Annual report : 1992/1993 / The Wellcome Trust, Cancer Research UK Gurdon Institute of Cancer and Developmental Biology.

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Publication/Creation

Cambridge : Wellcome Trust / Cancer Research UK Gurdon Institute, 1993

Persistent URL

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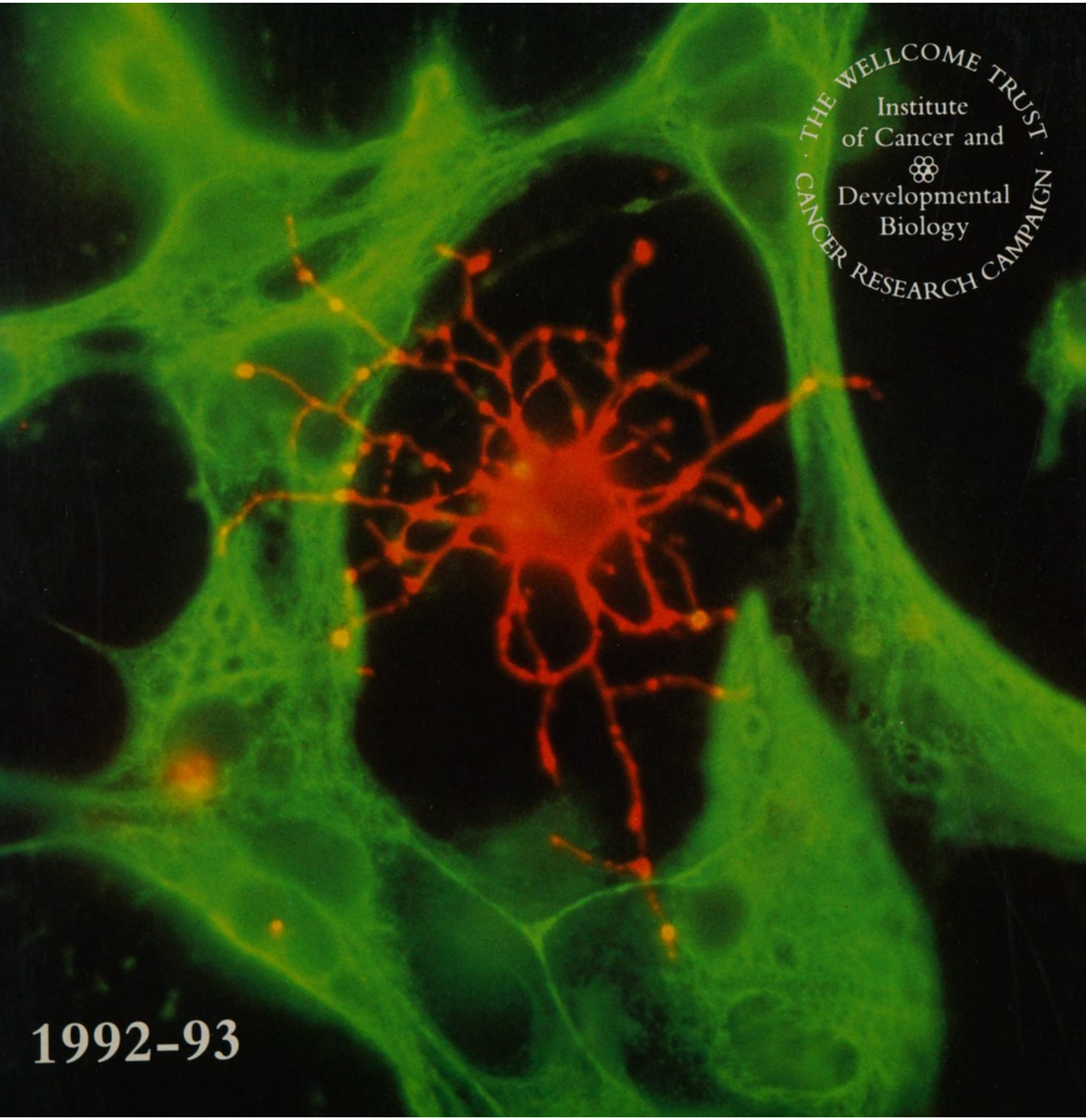
THE WELLCOME TRUST · CANCER RESEARCH CAMPAIGN ·
Institute
of Cancer and
Developmental
Biology
1992-93

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Institute of Cancer and Developmental Biology

PROSPECTUS

1993

ANNUAL REPORT 1992

University of Cambridge

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Front Cover Photograph:
Glial Cells in Culture
Photograph by Suzanna Scott-Drew

PROLEGOMENON

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 fifteen research groups, while the University of Cambridge maintains the building.

THE INSTITUTE IN 1992 It is a year and a half since we moved into our new Institute, and nearly all our laboratory space is now occupied. During this year we added greatly to our strength in mammalian developmental genetics. Azim Surani has been appointed to the Mary Marshall and Arthur

Walton Professorship of the Physiology of Reproduction in the University of Cambridge, and has moved his group into our Institute. He is a member of the Physiology Department and we are very pleased, in this way, to have an association with another major University Department to add to the associations we already have with Zoology, Genetics, Pathology, Biochemistry, and the Clinical School.

Professor Surani will continue his work on the molecular and genetic analysis of imprinting in mouse development.

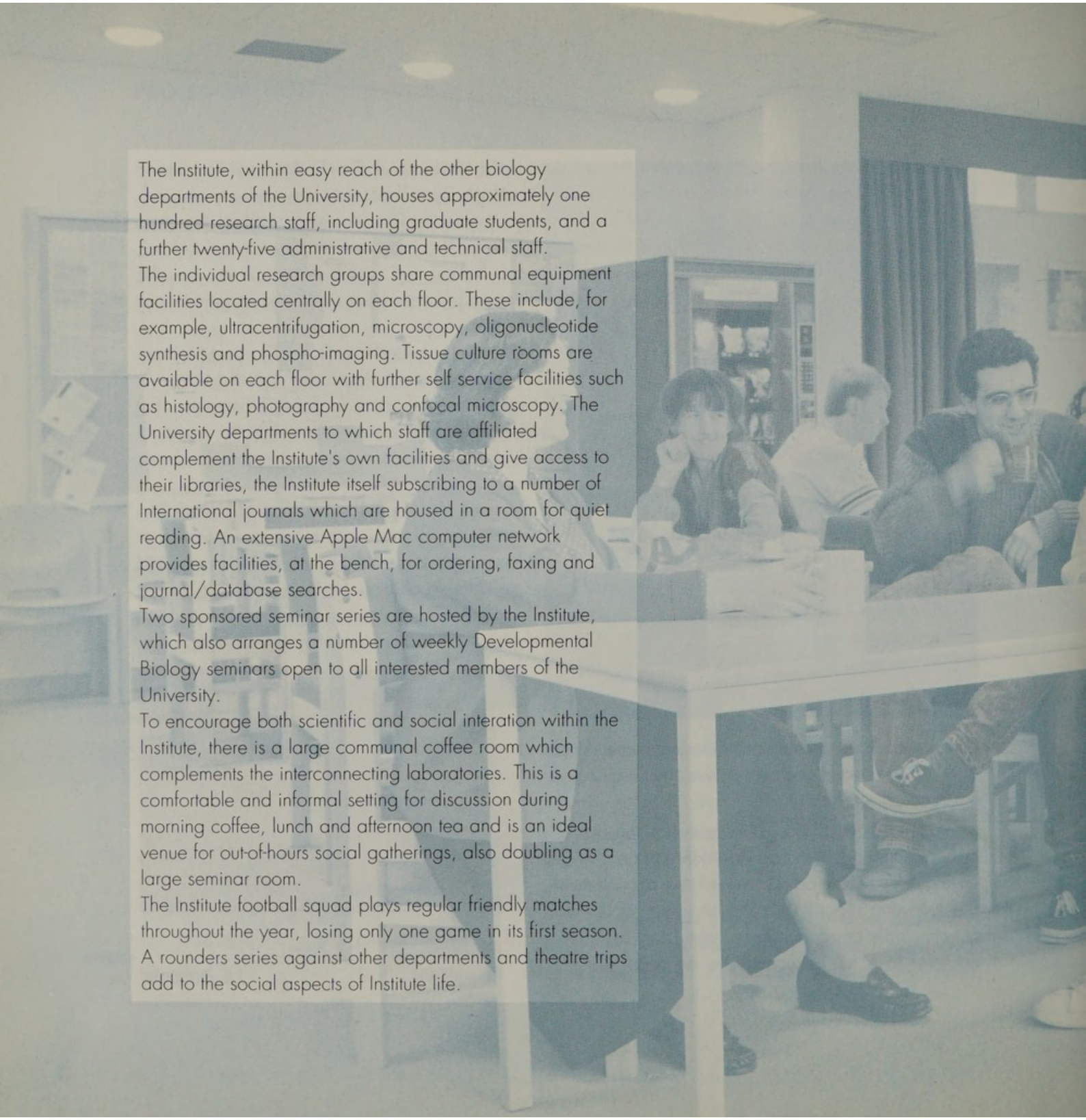
We are also very pleased to welcome Dr. Anne McLaren as a Principal Research Associate. Part of her time is spent at the Royal Society as Foreign Secretary, but in addition she has accommodation in the group of Chris Wylie and Janet Heasman, with whom she shares an interest in germ cells.

