Annual report : 1993/1994 / 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

1994

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Institute of Cancer and Developmental Biology

PROSPECTUS

1994

ANNUAL REPORT 1993

University of Cambridge

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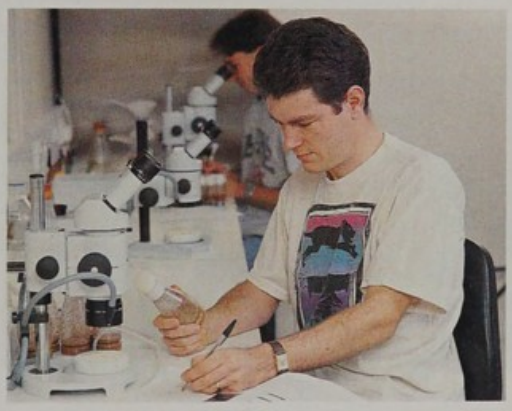
Front Cover Photograph:
A mutant Drosophila *egg chamber with the oocyte in the middle*
Photograph by Acaimo Gonzalez-Reyes
(See Page 31)

FOREWORD BY THE CHAIRMAN

HISTORICAL BACKGROUND The Institute, founded to promote research in the areas of Developmental Biology and Cancer Biology, represents a new type of research support within British Universities. It 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 each other.

In the present difficult economic climate we are grateful to the two charities, the Wellcome Trust and Cancer Research Campaign, who generously support most of the work of the seventeen research groups, while the University of Cambridge maintains the building.

THE INSTITUTE IN 1993 The one or two pages of this report devoted to each research group can give only a brief indication of its research interests, but further information of this kind is available from the recent publications of the group; these are referred to by numbers in the section on each group, and are cited fully in the Institute's publication list on page 47ff.



Since our last report, we have appointed Dr. J. Raff to a younger group leader position, and he will be taking up his Wellcome Senior Research Fellowship here in the Spring of 1994. He comes to us from the laboratory of Dr. Bruce Alberts in the University of California at San Francisco where he has held a postdoctoral fellowship for three years. He will develop a research group around his interest in the control of cell division in *Drosophila*. During the past year, Azim Surani has built his senior group up to full strength, and Andrea Brand will be doing so during the forthcoming year.

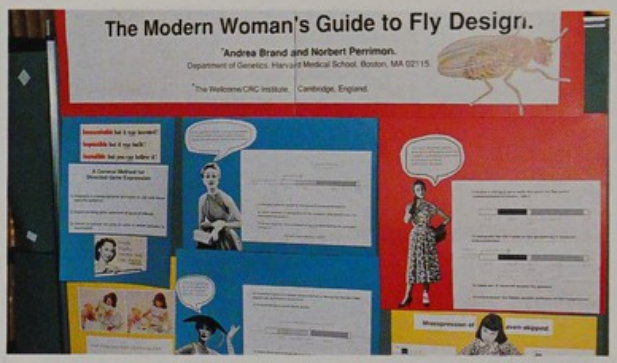
We shall be sorry to lose Chris Wylie and Janet Heasman during 1994, when they will take up professorships in the Medical School at the University of Minnesota. We are glad that their work has gone very well during their time in this Institute, and wish them success in establishing their new Department of Developmental Biology in Minnesota.

The pioneering work of Martin Evans in establishing mouse embryonic stem cells that can enter the germ line after prolonged culture and blastocyst implantation has been recognized by his election to Fellowship of the Royal Society, and by the award to him of the triennial William Bate Hardy Prize of the Cambridge Philosophical Society. Chris Wylie has continued to strengthen the international standing of the journal *Development*, in his capacity as Editor in Chief.

During the present year, we expect to make some further younger group leader appointments. These will be in the broad area of developmental biology, and will be at the level of Wellcome Senior Research Fellowships. These posts provide support for 5+5 years for those who have substantial postdoctoral experience and who wish to develop their own independent research group. The existence of these opportunities will be advertised in September, 1994, but enquiries to the Chairman will be welcomed in the meantime.

At present, we have some 30 graduate students, referred to on page 39ff. of this Report. A new scheme enabling prospective graduate students to work here for one year, before committing themselves to a particular research group, is currently under discussion.

J.B. GURDON *CHAIRMAN*



The Institute, located within the Biological Sciences area of the University, houses approximately one hundred research staff, including graduate students, and a further fifty technical and support staff.

The individual research groups share communal equipment facilities located centrally on each floor. These include, for example, ultracentrifugation, microscopy, oligonucleotide synthesis and phospho-imaging. Tissue culture rooms are available on each floor with further self service facilities such as histology, photography and confocal microscopy. In this past year our sponsors have kindly provided funds for the purchase of a fluorescent activated cell sorter.

The University departments to which staff are affiliated complement the Institute's own facilities and give access to their libraries, the Institute itself subscribing to a number of International journals which are housed in a room for quiet reading. An extensive Apple Mac computer network provides facilities, at the bench, for ordering, faxing and journal/database searches.

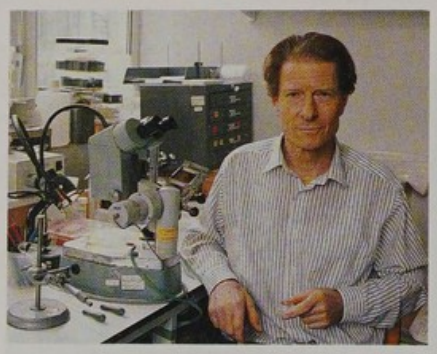
Two sponsored seminar series are hosted by the Institute, which also arranges a number of weekly Developmental Biology seminars open to all interested members of the University.

To encourage both scientific and social interaction within the Institute, there is a large communal coffee room which complements the interconnecting laboratories. This is a comfortable and informal setting for discussion during morning coffee, lunch and afternoon tea and is an ideal venue for out-of-hours social gatherings, also doubling as a large seminar room.

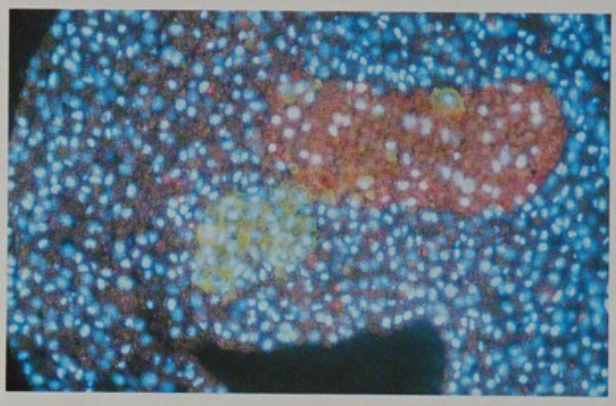
1993 saw the first gathering of staff for an Institute Scientific Retreat at Wye College in Kent. It is hoped that this will become an annual event as the talks and resulting discussions proved exrtremely beneficial to all participants.

The Institute football squad plays regular friendly matches throughout the year, losing only one game in its first season. A rounders series against other departments and theatre trips add to the social aspects of Institute life.

JOHN GURDON



BIRKE BARTOSCH
JULIAN BOWEN
AGNES CHAN
NIGEL GARRETT
PATRICIA HARGER
CHRISTINE HOLT
PATRICK LEMAIRE
DANIEL MAHONY
ANDREW MITCHELL
KEN RYAN
ELIZABETH TWEED



A reaggregate of message-injected signalling cells (red) and responding cells (yellow), enclosed in an ectoderm sandwich whose nuclei are shown in blue.

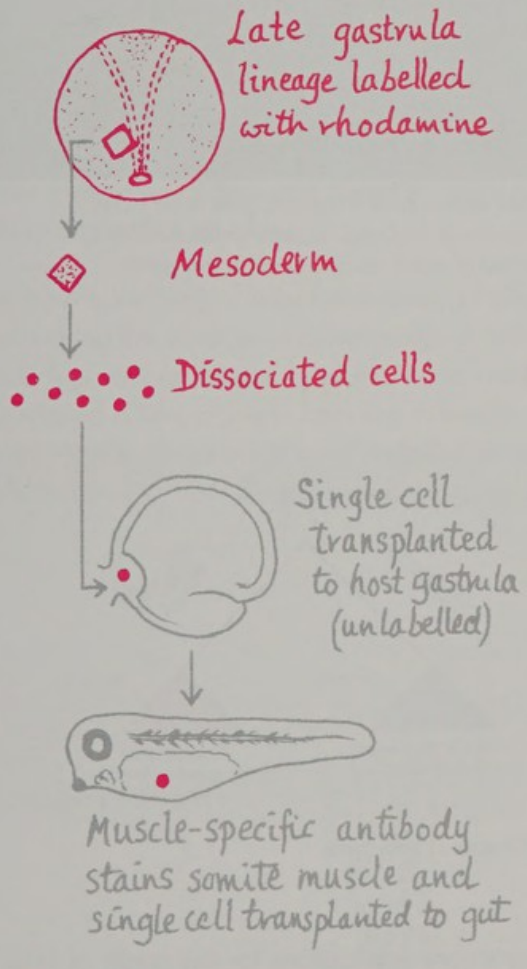
Gene enrichment in cDNA libraries using subtractive hybridization (Ref.47). (Relative abundance of cDNA clones assayed by reverse transcriptase PCR)			
Gene and expression	**Egg library**	**Gastrula library**	**Gastrula subtracted with egg library**
X. brachyury (Gastrula mesoderm)	0	1	30
X.GS17 (Post-zygotic ubiquitous)	0	10	200
X.FGF receptor (Egg & gastrula ubiquitous)	0.1	0.1	0.1

GURDON, J.B., TILLER, E., ROBERTS, J., and KATO, K. 1993. A community effect in muscle development. **Current Biology 3, 1-11.**

GURDON, J.B., KATO, K., and LEMAIRE, P. 1994. Community effects and related phenomena in development. **Cell**, in press.

See also nos. 27,29,30,39,47, page 47ff.

MECHANISMS OF CELL DIFFERENTIATION IN EARLY AMPHIBIAN DEVELOPMENT



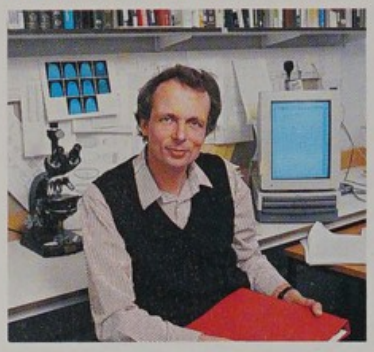
Single cell transplantation (Ref. 28)

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.

