Oxford Stem Cell Institute

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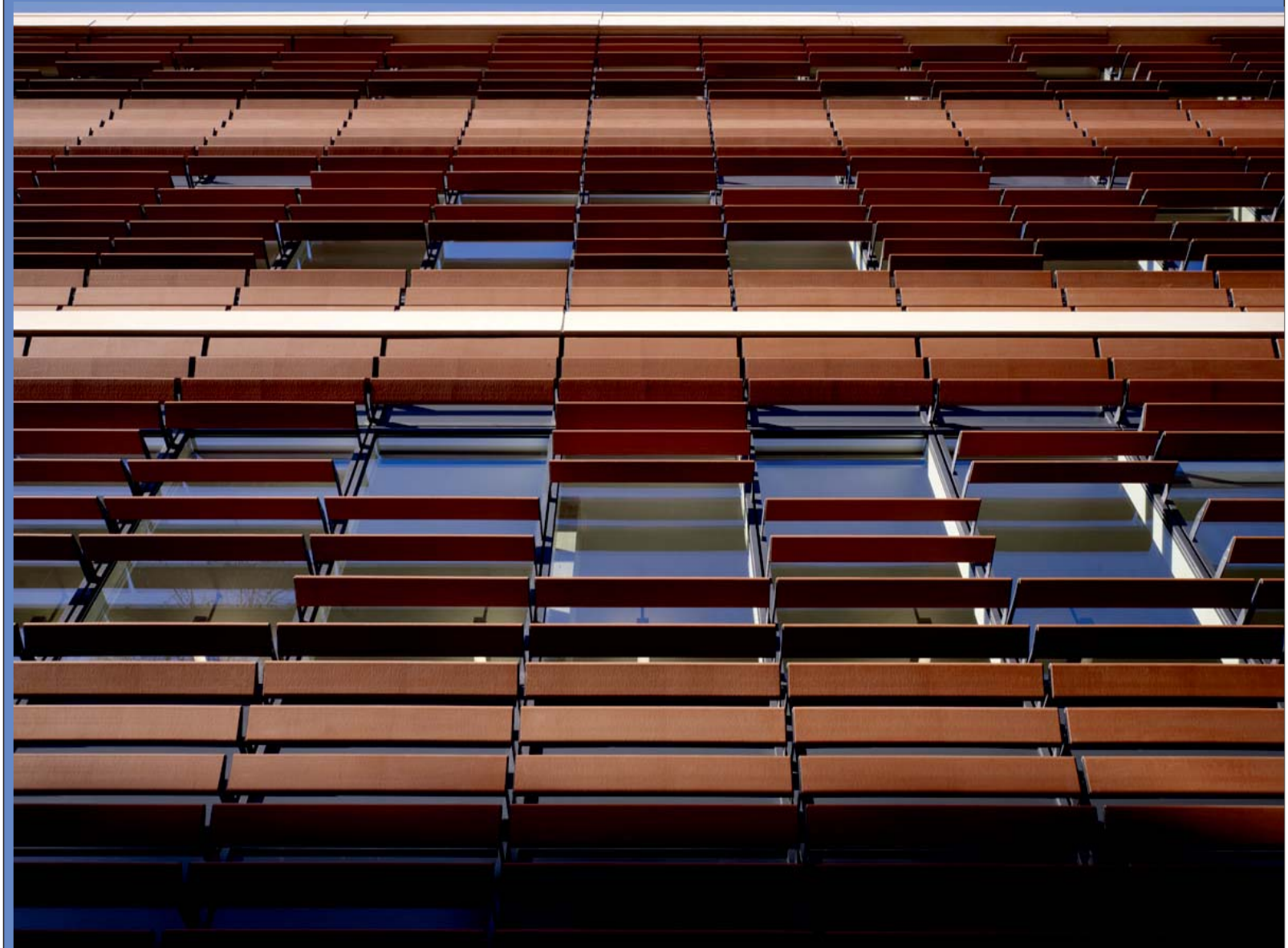
James Martin Stem Cell Facility
James Martin Stem Cell Research Fellows

Launch, June 2011



Welcome

The Oxford Stem Cell Institute is deeply indebted to the Oxford Martin School, not only for having the foresight and vision to enable its original establishment in 2008, but for the additional investment that the matched-funding scheme has since provided. On the basis of this funding, we are delighted to have appointment two James Martin Fellows, Dr Kenny Moore and Dr Michiko Yamasaki-Mann, whose research interests complement those already present within the Institute. Their establishment as independent researchers here in Oxford will bring new expertise and insight into the application of stem cells to intractable problems of significant clinical importance. We very much look forward to their integration into the OSCI and to appointing two further Fellows later in the year.

