Annual report : 1995/1996 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

THE WELLCOME TRUST
CANCER RESEARCH CAMPAIGN

Institute
of Cancer and
Developmental
Biology

UNIVERSITY OF CAMBRIDGE

1996

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PROSPECTUS 1996

ANNUAL REPORT 1995

University of Cambridge

CONTENTS

Front Cover Photograph

Hox gene expression in the developing larva of the brine shrimp Artemia

Photograph by Michalis Averof (see page 11)

FOREWORD BY THE 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 of 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 come to acquire and maintain their normal function; cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intracellular processes, which need to be analyzed 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 which ensure correct cell function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques which no one person can master, such as gene cloning, antibody preparation, cell culture, and embryological 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.

Photo by A. M. Photographic

INSTITUTE COMPOSITION AND NEW APPOINTMENTS Our Institute is now well established, with over 150 total personnel. We consist of 16 independent research groups, containing postdoctoral scientists, visitors, research assistants, and a total of 27 graduate students. Each group is affiliated to one of the University Departments. The teaching we do and our lists of publications are credited to our affiliated departments, and we have access to their workshops and equipment.

We are delighted to be joined, in January 1996, by Dr Enrique Amaya as a Wellcome Senior Research Fellow and Younger Group Leader within the Institute, and also by Dr Nancy Papalopolu. Enrique Amaya has worked in UCSF, Berkeley, and the Salk Institute. He will continue to work with Amphibia, concentrating on morphogenesis of the embryonic nervous system and on developing a genetic approach to *Xenopus* using sperm mutagenesis. Nancy Papalopulu will continue her work on neural induction in chick and mouse embryos.

One of our Group Leaders, Steve Jackson, has recently been appointed to a University Chair, the Quick Professorship of Biology, and we are delighted to have the prospect of his continuing to work in the Institute for many years.

Stephanie Wright, who joined us as a Younger Group Leader in 1992, left to take up a Lectureship in Leeds. We shall miss Stephanie, but wish her continued success in her new post.

THE INSTITUTE IN 1995 A highlight of the year was the visit by our International Advisory Board (page 44). The two-day visit was enthusiastically received by all member of the Institute. Several members of the Institute have received recognitions for their work, and these are listed on page 55. The increasing strength of our publication list (pages 45–53) is much influenced by the continuing enhancement of our younger groups.

EXPANSION OF THE INSTITUTE A new Biochemistry Department is under construciton next to our Institute and this enables us to take advantage of extra funding, previously awarded to us by the Wellcome Trust and the Cancer Research Campaign, for extension to our building. The extension should be complete by the end of 1996 and will allow the introduction of one or more new groups.

John Gurdon

JOHN GURDON
CHAIRMAN

Waiting for the Du Pont NEN Seminar

Besides this sponsored international seminar series which regularly attracts around one hundred scientists, the Institute hosts many internal and interdepartmental seminars.

Wine tasting

During 1995 various wine tasting events were arranged by members of staff, and also a Bangers and Beans evening, both of which we hope will be repeated in the coming year.

We are fortunate in having an Institute where research and support staff are highly interactive, their backgrounds and cultures varied; the atmosphere is both positive and friendly.

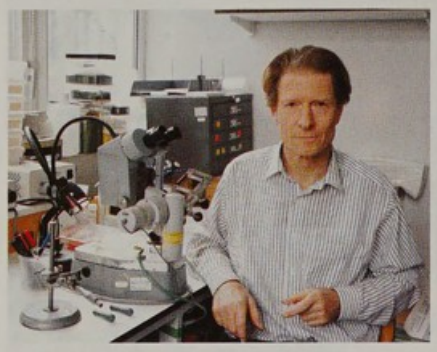
All members of staff are ecouraged to meet together over tea/coffee/lunch in our large coffee/seminar room which is also the venue for many social events. Meeting and cooperating both socially and academically with the science departments of the University is greatly facilitated by the groups of our Institute being affiliated to them.

Relaxing in the coffee room

The core staff play an important role in supporting the various research activities of the Institute

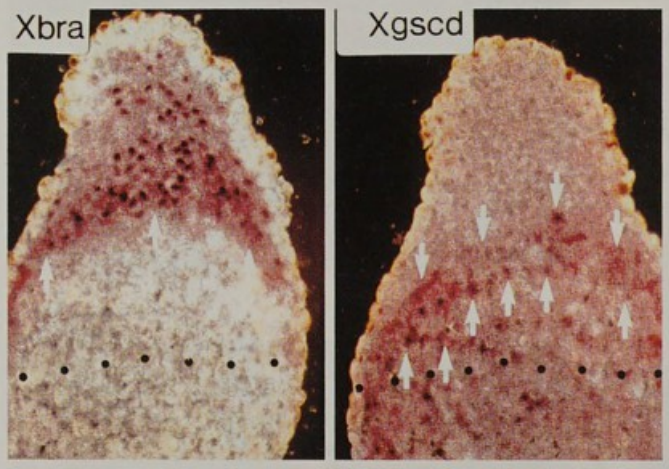
Team spirit is encouraged not only in the laboratory but also on the sports field. Besides the sporting events which help us to relax between sessions at the annual retreat, the Institute has its own football team, the Wellcome Wanderers, and in the summer regular matches of rounders are played with other University departments.

JOHN GURDON



GILLES CARNAC
AGNES CHAN
DEVANAND CREASE
STEVEN DYSON
NIGEL GARRETT
NATASHA MCDOWELL
ANDREW MITCHELL
KEN RYAN
FIONA STENNARD
ELIZABETH TWEED
AARON ZORN

Right hand tadpole has a double axis due to injection of Siamois mRNA. Normal uninjected control tadpole on right.



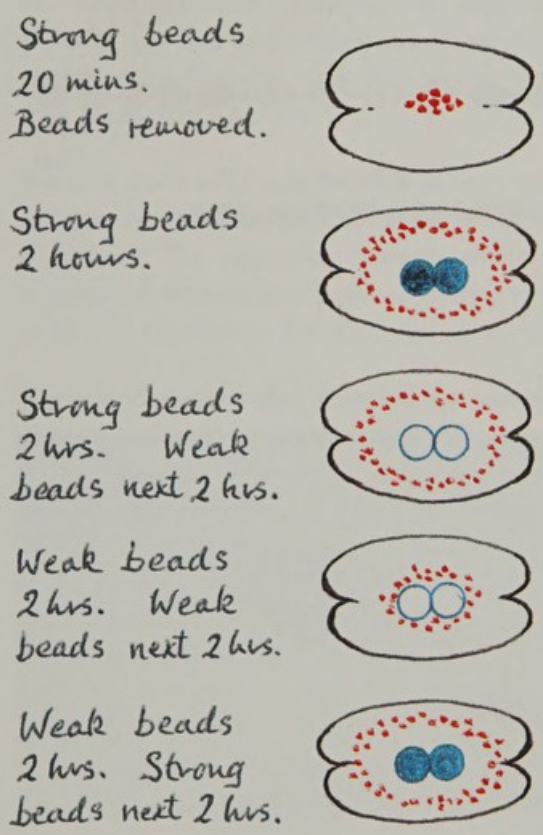
Sections through directional conjugates. Cells injected with activin mRNA are below the dotted line. Some of the cells above the line respond to activin signalling by expressing the gene Xbrachyury (left); other cells nearer the signalling source express Xgoosecoid (right)

LEMAIRE, P., GARRETT, N. and GURDON, J.B. 1995. Expression cloning of *Siamois*, a *Xenopus* homeobox gene expressed in dorsal-vegetal cells of blastulae and able to induce a complete secondary axis. **Cell 81**, 85-94.

GURDON, J.B., MITCHELL, A. and MAHONY, D. 1995. Direct and continuous assessment by cells of their position in a morphogen gradient. **Nature 376**, 520-521.

For further publications, see nos. 50,66, page 45ff.

MECHANISMS OF CELL DIFFERENTIATION IN EARLY AMPHIBIAN DEVELOPMENT



Activin loaded beads (blue) in animal cap sandwiches. Cells express Xbra (red) by a ratchet-like mechanism

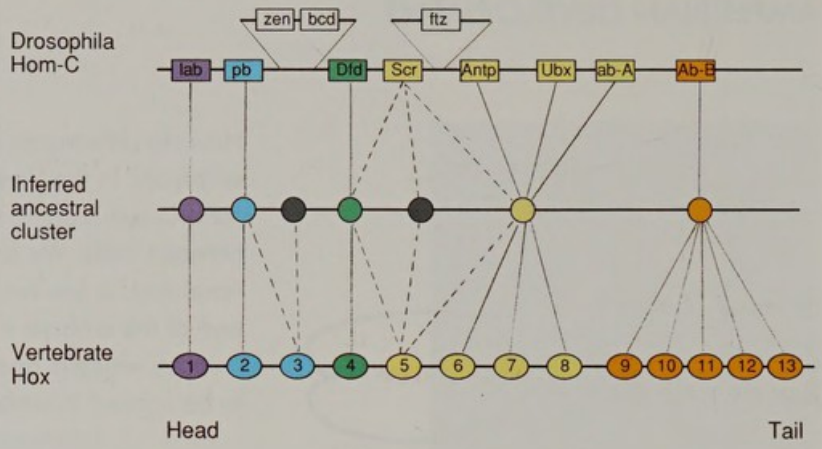
How do differences between cells first arise in early embryos? In the Vertebrates, much the most important mechanism leading to cell differences is interactions between cells. We are analysing this process in Amphibia: a few hours after fertilization, cells at one end of the embryo induce those at the other to become muscle, which is one of the first differentiated cell-types to be formed in embryos.

A particularly important aspect of this mesoderm-forming induction is that cells seem to respond to different concentrations of a signalling molecule such as activin, to form mesodermal cell-types like muscle, notochord, etc. We have obtained direct evidence for the operation of a morphogen gradient by using directional conjugates in which a concentration gradient of activin spreads from a source through a population of responsive cells. The decision of cells to respond to the gradient by expressing the genes *Xbrachyury* and *Xgoosecoid* is determined by their distance from the source, that is by the concentration of morphogen that they receive.

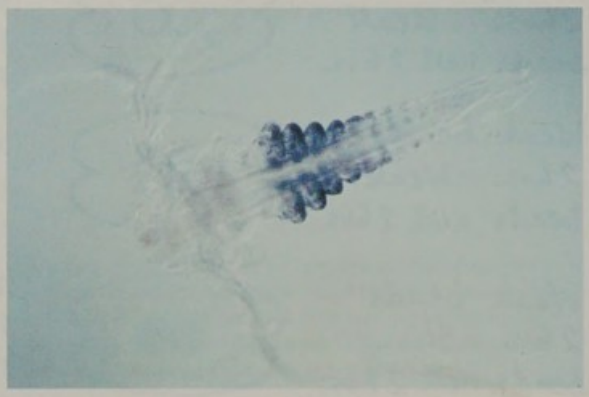
The mesoderm-forming induction is immediately followed in *Xenopus* by community effects in the notochord and muscle and by an inhibitory influence of ventral ectoderm – these processes are believed to refine early responses to a morphogen gradient by increasing uniformity within, and demarcation between, mesodermal cell-types. We are actively engaged in trying to identify new genes for these various mesodermal activities, using a functional screen of subtracted cDNA libraries.