To determine the time in development when cell interactions required for muscle differentiation are taking place, we have transplanted single embryo cells to different regions of an embryo. We find that, in order to complete the process of gene activation, cells need to receive a signal from neighbouring cells of their own kind. We are analysing this "community effect" type of cell:cell interaction by culturing reaggregates of cells from different sources, distinguished by yellow or red fluorescence. Gene expression characteristic of muscle or other cell types is revealed by antibodies or by gene-specific RNA probes.

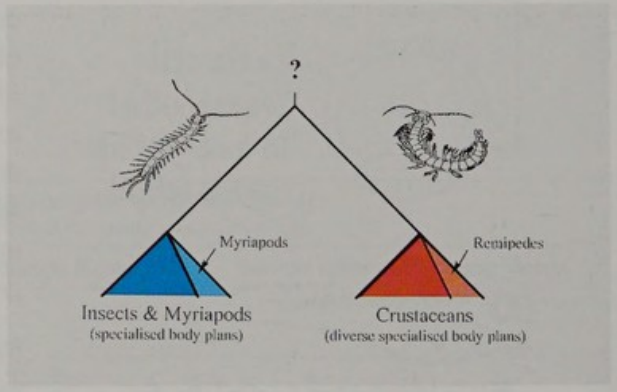
Our overall aim is to identify novel genes which encode signalling molecules. We are using subtracted libraries enriched for mesoderm-specific cDNAs. We have constructed two such libraries that contain inserts long enough to encode functional proteins. Messenger RNA is synthesized *in vitro* from these libraries and is microinjected into the animal pole of fertilized eggs. We look for genes that can convert animal cap ectoderm into mesoderm.

MICHAEL AKAM



MICHALIS AVEROF
JAIME CASTELLI-GAIR
RACHEL DAWES
FRANCESCO FALCIANI
DAVID FERRIER
KAREN HO
HILARY REED
LOUISE SMITH
SANDRA RYLANCE

The ectopic expression of a homeotic gene in the middle body segments of this Drosophila *embryo has modified the migration of cells in the peripheral nervous system.*



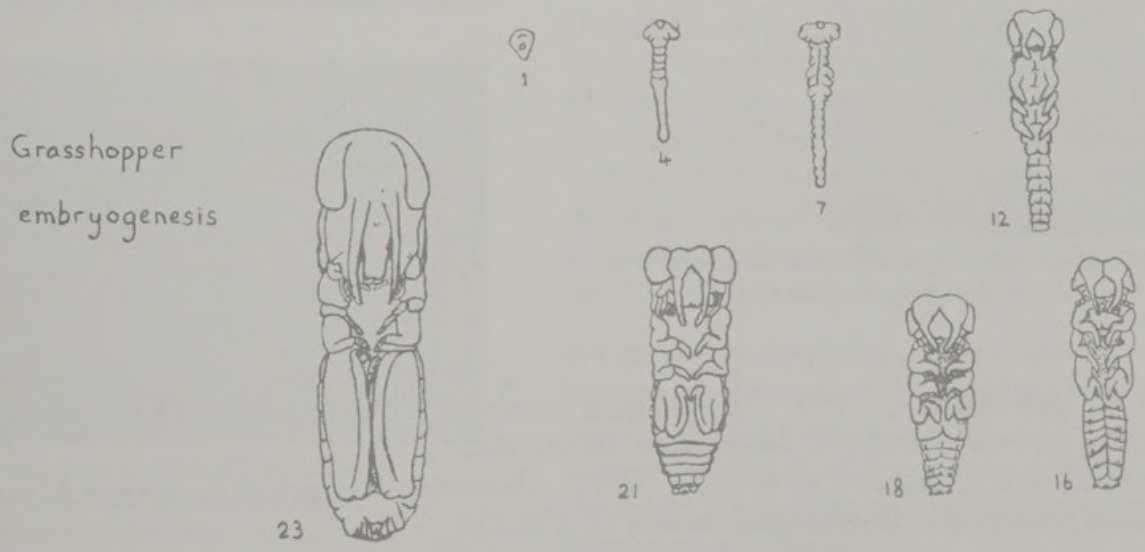
Insect/Crustacean body plans

AVEROF, M. and AKAM, M. 1993. Hom/Hox genes in a crustacean: implications for the origin of insect and crustacean body plans. **Current Biology 3**, 73-78.
GREIG, S. and AKAM, M. 1993. Homeotic genes autonomously specify one aspect of pattern in the *Drosophila* mesoderm. **Nature 362**, 630-632.
See also nos. 1,2,3,13,40, page 47ff.

HOMEOTIC GENES AND SEGMENT PATTERNING IN INSECTS AND CRUSTACEA

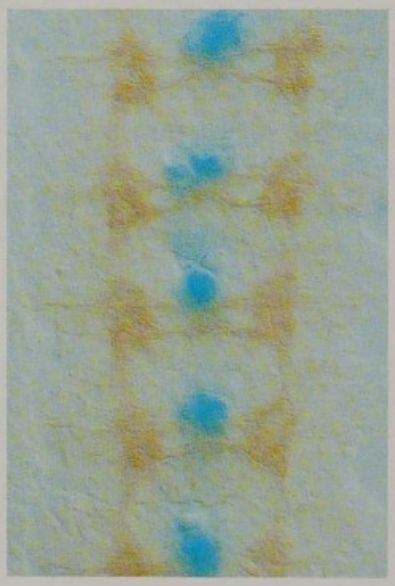
Our studies focus on the *Antennapedia*-like family of homeobox genes. In a wide range of organisms, these genes serve as labels to define different regions of the body. To investigate how the homeotic genes work in *Drosophila*, we have built constructs (utilising GAL 4 regulatory elements from yeast) that allow us to alter their patterns of expression in precisely controlled ways. With these we are testing where and when homeotic gene expression is required to define particular aspects of a complex pattern. For example, when we force transient expression of a homeotic gene in the ectoderm during a short period of early development, we can alter the migration of cells in the peripheral nervous system. Later expression of the same homeotic gene in the same cells has a different effect, changing the type of sense organ that develops.

To learn something of how the diversity of different body plans arose during evolution, we are comparing the structure and expression of homeotic genes in a range of different arthropod species, including various insects, myriapods and crustaceans. The regional specification of segments in Crustacea is very different from that in insects, and is believed to have evolved independently. We have recently isolated the set of Antp-like genes from one crustacean - the brine shrimp *Artemia* - and are now examining how these genes are expressed during its development.

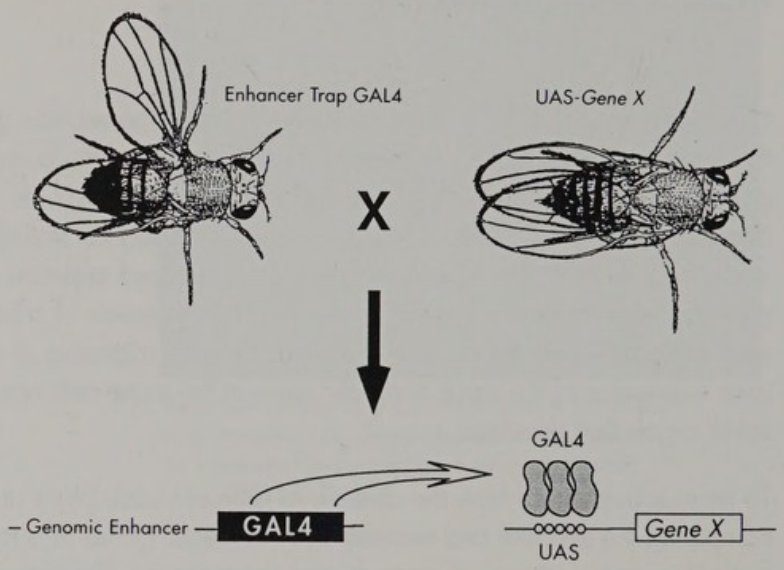


ANDREA BRAND

ALICIA HIDALGO



GAL4-directed expression of ß-galactosidase in cells along the ventral midline (stained blue). Axons are labelled in brown.

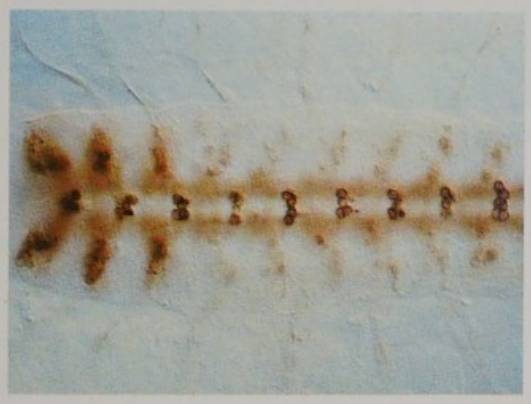


The GAL4 activation system for targeted gene expression

BRAND, A.H. and PERRIMON, N. 1993. Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. **Development 118**, 401-415.

PERRIMON, N., NOLL, E., McCALL, K. and BRAND, A. 1991. Generating lineage-specific markers to study *Drosophila* development. **Developmental Genetics 12**, 238-252.

THE DEVELOPMENT OF THE EMBRYONIC NERVOUS SYSTEM IN *DROSOPHILA*



An embryo expressing a tau-ß galactosidase fusion protein in the central nervous system. Two focal planes are shown.

To generate a functional nervous system requires the production of a large number of neurons, each with a specific identity. Each neuron must migrate to a characteristic position within the nerve cord from which it can extend an axon towards, and synapse with, an appropriate target cell. The expression of segmentation genes is known to be a necessary step in establishing certain neuronal identities. Later, the expression of specific cell surface molecules may direct neurons to extend their axons along the appropriate routes toward their target cells. Thus, nervous system development relies both on characteristic gene expression patterns and on cell-cell interactions.

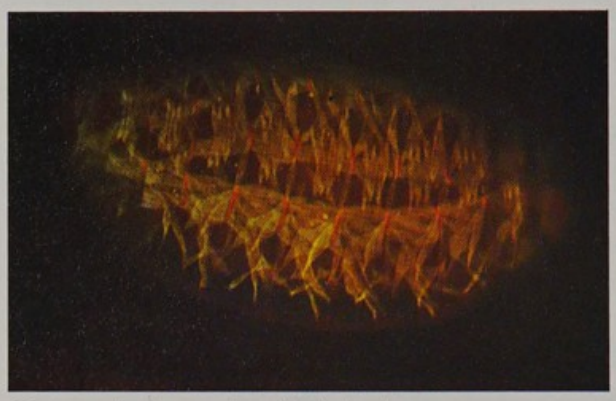
We have developed a general method for directed gene expression in *Drosophila* that allows transcription to be manipulated both spatially and temporally. Through the use of targeted gene expression, transcription patterns in neuronal precursor cells and in their progeny can be altered with the aim of eliciting specific cell fate changes. We have also expressed toxins in a restricted fashion as a means of targeted cell killing. Targeted cell ablation can be used to eliminate the local interactions involved in cell fate determination and in axon guidance.

