Decisions awaited on future of UK medical research funding

Decisions in the coming months will determine the future shape of medical research funding in the UK. In March, the Chancellor of the Exchequer, Gordon Brown, signalled a radical review of publicly funded health research. He proposed a single fund of more than a billion pounds to support the full spectrum of basic and applied research, training and infrastructure currently supported by the Department of Health in England and the MRC. The findings of the review, led by Sir David Cooksey, are expected this autumn.

For MRC Chief Executive Colin Blakemore, the Cooksey review presents a real chance to improve the interaction between basic and clinical research: “The UK has an outstanding track record in medical research. For its size it provides the best value for money of any public health research programme in the world. We must strive to maintain the best features of the present system, while searching for even better arrangements for the future. Any changes must give us at least the same freedom to support the best research. And we hope that there will be increased funding, so that we can fulfil our commitment to innovation and translation of research results.”

The MRC has now handed its submission to Sir David. It has suggested two options. The first is to merge completely the activities of the MRC and National Health Service R&D into a new arms-length body. The second would see a pair of ‘councils’ or organisations, one focused on research across the whole spectrum, and one on health service infrastructure and innovation, with a streamlined coordinating mechanism.

Declan Mulkeen, who organised the MRC response to the Cooksey review, explained: “Each of the MRC’s options has its own benefits and challenges. We think the first would offer the most long-term benefits for health research in the UK but the second would be simpler to implement in the short run, and might act as a route to full integration in the future.”

Colin Blakemore explained his hopes: “We want to see a long-term vision that will facilitate the translation between fundamental biomedical research and its clinical application. It will be important to avoid frequent tinkering with the system, which would make it difficult to attract and retain the best researchers.

We hope that the chosen model will improve planning and support for all areas of research, and will retain the commitment to the UK’s remarkable achievement in pre-clinical research, as well as the seamless linkage from bench to bedside. We have to strike a balance between creative discovery and the rapid response to health priorities.”

There have been hundreds of submissions to Sir David’s review, addressing the strengths and weaknesses of existing arrangements, how translation of research into better healthcare and innovation in industry could be improved, and possible future funding arrangements.

As Network goes to press, Sir David is analysing these submissions. Those that the MRC has seen have been generous in their praise of the major role that it has played in health research. They are generally supportive of the proposal to bring together funding, and they echo the MRC’s view that any new arrangements should build on past successes.

Sir David Cooksey, who is leading the review into publicly funded health research in the UK.
Sir John Skehel is widely acknowledged to be one of the world’s leading virologists. His research showing how the influenza virus sticks to and forces entry into its target cells is not only of fundamental scientific interest, but is also important in the search for better treatments for seasonal flu and in strategies to defend against the threat of a flu pandemic.

Viruses need to enter the cells of host organisms in order to make copies of themselves, which they do by hijacking the cell’s own machinery for replication. The virus must first bind to a receptor on the surface of the cell and enter it. Sir John has analysed the events in this process, studying the structure of the virus proteins involved in attachment of the virus particles to the outer surface of target cells. Once bound to the cell surface, a virus is drawn into the cell, into membrane-bound compartments called endosomes. Sir John and his collaborators discovered chemical changes that occur in the endosome and revealed how the genetic material of the virus is released.

Leading worldwide collaboration on flu research

From 1975 to 1993, Sir John was the director of the World Health Organization Collaborating Centre for Reference and Research on Influenza at the NIMR. This centre continues its crucial international role today under the leadership of Dr Alan Hay. Sir John has also been an advisor to several major institutes and public bodies including the Public Health Laboratory Service, the Animal Health Trust, and Cancer Research UK. He has collaborated with leading flu researchers worldwide. Thirty years ago, for example, Sir John embarked on a collaboration with Professor Don Wiley at Harvard University in the US. Their collaboration lasted 25 years, until Professor Wiley’s death in 2001.

During this time, they uncovered the mechanism of membrane fusion by haemagglutinin – the virus membrane glycoprotein that mediates the binding and fusion of the virus with endosomes. In 1981, Sir John and Professor Wiley published their discovery of the structure of haemagglutinin in Nature. The structure revealed the likely binding site and provided clues about the fusion mechanisms. The work also indicated how the structure of haemagglutinin varies between epidemic flu strains.

Further exploration of haemagglutinin

In 1982, Sir John showed that a low pH triggers a substantial conformational change in haemagglutinin, and that this leads to the fusion of the flu virus with the endosomal membrane of cells. He also elucidated the conformation of haemagglutinin after fusion, and the molecular mechanisms that launch part of the haemagglutinin molecule into the wall of the endosome so that the virus’s RNA can be injected into the cell. Sir John shows that the pH of the endosome is the critical factor that triggers membrane fusion by haemagglutinin.

Sir John has also studied the process by which the flu virus binds to the surface of a cell before it enters. The virus binds to sialic acid residues of cell surface glycoproteins, which vary among different types of cell. Haemagglutinin mediates this binding. Sir John’s work on this process has been important in the understanding of flu virus specificity – why some viruses infect only humans and others infect only birds.

Two years ago, a landmark paper in Science, led by Sir John, showed that the structure of the haemagglutinin of the 1918 human pandemic flu virus was able to bind to human cells even though the virus binding sites were characteristic of bird flu. This suggests one way in which the 1918 virus was able to adapt to and spread in the human population. There are important lessons from this research in the context of present concerns about another pandemic arising from an avian flu virus.

And in a Nature paper in August this year, Sir John elucidated the structure of the active site of the other defining protein of the H5N1 virus, neuraminidase. This may lead to the development of new drugs, potentially combating the problem of resistance to those currently available (see “Research Roundup”, page 16).

Career highlights

Born in 1941, Sir John obtained a BSc degree at the University of Wales (Aberystwyth) and a PhD from the University of Manchester. His post-doctoral positions were at the University of Aberdeen and Duke University Medical Centre, in North Carolina, USA. In 1969, he moved to the NIMR, where he was head of the Division of Virology and then head of the Infections and Immunity group, becoming the institute’s director in 1987.

Sir John was elected a fellow of the Royal Society in 1984 and was knighted in 1996. Among his many other distinctions, he was awarded the 1986 Wilhelm Feldberg Prize, which is presented each year to a German and a British scientist, and the Robert Koch Prize in 1989, awarded annually to international researchers whose innovative work in infectious diseases shows potential for new therapies. Sir John won the Royal Society’s Royal Medal in 2003.

Sir John is vice-president of the Academy of Medical Sciences and holds honorary professorships in virology at Glasgow University, Liverpool Sir John Moores’ University and the Department of Virology at University College London.
Public say prevention most important for ageing research

A strong emphasis on prevention and improving quality of life should be key factors in funding scientific research into ageing, according to a public consultation by Ipsos MORI for Research Councils UK.

By 2030, 14 million people in the UK will be over 65, outnumbering 20–39 year-olds by a fifth. With fewer people working and a pensions crisis looming, policymakers are taking note. The ageing population has been identified by the UK Treasury as a ‘Grand Challenge,’ and scientific crisis looming, policymakers are taking note. The ageing population has been identified by the UK Treasury as a ‘Grand Challenge,’ and scientific research into ageing has been identified by the UK Treasury as a ‘Grand Challenge,’ and scientific research into ageing was the subject of a House of Lords committee report in 2005.

The MRC spends around £130 million each year on research relevant to ageing. We commissioned the public study along with the Biotechnology and Biological Sciences Research Council (BBSRC) as part of our commitment to gathering different views in order to inform the decision-making processes.

The main outcomes of the consultation were that the public identified prevention of ill health as the most important area for research, and likelihood to contribute to improving quality of life as the most important criterion upon which to base funding decisions. The study also showed that although ageing and research into ageing may not be issues at the forefront of many people’s minds, there is strong support for such research to maximise people’s quality of life.

The full results of the study can be found on the Ipsos MORI website at www.ipsos-mori.com/polls/2006/rcuk.shtml.

