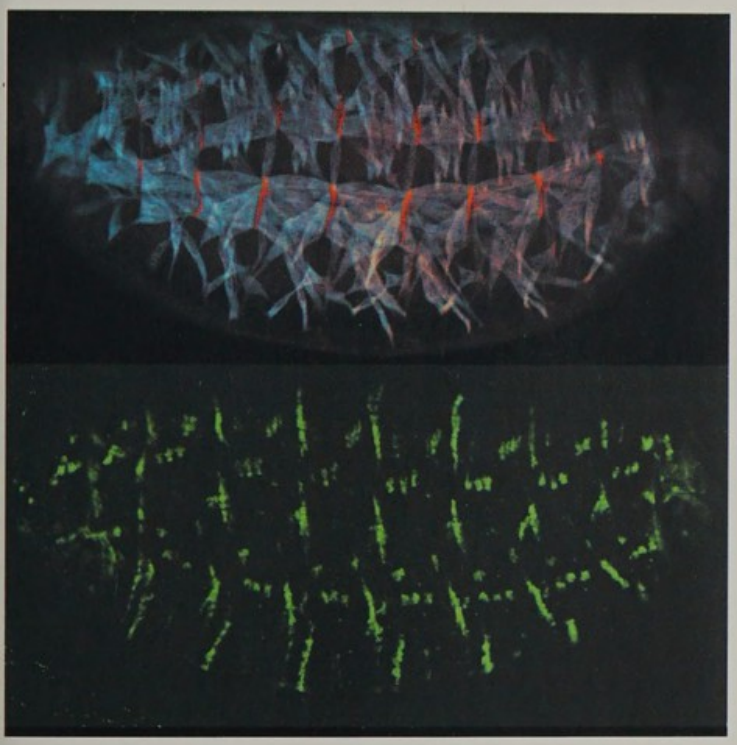
Expression of an integrin target gene in the larval midgut.

Gregory, S.L. and Brown, N.H. (1998) *Kakapo,* a gene required for adhesion between and within cell layers in *Drosophila,* encodes a large cytoskeletal linker protein related to plectin and dystrophin. **J. Cell Biol.** *143,* 1271–1282

Martin-Bermudo, M.D. and Brown, N.H. (1999) Uncoupling integrin adhesion and signalling: the βPS cytoplasmic domain is sufficient to regulate gene expression in the *Drosophila* embryo. **Genes Dev.** *13,* 729–739

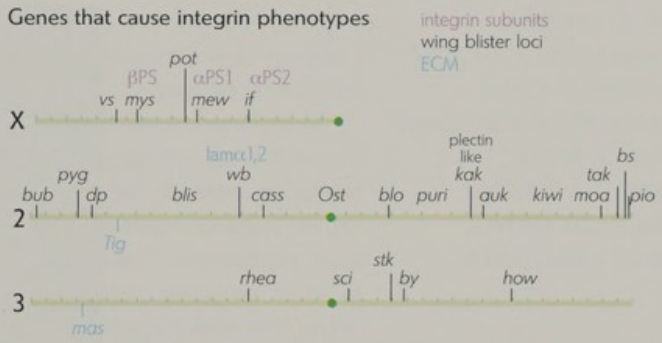
Martin-Bermudo, M. D., Alvarez-Garcia, I. and Brown, N. H. (1999). Migration of the *Drosophila* primordial midgut cells requires coordination of diverse PS integrin functions. **Development** *126,* 5161–5169

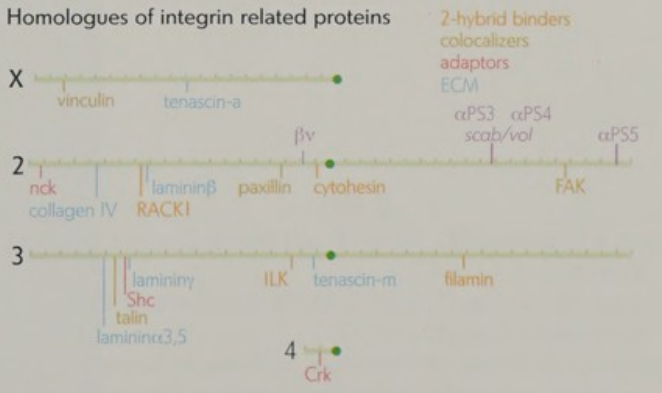
For further publications, see number 54 on page 51.



The cytoskeletal linker protein *Kakapo* (bottom panel, green) is expressed in the epidermal cells that require integrins (top panel, red) to attach to the muscles (top panel, blue).

Top, right: Loss of adhesion between the wing surfaces is caused by a mutation in an integrin gene.
Bottom, right: Genes related to integrin function on the four *Drosophila* chromosomes





CHARLES FFRENCH-CONSTANT

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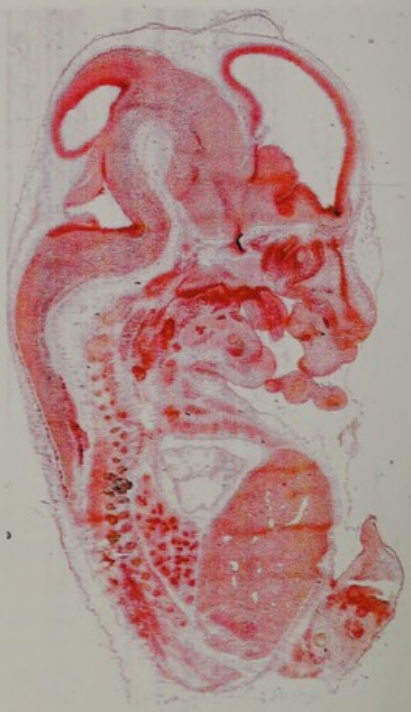
LAETITIA PRESTOZ
RICHARD MILNER
ALEX GOLDSMITH

Our interest is the role of cell adhesion receptors in mammalian neural development. We have examined receptors involved in both cell-extracellular matrix interactions (integrins) and cell–cell interactions (cadherins). By focusing on one neural cell lineage, the oligodendrocytes that form myelin, we have shown that integrins are 'switched' during differentiation and that this contributes to the regulation of proliferation, migration, survival and terminal differentiation in neural precursors. We have also identified the expression of the FAT protocadherin in these cells. As this protocadherin is a tumour suppressor gene in Drosophila we suggest that it may function to limit cell proliferation in the precursor cells of the mammalian CNS. Current work seeks 1) to test these putative functions by the generation and analysis of transgenic mice and 2) to determine how the signalling pathways downstream of these receptors interact with other intracellular pathways.

An important application of this work is neural repair in the adult brain, and ongoing work also asks 1) are developmental mechanisms reiterated during successful repair and 2) can we enhance repair by experimental re-expression of these mechanisms? These goals will be facilitated by the move of the group into the Cambridge Centre for Brain Repair that took place during October 1999.



FAT protocadherin expression in the mouse embryo

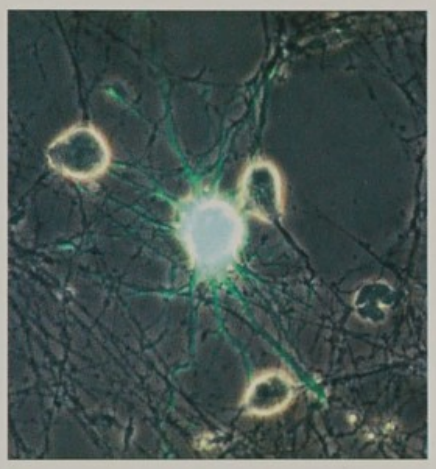
Frost, E.E., Buttery, P.C., Milner, R. and ffrench-Constant, C. (1999). Integrins mediate a neuronal survival signal for oligodendrocytes. **Curr. Biol.,** *9,* 1251-4

Ponassi, M., Jacques, T., Ciani, L. and ffrench-Constant, C. (1999). Expression of the rat homologue of the *Drosophila* fat tumour suppressor gene. **Mech. Dev.** *80,* 207–12.

Jacques, T.S., Relvas, J.B., Nishimura, S., Pytela, R., Edwards, G.M., Streuli, C.H. and ffrench-Constant, C. (1998) Neuroepithelial cell chain migration and division are regulated through different β1 integrins. **Development** *125,* 3167–3177.

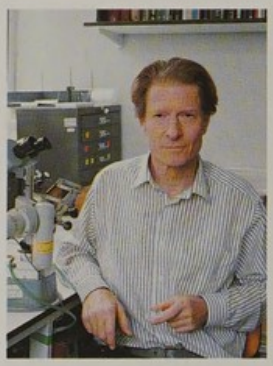
For further publications, see numbers 17–18, 31, 58, 81 and 115 on pages 49–54.

GFP-expressing oligodendrocyte precursor in co-culture with axons



Oligodendrocyte in cell culture

JOHN GURDON



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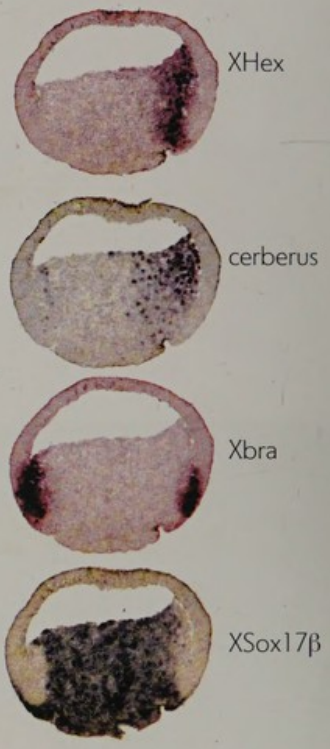
CAROLINE WEBB
AARON ZORN

The primary interest of this group is to analyse fundamental mechanisms of cell fate determination in early vertebrate development. In several cases, cells activate different genes according to the concentration of a single signalling molecule, which is therefore described as a morphogen. We have concentrated on a detailed analysis of how activin, a member of the transforming growth factor β-family of signalling molecules and a candidate for a natural Vertebrate inducer, can direct *Xenopus* blastula cells into many different cell fates. Three-fold increases in the concentration of activin to which a *Xenopus* blastula cell is exposed lead to equivalent increases in the absolute number of ligand-bound receptors, and to completely different pathways of differentiation. We currently determine how these signals are transduced quantitatively via *Smad2* to the promoters of two immediate *T-box* response genes, *Eomesodermin* and *Antipodean*.

As part of this work we analyse how gene activation leads to a uniform and demarcated expression of later genes, through the community effect, to create specialized tissues. This work aims to find ways of forcing dividing cells into differentiation pathways, thereby leading to the possibility of re-directing cancer cells into a non-proliferative state.

As an extension of this programme, we combine the redirection of cell fate with gene reprogramming by nuclear transplantation, thereby deriving a range of mesodermal cell types such as muscle from an adult skin cell. The experimental convenience of *Xenopus* enables us to improve the efficiency of such a procedure for the purposes of therapeutic cloning.



