THE INSTITUTE IN 2007

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INTRODUCTION

Most readers of our Annual Report will know of the tragic death of Anne McLaren and her companion Donald Michie in July last year. Anne’s death is a huge loss to the Institute. Her scientific achievements were many, and have been described in previous issues of this Annual Report as well as in the many obituaries that were written after her death. But in addition to this we miss her enormous energy and enthusiasm, her modesty and her generosity, and her knowledge and wisdom. We missed these qualities particularly at our last annual retreat, an event at which she was well known for her ability to discuss science and then dance well into the night, outdoing many of her younger colleagues. In addition, as Director of the Institute I shall greatly miss Anne’s quiet wisdom and advice, and her remarkable ability to put matters into perspective. Elsewhere in this report Azim Surani and I discuss Anne’s life and work. Readers may also be interested in the page devoted to Anne on our web site, where one can read the many messages of remembrance that were received and also learn how to contribute to the memorial fund that has been set up in her name. See http://www.gurdon.cam.ac.uk/anne-mclaren.html.

Anne’s death overshadows everything that has happened in the Institute this year, but as usual our science flourishes and our colleagues’ work is being recognised by many awards and prizes. In particular, we were very pleased that a founder member of the Institute, Sir Martin Evans, was awarded the 2007 Nobel Prize in Physiology or Medicine. Martin shared the award with Drs Mario Capecchi and Oliver Smithies for their ‘discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells’. We send Martin our warmest congratulations.

Of our current colleagues, Azim Surani was honoured for his pioneering work on genomic imprinting and the specification of primordial germ cells by the award of a CBE and of the 36th Annual Lewis S Rosenstiel Award for Distinguished Work in Basic Medical Science, while Steve Jackson received the Biochemical Society’s GlaxoSmithKline Award and an honorary degree from the University of Nottingham, the city of his birth. Magdalena Zernicka-Goetz was elected to EMBO and Julie Ahringer to the Academy of Medical Sciences, and Andrea Brand was elected to the Herchel Smith Chair in Molecular Biology in this University. And finally John Gurdon was awarded the honorary degree of Doctor of Science by Cambridge University, the Saxén and Toivonen Memorial Medal and Prize, and was made an honorary member of both the British and American Anatomical Societies. We congratulate all these members of the Institute.

After announcing the departure last year of Enrique Amaya and Nancy Papalopulu to the University of Manchester, we are delighted to welcome a new Group Leader to the Institute, Dr Thomas Down. Thomas joins us from the Wellcome Trust Sanger Institute. He is a bioinformatician interested in the mechanisms by which programs of gene expression are defined during the development of multicellular organisms, and is particularly well known for his new motif discovery tool, NestedMICA. We welcome Thomas, and look forward to working with him.

The Institute’s International Scientific Advisory Board visited the Institute at the end of November 2007. As usual the visit was enjoyable, thought provoking and helpful, and we thank the members of the Board, listed at the end of this report, for their hard work in helping to maintain the Institute’s scientific excellence.
HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance from the centre of the historic city. Founded in 1989 to promote research in the areas of developmental biology and cancer biology, the Institute 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, including stem cells, acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intra- and intercellular processes, which need to be analysed at the cellular and molecular levels. These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master, including molecular biology, biochemistry, microarray technology, bioinformatics, cell culture, imaging and embryonic manipulations. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another, as is the case in the Institute.

The Institute is an integrated part of Cambridge University, and all Group Leaders are also members of another University Department within the School of Biological Sciences and contribute to both undergraduate and graduate student teaching.

CENTRAL SUPPORT SERVICES

The Institute’s ‘core staff’ provides essential administrative, technical and computing support to our scientists, so that the scientists can spend as much time as possible on their research. We thank these colleagues for their flexible, helpful and positive attitude to their work, which has contributed in no small part to the smooth running of the Institute.
FUNDING

Our two major funding bodies, the Wellcome Trust and Cancer Research UK, continue to offer the Institute vital backing in the form of Fellowships, individual project grants, and programme and equipment grants, in addition to our invaluable core funding.

Other sources of financial support, both direct and indirect, include the European Union, the BBSRC, the MRC, the Royal Society, the Department of Trade and Industry, the Isaac Newton Trust, NIH, the European Molecular Biology Organisation, the National Alliance for Autism Research, KuDos, Volkswagen Stiftung, Applera Corporation and the March of Dimes. We are extremely grateful to all these organisations for their continuing support.

The University has also been very generous in its support of the Institute, particularly in funding equipment for the new building.

RETREAT

Our Annual Retreat this year was held for the first time at the University of Leicester on 27th and 28th September 2007; this provided an excellent venue, allowing members of the Institute every opportunity to interact both scientifically and socially. As always there was a strong attendance and we are grateful to the administrative team and to Jon Pines and Magdalena Zernicka-Goetz for organising it.

The Institute in Leicester, 2007. Photograph by John Overton (Brown group, front row right)
On 6 July, Anne McLaren spent a busy day at the Gurdon Institute in Cambridge, where she had worked since 1992. She prepared a talk for a meeting in Germany and answered a large number of e-mails. In the afternoon, she attended a group leaders’ meeting, as always paying close attention and ready to offer sensible advice. Towards the end of the day, she chatted with colleagues and asked questions about some recent stem-cell publications. She left promising to continue the discussion. Sadly, this was to be her last working day.

Anne McLaren had an extraordinary life, both personally and professionally. The daughter of industrialist Henry McLaren, Second Baron Aberconway, and his wife Christabel McNaughten, in 1945 she embarked on the study of zoology at the University of Oxford because for her this was an easier option than reading English, for which the entrance examination required too much reading in too little time. She completed her doctoral studies in 1952, and moved to University College London. There she began her studies on mouse genetics and reproduction with her colleague Donald Michie, whom she married that same year.

Initially, McLaren’s research interest was in the interactions between genes and the environment. One of her findings — now often ignored in bioassays and drug testing in mice — demonstrated that, compared with the offspring of a cross-strain mating, inbred strains of mice showed greater variability in their response to stress. These ideas were elegantly recaptured in a review, “Too late for the midwife toad”, written more than 40 years later. The article encompasses not only Conrad Waddington’s theories of canalisation and the inheritance of apparently acquired characteristics, but also the recent molecular explanations for morphological evolution based on studies in flies.

But McLaren’s abiding interest in “everything involved with getting from one generation to the next” began with an observation on the differences in the number of lumbar vertebrae in two strains of inbred mice. She wanted to know whether such variability was due to inherent differences between the embryos of the two strains or because of differences in their uterine environments. To answer this question, McLaren and her colleagues induced ovulation in mice, retrieved fertilised embryos from one strain and transferred them into females of the other. They found that the uterine environment influences the outcome.

This work was the precursor to a collaboration with John Biggers, with whom she showed that early mouse embryos could be cultured for a day or two in vitro and go on to develop into adult animals after transplantation into the uteri of surrogate females. This study was to capture the public imagination. And it provided an essential backdrop to reproductive research in humans that led to the development of in vitro fertilisation.

McLaren continued her flourishing work on reproductive biology and early development at the ARC Unit of Animal Genetics in Edinburgh, and in 1974 she returned to University College London as the director of the newly established MRC Mammalian Development Unit. During this period,
McLaren held many prominent offices. She was the first female officer of the Royal Society, serving as its foreign secretary from 1991 to 1996. In this capacity, she travelled extensively to stimulate and promote excellence in science. No matter where she went, she travelled with a single rucksack and a plastic bag full of research papers. Among many other offices, she was president of the British Association for the Advancement of Science, the Association for Women in Science and Engineering, and the British Fertility Society. In all of these capacities, McLaren particularly enjoyed the opportunity to engage with young and aspiring scientists. Indeed, she was an enthusiastic and popular teacher at the annual Mouse Embryology Course at Cold Spring Harbor Laboratory in New York.

She received many awards and prizes for her work; she was elected to the Royal Society in 1975 and received its Gold Medal in 1990. She was also a joint recipient of the Japan Prize, and of the March of Dimes Prize in Developmental Biology.

Anne McLaren was frugal in her personal life, but displayed great generosity towards those who sought her help; she always had a spare bed for a visitor or student who needed a refuge. She was passionate about social justice, and frequently emphasised that scientific advances should be for the welfare of all. She was a member of the Communist Party of Great Britain during the cold war, was committed to socialism, and enthusiastically participated in antiwar demonstrations. At the ceremony at which she received her joint award of the Japan Prize, Anne chose to hear Where have all the flowers gone? sung by Joan Baez as “a lament for all wars”, and John Lennon’s Imagine, which she said is “about a world of peace and love and social harmony”.

McLaren and Michie had three children together. Although they had divorced in 1959, they remained good friends and started to live together again in 2005. They died together in a car accident on 7 July 2007, while travelling from Cambridge to London. Memorial funds in support of young scientists have been established in their memories.

Azim Surani and Jim Smith, August 2007

See also: http://www.gurdon.cam.ac.uk/anne-mclaren.html

She wrote two highly influential books: *Mammalian Chimaeras* (1976) and *Germ Cells and Soma* (1981). She became increasingly interested in germ cells — the cells involved in reproduction — which she described as “the most fascinating cells of all”. She was also interested in sex determination, genetic imprinting and the X chromosome.

McLaren’s knowledge and wisdom made her a valuable member of many societies and committees. Of particular significance was her membership of the Warnock Committee, which advised the British parliament on potential developments in reproductive medicine and subsequently led to the 1990 Human Fertilisation and Embryology Act. For ten years, McLaren served with the Human Fertilisation and Embryology Authority, which regulated the practice of human in vitro fertilisation in Britain, and she continued to participate in many important debates on the ethics of reproductive technologies and stem cells. However, her concerns were not restricted to human welfare — she was also a co-founder of the Frozen Ark Project, which aims to collect the DNA and cells of endangered animals before they become extinct.

“In so many ways, Anne McLaren embodied the spirit of the Pugwash community and its fundamental credo, drawn from the Russell-Einstein Manifesto, of the social responsibility of scientists. Anne’s tenure on the Pugwash Council was marked by her liveliness of spirit, independence of thought, and warm collegiality. We will greatly miss her contributions to our work, while knowing full well that Anne transmitted these qualities to succeeding generations of scientists who will follow her.”