In addition to nurturing new careers in stem cell research, the matched funding scheme has provided permanent, state-of-the-art premises for the Stem Cell Facility. The Facility is embedded in the new Oxford Molecular Pathology institute, erected through the munificence of the EPA Research Fund. By offering support to many laboratories in Oxford and further afield, in the derivation and maintenance of human stem cells making, the Facility makes they technology accessible to those working primarily in other fields. The initiative has already made possible four interdisciplinary research themes that address key issues in human health and disease. On the following pages, we take a snapshot of these four themes, illustrating the reach of the initiative across Oxford and further afield. Importantly, the initiative is making strategic investments in a new generation of scientists, who will use the technology offered by the facility to break into new areas of science. The first two James Martin Stem Cell Research Fellows are now in post, and they describe their exciting work below.

We are sure that we speak for all within the OSCI when we thank the Oxford Martin School for their ongoing support and partnership in our vision of taking stem cell therapies from the laboratory to the clinic. Finally, we would like to express our gratitude to the dedication of Dr Sally Cowley and Cathy Browne, who make the core facility runs so effectively.

Paul Fairchild, Director, Oxford Stem Cell Institute
William James, Professor of Virology and James Martin Fellow

Key Personnel

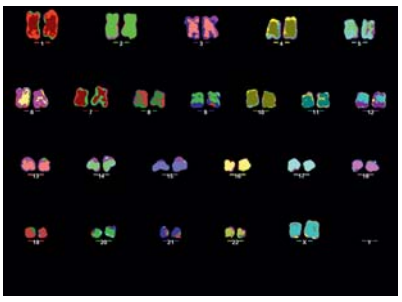
Sally Cowley, PhD. Head of the Facility

A graduate of Natural Sciences at Cambridge University, Sally completed her PhD on host–pathogen interactions in leprosy in 1990 at the Royal College of Surgeons, University of London. A postdoctoral position at the New England Deaconess Hospital in Boston led to her identifying and cloning a novel tyrosine kinase, MATK, which is expressed predominantly in megakaryocytes and implicated in their differentiation [JBC 1994 269 1068-1074]. A second postdoctoral post at the Institute of Cancer Research in London enabled her to be the first to demonstrate that the kinase MEK (/MKK), which is directly downstream from the products of the important cancer associated genes Ras and Raf, is critical for signal transduction from various growth factor receptors [Cell 1994 77 841-852 cited over 1500 times; EMBO J. 1994 13 1610-1619]. This was followed by a period in Ethiopia, as a senior researcher at AHRI, investigating the molecular mechanisms of drug resistance in mycobacteria and enteric pathogens, and subsequently a career break for raising children.

Sally is a Wellcome Trust Career Re-entry Fellow, whose research programme lies at the core of Theme 1, macrophages in Human Health and Disease. Together with William James, she set up the James Martin Stem Cell Facility, and now oversees its operation. She is an active collaborator in most of the research themes of the Facility.

Cathy Browne is the James martin Facility Research Assistant, who maintains the high level of quality control and information integrity required by the demanding and complex projects hosted by the Facility. She provides specialist training and maintains a core workflow of stem cell maintenance, expansion, and differentiation.

Jane Vowles is the Parkinson's Disease UK Research Assistant, specializing in the reprogramming of human skin cells to induced pluripotent stem cells, within the OPDC programme (Theme 3).



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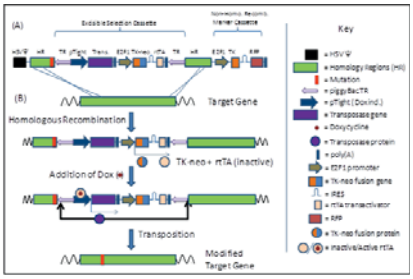
James Martin Stem Cell Research Fellows

Michiko Yamasaki-Mann, DDS, DPhil

After completing her doctorate in dental surgery at Kyushu University, Japan,in2001, Michiko undertook a detailed investigation of the role of cyclic ADP in cellular signalling through calcium. She completed her DPhil in the Pharmacology Department, University of Oxford under Professor Antony Gallione in 2005, and her post-doctoral training at the Department of Neurobiology and Behaviour, and the Department of Neurology, at the University of California's Irvine and Los Angeles campuses, respectively.

Michico's research project as a James Martin Fellow is entitled "Dissecting intracellular Ca^{2+} signalling pathways in Parkinson's disease (PD) using patient-specific human stem cell models". PD patients lose more than half of their key dopaminergic neurons, but the cause of this is unknown, limiting the prospects for prevention and cure. Michiko intends to use PD patient-derived iPS cells to study the calcium signalling pathways in neurons to see how cellular homeostasis is disturbed in disease. She hopes that elucidating these mechanisms will provide insights into PD pathogenesis that will eventually enable the early detection and prevention of disease progression.