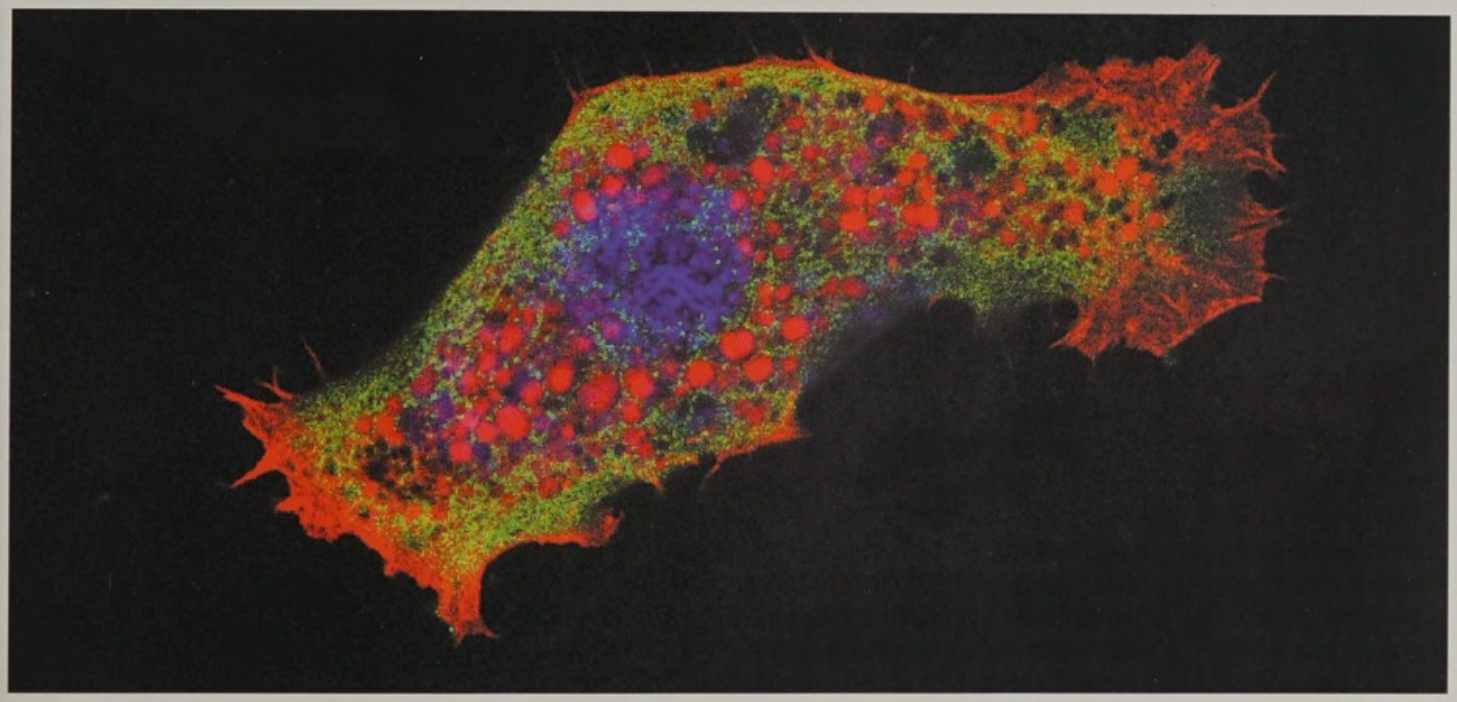
In situ hybridisation shows partially overlapping expression

Dyson, S. and Gurdon, J.B. (1998). The interpretation of position in a morphogen gradient as revealed by occupancy of activin receptors. **Cell** *93,* 557–568.

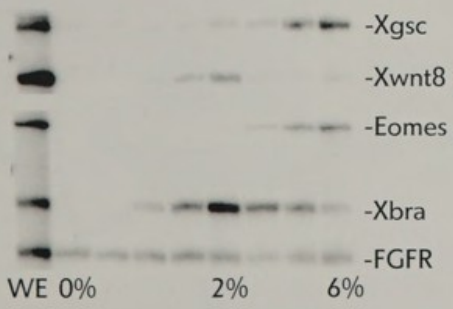
Gurdon, J.B., Standley, H., Dyson, S., Butler, K., Langon, T., Ryan, K., Stennard, F., Shimizu, K. and Zorn, A. (1999). Single cells can sense their position in a morphogen gradient. **Development** *126,* 5309–5317.

Gurdon, J.B. (1999). Developmental biology and the redirection or replacement of cells. **Philos. Trans. R. Soc. Lond. B Biol. Sci.** *354,* 1967–1976.

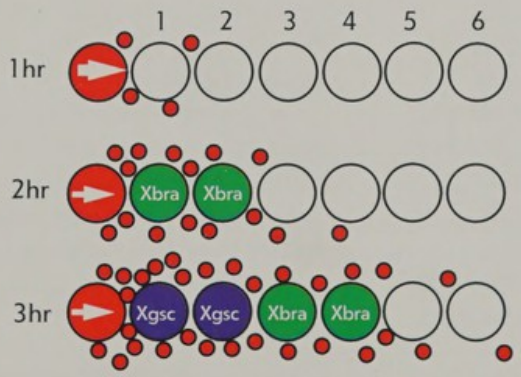
For further publications, see numbers 39–41, 43, 71, 96, 105–106, 123–124 on pages 50–54.



A cell that knows its position in a morphogen gradient



Increasing occupancy
of activin receptor II



Morphogen gradient formation

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By studying DNA repair and DNA damage signalling, we hope to understand how cells maintain their genomic integrity and how defects in these processes lead to cancer. One focus is the repair of ionising radiation-induced DNA damage by nonhomologous end joining (NHEJ; Fig. 1). Our recent achievements include mapping functional domains of the NHEJ proteins Ku and DNA-PKcs, establishing a link between NHEJ defects and human clinical radiosensitivity, and discovering that Ku functions in retrotransposition and retroviral integration.

An exciting new focus of our group is on the role of DNA repair proteins at telomeres. We discovered that yeast telomere homeostasis depends on Ku. Furthermore, defects in the DNA repair protein PARP lead to shortened telomeres and chromosomal instability in mice. Most recently, we demonstrated that transcriptional silencing proteins disperse from telomeres in response to DNA damage. This response depends on certain DNA damage-signalling proteins. We are currently analysing several components of DNA damage-signalling pathways. For example, we found that ATM and its relative ATR phosphorylate a key regulatory domain of the tumour suppressor protein p53. Also of particular importance is our recent discovery that FHA domains are phospho-dependent protein–protein interaction modules used both in DNA damage signalling (Fig. 2) and in other intracellular signalling pathways.

Our studies of transcription focus on Archaea, a domain of prokaryotic organisms distinct from Bacteria and Eucarya (Fig. 3). This work is demonstrating that the basal transcription machinery of Archaea is strikingly similar to, but much less complex than, that of Eucarya.

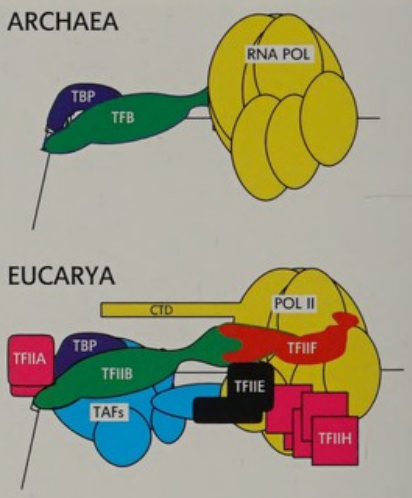


Fig. 3. Transcription in Archaea – the third domain of life. Through cloning archaeal transcription factors and establishing a defined *in vitro* transcription system, we have established that the fundamental mechanism of transcription in Archaea is akin to that of eukaryotic RNA polymerase II, although transcription in Archaea is considerably less complex. Depicted are the basal transcription machineries of the two groups of organisms.

d'Adda di Fagagna, F., et al. (1999). Functions of PARP in controlling telomere length and chromosomal stability. **Nat. Genet.** *23,* 76–80.
Durocher, D., Henckel, J., Fersht, A. R. and Jackson, S. P. (1999). The FHA domain is a phosphopeptide recognition motif. **Mol. Cell** *4,* 387–394.
Bell, S. D., and Jackson, S. P. (1999). Transcriptional regulation of an archaeal operon *in vitro* and *in vivo*. **Mol. Cell,** *4,* 971–982.

For further publications see numbers 7–9, 20, 25, 28–30, 36, 50–51, 64–65, 70, 82, 88, 93, 98–101, 111, 121 on pages 48–54.

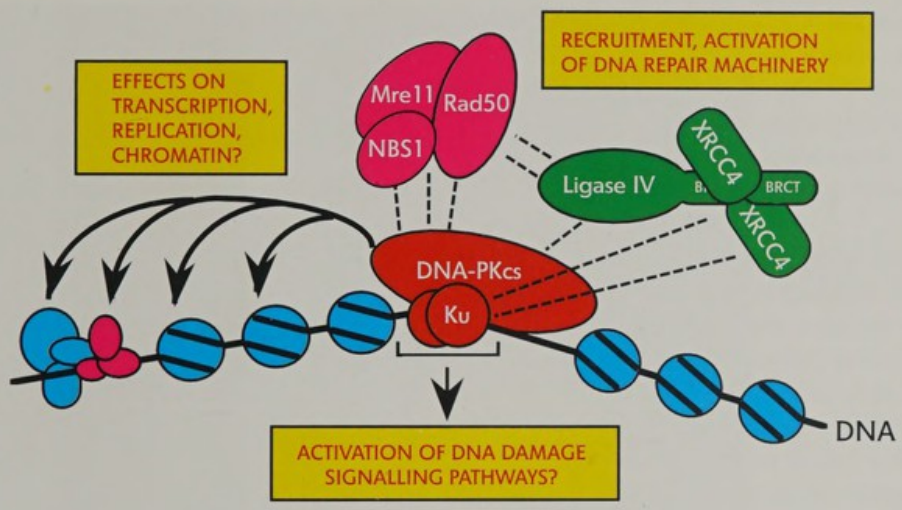


Fig. 1. Model for DNA NHEJ in mammalian cells. The DNA double-strand break is recognised by Ku, which then recruits and activates the DNA-dependent protein kinase catalytic subunit (DNA-PKcs). The DNA-PK holoenzyme may then potentiate NHEJ by the various mechanisms indicated. DNA-PK is depicted to recruit and/or activate the XRCC4-DNA ligase IV complex, and a nuclease complex containing Rad50, Mre11 and NBS1, the protein deficient in the human genetic disease Nijmegen breakage syndrome.