*Members of the Pugwash Conferences on Science and World Affairs*
Julie Ahringer

Developmental roles of chromatin regulatory complexes and the control of cell polarity

Co-workers: Yan Dong, Bruno Fievet, Paulina Kolasinska-Zwierz, Isabel Latorre, Costanza Panbianco, Stefania Ragone, David Rivers, Josana Rodriguez, Christine Turner, Shane Woods, Kathleen Xie

Our research is focused on two different biological questions: First, how is cell polarity established in the embryo and this information then transduced within the cell? Second, what are the functions of chromatin regulatory complexes in a developmental context? For both of these studies, we are taking advantage of a genome-wide RNAi library that we have constructed.

Cell polarity is an essential feature of most animal cells. For example, it is critical for epithelial formation and function and for correct partitioning of fate-determining molecules. In *C. elegans*, cell polarity is established during the first cell cycle and results in an asymmetric first division. Embryos are large and transparent, making these events easily visualised. Using genome-wide RNAi screening coupled with videomicroscopy of live embryos, we identified many new conserved cell-polarity genes, which we study using genetics, biochemistry, and real-time fluorescent cell imaging.

Transcriptional control is mediated through multiprotein chromatin regulatory complexes. However, little is known about the developmental roles and regulation of these complexes. In *C. elegans*, “synMuv” genes, which function together in several developmental contexts, encode components of different chromatin regulatory complexes, including the histone deacetylase complex NuRD, the retinoblastoma-containing complex Myb-MuvB and a TIP60 histone acetyltransferase complex. We are studying the function of these proteins in transcriptional control and development, and their relationships to each other using microarray expression profiling, chromatin immunoprecipitation and other techniques.

(Inset left): Expression profiling of synMuv mutants using microarrays shows widespread gene expression changes compared to wild-type (dark red and dark blue colour in last row).


For complete list of this lab’s publications since the last report, see numbers 5, 24, 54, 84 & 85 on pp 54-59
Abnormal distributions of polarity proteins PAR-3 (red) and PAR-2 (green) after RNAi of genes involved in establishing embryonic polarity. Top, wild-type, mutants below.

PAR proteins control cell cycle timing through generating asymmetry of the key cell cycle regulators Polo-like kinase PLK-1 and the CDK phosphatase CDC-25.1.

Early endosomes (green) are asymmetrically distributed in the one-celled embryo and are coincident with the domain of non-muscle myosin NMY-2 (red).

synMuv genes fall into functionally redundant genetic classes, as shown. Most synMuv genes encode homologs of chromatin regulators found in multiprotein complexes that modify histones or move nucleosomes.
Stem cells have the remarkable ability to give rise to both self-renewing and differentiating daughter cells. *Drosophila* neural stem cells segregate cell fate determinants from the self-renewing stem cell to the differentiating daughter at each division. We have shown that one such determinant, the homeodomain transcription factor Prospero, regulates the choice between self-renewal and differentiation. We identified the *in vivo* binding sites of Prospero throughout the genome and demonstrated, by expression profiling on DNA microarrays, that Prospero represses genes required for self-renewal and, surprisingly, is also required to activate genes for terminal differentiation. We have shown that Prospero acts as a binary switch between self-renewal and differentiation. In the absence of Prospero, differentiating daughters revert to a stem cell-like fate: they express markers of self-renewal, proliferate, fail to differentiate and form small tumours. By identifying neural stem cell-specific genes, and genes specific for differentiating daughters, we can begin to assess the potential for redirecting post-mitotic cells to divide in a regenerative manner, or to induce stem cells to differentiate.

In vertebrates, adult neural stem cells can proliferate in response to injury. We have discovered that *Drosophila* ventral midline cells, which normally divide only once, can undergo an extra cell division if a sibling midline cell is destroyed. Remarkably, the regenerated midline cell differentiates appropriately to replace the damaged cell. We aim to uncover the molecules that enable, or inhibit, neural regeneration. These molecules will be key targets for mutagenesis and targeted misexpression, as well as potential drug targets.

Further information is available on the Brand Lab website: [http://www.gurdon.cam.ac.uk/~brandlab](http://www.gurdon.cam.ac.uk/~brandlab)

Inset left: A brain lobe from a *Drosophila* third instar larva labelled with Dlg (red), BrdU (green) and DAPI (blue).
A neuromuscular synapse with synaptic boutons labelled in green, axon microtubules in red, and muscle actin in blue.

Three-dimensional visualisation of single cell clones in the adult brain. Dendritic and axonal projections are depicted in grey, cell nuclei in yellow, and cell outlines in blue.

Genome-wide mapping of transcription factor binding sites using the DamID technique.

Neural stem cells in the larval brain: on the right can be seen the symmetrically dividing neuroepithelial cells and asymmetrically dividing neuroblasts of the optic lobe, on the left, the large neuroblasts of the central brain (Dlg, green; L'sc, red; DNA, blue).
Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, which stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one family of cell surface receptors, called integrins, can perform both of these activities, and therefore provide a molecular link between cell adhesion and signalling. Our research is focused on determining how proteins inside and outside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers, and cell differentiation.

We use the genetics of the fruit fly *Drosophila* to elucidate integrin function within the developing animal, and to identify the proteins that work with integrins. The isolation of mutations in genes encoding proteins required for integrin function has been achieved using both forward genetics to identify genes that, like integrins, are required for adhesion between the two surfaces of the wing (inset picture), and using reverse-genetics to isolate mutations in genes encoding proteins that are associated with integrins in mammalian cells, such as paxillin (Fig 1). While some of these proteins are required in all cells where integrins function, others such as Bloated are restricted to epidermal cells (Fig 2). We continue to discover new functions for integrins in developmental processes, such as the anchoring of the hub cells, which provide the signals that maintain the stem cell character of the germ cells, to one end of the testes (Fig 3).

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For complete list of this lab’s publications since the last report, see numbers 18, 19, 23, 33 & 80 on pp 54-59
Fig 1: A major site of integrin function within the developing embryo is the muscle attachment site. Muscle myosin (red) shows the muscles, with integrins (blue) concentrated at the muscle ends, where they recruit a number of proteins that help link integrins to the cytoskeleton, such as paxillin (green).

Fig 2: Bloated, a novel integrin-associated protein, is part of a cytoskeletal structure within specialised epidermal cells (called tendon cells), which transmits force from the muscles to the exoskeleton. The figure shows the epidermis of a larva containing two *Drosophila* proteins that have been fused to green fluorescent protein (GFP); the green fluorescence (in white) shows the distribution of these proteins. Cadherin-GFP is at the plasma membrane, and shows the outline of all epidermal cells. Bloated-GFP is found in bright dots in the middle of a subset of cells (the tendon cells) which corresponds to the position of the cytoskeletal structure.

Fig 3: The hub cells (green) are normally anchored at one side of the gonad (left panel), where they signal to the germ line cells (blue); if integrins are not present, (right panel) the hub cells move into the middle.
We study the mechanisms by which programs of gene expression are selected during the development of multicellular organisms. Regulatory sequences contain clusters of binding sites for transcription factors, most of which interact with some specific DNA sequence motif. By discovering the repertoire of transcription factor binding sites, we can uncover an important part of the cell’s regulatory network. We are addressing this question using a new computational motif discovery tool, NestedMICA, to find DNA sequence motifs that are over-represented in larger sets of regulatory sequences from across the genome. Using this strategy, we have found 200 distinct candidate motifs in the fruitfly Drosophila, and can link many of them to specific patterns of embryonic gene expression. We are now applying the same strategy to other species. Results from this project will be made available via the BioTIFFIN database.

We would also like to understand how particular patterns of gene expression are stably maintained over time -- for instance, when a cell becomes committed to a particular developmental lineage. To this end, we are involved in studies of stable epigenetic modifications: particularly DNA cytosine methylation. New sequencing technologies allow epigenetic modifications to be studied on a genome wide basis. In the coming year, we hope to find out more about how the different modifications interact with one another, and with the machinery of transcription regulation.

Down TA and Hubbard TJP (2002) Computational detection and location of transcription start sites in mammalian genomic DNA. Genome Res 12:458-461


For complete list of this lab’s publications since the last report, see numbers 12, 25 & 63 on pp 54-59
A regulatory motif discovered from the *Drosophila* genome, and the embryonic expression pattern of a gene regulated by this motif. (P Tomancak et al. Genome Biology 3:research0088)

The Methyl DNA Immunoprecipitation (MeDIP) technique can be used to quantify the methylation state of genomic DNA on a large scale.

The BioTIFFIN interface for browsing regulatory sequence motifs.

Visualisation of DNA methylation state on the Ensembl genome browser; with yellow indicating unmethylated sequences and blue indicating highly methylated regions.
Embryonic stem cells have the remarkable property of being able to proliferate indefinitely or to differentiate into every different kind of cell-type. This makes them an ideal cell type for replacement therapy, if such cells can be derived from the accessible cells of adult humans. The direct conversion of adult skin cells to ES cells has been achieved by others but only at a very low frequency. Somatic cell nuclear transfer to eggs also achieves the production of ES cells from adult somatic cells. In Amphibia, the derivation of one cell type such as muscle or nerve from another unrelated tissue such as intestine never normally occurs. However, this process, which involves nuclear reprogramming, is relatively efficient by nuclear transfer, since this kind of switch in cell type is seen in up to 30% of all experiments.

We use growing amphibian oocytes to analyse the molecular basis of nuclear reprogramming. Oocytes have the special property of directly switching the transcriptional profile of an adult somatic cell nucleus to that of an embryo or stem cell. They do this directly, with no DNA synthesis or cell division and in the absence of protein synthesis; within a few hours, transcripts of Oct4, Nanog, and other stem cell marker genes increase by a factor of up to 100 times. To achieve this, somatic nuclei of mammals and other vertebrates are injected into the germinal vesicle of an oocyte. We analyse the DNA-association and exchange of DNA-binding proteins both by molecular methods and by fluorescence microscopy at the single nucleus level in real time. The long-term aim is to use molecules and mechanisms of eggs and oocytes to improve the efficiency of direct nuclear reprogramming in somatic cells. We hope to understand how to reverse the process of cell differentiation, and also to define more clearly the differentiated state of somatic cells.

Inset left: A growing (first mitotic prophase) oocyte of Xenopus with an injection needle.
A reporter DNA plasmic construct containing multiple repeats of protein binding sequences.