MICHAEL AKAM

JAIME CASTELLI-GAIR
CHUCK COOK
RACHEL DAWES
FRANCESCO FALCIANI
DAVID FERRIER
PHILIPPE GAUTIER
JEFFREY MARCUS
HILARY REED
LOUISE SMITH
SANDRA RYLANCE
DAVID STERN



Comparison of insect and vertebrate hox clusters



Hox gene expression in the developing larva of the brine shrimp Artemia. Genes that define both the thorax and abdomen of insects are restricted to the thorax in this crustacean, suggesting that differentiation of the insect trunk segments occurred after the split of insect and basal crustacean lineages.

AVEROF, M. and AKAM, M. 1995. Hox genes and the diversification of insect and crustacean body plans. **Nature 376**, 420-423.

CASTELLI-GAIR, J. and AKAM, M. 1995. How the Hox gene *Ultrabithorax* specifies two different segments: the significance of spatial and temporal regulation within metameres. **Development 121**, 2973-2982.

For further publications see nos. 1,2, page 45ff.

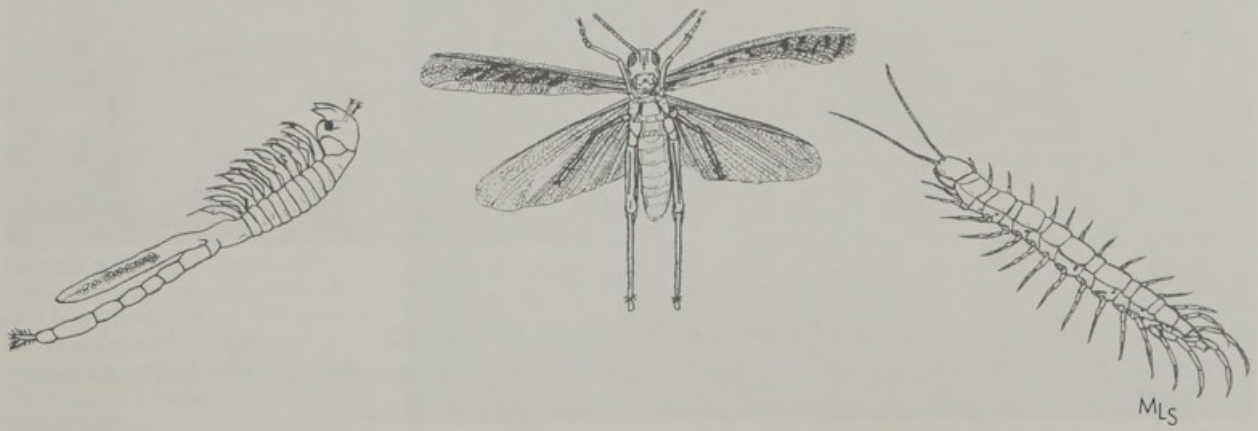
HOX GENES AND SEGMENT PATTERNING IN ARTHROPODS

Hox genes encode transcription factors that specify the position of cells along the antero-posterior axis of the embryo. In arthropods, they control the diversification and specialisation of segments.

Using the powerful genetics of *Drosophila*, we study how Hox genes control the morphogenesis of individual segments – how the Hox genes interact with the genetic systems that define the ground plan of limbs, gonads and other body elements; how transcriptional regulation of a single Hox gene can specify more than one type of segment; how the differential splicing of Hox encoded proteins may alter their biological function.

We also study what role the Hox genes may have played in the diversification of different arthropod groups. We have isolated homologues of Hox genes from other insects, from Crustacea, and from Myriapods. The expression domains of Hox genes in these diverse forms can be used as one criterion to establish homologies between different body parts. These patterns provide new models for the origins of tagmosis – the structural subdivision of the arthropod body into specialised regions.

These studies have also revealed the presence of rapidly evolving homeobox genes within the Hox clusters – genes represented by *fushi-tarazu* and *zen* in *Drosophila*. As the role of these genes appears to differ between insects, we are attempting to develop assays for their function in the locust *Schistocerca gregaria*, an insect only distantly related to *Drosophila*.



ANDREA BRAND

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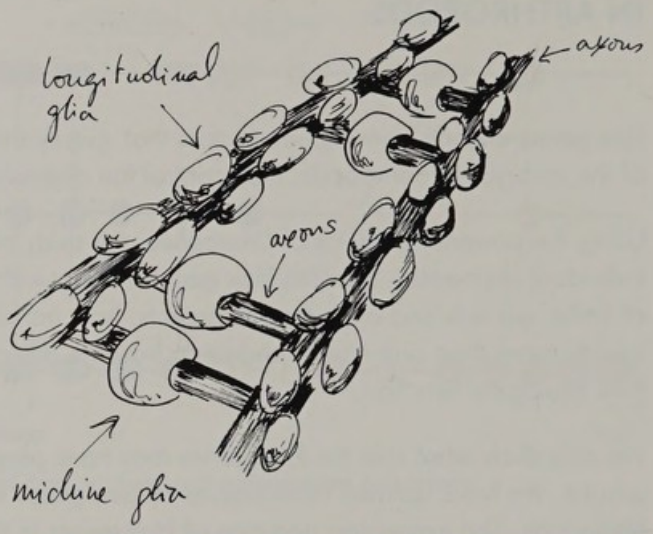
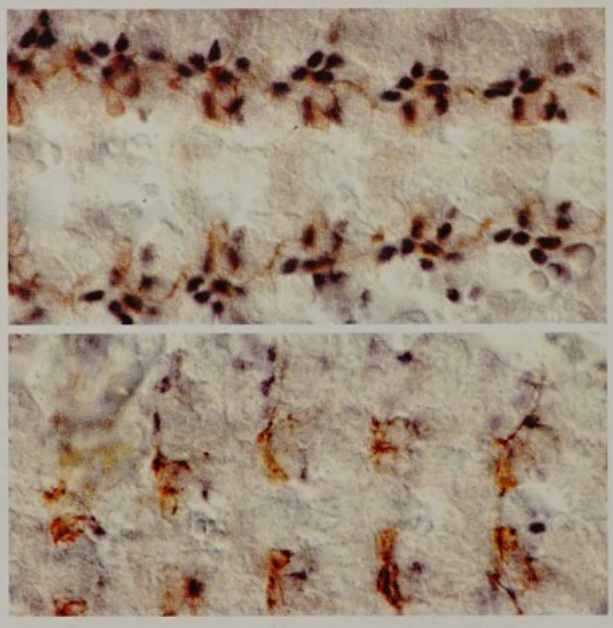
ALICIA HIDALGO
ULRIK JOHN
ALISON SCHULDT





Targeted ablation of glial cells disrupts axon tract formation, and maintenance, during embryonic development. A wild type nerve cord is shown at top (glial cells in black, axons in brown); at the bottom is a nerve cord in which the interface glia have been ablated.

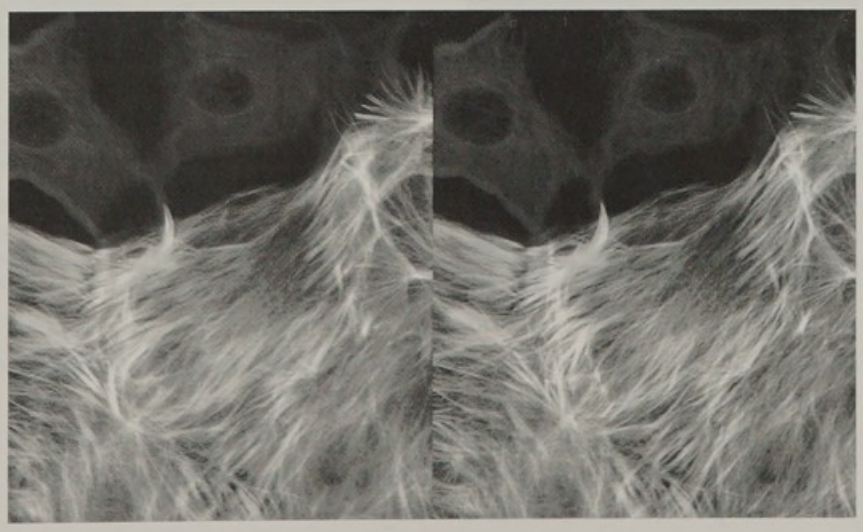
BRAND, A.H. 1995. GFP in *Drosophila*. **Trends in Genetics 11**, 324-325.
HIDALGO, A., URBAN, J. and BRAND, A.H. 1995. Targeted ablation of the longitudinal glia disrupts axon tract formation in the *Drosophila* embryonic CNS. **Development 121**, 3703-3712.
For further publications see nos. 10,107, page 45ff.

EMBRYONIC NERVOUS SYSTEM DEVELOPMENT IN *DROSOPHILA*

During nervous system development each neuron acquires a specific identity, directing it to extend an axon towards and synapse with an appropriate target cell. Cell identity arises in response to a specific pattern of gene expression and to cell-cell interactions. We have developed a general method for directed gene expression in *Drosophila*, the GAL4 system, that allows transcription to be manipulated both spatially and temporally. Using targeted gene expression, transcription patterns in neuronal precursor cells and in their progeny can be altered with the aim of eliciting specific cell fate changes. Directed expression of diphtheria toxin or ricin can be used to ablate cells and to eliminate the cell-cell interactions that may influence cell identity and axon outgrowth.

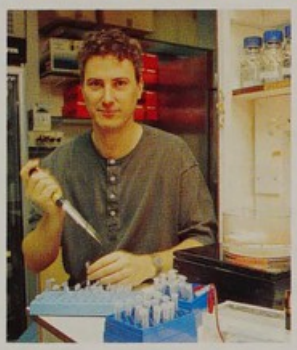
We are using targeted cell ablation to study the role of glial cells and pioneer neurons in establishing the axon scaffold. We are also killing specific subsets of the ventral midline cells, which may send out attractive or repulsive signals to migrating axons. For this reason the midline cells are thought to be analogous to the vertebrate floorplate.

To monitor the effect of cell ablation and cell fate changes *in vivo*, we are labelling neurons and glia in living embryos by expression of green fluorescent protein from the jelly fish, *Aequoria victoria*. Ultimately we aim to carry out all of our assays on living embryos, tracing individual cells through embryonic development.



Directed expression of a tau-GFP fusion protein in the epidermal cells of a living larva. The tau-GFP binds to microtubules and highlights the microtubule network within each cell. The image is a stereo pair of confocal micrographs.