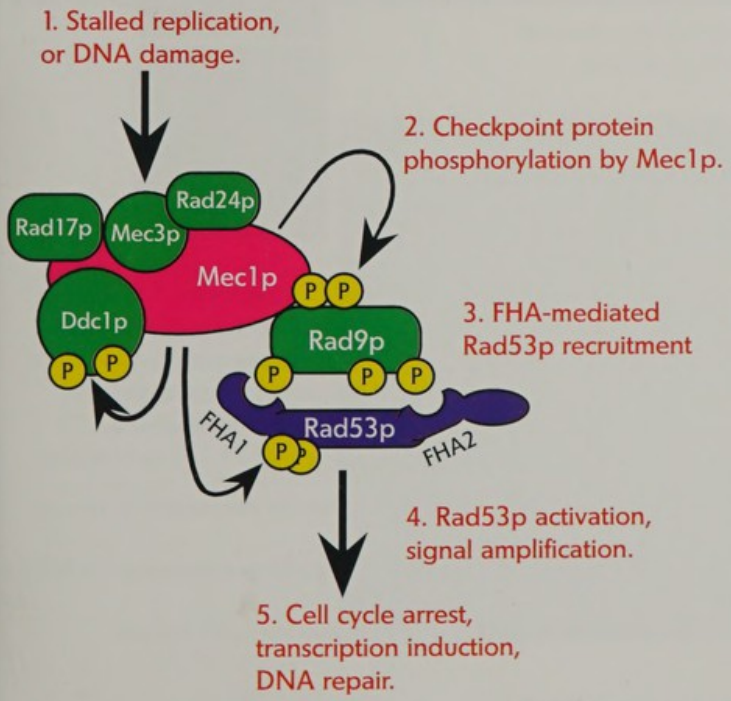
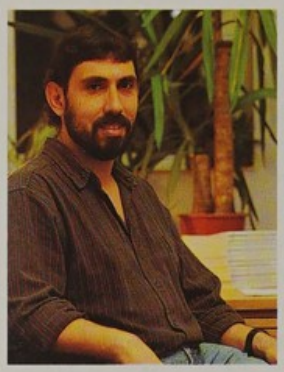


Fig. 2. The FHA domain is a phospho-dependent protein-protein interaction module. This model is based on genetic and biochemical data obtained from studies of the two FHA domains of *S. cerevisiae* Rad53p. DNA damage or blocked DNA replication are sensed by or transduced to Mec1p (a yeast homologue of ATM/ATR) which, in turn, phosphorylates Rad9p, Ddc1p and several other proteins. Phosphorylated residues on Rad9p, and possibly other proteins, are recognised by the FHA domains of Rad53p. Rad53p is next phosphorylated and activated by Mec1p, then active Rad53p phosphorylates downstream effectors of the DNA damage response.

TONY KOUZARIDES



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Many transcriptional regulators are found de-regulated in cancer. Our group is interested in defining the mechanisms by which such transcription factors function in normal cell proliferation and in cancer. Recently our attention has been focused on a new set of enzymes, acetylases and deacetylases, which regulate transcription by acetylating histones.

We have been analysing the process of acetylation since our discovery that a transcriptional co-activator protein CBP/p300 is a histone acetylase. We now know that this protein is found mutated in many different cancers. In an effort to establish the specificity of acetylation by CBP/p300 we have recognised that this enzyme can acetylate not only histones but also many other cellular proteins of diverse function, including transcription factors. An important acetylated factor, with respect to cell proliferation, is the S-phase-inducing transcription factor E2F1, whose activity we find is stimulated by acetylation. We have recently set out to identify chemical inhibitors of acetylases to help us in dissecting different acetylation pathways.

Our work on histone deacetylases has implicated these enzymes in the G1/S cell cycle checkpoint. We found that the RB tumour suppressor protein uses histone deacetylase activity to suppress E2F function and mediate G1 arrest. A connection has also been made to DNA-methylation, a process known to result in transcriptional repression. We have found that the DNA methyltransferase Dnmt1 is associated with deacetylase activity in the cell, suggesting an overlap in the repressive mechanism mediated by methylases and deacetylases.

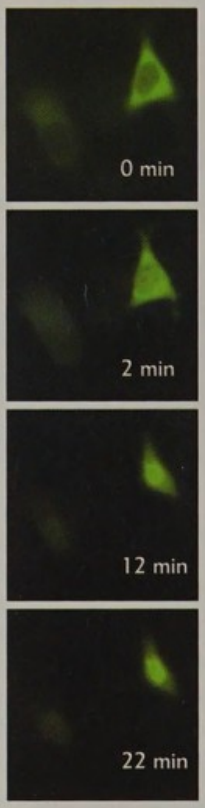

Figure 2.
GFP-HDAC4 translocates from the cytoplasm to the nucleus following the inhibition of nuclear export by leptomycin B treatment.

Brehm A, Miska EA, McCance DJ, Reid JL, Bannister AJ & Kouzarides T (1998). Retinoblastoma protein recruits histone deacetylase to repress transcription. **Nature** *391*, 597-601.

Miska, E.A., Karlsson, C., Langley, E., Nielsen, S.J., Pines, J. and Kouzarides T (1999). HDAC4 deacetylase associates with and represses the MEF2 transcription factor. **EMBO J.** *18*, 5099-5107.

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

For further references see numbers 5, 13–14, 47, 49, 59, 104 and 112 on pages 48–54.

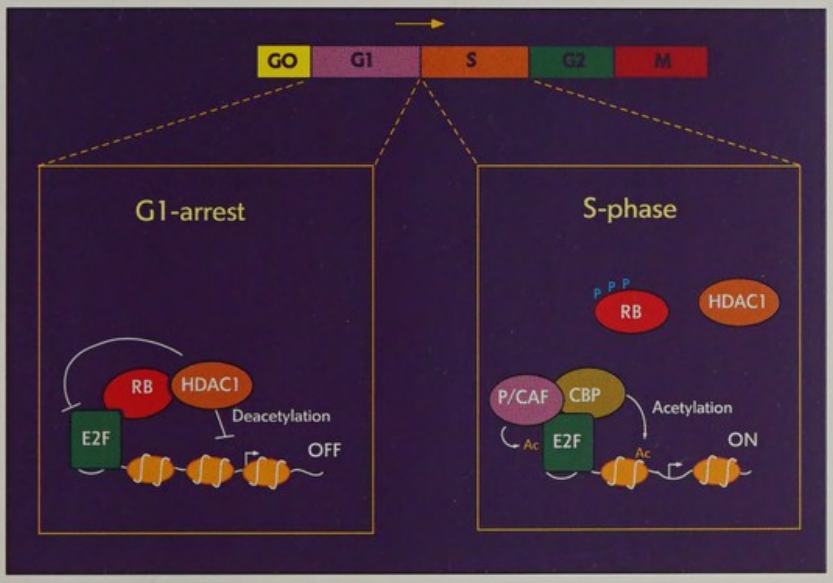

Figure 1. Acetylases and deacetylases regulate the activity of the E2F1 transcription factor.

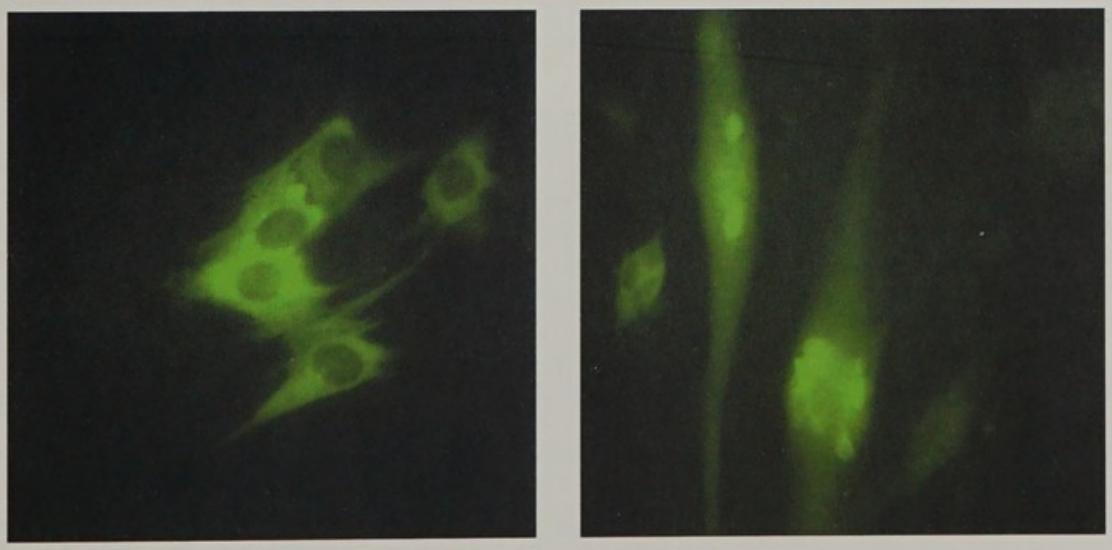

Figure 3. Differentiation of myoblasts (left) into myotubes (right) induces translocation of GFP-HDAC4 from the cytoplasm to the nucleus.

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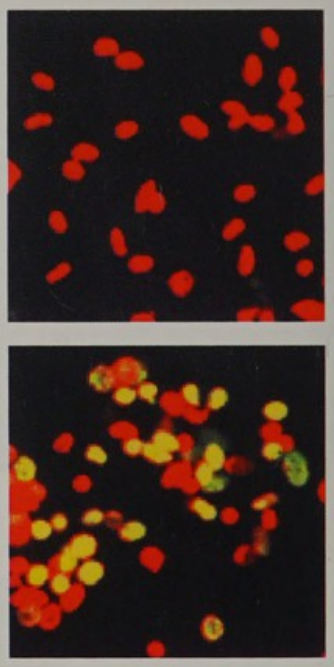
Our current research focuses on two topics, the control of eukaryotic chromosome replication and DNA replication proteins as diagnostic cancer markers.

We have used human cells grown in culture to develop a family of cell-free systems that initiate DNA replication efficiently *in vitro*. We use G1 nuclei as templates and S-phase extracts to induce replication. We have focused our attention on proteins that regulate DNA replication by assembling a pre-replication complex on unreplicated DNA. These proteins are the origin recognition complex ORC, Cdc6 and proteins of the MCM family. The presence of MCM proteins distinguishes replicated DNA from unreplicated DNA, as MCMs are displaced during replication.

Using the human DNA replication cell-free system, we have shown that competence of G1 nuclei to respond to S-phase factors arises suddenly in G1 at a time that coincides with synthesis of Cdc6 protein. Furthermore, addition of recombinant Cdc6 protein advances the time of initiation of DNA replication.

Cdc6 and MCM proteins can be used as markers for proliferating cells at any stage in the cell division cycle except quiescence (G0). We have exploited this to develop an immunoenhanced cervical smear test in order to decrease the frequency of false negative results in this important test. We are able to combine immunostaining for MCM5 or Cdc6 together with the conventional Papanicolaou stain. In this way both types of information can be read from the same slide. We are extending this approach to other forms of cancer, including cancer of the colon, lung, bladder and breast.



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

Krude, T., Jackman, M., Pines, J. and Laskey, R.A. (1997). Cyclin/Cdk-dependent initiation of DNA replication in a human cell-free system. **Cell** *88*, 109–119.

Stoeber, K., Mills, A.D., Kubota, Y., Krude, T., Romanowski, P., Marheineke, K., Laskey, R.A. and Williams, G.H. (1998). Cdc6 protein causes premature entry into S phase in a mammalian cell-free system. **EMBO J.** *17*, 7219–7229.