RT-PCR analysis of nuclear reprogramming.

Confocal monitoring of gene transcription in somatic nuclei undergoing reprogramming.
Our work focuses on the DNA-damage response (DDR): the set of events that optimises cell survival by detecting DNA damage, signalling its presence and mediating its repair. By working with both yeast and human cells, we aim to determine how these events occur, and how they are controlled and coordinated.

Much of our research concerns processes regulated by the DDR kinases ATM, ATR and DNA-PKcs. Previously, we showed that ATM and the MRN complex promote processing of DNA double-strand breaks (DSBs) into structures that activate ATR. Building on this, we recently discovered that the human CtIP protein physically and functionally interacts with the MRN complex to mediate DSB processing, ATR activation and DNA repair by homologous recombination. Furthermore, we discovered that CtIP has sequence homology with Sae2, which controls MRN-dependent DSB processing in yeast, thus highlighting the importance and evolutionary conservation of CtIP/Sae2-like proteins.

In collaboration with the laboratory of Daniel Durocher, we established that the human RNF8 protein promotes the G2/M DNA damage checkpoint and resistance to ionising radiation, and that RNF8 forms ubiquitin chains at sites of DNA damage that are required for recruitment of the DDR factors 53BP1 and BRCA1. Furthermore, we showed that RNF8 is itself recruited to DNA damage via its phospho-dependent interactions with ATM-target motifs in the MDC1 protein.

Finally, we discovered that the yeast Rtt109 protein is a histone acetyl-transferase required for genome stability and resistance to DNA-damaging agents. This further underlines the key links that exist between the DDR and the control of chromatin structure.


For complete list of this lab’s publications since the last report, see numbers 2, 9, 20, 26, 35, 40, 44, 52, 70 & 86 on pp 54-59
**Fig 1:** Common DNA-damage recruitment and activation mechanisms for ATM, DNA-PKcs and ATR. These proteins are recruited and activated at sites of damage through interactions with their partner proteins – NBS1 that is part of the MRE11-RAD50-NBS1 (MRN) complex, Ku80 and ATRIP – to bring about DDR signalling or repair, as indicated. Model derived from Falck J, Coates J, Jackson SP. (2005). Nature 434:605-611.

**Fig 2:** Cell-cycle coordination of DSB signalling and repair. In G1, cells carry out little DSB resection, leading to activation of ATM-dependent signalling and DSB repair by non-homologous end-joining (NHEJ). In S and G2 cells, ATM signalling also occurs but in these circumstances, CtIP – in conjunction with the MRN complex – promotes DSB processing to generate single-stranded DNA that triggers ATR activation and leads to repair by homologous recombination (HR).

**Fig 3:** Model for the mode of action of RNF8 at DSBs. Following recruitment to DBSs by ATM-phosphorylated MDC1, RNF8 ubiquitinates an unknown protein (X). Ubiquitination is required for the subsequent recruitment and retention of the repair factors RAP80-BRCA1 and 53BP1. These findings thus reveal how the DDR is controlled by both ATM-dependent phosphorylation of MDC1 and RNF8-mediated ubiquitination.
Our group is interested in defining the mechanisms by which chromatin modifications function to regulate cellular processes. Our attention is focused on a set of enzymes (acetylases, deacetylases, methylases and kinases), which regulate transcription by covalently modifying histones. We would like to understand what biological processes these enzymes control and the precise role of each modification on chromatin dynamics. In addition, a number of chromatin-modifying enzymes have been implicated in the genesis of cancer so we are dissecting, as far as possible, the pathways misregulated in cancer cells.

We are taking a number of complementary approaches in both yeast and human cells to characterise chromatin modifications. We use yeast as a model system whenever possible, to investigate their mechanism of action. The recently developed Chromatin Immunoprecipitation-sequencing technology is used to map the global position of histone modifications in both yeast and human cells. Recombinant nucleosome arrays carrying specific modifications are being constructed, in order to understand how they affect compaction of chromatin.

Histones are very highly modified. Despite their abundance, we believe that more modifications are likely to exist on histones. This complexity is probably necessary because histones integrate many signalling pathways with biological processes involving DNA metabolism and function. A major drive at the moment is to identify new histone modifications, as the pathways that control them may well be deregulated in cancer. In recent years, we have identified two novel pathways that modify chromatin, arginine deimination and proline isomerisation. Both of these modifications appear to have a negative effect on transcription. Most recently we have defined a new arginine methylation pathway that modifies histone H3R2. This methylation acts to inhibit the enzyme which tri-methylates H3K4 and therefore is a gatekeeper for transcriptional activation.


For complete list of this lab’s publications since the last report, see numbers 6, 7, 15, 39, 41, 42, 57 & 86 on pp 54-59
Isomerisation of proline 38 in the histone H3 tail has the potential to bend the tail and affect chromatin structure.

Genomic pattern of methylation at all currently known methylation sites in yeast (part of chromosome 1 shown).

Methylation of H3R2 prevents the binding of the SPP1 component of the Set1 methylase complex and in doing so controls the deposition of H3K4 tri-methylation and subsequent gene activity.
The neocortex is the part of the mammalian brain that integrates sensations, executes decisions and is responsible for cognition and perception. Altered neocortical development results in a range of human diseases, including epilepsy and learning disabilities. Neocortical neurons have two identities that dictate their connections. They belong to one of six layers of neurons, each of which is generated in a stereotyped order, and each of which has characteristic connectivity to other layers and parts in the cortex and to subcortical parts of the nervous system. Cortical neurons also belong to a discrete piece or area of the cortex that is dedicated to a single function, such as visual processing or motor control, and this also dictates the long-range connectivity of cortical neurons so that those areas communicate effectively with one another and subcortical structures.

All of the neurons in the cortex are generated from a population of multipotent neocortical stem and progenitor cells. The majority of the research in the lab centres on the biology of neocortical stem cells and in particular how neocortical stem cells produce layer-specific neurons in order (the timing problem) and for the correct area (the patterning problem). Our current work on the patterning problem is focused on how a transcription factor-based map that controls spatial identity is set up in neocortical stem cells and subsequently used to produce spatially discrete populations of neurons. Current projects include characterisation of how the transcription factor map is generated and how the gradient-based map is used to generate spatially discrete populations of neurons. For example, we are identifying the target genes of each transcription factor by combining in vivo location analysis by chromatin-IP (ChIP-on-chip and ChIP-seq) with gene expression profiling.

How neurons for specific layers are generated in order is a timing problem, in that it is controlled by a cellular mechanism intrinsic to neocortical stem cells. Our work in this area concentrates on testing candidate genes and mechanisms for controlling developmental timing in neocortical stem cells in vivo. Examples of projects in this area include generating mice mutant for key transcription factors regulating timing in the cortex and studies of the roles of epigenetic, chromatin-based processes in controlling self-renewal, neurogenesis and cell fate determination.


For an additional publication since the last report, see number 69 on pp 54-59
Cortical neural stem cells in monolayer culture.

Cortical neurons (green, GFP) migrating and differentiating in slice culture.

Layer 5 and 6 neurons (green) and their thalamic projections (red).

Coronal section of the embryonic mouse forebrain, showing the position of neocortical stem cells (red) and post-mitotic neurons (green).
Cytokinesis is essential for cell proliferation. Failure of cytokinesis leads to aneuploidy or chromosomal instability, which has been associated with human cancers. Successful cytokinesis relies on a dynamic interplay between microtubules, the actin cytoskeleton, and membrane compartments under the control of the cell cycle machinery. In spite of its importance, the molecular mechanism of cytokinesis in animal cells has not yet been fully clarified.

We would like to understand cytokinesis more fully, in terms of the dynamic assembly of molecular machinery. The central spindle is a microtubule-based molecular assembly that forms between the segregating chromosomes during anaphase. During telophase, it associates with the ingressing cleavage furrow and matures into the midbody. These microtubule-based structures have crucial roles through all the steps of cytokinesis from initiation to completion. We will address the following questions:

• How is the central spindle/midbody assembled?

• How does the central spindle/midbody contribute to the progression of cytokinesis at the molecular level?

We will focus on centralspindlin, a stable protein complex of a mitotic kinesin-like protein and a Rho-family GTPase-activating protein (RhoGAP), which is crucial for assembly of the central spindle and the midbody. We will characterise the dynamic behaviour of centralspindlin and investigate centralspindlin-interacting proteins by using mammalian cultured cells and Caenorhabditis elegans embryos as model systems. In addition to biochemical and genetical analyses, live imaging both at single molecule level in vitro and at subcellular level in vivo will be performed. We will also develop experimental strategies to (in)activate molecules of interest in vivo in a reasonable time resolution to dissect the molecular mechanism of cytokinesis.

Inset left: A C. elegans embryo finishing cytokinesis. Centralspindlin (red) is highly concentrated to the midbody when chromosomes are reforming nuclei (cyan).

For an additional publication since the last report, see number 60 on pp 54-59
Centralspindlin is an evolutionarily conserved protein complex of a mitotic kinesin and a RhoGAP critical for the assembly of the central spindle. Being in a complex is essential both for the formation of the central spindle and for the in vitro microtubule-bundling activity. When incubated with microtubules, the complex causes the strong bundling of microtubules (arrowheads), while neither the kinesin subunit alone nor the RhoGAP subunit alone does.

Centralspindlin dramatically changes its localisation at metaphase/anaphase transition under the control of a master cell-cycle regulating protein kinase, CDK1. The kinesin subunit is phosphorylated by CDK1 at the sites flanking its catalytic core (P). This phosphorylation reduces the affinity for microtubules and contributes to the prevention of premature formation of the central spindle before anaphase onset, ensuring proper segregation of genetic materials.
The recent discovery of microRNAs has added a completely new dimension to the control of eukaryotic gene expression. MicroRNAs are a large class of 18-26 nucleotide short regulatory RNAs. Approximately 1% of all known human genes encode microRNAs, but very little is known about their biological roles. Our laboratory is interested in understanding how microRNAs contribute to the determination of cell fate, i.e., the decision to divide, die or differentiate, and how deregulation of microRNAs may contribute to disease, in particular to cancer.

We use the powerful genetics of the nematode Caenorhabditis elegans to study the function of microRNAs. Our starting point is a collection of microRNA knockout strains covering the majority of all known microRNA genes in this organism. To place microRNAs into biological pathways we combine phenotypic analysis, expression studies, genetic screens and bioinformatics.