Michael D (Kenny) Moore, MA, PhD



Kenny studied Biological Sciences at St Catherine's College, Oxford. He obtained his PhD at Imperial College London under Professor Myra McLure, pursuing gene therapeutic interventions for Hepatitis. His post-doctoral training was with Dr. Wei-Shau Hu, at the NIH National Cancer Institute, Frederick, MD, USA ,where he worked on HIV-1 recombination. He recently returned to Oxford, on an NIH-sponsored microbicide program in the James lab, where he successfully isolated neutralizing aptamers to genital herpes virus.

Kenny's research programme as a James Martin Fellow includes the development of a novel transposon-based genetic manipulation platform to accurately and cleanly correct gene mutations. He hopes this will not only enable to use stem cell technology to investigate molecular mechanisms of disease more precisely, but might lead to methods for gene therapy in the future. He works in Theme 2, investigating the interplay between macrophages and HIV-1, with particular emphasis on the virus's evasion of innate immune mechanisms within these cells. To achieve these aims Kenny is exploiting stem cell technology combined with directed-differentiation of the stem cells into monocytes and macrophages.

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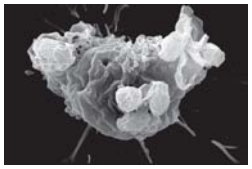
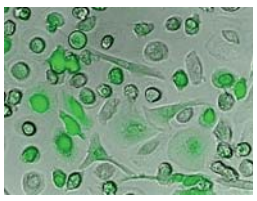
Research Theme 1:

Macrophages in Human Health and Disease





Sally Cowley, together with DPhil student, **Bonnie van Wilgenburg**, is working on the linkage between cell surface molecules on macrophages and the intracellular signalling pathways that lead to effector functions, such as immune modulation, bacterial killing and inflammation. They are using a range of novel genetic vectors to introduce changes to surface molecules such as CD4 in stem cell-derived macrophages in order to study these interactions in molecular detail and identify pathways for potential therapeutic modulation of macrophage activity.

The Stem Cell Facility has been crucial in bringing together the groups of **Reinhart Seger** and **Janine Reichenbach**, from the University Children's Hospital, Zurich, and **Majlinda Lako** and **Lyle Armstrong**, from the Centre for Genetic Therapy, University of Newcastle in a project to evaluate gene therapy approaches to chronic granulomatous disease (CGD). CGD is a serious hereditary illness in which certain cells of the immune system are unable to kill pathogens. This leads to recurrent infections such as Pneumonia and abscesses, which severely reduce the quality and length of life. In normal individuals the pathogen killing function relies on the ability of the immune cells to produce free radicals that are toxic to the invading bacteria or fungi but in CGD, mutations in a specific gene stop this happening which in turn makes the immune system work less effectively. Current treatments for CGD rely upon antimicrobial drugs are proving decreasingly effective, so an alternative approach, based on tacking the root genetic cause, is needed. Development of such gene therapies using mouse models or patients' bone marrow cells have proved very ineffective, so the group is using patient-derived induced pluripotent stem cells, from which we can differentiate macrophages in vitro, as a more experimentally tractable model system.

Eva Gluenz, Royal Society University Research Fellow, has begun a project to study the interactions between the Leishmania parasite and human macrophages. These parasites are transmitted by the bite of the sand fly and cause disfiguring cutaneous lesions and life-threatening visceral infections in about 12 million people in the poorest countries of the world. In the human body, Leishmania parasites are taken up by macrophages and proliferate within the harsh conditions of the phagolysosome. Eva is testing the hypothesis is that the parasite flagellum acts as a 'cellular antenna' which is required to cause infection in human stem cell derived macrophages.

In a future planned collaboration with the Facility, **David Greaves** plans to use the ability it offers to genetically manipulate stem cell-derived macrophages in order to investigate the potential to specifically modulate their key role in inflammatory disorders and cardiovascular disease. The Facility is also establishing links with the **Kennedy Institute for Rheumatology**, which is moving from London to oxford next year.