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

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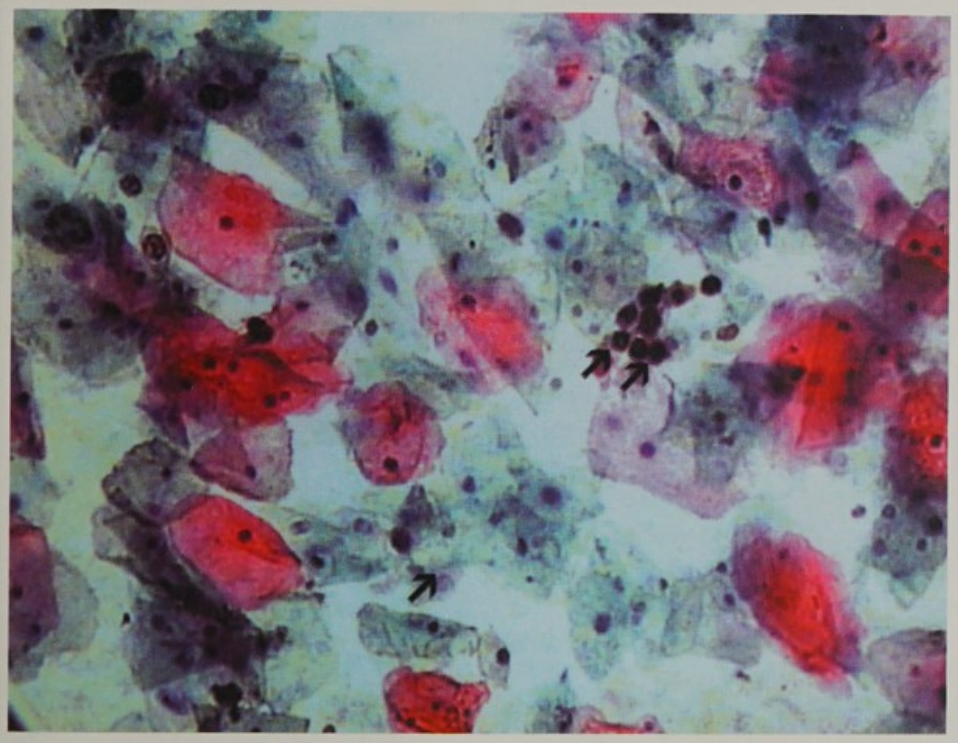
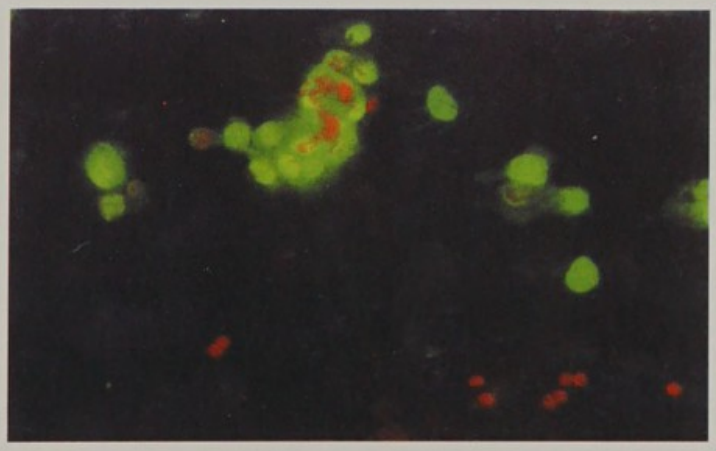


Enhanced cervical smear (Pap) test



Enhanced cervical smear (Pap) test by fluorescence microscopy

NANCY PAPALOPULU

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LUCY HAYTER

During embryonic development, neuronal differentiation (neurogenesis) takes place within the proliferating neuroectoderm in a stereotypical spatial and temporal pattern. The spatial and temporal control of neurogenesis is important for neural cell type specification, controlled growth and formation of appropriate neural connections. The central interest in our lab is to understand the role that transcription factors play in temporally and spatially controlling neuronal differentiation in the vertebrate nervous system. As a model system, we use the frog *Xenopus laevis* and a combination of molecular and classical embryology.

We have shown that *XBF-1*, a winged helix transcription factor that is expressed in the anterior neural plate, positions neurogenesis around the border of its expression. Analysing the activity of *XBF-1* we have found that it is bifunctional, acting as a suppressor or an activator of neuronal differentiation at a high and low concentration, respectively. The molecular mechanism by which *XBF-1* exerts a dose dependent dual effect on neurogenesis is currently being investigated. Recently, we have found that XBF-1 also affects the proliferation of neuroectodermal cells by controlling the transcription of a cell cycle regulating molecule.

We are analysing additional early neural genes such as a homeobox gene similar to the *Drosophila distal-less* gene, *X-dll3*, which is also expressed in the anterior neural plate and its derivatives. Through functional analysis of these early neural genes and identification of their targets, we aim to understand how the processes of patterning and neurogenesis are integrated.

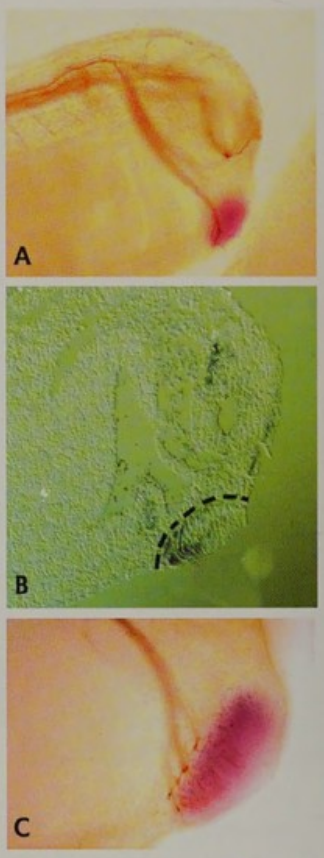

Figure 1. Trigeminal axons (brown in A, C) reach the cement gland (purple in A, C) and branch in the posterior half, where X-dll3 is expressed (dark blue in B).

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,** in press

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

Bellefroid, E. J., Kobbe, A., Gruss, P., Pieler, T., Gurdon, J., and Papalopulu, N. (1998). *Xiro3* encodes a *Xenopus* homolog of the *Drosophila Iroquois* genes and functions in neural specification. **EMBO J.,** *17,* 191-203.

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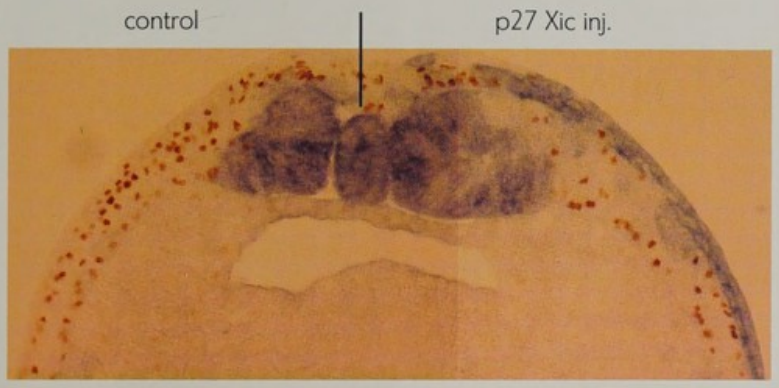

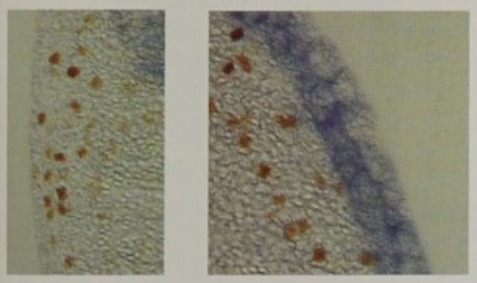

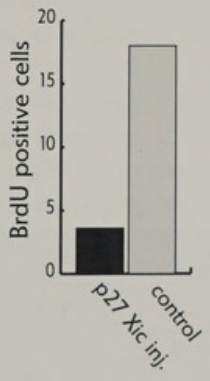

Figure 2. A cyclin dependent kinase (cdk) inhibitor, p27 Xic, (blue/purple) is not expressed in dividing cells (brown nuclei) and stops cell division when misexpressed in the embryo.

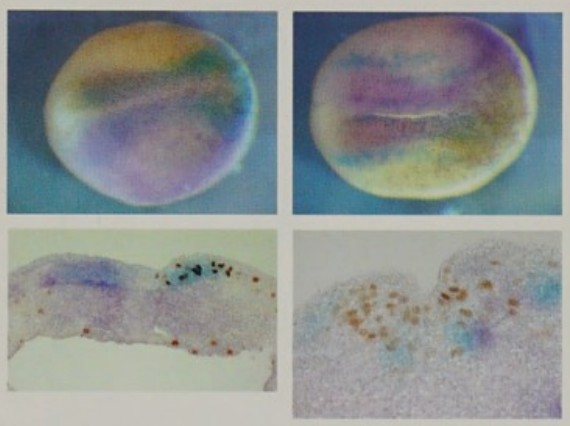

Figure 4. Cells that express ectopic cdk inhibitor (purple) stop dividing, as seen by lack of BrdU incorporation (brown nuclei) but do not express ectopic neural or neuronal markers (light blue).

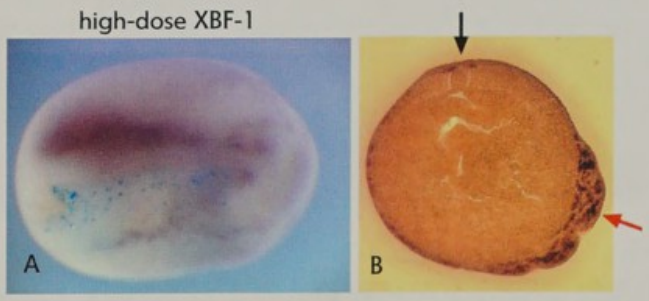

Figure 3. A high dose of XBF-1 (light blue in A) suppresses the expression of a cdk inhibitor (purple in A) and causes dramatic outgrowths in the ectoderm that contain ectopic neurons (brown; red arrow in B). Black arrow in B points to endogenous neural tissue for comparison.

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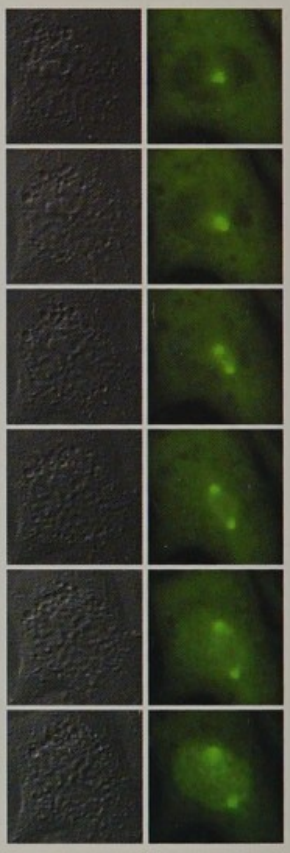
The dramatic changes in the architecture of the cell as it prepares to divide are orchestrated by the cyclin-dependent kinases (CDKs) and their cyclin partners. Our goal is to determine how cyclin-CDK activities are coordinated in space and time to reorganise the cell at mitosis.