Thus, with Martin Evans and his group, we are now very well represented in the area of mammalian development. One highlight in this area has been the generation of mice with a targeted mutation in *cftr*. Mutations at this locus in humans are responsible for the genetic syndrome of cystic fibrosis and the homozygous *ctfr* mice show the same primary loss of chloride channel function and many of the same symptoms as severe forms of the human condition. The creation of animal models of human genetic disease such as these mice will greatly facilitate further understanding of human syndromes and the development of new approaches to treatment, particularly that of gene therapy (see pages 14, 15).

Others who have joined us include Stephanie Wright working on transcriptional attenuation, and Kerstin Meyer on B cell diversity.

An important event during the year was the first visit by our International Advisory Board (see page 39) who have given valuable advice on the future of our Institute. The following reports indicate the range of research activities now being pursued. These have been presented in a concise and relatively simple form, but we refer to a full publication list on page 40ff.

J.B. GURDON
CHAIRMAN



The Institute, within easy reach of the other biology departments of the University, houses approximately one hundred research staff, including graduate students, and a further twenty-five administrative and technical 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. 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 interation 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.

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

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PATRICK LEMAIRE
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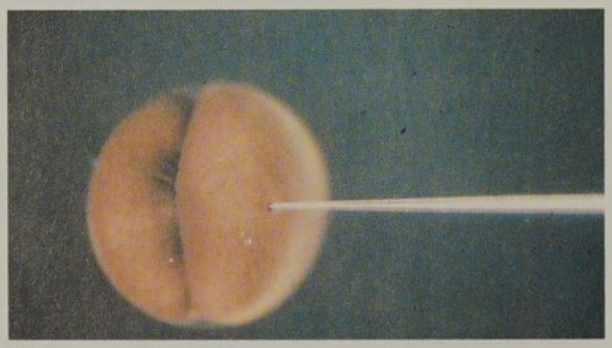
TOBY SYKES
EMMA TILLER
ELIZABETH TWEED

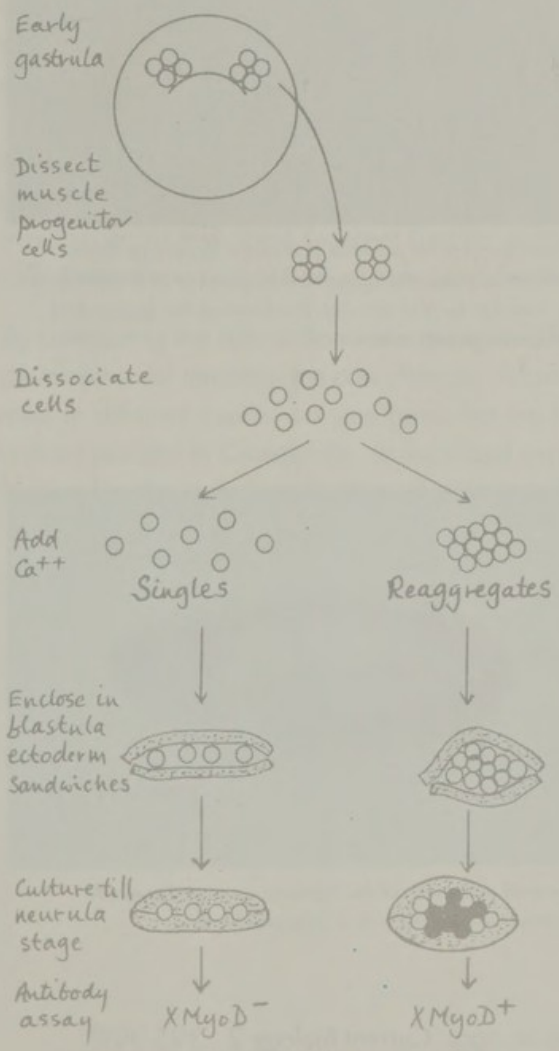
Expression of muscle actin (red) and XMyoD (black), from head (left) to tail (right)



Microinjection of a 2-cell embryo

GURDON, J.B. 1992. The generation of diversity and pattern in animal development. **Cell 68**, 185-199.
GURDON, J.B. 1993. A community effect in normal muscle development. **Current Biol. 3**, 1-11.
See also nos. 22,23,24,26,32,36,46, page 40ff.

MECHANISMS OF CELL DIFFERENTIATION IN EARLY AMPHIBIAN DEVELOPMENT



Community effect: experimental design

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.

Using a muscle-specific actin gene as an early marker of muscle differentiation, we have identified two regulatory myogenic genes, XMyoD and XMyf5, whose products bind to the actin gene promoter. Furthermore, these regulatory genes can activate muscle genes when overexpressed in embryonic cells of non-muscle type.

We transplant gastrula muscle progenitor cells, either singly or as a group, into a non-muscle region of an embryo or into sandwiches of blastula ectoderm. Only cells within the reaggregated groups activate MyoD and later muscle genes. We believe that this represents a "community effect", in which like cells induce and respond to each other, to achieve a uniform and coordinated activation of muscle genes. The molecules which mediate the community effect are different from those involved in mesoderm induction. To identify genes responsible for the community effect and for other early events, we are using subtracted cDNA libraries, which we express in various combinations of inducing and responding embryonic cells.

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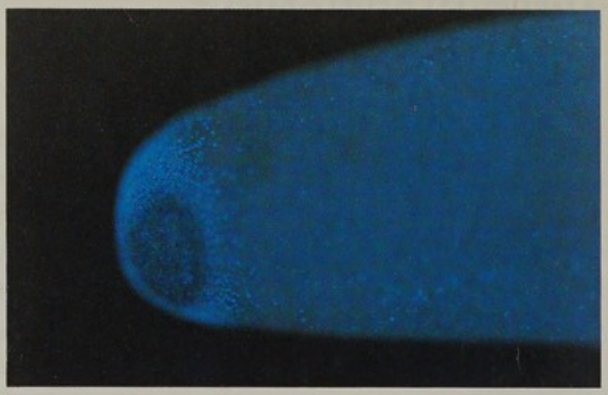
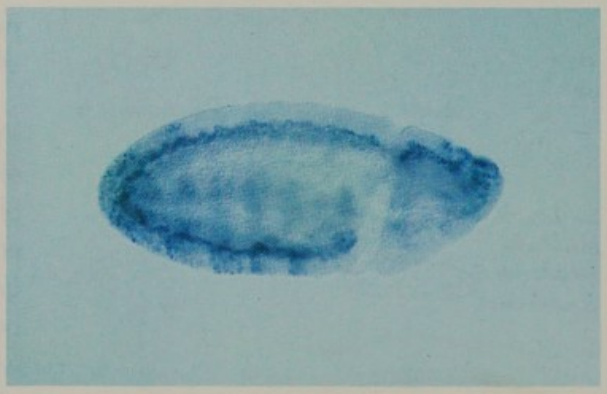


Clustered nuclei at the posterior pole of the locust egg define the embryonic primordium. Localized expression of a homeobox gene, revealed by dark staining, foreshadows the appearance of a posterior growth zone.



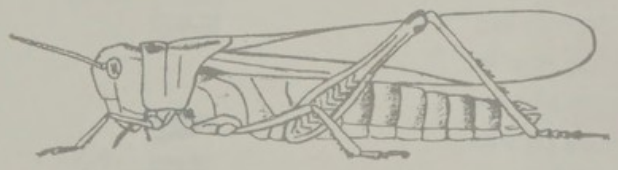
Engineered expression of the homeotic gene abdominal-A *throughout the mesoderm of a* Drosophila *embryo.*

AKAM, M. and DAWES, R. 1992. More than one way to slice an egg. **Current Biology 2**, 395-398.
KELSH, R.N, DAWSON, I.A. and AKAM, M. 1993. An analysis of *Abdominal-B* expression in the locust *Schistocerca gregaria*. **Development 117**, 293-305.
See also nos. 1,3,4,11, page 40ff.