Seeing the light – Diamond update

The accelerator team at Diamond Light Source, the soon-to-be-completed third generation synchrotron at Harwell in Oxfordshire, is celebrating after accumulating the first stored beam in the facility’s 562-meter storage ring, which in turn allowed the first observation of synchrotron light.

This latest milestone for the synchrotron means that the machine is well on target to becoming operational by January 2007. Dr Riccardo Bartolini, Diamond’s Head of Accelerator Physics, said: “We are successfully taking the first steps in climbing the ladder up to our eventual beam current target of 300 mA and are very encouraged by these early date results.”

Diamond is the size of five football pitches and strikes an impressive profile on the Harwell Chilton science campus. When it opens for business in January eight beamlines will be available, and an additional fifteen – part-funded by the MRC – will be completed by 2012.

MRC Medical Sciences Workshop

In spring 2006, MRC scientists, corporate representatives and senior unit administrators joined colleagues from Oxford University for a one-day Medical Sciences Workshop at Diamond. The workshop gave delegates (pictured above right) the opportunity to discover more about the synchrotron and its scientific capabilities and share their ideas on its potential as a research tool for the MRC.

The central learning point of the workshop was that there must be continuing and open dialogue between key user communities in order to maximise the facility’s capabilities. Professor Louise Johnson, Director of Life Sciences at Diamond, spoke of the essential part the scientific community has played in driving forward the synchrotron’s development and how discussion between stakeholders must be ongoing. She said: “Open dialogue with its key user communities is critical to Diamond’s success. We need to have a clear picture of both current and future research requirements.”

Another theme of the day’s discussions was the need for more interaction and understanding between biologists, physicists and engineers. Dr Megan Davies, Head of the Cambridge Centre, said: “Biologists do not necessarily understand enough about the synchrotron’s potential to ask for it, and physicists and engineers do not necessarily know enough about the biological questions, or constraints in working with biological materials, to be able to offer well-developed new technologies. Success will require new ways of catalysing interactions between these communities.”

Diamond Research Complex

One very effective way of uniting these communities comes in the form of the new Research Councils UK Research Complex. This will provide essential laboratory facilities for life and physical scientists to undertake new cutting-edge research. Its main purpose is to promote challenging interdisciplinary research that will fully exploit the capabilities of Diamond, and of site residents ISIS and the Central Laser Facility.

Dr Kevin Moreton, Project Sponsor of the Research Complex and Head of MRC Research Career Awards, said: “Experience at other synchrotrons around the world has shown that research facilities located close to the source have allowed visiting and resident research teams to achieve remarkable advances; benefiting from close collaboration with the beamline scientists and other technical experts at the facility.”
An interview with...

Sir John Chisholm, new MRC Chairman

Sir John Chisholm becomes Chairman of the MRC in October. Sir John is widely credited with transforming a collection of government research laboratories into the highly successful defence and security technology company QinetiQ, which floated on the London Stock Exchange in February. Network finds out more about him…

With a background in engineering, defence and technology, what attracted you to the MRC?

It is true that when I was first approached it did not seem the most obvious thing to do, but the more I looked into it the more interesting it became. Of course the distinction of the MRC’s scientific record is attraction enough, but I am more focused on the potential for the future, and there is no area of scientific endeavour more likely to change the course of human civilisation for the better over the next 20 years than medical research.

It is an interesting time for the MRC – what was your reaction to Gordon Brown’s announcement of a single health research fund for the UK?

The UK has enormous potential to raise still further its contributions to medical science by exploiting in a more coherent way its assets in the medical research and clinical arenas. It is not surprising to me as an outsider that Gordon Brown has been drawn to a single fund – I look forward in due course to working with others to maximise the opportunities that a single fund can deliver.

What aspects of your past experience will help you take the MRC in the direction you think it needs to go?

I was lucky to discover early in my career that computers could be immensely helpful in tackling physical problems. That led me into all sorts of interesting areas of application and into a career spent helping very able people to do extraordinary things. Being asked as a complete outsider to take on the Defence Research Agency and make it survive and thrive as a stand-alone business was an important challenge.

The challenges and opportunities of the MRC are quite different but the generic concerns of research leadership, such as motivation, infrastructure, funding and translation, are all very familiar:

You have considerable experience in research exploitation. How do you plan to apply this to the MRC, which is aiming to speed the translation of research to achieve clinical benefits?

There is no single answer for translation and no simple model. I have my own war chest of dos and don’ts, but apart from enduring issues such as incentivisation and communication my experience is that you have to understand the detailed exploitation path of a particular scientific application. So for the moment I want to learn much more about the special characteristics of the various fields in which the MRC is engaged.

The privatisation of QinetiQ met with a degree of criticism from people concerned that a lot of money was made, particularly by the Carlyle Group, at the taxpayer’s expense – what is your view about this?

When I first came into a government job in the 1990s it was towards the end of the 1979–1997 Conservative Government. At the time, it seemed that there was no Government initiative for which a negative angle would not be reported by the press, a phase we seem to now be in with this Government. The QinetiQ story is a huge triumph and I am confident the history books will record it that way. A moribund and neglected set of government research establishments was transformed into a thriving company worth over £1 billion.

To help achieve this, the Government brought in a private equity partner, Carlyle, with its stake restricted to less than 30 per cent, and allowed QinetiQ staff to invest in nearly 20 per cent of the business. So the big winner was the taxpayer through the Government’s stake of more than 50 per cent. But the work to create the value had been done by Carlyle, and particularly by QinetiQ staff. I doubt that history will begrudge them their reward!

And finally, on a lighter note, can you tell us more about your interest in old cars?

I love old cars, particularly taking them apart and making them work. In recent years I have added the extra challenge of then racing them. There is no better way of finding out if you have got it right. I guess that could also be considered an especially vigorous form of translation!
And farewell to...
Sir Anthony Cleaver

It was with appreciation and admiration that the MRC said farewell to Sir Anthony Cleaver, chairman of the Council since 1998, at an event in July at the Royal Society of Medicine (RSM) in London. The RSM atrium was filled with well-wishers expressing their sadness at his departure, including council and board members and staff, and other colleagues and friends of Sir Anthony.

In appreciative speeches, current and previous MRC Chief Executives Professor Colin Blakemore and Sir George Radda paid tribute to Sir Anthony’s leadership and guidance over the years and wished him well for the future. Sir George spoke of how Sir Anthony “demonstrated his enthusiasm for research and for communicating with scientists right from the start,” while Colin spoke of his “repository of knowledge and wisdom.”

“Sir Anthony has overseen the governance of the MRC with diplomacy, wisdom and skill. His wise stewardship has been widely appreciated across the MRC and among our key stakeholders. He has been a steady hand during times of change. He will be missed and we wish him well for the future.”

MRC Chief Executive Colin Blakemore pays tribute to outgoing chairman Sir Anthony Cleaver

New faces

The Government has appointed Professor Christopher Kennard as a member of the MRC’s Council. Professor Kennard is the deputy principal of the Faculty of Medicine at Imperial College London and has been professor of clinical neurology at the University of London since 1991. As chair of the MRC Neuroscience and Mental Health Board, he will be responsible for guiding the management and development of the board’s scientific portfolio and will oversee decisions about awards of grants to scientists and funding of units and institutes.

A similar role will once again be played by Dr David Armstrong who has been reappointed as a Council member and chair of the MRC Health Services and Public Health Research Board. Dr Armstrong is reader in sociology as applied to medicine at Guy’s, St Thomas’s and King’s Medical School at King’s College London. He is also an honorary consultant in public health medicine at the Guy’s and St Thomas’s Hospitals Trust. His research interests embrace health services research, especially in primary care, and the sociology of medical knowledge.

Coming soon – the new MRC website

Behind the scenes at head office, the MRC corporate web communications team and IT service provider, Logica CMG, are hard at work, putting the finishing touches to the new MRC website, which is due to launch in late September.

The MRC site has been completely redeveloped, following a comprehensive review of its information architecture and content. As is often the case with sites of information-heavy organisations with a range of different audiences, the MRC website had grown to the point where navigation had become complex and insufficiently intuitive for users. Internal users tended to be less handicapped by this, as familiarity with the site and the MRC helped to overcome obstacles. But for external users, the experience had become much more challenging.