NICHOLAS BROWN



JAMES BLOOR
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JOHN OVERTON
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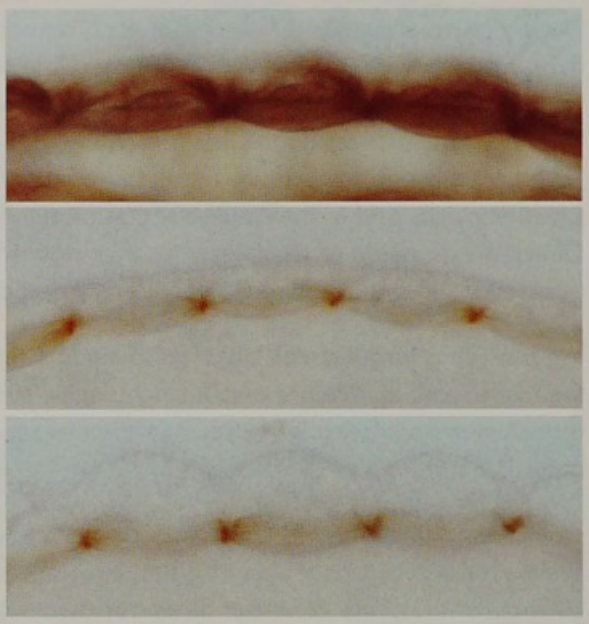
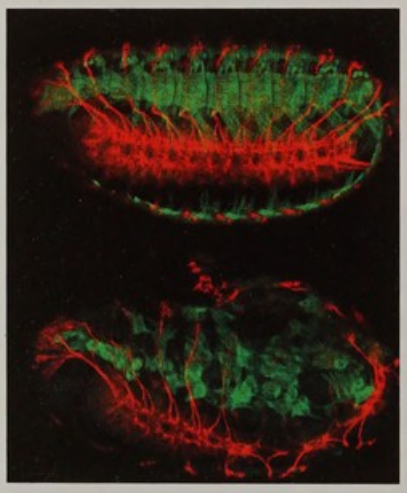


Mapping a domain of the β_{PS} protein that can shift the localisation of the CD2 protein from uniform expression on the muscle cell surface (top) to the ends of the muscles (middle) where the β_{PS} integrin is normally found (bottom)



Defects in morphogenesis are found in embryos mutant for the gene encoding the β_{PS} integrin subunit. A normal embryo (top) and a mutant embryo (bottom) are stained to show the muscles (green) and the nervous system (red)

BROWN, N.H. 1994. Null mutations in the α_{PS2} and β_{PS} integrin subunit genes have distinct phenotypes. **Development 120**, 1221-1231.

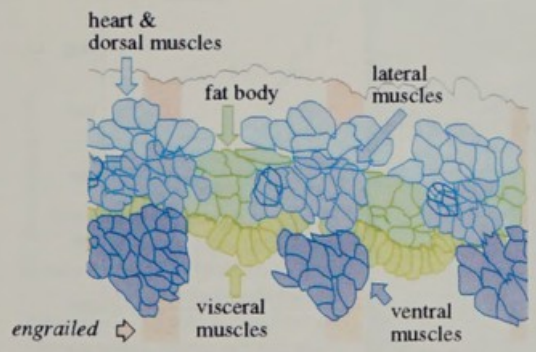
DUNIN-BORKOWSKI, O.M, BROWN, N.H. and BATE, M. 1995. Anterior-posterior subdivision and the diversification of the mesoderm in *Drosophila*. **Development 121**, in press.

For further publications see no. 26, page 45ff.

MOLECULAR ANALYSIS OF CELL ADHESION

The development of a multicellular organism requires numerous molecular interactions between proteins on the cell surface. These proteins mediate both adhesion and signalling between cells. Our aims are to characterise the cellular interactions and shape changes that occur during the development of the fruit fly *Drosophila*, identify the proteins that mediate these events and understand how they function.

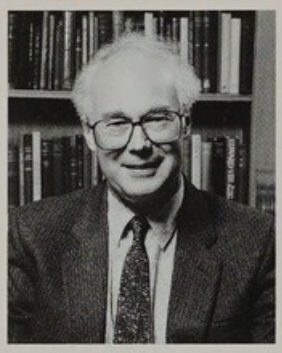
We have developed a new marker that allows us to see the shapes of cells within the developing embryo. By generating embryos that express this marker in the developing mesoderm we have been able to see how cell shape changes accompany the early segregation of the populations of cells that give rise to the different mesodermal derivatives. We now wish to identify the proteins that specify the changes in shape and adhesiveness that accompany this segregation.



Identification of the progenitors of the different muscle derivatives by visualising cell shape with the marker CD2

Members of the integrin family of adhesion receptors are required for the adhesion of different cell layers to each other in the developing embryo. By manipulating the genes encoding these integrins we are examining how these proteins function to achieve this. We have recently completed a screen for mutations in genes which are required for integrin mediated adhesion, and have identified 12 new genes. The cloning and characterisation of these genes will illuminate the links between the inside and outside of the cell.

MARTIN EVANS



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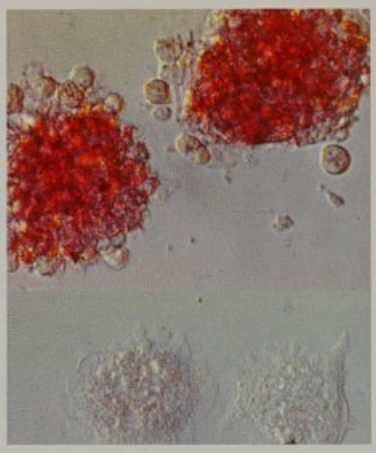
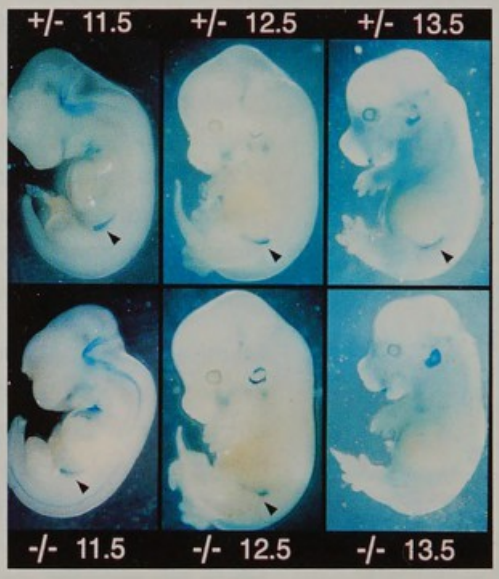
SUSAN HUNTER
JODIE MACOUN
VENKATA NARAYANA PISUPATI
ROSEMARY RATCLIFF
EMILY SCOTT
CHUL SOHN
GORDON STOTT
EVA STRAETLING
FIONA THISTLETHWAITE
JOANNE WILSON
MAGDALENA ZERNICKA-GOETZ



The purple acid phosphatase locus Acp5 knock out gives mice with a deficit of endochondrial ossification and bone re-modelling. This tartrate resistant acid phosphatase (TRAP) is specifically expressed in macrophages and osteoclasts. Shown here are osteoclasts isolated from normal (a) and from Acp -/- mouse femurs (b). They are stained for acid phosphatase. [Work in collaboration with Prof. Tim Cox & Dr Alison Hayman.]



Hox11 in spleen development Lac-Z staining (under the control of Hox11) shows onset of spleen development is normal in the Hox11 –/– mutant mice but the organ subsequently fails to develop and undergoes apoptosis.

COLLEDGE, W.H., ABELLA, B.S., SOUTHERN, K., RATCLIFF, R., JIANG, J., CHENG, S.H., MacVINISH, L.J., ANDERSON, J.R., CUTHBERT, A.W. and EVANS, M.J. 1995. Generation and characterization of a ΔF508 cystic fibrosis mouse model. **Nature Genetics 10**, 445-452.

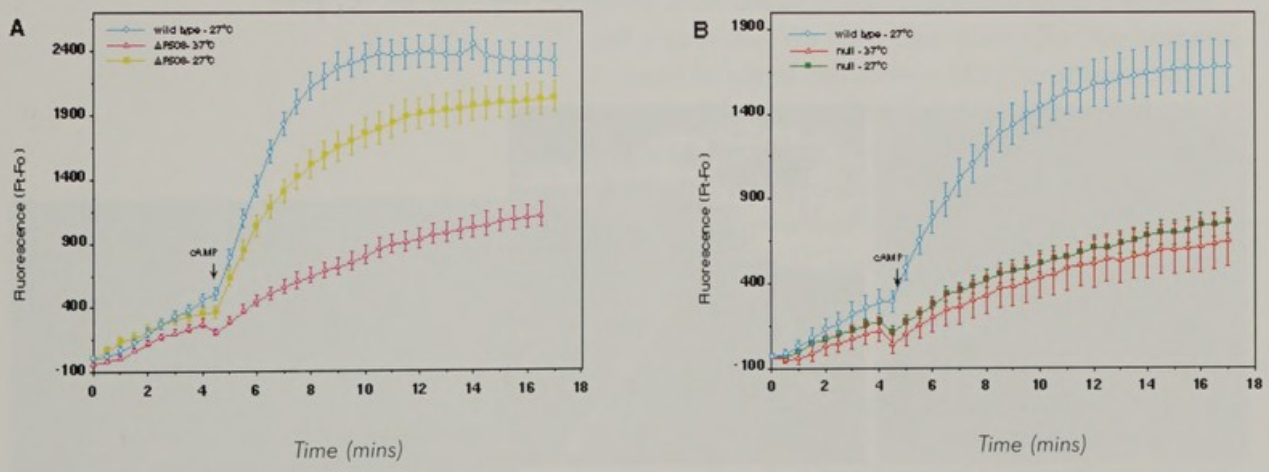
DEAR, T.N., COLLEDGE, W.H., CARLTON, M.B.L., FORSTER, A., LAVENIR, I., LARSON, T., SMITH, A., WARREN, A., EVANS, M.J., SOFRONIEW, M.V. and RABBITTS, T.H. 1995. HOX11 is essential for cell survival during spleen development. **Development 121**, 2909-2915.

For further publications see nos. 14,18,19,22,27,28,79,93,94,95,106, page 45ff.

MAMMALIAN DEVELOPMENTAL BIOLOGY AND GENETICS THROUGH THE CULTURE OF EMBRYONIC STEM CELLS

The use of embryonic stem (ES) cells of mice as a route to somatic and germ line transgenesis has opened up the route to experimental mammalian genetics. Because these cells provide a bridge between the whole animal and tissue culture, specific genetic modification which may be induced, screened or selected in culture, can be tested and recombined within the context of the physiology and genetics of the whole animal.

We are creating mouse mutants resulting from random integration of viral DNA into the genome and are using homologous recombination to introduce specific mutations into ES cells to study the results of such gene targeting *in vivo* and generate animal models of human diseases.