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 (utilizing GAL 4 regulatory elements from yeast) that allow us to alter their patterns of expression in precisely controlled ways. With these we are testing which cells define particular aspects of a complex pattern. For example, we can force the muscle cells of a segment to express a gene specifying abdomen, while the epidermal cells carry a "thorax" label. The development of an abdominal pattern of muscles shows that some segment specific differences depend on signals carried by the muscle cells themselves, and not on signals provided by the epidermis.

By comparing the role of homeotic genes in different arthropod species, we hope to learn how developmental mechanisms can change. Most homeotic genes appear to have conserved roles in different insects, but one gene that we have isolated from the locust *Schistocerca* appears to be without parallel in *Drosophila*. Its localized expression in the very early embryo suggests that it may be involved in the early specification of polarity in the embryo.



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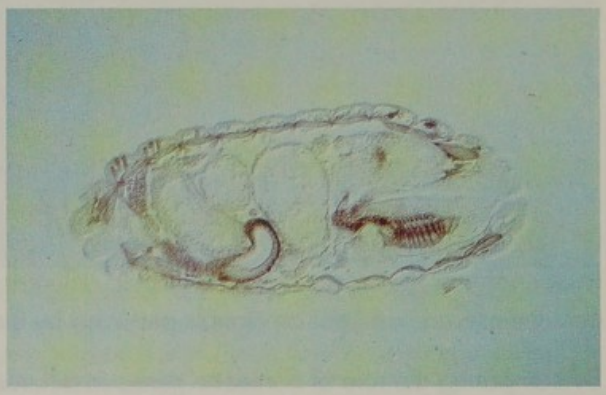
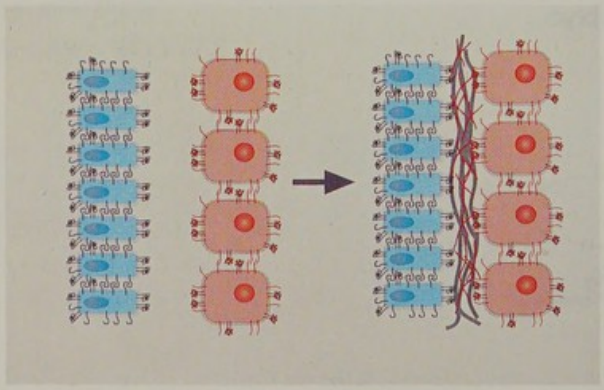


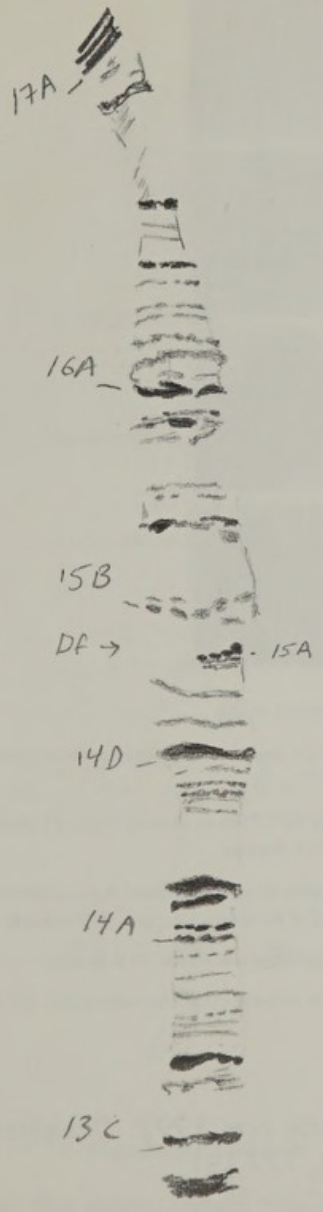
Surface staining of the embryonic mesoderm



Adhesion of cell layers via the extracellular matrix

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.
BOGAERT, T., BROWN, N. and WILCOX, M. 1987. The *Drosophila* PS2 antigen is an invertebrate integrin that, like the fibronectin receptor, becomes localized to muscle attachments. **Cell 51**, 929-940.
See also no. 52, page 40ff.

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.

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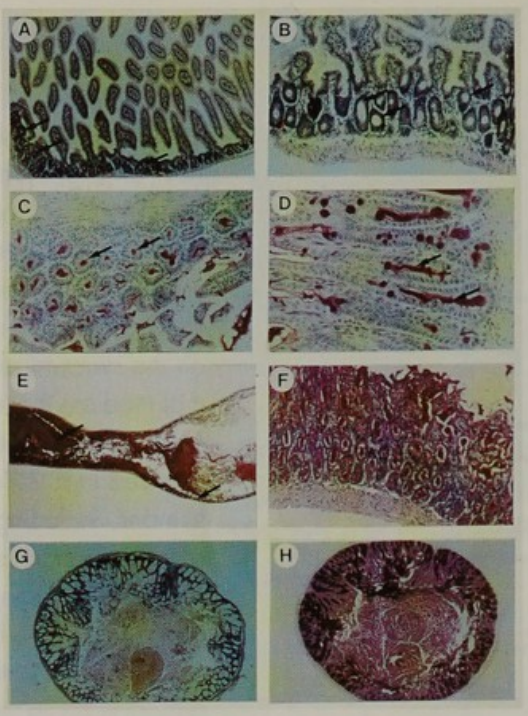
SAM DAINES
JOHN DIXON
JOANNE DORAN
DIANE FOSTER
DARREN GILMOUR
DIPA NATARAJAN
ROSEMARY RATCLIFF



Gastrointestinal histopathology in cystic fibrosis mice

A. *Transverse section of small intestine from a normal 21 day old mouse showing villous architecture and the appearance of crypts of Lieberkühn. (H & E)*

B,C,D. *Transverse sections of small intestine from a 21 day old CF mouse showing crypts of Lieberkühn distended with mucus (arrowed). (B,C - H&E, D - PAS diastase)*

E. *Longitudinal section of small intestine from a CF mouse showing inspissated mucus distending the bowel lumen and causing villous atrophy (arrowed) of the intestinal mucosa. (PAS diastase)*

F. *Higher magnification of E illustrating distended crypts filled with mucus. (PAS diastase)*

G,H. *Transverse sections of large intestine from CF mouse showing crypts filled with mucus. (G - H&E, H - PAS diastase)*

RATCLIFF, R., EVANS, M.J., DORAN, J., WAINWRIGHT, B.J., WILLIAMSON, R. and COLLEDGE, W.H. 1992. Disruption of the cftr gene in embryonic stem cells by gene targetting. **Transgenic Res. 1**, 177-181.
COLLEDGE, W.H., RATCLIFF, R., FOSTER, D., WILLIAMSON, R. and EVANS, M.J. 1992. Cystic fibrosis mouse with intestinal obstruction. **Lancet 340**, 680.
See also nos. 7,45, page 40ff.

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

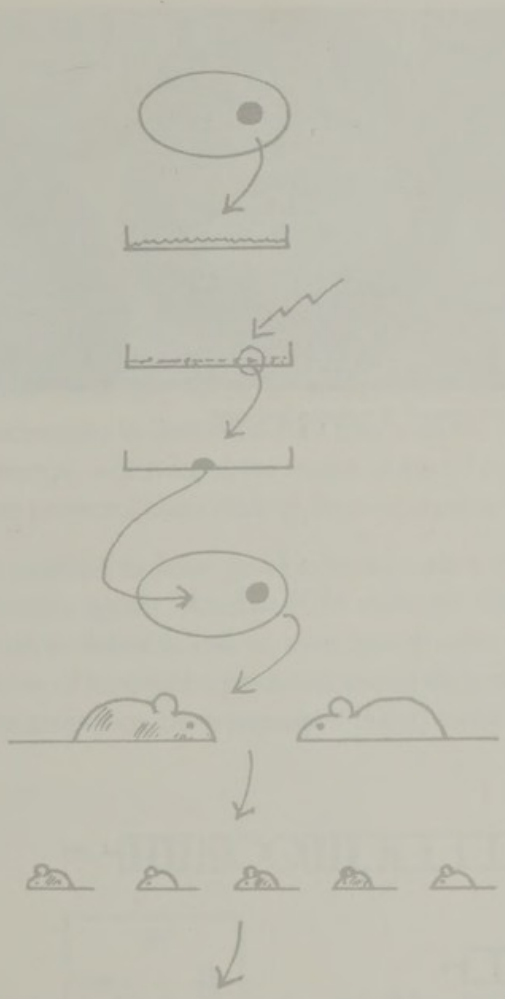


Diagram of ES cell route

The use of embryonic stem (ES) cells of mice as a route to somatic and germ line transgenesis has allowed several new approaches 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 analysing 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. Genes of interest in the laboratory, which have been targeted, include the cystic fibrosis gene, adenosine deaminase, mos and the oestrogen receptor, and after selection and analysis of homologous recombination events these clones are being introduced into mice.