Aware of these growing ‘usability’ issues, the web communications team worked with a web usability consultancy to get to the heart of the problem, as a starting point towards developing a new, user-friendly site. This included giving volunteers a set of tasks on the site, with a facilitator recording their responses as they moved through the navigation in search of their information goals. The results informed the development of a new, streamlined navigational structure, which in turn was user-tested in prototype to ensure that it reflected target audiences’ needs.

Scientists are a key audience for the MRC site, so the sections on MRC grant funding and career award schemes have been a priority for upgrade, to give a clear overview of the different routes to funding and step-by-step guides to the application and assessment processes. And researchers will now be able to register to receive email and RSS alerts about the latest MRC funding and policy news as it happens, and future editions of Network and other publications.

Visit www.mrc.ac.uk from late September onwards to see the results and give the MRC web communications team your feedback.
Mutagenesis news

The MRC has recently funded four new projects using mouse mutagenesis to study genetic aspects of human diseases. *Network* takes a look at this technique and its potential benefits for research and health…

In recent years, large-scale research projects have revealed that humans and mice share many genes. And functional genomics, which involves studying the function of genes and other parts of the genome, has demonstrated that a large proportion of these genes carry out similar functions. With its highly characterised genome, the mouse is now the model of choice for many researchers investigating the underlying cause of several important human diseases.

As mouse mutagenesis is one of the key methods used to generate new mouse models, the MRC opened a state-of-the-art facility dedicated to this activity in 2004. Located at Harwell, Oxfordshire, the Mary Lyon Centre provides mouse mutagenesis, characterisation and breeding services to other MRC units, including the nearby Mammalian Genetics Unit and Radiation and Genome Stability Unit. One-third of the centre’s resources are available for collaboration with other MRC-funded research groups, providing a platform for the wider development of functional genomics in the UK. The centre is able to house 65,000 animals with advanced environmental engineering and an extensive quarantine capability.

Mouse mutagenesis science

Mouse mutagenesis is carried out in two ways, known as forward and reverse genetics. In reverse genetics, scientists disrupt, knock-out (remove) or knock-in (insert) a specific gene and examine the effect this has on the mouse. Forward genetics involves starting with an observable characteristic, such as eye colour or disease feature, and then working to identify the gene responsible for that characteristic (phenotype). In an enhanced version of forward genetics, a powerful chemical called ethynitrosourea (ENU) is used to induce random mutations throughout the mouse genome. Mice born with interesting phenotypes are then identified and analysed to find out which gene or genes caused the effect.

Detecting subtle changes in mouse phenotypes can be difficult. At the Mary Lyon Centre our scientists screen mice born to ENU-treated fathers for sensory, developmental, behavioural, clinical chemistry, and physical abnormalities, as well as more specialised screens for heart, immune system and other disease-related irregularities.

Although ENU-driven mutagenesis is expected to play a significant role in uncovering new genes, there are some uncertainties about the approach. Some clinical and physiological scientists are not completely convinced that mouse models are appropriate for understanding human gene function, believing that humans are the best experimental animals. There are also concerns that the technique might not be appropriate for modelling late-onset diseases such as Alzheimer’s or cancer; which may be caused by a combination of genes and environmental factors such as diet. As the technique is ‘high-throughput,’ with large numbers of animals screened for unusual characteristics, there is also the potential that some of the more subtle changes may be missed.

Mutagenesis workshop

During the Mary Lyon Centre’s first year, the MRC received a number of mouse mutagenesis proposals from well-established researchers. Unfortunately, independent peer-review showed that the majority were not competitive enough to warrant funding. In July 2005 the MRC held a workshop to explore the reasons for this, involving members of the MRC’s research boards and international experts in ENU mutagenesis and other key fields of mouse genetics.

The day involved in-depth discussion of the benefits of ENU mutagenesis, highlighting its versatility for modelling human gene function and disease. One key advantage is that no assumptions are made at the outset about the genes involved in a disease, so the technique provides a powerful method for discovering the function of completely new genes. Another advantage of ENU mutagenesis is that it causes mutations only in single DNA ‘bases’. How the different mutations alter the function of a gene therefore vary, from slightly diminishing or increasing its activity to disabling it completely. This can give a more accurate reflection of what happens in human diseases than if a gene is ‘knocked out’ completely.

Mutagenesis in the future

The participants suggested that long-term, cross-disciplinary training at the fellowship level would increase the scientific community’s awareness of the different approaches available for generating and investigating new models of disease. And because these studies involve large numbers of mice, they recognised that it may be necessary to prioritise the diseases or physiological systems to be worked on. There was general agreement that the most successful approach would probably be to develop a ‘one-stop shop’ for characterising a wide range of mouse phenotypes.

Looking at the shorter term, the delegates suggested that the MRC should provide strategic funding to support mutagenesis projects proposed by consortia of UK investigators, which would show the demand within particular specialist areas or diseases. These projects would build a broader platform of mouse phenotyping specialists at Harwell and provide valuable evidence to inform the MRC’s longer-term mutagenesis strategy.

As a result, the MRC put out a call for collaborative proposals in ENU mutagenesis in February this year; see below for outcomes of this call.

ENU mouse mutagenesis projects approved in August 2006:

**Consortia led by:**
- **Professor Rajesh Thakker’s team at the University of Oxford** will study new models of bone and mineral disorders.
- **Professor Howard Thomas and colleagues at Imperial College London** will investigate a genetic approach to developing novel mouse models of liver disease.
- **Professor Sianon Gordon and team at the Sir William Dunn School of Pathology at the University of Oxford** will research genetic dissection of immunity and inflammation.
- **Dr Michel Goedert and co-workers at the Laboratory of Molecular Biology** will investigate genetic modifiers in a model of tauopathy.
Strengthening best practice in animal research

In a partnership between the MRC, other public funders and industry, four UK research centres have been awarded more than £111 million to regenerate training in animal research skills...

Capacity Building Awards in Integrative Mammalian Biology have been made to the Centre for Integrative Mammalian Physiology and Pharmacology at Imperial College London, the Centre for Integrative Biomedicine at King’s College London, and to consortia between Glasgow and Strathclyde Universities and the Universities of Manchester and Liverpool.

Integrative mammalian biology is the study of how genes influence the body; it is central to the development of new therapies for human and animal diseases. A recent survey of UK higher education institutes (HEIs) revealed the emergence of a skills gap in integrative mammalian biology thought to be caused by a decline in animal physiology education. The Capacity Building Awards aim to address this by providing funding for academic centres to rebuild their capacity for research training.

Increasing research and training capacity

Announced in June 2006, the awards were jointly funded by the MRC, the Biotechnology and Biological Sciences Research Council (BBSRC), the Department of Trade and Industry, the Higher Education Funding Council for England, and the Scottish Funding Council. These funders believe that UK biomedical research urgently needs scientists who are experts in integrative mammalian biology to translate biological and medical research into treatments for human and animal diseases. The awards will enable the four centres to offer research and training opportunities in areas including heart disease, cancer, neuroscience, reproduction and metabolism. They will also provide a ‘springboard’ to support the long-term sustainability of UK research and training capacity in integrative mammalian biology. Another important outcome will be the creation of an enhanced environment to attract top-level scientists, both to conduct research and to train the next generation of researchers.

Of 20 expressions of interest received in the second half of 2005, six were invited to submit full proposals. These underwent peer review in April 2006, before a cross-funder panel decided on the final four awards. The criteria for assessment included a track record of excellent mammalian biology research and training, evidence of an HEI commitment to management and sustainability.

Lord Sainsbury of Turville, Parliamentary Under Secretary of State for Science and Innovation, said: “The UK is a world leader in medical research and it is essential that we train the next generation of researchers in practical animal research skills so that we can maintain our position. I therefore welcome this excellent joint partnership of the private and public sectors.”

Stem cell science – hope not hype...