We are studying the dynamic behaviour of the cell cycle machinery during cell division in real time, in living cells by time-lapse fluorescence and DIC video microscopy. By using GFP-fusion proteins we are able to determine the changes in localisation of specific cell cycle regulators, such as the cyclins, the CDKs and the Cdc25 phosphatases as cells progress through the cell cycle. We use this assay to define the domains of the proteins that target them to specific subcellular structures and to determine how localisation is regulated depending on the stage of the cell cycle. In complementary experiments we are isolating the proteins responsible for targeting and controlling the subcellular location of cyclin-CDK complexes.

We are also using the time lapse fluorescence assay to study the role of proteolysis in mitosis. The amount of fluorescence of a GFP-chimaera is directly related to the amount of protein, therefore by quantitating the fluorescence we are able to determine when, and where, proteolysis is activated in the cell. These studies have shown that cyclin B1 destruction is coordinated, both temporally and spatially, with the spindle assembly checkpoint.



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

Hagting, A., Karlsson, C., Clute, P., Jackman, M. and Pines, J. (1998) MPF localisation is controlled by nuclear export. **EMBO J.** *17,* 4127-4138.

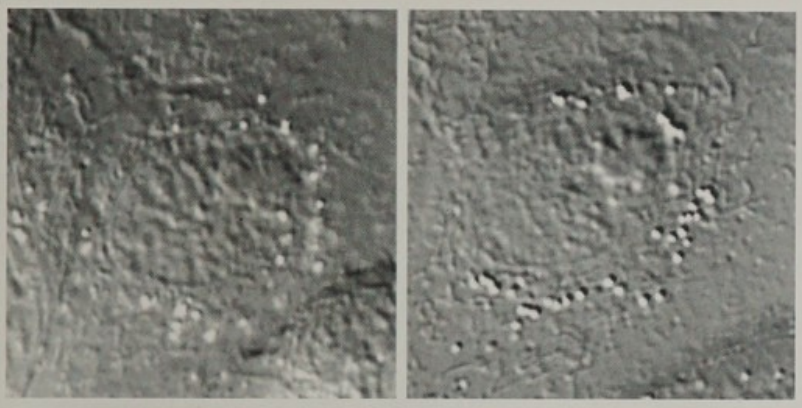
Clute, P and Pines, J. (1999) Temporal and spatial control of cyclin B1 destruction in metaphase. **Nat. Cell Biol.** *1,* 82–85.

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

Karlsson, C., Kaitch, S., Hagting, A., Hoffmann, I. and Pines, J. (1999) Cdc25B and Cdc25C differ markedly in their properties as initiators of mitosis. **J. Cell Biol.** *146,* 573–584.

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

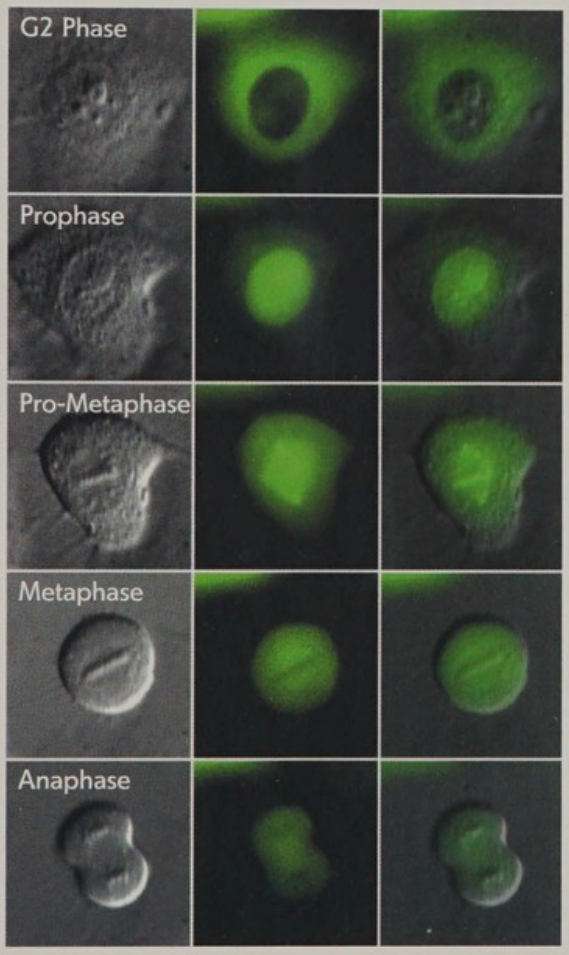
For further references please see numbers 4, 86–87 and 122 on pages 48–54.



Before injection After injection

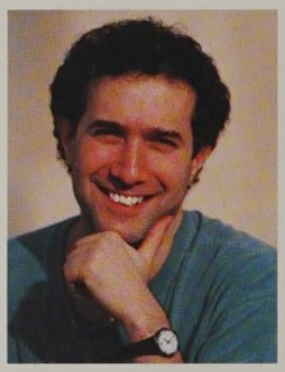
Cyclin A is required for prophase. A prophase cell (left) injected with an inhibitor of cyclin A-dependent kinases returns to G2 phase (right). Note that the cell decondenses its chromosomes and flattens out.

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



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

JORDAN RAFF



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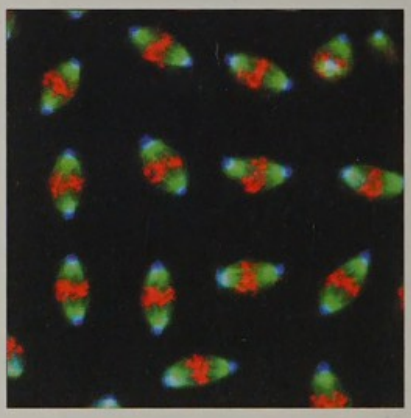
KIM JEFFERS
MICHAEL LEE
CHODAGAM SASIDHAR

The centrosome is the main microtubule organising centre in animal cells. Despite its central role in organising many cellular events, very little is known about how centrosomes function. We have taken a reductionist approach to this problem, isolating proteins that bind to microtubules *in vitro* and are associated with centrosomes *in vivo*. By studying these proteins we hope to gain a better understanding of how the centrosomes function at the molecular level. One of these proteins, called D-TACC, is associated with centrosomes in interphase, and with centrosomes and spindles in mitosis. Centrosomal microtubules are too short in embryos carrying a mutation in the d-tacc gene, suggesting that D-TACC is normally required to nucleate or stabilise centrosomal microtubules (Figure 1). D-TACC is related to the mammalian transforming acidic-coiled-coil containing (TACC) proteins, that have been implicated in cancer. We have shown that at least two of the TACC proteins are localised to centrosomes and/or microtubules in human cells. When overexpressed in human cells, the TACC proteins form huge polymers in the cytoplasm, that can interact with microtubules (Figure 2). We are currently investigating the function of these proteins in human cells.



The distribution of D-TACC (blue), microtubules (green) and DNA (red) in WT embryos at metaphase.

Many cell cycle regulators are associated with centrosomes and we have started to analyse the potential role of the centrosome in regulating cell cycle events. We have made a cyclin B-GFP construct and shown that the degradation of cyclin B (an event that is crucial for the exit from mitosis) is spatially regulated within cells. Cyclin B-GFP accumulates at centrosomes in interphase, in the nucleus in prophase, on the mitotic spindle in prometaphase, and on the microtubules that overlap in the middle of the spindle in metaphase. In cellularised embryos, the protein is degraded in two phases: toward the end of metaphase, degradation of the spindle-associated protein initiates at the spindle poles and spreads to the spindle equator; once complete, the chromosomes enter anaphase, and the remaining cytoplasmic cyclin B is degraded. These observations suggest that cyclin B degradation may be initiated at the centrosomes/spindle poles.

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

Raff, J.W. (1999). Nuclear migration: the missing (L)UNC? **Curr. Biol.** *9*, R708-R710.

Huang, J-Y., and Raff, J.W. (1999). The disappearance of cyclin B at the end of mitosis is regulated spatially in *Drosophila* cells. **EMBO J.** *18*, 2184-2195.

For further references see number 92 on page 53.

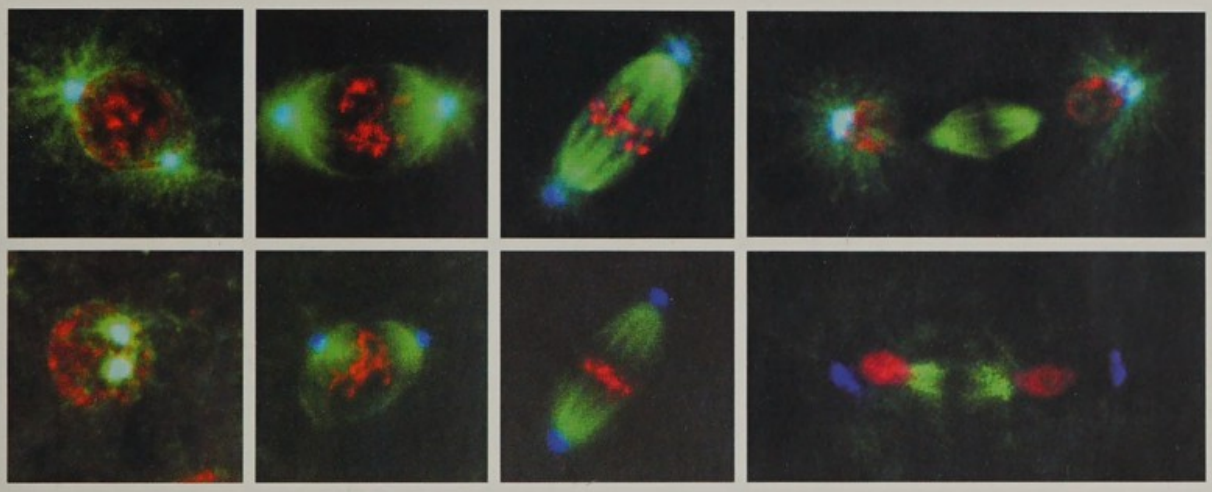


Figure 1
The distribution of DNA (red), microtubules (green), and centrosomes (blue) in normal (top panels) and d-tacc mutant (bottom panels) embryos. In the mutant embryos the microtubules associated with the centrosomes are too short at all stages of the cell cycle.

Figure 2
The distribution of microtubules (red) and a human TACC protein (green) in human cells that are overexpressing the TACC protein. The overexpressed TACC protein forms large fibres in the cytoplasm that interact with the microtubules.

DANIEL ST JOHNSTON

Co-workers:

SUSAN BEGG
RICHARD BENTON
JEAN-RENÉ HUYNH
UWE IRION
VINCENT LECLERC
HERNAN LOPEZ-SCHIER
KATIA LITIÉRE
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SOPHIE MARTIN
RUTH MCCAFFREY
MARK SHEPPARD
JOSHUA SHULMAN
LUCIE WHITEHEAD

The generation of polarity within a cell plays an essential role in many developmental events, such the determination of body axes, and the asymmetric divisions that generate new cell-types. Cell polarity is established by the localisation of specific proteins to each end of the cell, and this is often achieved by localising the mRNAs that encode them. A striking example of this phenomenon is provided by the localisation of *bicoid, oskar* and *gurken* mRNAs to three distinct positions within the *Drosophila* oocyte, where they define the anterior-posterior and dorsal-ventral axes of the embryo. My group is using this system to investigate the molecular mechanisms that underlie cell polarity and mRNA localisation, because the oocyte is about 1000 times larger than the average somatic cell, making it amenable to cell-biological approaches, and because mutations that disrupt the localisation of these mRNAs cause pattern defects in the resulting embryos, and this makes it possible to identify the genes required for these processes in genetic screens.