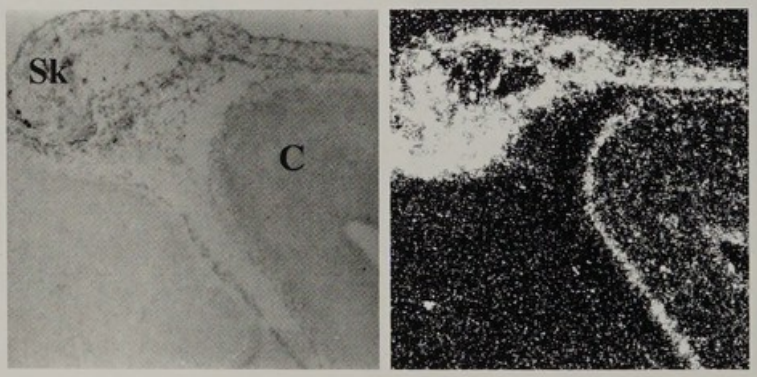


In mice ΔF CFTR is a temperature sensitive mutant. Cells grown from the trachea of normal mice demonstrate cyclic-AMP stimulated halide transport when grown at either 27°C or 37°C. Cells from null mutant mice do not show this activity at either temperature but tracheal cells from ΔF508 homozygous mice show reactivation of the cyclic AMP stimulated channel at 27°C. (Colledge et al., Ref. opposite)

CHARLES FFRENCH-CONSTANT

KATHERINE BLASCHUK
PHIL BUTTERY
EMMA FROST
THOMAS JACQUES
RICHARD MILNER

Myelin sheath formation in xenocultures of mouse oligodendrocytes and rat neurons



Thrombospondin-1 expression in the embryonic central nervous system.

MILNER, R. and FFRENCH-CONSTANT, C. 1994. A developmental analysis of oligodendroglial integrins in primary cells: changes in av-associated β subunits during differentiation. **Development 120**, 3497-3506.

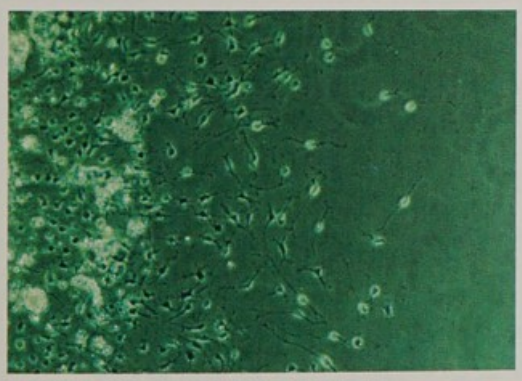
FFRENCH-CONSTANT, C. 1995. Alternative splicing of fibronectin – many different proteins but few different functions. **Exp. Cell Res. 221**, in press.

For further publications see nos. 34,35,67, page 45ff.

DEVELOPMENT AND REPAIR OF THE VERTEBRATE CENTRAL NERVOUS SYSTEM

The focus of our group is the role of cell-extracellular matrix (ECM) interactions in mammalian central nervous system (CNS) development. These interactions have received less attention than the effects of neurotrophins and other growth factors, but evidence from other developmental systems suggests that they will play key roles in controlling cell behaviour. We study the oligodendroglial cells (which form myelin in the mature CNS) as these cells can be identified and manipulated in cell culture.

We have shown that different ECM molecules can either stimulate or inhibit oligodendroglial precursor cell migration. We have also shown that the integrins, a major family of cell surface ECM receptors, are regulated during development in a pattern that demonstrates a role in the control of cell migration. We are presently constructing cell lines with different chimeric integrins and also analysing transgenic mice lacking different ECM molecules so as to test directly the roles of these molecules and their receptors.



Oligodendrocyte precursor migration assay

In addition to these developmental studies we also study repair in the nervous system. Another ECM molecule, fibronectin, appears during peripheral nerve repair and we find that forms of fibronectin produced during early development by alternative splicing of the primary gene transcript are re-expressed during repair. This suggests that efficient repair may require re-use of developmental mechanisms. We hope to use our knowledge of CNS development to devise strategies for repair of the CNS.

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SUSAN CRITCHLOW
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DAVID GELL
NICHOLAS LAKIN
SOHAIL QURESHI
SCOTT ROTTINGHAUS
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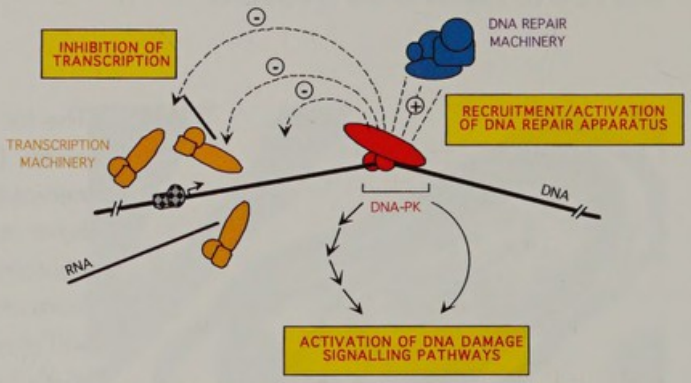
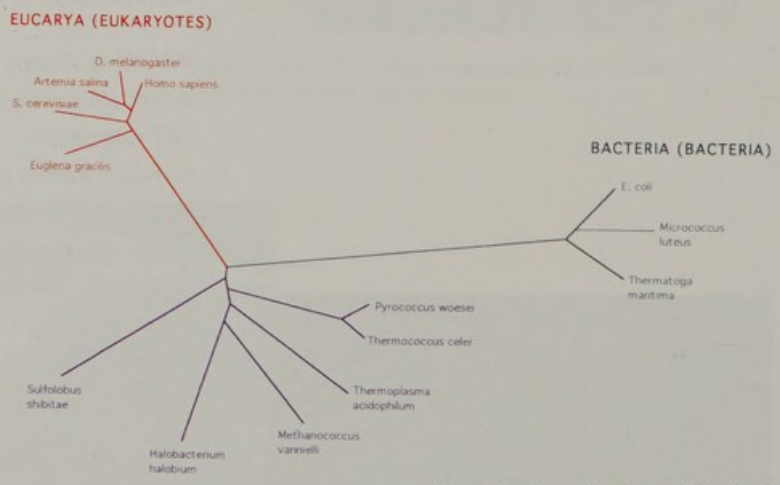
SOO-HWANG TEO
UGUR YAVUZER



Possible functions for DNA-PK at sites of DNA damage



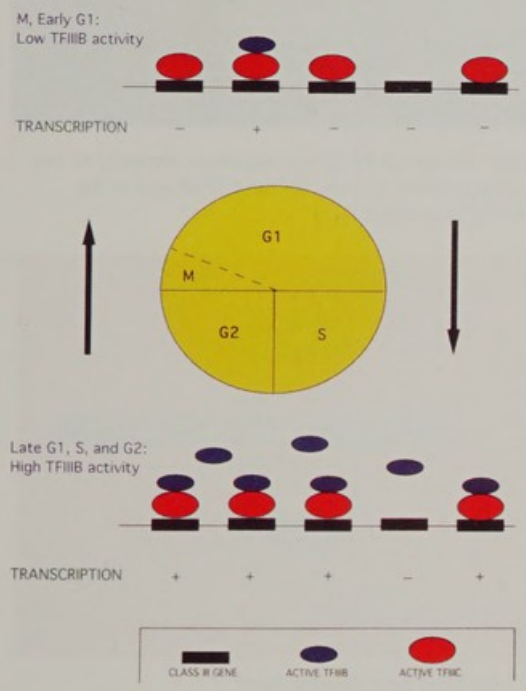
Archaebacteria (Archaea): the third domain of life

BLUNT, T., FINNIE, N.J., TACCIOLI, G.E., SMITH, G.C.M., DEMENGEOT, J., GOTTLIEB, T.M., MIZUTA, R., VARGHESE, A.J., ALT, F.W., JEGGO, P.A. and JACKSON, S.P. 1995. Defective DNA-dependent protein kinase activity is linked to V(D)J recombination and DNA repair defects associated with the murine *scid* mutation. **Cell 80**, 813-823.

HARTLEY, K., GELL, D., SMITH, G.C.M., ZHANG, H., DIVECHA, N., CONNELLY, M.A., ADMON, A., LEES-MILLER, S.P., ANDERSON, C.W. and JACKSON, S.P. 1995. DNA-dependent protein kinase catalytic subunit: a relative of phosphatidylinositol 3-kinase and the ataxia telangiectasia gene product. **Cell 82**, 849-856.

For further publications, see nos. 7,32,33,49,52,53,54,61,77,83,84,87,103,104,105, page 45ff.

TRANSCRIPTION, GENETIC RECOMBINATION, AND DNA REPAIR



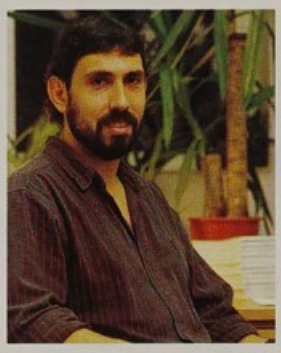
Cell cycle regulation of RNA polymerase III transcription

One of our major goals is to define fundamental mechanisms of transcriptional control. For example, we have elucidated the basis for cell cycle regulated transcription by RNA polymerase III. We are now defining the precise mechanistic basis for this control, assessing the involvement of tumour suppressor proteins in this regulation, and extending our work to RNA polymerases I and II.

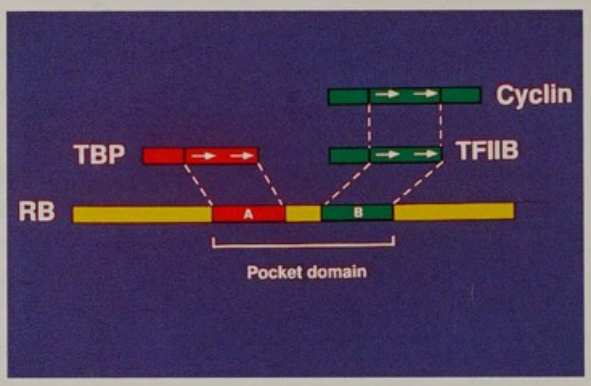
In addition, we study transcription in Archaea. Our results indicate that the transcriptional machineries of Archaea and eukaryotes are fundamentally homologous. Current directions include establishing a fully defined archaeal *in vitro* transcription system and mapping interactions between various transcriptional components.