Health minister Andy Burnham joined parliamentarians and scientists from the MRC and the Biotechnology and Biological Sciences Research Council (BBSRC) at the launch of a public exhibition on stem cell science at the Houses of Parliament in June.

The exhibition, which is now touring the country, explains why and how stem cells offer hope to sufferers of incurable diseases such as Alzheimer’s and Parkinson’s. It also conveys the challenges for both policymakers and scientists in balancing public expectation with scientific reality.

Speakers at the event included Lord Patel, chair of the Stem Cell Steering Committee, Andy Burnham and two leading scientists in stem cell research, Professor San Harding and Professor Tariq Enver.

Professor Harding, from the National Heart and Lung Institute, explained the advances that have been made in the development of embryonic stem cells to generate cardiomyocytes (beating heart cells) from both human and mouse cell lines. Contraction of these cardiomyocytes is measured by methods adapted from those used for adult cells. The beating cells can be seen online at www.fom.sk.med.ic.ac.uk/medicine/about/divisions/ntll/heart/molcell/fm/.

Professor Enver, from the MRC Molecular Haematology Unit in Oxford, described his work trying to understand the molecular events associated with the self-renewal of haematopoietic (blood) stem cells and their decision to form blood cells, and what goes wrong in leukaemia.

The exhibition has been developed by the BBSRC and the MRC as part of the research councils’ response to the Paterson report recommendation for a “sustained and coordinated programme of public dialogue on stem cell research over the next decade.” The exhibition began in Newcastle at the Centre for Life in July, and will be in Scotland from September. There are also plans for it to travel to the UK Stem Cell Bank in Hertfordshire and to Cambridge.
MRC training review

An expert working group is reviewing the training the MRC provides for the scientific community, to help ensure that the right amount of money is being spent in the right areas…

As well as being an important part of the MRCs mission, training skilled researchers is a priority in the Government’s Science and Innovation Investment Framework 2004-2014, which emphasises the importance of a skilled R&D workforce to the competitiveness of the UK economy. The MRC’s remit includes meeting the needs of the UK academic sector and the National Health Service for skilled researchers, as well as supporting industry in this respect. About 12 per cent of our overall funding is spent on research training and career development awards, such as studentships and fellowships. To review and evaluate this investment, the MRC’s Council set up an independent working group earlier this year (see box for details of members).

The working group will make recommendations to the MRC about its overall level of spending on training and the appropriate balance of support across different career stages and groups, for example, between postgraduate and postdoctoral awards, between training for clinical and non-clinical scientists, between scientists in the MRC’s units and universities, and between basic and applied research.

MRC training in context

In the UK there are a number of organisations that fund medical research training, so the group is looking at the MRC’s support in the context of this larger picture. It will not assess specific schemes in detail, but will take into account the recent review of MRC support for early-career non-clinical scientists led by the Training and Career Development Board, and recent reviews by organisations such as the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry.

The MRC’s five research boards have their own budgets for research grants and responsibility for managing their individual portfolios, while the Training and Career Development Board is responsible for training and career development awards in all scientific areas within the MRC’s remit. The training review will consider whether the mechanisms for oversight and governance of investment in training could be improved, to help ensure that training and career development support is in line with the MRC’s scientific and strategic priorities.

Consultation and reporting

The working group has already consulted a variety of stakeholders, including universities, academic societies, the health departments, other government departments, research charities, and industry. It aims to complete its report during autumn for consideration at a meeting of the MRC’s Council in December 2006. Look out for an article summarising the report in a future edition of Network.

MRC Training Review Working Group

- Chair: Professor Herb Sewell, professor of immunology and pro-vice-chancellor for research at Nottingham University and MRC Council member.
- Dr Tony Bradshaw of the Bioindustries Association and director of bioProcess UK.
- Professor Keith Gull, principal research fellow at Oxford University and member of the MRC Basic Research Overview Group.
- Professor Stephen Holgate, MRC clinical research professor at Southampton University and member of the MRC Clinical Research Overview Group.
- Professor Sally Macintyre, director of the MRC Social and Public Health Sciences Unit and a member of the MRC Population Health Research Overview Group.
- Professor Dave Moore, director of the MRC Institute of Hearing Research.
- Dr Philip Wright of the Association of the British Pharmaceutical Industry.

New MRC centre to research cancer diet link

The MRC has awarded £2.3 million to fund research into the impact of diet on cancer at the newly established MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival (CNC) at the University of Cambridge. Dr Sheila Bingham of the MRC Dunn Human Nutrition Unit will direct the new centre.

Cancer remains one of the most common causes of death in most western countries, including the UK. The new centre will provide international leadership in research into the molecular origins of dietary links to cancer; through its work spanning the basic molecular science of cancer; the role of nutrition and epidemiological techniques.

The CNC will conduct epidemiological studies into links between cancer and diet and will provide a UK focus for multidisciplinary training in nutrition and monitoring cancer in the population. Initial research will build on the findings of the European Prospective Investigation of Cancer (EPIC) study, and will provide sound scientific evidence to underpin intervention studies, public health advice and clinical guidelines for patient treatment.

At the CNC’s opening on 7 July 2006, MRC Chief Executive Colin Blakemore said: “MRC funding for the centre is a response to evidence suggesting a causal link between diet and cancer risk. Future research results will help scientists to better understand the relationship between diet and ill health. In the long term, research conducted at the CNC will contribute to public health advice and clinical treatment guidelines to benefit people who suffer from cancer.”
National Centre for the Replacement, Refinement and Reduction of Animals in Research: 3Rs Research Funding Scheme

Funding is available for research which advances knowledge in the replacement, refinement or reduction of animals in research. The deadline for applications is 14 February 2007. For further information please visit www.nc3rs.org.uk or email enquiries@nc3rs.org.uk.

Translating antibody targets into therapies

The Therapeutic Antibody Group (TAG) at MRC Technology collaborates with MRC scientists to translate novel antigenic targets they have identified into potent and selective therapeutic antibody candidates. TAG is now looking for the next generation of potential antibody-based therapies. If you have an antigen or antibody that you think might be important then please complete our short online questionnaire. Entries will be placed into a draw for a grant of £500, to be put towards sending the winner to a conference of their choice. For further information visit www.mrctechnology.org/abq.htm. Deadline 31 Oct 2006.
Haematological diseases present numerous challenges to researchers and clinicians who are trying to understand how mutations in blood cell development can cause such devastation to the human body. The MRC Molecular Haematology Unit is a key player in this quest for understanding...

In the next year, over 100,000 children around the world will be born with thalassaemia, an inherited blood disorder that affects haemoglobin, the oxygen-carrying protein in the blood. Over the same 12 months, some seven thousand people in the UK will be diagnosed with leukaemia and the parents of a thousand UK children will be told that their child has sickle-cell anaemia.

Blood disorders are widespread throughout all ethnic groups and their treatments are often high-maintenance. An important approach to understanding them is by studying haemopoietic (blood) stem cells. The process by which these undeveloped cells divide, replicate and form mature red and white blood cells and platelets, called haemopoiesis, is the focus of research at the MRC Molecular Haematology Unit (MHU) in Oxford. By studying how haemopoietic stem cells develop and differentiate, scientists at the unit hope to learn more about the causes and evolution of common blood diseases. Ultimately, their goal is to improve treatment options for patients who have acquired or inherited such diseases.

The MHU is housed within the Weatherall Institute of Molecular Medicine in the grounds of the John Radcliffe Hospital in Oxford. It was established in 1980 under the directorship of Sir David Weatherall. At that time the unit focused on understanding the molecular basis of the globin gene disorders, which involve the group of proteins called globins that help transport oxygen in the blood.

This work had been largely completed by the time Professor Doug Higgs (right) was appointed MHU director in 2001. Under Doug's directorship and following on from the unit's previous success, the MHU began a new scientific programme based on the continued study of the globin genes and the broader study of the process of haemopoiesis. He drew together a team of international experts in the field: the unit now comprises nine research programmes that, says Doug, "bring together a multidisciplinary, interactive team of scientists and clinicians dedicated to understanding the normal process of haemopoiesis and the diseases that occur when this process is disrupted."