1) The dsRNA-binding protein, Staufen, is required for the localisation of both *bicoid* and *oskar* mRNAs, and co-localises with each transcript. Furthermore, Staufen targets *prospero* mRNA to the basal side of dividing neuroblasts. We are currently studying how Staufen recognizes these different mRNAs, and are characterising proteins that interact with Staufen to mediate both actin- and microtubule-dependent mRNA transport.

2) We have carried out several genetic screens for mutants that disrupt cell polarity or mRNA transport, and are analysing a number of new proteins involved in each process.

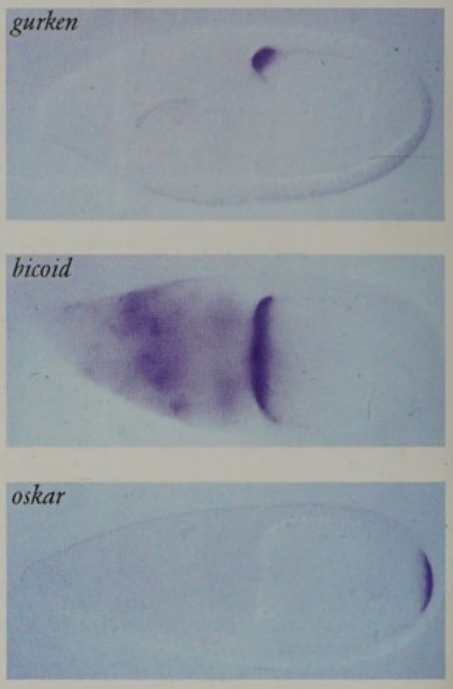


Figure 3.
Gurken, bicoid and *oskar* mRNA localisation

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

Shulman, J.M. and St Johnston, D. (1999). Pattern formation in single cells. **Trends Cell Biol.** *9,* M60–64.

Van Eeden, F., and St Johnston, D (1999). The polarisation of the anterior-posterior and dorsal-ventral axes during *Drosophila* oogenesis. **Curr. Opin. Genet. Dev.,** *9,* 396–404.

González-Reyes, A., and St. Johnston, D. (1998). The *Drosophila* AP axis is polarised by the Cadherin-mediated positioning of the oocyte. **Development,** *125,* 3635–3644.

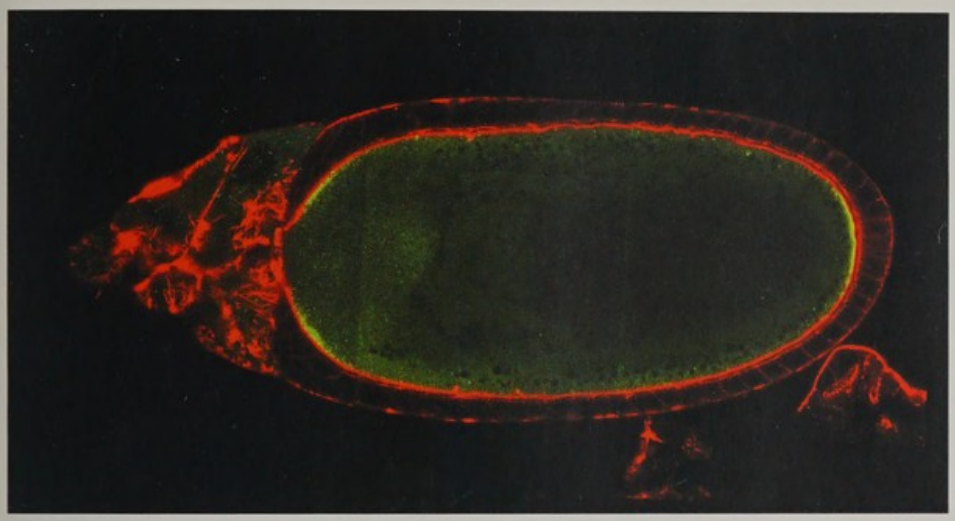


Figure 1
Wildtype egg chamber showing the localisation of GFP-Staufen at the anterior of the oocyte with bicoid mRNA and at the posterior with oskar mRNA. The egg chamber has been counterstained with Rhodamine-phalloidin (red) to reveal the organisation of the actin cytoskeleton.

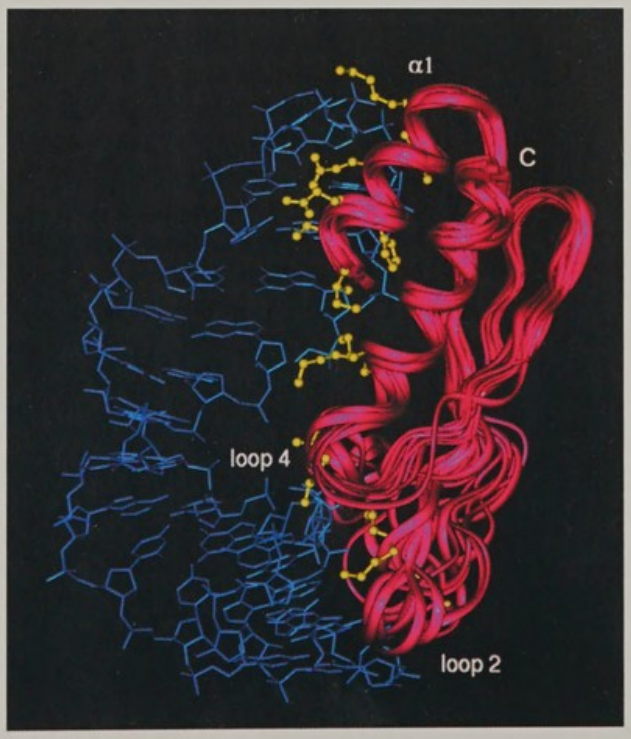
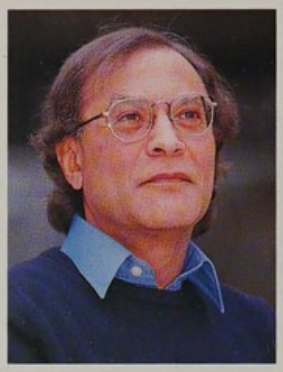


Figure 2
NMR structure of one double-stranded RNA binding domain from Staufen protein (red) bound to a 12bp RNA stem-loop (blue). The amino acid side chains that contact the RNA are shown in yellow. Collaboration with Andres Ramos and Gabrielle Varani (LMB-MRC).

AZIM SURANI



Co-workers:

JUSTIN AINSCOUGH
SAM APARICIO
TAKAHIRO ARIMA
KATHARINE ARNEY
SHEILA BARTON
ROBERT DREWELL
SYLVIA ERHARDT
KELVIN HAWKER
KATHY HILTON
ROSALIND JOHN
MARY MALKIN
MITINORI SAITOU
IRENE SZETO

The mammalian germ line originates from the pluripotent epiblast cells. Primordial germ cells (PGC) remain pluripotent at the time when neighbouring cells acquire a somatic cell fate. We are investigating the mechanism by which PGCs escape from acquiring a somatic cell fate. Pluripotent embryonic stem cells (ES) and embryonic germ cells (EG) are derived from epiblast and PGC, respectively. A somatic nucleus can revert to a pluripotent state in germ cell-somatic cell hybrids. We are using genetic and biochemical approaches to investigate how a somatic nucleus reverts to a pluripotent state.

The mammalian germ line also regulates development through 'imprinting' of germline-specific epigenetic modifications later during gametogenesis. Parental genomes are functionally non-equivalent during development because of the differential monoallelic expression of imprinted genes. Evolutionary theories are being developed to account for this unusual mode of regulation of development.

Imprinting is conferred by *cis* regulatory elements within large chromosomal domains in which imprinted genes are arranged in clusters. These *cis* elements effect heritable epigenetic modifications, such as DNA methylation, to regulate imprinted gene expression. We are investigating mechanisms by which these *cis* control elements regulate expression of specific parental alleles.

The imprinted gene dosage may be critical for development. We are focusing on neural development to investigate functions of imprinted genes since the parental genomes contribute unequally to cell allocation in the central nervous system. Studies on two imprinted genes, *Mest* and *Peg3*, demonstrate that they affect adult behaviour, including maternal behaviour.

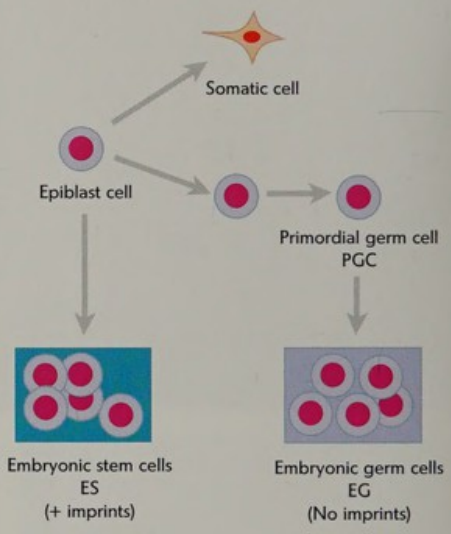


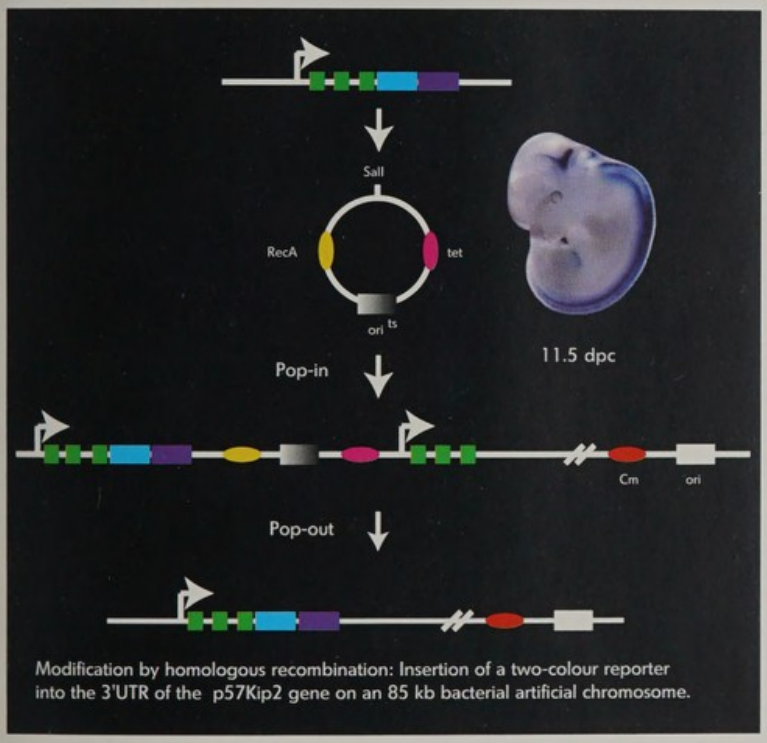
Fig.1. Relationship between epiblast cells, primordial germ cells and stem cells. All these cells are pluripoitent. A somatic nucleus when fused with an EG cell undergoes epigenetic modifications, including demethylation, so that it resembles the pluripotent germ cell.