We also study DNA-dependent protein kinase (DNA-PK). Interestingly we find that DNA-PK is activated by DNA ends. Consistent with this, we have made the important discovery that cells deficient in DNA-PK are defective in DNA repair and are unable to perform V(D)J recombination. Thus, DNA-PK is a crucial component of the DNA repair/ recombination apparatus. Cloning of DNA-PK_{CS} reveals homologies to several other proteins involved in the recognition and repair of DNA damage. We are currently using the combination of biochemistry, mammalian cell culture and yeast molecular genetics to define the mechanism of action of DNA-PK and its relatives, and to study how these proteins may prevent carcinogenesis.

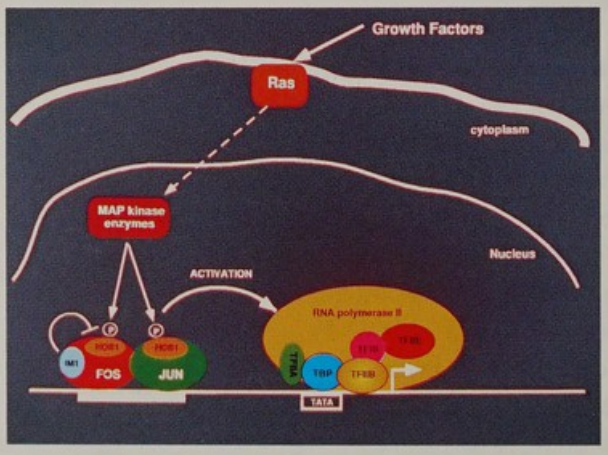
TONY KOUZARIDES



ANDREW BANNISTER
HELEN BROWN
CATHERINE LE CHALONY
ALISTAIR COOK
PAUL LAVENDER
KLAUS MARTIN
JONATHAN MILNER
JULIET REID
DIDIER TROUCHE



The pocket domain of RB shows sequence similarity to two general transcription factors, TBP and TFIIB and to the Cyclin family of proteins



c-Fos and c-Jun have an activation motif (HOB1) which is phosphorylated by MAP kinase-like enzymes in response to Ras and is inhibited by the IM1 motif.

MARTIN, K., TROUCHE, D., HAGEMEIER, C., SØRENSEN, T.S., LA THANGUE, N.B. and KOUZARIDES, T. 1995. Stimulation of E2F1/DP1 transcriptional activity by MDM2 oncoprotein. **Nature 375**, 691-694.

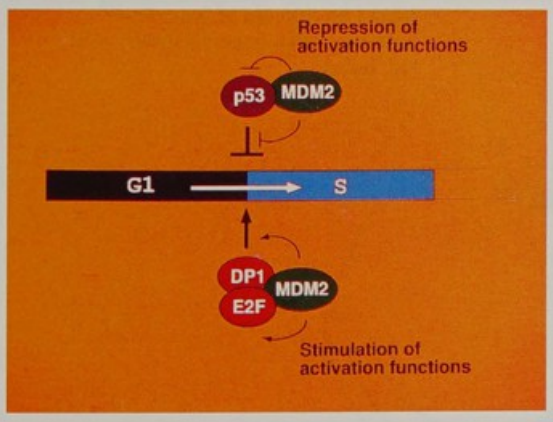
BANNISTER, A.J. and KOUZARIDES, T. 1995. CBP-induced stimulation of c-Fos activity is abrogated by E1A. **EMBO J. 14**, 4758-4762.

For further publications see nos. 5,6,13,58,92, page 45ff.

TRANSCRIPTIONAL REGULATION BY ONCOGENE PRODUCTS AND TUMOUR SUPPRESSOR PROTEINS

Our group is interested in defining the mechanisms by which transcription factors modulate gene expression and how these functions correlate with oncogenic capacity. We are currently concentrating on two oncogenic transcriptional activators, c-Fos and c-Jun, and a transcriptional repressor, the Retinoblastoma tumour suppressor protein, RB.

Our analysis of c-Fos and c-Jun indicates that they possess a homologous activation domain containing two motifs, HOB1 and HOB2. The activity of the HOB1 motif is regulated by Ras-induced phosphorylation and is silenced by an inhibitor motif (IM1) present within c-Fos. We have recently shown that a co-activator protein, CBP, can bind to c-Fos and c-Jun and stimulate their activation capacity.



MDM2 represses p53 and stimulates E2F1/DP1, resulting in S phase progression

The tumour suppressor functions of the RB protein correlate with its ability to bind and silence the E2F transcription factor. This repression is mediated via a domain which we find has sequence similarity to two general transcription factors, TBP and TFIIB as well as the family of Cyclins. We have presented evidence that RB may use this similarity to displace TBP from E2F. Recently, we discovered a functional connection between the E2F oncoprotein and the p53 tumour suppressor protein: both proteins are contacted by MDM2, a protein which represses p53 but stimulates E2F activity. These results provide a mechanism for the oncogenic capacity of MDM2.

RON LASKEY

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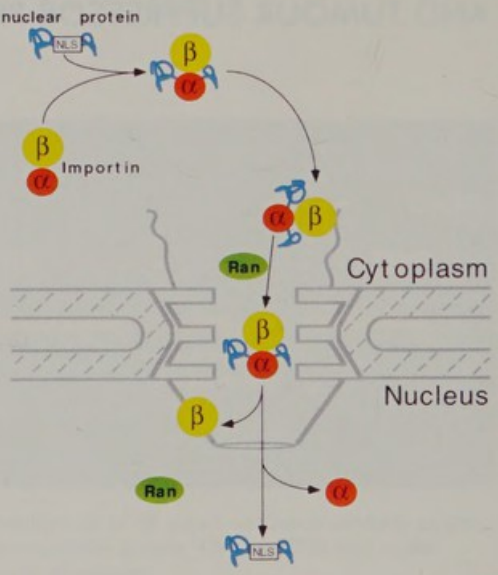
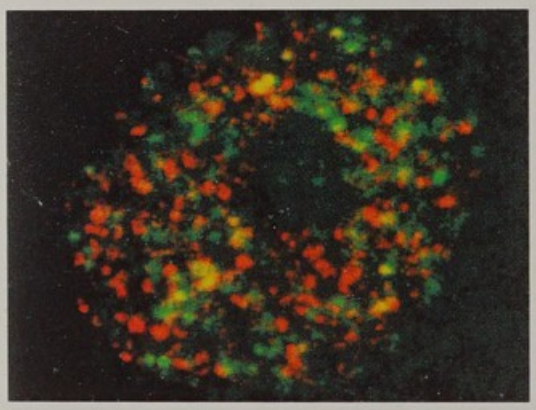
DIRK GÖRLICH
TORSTEN KRUDE
YUMIKO KUBOTA
MARK MADINE
KATHRIN MARHEINEKE
JACKIE MARR
TONY MILLS
KEITA OHSUMI
PIOTR ROMANOWSKI
HANNAH WILKINSON



Model for the role of Importin in nuclear protein import (Görlich et al., Ref. below)



MCM3 (green) marks unreplicated DNA and is displaced by replication (red)

GÖRLICH, D., VOGEL, F., MILLS, A.D., HARTMANN, E. and LASKEY, R.A. 1995. Distinct functions for the two importin subunits in nuclear protein import. **Nature 377**, 246-248.

MADINE, M.A., KHOO, C-Y., MILLS, A.D. and LASKEY, R.A. 1995. MCM3 complex required for cell cycle regulation of DNA replication in vertebrate cells. **Nature 375**, 421-424.

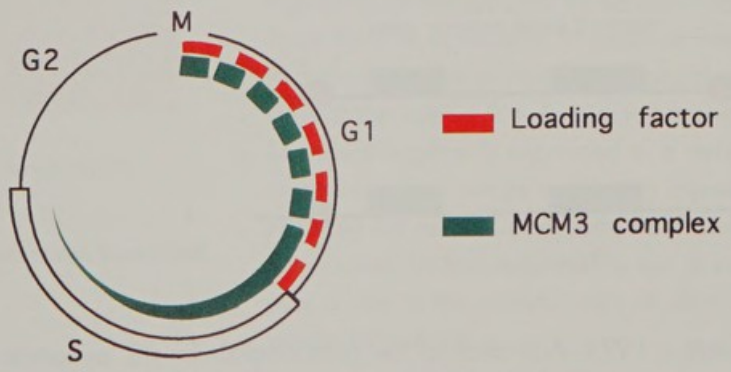
For further publications see nos. 16,24,41,42,59,60,62,64,78,88, page 45ff.

CONTROL OF EUKARYOTIC CHROMOSOME REPLICATION AND NUCLEAR PROTEIN IMPORT

We are analysing the control of eukaryotic chromosome replication and the mechanism of nuclear protein import using cell-free systems derived from eggs of *Xenopus laevis*.

Replication is coupled to the cell cycle so that DNA replicates only once between consecutive divisions. Disrupting the nuclear membrane overcomes this mechanism allowing a further cycle of complete replication. This observation can be explained by a licensing factor model. We have found that the replication capacity of nuclei from synchronised human cells can be accounted for by a similar model. We have shown that a family of known proteins, the Mcm3 family, are components of the licensing system, and that another "loading" factor regulates their binding to chromatin. The nuclear membrane regulates entry of the loading factor and hence the binding of the Mcm proteins.

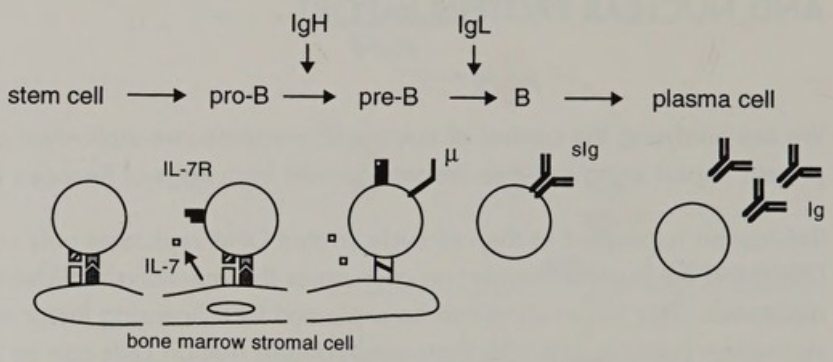
We are also investigating how nuclear proteins are targeted to the cell nucleus. We have identified a protein, importin, which acts as a receptor for nuclear localization signals. It causes them to bind to the nuclear pore complex. One subunit of importin enters the nucleus with its passenger nuclear protein.