Gene regulation

Doug and his colleague Professor Bill Wood are carrying out research into gene regulation, the process by which genes are switched on and off. They are also interested in the diseases that occur when gene regulation goes awry. Doug explains: "Within the region of one of our chromosomes, called chromosome 16, lie the alpha globin genes – the genes that direct the production of part of the haemoglobin molecule. When something affects the regulation of the alpha globin genes, patients develop alpha thalassaemia, which is one of the world’s most common genetic diseases. As well as suffering from alpha thalassaemia, rare patients are also born with mental retardation and other developmental problems. Some of these patients have a piece of chromosome 16 missing from the region we are looking at. With the information from our studies, we are identifying precisely which genes are missing in these patients and how that loss contributes to their mental and developmental difficulties."

Blood stem cells

Most cells in the body have a particular purpose which cannot be changed. For instance, a liver cell has developed to perform specific liver functions and cannot suddenly take on the role of a heart cell. But stem cells, which are still at an early stage of development, retain the potential to turn into many different types of cell. When a stem cell divides, each new cell can either remain a stem cell or become another type of cell with a more specialised function. When a haemopoietic (blood) stem cell divides it creates two daughter cells: one is a replica of the original stem cell while the other develops and differentiates into a mature blood cell, such as a red or white blood cell or a platelet.
From pre-leukaemic disorders to leukaemia

Anaemia is usually due to a deficiency of the red blood cells that are needed to carry oxygen around the body. It causes symptoms ranging from tiredness and breathlessness to an irregular heartbeat and dizziness. Severe anaemia can be caused by myelodysplasia, a condition in which haemopoietic stem cells fail to mature properly and therefore do not function correctly. A diagnosis of myelodysplasia can then lead to other problems. Imagine all these malfunctioning cells being transported around the body through the blood stream as faulty buttons in a button factory. While correctly-manufactured buttons pass through the factory machinery, get sorted into boxes and go on to distribution, the faulty buttons go nowhere. They accumulate on the ‘rejects’ pile and unless disposed of, can block the factory machinery. When this happens in the human body, the build-up of immature, malfunctioning blood cells can eventually lead to leukaemia. In around 40 per cent of patients, myelodysplasia is a preleukaemic disorder that eventually leads to leukaemia.

Understanding myelodysplasia depends on knowing how blood cells are normally made and mature in the bone marrow, and this is the role of Dr Paresh Vyas’s group. He says: “Over the last few years we have found a common cellular defect at the first stages of haemopoietic differentiation in adult patients diagnosed with early myelodysplasia. In addition, our group has focused on one critical factor that is required in blood production: GATA1. GATA1 coordinates many aspects of the normal maturation programme of blood cells and we are studying various aspects of its biology.”

The group now knows that mutations in GATA1 help to cause a preleukaemic disorder in newborn infants with Down syndrome called Transient Myeloproliferative Disorder. In approximately 20 per cent of cases, this condition will progress to acute megakaryoblastic leukaemia (AMKL). Overall, AMKL occurs in about one per cent of children born with Down syndrome. Paresh says: “Our overall aim is to improve the diagnostic, prognostic and therapeutic aspects of the management of AMKL in Down syndrome children and myelodysplasia in adults.”

Clinical links

Paresh is one of a number of scientists within the MHU who also has clinical responsibilities. He’s a consultant haematologist at the John Radcliffe Hospital, as are several of his research colleagues. He explains: “Haematology lends itself to science as much of our clinical work is lab-based anyway; haematologists are always looking down microscopes. Furthermore, if you want to carry out research into abnormal cells, blood cells and bone marrow samples are easy to get hold of.”

Integrating the MHU scientific programme with clinical departments of haematology in Oxford and across the UK is a high priority for Doug Higgs. The unit now has monthly scientific/clinical meetings and works closely with haematologists nationwide. “We are working towards making the MHU an internationally recognised centre of excellence in haemopoiesis and haematology,” he says. Part of the unit’s ongoing work to meet this aim is the establishment of an academic department of haematology in Oxford, and the future appointment of a chair of haematology.

T-ALL order

The haemopoietic system works hard to keep up with the body’s demands. It has to keep the number of blood cells in our body constant and so must run efficiently and be highly regulated. Dr Catherine Porcher’s group studies the role of one regulator of this system, a protein called SCL. It is crucial for the formation of the first haemopoietic stem cells during embryonic development and for the production of red blood cells and platelets. If SCL is not regulated, the blood cells do not mature properly. Through a process called leukaemogenesis, this can then lead to the development of a type of leukaemia called T-cell acute lymphoblastic leukaemia (T-ALL).

Catherine and her colleagues are trying to understand how SCL works in normal haemopoiesis. She says: “This will then give us insight into how deregulation of SCL might promote leukaemogenesis, with the aim of developing new therapeutic approaches in T-ALL.”

We are working towards making the MHU an internationally recognised centre of excellence in haemopoiesis and haematology.

Professor Doug Higgs
MHU director
Exploring stem cells

Often, the only treatment for leukaemia and aggressive cancers is a stem cell transplant. Around 45,000 of these procedures are carried out worldwide every year. It is already known that stem cells have the ability to self-renew, and it is now suspected that this may also be the case for cancer cells. Professor Roger Patient's group is trying to understand better how and where stem cells are made and controlled, with a view to learning more about how other types of cells, such as cancer cells, are controlled.

Roger explains: “We are working out the genetic programming of stem cells which takes place during embryonic development. We study amphibian and fish embryos because, firstly, they develop externally in large numbers rendering them ideal for study and, secondly, because the processes involved have been highly conserved during evolution and therefore what we discover in these model organisms has direct relevance to humans.”

Haemopoietic stem cells come from the same population of cells in the embryo that gives rise to the cardiovascular system. So anything that the group discovers about blood programming may also have direct relevance to heart tissues and the diseases that affect these tissues.

It's fascinating stuff and the potential of Roger's work is reflected in the research programme of Dr Marella De Bruijn. Her group is studying one element of the stem cell generation process — Runx1. Runx1 is a transcription factor, meaning it controls the expression of genes and so can determine whether a cell will become a blood cell and, if so, what type. Marella says: “Mutations of Runx1 are found in approximately 25 per cent of acute leukaemias. Studying how Runx1 works in normal blood stem cell formation and how it relates to other transcription factors will hopefully help the group to contribute to a better understanding of leukaemogenesis and ultimately to the development of new therapies.”

Transcription factors and gene expression

To learn more about how transcription factors work and how they affect gene expression, it's necessary to get right back to basics and study what is going on inside the nucleus of the cell. Dr Veronica Buckle and Dr Francisco Iborra are doing just that. They are looking at how the organisation of DNA within a cell nucleus and the presence of transcription factors can influence how a gene is expressed. Veronica says: “We use the development of blood cells as a model system because this is a well-characterised process. We can easily link changes in nuclear structure and transcription factor levels with gene expression.”

Despite the revolution in genetics in the last decade and in particular the sequencing of the human genome, the regulation of gene expression remains largely a mystery. Although every cell of the body contains a full complement of genes, each cell only expresses a small range that are required for its specific function, such as the oxygen-carrying protein haemoglobin in red blood cells.

Dr Richard Gibbon's group aims to determine the role of proteins in the regulation of gene expression and their involvement in human disease. Richard is a clinical geneticist who specialises in inherited syndromes that affect intelligence. Many diseases have now been identified which are caused by disruption to proteins involved in regulating gene expression.

In one such condition, ATR-X syndrome, affected children have profound learning difficulties, a characteristic facial appearance, physical abnormalities and thalassaemia. Richard explains: “It arises because of mutations in a protein involved in the regulation of gene expression. The diverse problems suffered by children with ATR-X probably reflect the many different genes whose expression is disrupted.”