We are specifically altering gene expression during neurogenesis to investigate the role of segmentation genes in directing neuronal cell fate, and are using targeted cell killing to analyse the role of cell-cell interactions in influencing neuronal identity and in directing axon guidance.

NICHOLAS BROWN

JAMES BLOOR
OLGA DUNIN-BORKOWSKI
LOLA MARTIN-BERMUDO
JOHN OVERTON
PHIL WALSH

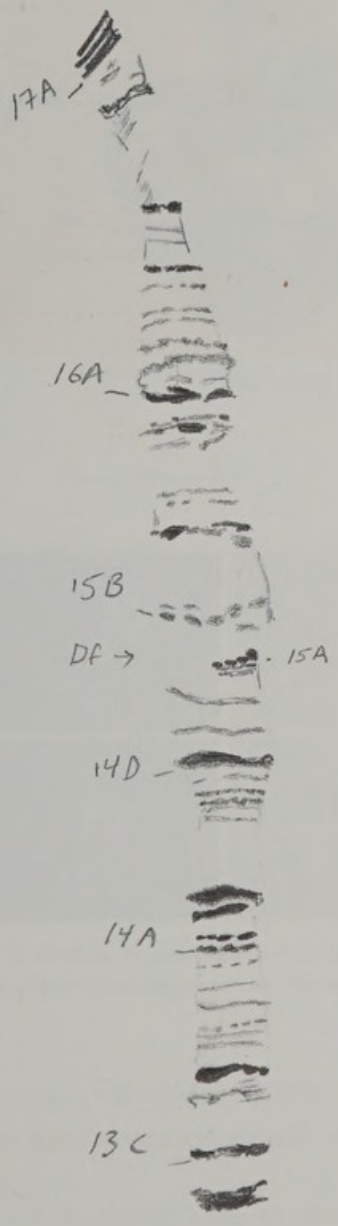
Surface staining of the embryonic mesoderm



PS integrins (red staining) are localised at the embryonic muscle attachment sites

BROWN, N.H., KING, D.L., WILCOX, M. and KAFATOS, F.C. 1989. Developmentally regulated alternative splicing of *Drosophila* integrin PS2α transcripts. **Cell 59**, 185-195.
BROWN, N.H. 1993. Integrins hold *Drosophila* together. **Bioessays 15**, 383-390.

MOLECULAR ANALYSIS OF CELL ADHESION

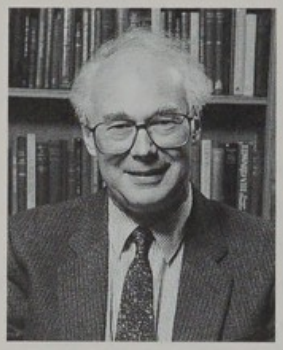


Polytene chromosome showing a deficiency (Df) at the PS2α/inflated locus

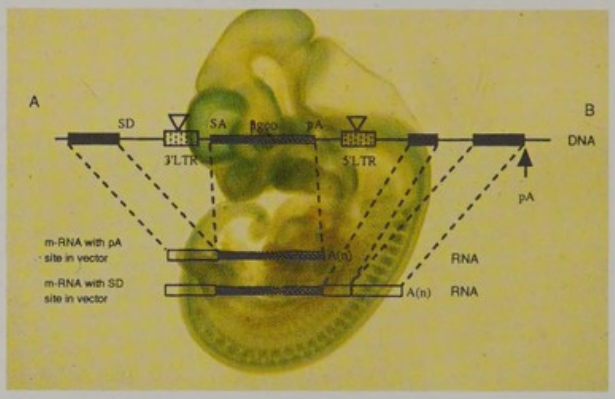
The major interest of our group is to comprehend how an organism is formed through cell interactions during embryogenesis. Cells adhere to each other during embryogenesis to form coherent masses (tissues), and these tissues adhere to each other to form the recognizable organism. We are pursuing studies on the structure and function of cell surface proteins that mediate these events, in particular a family of proteins called the integrins. These proteins are involved in a variety of essential adhesive events in humans, including the migration of leukocytes to sites of inflammation and the formation of blood clots. In the fruit fly, *Drosophila melanogaster*, the particular integrins that we have identified and characterised appear to mediate adhesion between tissues (e.g. the adhesion of muscles to the epidermis), judging from the failure of this adhesion to occur in embryos that are mutant for the integrin genes. One avenue that we are currently investigating is the examination of the role of specific regions of the α_{PS2} integrin by replacing the wild type gene with copies that have been specifically altered by *in vitro* mutagenesis.

By studying the effect of these changes on the development of the embryo we hope to relate the structure of the protein to its role in orchestrating the adhesion of cell layers to produce a functional organism.

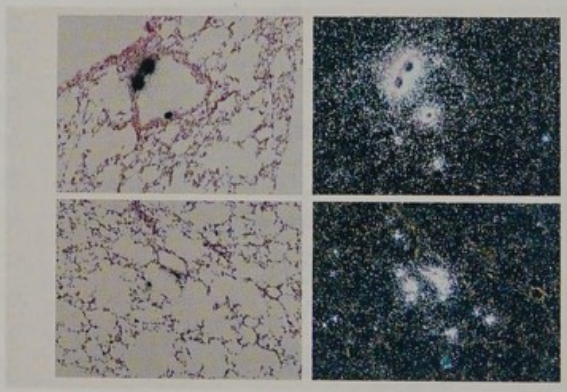
MARTIN EVANS



SUSAN BROWN
HELEN BURRELL
MARK CARLTON
BILL COLLEDGE
JOHN DIXON
JOANNE DORAN
DIANE FOSTER
DARREN GILMOUR
JODIE MACOUN
ROSEMARY RATCLIFF
SOPHIE VAULONT



Diagrams of gene trapping protocols



Human Cftr expressed in airway and alveolar epithelia of a cystic fibrosis mouse after liposome-mediated gene therapy

HYDE, S.C., GILL, D.R., HIGGINS, C.F. TREZISE, A.E.O., MacVINISH, L.J., CUTHBERT, A.W., RATCLIFF, R., EVANS, M.J. and COLLEDGE, W.H. 1993. Correction of the ion transport defect in cystic fibrosis transgenic mice by gene therapy. **Nature 362**, 250-255.

RATCLIFF, R., EVANS, M.J., CUTHBERT, A.W., MacVINISH, L.J., FOSTER, D., ANDERSON, J.R. and COLLEDGE, W.H. 1993. Production of a severe cystic fibrosis mutation in mice by gene targeting. **Nature Genetics 4**, 35-41.

See also no. 68, page 47ff.

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

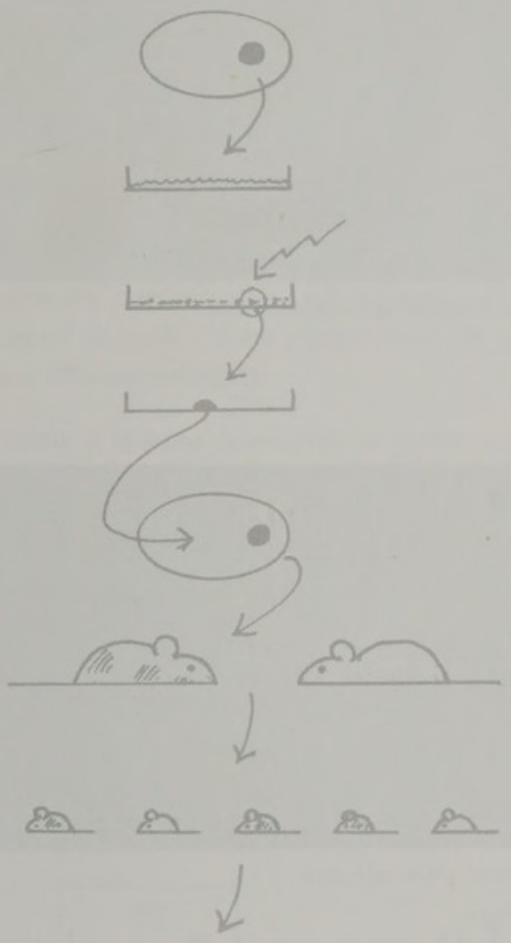


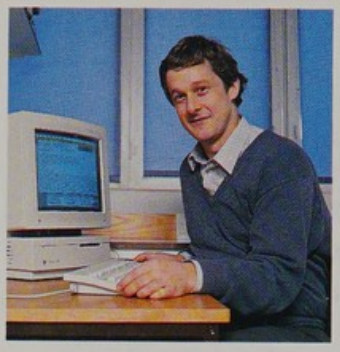
Diagram of ES cell route

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.

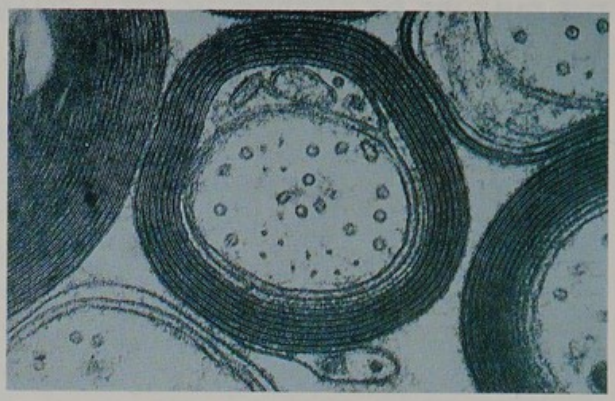
Injection of ES cells into 2.5 day host blastocysts results in chimaeric mice with the ES cells having the ability to contribute to all organs. Germline transmission of the ES cell clone results in multiple transgenic mice which can be analysed to determine the function of transgenes in the development of the mouse.

We are creating a systematic library of 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. We are concentrating mainly on creating animal models of human disease by specific gene targeting and using retroviral vector mutated insertional mutagenesis.