CHARLES FFRENCH-CONSTANT

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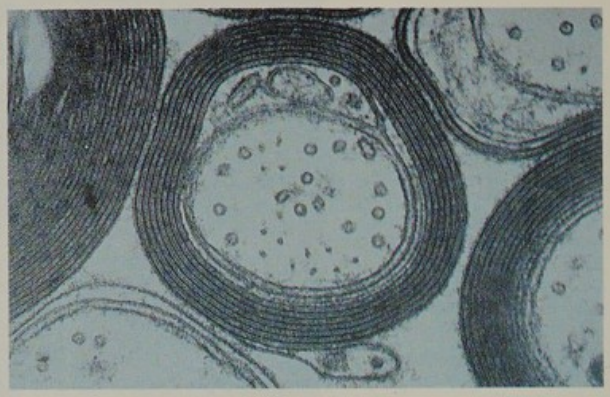
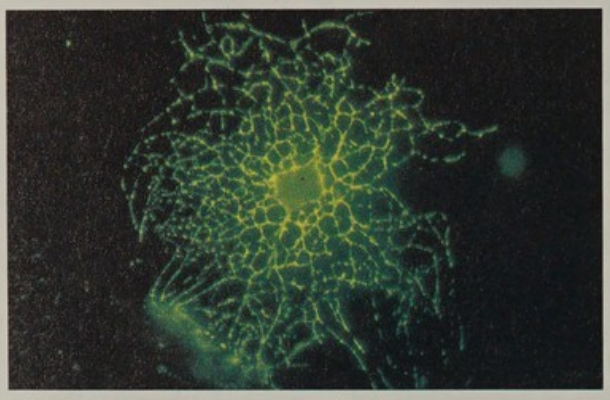


Electron micrograph of a myelinated axon



Oligodendrocyte and astrocytes 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.

FFRENCH-CONSTANT, C., VAN DE WATER, L., DVORAK, H.F. and HYNES, R.O. 1989. Reappearance of an embryonic pattern of fibronectin splicing during wound healing in the adult rat. **J. Cell Biol. 109**, 903-914.

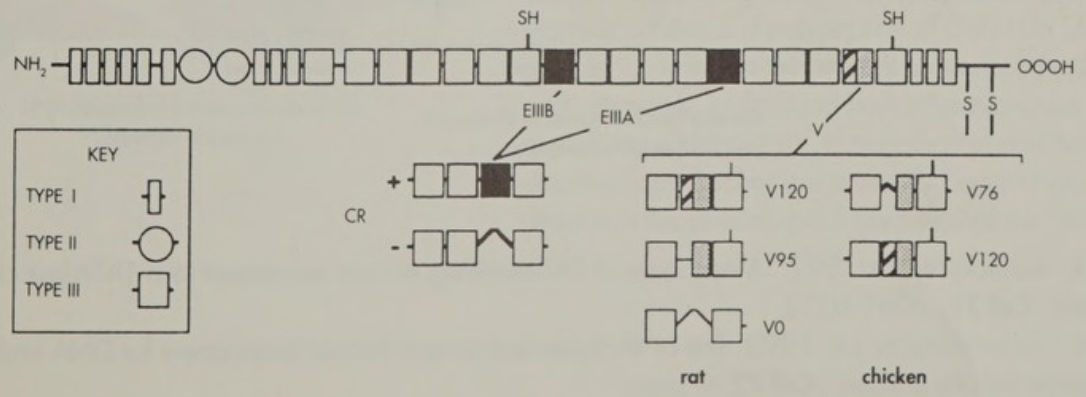
See also nos. 9,16,17,18,19 page 40ff.

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 one important aspect of this development, cell migration. The nervous system develops from a two-dimensional sheet of cells into a complex three-dimensional structure, but a striking feature throughout this development is that most of the different cell types appear first in the innermost layer of cells and subsequently migrate long distances to their final destinations.

In order to elucidate the mechanisms responsible for this migration 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. Initially we have focused on three molecules, tenascin, thrombospondin and the integrin family of receptors, and use cell culture techniques to determine their effects on the migration of oligodendrocytes and their precursors. This cell lineage, which forms the myelin of the CNS, was chosen as the precursor cells migrate extensively in the postnatal brain making them accessible for study.

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 nerve growth cone migration. Specifically we are testing the hypothesis that forms of fibronectin produced during early development by alternative splicing of the primary gene transcript may be re-expressed during repair and may be essential for efficient repair.



Alternative splicing of fibronectin

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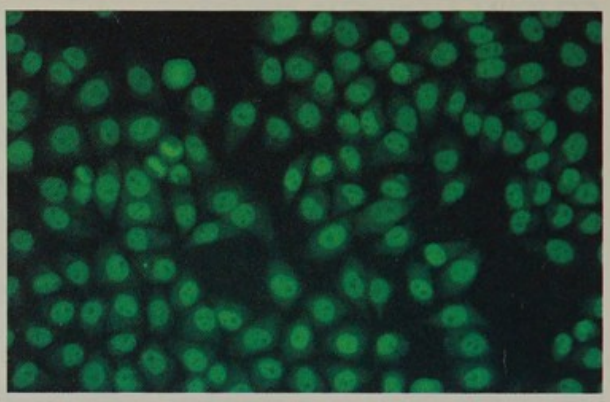
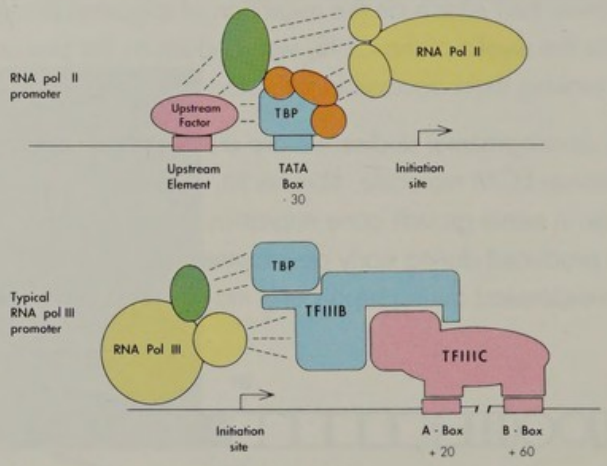
KATHARINE HARTLEY
ROBERT WHITE



Nuclear localisation of transcription factor Sp1



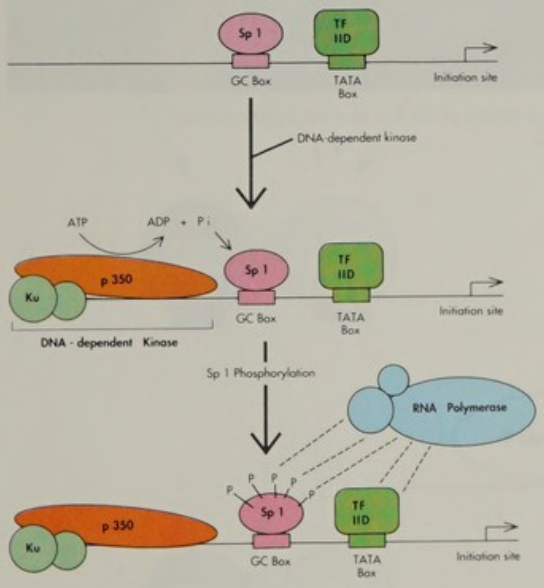
General factors involved in RNA pol II and RNA pol III transcription

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**, in press.

See also nos. 33,34,35,59,60, page 40ff.

MECHANISMS AND REGULATION OF MAMMALIAN GENE TRANSCRIPTION



DNA-dependent kinase phosphorylates promoter-bound Sp1

Our aims are to determine the mechanism of gene transcription and to understand how transcriptional initiation is regulated. One approach taken has been to study TBP, the TATA-binding protein, required for transcription by RNA polymerase II (pol II). Surprisingly, we have found that TBP is also a general factor for RNA pol III, even though most class III promoters lack TATA boxes. Biochemical analysis reveals that TBP is a component of the pol III general factor, TFIIIB. We are currently analysing TFIIIB further to determine its polypeptide composition, its role in transcriptional initiation, and how it might mediate activation by upstream factors.