Since geneticists became aware of ATR-X, some 150 affected people from 120 families around the world have been identified as carriers. Of these, approximately 40–50 are British. As there's no provision for ATR-X testing within the National Health Service (NHS), the MHU provides a valuable diagnostic service and reference centre for the country's geneticists and paediatricians. Pregnant women at risk are offered in utero testing for the syndrome and families can obtain information and advice via a bespoke website or by contacting the research group directly. Richard says: “We have built up good relationships with many families and our research has benefited greatly through their goodwill and participation.”

Working decisions

Professor Taqir Erver is internationally recognised as an expert in haemopoiesis and his group is researching how and why stem cells decide whether to self-renew or to differentiate into mature blood cells. They're also looking at how a blood stem cell becomes a specific type of cell, such as a red blood cell or a platelet. Taqir says: “These ‘working decisions' that stem cells make are ultimately effected at the level of differential gene activity or usage, and understanding how this process works is an important challenge in developmental biology, transplantation medicine, stem cell-based gene therapy and blood cancers.” He adds: “We anticipate that our research will illuminate how normal cell fate decisions are instigated. This in turn should inform our approach for manipulating stem cells and their fate for therapeutic purposes.”

Steps towards a centre of excellence

The MHU's work is providing invaluable insights into haemopoiesis and the development of best practice in scientific and clinical collaborations. With multiple potential therapeutic outcomes of the unit's research, its scientists are driven in their desire to identify the fundamental processes involved in the development and mutation of blood cells. Doug Higgs sums up: “Over the past five years the very fruitful collaboration between the MRC-funded MHU and our NHS colleagues has made the first important steps towards creating a centre of excellence in haemopoiesis and blood disorders. Over the next five years we hope to develop this further and increase the flow of our basic science into the clinic.”
The MRC achieved an important milestone in its plan for improved administrative efficiency with the official opening of its new Shared Service Centre (SSC) in May by MRC Chief Executive Colin Blakemore. Colin paid tribute to the MRC staff who had contributed to the project and welcomed the newly recruited staff working in the SSC.

Based in Swindon, the SSC is now fully staffed and operational and has already taken on finance, HR and procurement work from MRC units in London and Scotland and from MRC Head Office. Work from other units and institutes will transfer in a planned programme over the coming months. Ultimately, the staff of nearly 100 in Swindon will provide support services to just under 40 MRC units. They will handle transactional work, allowing people in the units to concentrate on providing support for their directors on strategic and management issues. The recruitment of additional professional regional finance and HR staff will also help to ensure that units have effective administrative support. The aim is to release as much of the MRC’s financial resources as possible for spending on research.

The MRC has also recently commenced the roll-out of its new electronic purchasing system, EBP, across its units. This will further streamline purchasing and contribute to the cost-savings target.

The MRC is now working closely with the other research councils to develop a shared service centre structure that will provide a wide range of support services to all the councils by 2009. Phil Lambert, director of the SSC says: “The new MRC SSC will provide valuable experience for the project teams developing this wider structure, and we will aim to ensure that the joint facility builds on the considerable work in building infrastructure and mapping business processes that many MRC staff contributed to when building our SSC.”

## NIMR update

Since our last update on the National Institute for Medical Research (NIMR) in autumn 2005, plans for the institute’s renewal have continued apace…

With the retirement of Sir John Skehel at the end of September 2006, the appointment of a new director has been a hotly debated topic. The announcement that Professor Scott Fraser of the California Institute of Technology had been invited to take over the directorship came at the beginning of July, along with the news that Sir Keith Peters had agreed to serve as transitional acting director. The MRC has started formal negotiations with Professor Fraser, who is keen to respond to input from members of staff at NIMR and has set up an email address specifically for this purpose: fraser.caltech@gmail.com.

The project board, responsible for the day-to-day oversight of the renewal process and delivery of the detailed business case, has now met five times and will continue to meet at least monthly until its work is completed in October. The business case must be completed in time for submission to the MRC’s Council at its meeting on 11 October. The document will then be revised in the light of the Council discussion and be submitted to the Office of Science and Innovation and the Treasury. It will provide the material to enable them to make their decision on the capital investment that the MRC is proposing.

The first issue of a quarterly newsletter providing the latest developments and progress of the renewal project was published in July. The newsletter is circulated to all NIMR staff and available electronically on the MRC website. In addition, a series of consultations with NIMR staff are planned as part of the MRC’s ongoing communications strategy for the renewal.

### DNA workshops

Scientists from the MRC’s Virology Unit in Glasgow will run a series of DNA workshops at the city’s Science Centre this autumn. The workshops will give advanced students the opportunity to try out the latest molecular biology techniques and to meet and talk to MRC scientists about research and careers in biomedical science.

This is the second year the unit has run the workshops, and last year’s event was a great success. As one student reported later, “I really enjoyed the whole experience – it was a great opportunity to gain some inside information on careers and some great hands-on practical work. I have decided to pursue a career in medical research.”

The workshops run daily from 24–27 October. For further information visit www.glasgowsciencencentre.org or call the education team on 0871 540 1003.

### NICE conference

The MRC will be part-sponsoring the NICE (National Institute for Health and Clinical Excellence) conference in Birmingham in December this year. Further information about the MRC’s part in this annual event will be available later in the year.

More details are available at www.mrc.ac.uk and www.nice.org.uk.
Building international links for UK scientists

The MRC has refined its international strategy, defining and promoting its role in global research and increasing opportunities for collaboration and input into the global science agenda…

The revised international strategy will provide a framework for the MRC to coordinate and prioritise international activities so that we gain maximum advantage from the many emerging international opportunities for researchers. It was developed by the Council’s International Strategy Overview Group (ISOG) and will be published later this year. Professor Chris Higgins, chair of ISOG, says: “Healthcare and biomedical research are truly international activities and the MRC is an international leader. Establishing a specific international overview group enables the MRC to increasingly play a leading role, and MRC researchers to benefit from new scientific applications.”

Biomedical and healthcare research and policy have become global activities. Increasingly, the MRC recognises that much is achieved through partnerships with others, and that research overseas often has immediate implications for work in the UK.

International leadership

As a worldwide leader in science, the MRC aims to influence international research strategies, policies, ethical and governance frameworks, and legislation in ways that will enhance UK research and encourage collaborations. Professor Higgins says:

“The UK, and the MRC in particular, is at the forefront of biomedical research and it is important we provide leadership and also transfer our expertise to developing countries.”

Therefore, the first element of the strategy will include promoting the MRC’s role to international organisations with interests in medical research. In turn, this will ensure that we continue to help shape the international research agenda, and benefit from and contribute to international collaborations.

Joining forces worldwide

MRC-supported international collaborations enable our scientists to work with researchers in other countries. For example, the MRC has contributed significantly to the international effort in understanding the potential threat from flu – an emerging global problem – by making additional funding of up to £15 million available for commitments to research over the next two years. Several new projects involve collaboration with scientists overseas, including the USA, Vietnam, China and Australia.

MRC researchers are also successful in winning funds for collaborations from other organisations. For instance, Professor Tim Aitman, who leads a group at the MRC Clinical Sciences Centre in London, won funding from Fondation Leducq – a not-for-profit foundation in Paris – to investigate the genetic causes of cardiovascular disease, in collaboration with Harvard University and groups in France, Sweden and the Czech Republic. Professor Aitman says: “Progress will be greatly accelerated by international collaborations such as the Leducq.”

A great deal of biomedical research is now conducted on a scale that is not achievable by a single country and can be accomplished only through international collaboration. For example, the MRC helps fund the Cambridge-based European Bioinformatics Institute (part of the European Molecular Biology Laboratory).

This is Europe’s leading provider of biological databases, containing information such as DNA and protein sequences and structures, and providing freely available data and bioinformatics services to researchers.

Developing research capacity overseas

An outcome of international collaboration can be the development of research capacity – the third part of the strategy. This is especially important in lower and middle-income countries where the MRC identifies unique opportunities for undertaking particular research. This may include a community where there is greater incidence of a disease than in the UK, thus allowing larger studies and quicker assessment of treatments or changes in behaviour. This helps to provide local solutions to healthcare issues that are also applicable to the UK. For example, the MRC funds a research grant based in India, led by Dr Caroline Fall at the University of Southampton, investigating whether adult disease is preventable by measures that optimise fetal, infant and childhood nutrition. Dr Fall’s team has found that there is a link between diabetes in the mother and diabetes in the child.