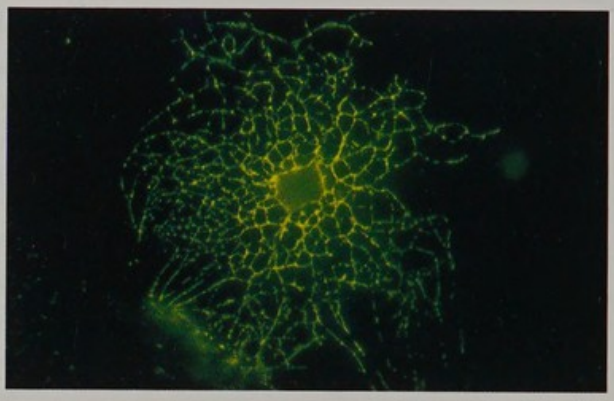
CHARLES FFRENCH-CONSTANT



THOMAS JACQUES
BRENT KIERNAN
GRETA MATHEWS
RICHARD MILNER
SUZANNA SCOTT-DREW



Electron micrograph of a myelinated axon



Oligodendrocyte in cell culture

FFRENCH-CONSTANT, C., MILLER, R.H., BURNE, J.F. and RAFF, M.C. 1988. Evidence that migratory oligodendrocyte-type-2 astrocyte (O-2A) progenitor cells are kept out of the rat retina by a barrier at the eye-end of the optic nerve. **J. Neurocytology 17**, 13-15.

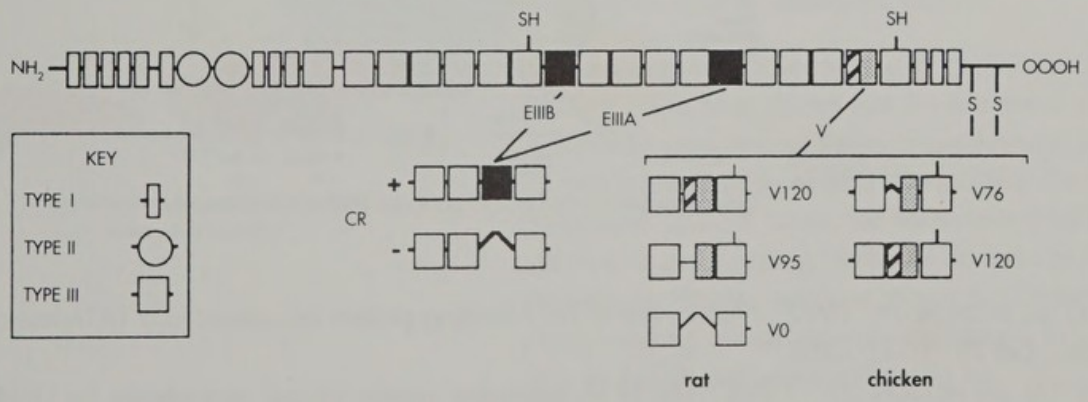
KIERNAN, B.W. and FFRENCH-CONSTANT, C. 1993. Oligodendrocyte precursor (O-2A) progenitor cell migration; a model system for the study of cell migration in the developing CNS. **Development Supplement**, in press.

See also nos. 11,19, page 47ff.

DEVELOPMENT AND REPAIR OF THE VERTEBRATE CENTRAL NERVOUS SYSTEM

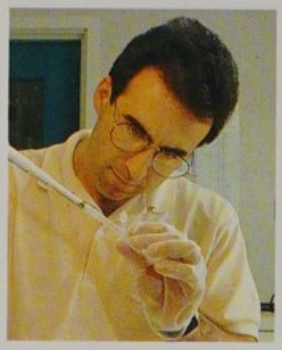
The goal of our research is to understand the development and repair of the vertebrate central nervous system (CNS). Our work focuses on cell migration. In order to elucidate the mechanisms responsible for migration during development we are examining the extracellular matrix (ECM) molecules present in the CNS, as these molecules and their cell-surface receptors play a central role in the control of migration elsewhere in the developing embryo. We have focused on the migration of oligodendrocytes and their precursors as this cell lineage, which forms the myelin of the CNS, migrates extensively in the post-natal brain. We find that different ECM molecules in the migratory pathway stimulate migration while those outside the pathway inhibit this migration. Experiments under way to alter the expression of the ECM receptor molecules of the integrin family on oligodendrocyte precursors will allow us to test the roles of these different molecules.

In addition to these developmental studies we are also examining migration during repair in the nervous system. Another ECM molecule, fibronectin, appears during peripheral nerve repair and we wish to define its role in axon regrowth. 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. A long term goal of our laboratory is to use our knowledge of CNS development to devise strategies that enhance the normally very poor repair that occurs following damage to the CNS.

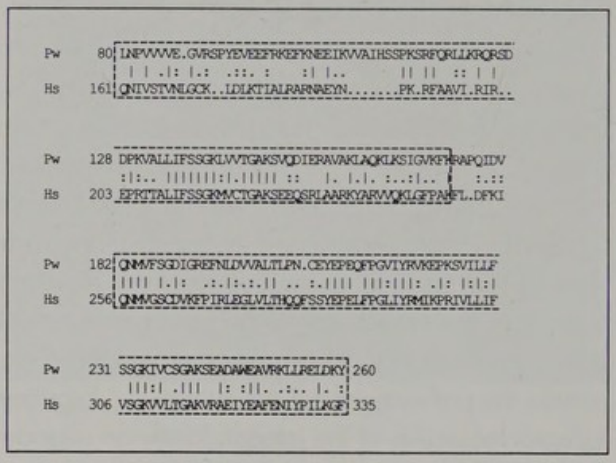


Alternative splicing of fibronectin

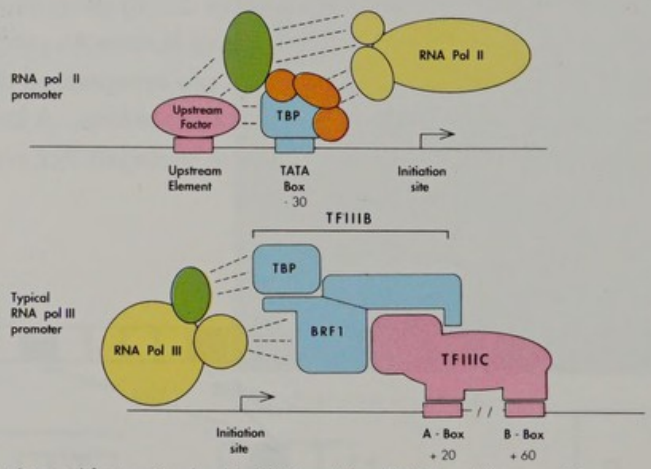
STEPHEN JACKSON



PETER BAUMANN
DAVID GELL
NICHOLAS FINNIE
TANYA GOTTLIEB
BERNARD KHOO
TRACEY ROWLANDS
ROBERT WHITE
MARK YOULES



Striking conservation between the TBP proteins of the archaebacterium Pyrococcus woesei (Pw) and human (Hs)



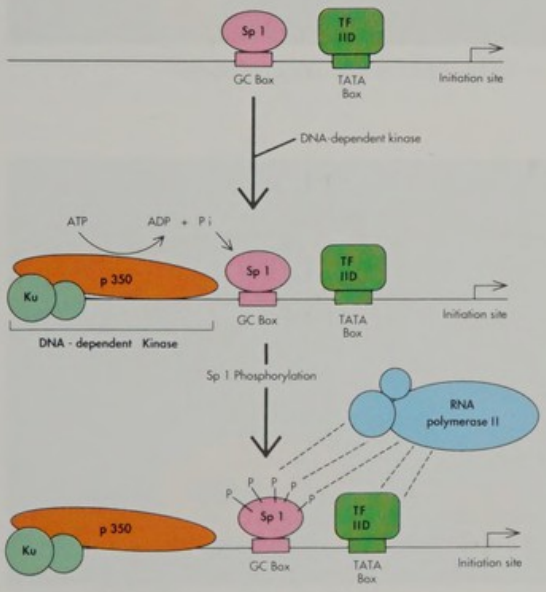
General factors involved in RNA pol II and RNA pol III transcription

WHITE, R.J. and JACKSON, S.P. 1992. Mechanism of TATA-binding protein recruitment to a TATA-less class III promoter. **Cell 71**, 1041-1053.

GOTTLIEB, T.M. and JACKSON, S.P. 1993. The DNA-dependent protein kinase: requirement for DNA ends and association with Ku antigen. **Cell 72**, 131-142.

See also nos. 5,20,37,38 page 47ff.

STRUCTURE, REGULATION AND EVOLUTION OF THE TRANSCRIPTIONAL APPARATUS



DNA-dependent kinase phosphorylates promoter-bound Sp1

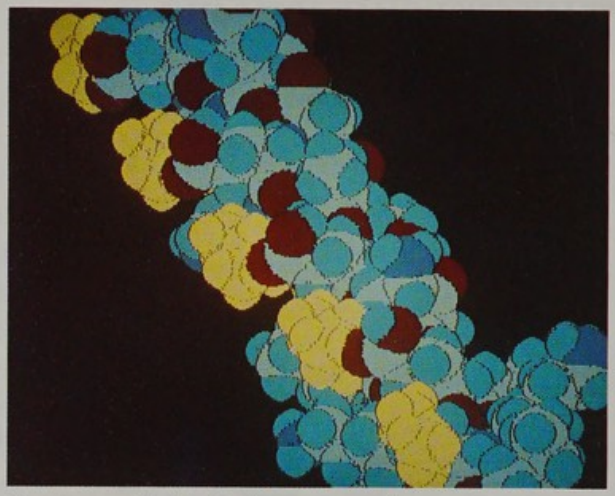
To investigate the mechanism of transcription, we employ *in vitro* transcription assays. Thus, we discovered that the TATA-binding protein, TBP, is essential for transcription by RNA pol III, even though most class III promoters lack TATA boxes. Biochemical analysis reveals that TBP is part of the pol III general factor, TFIIIB. We are currently investigating TFIIIB further: analysing its mode of action, the functions of its TBP and BRF1 subunits, and studying its regulation.

The requirement of TBP for all nuclear transcription suggests its role was set early in evolution. Interestingly, TATA boxes are present in promoters of archaebacteria, a kingdom of organisms distinct from both eukaryotes and eubacteria. By PCR, we isolated the gene for a TBP homologue from archaebacterium *Pyrococcus woesei*, indicating that TBP evolved before the archaebacterial and eukaryotic lineages diverged. Attempts are under way to identify archaebacterial homologues of other eukaryotic factors.