We are also interested in the mechanism of microRNA action. Currently we are focusing on the Argonaute family of RNA-binding proteins, which have been implicated in both the mechanism of RNAi and microRNA pathways. Of particular interest to us are the orthologues of two Drosophila Argonaute family members, Aubergine and Piwi that define germ line identity in the fly. We use a combination of biochemical and genetic approaches to understand their function.

In invertebrates microRNAs have been implicated as regulators of developmental timing (e.g., lin-4), neuronal differentiation, cell proliferation, programmed cell death and fat metabolism. In contrast, no in vivo function for any microRNA has been established in mammals. To help uncover the biological roles of microRNAs in mammals we first ask the question where and when microRNAs are expressed using microarray profiling. One focus is the analysis of microRNA expression in primary human tumours. This work is being carried out as a collaboration with the Cancer Genomics Group at the Broad Institute of MIT, and Harvard.

Inset left: We have developed microRNA microarrays to profile microRNA expression in C. elegans and mammals (insert). We compare the expression of microRNAs in different tissues, at different stages during development and under a variety of physiological conditions to understand where microRNAs act and how their expression is regulated. Shown here is a correlation heat map.


For complete list of this lab’s publications since the last report, see numbers 3, 13, 46, 54, 58 & 66 on pp 54-59
The first microRNA to be identified was the product of the *C elegans* gene *lin-4*. Loss of function of *lin-4* leads to an over-proliferation defect of the seam cells, which are part of the outer epithelial covering of the worm. The cell divisions of the first larval stage (1) are reiterated in these mutants: 1, 1, 1, 1, …

A: we are using a functional genomics approach in *Caenorhabditis elegans* to study microRNA function.

B: the microRNA miR-84 is expressed in a number of cell types including the seam cells, as assayed by a GFP reporter in the living animal.

Short RNAs as key players of gene regulation: Primary microRNA gene transcripts contain stem-loop structures that are processed by RNAse type III enzymes such as Dicer to give rise to the mature microRNA. Dicer is also required for the processing of double-stranded viral RNA and for generating siRNAs in RNAi. microRNAs can act through the inhibition of translation, mRNA degradation and possibly transcriptional gene silencing.
How do cells control mitosis?

Co-workers: Caroline Broad, Barbara Di Fiore, Olivier Gavet, Anja Hagting, Daisuke Izawa, Mark Jackman, Paola Marco, Takahiro Matsusaka, Jakob Nilsson, Bernhard Strauss, Felicia Walton, Mona Yekezare

How do cells regulate entry to mitosis? And, once in mitosis, how do cells coordinate the remarkable events of chromosome alignment and segregation with cell division itself (cytokinesis) to ensure that the two daughter cells receive an equal and identical copy of the genome? The answer is the interplay between protein kinases, phosphatases and ubiquitin-mediated proteolysis, in particular ubiquitination by the Anaphase Promoting Complex/Cyclosome (APC/C), and this is the focus of our research. Because mitosis is a highly dynamic process we study living cells by time-lapse fluorescence microscopy. We use FRAP and photo-activation to gain a better understanding of the kinetics of protein behaviour, deconvolution to improve the spatial resolution and FRET to assay protein-protein interactions and kinase activity.

To understand how cells first initiate mitosis we are analysing the behaviour of the mitotic cyclin-CDKs, cyclins A and B1, and their regulation by phosphorylation and subcellular localisation. We use GFP-fusion proteins to reveal the dynamics of protein localisation through the cell cycle, and to define how proteins are targeted to specific subcellular structures. To identify the proteins responsible for targeting the cyclins, and to provide insights into Cdk substrates, we are analysing protein complexes by mass spectrometry. Recently, we have developed a biosensor to assay Cyclin B1-Cdk1, the major mitotic kinase activity, in vivo.

To understand how proteolysis is used to regulate progress through mitosis we measure the degradation of GFP-fusion proteins in living cells. These studies are revealing how the APC/C is first activated and, most importantly, how it is able to select a particular protein for destruction at a specific time in mitosis - essential to coordinating events such as chromosome segregation and cytokinesis. We have strong evidence that the ubiquitination machinery is spatially regulated in mitosis and we are investigating whether this is responsible for the exquisite control on protein degradation exerted by the spindle assembly checkpoint. We hope that these studies will increase our understanding of how cells control their division to prevent improper chromosome segregation (aneuploidy) that is the hallmark of many cancers.

Inset left: A prophase cell stained for MCAK (green), microtubules (red) and DNA (blue). (Catherine Lindon)


For complete list of this lab’s publications since the last report, see numbers 1, 11 & 21 on pp 54-59
Plk: Deconvolved images of Hela cells progressing through mitosis stained for Polo-like kinase 1 (green), tubulin (red) and DNA (blue). (Catherine Lindon).

Aurora_Cdc20: Pro-metaphase Hela cell stained for Cdc20 (left and green), Aurora A (middle and red), DNA (right and blue). (Lorena Clay).

Montage of cyclin B1-Cdk1 kinase activity detected in mitosis using a novel FRET biosensor. (Red, high activity, green, low activity). (Olivier Gavet)
The centrosome is the main microtubule organising centre in animal cells, and it plays a major role in many aspects of cell organisation. Surprisingly, we showed that flies could develop nearly normally without centrioles or centrosomes. We have been investigating how flies compensate for the lack of centrosomes and find that ~15% of the asymmetric divisions of the neural stem cells (neuroblasts) occur symmetrically, potentially generating extra stem cells. In contrast, the asymmetric divisions of the female germline stem cells occur normally without centrosomes, as do the complex MT rearrangements that are required for oogenesis. We are currently using these flies to investigate the role of the centrosome in several cell processes.

We have now shown that overexpressing certain proteins required for centriole replication can lead to centriole overduplication and to de novo centriole formation. We have generated flies that constitutively have too many centrioles in most of their cells. Surprisingly, this does not lead to a massive increase in genetic instability as these cells usually divide in a bipolar fashion due to clustering and/or inactivation of the extra centrosomes during mitosis.

We have recently performed a genome-wide RNAi screen to identify all of the components required for centriole duplication and PCM recruitment to the centrosomes during mitosis. This screen has identified almost all of the known proteins required for these processes (such as Cnn and DSpd-2) as well as several new ones. We are now investigating how these proteins cooperate to ensure proper centriole/centrosome function.

Inset left: Mitotic spindles in a Drosophila embryo. Microtubules (green); centrosomes (red); DNA blue.
The overexpression of centriole duplication proteins can drive de novo centriole formation in unfertilised eggs. GFP fusions of the centriole duplication proteins Sak, DSas-4, and DSas-6 have been overexpressed in unfertilised eggs (that normally lack centrioles) and this leads to the formation of centriole-like structures (green) that can organise PCM markers (red).

A genome-wide RNAi screen to identify proteins required for centriole duplication and PCM recruitment. This figure shows fields of Drosophila S2R+ cells fixed and stained to reveal the distribution of DNA (blue), mitotic chromatin (red) and centrosomes (green). In control cells, each mitotic cell is associated with centrosomes. In the absence of Cnn or Polo, no centrosomes are detectable in the mitotic cells.

\textit{Drosophila} Spd-2 (DSpd-2) mutant testes cells have too many centrosomes. RNAi screens in worms have shown that SPD-2 is required for centriole duplication. Surprisingly, we find that in flies, DSpd-2 mutant testes have too many centrioles (shown here in green; DNA in blue, microtubules in red), indicating that this protein is not essential for centriole duplication in flies.

Centrosomes are not required for the asymmetric division of female germline stem cells. It has been proposed that an asymmetry between the two centrosomes may play an important role in determining the self-renewing capacity of stem cells, and our studies show that centrosomes play an important role in the asymmetric divisions of \textit{Drosophila} neural stem cells. In female germline stem cells, however; the spindle (green) can line up correctly with positional information (the spectrosome, red) even in the absence of centrosomes (blue).
We aim to understand the molecular basis of mesoderm formation in the vertebrate embryo. As well as shedding light on fundamental developmental mechanisms, our work should assist in efforts to direct embryonic stem cells down particular developmental pathways, and it might even allow us to make differentiated cells move backwards in developmental time, so that they can then be re-programmed as the experimenter desires.

We make use of *Xenopus* species (both *X. laevis* and *X. tropicalis*) and the zebrafish. One interest concerns the mechanisms by which inducing factors exert long-range effects, and we are studying this by means of tagged forms of inducing factors such as Xnr2 and by using novel approaches to identify, in real time, the cells that respond to such signals. Like other members of the transforming growth factor type β family, Xnr2 exerts its effects by causing Smad proteins to form heteromeric complexes, and another aspect of our work has been to identify and characterise Smad-interacting proteins such as Smicl.

A second line of work involves elucidating the genetic regulatory networks that underlie mesoderm formation, and to this end we are carrying out ChIP-on-Chip and ChIP-Seq experiments, focusing on members of the T box family of proteins. The founder member of this family, Brachyury, is both necessary and sufficient for mesoderm formation in the early amphibian embryo. We shall go on to study gene function by use of antisense morpholino oligonucleotides, and we are also asking to what extent our results will apply to mammalian embryos.

Inset left: Dissociated animal pole cells expressing nuclear cyan fluorescent protein (blue) and Rab5 tagged with green fluorescent protein


For complete list of this lab’s publications since the last report, see numbers 14, 59, 64, 67, 68, 73, 74 & 77 on pp 54-59
Overexpression of dominant negative Activin receptor type IIB (DNActRIIB) sequesters fluorescent Activin released from a bead and prevents long-range signalling. Activin signalling is visualised by nuclear fluorescence derived from Smad2/Smad4 bimolecular fluorescence (Smad2&4 BiFC).

A control morpholino oligonucleotide (CoMo) has no effect on muscle or notochord differentiation in *Xenopus tropicalis*, as visualised using monoclonal antibodies 12/101 and MZ15 respectively. Use of an antisense morpholino oligonucleotide directed against Elk-1 (Xtelk-1 Mo) causes these tissues to differentiate poorly, and the specificity of this effect is demonstrated in a rescue experiment in which Xtelk-1 is re-introduced by RNA injection.

Chromatin immunoprecipitation combined with genomic microarrays identifies actively transcribed genes in the zebrafish gastrula embryo.