Surani M. A. Imprinting and the initiation of gene silencing in the germ line (1998). **Cell** *93,* 309–312.

Li L.-L., Keverne, E. B., Aparicio, S. A., Ishino, F., Barton, S. C., Surani, M. A. Regulation of maternal behaviour and offspring growth by paternally expressed *Peg3* (1999). **Science** *284,* 330–333

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

For further references see numbers 3, 15, 19, 46, 52–53, 55, 90, 94 and 108–110 on pages 48–54.



Modification by homologous recombination: Insertion of a two-colour reporter into the 3'UTR of the p57Kip2 gene on an 85 kb bacterial artificial chromosome.

Fig. 2. A. Modification by homologous recombination of the bacterial artificial chromosome with the *p57Kip2* gene, by insertion of a two-colour reporter into the 3'UTR. The modified gene was used to generate transgenic mice to examine expression (d11.5 embryo is shown) and imprinting of the transgene in ectopic sites.
B. Analysis of the H19 imprinting *cis* control element. The H19 maternal allele is expressed and the paternal allele is silent and methylated (closed circles depicting *Cfo1* sites). Deletion of 1.2 kb region (shown in red) caused expression of the normally silent paternal allele.

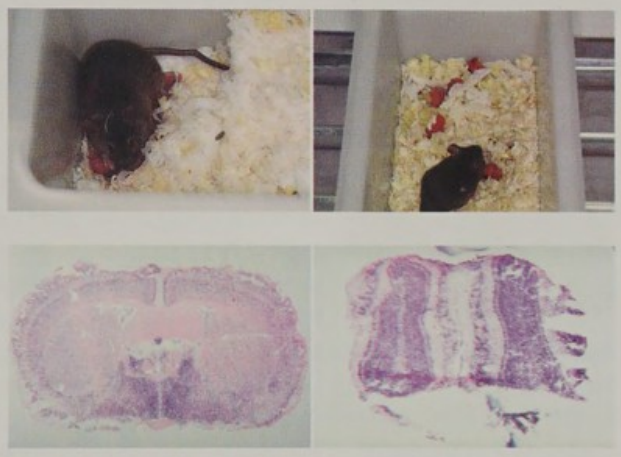
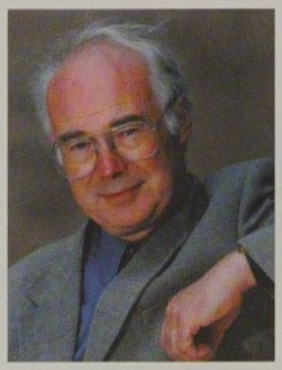


Fig. 3. Imprinted genes affect aspects of development and behaviour in mammals. Mutations in the *Peg3* and *Mest* genes affect maternal behaviour. The wild-type animal shows appropriate maternal care (a) whereas the mother with the mutation in these genes fails to respond appropriately to the new born offspring (b). The genes are expressed in the adult brain including the hypothalamus (c) and the olfactory bulbs (d). Both genes are expressed only when inherited from the father, whereas the maternal allele is repressed. These studies have implications for evolutionary theories of genomic imprinting, and the role of paternally inherited genes affecting behaviour.

MARTIN EVANS

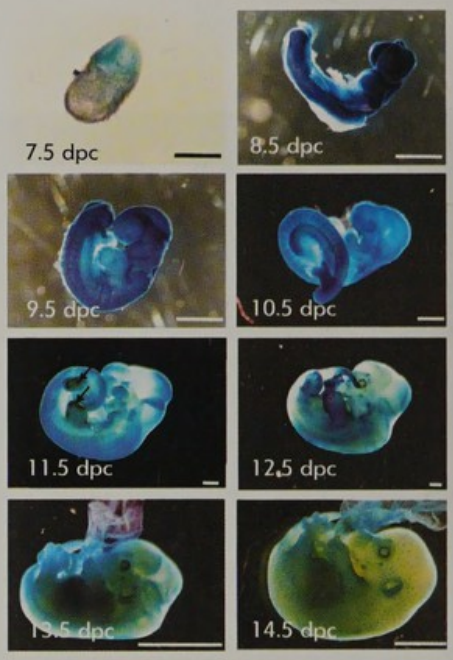


Co-workers:

SUSAN BROWN
HELEN BYE
MARK CARLTON
CHRISTINE COULDREY
JOHN DIXON
GEORGE MILLINGTON
JONATHAN PEARCE
VENKATA NARAYANA PISUPATI
ANDREAS RUSS
GORDON STOTT
JOANNE WILSON
MAGDALENA ZERNICKA-GOETZ

We are studying the development and physiology of the mammalian organism by using embryonic stem cells as a route to somatic and germ-line transgenesis. These cells provide a bridge between tissue culture and the whole animal, allowing specific genetic modifications to be introduced and selected in cell culture, and their effects to be tested in the context of the physiology and genetics of a whole animal.

Embryonic stem cells can be genetically modified by various techniques. By gene trapping, we generated and analysed mutations in the genes encoding Histone 3.3a, which causes neuromuscular deficits and male infertility. Several members of the *T-box* gene family, a class of putative transcription factors controlling essential events in early development, were mutated by gene targeting (homologous recombination). We found that the murine orthologue of *Eomesodermin*, a *Xenopus T-box* gene identified in the laboratory of John Gurdon, is required for the development of the trophoblast lineage and the morphogentic movements of gastrulation in the mouse embryo. *Tbx4* and *Tbx14*, two other members of this gene family, are essential for the formation of specific subsets of mesodermal tissue later in development.



Gene trap mutation of the Histone 3.3a gene.

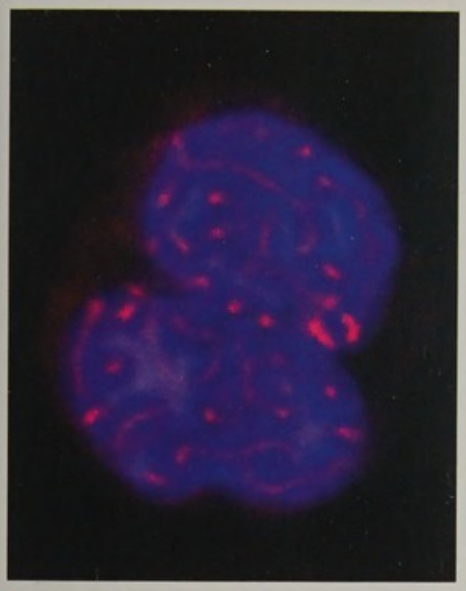
Russ, A.P., Wattler, S. Colledge, W.H., Aparicio, S.A., Carlton, M.B., Pearce, J.J. Barton, S.C., Surani, M.A., Ryan, K., Nehls, M.C., Wilson, V. and Evans, M.J. (2000). *Eomesodermin* is required for mouse trophoblast development and mesoderm formation. **Nature,** in press.

Couldrey, C, Carlton, M. B., Nolan, P.M., Colledge, W.H., and Evans M.J. (1999). A retroviral gene trap insertion into the histone 3.3A gene causes partial neonatal lethality, stunted growth, neuromuscular deficits and male sub-fertility in transgenic mice. **Hum. Mol. Genet.** *8(13),* 2489–2495.

Lee H., Trainer, A.H., Friedman, L.S., Thistlethwaite, F.C., Evans, M.J., Ponder, B.A., Venkitaraman, A.R. (1999). Mitotic checkpoint inactivation fosters transformation in cells lacking the breast cancer susceptibility gene, *Brca2*. **Mol. Cell** *4(1),* 1–10.

Pearce, J.J. and Evans, M.J. (1999). *Mml,* a mouse mix-like gene expressed in the primitive streak. **Mech. Dev.** *87,* 189–92.

Pearce J.J., Penny, G. and Rossant, J. (1999). A mouse cerberus/Dan-related gene family. **Dev. Biol.** *209,* 98–110.



Immunofluorescence of a mouse oocyte at the pachytene stage of meiosis. Pairing of homologous chromosomes is shown by the presence of synaptonemal complex in red. Germ cell nuclear antigen, a germ cell marker, is shown in blue.

The germ cell lineage in mice is established about a week after fertilisation, in the extraembryonic region proximal to the posterior end of the primitive streak. After migrating to the genital ridges, the site of the future gonads, the primordial germ cells can follow three alternative developmental pathways. Which they pursue depends upon signals from their surroundings. In a female embryo they enter first meiotic prophase. In a male embryo they stop proliferating and remain in G1 or G0 until birth, after which the cell cycle resumes. If they are removed from the genital ridge and cultured in the presence of certain growth factors, they develop into pluripotential stem cells, termed EG (embryonic germ) cells, which can be maintained indefinitely in culture. If replaced in an early embryo, EG cells will colonise all cell lineages.

We are studying the transition in vitro from primordial germ cells to EG cells, and the resumption of proliferation in male germ cells after birth. An EG cell line derived from the spermatogonial stem cell population could throw valuable light on the establishment of new methylation patterns associated with imprinted genes. We are also attempting to identify genes responsible for the entry of female germ cells into meiosis, using subtractive hybridisation and homologies with other organisms.

Co-workers:

IAN ADAMS
GABRIELA DURCOVA-HILLS

McLaren, A. (1999) Signalling for germ cells, **Genes Dev.** *13,* 373–376.
McLaren, A., (1999) Role of the state in genetics and reproduction in the 21st century. In: *Towards Reproductive Certainty: Fertility and genetics beyond 1999.* Parthenon.
McLaren, A. (1999) Too late for the midwife toad: stress, variability and Hsp 90. **Trends in Genetics** *15,* 169–171.
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Adams, I.R., and Kilmartin, J.V. (1999) Localisation of core spindle pole body (SPB) components during SPB duplication in *Saccharomyces cerevisiae.* **J. Cell Biol.** *145,* 809–823.

For further references see numbers 72, 76–78 and 119–120 on pages 52–54.

SAMUEL APARICIO

Co-workers:

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ARLETTE FRANCHI
PATRICIA HUNTER
SARAH JONES

Our interests are in the areas of development and evolution and in the study of cell behaviours in development which may relate to a better understanding of cell behaviour in cancers. In evolution, our work has shown that teleost fish have undergone additional rounds of genome duplication and subsequent gene loss from an analysis of *Hox* complex structure in *Fugu rubripes* (pufferfish). We have also shown that sequence comparisons using non-coding sequences of this fish are an efficient means to detect regulatory elements in mammals. In the area of cell behaviour in development, we are studying the molecular basis for cellular memory and investigating the role of Staufen proteins in mammalian development. In close collaboration with Azim Surani we are using mouse genetics to try to address the kinetics of cell memory mediated by novel *polycomb* and *trithorax* group homologues in mammals.