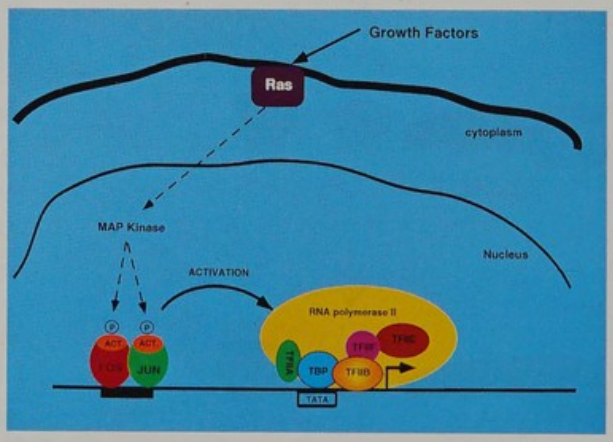
We also study the DNA-dependent protein kinase, DNA-PK. We have shown that this enzyme is a multiprotein complex consisting of autoimmune antigen Ku and a polypeptide of 350 kDa (p350). To understand DNA-PK better, we have cloned the p350 cDNA and are mapping functional domains of DNA-PK subunits. Finally, we have shown that DNA-PK phosphorylates several transcription factors, including Sp1 and p53, and are investigating the consequences of these modifications.

TONY KOUZARIDES

ANDREW BANNISTER
HELEN BROWN
ALISTAIR COOK
CHRISTIAN HAGEMEIER
KLAUS MARTIN
DIDIER TROUCHE
MARK YOULES



Graphics model of the Fos leucine zipper domain

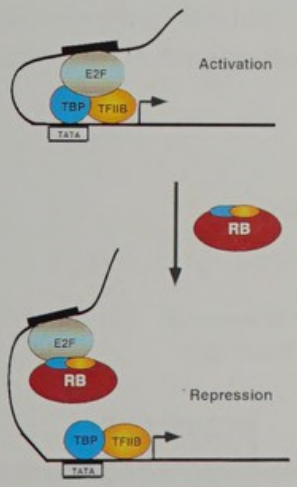


SUTHERLAND, J.A., COOK, A., BANNISTER, A.J. and KOUZARIDES, T. 1992. Conserved motifs in Fos and Jun define a new class of activation domain. **Genes Dev. 6**, 1810-1819.

HAGEMEIER, C., BANNISTER, A.J., COOK, A. and KOUZARIDES, T. 1993. The activation domain of transcription factor PU.1 binds the retinoblastoma (RB) protein and the transcription factor TFIID *in vitro*: RB shows sequence similarity to TFIID and TFIIB. **Proc. Natl. Acad. Sci. USA 90**, 1580-1584.

See also nos. 5,10,21,32,43, page 47ff.

TRANSCRIPTIONAL REGULATION IN EUKARYOTES



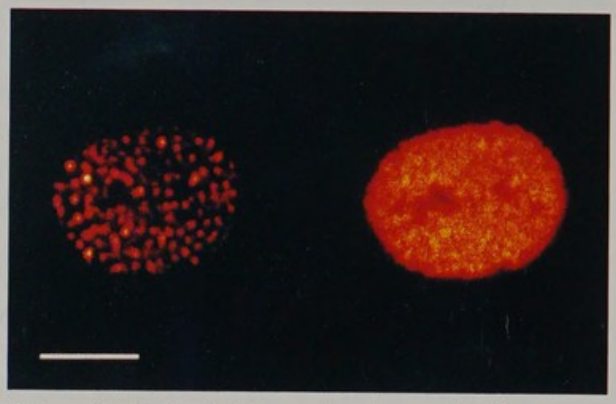
Our group is interested in defining the mechanisms by which regulatory transcription factors modulate gene expression. We are currently concentrating on two transcriptional activators, the c-Fos and c-Jun oncoproteins, and a transcriptional repressor, the Retinoblastoma tumour suppressor protein.

Our analysis of c-Fos and c-Jun indicates that these two activators have a homologous activation domain which is regulated by MAP kinase phosphorylation. We have identified an inhibitor sequence within c-Fos which will specifically silence this activation domain and are now trying to isolate the protein(s) which contact the inhibitor sequence. We have also shown that c-Fos has an additional activation domain which functions by contacting the TATA-box binding protein, TBP.

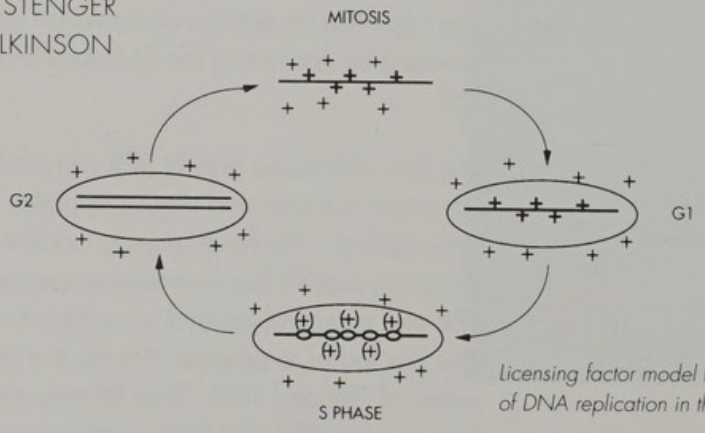
The Retinoblastoma protein (RB) can bind to the E2F transcription factor and silence its ability to activate transcription. We have recently made the exciting discovery that RB has extensive sequence similarity to TBP and a second general transcription factor TFIIB. This has led us to propose that RB is a molecular mimic of TBP and TFIIB. Thus RB may prevent E2F from binding TBP and TFIIB, leading to transcriptional repression. Consistent with this model, we find that residues within E2F which are required for binding RB, are also required to bind TBP, suggesting that these two interactions are mutually exclusive.

RON LASKEY

DAWN COVERLEY
DIRK GOERLICH
CHONG YEE KHOO
MARK MADINE
JOE MAKKERH
TONY MILLS
JACKIE ROBBINS
ANNAMARIA STENGER
HANNAH WILKINSON



Clusters of replication forks in pseudonuclei assembled from bacteriophage DNA



Licensing factor model for the control of DNA replication in the cell cycle

LENO, G.H., DOWNES, C.S. and LASKEY, R.A. 1992. The nuclear membrane prevents replication in Human G2 nuclei but not in G1 nuclei in *Xenopus* egg extract. **Cell 69**, 151-158.

COVERLEY, D., DOWNES, C.S., ROMANOWSKI, P. and LASKEY, R.A. 1993. Reversible effects of nuclear membrane permeabilization: evidence for a positive licensing factor. **J. Cell Biol. 122**, 985-992.

See also nos. 14,44,45,46,48,49,60, page 47ff.

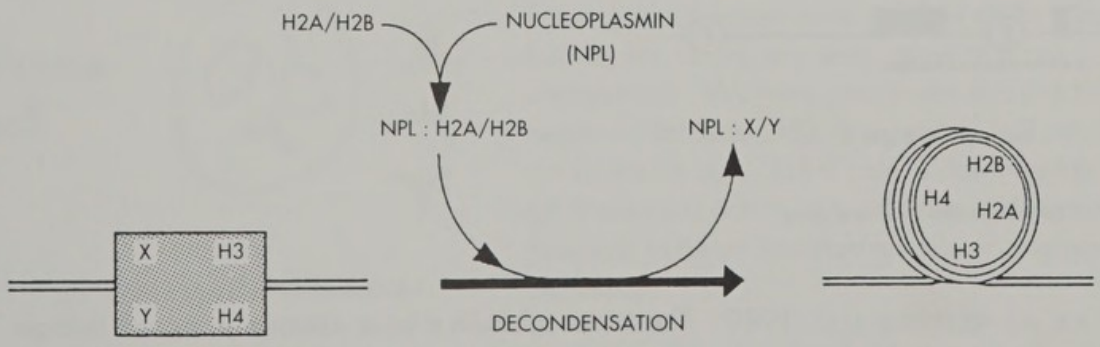
CONTROL OF EUKARYOTIC CHROMOSOME REPLICATION

We are analysing the control of eukaryotic chromosome replication using a cell-free system 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 the licensing factor model of Blow and Laskey shown opposite. We have found that the replication capacity of nuclei from synchronised human cells can be accounted for by a similar model. Membrane repair experiments have demonstrated the existence of a factor with these properties and provided an assay for its isolation.

In addition we are investigating how nuclear proteins are targeted to the cell nucleus. We have identified a bipartite class of nuclear targeting sequence which appears to be common in nuclear proteins and proposed how this might be recognised. We are investigating proteins and mechanisms involved in nuclear protein transport.

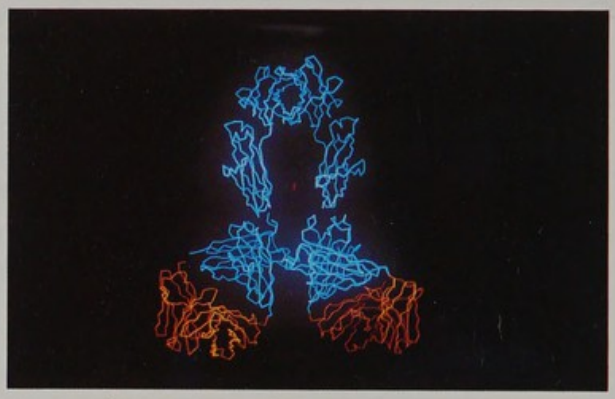
We have also shown that *Xenopus* sperm nuclei are decondensed at fertilization by the acidic protein nucleoplasmin which removes sperm basic proteins and replaces them with histones. Remodelling sperm chromatin in this way requires intense phosphorylation of nucleoplasmin.