A *Xenopus* embryo expressing both Green Fluorescent Protein and mCherry under the control of the CMV promoter.
mRNA localisation and the origin of polarity in *Drosophila*

**Co-workers:** Rebecca Bastock, Katsiaryna Belaya, Sue Croysdale, Eurico De Sa, Helene Doerflinger, Celia Faria, Alejandra Gardiol, Jacqueline Hall, Nick Lowe, Dmitry Nashchekin, Ross Nieuwburg, Alexandre Raposo, Isabel Torres, Antonio Vega Rioja, Lucy Wheatley, Tongtong Zhao

The localisation of *bicoid* and *oskar* mRNAs to the anterior and posterior poles of the *Drosophila* oocyte defines the AP axis of the embryo, and provides an excellent model for analysing the molecular mechanisms that underlie cell polarity and mRNA localisation. We are taking a combination of cell-biological, genetic and molecular approaches to investigate these mechanisms:

1) Since many proteins involved in mRNA transport or cell polarity are required throughout development, they were not identified in the classical screens for mutations that disrupt axis formation. To overcome this problem, we are performing screens in germline clones for mutants that affect the localisation of GFP-labelled *bicoid* mRNA and RFP-labelled *oskar* mRNA in living oocytes. We have identified many novel genes required for cell polarity or mRNA localisation, and are now examining their functions.

2) We have shown that the anterior-posterior polarity of the oocyte and the apical-basal polarity of epithelial cells depend on the formation of reciprocal domains of PAR proteins, with Bazooka (PAR-3), PAR-6 and aPKC marking anterior and apical cortical domains, and PAR-1 marking posterior and lateral domains. Furthermore, these domains are maintained by mutual inhibitory interactions, in which PAR-1 phosphorylates and disrupts the Bazooka complex, whereas aPKC phosphorylates PAR-1 to remove it from the cortex. We are now analysing how this asymmetry is established, and how the PAR proteins polarise the cytoskeleton.

3) We are making time-lapse films of mRNA movement *in vivo* to determine how *bicoid* and *oskar* mRNAs are transported to opposite poles of the same cell. We are also attempting to purify mRNA localisation complexes and to reconstitute mRNA transport in vitro.

Inset left: The localisation of *bicoid* (black) and *oskar* (red) mRNAs in a stage 10A *Drosophila* oocyte


For complete list of this lab’s publications since the last report, see numbers 17, 29, 38, 53, 76 & 87 on pp 54-59
Starvation-dependent tumour formation. Removal of the AMP-dependent protein kinase from clones of follicle cells (marked by the absence of GFP; green) causes the cells to lose their polarity and over-proliferate, resulting in small tumours. This phenotype is only observed under starvation conditions. Collaboration with Jay Brenman (University of North Carolina).

Miranda targets Staufen and oskar mRNA to the anterior of the oocyte. Staufen (green) and oskar mRNA localise to the posterior of wildtype oocytes, where Oskar protein defines the abdomen (bottom). Ectopic expression of Miranda targets some Staufen and oskar mRNA to the anterior of the oocyte, resulting in bicaudal embryos. In mago nashi mutants, which disrupt posterior localisation, Miranda directs all Staufen and oskar mRNA to the anterior, leading to reversed embryos with an anterior abdomen and no head.

Drosophila anterior-posterior axis formation. Left panel: A stage 10A egg chamber showing the localisation of PAR-6 (red) and PAR-1 (green) to define anterior-posterior polarity in the oocyte. The nuclei are stained in blue. Right panel: The PAR protein polarity directs the localisation of the anterior determinant, bicoid mRNA (green) and the posterior determinant, oskar mRNA (red) to opposite poles of the oocyte.

Drosophila oogenesis. A Drosophila ovariole, containing a series of germline cysts (green, BicD) that progress through oogenesis as they move posteriorly. The cysts are born at the anterior of the ovariole, and become surrounded by somatic follicle cells (red, FasIII) as they exit the germarium. Each cyst contains 16 germ cells, and one of these is selected to become the oocyte and accumulates higher levels of BicD protein.
We aim to elucidate the genetic programme that regulates specification of mouse primordial germ cells (PGCs), which includes active repression of the somatic programme adopted by the neighbouring cells. We discovered that the transcriptional repressor, Blimp1/Prdm1, is the key regulator of PGC specification. We are exploring the role of this and other key genes involved in PGC specification. Furthermore, Blimp1 forms a novel complex with Prmt5 arginine methylase that is apparently critical for the specification and maintenance of early PGCs, while PRMT5 itself is independently implicated in regulating pluripotency in stem cells, which underlines the relationship between germ cells and pluripotent stem cells.

Following PGC specification, extensive epigenetic reprogramming of the genome follows, which is an essential first step towards the eventual generation of totipotency. In particular, when PGCs migrate into developing gonads at E11.5, they undergo extensive epigenetic modifications, including genome-wide DNA demethylation, erasure of imprints and reactivation of the X chromosome. Dedifferentiation of PGCs into pluripotent EG cells also results in a similar epigenetic reprogramming event following the loss of Blimp1 (Fig 4). We are investigating the mechanism, including the identity of intrinsic factors involved in the epigenetic reprogramming of PGCs, together with the nature of the external signals that trigger it.

Our broader objectives are to develop model systems that will attempt to mimic the key aspects PGC specification and epigenetic reprogramming in vitro. The key factors and mechanisms that govern erasure of epigenetic information in PGCs could be relevant for investigations of genomic reprogramming of somatic cells towards pluripotency in vitro. This knowledge could also contribute to advances in human medicine, including the causes of cancers, as well as for the repair and rejuvenation of somatic tissues.

Inset left: Expression of Stella-GFP at E7.8. PGCs are detected at the base of the allantois. Stella is located within a cluster of pluripotency genes, including nanog and Gdf3 that are expressed in ES and EG cells.
Blmp1, the key determinant of germ cell specification in mice, with a SET/PR domain and five Krueppel-like zinc fingers, which bind to DNA. BLMP1 can potentially interact with several co-repressors to repress target genes. In germ cells, BLMP1 forms a novel complex with an arginine methylase, PRMT5.

Role of Blmp1 in PGC specification. Shown are early embryos from E5.0 to E7.5 depicting the formation of PGCs. The proximal epiblast respond to signals from extraembryonic tissues that induce expression of fragilis in the epiblast, and of Blmp1 in the lineage restricted PGC precursors, which develop as founder PGCs and show expression of Stella.

During dedifferentiation of PGCs into pluripotent embryonic germ cells (EG), Blmp1 is down regulated resulting in the expression of the repressed targets of BLMP1, and epigenetic reprogramming in EG as observed in gonadal PGCs in vivo. Prmt5 expression is maintained and may have an independent role in pluripotency.

Genetic regulators, expression of pluripotency genes and epigenetic modifications in nascent PGCs
We are investigating the cellular and molecular mechanisms underlying cell allocation and commitment in the mouse embryo.

First, how is the polarity of the egg established to permit the asymmetric, meiotic divisions and then re-organised following fertilisation to allow symmetric embryonic divisions? We are addressing this by combining experimental embryology with molecular techniques to disturb spatial organisation of the embryo. Time-lapse imaging of spindle positioning and cell division allows us to follow these processes in live embryos; ectopic expression or down-regulation of regulatory proteins enables us to perturb them. Our findings have revealed that cells start to differ already in the 4-cell embryo. We have therefore begun to investigate the molecular basis of these differences.

Second, what is the interplay between cell polarity, position and potency in directing cell-fate in the mouse? This relationship appears instrumental in generating pluripotent, inside cells that give rise to the animal body and outside cells differentiating into the extra-embryonic tissues. We found that we can influence these cell-fate decisions by affecting the function of cell polarity proteins such as Par3 and aPKC. We have also discovered that we can direct cells to pluripotency by manipulating a specific chromatin modification. We wish to understand the molecular mechanism of this relationship.

Third, when and how do the first signalling centres become established to determine the anterior-posterior axis? To address this we are undertaking expression profiling and lineage tracing combined with clonal RNAi to down-regulate signalling genes. Since our screens revealed novel asymmetrically expressed genes shortly after implantation, we are characterising their function and developing reporter lines to follow their expression in vivo.

Inset left: 3D reconstruction of mouse blastocyst. Yellow: pluripotent cells of the inner cell mass; blue and green: outside cells of trophectoderm. (Image from Emlyn Parfitt and Magdalena Zernicka-Goetz)

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For complete list of this lab’s publications since the last report, see numbers 34, 55, 62, 82 & 83 on pp 54-59
THE GURDON INSTITUTE

Post-implantation mouse embryo with migrating anterior visceral endoderm cells expressing Crl (in green). Boundaries between cells shown in red. (Image from Lucy Richardson)

3D reconstructions of mouse embryos. 4-cell to morula stage. Red-polar body, blue, yellow and green – blastomeres. (Images from Maria Skamagki).