<table>
<thead>
<tr>
<th>MRC International Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>The MRC’s strategy is split into three parts:</td>
</tr>
<tr>
<td>• Shaping the international research agenda through the MRC’s scientific leadership.</td>
</tr>
<tr>
<td>• Encouraging international collaboration in biomedical research.</td>
</tr>
<tr>
<td>• Assisting in the development of research capacity, especially in less developed countries so that they may become effective partners with the UK.</td>
</tr>
</tbody>
</table>
Global health funders forum

Together with the Wellcome Trust, the Department for International Development and the Economic and Social Research Council, the MRC is part of a UK funders forum on health research in developing countries that was set up in 2004. One of the forum’s key roles is to ensure that these funding partners coordinate their activities and respond effectively to international initiatives and emerging health issues. With their similar research objectives in this area, they share interests in capacity building and in developing ways to translate the outcomes of research into public healthcare policy and practice. And from the outset, forum partners have attended international meetings on behalf of each other when necessary, to present a coherent UK presence and perspective.

In November 2004 the forum hosted a meeting of UK researchers involved in the development of HIV vaccines. The aim was to determine how the UK could best contribute to the Global HIV Vaccine Enterprise, a G8 consortium aimed at speeding the development of an HIV vaccine. Following the meeting, the forum funded a scoping exercise of UK activities, which has led to the development of a consortium-based research strategy and a coordinated mechanism for taking forward the resulting research proposals. And in March 2006 the forum supported a workshop on the social impacts of antiretroviral therapy (ART) for people with HIV/AIDS in Africa. This workshop brought together social scientists from a range of disciplines to discuss issues relating to stigma, sexual risk behaviour, prevention, macro- and micro-economic impacts of ART, and impacts on healthcare systems. Several of the issues that arose at the meeting will be followed up in more detail by researchers.

Effective and fair delivery of HIV therapy

In May 2006, the MRC/Ugandan Virus Research Institute and the London School of Hygiene and Tropical Medicine held a workshop on AIDS in Uganda. The event, which focused on developing strategies for the effective and fair delivery of ART in sub-Saharan Africa, brought together researchers, policymakers and funders from Uganda and internationally. The aim was to define the priorities for research into ART delivery that are needed to inform public health, and to discuss how this research might be funded. The participants gave highest priority to research looking at ways in which health services can deliver ART, both from hospitals and health centres; strategies for supporting healthcare workers to improve professional practice; identifying new strategies for HIV prevention; and determining how these strategies should be integrated with treatment programmes.

Global health research update

The MRC has been carrying out pioneering research into infectious diseases in Africa for more than 90 years. Read on to learn about current and recent activities…

Also, if the child has a low birth weight, doesn’t grow well during the first year and then grows rapidly after the age of two – even without being obese – there is an increased risk of diabetes. These results are “more startling in the developing world,” says Dr Fall, because there is a higher incidence of diabetes. Her grant also contributes to better infrastructure in the Indian centres and allows exchanges of UK and Indian scientists.

The MRC also represents the UK on the European and Developing Countries Clinical Trials Partnership (EDCTP), and Dr Diana Dunston, director of the MRC’s Research Management Group, is the current chair of the European Economic Interest Grouping (EEIG) Assembly. EDCTP aims to tackle poverty-related diseases such as HIV/AIDS, tuberculosis and malaria, as well as setting up self-sustaining infrastructure in developing countries once particular research programmes end.

The need to continue to invest in such opportunities for funding research capacity is an important part of the MRC’s international strategy. Professor Higgins says: “Scientists have many bright ideas, but we need to ensure the MRC has effective mechanisms to identify, prioritise and fund this excellence in science.”

Find out more online

A new booklet, Improving health, improving lives: MRC-funded research in Africa, looks at how the MRC’s units in The Gambia and Uganda are tackling diseases that have a major impact in Africa and other developing countries. To download or order a copy visit www.mrc.ac.uk/index/publications-general_publications.htm.
Antiviral proteins could reduce asthma risk

Low levels of antiviral proteins may be to blame for causing people with asthma to have more severe attacks if they catch a common cold virus, say MRC-funded scientists. They hope that the finding will lead to a new method of asthma treatment. Professor Sebastian Johnston, of the MRC and Asthma UK Centre in Allergic Mechanisms of Disease at Imperial College London, and his team tested cells from the lungs of volunteers with and without asthma. They found that, when infected with the rhinovirus, the lung cells from asthmatics produced half the levels of a newly identified family of interferons – proteins with antiviral properties generated by the immune system. “People with asthma are particularly susceptible to rhinoviruses, which are the major cause of severe asthma attacks. When we tested volunteers with and without asthma, we found these new interferons, which would tackle the infection, were not being produced as effectively in people with asthma,” said Professor Johnston. “The discovery of this mechanism could be of huge importance in how we treat asthma attacks. Delivery of the deficient interferons by inhalers could be an ideal way to treat and prevent severe attacks of asthma, potentially vastly improving the quality of life for many asthma patients.”

Nature Medicine 2006: Advance online publication

Self-harm and the Goth subculture

Between seven and 14 per cent of young people in the UK deliberately harm themselves. MRC researchers have shown that those who identify with the ‘Goth’ subculture are more likely to self-harm or attempt suicide than other young people. Led by Robert Young of the MRC Social and Public Health Sciences Unit in Glasgow, the team tracked more than 1,200 young people who were aged 11 in 1994 for eight years. Around seven per cent claimed to identify with the Goth subculture. Of those who identified most strongly, more than half admitted to self-harming at some point in their lives, compared with only six per cent of young people who did not associate with the subculture. Other factors that increased the likelihood of self-harm or attempted suicide were being female, having separated or divorced parents, smoking and drug use, and previous depression. Nevertheless, the scientists suggest that the Goth subculture may actually protect some vulnerable children by offering them valuable social and emotional support from their peers.

British Medical Journal 332: 1058–1061

Bird flu’s Achilles heel

Scientists at the National Institute for Medical Research in London have discovered subtle variations in the structure of the bird flu virus H5N1 that could lead to more effective anti-flu drugs. All flu viruses have the proteins haemagglutinin and neuraminidase on their coats – the H and the N in their name. There are nine forms of neuraminidase, which allows the virus to be released from a cell so it can infect new cells. The anti-flu drugs oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differs from the active sites of N2 and N9. So although oseltamivir and zanamivir are both designed to block neuraminidase, but are based on the N2 and N9 forms of the protein as these were the only ones available when the drugs were developed. Led by Sir John Skehel, the scientists used X-ray crystallography to show that the active site of N1 differ...
Common painkillers could raise heart attack risk

Last year a drug called Vioxx®, a COX-2 inhibitor, was withdrawn from the market after it was shown to increase the risk of heart disease. And now an MRC study involving more than 140,000 people has revealed that high doses of common painkillers called non-steroidal anti-inflammatory drugs (NSAIDS) could also increase people’s heart attack risk. Researchers at the MRC- and Cancer Research UK-funded Clinical Trial Service Unit, based at the University of Oxford, collaborated with colleagues at the University of Rome to study the results of 138 trials that examined the cardiovascular effects of COX-2 inhibitors or NSAIDS. They found that both COX-2 inhibitors and high doses of the NSAIDS ibuprofen and diclofenac were associated with around a two-fold increased risk of heart disease. However, researcher Dr Colin Baigent said: “Many patients with severe chronic arthritis depend on these drugs to stay physically active, so it is important that they and their doctors can weigh up their benefits and potential harm. This research summarises what is known about cardiovascular risks, but doctors also need to consider the gastrointestinal and other potential risks of these drugs before deciding which is best for a particular patient.”