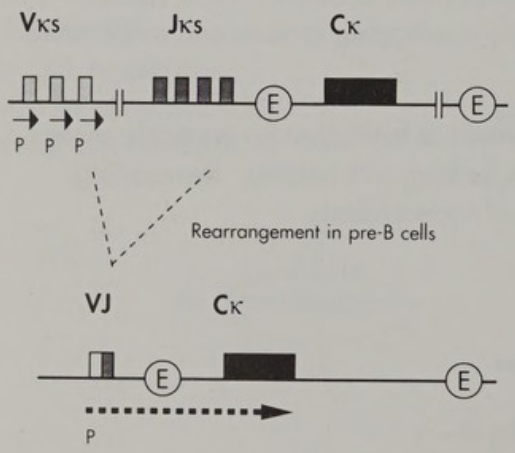
Model illustrating the modulation of sperm chromatin, mediated by nucleoplasmin during decondensation

KERSTIN MEYER

JOHN IRELAND



Structure of an Ig molecule with the variable regions shown in red

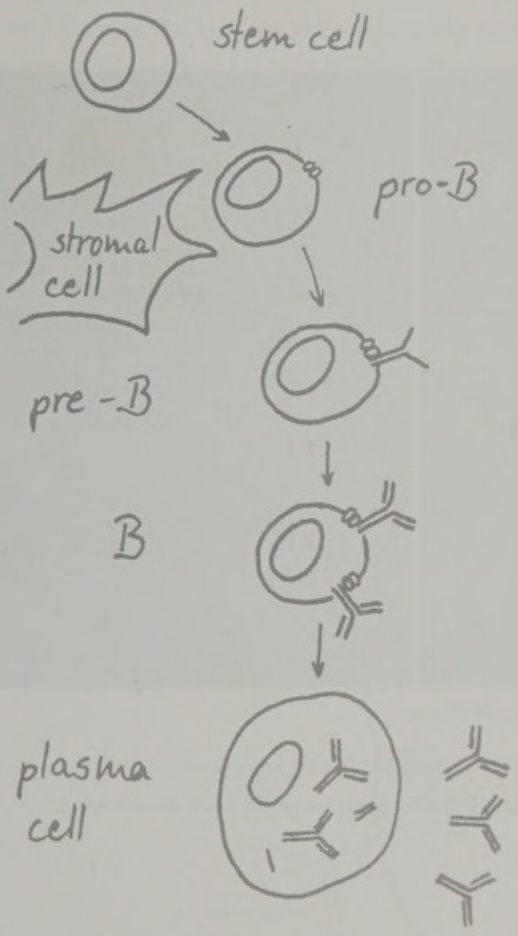


Rearrangement of the Igκ gene

MEYER, K.B. and NEUBERGER, M.S. 1989. The immunoglobulin κ locus contains a second stronger B-cell-specific enhancer which is located downstream of the constant region. **EMBO J. 7**, 1959-1964.

MEYER, K.B., SHARPE, M.J., SURANI, M.A. and NEUBERGER, M.S. 1990. The importance of the 3'-enhancer region in immunoglobulin κ gene expression. **Nucleic Acids Res. 18**, 5609-5615.

REGULATION OF TRANSCRIPTION IN DEVELOPING B LYMPHOCYTES

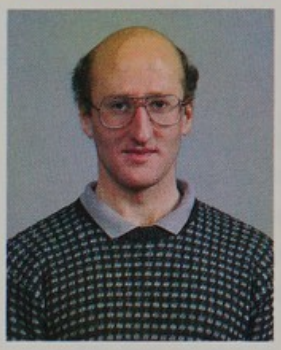


Schematic representation of B cell development

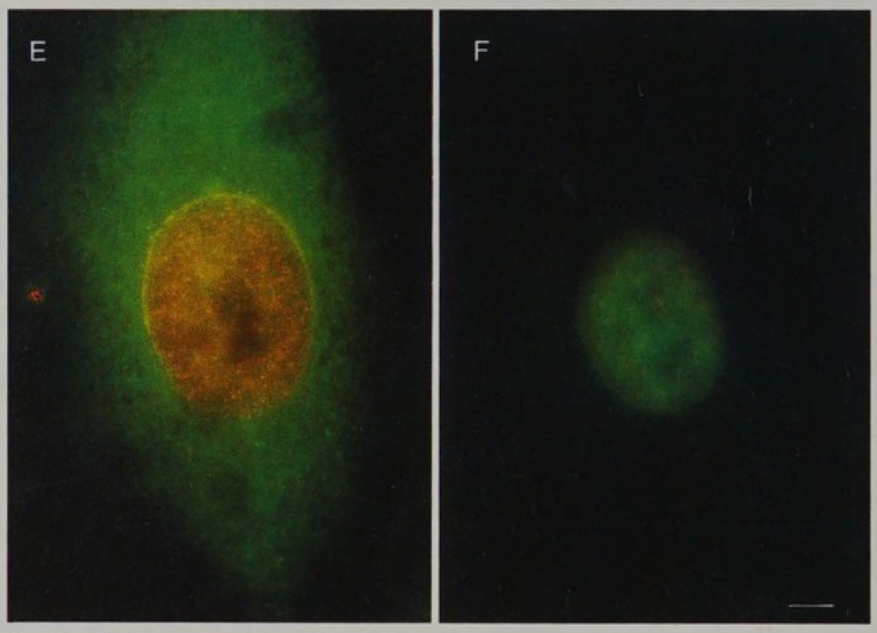
During the development of a mature B cell from a haematopoietic stem cell, immunoglobulin (Ig) genes undergo a complex pattern of gene rearrangement and subsequent expression. Our work focuses on the activation of the Igκ gene at the developmental switch from a pre-B to a B cell. In pre-B cells the activity of the κ3′ enhancer, which was described in our previous work, is silenced by a region flanking an active core element. We have now identified a lymphoid specific nuclear factor that binds to a site within this repressor region. Developmental studies of this factor show a pattern of expression consistent with a role as a transcriptional repressor of the Ig enhancer. We are currently attempting to clone the factor and examine the role phosphorylation plays in its regulation.

In addition, we are studying the involvement of HLH (helix-loop-helix) proteins in the control of Ig gene expression. The formation of either homo- or heterodimers is known to control their ability to activate transcription during very early stages of B cell development. We have now shown that a dominant negative HLH factor, Id3, is expressed in B cells but not in plasma cells. Id3 is able to downregulate IgH3′enhancer activity in transfection studies and is thus likely to be an important modulator of Ig gene expression.

JONATHON PINES



MALCOLM FIRTH
MARK JACKMAN
EMMA KELLY
ANNA MEDDINS



Human cyclin B moves into the nucleus at mitosis.

E. *Cyclin B (green) is a cytoplasmic protein in interphase. Nuclear lamina in red.*

F. *Cyclin B (green) moves into the nucleus before the nuclear lamina (red) breaks down in mitosis.*

PINES, J. and HUNTER, T. 1990. Human cyclin A is adenovirus E1A associated protein p60 and behaves differently from cyclin B. **Nature 346**, 760-763.

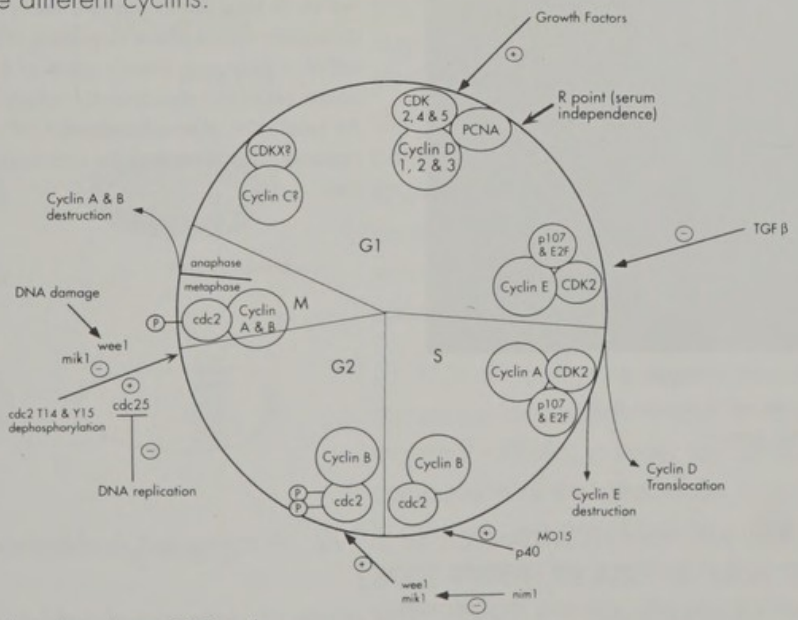
PINES, J. and HUNTER, T. 1991. Human cyclins A and B are differentially located in the cell and undergo cell cycle dependent nuclear transport. **J. Cell Biol. 115**, 1-17.

See also nos. 51,52, page 47ff.

REGULATION OF THE MAMMALIAN CELL CYCLE BY CYCLIN-DEPENDENT KINASES

Dividing cells must ensure that the processes of DNA replication and cell division are separate and sequential. To ensure this, DNA synthesis and mitosis follow one another in a regulated series of steps called the cell cycle. Several steps in the cell cycle are regulated by a family of protein kinases called the cyclin-dependent kinases (CDKs) which require a partner cyclin protein for their activity; the cyclins also localise their CDK partner to the correct sub-cellular structures.

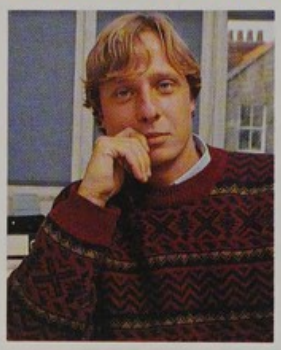
We wish to determine how cyclins localise different CDKs to particular parts of the cell. We have shown that cyclin A is a nuclear protein, and is associated with a transcription factor complex. By contrast cyclin B is cytoplasmic throughout interphase but moves rapidly into the nucleus at the beginning of mitosis where it associates with the mitotic apparatus. Our research focuses on defining which parts of the cyclins are responsible for their nuclear or cytoplasmic location, for binding to transcription factors and for association with the mitotic apparatus. We have defined a region in B-type cyclins responsible for their localisation to the cytoplasm, and have identified a potential means by which they are released to enter the nucleus at mitosis. We are presently searching for proteins that are able to interact specifically with the different cyclins.



The cell cycle as a CDK cycle

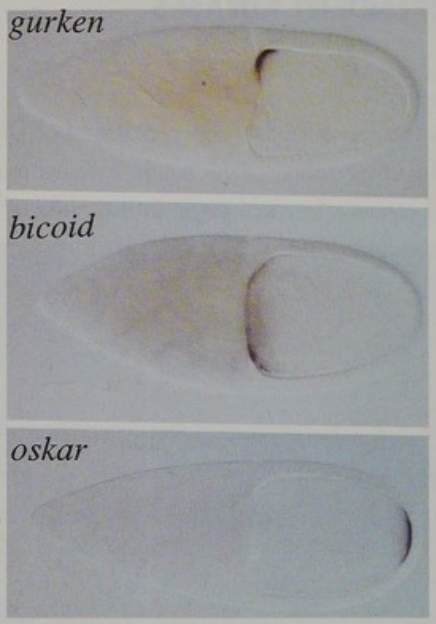
The putative points of action of the different cyclins and their partner kinases in the mammalian cell cycle

DANIEL ST JOHNSTON



LISA ELPHICK
ACAIMO GONZALEZ-REYES
STEFAN GRÜNERT
SARAH JOSEPH
DAVID MICKLEM
MATTHEW WESTON

Staufen protein (red) associates with injected bicoid RNA to form particles which migrate to the poles of the mitotic spindles (green)