Tracking pluripotent inner cell mass cells as blastocyst develops. (Image from Sigolene Meilhac and Richard Adams)

First cleavage division of the mouse zygote. Chromatin in blue, microtubules in green, actin in red. (Image from Jie Na)
CATEGORIES OF APPOINTMENT / SENIOR GROUP LEADERS

CATEGORIES OF APPOINTMENT

SENIOR GROUP LEADER
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GROUP LEADER
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CAREER DEVELOPMENT FELLOW
4-year grant-funded appointment, within individual groups

INDEPENDENT SENIOR RESEARCH ASSOCIATE
3-year grant-funded appointment, within individual groups

RESEARCH ASSOCIATE/FELLOW
Postdoctoral Fellow, within individual groups, appointed by group leader

RESEARCH ASSISTANT
Postgraduate, within individual groups, mainly grant-funded

GRADUATE STUDENT
3 or 4 year studentship within individual groups, mainly grant-funded

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Within individual groups, mainly grant-funded

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Within individual groups or part of core support, grant-funded

POSTGRADUATE OPPORTUNITIES

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

JIM SMITH PhD FRS FMedSci, Director
John Humphrey Plummer Professor of Developmental Biology
Member European Molecular Biology Organization
Member Academia Europaea
(Member of the Department of Zoology)

JOANNA ARGASINSKA PhD
Wellcome Trust Research Associate

JULIA BATE
Personal Assistant

CLIFFORD BOGUE PhD
Sabbatical Visitor

LIZ CALLERY PhD
Wellcome Trust Research Associate

CLARA COLLART PhD
Wellcome Trust Research Associate

KEVIN DINGWELL PhD
Wellcome Trust Research Associate

AMANDA EVANS HNC
Wellcome Trust Research Assistant

GEORGE GENTSCH MPhil
Wellcome Trust Graduate Student

ANJA HAGEMANN
Graduate Student

STEVE HARVEY PhD
VolkswagenStiftung Research Associate
KIM LACHANI  
EU Chief Research Lab Technician

NIGEL MESSENGER  
Wellcome Trust Research Associate

OLIVER NENTWICH PhD  
Wellcome Trust Research Associate

AMER RANA PhD  
Wellcome Trust Research Associate

STEFAN TÜMPEL PhD  
DFG Fellow

FIONA WARDLE PhD  
Wellcome Trust Senior Research Associate

XIN XU  
EU Graduate Student

ANDREA BRAND PhD FMedSci
Herchel Smith Professor of Molecular Biology  
Member European Molecular Biology Organization  
(Member of the Department of Physiology, Development and Neuroscience)

TORSTEN BOSSING PhD  
Wellcome Trust Research Associate

ADRIAN CARR MPhil  
Graduate Student

JAMES CHELL MPhil  
Wellcome Trust Graduate Student

MELANIE CRANSTON BA  
Wellcome Trust Research Assistant

CATHERINE DAVIDSON BSc  
Wellcome Trust Research Associate

JAMES DODS BSc  
Wellcome Trust Graduate Student

KARIN EDOFF PhD  
MRC Stem Cell Career Development Fellow

BORIS EGGER PhD  
Wellcome Trust Research Associate

DAVID ELLIOTT PhD  
Wellcome Trust Research Associate

KATRINA GOLD MPhil  
Wellcome Trust Graduate Student

BOB GOLDSTEIN PhD  
Visiting Academic from University of North Carolina

UGO MAYOR PhD  
Royal Society Dorothy Hodgkin Fellow

ANNE PELISSIER PhD  
EMBO Fellow

TONY SOUTHALL PhD  
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MRC Graduate Student

CHRISTINE TURNER  
Secretary

JAKOB VON TROTHA  
Graduate Student

PAO-SHU (PAUL) WU  
Graduate Student

NICK BROWN PhD  
Reader in Cell Biology  
(Member of the Department of Physiology, Development and Neuroscience)

ISABELLE DELON PhD  
BBSRC Research Associate

JONATHAN FRIEDLANDER  
Gates Scholarship Graduate Student

SAMANTHA HERBERT BSc  
Wellcome Trust Research Assistant
SENIOR GROUP LEADERS

SVEN HUELSMANN PhD
Wellcome Trust Research Associate

YOSHIKO INOUE PhD
Wellcome Trust Research Associate

SUSHMITA MAITRA PhD
Wellcome Trust Research Associate

JOHN OVERTON HNC
Wellcome Trust Chief Research Technician

DORA SABINO
Graduate Student

XIAOTAN PhD
Graduate Student/Wellcome Trust Research Associate

JUTTA WELLMANN
DAAD and European Trust Graduate Student

JOHN GURDON Kt DPhil DSc FRS
Distinguished Group Leader
Foreign Associate, US National Academy of Sciences
Foreign Associate, US Institute of Medicine of the National Academies
Member European Molecular Biology Organization
Member Academia Europaea
Honorary Member of American Anatomical Society
Honorary Member of Anatomical Society of Great Britain
(Member of the Department of Zoology)

CAROLINA ÅSTRAND PhD
Swedish Research Council Fellow

JEROME JULLIEN PhD
Wellcome Trust Research Associate

MAGDALENA KOZIOL BSc
Wellcome Trust Graduate Student

NICOLE LANT
Secretary

KAZUTAKA MURATA BSc
Graduate Student

VINCENT PASQUE BSc
Wellcome Trust Graduate Student

ILENIA SIMEONI PhD
EU Research Associate

HENRIETTA STANDLEY PhD
BBSRC Research Associate
STEVE JACKSON PhD FMedSci
Frederick James Quick Professor of Biology
Head of Cancer Research UK Labs
Member European Molecular Biology Organization
(Member of the Department of Zoology)

RIMMA BELOTSEVKOVSKAYA PhD
Cancer Research UK Research Associate

RICHARD CHAHWAN
Graduate Student

ROSS CHAPMAN BSc
Cancer Research UK Research Assistant

JULIA COATES MA
Cancer Research UK Chief Research Technician

ROBERT DRISCOLL BSc
BBSRC Graduate Student

KATE DRY PhD
Cancer Research UK Senior Research Associate

SONJA FLOTT PhD
Cancer Research UK Research Associate

JOSEP FORMENT PhD
Cancer Research UK Research Associate

YARON GALANTY PhD
EU Research Associate

SABRINA GIAVARA PhD
EU Research Associate

SIMONA GIUNTA BSc
BBSRC CASE Graduate Student

SERGE GRAVEL PhD
Cancer Research UK Research Associate

JEANINE HARRIGAN PhD
Cancer Research UK Research Associate

PABLO HUERTAS PhD
BBSRC Research Associate

ABDERRAHMANE KAIIDI PhD
Cancer Research UK Research Associate

CHRISTINE MAGILL BSc
Cancer Research UK Research Assistant

ANDREAS MEIER PhD
Swiss National Foundation Research Associate

KYLE MILLER PhD
EU Research Associate

TOBIAS OELSCHLAGEL PhD
EU Research Associate

SOPHIE POLO PhD
HFSP Fellow

HELEN REED
Secretary

ALEX SARTORI PhD
Swiss National Science Foundation Fellow

PHILIPPA SMITH BSc
Cancer Research UK Lab Manager

JORRIT TJEERTES
BBSRC CASE Graduate Student

TONY KOUZARIDES PhD FMedSci, Deputy Director
Royal Society Napier Professor
Member European Molecular Biology Organization
(Member of the Department of Pathology)

HATICE AKARUSU PhD
EU Research Associate

ANDREW BANNISTER PhD
Cancer Research UK Senior Research Associate

TILL BARTKE PhD
HFSP Research Fellow

MARIA CHRISTOPHOROU PhD
HFSP Research Fellow

ALISTAIR COOK GIBiol
Cancer Research UK Chief Research Technician

SOPHIE DELTOUR PhD
Cancer Research UK Research Associate
SENIOR GROUP LEADERS

KAREN HALLS BSc
Royal Society Research Assistant

PAUL HURD PhD
Cancer Research UK Research Associate

ANTONIS KIRMIZIS PhD
Marie Curie Intra-European Fellow

DAVID LANDO PhD
Cancer Research UK Research Associate

SUSANA LOPES PhD
Cancer Research UK Research Associate

CHRIS NELSON PhD
CIHR Research Fellow

NIKKI OLIVER BA
Secretary

CLAIRE PIKE BSc
Cancer Research UK Graduate Student

HELENA SANTOS ROSA PhD
Cancer Research UK Senior Research Associate

BLERTA XHEMALCE PhD
EU Research Associate

ANNE McLAREN DBE DPhil FRS
BBSRC Distinguished Group Leader
Member European Molecular Biology Organization
(Member of the Department of Zoology)

DILLY BRADFORD
Secretary

CRISTINA EGUIZABAL PhD
BBSRC Research Associate

TANYA SHOVLIN PhD
BBSRC Research Associate

JON PINES PhD FMedSci
Director of Research in Cell Division
Member European Molecular Biology Organization
(Member of the Department of Zoology)

CAROLINE BROAD
Cancer Research UK Lab Manager

FAY COOKE
MRC Graduate Student

BARBARA DI FIORE PhD
Cancer Research UK Research Associate

SUZANNE FLOYD PhD
MRC Research Associate

OLIVIER GAVET PhD
Marie Curie Experienced Researcher

ANJA HAGTING PhD
Cancer Research UK Research Associate

DAI SUKE IZAWA PhD
JSPS Research Fellow
KATHRIN BRUNK PhD
Cancer Research UK Research Associate

PAUL CONDUIT BSc
Cancer Research UK Graduate Student

CARLY DIX MPhil
Cancer Research UK Research Assistant/Graduate Student

JEROEN DOBBELAERE PhD
HFSP Research Fellow

ANNA FRANZ BSc
Wellcome Trust Graduate Student

GILLIAN HOWARD
Cancer Research UK Senior Research Technician

MARK JACKMAN PhD
Cancer Research UK Research Associate

LARS KOOP
BBSRC CASE Graduate Student

CATHERINE LINDON PhD
MRC Career Development Fellow

PAOLA MARCO
BBSRC CASE Graduate Student

TAKAHIRO MATSUSAKA PhD
Cancer Research UK Research Associate

JAKOB NILSSON PhD
Danish Cancer Society Fellow

BERNHARD STRAUSS PhD
Newton Trust Research Associate

FELICIA WALTON
Marshall Scholar

MONA YEKEZARE
Yousef Jameel Graduate Student

JORDAN RAFF PhD
Director of Research in Cancer Cell Biology
Cancer Research UK Programme Grant Holder
(Member of the Department of Genetics)

JULIET BARROWS BA
Secretary

RENATA BASTO PhD
Royal Society Dorothy Hodgkin Fellow

JOYCE LAU MPhil
Cancer Research UK Senior Research Technician

ELIANA PIRES LUCAS MSc
Cancer Research UK Research Assistant/Graduate Student

NINA PEEL MPhil
Cancer Research UK Research Assistant/Graduate Student

RICHARD RESCHEN BSc
MRC Graduate Student

NAOMI STEVENS MPhil
Wellcome Trust Graduate Student
SENIOR GROUP LEADERS

DANIEL ST JOHNSTON PhD FRS FMedSci
Wellcome Trust Principal Research Fellow
Professor of Developmental Genetics
Member European Molecular Biology Organization
(Member of the Department of Genetics)