We are also studying the DNA-dependent protein kinase (DNA-PK) that phosphorylates Sp1 and a variety of other transcription factors. This is an unusual kinase in that it binds DNA. Recently we have discovered that the DNA-PK is a multiprotein complex. The DNA binding component of the enzyme is Ku, a human autoimmune antigen, whereas the catalytic subunit is a polypeptide of 350 kDa (p350). In order to ascertain the primary sequence of p350 and, ultimately, understand how it functions, we have cloned the p350 cDNA. Immunological and biochemical approaches are presently being employed to determine the physiological function(s) of the DNA-PK.

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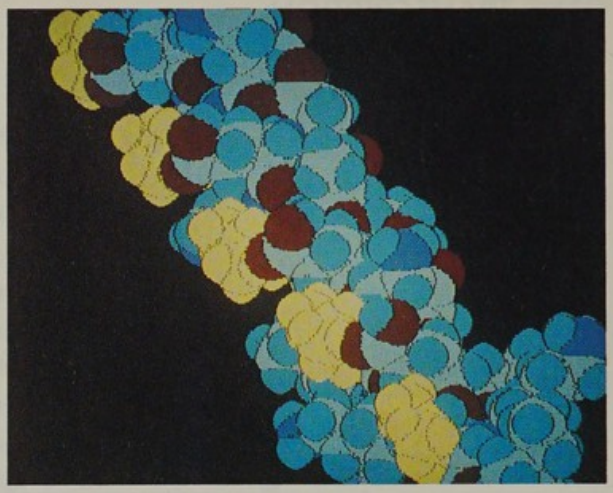
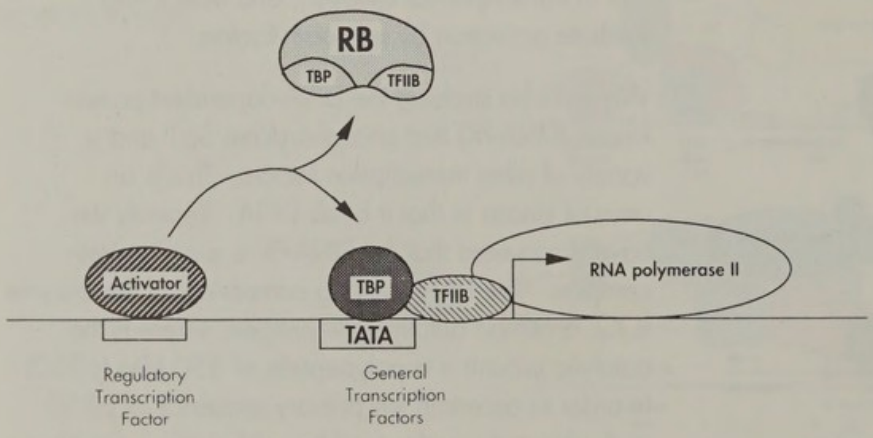


Graphics model of the Fos leucine zipper domain



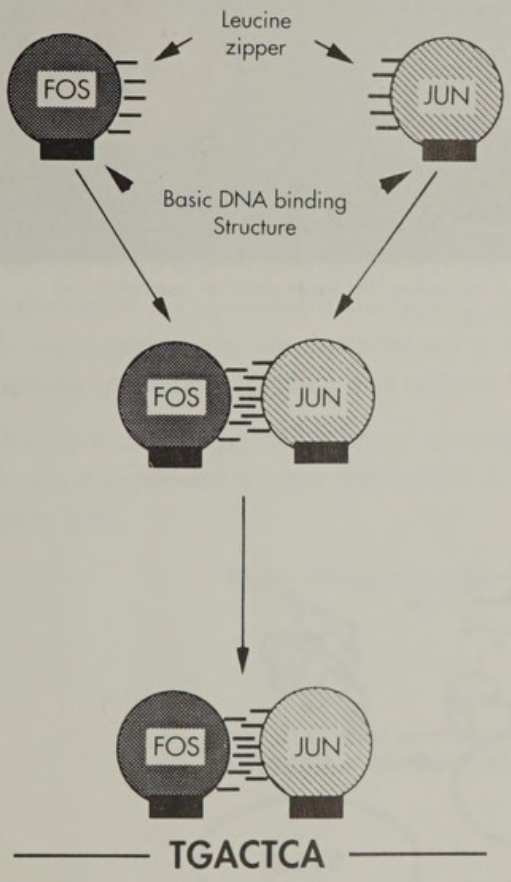
Model for RB function: Binds regulatory transcription factors that also contact TBP and TFIIB

KOUZARIDES, T. and ZIFF, E.B. 1988. The role of the leucine zipper in the Fos-Jun interaction. **Nature 336**, 646-651.

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.

See also nos. 5,6,28,29, page 40ff.

TRANSCRIPTIONAL REGULATION IN EUKARYOTES



Our group is interested in the mechanisms by which "regulatory" transcription factors activate gene expression. DNA bound regulatory factors are thought to activate transcription by contacting and stabilising "general" transcriptional factors assembled at the initiation site. In order to establish the points of interaction between "regulatory" and "general" transcription factors we are characterizing regulatory factors, such as Fos and Jun, and general factors, such as the TATA box binding protein TBP.

Our previous work has shown that the Fos and Jun proteins can form a complex, via a leucine zipper and can bind DNA via a basic structure. More recently, we have shown that Fos and Jun have an activation domain which is structurally and functionally homologous. Our efforts are now concentrated towards identifying any protein(s) that bind to this domain and mediate the activation process.

Our work on TBP has revealed that several regulatory transcription factors can directly contact TBP. In addition, we find that these factors can bind Retinoblastoma (RB) tumour suppressor protein. This has led to the exciting discovery that RB has extensive sequence similarity to two general transcription factors, TBP and TFIIB. Our current model is that RB uses these similarities to bind (and regulate) regulatory transcription factors that contact TBP and TFIIB.

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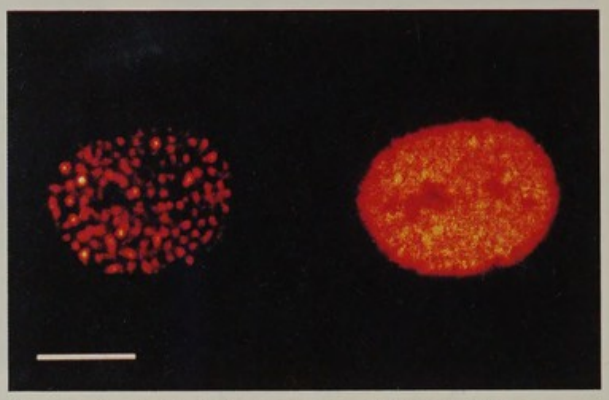
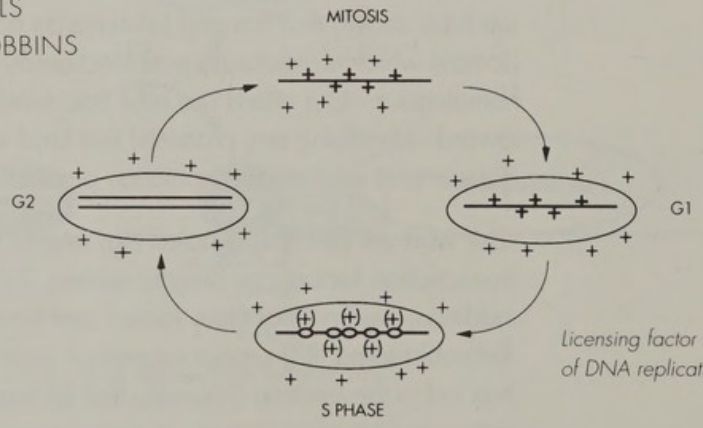
MARIE MACK
MARK MADINE
JOE MAKKERH
TONY MILLS
JACKIE ROBBINS



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.

PHILPOTT, A. and LENO, G.H. 1992. Nucleoplasmin remodels sperm chromatin in *Xenopus* egg extracts. **Cell 69**, 759-767.

See also nos. 12,13,14,38,39,40,41,43,48,49,50, page 40ff.