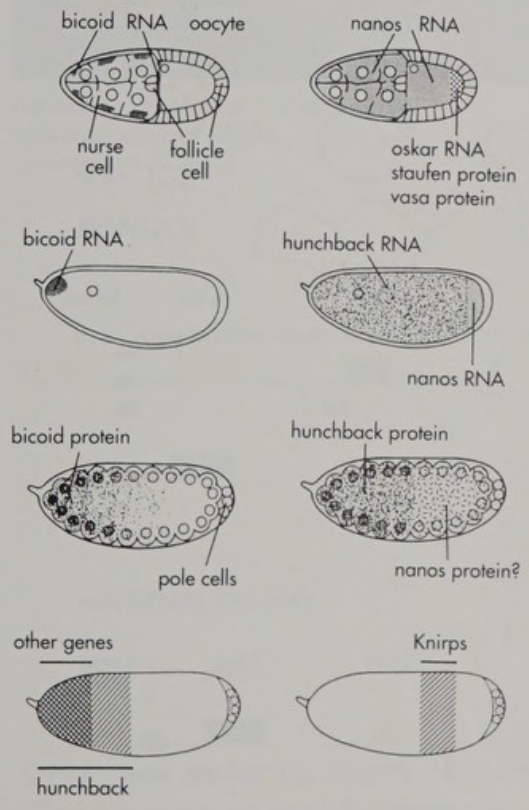


The localisation of gurken, bicoid *and* oskar *mRNAs to three distinct positions within the Drosophila oocyte. The accumulation of* gurken *mRNA in the dorsal/anterior corner of the oocyte establishes dorsal-ventral polarity, while the localisation of* bicoid *and* oskar *mRNAs to opposite poles determines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

ST JOHNSTON, D., BROWN, N.H., GALL, J.G. and JANTSCH, M. 1992. A conserved double-stranded RNA-binding domain. **Proc. Natl. Acad. Sci. USA 89**, 10979-10983.

ST JOHNSTON, D. and NÜSSLEIN-VOLHARD, C. 1992. The origin of pattern and polarity in the *Drosophila* embryo. **Cell 68**, 201-219.

THE LOCALISATION OF MATERNAL DETERMINANTS IN THE *DROSOPHILA* EGG



The determination of the anterior-posterior axis of the Drosophila *embryo*

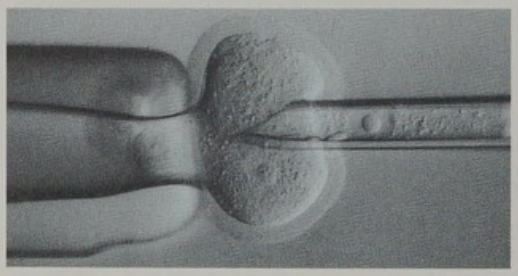
In many organisms, the formation of the primary body axes is controlled by cytoplasmic determinants which are localised during the development of the egg. These signals have been best characterized in *Drosophila*, where the localisation of *bicoid*, *oskar* and *gurken* maternal mRNAs determines the polarity of both the anterior-posterior and the dorsal-ventral axes. Our group is taking several different approaches to investigate how these mRNAs are transported within the oocyte, with a view to understanding both the basic mechanisms of mRNA localisation, and the origins of polarity within the egg.

1) The maternal gene *staufen* is required for both the anchoring of *bicoid* RNA at the anterior pole of the egg, and for the transport of *oskar* RNA to the posterior pole. Staufen protein acts as a chaperon during the localisation of these transcripts, and contains several copies of a novel double-stranded RNA-binding domain. We are now using a combination of genetic and biochemical approaches to investigate how these domains bind in a sequence-specific manner to two different mRNAs.

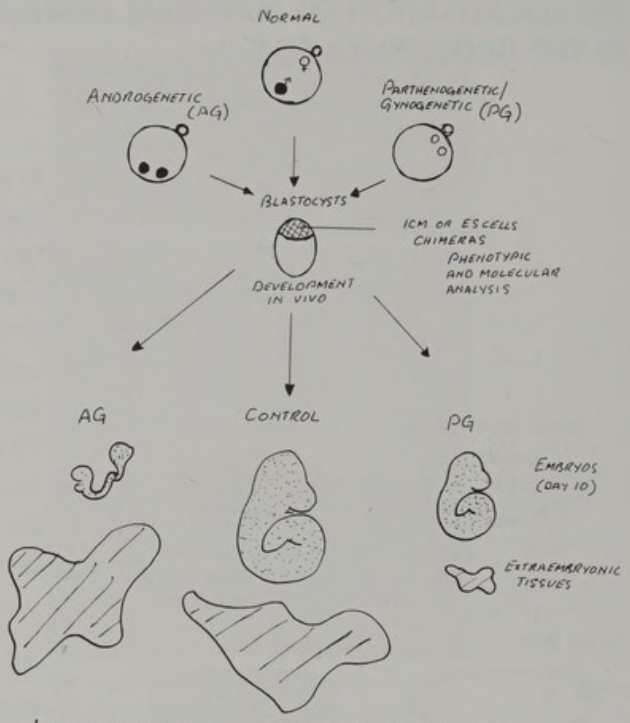
2) We are analysing several new mutations which disrupt the localisation of one or more of these maternal mRNAs, in order to identify further components of the intracellular transport machinery. In addition, we are characterising a group of genes which seem to be involved in the earliest step in the generation of polarity, the positioning of the oocyte within the follicle.

AZIM SURANI

JUSTIN AINSCOUGH
SHEILA BARTON
JAMES BRENTON
ANNE FERGUSON-SMITH
KATHY HILTON
TSUYOSHI KOIDE
LI-LAN LI
MAITHREYI NARASIMHA
FAY SHAMANSKI
STÉPHANE VIVILLE



Transplantation of pronucleus in the mouse zygote



INFLUENCE OF IMPRINTED GENES ON DEVELOPMENT

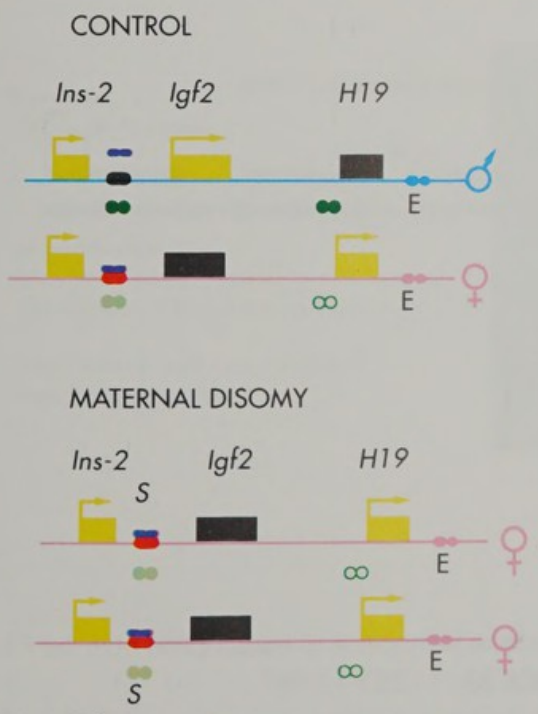
SASAKI, H., JONES, P.A., CHAILLET, J.R., FERGUSON-SMITH, A.C., BARTON, S.C., REIK, W. and SURANI, M.A. 1992. Parental imprinting: potentially active chromatin of the repressed maternal allele of the mouse insulin-like growth factor II (*Igf2*) gene. **Genes Dev. 6**, 1843-1856.

FERGUSON-SMITH, A., SASAKI, H., CATTANACH, B.M. and SURANI, M.A. 1993. Parental-origin-specific modification of the mouse H19 gene. **Nature 362**, 751-755.

See also nos. 6,15,17,18,22,42,54,55,57,62,63,64,65, page 47ff.

MAMMALIAN DEVELOPMENTAL GENETICS AND GENOMIC IMPRINTING

Expression of a transgene in neural crest cells and spinal ganglia



Control of gene expression by parental imprinting

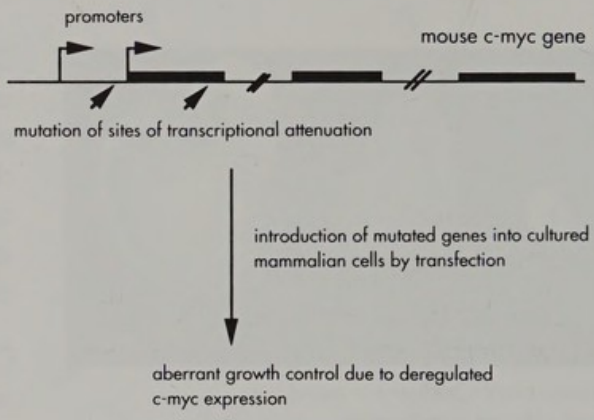
Development in the mouse requires both maternally and paternally inherited sets of chromosomes, because expression of some genes, called imprinted genes, is determined by their parental origin. The transcriptional control of imprinted genes is achieved by germline specific heritable modifications to the DNA or chromatin.

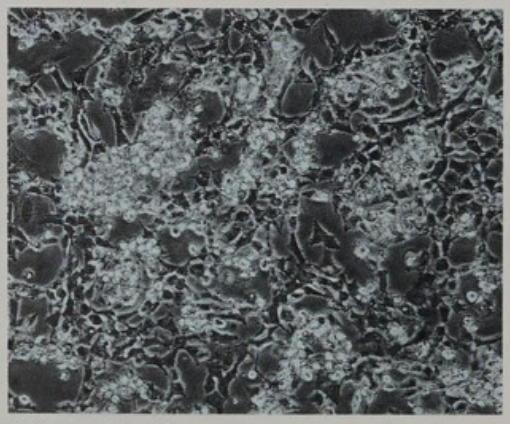
Cumulative effects of imprinted genes can be examined in androgenetic (AG: duplicated paternal genome) and parthenogenetic/gynogenetic (PG: duplicated maternal genome) embryos. AG cells in chimeras with normal embryos contribute disproportionately to skeletal muscle and cartilage and produce skeletal abnormalities. PG cells are largely excluded from these tissues but instead they contribute to neural tissues. Embryonic stem cells derived from AG and PG blastocysts provide opportunities to investigate the molecular characteristics of parental imprints and their influence on the pluripotency/totipotency of these cells.

Distal Chromosome 7 has at least two closely linked, reciprocally imprinted genes; the paternal gene of *Igf2* and the maternal gene of *H19* are expressed. Within the *Igf2/H19* domain, there are regions with parental origin dependent differences in DNA methylation and chromatin structure which probably influence expression of *Igf2* and *H19*. The combined developmental and molecular approaches will show how the parental genomes interact during normal embryogenesis.