REBECCA BASTOCK PhD
Wellcome Trust Research Associate

KATSIARYNA BELAYA BSc
Graduate Student

SUE CROYSDALE
Secretary

KATJA DAHLGAARD
Graduate Student

EURICO DE SA
Portuguese Foundation of Science and Technology Graduate Student

HELENE DOERFLINGER PhD
Wellcome Trust Research Associate

CELIA FARIA
Wellcome Trust Graduate Student

ALEJANDRA GARDOIOL PhD
Wellcome Trust Research Associate

JACQUELINE HALL MSc
Wellcome Trust Senior Research Technician

NICK LOWE PhD
Wellcome Trust Research Associate

VINCENT MIROUSE PhD
EMBO Fellow

DMITRY NASHCHEKIN PhD
Swedish Research Council Fellowship

ROSS NIEUWBURG
Graduate Student

ALEXANDRE RAPOSO
Graduate Student

ISABEL TORRES
Graduate Student

ANTONIO VEGA RIOJA PhD
FEBS Fellow

LUCY WHEATLEY
Wellcome Trust Research Assistant

TONGTONG ZHAO
Graduate Student

MAARTEN ZWART
Wellcome Trust Research Assistant

AZIM SURANI PhD FRS FMedSci
Mary Marshall & Arthur Walton Professor of Physiology and Reproduction
Member European Molecular Biology Organization
Member Academia Europaea
Associate Fellow, Third World Academy of Sciences
(Member of the Department of Physiology, Development and Neuroscience)

SHEILA BARTON
Wellcome Trust Senior Research Associate

SUZAN BER PhD
Newton Trust Research Associate

FRANCESCA CESARI WEIMAR PhD
Marie Curie Fellow

GABRIELA DURCOVA-HILLS PhD
MRC Research Fellow

LYNN FROGGETT
Secretary

SAM GOSSAGE MSc
Wellcome Trust Research Assistant

PETRA HAJKOVA PhD
Wellcome Trust Research Associate

SOPHIE HANINA
MRC Graduate Student

KATSUHIKO HAYASHI PhD
DTI Research Associate
SENIOR GROUP LEADERS / GROUP LEADERS

SEAN JEFFRIES
NIH Graduate Student

MASAHIRO KANEDA PhD
Uehara Memorial Foundation Research Fellow

SHINSEOG KIM PhD
Wellcome Trust Research Associate

CAROLINE LEE ONC
Wellcome Trust Chief Research Technician

ERNA MAGNUSDOTTIR PhD
Wellcome Trust Research Associate

WILLIAM MIFSUD
Wellcome Trust Graduate Student

QIN SI PhD
Wellcome Trust Research Associate

FUCHOU TANG PhD
Applera Research Associate

WEE WEITEE
Wellcome Trust Graduate Student

LENG SIEW YEAP
BBSRC Dorothy Hodgkin Graduate Student

BRUNO FIEVET PhD
HFSP Research Fellow

PAULINA KOLASINSKA-ZWIERZ
Gates Scholarship Graduate Student

TAEJOON KWON
Wellcome Trust Research Assistant

ISABEL LATORRE PhD
NIH Research Associate

NEERAJ MANDHANA
Graduate Student

COSTANZA PANBIANCO PhD
Wellcome Trust Research Associate

GINO POULIN PhD
Wellcome Trust Research Associate

STEFANIA RAGONE PhD
NIH Research Associate

DAVID RIVERS PhD
Wellcome Trust Research Associate

JOSANA RODRIGUEZ PhD
HFSP Research Fellow

CHRISTINE TURNER
Secretary

SHANE WOODS
Gates Scholarship Graduate Student

KATHLEEN XIE
Exchange student from MIT

JULIE AHRINGER PhD FMedSci
Wellcome Trust Senior Research Fellow
Director of Research in Genetics & Genomics
Member European Molecular Biology Organization
(Member of the Department of Genetics)

YAN DONG MSc
Wellcome Trust Research Assistant
GROUP LEADERS

THOMAS DOWN PhD
Wellcome Trust Research Career Development Fellow (Bioinformatics) (Member of the Department of Genetics (provisional))
Thomas will be recruiting group members throughout 2008

RICK LIVESEY MB BChir PhD
Wellcome Trust Group Leader
(University Senior Lecturer in Biochemistry)

JESSICA ALSIO BSc
Wellcome Trust Graduate Student

JULIET BARROWS BA
Secretary

DEAN GRIFFITHS PhD
MRC Research Associate

JOAO PEREIRA BSc
Graduate Student

GRACE NISBET BSc
Jean Shanks Graduate Student

SABHI RAHMAN BSc
EU Research Assistant/Graduate Student

STEPHEN SANSOM BSc
NAAR Research Assistant

JAMES SMITH BSc
March of Dimes Research Assistant

TATIANA SOUBKHANKOULOVA PhD
EU Research Associate

URUPORN THAMMONGKOL BSc
Graduate Student

MASANORI MISHIMA PhD
Cancer Research UK Group Leader
(Member of the Department of Biochemistry)

SUE CROYSDALE
Secretary

TIM DAVIES BSc
BBSRC Graduate Student

MAX DOUGLAS MBiochem
BBSRC Graduate Student

ANDREA HUTTERER PhD
HFSP Research Fellow

KIANDYONG LEE BSc
Cancer Research UK Graduate Student

JULIA MASON BSc
Cancer Research UK Research Assistant

ERIC MISKA PhD
Cancer Research UK Group Leader
(Member of the Department of Biochemistry)

JULIE ADDISON BA MPhil
Cancer Research UK Student

JAVIER ARMISEN GARRIDO PhD
BBSRC Research Associate
GROUP LEADERS

MAGDALENA ZERNICKA-GOETZ PhD
Wellcome Trust Senior Research Fellow
Member European Molecular Biology Organization
Reader in Developmental Biology
(Member of the Department of Genetics)

ALEX BRUCE PhD
Wellcome Trust Research Associate

TAGBO ILOZUE
AstraZeneca Graduate Student

MARLOES BAGIJN MSc
Graduate Student

CHERI BLENKIRON PhD
EU Research Associate

HEERAN BUHECHA BSc
Cancer Research UK Graduate Student

ALEJANDRA CLARK PhD
Cancer Research UK Research Associate

PARTHA DAS MSc
Cancer Research UK Chief Research Technician

ETHAN KAUFMAN BSc
Gates Graduate Student

NIC LEHRBACH MPhil
Wellcome Trust Graduate Student

ALEXANDRA SAPETSCHNIG PhD
Herchel Smith Research Fellow

FUNDA SAR PhD
Cancer Research UK Research Fellow

STEFANIE SASSEN Dr med
Visiting Academic

ROBERT SHAW BA MPhil
Wellcome Trust Graduate Student

AGNIESZKA JEDRUSIK
Graduate Student

EUNICE LIN
Gates Graduate Student

JULIA LINDROOS
BBSRC Research Technician

RUI MARTINS PhD
EMBO Research Fellow

SAMANTHA MORRIS PhD
BBSRC Research Associate

EMLYN PARFITT
MRC Graduate Student

LUCY RICHARDSON
Graduate Student

BEDRA SHARIF
Visiting Academic

MARIA SKAMAGKI
Graduate Student
GROUP LEADERS / SUPPORT STAFF

SAMLY SRUN
Visiting Student

BERNHARD STRAUSS PhD
Newton Trust Research Associate

QIANG WU PhD
Wellcome Trust Research Associate

ADMINISTRATION

ANN CARTWRIGHT MPhil
Institute Administrator

GEORGE BROWN
Accounts Manager

SUZANNE CAMPBELL BSc
Administration Assistant

JANE COURSE
Accounts/Admin Assistant

DIANE FOSTER
Deputy Administrator

KATHY HILTON DipMgm
CBSG Manager

LYNDA LOCKEY
Office Manager

NIKKI OLIVER BA
Receptionist

JACKIE SIMCOX
Receptionist

COMPUTING

ALASTAIR DOWNIE
Computer Associate

NICOLA LAWRENCE PhD
Computer Associate

NIGEL SMITH
Computer Associate

ALEX SOSSICK BSc
Computer Imaging Associate

PETER WILLIAMSON BSc
Computer Associate

BIOINFORMATICS

MIKE GILCHRIST PhD
Computer Associate (Bioinformatics)

MIKKEL CHRISTENSEN PhD
Computer Associate (Bioinformatics)

JIA TIAN PhD
Computer Associate (Bioinformatics)

ACCOUNTS/PURCHASING/STORES

IAN FLEMING
Stores/Purchasing Manager

SIMON ALDIS
Purchasing/Accounts Assistant
SUPPORT STAFF

RICHARD ETTERIDGE
Stores Technician
LEN SYMONDS
Senior Stores Technician
ANDY VINCENT
Stores Technician
MICK WOODROOFE
Purchasing/Accounts Assistant

TECHNICAL SUPPORT
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CRISTIAN GUZMAN-QUEIROLO
STEPHEN SALT
PAUL TURRELL

MEDIA/GLASS WASHING
JUANITA BAKER-HAY
Media/Glass Washing Manager

CATERING
DARIA SKRODZKA
AGNIESZKA SURLES

THE GURDON INSTITUTE
The following is a list of articles by members of the Institute that were either published or accepted for publication, since the date of publication of the last Annual Report.

* Indicates equal priority.


2. Ahnesorg P and Jackson SP (2007) The non-homologous end-joining protein Nej1p is a target of the DNA damage checkpoint. *DNA Repair* 6, 190-201


21 Di Fiore B and Pines J (2007) Emi1 is needed to couple DNA replication with mitosis but does not regulate activation of the mitotic APC/C. J Cell Biol 177, 425-437

29 Efrat AK, Torres IL, Schejter ED, St Johnston D and Shilo B-Z (2007) Drosophila follicle cells are patterned by multiple levels of Notch signalling and antagonism between the notch and JAK/STAT pathways. Development, 134, 1161-1169


Actin stainings of Drosophila eggchambers. The oocytes contain a dense actin mesh. (Vincent Pasque, St Johnston lab, 2007)

Isabel Torres (St Johnston Group), winner of this year’s cover image competition, receiving the prize from Tina Howe of Olympus UK. (Anatomy Visual Media Group, 2007)
INSTITUTE PUBLICATIONS


Teratoma induced by injecting pluripotent EG cells under kidney capsule (Cristina Eguizabal and Gabriela Durcova-Hills, Former McLaren lab, 2007)

Neuromuscular junctions and nuclei in a third instar Drosophila larva hemisegment. (Alejandra Gardiol, St Johnston lab, 2007)
INSTITUTE PUBLICATIONS


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54 Drosophila ovarian stem cell in mitosis (Naomi Stevens, Raff lab, 2007)

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C elegans cyk-4 (RNAi) embryo after failed cytokinesis (DNA in bue, PAR-3 in green and alpha-tubulin in red). (Anna Franz, Raff lab, 2007)

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64 Ramis JM, Collart C and Smith JC (2007) Xnrs and Activin regulate distinct genes during Xenopus development: Activin regulates cell division. PLoS ONE 2, e213


68 Saka Y and Smith JC (2007) A mechanism for the sharp transition of morphogen gradient interpretation in Xenopus. BMC Developmental Biology 7, 47


79 Surani MA (2007) Germ cells: The eternal link between generations. The Pontifical Academy of Sciences, Vatican City


OTHER INFORMATION

STAFF AFFILIATIONS

JULIE AHRINGER is a member of the Scientific Advisory Board of Reactome.