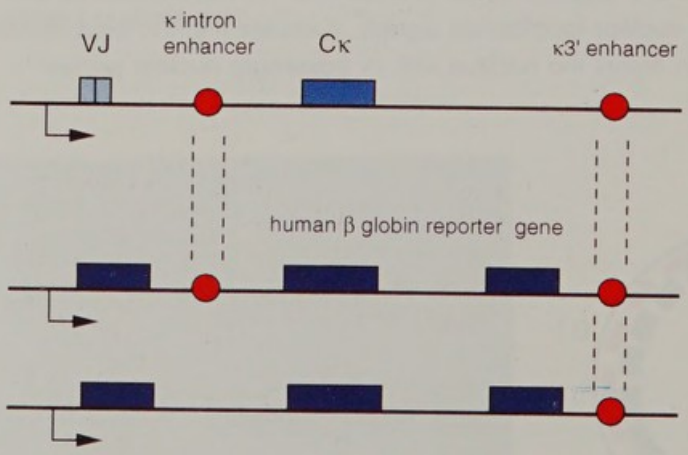
Two step model for replication licensing

KERSTIN MEYER

JOHN IRELAND



Schematic representation of B cell development



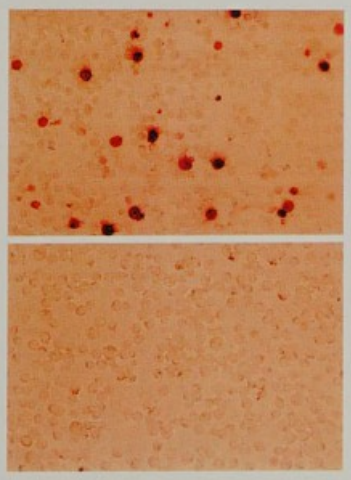
Structure of constructs introduced into transgenic mice

MEYER, K.B. and IRELAND, J. 1994. Activation of the immunoglobulin κ3′ enhancer in pre-B cells correlates with the suppression of a nuclear factor binding to a sequence flanking the active core. **Nucleic Acids Res. 22**, 1576-1582.

MEYER, K.B.,SKOGBERG, M., MARGENFELD, C., IRELAND, J. and PETTERSSON S. 1995. Repression of the immunoglobulin heavy chain 3′ enhancer by helix-loop-helix protein Id3 via a functionally important E47/E12 binding site: implications for developmental control of enhancer function. **Eur. J. Immunol. 25**, 1770-1777.

For further publications sees nos. 21,76, page 45ff.

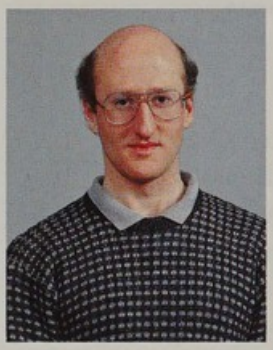
REGULATION OF TRANSCRIPTION IN DEVELOPING B LYMPHOCYTES



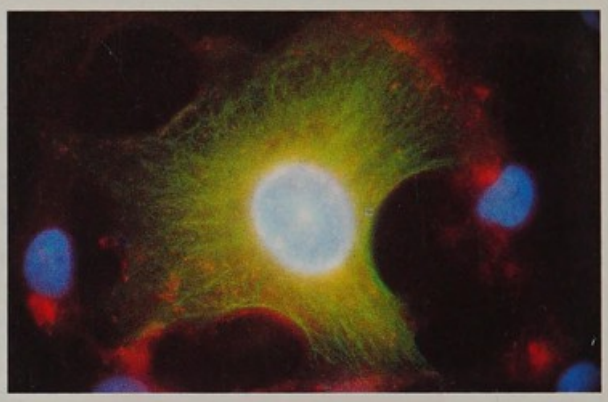
Transient expression of a tagged transcriptional regulator in plasmacytoma cells

The development of a mature B cell from a haematopoietic stem cell proceeds through a number of distinct stages, defined by the expression of surface markers. Our work focuses on examining the molecular basis for the tissue-restricted and developmentally controlled activity of some of these genes. In particular, we have studied the control of the immunoglobulin (Ig) genes. Initial experiments examined the transcription factors responsible for the activity of the Igκ3′ enhancer in cell lines. More recently this work has been extended to studying the activity of the κ3′ enhancer in transgenic mice. These experiments revealed a function of this enhancer early in B cell development and strong inducibility of the 3′ enhancer at the final stage of B cell differentiation. Cells from these animals will now be used to examine the signals, signalling pathways and transcription factors responsible for enhancer activation. In addition we have initiated experiments to examine the lymphoid-specific expression of the interleukin-7 receptor α chain. In the B lineage this gene is expressed in a defined developmental window before surface Ig expression, and is required for normal early lymphoid development. Thus the nuclear factors responsible for its activation may play a role in the commitment of stem cells to the lymphoid lineage.

JONATHON PINES



MALCOLM FIRTH
MARK JACKMAN
CHRISTINA KARLSSON
ANNA MEDDINS
MARY NAPIER
KAREN SIMPSON



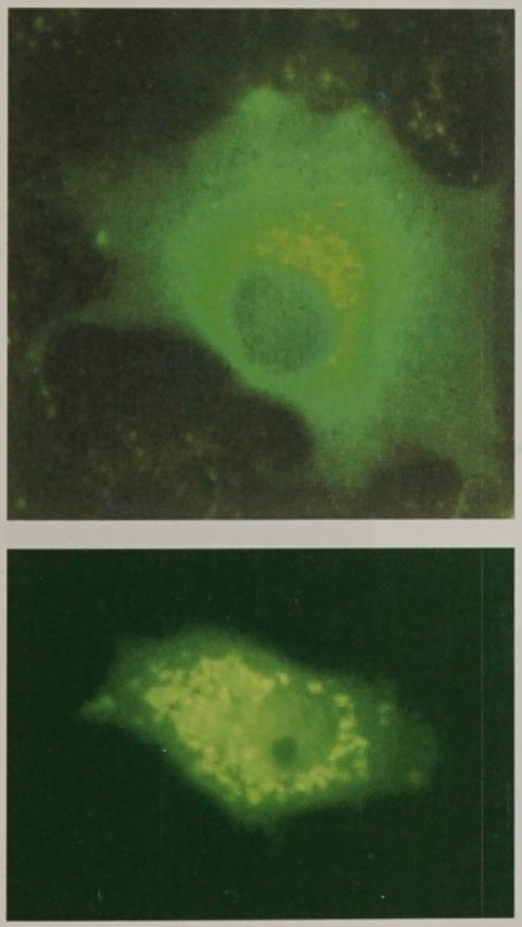
Cell stained with anti-cyclin B1 (green)
Höchst 33342 (blue) and wheatgerm agglutinin (red)

Cell stained with anti-cyclin B2 (red)

Cyclin B1 and B2 localised to different sub-cellular structures. It is clear that cyclin B1 binds to microtubules and cyclin B2 localises to the golgi and vesicle compartment

PINES, J. and HUNTER, T. 1994. The differential localisation of human cyclins A and B is due to a cytoplasmic retention region in cyclin B. **EMBO. J.** 13, 3772-3781.
JACKMAN, M., FIRTH, M. and PINES, J. 1995. Human cyclins B1 and B2 are localised to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus. **EMBO J. 14**, 1646-1654.
For further publications see nos. 81,82, page 45ff.

REGULATION OF THE MAMMALIAN CELL CYCLE BY CYCLIN-DEPENDENT KINASES



Living COS cells expressing (top) cyclin B1-GFP chimaera, which localises to the cytoplasm and in part to microtubules; (bottom) cyclin B2-GFP chimaera, localising to the endosomes and Golgi apparatus

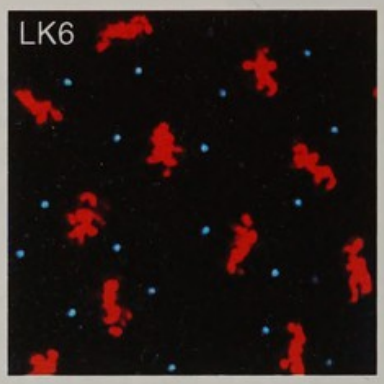
The cell cycle ensures that DNA replication and mitosis are discrete and sequential. Critical steps in the cell cycle are regulated by the cyclin-dependent kinases (CDKs). CDKs are activated and localised to the correct sub-cellular structures by their cyclin partner.

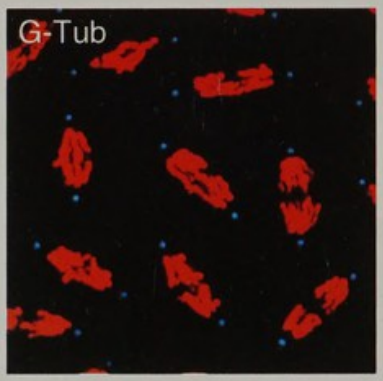
We are studying how cyclins localise CDKs to particular parts of the cell. Cyclin A is a nuclear protein, whereas cyclins B1 and B2 are cytoplasmic throughout interphase. Cyclin B1 associates with microtubules, whereas cyclin B2 localises to the Golgi apparatus suggesting that cyclin B1-cdc2 is responsible for re-organising the cytoskeleton, and cyclin B2-cdc2 for disassembling the Golgi and ER at mitosis.

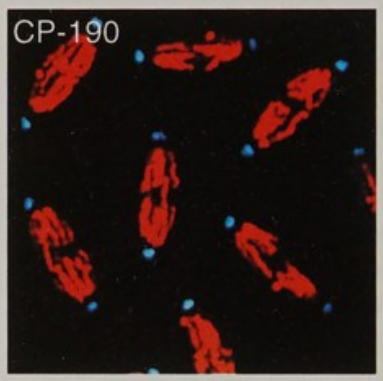
Using chimaeric proteins and point mutants we have defined the regions of the cyclins required for their localisation. We have found a number of proteins that are able to interact specifically with different cyclins using the yeast 2 hybrid screen, and are looking for substrates that are specific to each type of cyclin. We are using Green Fluorescent Protein (GFP) as an *in vivo* marker for cyclin localisation. Cyclin-GFP chimaeras are correctly localised, and we are able to observe them in living cells over several hours. We hope to gain a better understanding of cyclin function in the cell cycle by studying their behaviour in living cells.