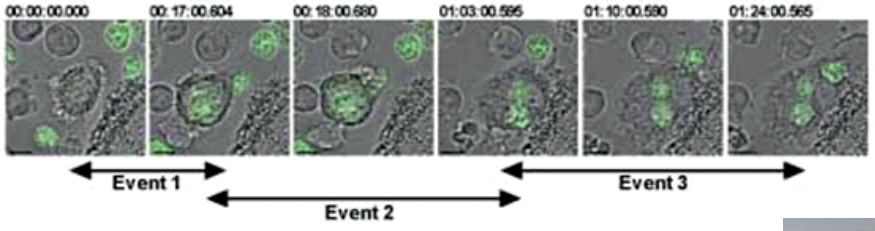
Research Theme 2:

HIV and AIDS

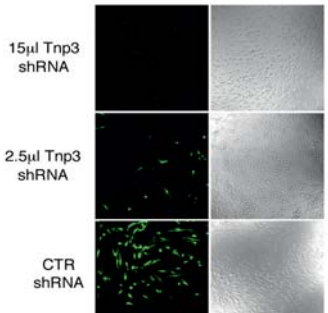
Macrophages are a key target for HIV during infection, setting up what is known as a viral reservoir in these cells, as they are long-lived. Since macrophages exist in almost every tissue in the body including the brain, this allows long-term HIV-1 establishment in these tissues, and onward transmission to other cell types. Until the development of stem cell technologies, it was extremely difficult to undertake precise genetic experiments to investigate the molecular interactions between HIV and the macrophage in order to understand disease pathogenesis and identify potential therapeutic pathways. In a co-ordinated set of complementary projects, many undertaken in collaboration with others, the aim of the James Martin Stem Cell Facility is to tackle the big questions using its unique stem cell-based methods.

In conjunction with DPhil student, **Darshan Baskaran**, **Kenny Moore** is developing a new set of powerful genetic vectors both to engineer precise genetic corrections into stem cells (see figure), and to express potentially therapeutic genes in a controlled manner. he is using these methods, amongst other things, to investigate molecular pathways during macrophage infection by HIV.

Professor Quentin Sattentau (James Martin Fellow) leads an MRC-funded programme to investigate the interactions between lymphocytes and macrophages during cellular infection by HIV They have recently shown that whilst carrying out one of their major functions, eating infected and dead and dying cells, macrophages avidly ingest HIV-1-infected T cells and become infected with the virus. This pathway of infection is substantially more efficient that the conventional model of cell-free virus infection and is probably the major mechanism of macrophage infection in vivo. They have used embryonic stem cell-derived macrophages to probe the uptake of HIV-1-infected CD4+ T cells in real time (Figure 1), and have found this an invaluable tool for reproducible production of macrophages, their live cell imaging and their infection by HIV-1.



Sally Cowley and Kenny Moore are collaborating on separate projects with **Professor Areiberto Fassati** (pictured, right) and **Professor Greg Towers**, at University College London, on the molecular pathways by which the HIV core reaches the nucleus of infected macrophages. Ariberto is Director of the Wohl Viron Centre and Greg is Professor of Molecular Virology at UCL. By taking complementary approaches, the two groups have identified key cellular transport proteins that are important to HIV infection in cell lines. By working with the James Martin Stem Cell Facility, they have been able to test the relevance of these proteins for HIV infection of authentic macrophages, and the results (see figure) are proving the crucial role of defined pathways of nuclear import in vivo.



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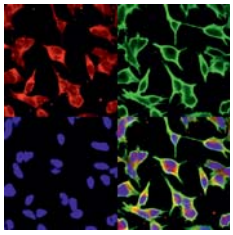
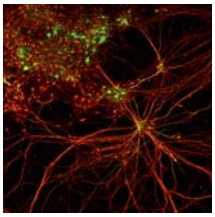
MRC Medical Research Council

Research Theme 3:

Neurodegenerative Diseases

Richard Wade-Martins, MA DPhil (pictured, right), leads the Oxford Parkinson's Disease Centre (OPDC), a new group of internationally-leading scientists and clinicians working together to better understand the causes of Parkinson's disease. Richard graduated from Cambridge in Natural Sciences (Genetics) and obtained his DPhil at the Wellcome Trust Centre for Human Genetics in Oxford. In 2000 Richard moved to Massachussetts General Hospital, Harvard Medical School as a Wellcome Trust Travelling Research Fellow. He returned to Oxford, and in 2007 moved to the Department of Physiology, Anatomy and Genetics, University of Oxford. Funded by a Monument Trust Discovery Award from Parkinson's UK, the aim of OPDC is to develop therapies to halt the disease progression at the earliest stages. This world-class research centre uses the latest methodologies in brain imaging, genetics, biomarkers, and animal models. Induced pluripotent stem cells (iPSCs) offer great potential for research into human diseases and play a central role in the OPDC program. A small sample of skin is taken from a patient and reprogrammed into iPSCs by **Jane Vowles** in the James Martin Facility. The iPSCs are then directed to generate nerve cells by OPDC Fellow, **Elizabeth Hartfield,** PhD (right), and in order to study the pathology of Parkinson's. The availability of human nerve cells from patients is currently extremely limited, and so iPSC technology allows human nerve cells to be studied in much more detail than ever before. By using this cutting edge technology, we will for the first time be able to understand the mechanism behind this cell loss. Increasing our understanding of what goes wrong can potentially lead to improved therapeutics to help suffers of this disease.