ANDREA BRAND is a Founding Board Member of The Rosalind Franklin Society, USA, a member of the Scientific Advisory Board of the MRC Centre for Developmental Neurobiology, King’s College London, a member of the University of Cambridge Neuroscience Committee, a member of the steering committee of the University of Cambridge Women in Science, Engineering and Technology Initiative.

JOHN GURDON is a member of the Conseil Scientifique of the Institut Curie, Paris, a member of the Scientific Advisory Board of the Max-Planck-Institut für Biophysikalische Chemie, Göttingen, a member of the British and American Anatomical Societies, Chairman of the Company of Biologists and a member of the Board for Diagnostics of the Real World. He also sits on the Advisory Board of the new Harvard Stem Cell Institute, and is a Board member for the Daiwa Anglo-Japanese Foundation.

STEVE JACKSON is a member of the Radiation Oncology and Biology External Advisory Board, University of Oxford Steering Committee for the UK Research Network on the Biomedical Applications of High Energy Ion Beams, University of Cambridge Advisory Group on Translation of Research, and is Chief Scientific Officer, KuDOS Pharmaceuticals Ltd.

TONY KOUZARIDES is a member of the Cancer Research UK Science and Strategy Advisory Group, a member of the Marie Curie Institute Scientific Committee, and non-executive director of AbCam Plc.

ANNE McLAREN was a member of the international Scientific Advisory Board (Fachbeirat) of The Max Planck Institute for Molecular Biomedicine in Munster, Germany and the Scientific Advisory Committee of the Institute for Molecular Bioscience in Brisbane, Australia, and an Honorary Fellow of King’s College, Cambridge.

JONATHON PINES is the Membership Secretary of the British Society for Cell Biology and a member of the HFSP Fellowship Committee.

JORDAN RAFF is a member of the Academy of Medical Sciences’ working group on the Careers of Basic Scientists, a Non-Executive Director of the Company of Biologists, a life-long member of the Royal Institution, and a Committee Member and Honor Fell Travel Award Secretary of British Society for Cell Biology.

DANIEL ST JOHNSTON is a Director of the Wellcome Trust Four-Year PhD programme in Developmental Biology at the University of Cambridge, and is a non-executive Director of the Company of Biologists.

JIM SMITH is a member of the Board of Directors of the Babraham Institute and a member of the Cancer Research UK Assessment Panel for Senior University Salaries. He is also Chairman of the Royal Society Research Appointment Panel (Bi), Chairman of the Wellcome Trust Sir Henry Wellcome Postdoctoral Fellowship Committee and a member of the Wellcome Trust Molecular and Physiological Sciences Strategy Committee. He is Chairman of the Scientific Advisory Board of The Max-Planck-Institut für Immunbiologie and Institute for Toxicology and Genetics, Karlsruhe. His University commitments include being a member of the University of Cambridge Sub-Committee for Biological Sciences and Clinical Medicine (Senior Academic Promotions), the School of Biological Sciences External Relations & Collaborations Group, and the Consultative Committee for Safety. He is also Chairman of the Darwin at Christ’s 2009 College Committee.

AZIM SURANI is the Sir Dorabji Tata Visiting Professor, Tata Institute for Fundamental Research, NCBS, Bangalore, India (2005-2010), a member of the Royal Society Working Group on Stem Cells, a member of the German Stem Cells Initiative, and Founder and Consultant for CellCentric Ltd, a member of the International Scientific Advisory Board of the Wellcome Trust Centre for Stem Cell Research, University of Cambridge, and Chairman of the Scientific Advisory Board of the Centre for Trophoblast Research, University of Cambridge.

MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Research Fellow at Sidney Sussex College and Board Member of the Cambridge Philosophical Society.
HONOURS AND AWARDS

STEVE JACKSON - Honorary degree Nottingham University (Doctor of Science)

JOHN GURDON - Saxen and Toivonen Memorial Medal and Prize, Honorary degree University of Cambridge (Doctor of Science)

EDITORIAL BOARDS OF JOURNALS

JULIE AHRINGER – Public Library of Science Biology, Molecular Systems Biology, EMBO Journal, EMBO Reports, Phil. Transactions of the Royal Society B

ANDREA BRAND – Neural Development, BioEssays, Fly, Biology Image Library

JOHN GURDON – Current Biology, Development, Growth and Differentiation, International Journal of Developmental Biology, Proceedings of the National Academy of Sciences of the USA.

STEVE JACKSON – Carcinogenesis, EMBO Journal, EMBO Reports, Nature Reviews, DNA Repair, Faculty of 1,000, Science, Genes and Development, Current Biology, The Scientist.

ANNE McLAREN – Gene Therapy, Current Opinion in Genetics and Development.

JON PINES – EMBO Journal, EMBO Reports.

DANIEL ST JOHNSTON – Development, EMBO Journal, EMBO Reports.

JIM SMITH – Development (Editor-in-Chief), Trends in Genetics, EMBO Reports.

AZIM SURANI – Cell Stem Cell, Regenerative Medicine, Epigenetics

MAGDALENA ZERNICKA-GOETZ – Developmental Dynamics, BioMed Central, Developmental Biology, Reproduction, Development.

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PROF ERICH NIGG, Max Planck Institute for Biochemistry, Martinsried, Germany

CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR SIR TOM BLUNDELL, Head, Department of Biochemistry and Chair of the School of Biological Sciences, University of Cambridge, UK
LEAVERS DURING 2007

SHEILA BARTON retired from the Institute

CLIFFORD BOUGE completed sabbatical visit and returned to USA

TORSTEN BOSSING has accepted a position at the University of Southampton

HEERAN BUHECHA decided on career change

FRANCESCA CESARI-WEIMAR left to take up the position of Development & Stem Cell editor at Nature publishing

RICHARD CHAHWAN completed Studentship

CHIN-WEN CHANG returned to Taiwan as project completed

FAY COOKE left to take up a postdoctoral position in Paul Martin’s lab in Bristol

KATJA DAHLGAARD left to take up postdoctoral fellowship with the Faculty of Health Sciences, University of Copenhagen, Denmark

DAVID ELLIOTT moved to Melbourne, Australia, to accept a position at the Monash Immunology and Stem Cell Laboratory

SUSIE FLOYD moved to the Department of Genetics to work in Cath Lindon’s research group

RICHARD GARDNER completed Vacation Studentship and returned to full time studies

SABRINA GIARARA moved to Australia to carry out postdoctoral work in the Walter and Eliza Hall Institute of Medical Research, Victoria

DEAN GRIFFITHS left to take up new position in Göttgens lab at CIMR

KAREN HALLS completed her PhD and took up a position at ABCAM

MASAHIRO KANEDA returned to Japan to take up research position at the National Institute of Livestock & Grassland Science, Japan

LARS KOOP completed Studentship and joined Roche in Germany

MAGDALENA KOZIOL completed her Studentship and moved to the Boston Consulting Group in Frankfurt

TAEJOON KWON left to start PhD at University of Texas

JOYCE LAU returned to Hong Kong

CATH LINDON took up a Group Leader position in the Department of Genetics

SUSANA LOPES left to pursue a career in pharmaceutical regulatory affairs

ELIANA PIRES LUCAS took up postdoctoral position in London

NEERAJ MANDHANA completed his Studentship and has taken up a post as Biotechnology Manager at Videocon Industries Limited in Mumbai India

ANDREAS MEIER returned to Baden, Switzerland to take up a teaching position

NIGEL MESSENGER left to start up own business in South of France

VINCENT MIROUSE left to take up postdoctoral fellowship with Clermont-Ferrand in France

NINA PEEL left to start postdoctoral position in USA

GINO POULIN took up Group Leader position at University of Manchester

SABHI RAHMAN completed his PhD and took up a post at GlaxoSmithKline

LUCY RICHARDSON completed her Studentship and went to work as an Embryologist in The London Bridge Centre for Fertility, Genetics and Gynaecology

ALEX SARTORI left to take up a position with University of Zurich, Switzerland

STEPHANIE SASSEN returned to Germany to continue her medical career

TATIANA SOUBKHANKOULOVA moved to The Royal London Hospital to take up postdoctoral position

SAMLY SRUN visiting student who returned to Paris to complete full time studies

HENRIETTA STANDLEY took up professional tutor position in School of Biosciences at Cardiff University

XIAO TAN moved to USA to study medicine at Stanford University

JIA TIAN took up new position in London

FIONA WARDLE took up Career Development award at Department of Physiology, Development and Neuroscience.

MAARTEN ZWART started Wellcome Trust PhD Studentship
“Just one more thing before you go home...” (Shane Woods, Ahringer lab, 2007)

**ACKNOWLEDGEMENTS**

Prospectus produced in the Wellcome Trust/Cancer Research UK Gurdon Institute. Edited by Ann Cartwright, production by Alastair Downie

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Front cover: *Drosophila* egg chamber with microtubules in green, nuclei in blue and a microtubule-binding protein in red. (Isabel Torres, St Johnston Group, 2007)

Back cover: Images from the Annual Retreat (University of Leicester). (Photos by John Overton, Jim Smith and James Smith)
Wellcome Trust/Cancer Research UK Gurdon Institute

The Henry Wellcome Building of Cancer and Developmental Biology
University of Cambridge, Tennis Court Road, Cambridge CB2 1QH, United Kingdom

Telephone: +44 (0)1223 334088
Fax: +44 (0)1223 334089
http://www.gurdon.cam.ac.uk
e-mail: info@gurdon.cam.ac.uk