STEPHANIE WRIGHT

CRAIG LUCCARINI



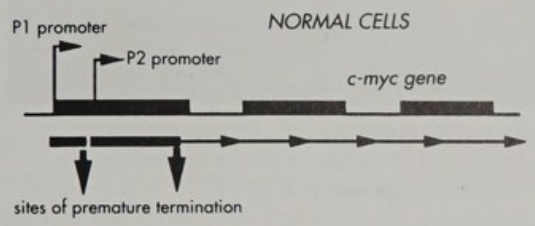


Cells transformed by over expression of the c-myc oncogene

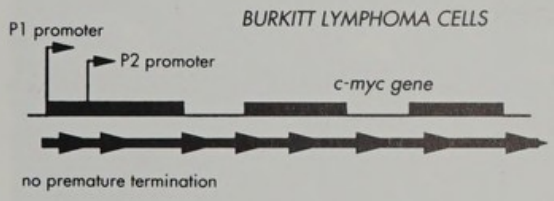
WRIGHT, S., CALAYAG, M., MIRRELS, L. and BISHOP, J.M. 1991. Premature termination of transcription from the P1 promoter of the mouse c-myc gene. **Proc. Natl. Acad. Sci. USA 88**, 11383-11387.

WRIGHT, S. 1993. Regulation of eukaryotic gene expression by transcriptional attenuation. **Mol. Biol. of the Cell 4**, 661-668.

REGULATION OF PROTO-ONCOGENE EXPRESSION IN NORMAL AND TUMOUR CELLS



Low c-myc expression due to premature termination



Over expression of c-myc due to loss of attenuation

Transcription through the c-myc gene in normal and tumour cells

The development of neoplasia is often a result of the aberrant expression of genes that normally act to control cellular proliferation and differentiation. The aim of our work is to determine the mechanism whereby transcriptional attenuation is used to regulate expression of three such genes (c-myc, c-fos and c-myb) in normal cells, and to characterise the events leading to the loss of ability to regulate attenuation within the c-myc gene in a variety of tumours.

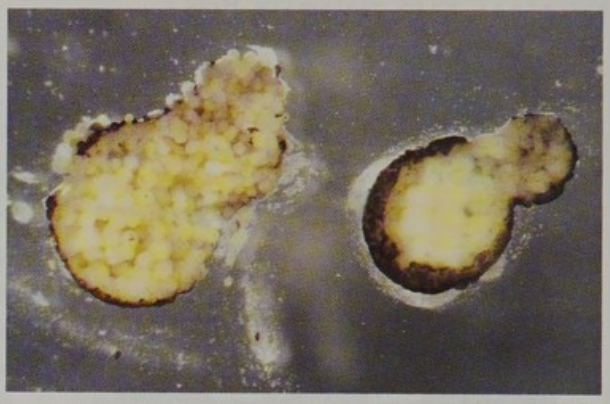
We have previously shown that the c-myc, c-fos and c-myb genes are normally regulated via the modulation of transcriptional elongation through discrete sites of premature termination within the gene, with the degree of transcriptional attenuation being controlled in response to different physiological signals. We have characterised common sequence elements and factors interactions at sites of premature termination within these genes, and have analysed the *regulatory* elements that enable the *degree* of attenuation within different genes to be independently controlled.

We are currently determining whether aberrant regulation of transcriptional attenuation within the c-myc gene in tumours is due to alterations in protein interactions at such regulatory elements.

CHRIS WYLIE

JANET HEASMAN

CLARE BAKER
JULIE COOKE
AARON CRAWFORD
MARTIN GARCIA-CASTRO
KIM GOLDSTONE
MIRANDA GOMPERTS
JOS RAATS
LUBA RYABOVA
LUCINDA VICKERS
TANYA WHITFIELD
(COLIN SHARPE)



A comparison of the appearance of a Xenopus blastula after the depletion of EP cadherin molecules (LHS) and a normally adherent control embryo (RHS)

A confocal image of two linked primordial germ cells within a 10.5 day mouse embryo. The embryo was stained using an antibody which recognises a sugar present on the surfaces of germ cells

GOMPERTS, M., GARCIA-CASTRO, M., WYLIE, C.C. and HEASMAN, J. 1994. Adhesive interactions between primordial germ cells play a role in their migration in mouse embryos. **Development**, in press.

HEASMAN, J., GINSBERG, D., GEIGER, B., GOLDSTONE, K., PRATT, T., YOSHIDA-NORO, C. and WYLIE, C.C. 1994. A functional test for maternally inherited cadherin in *Xenopus* shows its importance in cell adhesion at the blastula stage. **Development 120**, in press.

See also nos.11,24,35,66,67,70,71,72, page 47ff.

THE ESTABLISHMENT OF CELL BEHAVIOUR IN EARLY EMBRYOS

We study the molecules that are responsible for the changes in cell behaviour that underlie morphogenesis. We use two model systems:

Primordial germ cells, which ultimately give rise to the eggs and sperm of the adult animal, are migratory. We are interested in the factors and processes that guide these cells from the site where they arise in the early mouse embryo to their target tissue, the genital ridges. Until recently it was considered that germ cells migrate independently of each other. By using confocal microscopy we have studied germ cells *in situ* in their three dimensional environment. We have found that germ cells associate with each other as they migrate via fine cytoplasmic processes, forming extensive networks. A similar sequence of events occurs when isolated germ cells are cultured *in vitro*. We are currently trying to identify the molecules that mediate germ cell-germ cell and germ cell-substratum adhesion to see how these may influence germ cell migration.

***Xenopus* oocytes and early embryos**. Events at the earliest stages of *Xenopus* development are largely controlled by mRNAs and proteins inherited from the oocyte. We are characterising examples of several classes of such gene products, and analysing their specific roles by analysing the effects in the early embryo of perturbing their expression in the oocyte:

i) Cell adhesion molecules that control early segregation of cells to specific regions of the embryo during the blastula stage.

ii) Cytoskeletal molecules that control the distribution of informational molecules in the egg, and early cell division cycles.

iii) Transcription factors involved in controlling the earliest patterns of gene expression.

During 1994 Chris Wylie and Janet Heasman will be leaving the Institute. Their new address will be: Institute of Human Genetics, University of Minnesota School of Medicine, Box 206 Mayo, 420 Delaware St. SE, Minneapolis, MN 55455-0392, USA.
Miranda Gomperts and Martin Garcia-Castro will continue to work in the laboratory until October 1995.

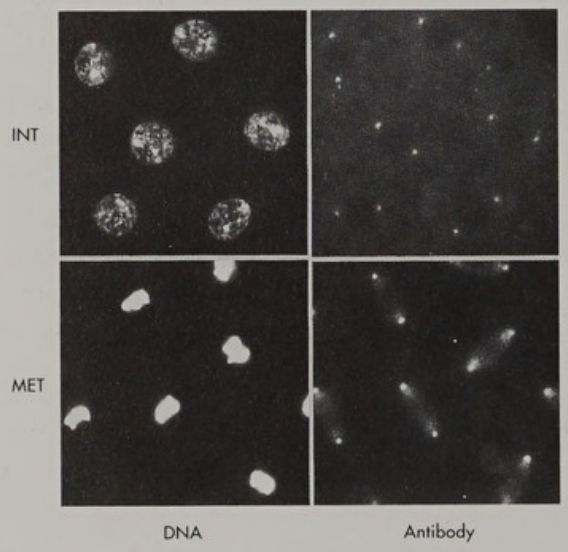
JORDAN RAFF

MOLECULAR ANALYSIS OF THE CENTROSOME

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 *Drosophila* 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, called DMAP190 and DMAP60, form a tight complex with γ-tubulin, a highly conserved centrosomal protein thought to be involved in microtubule nucleation. Another is a protein kinase - the first protein kinase shown to be located in the centrosome and to interact with microtubules. This protein kinase phosphorylates DMAP60 *in vitro*.

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



The localisation of the LK6 protein kinase to centrosomes in interphase

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SCIENTIFIC STAFF OF THE INSTITUTE

CATEGORIES OF APPOINTMENT

PRINCIPAL GROUP LEADER	Professor/Reader/Lecturer Level
YOUNGER GROUP LEADER	5 year grant-funded appointment (maximum 10 years)
INDEPENDENT SENIOR RESEARCH ASSOCIATE	3 year grant-funded appointment
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RESEARCH TECHNICIAN	Within individual groups, mainly grant-funded
LABORATORY ASSISTANT	Within individual groups, mainly grant-funded

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

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OTHER ACTIVITIES

MICHAEL AKAM is Chairman of the British Society for Developmental Biology, and a member of the Wellcome Cell & Molecular Biology Board, and of the International Review Committee, CSIC, Madrid.

CHARLES FFRENCH-CONSTANT gave the "Sir Richard Cave Memorial Lecture" to the Multiple Sclerosis Society in 1992.

MARTIN EVANS is Chairman of the AFRC Stem Cell & Molecular Biology Working Party, Founder and Director of Genesys Instruments Ltd, Founder Member of Animal Biotechnology, Cambridge Ltd. He was the Walter Cottman Fellow at Monash University, Melbourne for 1993.

JOHN GURDON is President of the International Society for Developmental Biology, and a member of the Councils of the Royal Society and the Cancer Research Campaign.

RON LASKEY is Subject Convenor for Cell and Developmental Biology, Academia Europaea, a member of the Cancer Research Campaign Scientific Committee, and Chairman of the Board of Trustees of the Strangeways Research Laboratories.

CHRIS WYLIE has continued as Chief Editor of *Development*.

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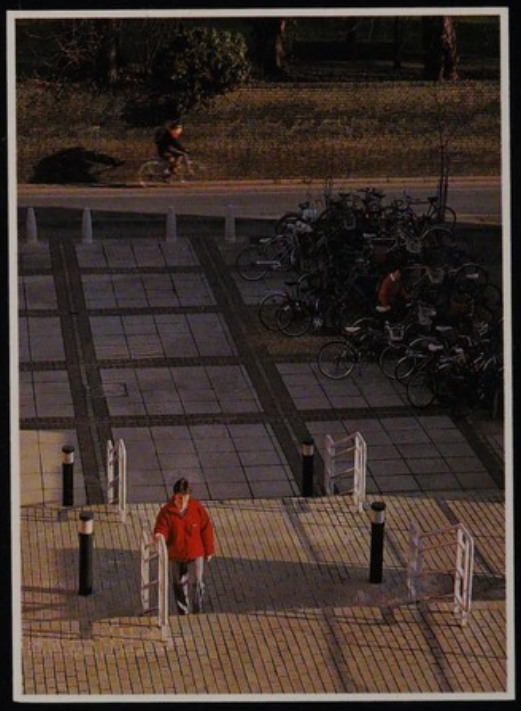

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