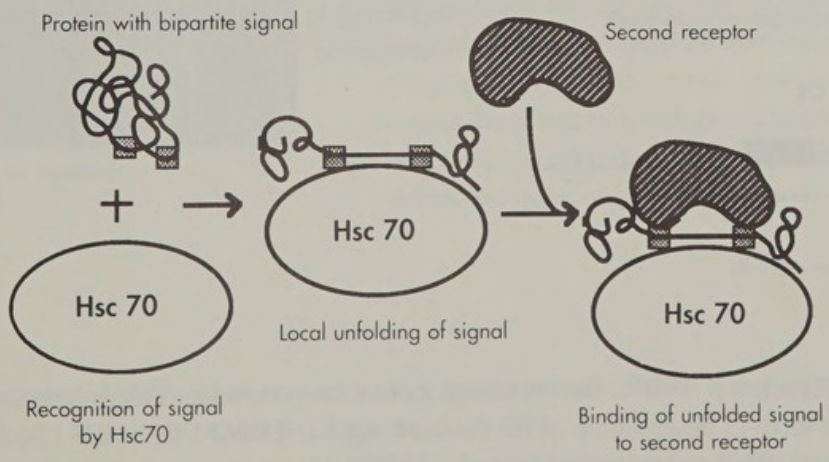
CONTROL OF EUKARYOTIC CHROMOSOME REPLICATION

We have analysed 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. These experiments have produced a possible assay for the hypothetical licensing factor.

In addition we have identified a bipartite class of nuclear targeting sequence which appears to be common in nuclear proteins and proposed that this might be recognised in a locally unfolded conformation by a member of the hsp 70 heat shock protein family. 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 by histones.

We have cloned and characterized the proto-oncogenes ski and A myb from *Xenopus* and found that A myb is expressed in ovary and testis in a manner which suggests it may be specific for proliferating germ cells.



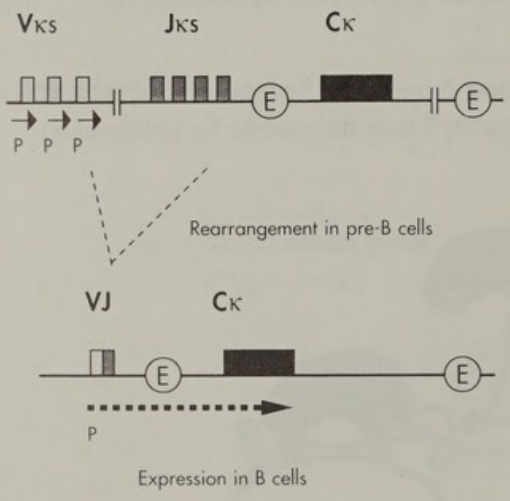
Signal presentation model for role of Hsc 70 in nuclear protein targeting

KERSTIN MEYER

REGULATION OF TRANSCRIPTION IN DEVELOPING B LYMPHOCYTES

During the development of a mature B cell from its precursor, immunoglobulin (Ig) genes undergo a complex pattern of gene rearrangement and subsequent expression. My work focuses on the activation of the Igκ gene at the developmental switch from a pre-B to a B cell. This involves further characterization of the 3' enhancer described in my previous work. The aim is to identify novel transcription factors that bind the enhancer and thereby contribute to stage and tissue-specific expression of the Igκ gene.

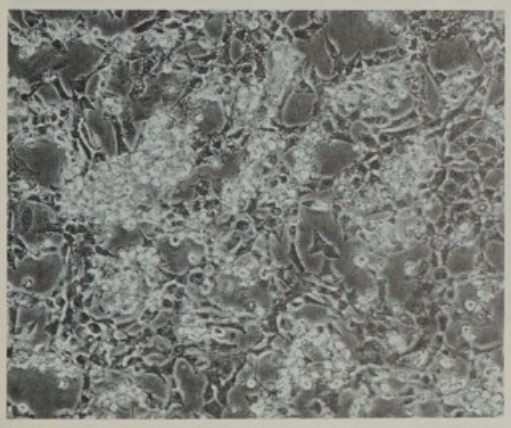
Furthermore, many transcription factors, like those belonging to the helix-loop-helix family, have to form dimers in order to bind DNA. The formation of either homo- or heterodimers is known to control their ability to activate transcription during the early stages of B cell development. The importance of dimerization in regulating Ig expression in more mature cells is being investigated.



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.

STEPHANIE WRIGHT

CRAIG LUCCARINI



Cells transformed by over expression of the c-myc oncogene

REGULATION OF PROTO-ONCOGENE EXPRESSION IN NORMAL AND TUMOR CELLS

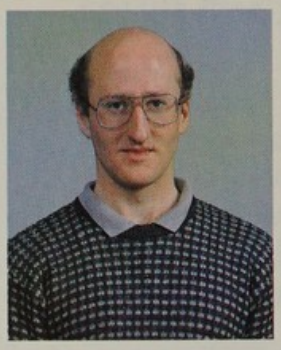
Regulation of the expression of a variety of proto-oncogenes is important in the control of normal cellular proliferation and differentiation; aberrant expression of proto-oncogenes is associated with the development of a variety of neoplasms.

We have shown that expression of the c-myc, c-myb and c-fos proto-oncogenes is controlled to a large extent by the modulation of transcriptional elongation through discrete sites of premature termination within the gene. We have defined common nucleotide sequences and features at sites of premature termination and are determining whether specific proteins interact with these regions. We are determining the mechanism whereby use of premature termination signals in different genes is regulated independently according to physiological signals that govern cellular proliferation and differentiation. In addition, we are defining the mechanism underlying the loss of ability to regulate termination within the c-myc gene in certain tumors. Lastly, we intend to assess the extent to which premature transcriptional termination is used as a general mechanism to control eukaryotic gene expression.

WRIGHT, S. and BISHOP, J.M. 1989. DNA sequences that mediate attenuation of transcription from the mouse proto-oncogene myc. **Proc. Natl. Acad. Sci. USA 86**, 505-509.

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

JONATHON PINES



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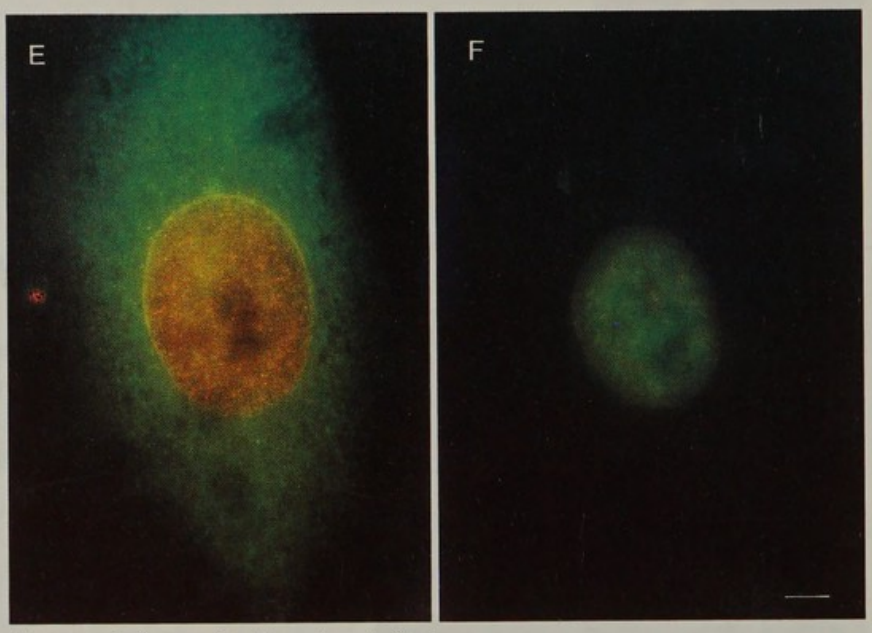


Human cyclin B moves into the nucleus at mitosis.

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.*

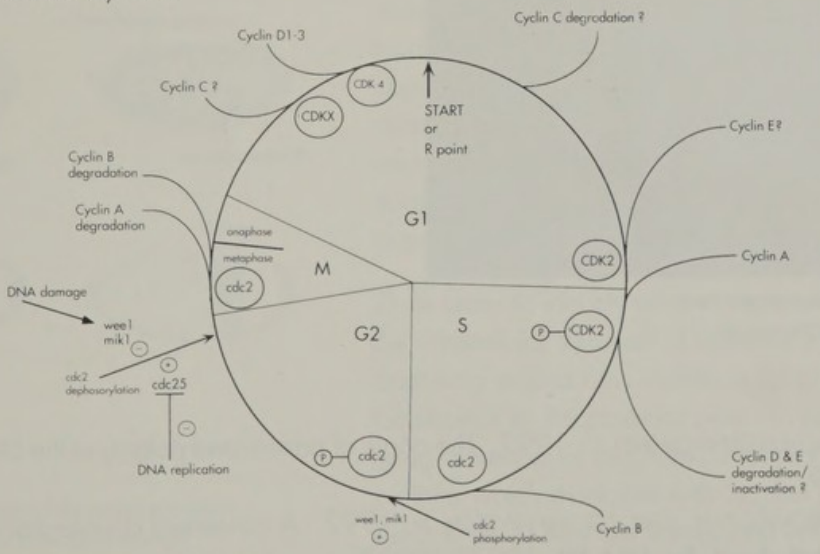
PINES, J. and HUNTER, T. 1990. Human cyclin A is adenovirus E1A associated protein p60 and behaves differently from cyclin B. **Nature 346**, 760-763.