JORDAN RAFF

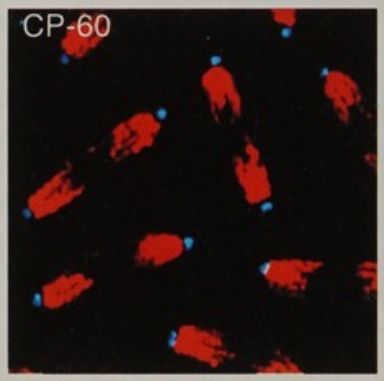
JUNYONG HUANG
DEBORAH KIDD
JAMES WAKEFIELD





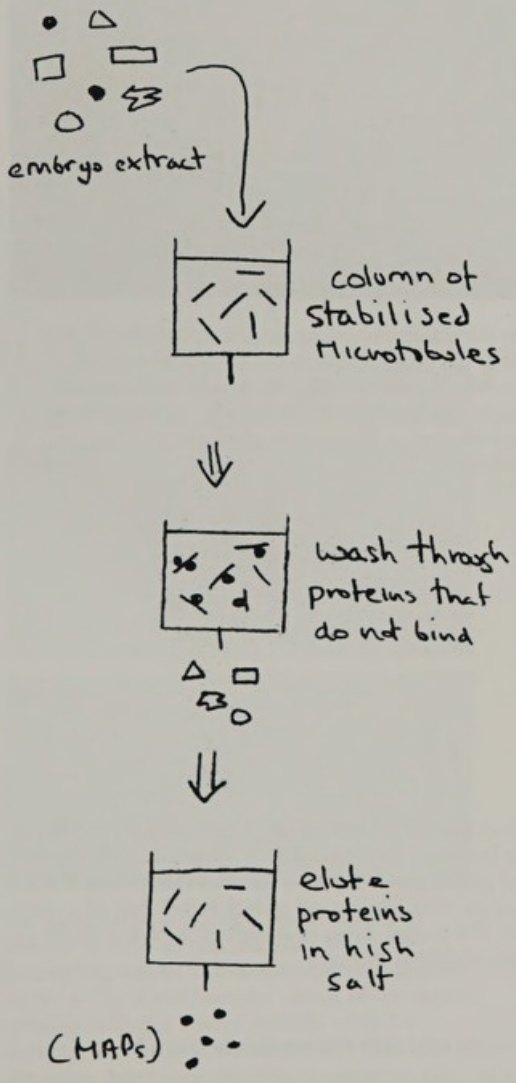


Centrosomes (blue) and chromosomes (red) during mitosis in an early Drosophila embryo



GLOVER, D.M., GONZALEZ, C. and RAFF, J.W. 1993. The centrosome. **Scientific American 268**, 62-68.
RAFF, J.W., KELLOGG, D.R. and ALBERTS, B.M. 1993. *Drosophila* γ-tubulin is part of a complex containing two previously identified centrosomal MAPs. **J. Cell Biol. 121**, 823-825.
For further publications see nos. 56,85, page 45ff.

MOLECULAR ANALYSIS OF THE CENTROSOME



Microtubule column affinity chromatography

The centrosome is the main microtubule organising centre in animal cells. This organelle plays a crucial role in many aspects of cellular organisation, yet very little is known about its structure or how it functions. Using the early *Drosophila* embryo as a model system, we have begun a molecular dissection of the centrosome by isolating a number of proteins that bind to microtubules *in vitro* and are located in the centrosome *in vivo*. Using antibodies raised against these proteins we have cloned cDNAs that encode four of them.

Two of these proteins, called CP190 and CP60, bind directly to each other and to microtubules. Both proteins are components of a larger protein complex that includes γ-tubulin, a highly conserved centrosomal protein that is thought to be involved in the interaction between centrosomes and microtubules. Another is a protein kinase – the first protein kinase shown to be located in the centrosome and to interact with microtubules. Phosphorylation events are known to regulate the microtubule nucleating properties of centrosomes, and this protein is an excellent candidate for a protein involved in this process. Interestingly, the kinase phosphorylates CP60 *in vitro*.

We are using a variety of molecular, biochemical, cell biological, and genetic approaches to study the functions of these centrosomal proteins and to isolate new proteins that associate with them.

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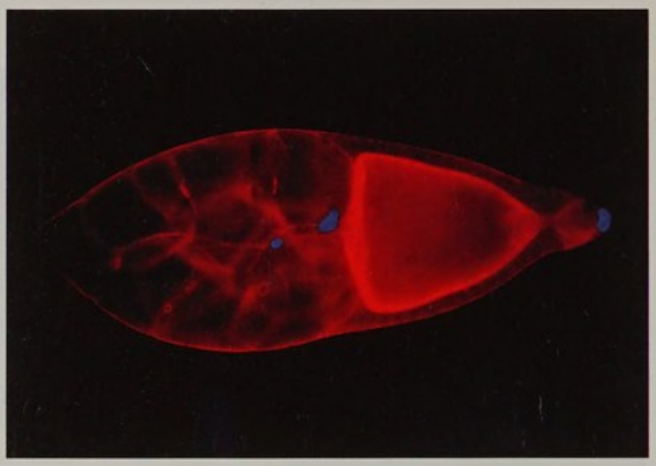
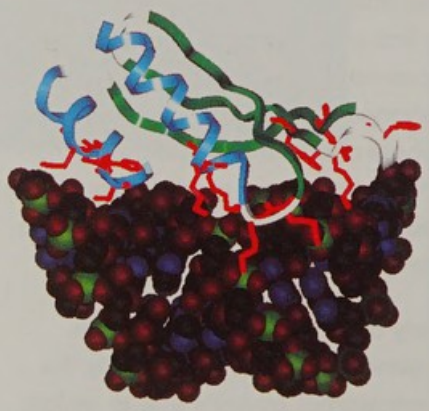
STEFAN GRÜNERT
DAVID MICKLEM
RACHEL SMITH
MATTHEW WESTON
CHIHIRO YAMADA



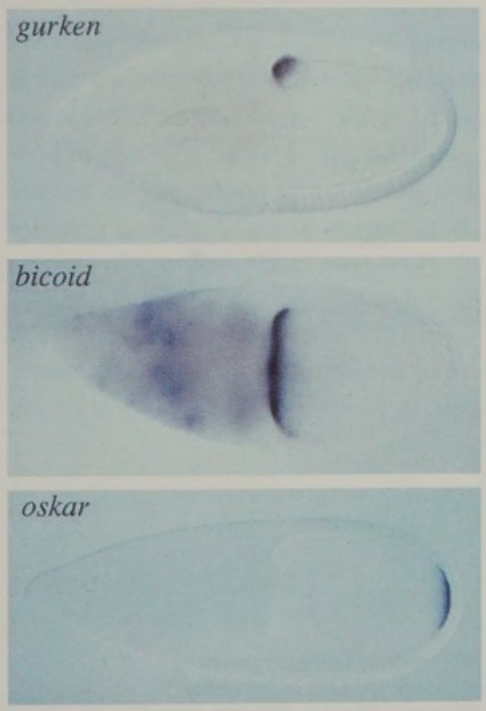
gurken encodes the signal that induces posterior follicle cell fate. In gurken mutants, the anterior follicle cell marker slbo *(blue) is expressed in the follicle cells on both the anterior and posterior sides of the oocyte. The positions of the oocyte, nurse cells and follicle cells are indicated by Rhodamine-phalloidin staining (red) of the actin cytoskeleton*



A model for how a single double-stranded RNA binding domain from Staufen protein contacts dsRNA. The backbone of the domain is shown as a ribbon with α helices in blue, ß sheets in green, and loops in white. The side chains of the amino acids that are required for RNA-binding are shown in red, and all project from one side of the domain. The model shows how these side chains might contact a 12 base pair region of dsRNA (bottom)

GONZÁLEZ-REYES, A., ELLIOTT, H. and ST JOHNSTON, D. 1995. Polarization of both major body axes in *Drosophila* by *gurken-torpedo* signalling. **Nature 375**, 654-658.
ST JOHNSTON, D. 1995. The intracellular localisation of messenger RNAs. **Cell 81**, 161-170.
For further publications see no. 30, page 45ff.

mRNA LOCALISATION AND THE ORIGIN OF POLARITY IN DROSOPHILA



The localisation of gurken, bicoid *and* oskar *mRNAs to three distinct positions within the* Drosophila *oocyte. The accumulation of* gurken *mRNA in the dorsal/anterior corner of the oocyte establishes dorsal-ventral polarity, while the localisaion of* bicoid *and* oskar *mRNAs to opposite poles determines the anterior-posterior axis.*

The intracellular localisation of mRNA is a general mechanism for protein targeting which is now thought to occur in all polarised cell types. A striking example of this phenomenon is provided by the *Drosophila* oocyte, where the localisation of *bicoid, oskar,* and *gurken* mRNAs to three distinct positions within the cell determines the polarity of the anterior-posterior and dorsal-ventral axes of the embryo. We are taking several approaches to investigate how these mRNAs are transported within the oocyte in order to understand both the mechanism of mRNA localisation and the origin of polarity.

1) Staufen protein is required for the localisation and translational control of both *bicoid* and *oskar* mRNAs, and co-localises with each transcript. We have identified a novel dsRNA-binding domain that occurs five times within Staufen, and are now studying how these domains allow the protein to recognise two distinct mRNAs.

2) We are carrying out genetic screens to identify other genes involved in mRNA localisation, in particular the motor proteins that transport these transcripts.

3) We have recently shown that anterior-posterior polarity originates from the movement of the oocyte to the posterior of the egg chamber, and the subsequent induction of posterior fate in the adjacent follicle cells. We are currently cloning two genes that are required for oocyte migration.

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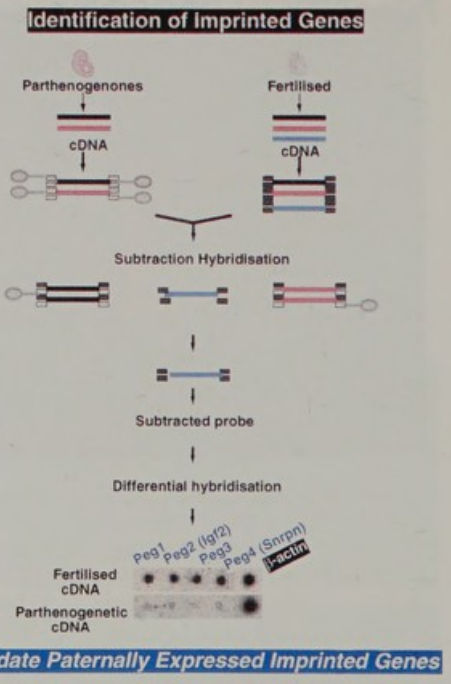
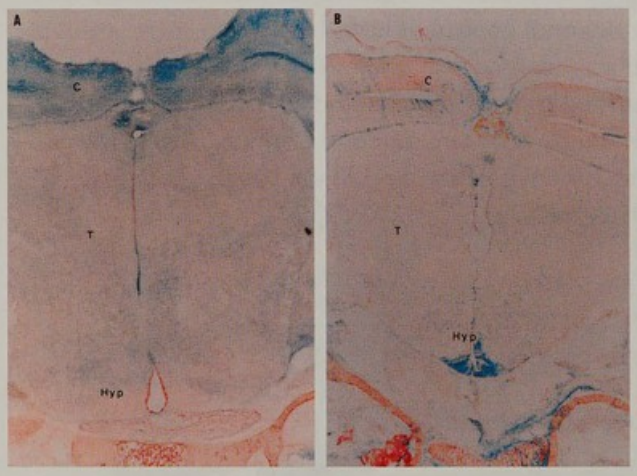
KATHY HILTON
ROSALIND JOHN
NOBUAKI KIKYO
LOUIS LEFEBVRE
LI-LAN LI
MAITHREYI NARASIMHA
WILLIAM RIDEOUT III
MASAKO TADA
TAKASHI TADA





Reciprocal distribution of parthenogenetic (A) and androgenetic (B) cells in the cortex (c) and hypothalamus (Hyp) in chimeras with uniparental cells

KAY, G.F., BARTON, S.C., SURANI, M.A. and RASTAN, S. 1994. Imprinting and X chromosome counting mechanisms determine *Xist* expression in early mouse development. **Cell 77**, 171-182.