Matthew Wood, BM, DPhil is developing gene silencing therapies for human neurodegenerative diseases including PD and Spinocerebellar ataxia type 7. A crucial requirement is demonstrating activity and benefit in relevant human cell models, prior to proceeding to clinical trials in patients. A major challenge with human neurodegenerative disease is obtaining relevant human cells from the brain that display a relevant defect and which can be studied and modelled in the laboratory. With the advent of methods to generate induced pluripotent stem (iPS) cells using skin cells directly obtained from patients, and with Martin School funding, Matthew and **Janine Scholefield**, PhD, can now produce relevant brain cells in vitro which can then be used in the laboratory to monitor the effects of potential new treatments, such as gene silencing therapies.

In planned developments in this theme**, Jo Poulton,** DM DPhil is planning to work with the Facility on the mitochondrial genetics of neurological diseases.

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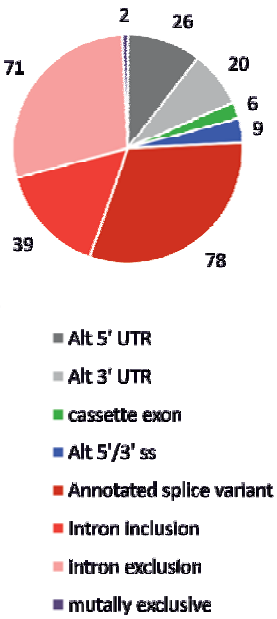
Research Theme 4:

Developmental Molecular Biology

Shona Murphy, PhD, Reader in Molecular Biology, has been investigating the genes encoding small non-Coding RNAs since her graduate studies in Heidelberg and her post-doctoral work at the Rockefeller University, New York. The collection of genes referred to as the genome contains all the information required for our growth and development. The DNA that makes up the genes is copied into RNA for the information to be decoded, for example into proteins, which can be structural or catalytic. In many genes, the RNA copies contain protein-coding regions (exons) interspersed with non-protein coding segments (introns) and the RNA is processed to remove introns and join exons together in a process known as splicing, directed by standard signals within exons and introns. In many cases, exons can also be excised or introns retained, altering the RNA such that different proteins are generated from the same gene. This process in known as alternative splicing and is fundamental to generating protein diversity in different cells. Failure to correctly regulate alternative splicing can result in disease due to the appearance of the wrong product in the wrong place and/or at the wrong time. Together with **Dawn O'Reilly**, PhD, and graduate student, Pilar Vasquez Arango, Shona aims to determine the function of a novel group of small RNAs in alternative splicing, which will 1) elucidate how misregulation of their expression could lead to disease and 2) allow their development as drugs to combat disease. Several of these novel small RNAs are differentially expressed in human embryonic stem cells (HESCs), suggesting they play a role in stem cell maintenance and/or early development. Using the protocols established by the group of William James to differentiate HESCs, we are able to study the function of these RNAs during differentiation.



Zoia L. Monaco, Ph.D. is Head of the Mammalian Chromosome Group at the Wellcome Trust Centre for Human Genetics. Zoia's group is interested in understanding the mechanisms of genome stability in stem cells as a prerequisite to develop strategies for gene therapy. The focus is to investigate human chromosome organization and function using artificial chromosomes (HAC) as a research model. HAC are extrachromosomal elements, which behave as normal chromosomes within cells, and are successful as gene vectors, since they have the capacity to accommodate larger genes and regulatory regions for long term expression studies. For the first time, they recently showed that newly formed and stable artificial chromosomes that expressed genes were successfully generated in human embryonic stem (hES) cells. A major finding was that the host ES genome remained intact in contrast to previous studies in tumour. HAC will be an important marker in patient therapeutic strategies for monitoring chromosome stability in different cell types including induced pluripotent stem (iPS) cells.

The Facility has helped Professor **Helen Mardon**, DPhil, isolate and characterize new embryonic stem cell lines, and is working with **Zam Cader**, BM DPhil, on the epigenetic regulation of aminocyl tRNA synthases. It is planning a programme of work in collaboration with **Doug Higgs**, FRS and the MRC Haematology Unit, on epigenetic regulation during myeloid differentiation from stem cells in vitro.

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