For recent publications see numbers 3, 19, 55, 67 and 90 on pages 48–53.

staufen1 expression in the dorsal root ganglion

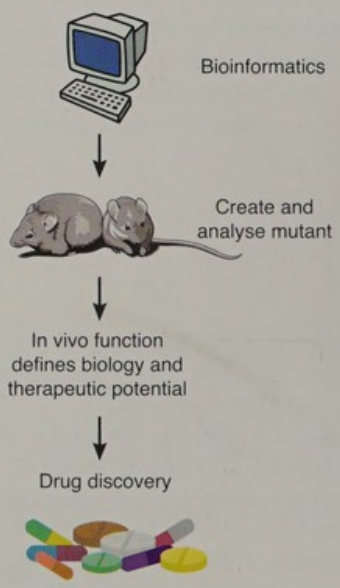
MARK CARLTON

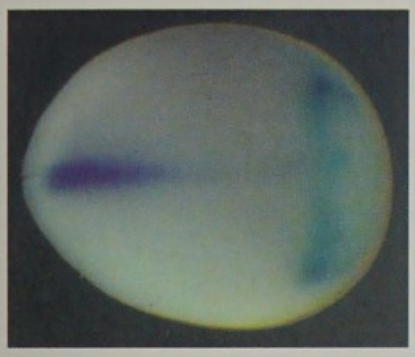
Co-workers:

JOHN DIXON
ALAN HENDRICK
ANDREAS RUSS
DIRK ZAHN

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

For recent publications see number 22 on page 49.





Xenopus embryo showing notochordal and epiphysial expression of the *not/flh* gene (dark blue stain).

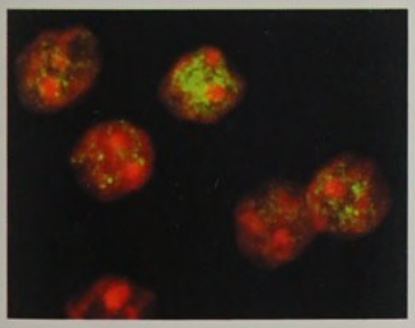
A major issue in developmental biology is how the embryo subdivides into progressively smaller regions, each with a unique identity. This project concerns the mechanism by which two such regions are specified, the notochord and the epiphysis. The earliest known transcription factor expressed by these 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. The aim of the project is to identify the direct regulators of the *not/flh* gene because this, in turn, will reveal the signal transduction pathways and developmental processes by which the notochord and epiphysis are formed.

M.Branon, M.Gomperts, L.Sumoy, R.T.Moon and D.Kimelman. β-catenin binds to the *siamois* promoter via transcription factor Lef/Tcf to regulate specification of the dorsal embryonic axis in *Xenopus*. (1997) **Genes Dev.** *11*, 2359–2370.

MIRANDA GOMPERTS

Co-worker:

KIM GOLDSTONE



Initiation of human DNA replication *in vitro*

My research focuses on the cell cycle control of initiation of DNA replication and of chromatin assembly, using cell-free systems derived from human tissue culture cells.

Initiation of DNA replication is triggered in nuclei, isolated from late G1 phase cells arrested by mimosine, upon incubation in cytosolic extract from proliferating cells. The protein kinases cyclin A/Cdk2 and cyclin E/Cdk2 are bound to nuclei from mimosine-arrested cells and their activity is required for triggering initiation. Initiation also depends on soluble factors, which we are currently purifying by biochemical fractionation of the cytosolic extract.

Chromatin assembly factor CAF-1 mediates regulated nucleosome assembly on replicating DNA. We are currently analysing the coupling of CAF-1 activity to DNA replication, which depends on cyclin-dependent kinase and on protein phosphatase activities.

For recent publications see numbers 61–63 on page 51.

TORSTEN KRUDE

Co-workers:

AIDAN BUDD
CHRISTIAN KELLER
DAVID SZUTS

SOO-HWANG TEO

DNA may be damaged by sunlight, ionizing radiation, chemical mutagens and many other agents. Unrepaired or inaccurately repaired DNA damage often features in the development of cancer. Very efficient mechanisms have evolved, therefore, to repair various forms of damage. My research focuses mainly on the final step in the repair of DNA double-strand breaks – the joining of DNA ends catalysed by DNA ligases. I have found that the yeast DNA ligase, Lig4p, repairs DNA double-strand breaks, and that its activity is regulated in several ways by its partner protein, Lif1p. For example, Lif1p targets Lig4p to DNA ends and this, in turn, is regulated by another DNA-binding protein, Ku. I am currently characterising how this occurs within chromatin. In collaboration with colleagues, I am also studying how Ku regulates telomere length.

For recent publications see numbers 93, 101 and 111 on pages 53–54.

MAGDALENA ZERNICKA-GOETZ

The aim of our research is to determine when and how the body plan of mammals is established. Until now it was believed that mammalian embryo polarity is established only after implantation. However, our studies using a novel strategy to trace cell lineages challenge this view. They indicate that mouse embryo polarity is anticipated before implantation and is related to the polarity of the egg. To understand the origin of polarity and mechanisms of axis formation in mammals, we are combining experimental embryology and molecular techniques to ask:

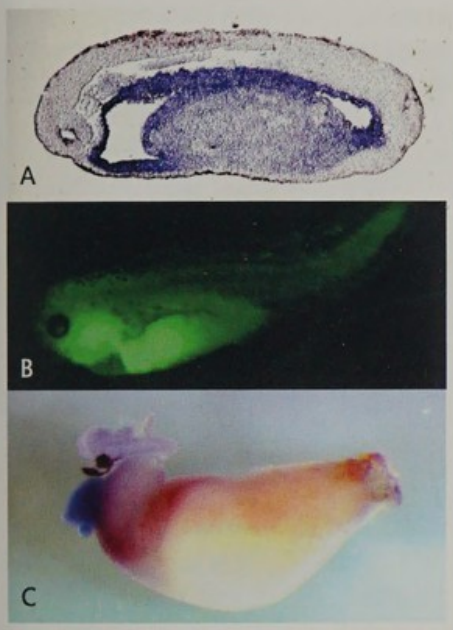
- what underlies asymmetric division of the egg and how is egg asymmetry related to embryonic polarity?
- what is the developmental role of embryo pre-patterning and how does early polarity transform into that of the definitive embryo?
- how are signalling centres established and what are the molecular mechanisms specifying polarity?

For recent publications see numbers 117–118 and 122 on page 54.

Co-workers:

DANIEL MESNERD
BERENIKA PLUSA
ROBERTA WEBER
FLORENCE WIANNY

Postimplantation mouse embryo (E6.5) showing the fate of a blastocyst ICM cell microinjected with GFPmRNA. These studies demonstrate that polarity of the embryo is established already before implantation.



A) *XSox17β* (blue) in the naïve endoderm. (B) Transgenic *Xenopus* embryos expressing GFP in the developing foregut. (C) Homeobox genes *Hex* in the liver bud (blue) and *Pdx* in the pancreatic region (brown) of the embryonic gut.

Our research focuses on the molecular mechanisms underlying the formation of internal organs such as the liver and pancreas. In vertebrate embryos, signalling by growth factors patterns naïve endodermal tissue into broad territories. This basic pattern is elaborated by a complex series of tissue interactions, so that some endodermal cells 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, to uncover the genetic programs responsible for this poorly understood process of organogenesis. 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 development.

For recent publications see numbers 38, 106 and 123–124 on pages 50–54.

AARON ZORN

Co-worker:

JULIA MASON

CATEGORIES OF APPOINTMENT

Senior Group Leader
Professor, Reader or Lecturer Level

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

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

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

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

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

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

Research Technician
Within individual groups, mainly grant-funded

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

POSTGRADUATE OPPORTUNITIES

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

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INSTITUTE PUBLICATIONS

1. Adams, I.R. and Kilmartin, J.V. (1999). Localisation of core spindle pole body (SPB) components during SPB duplication in *Saccharomyces cerevisiae*. **J. Cell Biol.** *145,* 809–823.
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OTHER ACTIVITIES

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

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

JOHN GURDON is a governor of the Wellcome Trust, Master of Magdalene College, Cambridge, Member, Conseil Scientifique and of the Institut Curie, France.

STEVE JACKSON is a member of the Biochemical Society Nucleic Acids and Molecular Biology Group Committee, the Biochemical Society Council, and the European Molecular Biology Organisation.

TONY KOUZARIDES is a member of the Cancer Research Campaign Grants Committee and the European Molecular Biology Organisation.

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

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

DANIEL ST JOHNSTON is a Board Member of the British Society of Developmental Biology, a non-executive Director of the Company of Biologists and is a member of the European Molecular Biology Organisation.

AZIM SURANI is a member of the Royal Society International Exchange Panel.

HONOURS AND AWARDS

ANNE McLAREN, elected Foreign Member of the Russian Academy of Sciences.

JOHN GURDON Doctor of Science, *Honoris causa,* University of Hull. Special lectures: Rodney Porter Memorial Lecture, University of Oxford. University Lecture Series, University of Texas Southwestern Medical Center.

RON LASKEY received the University Medal of Charles University, Prague.

MARTIN EVANS received the 1999 March of Dimes Prize in Developmental Biology.

AZIM SURANI received the Wellcome-Burroughs and National Institute of Child Health Research Pioneer Award. Special lectures: Amoroso Lecture, British Society for the Study of Fertility.

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LEAVERS DURING 1999

DR KATHARINE BLASCHUK, former MS Society Research Associate, is now undertaking research at the Miami Project to Cure Paralysis, 1611 NW 12th Avenue, Miami, Florida 33136, USA.

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DR LORENZA CIANI, former CRC Research Associate, has moved to the Cambridge Centre for Brain Repair, University of Cambridge.

PROF MARTIN EVANS, former Senior Group Leader, is now Dean of Biological Sciences, Cardiff School of Biosciences, Cardiff University.

DR CAROL FEATHERSTONE, former CRC Senior Research Associate, has joined her husband in France.

PROF CHARLES FFRENCH-CONSTANT, Junior Group Leader is now an Honorary Consultant at the Cambridge Centre for Brain Repair, University of Cambridge.

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DR MARIAN MARTINEZ, former EMBO Fellow, has returned to Spain.

DR RICHARD MILNER, former Wellcome Research Associate, is now at the Cambridge Centre for Brain Repair.

DR KERSTIN OTTE, former EC Marie Curie Fellow, is now working for Lion Bioscience AG in Heidelberg as a Project Manager.

DR LAETITIA PRESTOZ, MRC Research Associate, has moved to the Cambridge Centre for Brain Repair.

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SARAH TREWICK, former Research Assistant, is now a graduate student at the ICRF, London.

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DR JAMES WAKEFIELD, former Welcome Research Associate, is now at the University of Rome 'La Sapienza', Departmento di Genetica e Biologica Moleculare, Roma, Italy

ROBERTA WEBER, former Research Assistant, is now at the ICRF London.

ACKNOWLEDGEMENTS

Prospectus produced in the Wellcome/CRC Institute, by Desmond Schmidt, Caroline Webb, John Gurdon, David Dunbar, Linda Millett, John Overton (Photography). Printed by Cambridge University Press.

Cover

TACC2, a centrosomal human protein, overexpressed in taxol-treated HeLa cells. Image by Fanni Gergely, Raff Group.

Annual Retreat, Canterbury 1999

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