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.

REGULATION OF 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 of the phases of the cell cycle are regulated by a family of protein kinases called the cyclin-dependent kinases (CDKs). These protein kinases share a high degree of structural homology and require a partner cyclin protein for their activity. Cyclins both activate and localise their CDK partner to the correct sub-cellular structures.

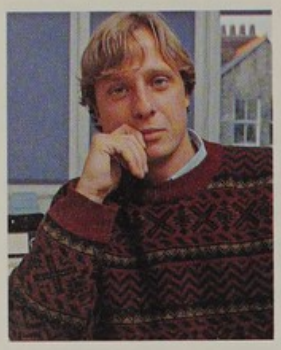
We wish to determine how cyclins localise different CDKs to particular parts of the cell. Our previous work has shown that cyclin A is a nuclear protein, and associated with a transcription factor complex. By contrast cyclin B is cytoplasmic throughout interphase but moves rapidly into the nucleus at the beginning of mitosis. During mitosis cyclin B 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 are creating various chimeric proteins and point mutations in the cyclins, expressing them in tissue culture cells and looking at their localisation, and we are searching for proteins that are able to interact specifically with 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



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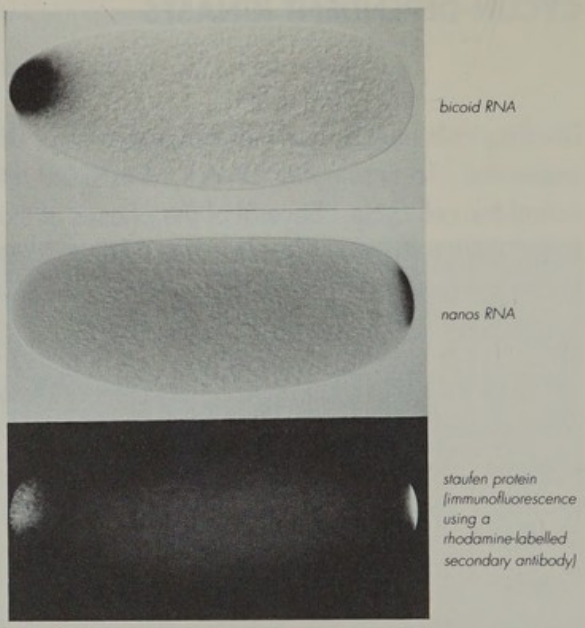
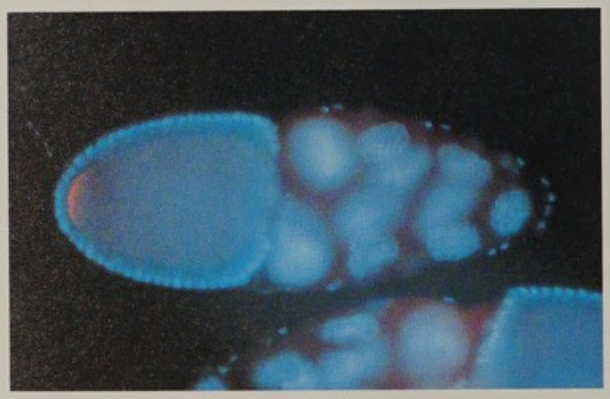
DAVID MICKLEM



The colocalisation of staufen protein with maternal RNAs at both poles of the egg



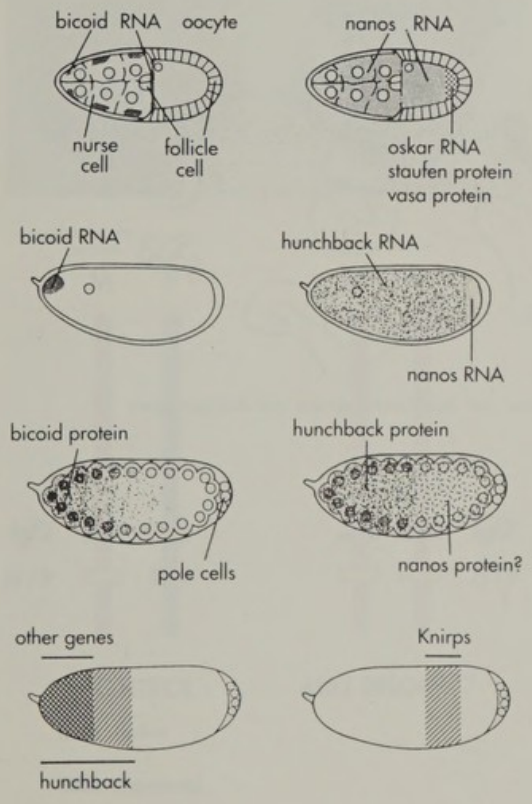
The localisation of staufen protein (red) to the posterior pole of the oocyte

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

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.

See also no. 15, page 40ff.

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 one of the primary body axes is controlled by cytoplasmic determinants which are localised in the unfertilised egg. These signals have been best characterized in *Drosophila*, where the pattern and polarity of the anterior-posterior axis is determined by the products of localised maternal mRNAs such as *bicoid* RNA which is localised to the anterior pole of the egg and *oskar* and *nanos* RNAs which are found at the posterior pole. Our group is taking several different approaches to investigate how these RNAs are localised during oogenesis.

1) The maternal gene *staufen* is required for both the anchoring of *bicoid* RNA at the anterior pole of the egg, and the transport of *oskar* RNA to the posterior pole. Staufen seems to act 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 might interact to bind to two different mRNAs in a sequence-specific manner .

2) In order to identify other components involved in the intracellular transport of maternal mRNA, we are analysing several new mutations which disrupt localisation to the posterior pole. In parallel, we are using a number of biochemical approaches to purify proteins which associate with Staufen protein and *oskar* RNA as they are transported within the egg.

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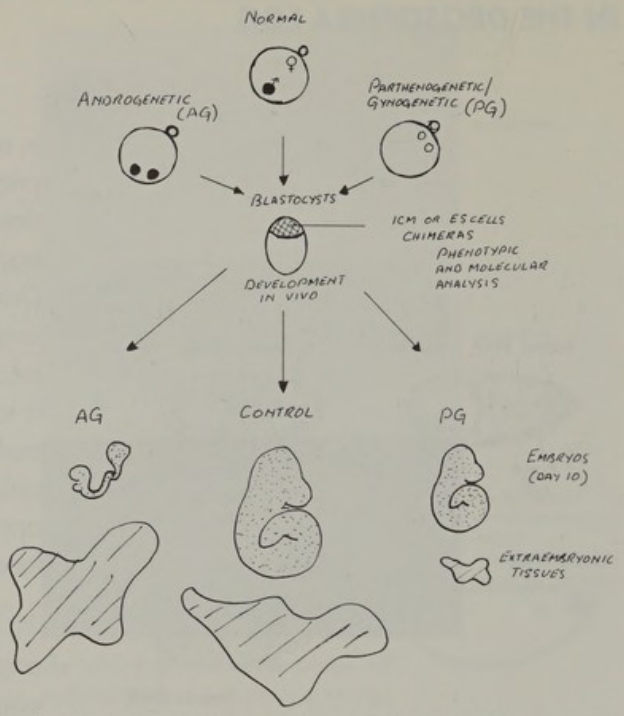
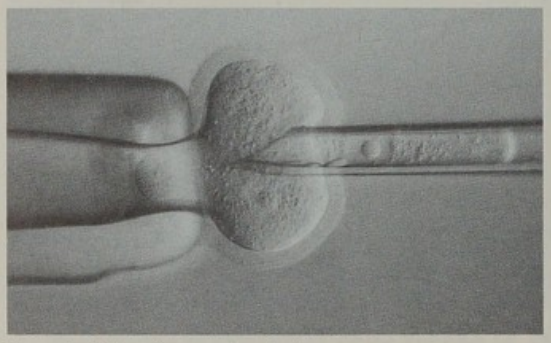