KANEKO-ISHINO, T., KUROIWA, Y., MIYOSHI, N., KOHDA, T., SUZUKI, R., YOKOYAMA, M., VIVILLE, S., BARTON, S.C., ISHINO, F. and SURANI, M.A. 1995. *Peg/Mest* imprinted gene on chromosome 6 identified by cDNA subtraction hybridization. **Nature Genetics 11**, 52-59.

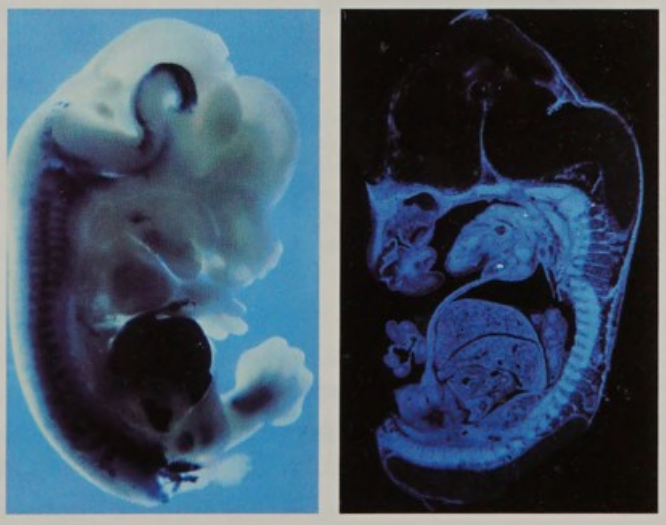
For further publications see nos. 8,12,20,29,36,37,38,57,80,86,90,91,97,98,99,100,101,102, page 45ff.

MAMMALIAN DEVELOPMENTAL GENETICS: THE INFLUENCE OF GENOMIC IMPRINTING

Parental genomes are functionally non equivalent during development because the expression of a number of genes, known as imprinted genes, is dependent on their parental origin. The transcriptional control of the appropriate parental allele is determined by germ line-specific heritable epigenetic modifications such as DNA methylation. These epigenetic modifications are being analysed in germ cells and early embryos, as well as in embryonic stem cells and embryonic germ cells derived from the epiblast and primordial germ cells, respectively.

We have identified several novel candidate imprinted genes. Amongst these are *Peg 1* on chromosome 6 that encodes for an Epoxide Hydrolase, and *Peg 3* on proximal chromosome 7 that encodes for an unusual C2H2 zinc finger protein. Their expression patterns and role in development are being examined in embryos by mutating the genes to induce a loss of expression. Imprinted genes are of particular interest during development of the limbs, brain and of the germ line, as indicated by the reciprocal distribution patterns of androgenetic and parthenogenetic cells in chimeric embryos.

The key control elements that regulate large imprinted chromosomal domains and the individual imprinted genes within them are being identified in transgenic experiments. For example, transgene constructs, including YAC clones, with the reciprocally imprinted *Igf2* and *H19* genes have been introduced in the mouse genome to analyse the functions of *cis*-elements.



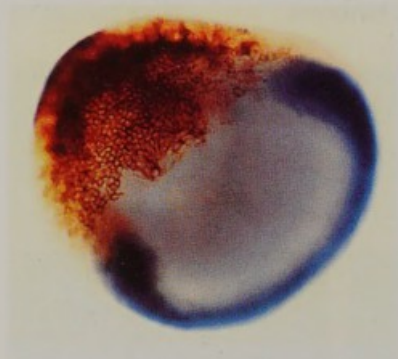
Transgenic and in situ expression of an imprinted gene

ENRIQUE AMAYA

SIGNALS THAT ORGANIZE THE VERTEBRATE EMBRYO

The vertebrate embryo is organized and patterned following a series of inductive events. The first of these signalling events results in the formation of the mesoderm at the blastula stage. The second event occurs when the dorsal mesoderm patterns the rest of the mesoderm at the gastrula stage. As a long term goal we would like to understand the molecular basis of the inductions that organize the vertebrate embryo. In addition we would like to better understand how localised production of signalling molecules gets translated into organized changes in cell movement and differentiation.

To this end we have been investigating the role of fibroblast growth factor (FGF) during mesoderm formation in the frog, *Xenopus laevis*. We have found that inhibiting FGF signalling in the embryo, by expressing a dominant negative version of the FGF receptor, disrupts mesoderm formation. In addition we have recently developed a very efficient method for making transgenic frog embryos. This technology will allow us to manipulate the expression of developmental genes in the embryo with much better precision than ever before.



Expression of the dominant negative FGF receptor (dark red) inhibits the expression of Brachyury *(blue), a gene which is normally expressed in a ring around the gastrula and is a marker of mesoderm.*

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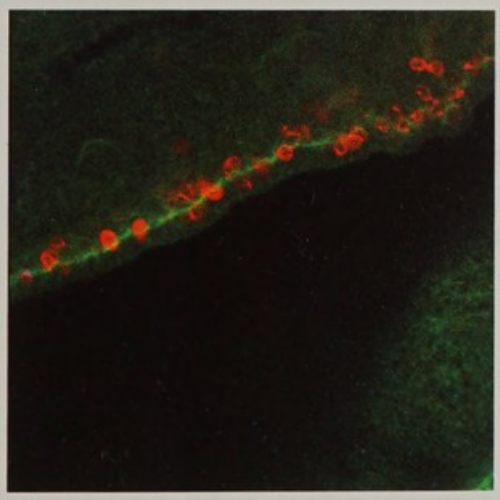

Here primordial germ cells (red) and laminin (green) are shown in the border of the developing genital ridge of a 10.5 days post coitum mouse embryo.

GERM CELLS IN THE MOUSE EMBRYO

Embryonic germ cells, the cells whose descendants give rise to eggs in the female, sperm in the male, move from the extra-embryonic region where they are located during gastrulation, to the genital ridges, the site of the future gonads.

For part of their journey, they appear to be migrating actively. We have studied the changing interaction between the germ cells and extracellular matrix molecules on their migration pathway, with particular reference to laminin. The domain recognised by germ cells has been mapped to the GD2 peptide within the globular region of the A chain.

Once in the genital ridges, germ cells in female embryos enter meiotic prophase and develop as oocytes. In male embryos, on the other hand, the first spermatogenic cells do not enter meiosis until a week after birth. If, however, they are removed sufficiently early from the genital ridge environment, they too will enter meiosis and develop as oocytes. By explanting germ cells into cultured reaggregates of embryonic lung, we have identified the critical time for commitment to spermatogenesis. We are now attempting to identify the somatic signals involved in this commitment.

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For further publications see nos. 69,70,71,72,73, page 45ff.

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PRINCIPAL GROUP LEADER	Professor/Reader/Lecturer Level
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As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of a Biological or Medical Sciences Department with which their group is affiliated.

Graduate studentships are supported mainly by the Wellcome Trust or the Cancer Research Campaign but additional sponsorship may be applied for from a variety of sources, including the Government Research Councils.

Applicants should write, in the first instance, to the leader of the group whose work interests them.

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INSTITUTE PUBLICATIONS

1. *AKAM, M.* 1995. Hox genes and the evolution of diverse body plans. **Phil. Trans. Roy. Soc. Lond. B 349**, 313-319.

2. *AVEROF, M. and AKAM, M.* 1995. Hox genes and the diversification of insect and crustacean body plans. **Nature 376**, 420-423.

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13. *BROWN, H., SUTHERLAND, J.A., COOK, A., BANNISTER, A.J. and KOUZARIDES, T.* 1994. An inhibitor domain in c-Fos regulates activation domains containing the HOB1 motif. **EMBO J. 140**, 124-131.

14. *CARLTON, M.B.L., COLLEDGE, W.H. and EVANS, M.J.* 1995. Generation of a pseudogene during retroviral infection. **Mammalian Genome 6**, 90-95.

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27. *EVANS, M.J., AFFARA, N. and LEVER, A.M.L.* 1995. Gene therapy – future prospects and the consequences. *In:* **Gene Therapy, British Medical Bulletin, Vol. 51, no. 1** (A.M.L. Lever & P. Goodfellow, Eds.), Churchill Livingstone, London, 226-234.

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39. *GONZÁLEZ-REYES, A., ELLIOTT, H. and ST JOHNSTON, D.* 1995. Polarization of both major body axes in *Drosophila* by *gurken-torpedo* signalling. **Nature 375**, 654-658.

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OTHER ACTIVITIES

MICHAEL AKAM is a member of the Wellcome Cell & Molecular Biology Board.

JOHN GURDON is currently a member of the Council of the Cancer Research Campaign, and is a Governor of the Wellcome Trust.

RON LASKEY is President of the British Society of Cell Biology, Subject Convenor for Cell and Developmental Biology of Academia Europaea, a member of the Cancer Research Campaign Scientific Committee, and a Trustee of Strangeways Research Laboratories.

ANNE McLAREN is Foreign Secretary of the Royal Society.

HONOURS AND AWARDS

JOHN GURDON was created a Knight in the June 1995 list of Honours

STEVE JACKSON has been appointed to the Quick Professorship of Biology; he was awarded the Eppendorf Award for 1995 "in acknowledgement of an outstanding contribution to biomedical research based on methods of molecular biology".

RON LASKEY was elected Honorary Foreign Member of the Japanese Biochemical Society.

ANNE McLAREN was invited by St John's College, Cambridge to give the 1995 Linacre Lecture, entitled "Social Equity and the RDP".

AZIM SURANI was awarded an Honorary Doctorate by the University of Uppsala, Sweden.

MEMBERS OF STAFF ON THE EDITORIAL BOARDS OF JOURNALS

MICHAEL AKAM – *Current Biology, Development, EMBO Journal, Insect Molecular Biology, Journal of Evolutionary Biology, Roux's Archives of Developmental Biology*

MARTIN EVANS – *Biological Reviews, Molecular Reproduction & Development*

CHARLES FFRENCH-CONSTANT – *Development*

JOHN GURDON – *Development, International Journal of Developmental Biology*

RON LASKEY – *Cell, Current Opinion in Genetics & Development (Editor), Current Biology*

AZIM SURANI – *Development, Transgenic Research*

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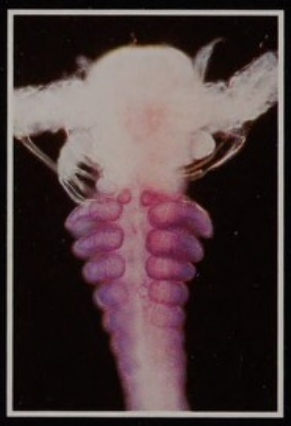

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