INFLUENCE OF IMPRINTED GENES ON DEVELOPMENT

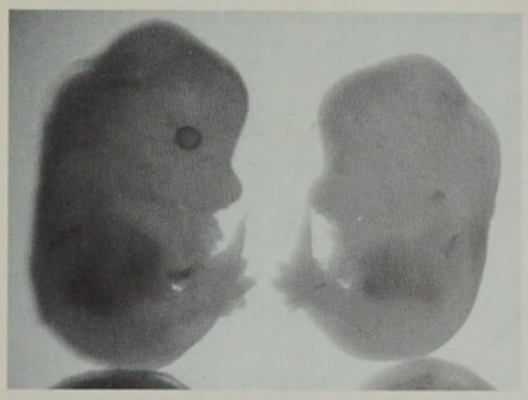


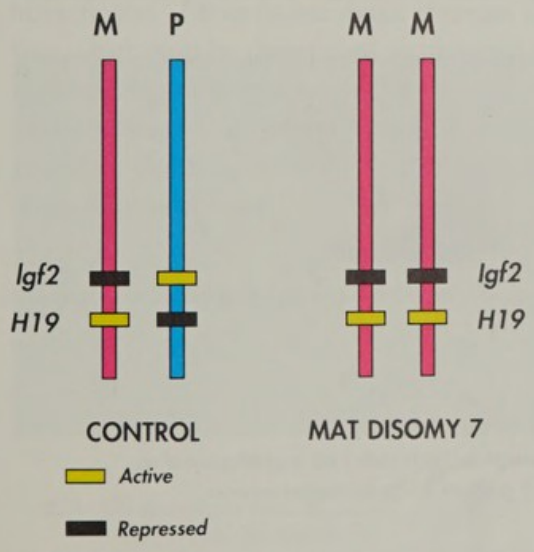
Transplantation of pronucleus in the mouse zygote

FERGUSON-SMITH, A., CATTANACH, B.M., BARTON, S.C., BEECHEY, C.V. and SURANI, M.A. 1991. Embryological and molecular investigations of parental imprinting on mouse chromosome 7. **Nature 351**, 667-670.

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.

MOUSE DEVELOPMENTAL GENETICS: GENOMIC IMPRINTING AND EPIGENETIC INHERITANCE FROM THE GERMLINE





Expression of imprinted genes: The paternal gene of Igf2 *and the maternal gene of* H19 *on distal chromosome 7 are expressed. In embryos with maternal duplication of the distal chromosome 7 (MatDi7), there is an excess of* H19 *and no* Igf2 *transcripts. These embryos die by day 16 of gestation.*

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.

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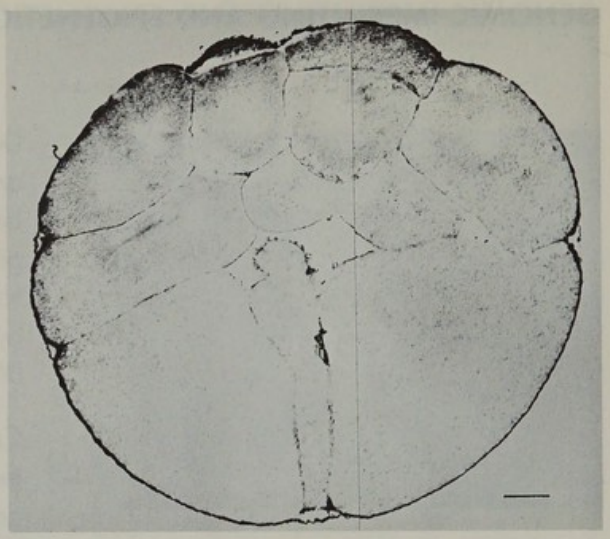
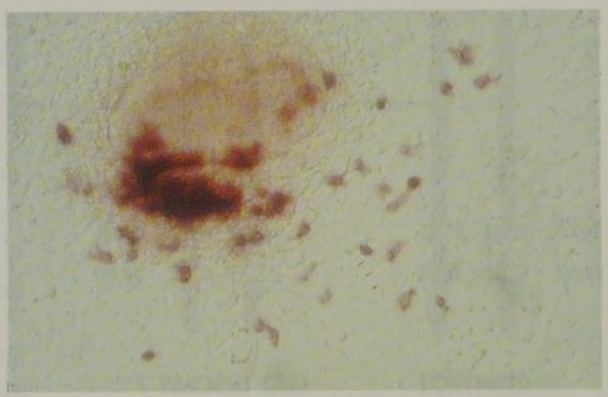
(COLIN SHARPE)



Antibody M4B stains the surface of cells of early Xenopus blastula



Mouse primordial germ cells (red) migrating out of an explant of gut from a 9½day mouse embryo

TORPEY, N.P., HEASMAN, J. and WYLIE, C.C. 1992. The function of maternal cytokeratin in *Xenopus* development. **Nature 357**, 413-415.

TURNER, A.P., BROWN, D., HEASMAN, J., COOK, G.M.W., EVANS, J., VICKERS, L. and WYLIE, C.C. 1992. Glycolipid-mediated cell adhesion in the early *Xenopus* embryo. **EMBO J. 11**, 3845-3856.

See also nos. 9,17,20,30,31,55,61, page 40ff.

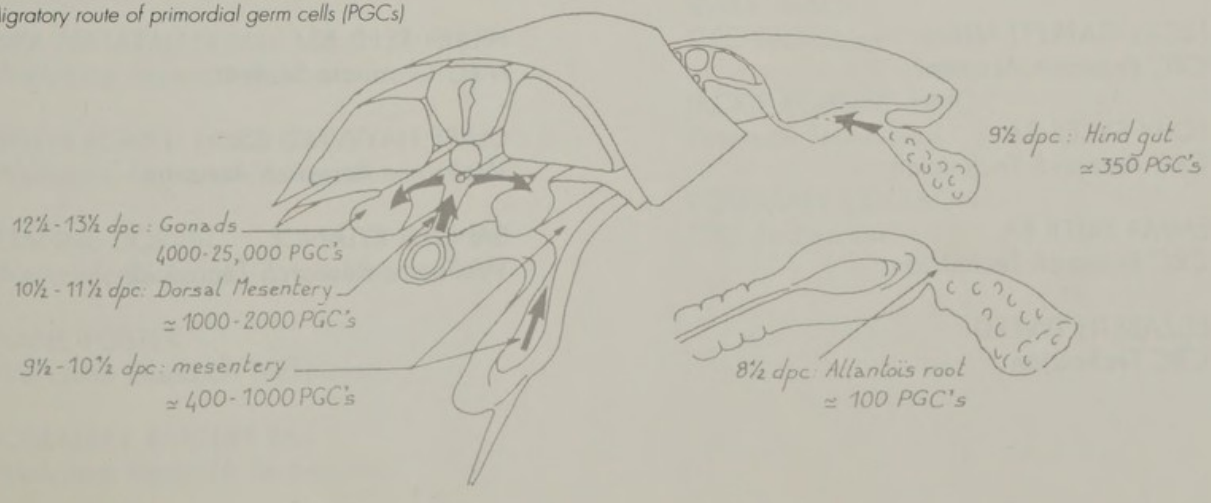
THE ESTABLISHMENT OF CELL BEHAVIOUR IN EARLY EMBRYOS

Morphogenesis is controlled by changes in cell behaviour. We study the molecules that underlie these changes, focusing on the cell surface and the cytoskeleton using two model systems.

1. **Primordial germ cells.** These give rise eventually to the functional gametes. In all vertebrates these cells migrate from elsewhere to the developing gonad. We are interested in the factors that control the survival, proliferation, migration, and targeting of these cells. Using an *in vitro* culture system we have identified several growth factors involved in their guidance (TGFβ), survival (Steel factor) and proliferation. We have also shown that germ cells modulate their adhesion to fibronectin during migration. These studies aim to show how the properties of a migratory cell population in the embryo are controlled.

2. ***Xenopus* oocytes and early embryos.** For the first 8 hours of *Xenopus* development there is no transcription. Nevertheless major changes occur at the cell surface and in the cytoskeleton during this time which must be dependent on maternal mRNAs and proteins. We have devised a technique to remove selectively from the oocyte specific mRNAs, and then to fertilise them to look for developmental abnormalities. We use this method to study the roles of intermediate filament proteins and cell surface proteins. We recently identified a novel cell surface molecule involved in cell adhesion during the first hours of development.

Migratory route of primordial germ cells (PGCs)



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INSTITUTE PUBLICATIONS

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OTHER ACTIVITIES

MICHAEL AKAM has been Chairman of the British Society for Developmental Biology since 1989.

JOHN GURDON is President of the International Society for Developmental Biology.

RON LASKEY is Subject Convenor for Cell and Developmental Biology, Academia Europaea.

CHRIS WYLIE has continued as Chief Editor of Development.

ACKNOWLEDGEMENTS

Photography by Peter Addis, Dudley Simons, Neville Taylor (colour printing by the Photographic Department of the Audio Visual Aids Unit of the University of Cambridge), and members of the Institute.

Prospectus designed and produced by Zoë Conway Morris.

Printed by Chapman & Harvey Limited Ely.

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