British Medical Journal 332: 1302–1305

New gene link to dementia

Approximately 750,000 people in the UK have some form of dementia. The second most common type after Alzheimer’s disease is frontotemporal dementia (FTD), which affects one in 5,000 people, mostly aged between 50 and 60. Research by MRC scientist Dr Stuart Pickering-Brown and colleagues at the University of Manchester has identified a gene linked to FTD, opening up new possibilities for diagnosis and treatment. The team discovered a link between FTD and a gene called granulin, which is on the same chromosome as the tau gene, which has previously been linked to the disease. “While a lot of progress has been made in understanding Alzheimer’s disease, relatively little was known about the genes linked to FTD. Yet about half of all people with FTD have other family members with the disease,” said Dr Pickering-Brown. “We now know that many other cases are caused by errors in the gene granulin. These results mean that we should be able to develop therapies and treatments to tackle this form of dementia.”

Nature 2006: Advance online publication

Resisting anything but temptation

Different people have higher or lower ‘reward sensitivity’, a personality trait that reflects their drive to pursue rewarding or pleasurable experiences. And now researchers have shown that individuals with higher reward sensitivity show increased activity in the parts of the brain implicated in reward when looking at pictures of appetising food. In an attempt to explain why some people are more likely than others to become overweight or obese, Drs John Beaver, Andy Calder and Andrew Lawrence of the MRC Brain Science and Cognition Unit in Cambridge used functional magnetic resonance imaging to measure people’s brain activity in the areas involved in motivation or reward when they were shown pictures of highly appetising foods such as chocolate cake, bland foods such as broccoli and disgusting foods such as rotten meat. Afterwards they completed a questionnaire that assessed their levels of reward sensitivity. The participants’ scores on the reward sensitivity questionnaire predicted the extent to which the appetising food images activated their brain’s reward network. “The new findings demonstrate that even in healthy individuals some people’s brain reward centres are more sensitive to appetising food cues. This helps explain why some individuals are more vulnerable to developing certain disorders like binge eating,” said Dr Beaver.

Journal of Neuroscience 26: 5160–5166
Money matters

A major challenge for the MRC is planning what to commit to spend in future years, so that the money matches the MRC’s allocation from Government during each of those years. Nigel Watts, MRC finance director, told Network more about what’s involved...

Our year-on-year spending – the money that the research community sees – depends on commitments that we make several years before. This is where good financial planning and modelling comes in. What we commit in the current year won’t have an impact until later years: we have to aim for a spend that matches income in any given year. This is hard to balance exactly, but we are usually allowed to carry forward any surplus money left over from previous years, which helps to smooth out expenditure.

We did well last year: Our income from the Office of Science and Innovation (OSI) was £444m and we spent £459m, which was close to our prediction. The difference was funded out of our brought-forward surplus.

Financial planning involves taking some risks. Judging what risks to take is what we’re getting out of our brought-forward surplus.

By the end of next year, we will aim to have used up a lot of the £50m surplus, and we have improved our modelling to reduce the risk of it building up another large surplus.

In 2005/06 we increased our spending by 17 per cent, compared with the previous year; and increased external grant payments by 20 per cent. We have also committed substantially more money to new grants. The value of new grants awarded to universities rose from £94m in 2003/04 to £170m in 2004/05 and to £194m in 2005/06.

Subject to the outcome of future expenditure reviews, we anticipate that overall spend will increase by a third over the next six years, spending on grants will double, and spending on fellowships and studentships will increase by over 70 per cent.

A more balanced view of risk, together with good modelling and careful planning of commitments means that we will be more able to fund the best science, consistently and efficiently, and capitalise on the growing OSI contributions that reflect the Government’s strong focus on UK science.

Cheltenham Science Festival 2006

In June 2006 the MRC once more played an important role in the Cheltenham Science Festival. The festival was first held in 2001, so to mark its fifth anniversary three of the big science issues at the first festival – cloning, human genetic and electricity – were revisited in a series of lectures. The MRC sponsored one of these, ‘Genetics – Five Years On’, which was hosted by Lord Robert Winston with contributions from Imperial College London geneticist Dr Armand Leroi, Professor Marcus Pembrey of the Institute of Child Health and Dr Mark Ross of the Wellcome Trust Sanger Institute. The four experts looked at how scientists learnt the sequence of the human genome – hailed as the blueprint for life – and asked whether it has turned out to be as useful as predicted.

To coincide with its imminent publication of the findings of a public consultation into ageing research, the MRC sponsored an event entitled ‘The Ageing Population’. Professor Raymond Tallis, a leading expert in geriatric medicine, looked at some of the issues around growing older in the UK in the 21st century. Reassuringly, he summarised new evidence that shows that people are not only living longer but are also staying healthier for longer than ever before.

An estimated 45,000 people took part in the festival during its five days, including the 15,000 visitors who attended its 60-odd lectures and events. A big draw was the Discover Zone, a huge space in the city’s Town Hall that was dedicated to bringing hands-on science to the general public.

The festival hosted the final of Famelab, a nationwide search to find the UK’s best new talent in science communication. MRC-funded PhD student Sarah Forbes-Robertson was among ten national finalists, each of whom had just five minutes to explain a difficult scientific idea to a panel of judges that included festival director Kathy Sykes, Daily Telegraph science correspondent Roger Highfield, and Mark Lythgoe, a neurophysiologist at London’s Institute of Child Health. Sarah gave a fascinating explanation of an area of genetics – specifically what makes an octopus different from other sea life and from most other life on Earth. And although she didn’t win the closely-fought final, Sarah won the public vote for the best science podcast on the Channel 4 Famelab website. Many congratulations!
A pioneer in public health and tuberculosis research, Dr Philip D’Arcy Hart died in July 2006 aged 106. At a time when the necessity of clinical trials was debated, he used a trial to show that antibiotics could be used as a non-surgical therapy for TB. Later he established current public health policy by trialling the BCG vaccine in thousands of school children.

Philip Montague D’Arcy Hart was educated at Clifton College, Bristol, and Gonville and Caius College, Cambridge. He trained in clinical medicine at University College Hospital Medical School, London, where he thrived in the academic atmosphere and gained an MD by thesis in 1930. In 1939, he left his prestigious clinical teaching post to join the MRC to concentrate on research. His first task was to lead a group investigating the prevalence of the fatal lung disease pneumoconiosis in Welsh coal miners. By linking the hardness of coal (and thus the amount of dust generated by mining) to geographical correlation of the disease, the group showed that coal dust was harmful.

In 1946 Philip transferred to the Tuberculosis Research Unit in London. He led the unit from 1948, splitting his time between administrative and research duties until his retirement in 1965. Such was his devotion to research, upon retirement he took up an MRC grant at the National Institute for Medical Research and sought to understand the mechanisms of the tuberculosis bacterium that he had not had time to challenge in his first career.

Colleagues remember Philip as a remarkable person who achieved two quite distinct careers in one lifetime. In this new century, tuberculosis is as relevant to international public health as it was to the UK when Philip’s research began. His discoveries and research achievements continue to guide scientists today.

Priorities in population health research

The Population Health Research Overview Group was set up last year to develop the MRC’s future strategy for population health research. Network reports on progress so far…

In 2004 the MRC identified public health research and clinical research as crucial domains for investment, and has therefore shifted spending priorities towards these linked areas. A year later it set up the Population Health Research Overview Group (PHROG), which was tasked with developing the MRC’s future role in population health research.

The PHROG has met four times since June 2005. During this time it has developed a vision of the MRC’s portfolio of research that it believes should be expanded to include the full range of research that makes up the ‘landscape’ of population health research. In order to provide a robust evidence base for policy and practice, research is required across the entire spectrum, from basic biomedical and social sciences through underpinning and applied population health research to policy evaluation. In developing this broad public health research portfolio, the PHROG recognises the importance of identifying areas where the MRC can add the most value and support to others’ activities in research, policy or practice, as well as identifying and filling any gaps in the current public health evidence base.

Turning a vision into reality

Having developed this top-level vision, the group is now working on a strategy to make it a reality. And for the MRC to add value to the activities of external organisations with a public health remit, it will be crucial that the PHROG engages with them while developing its strategy. This will help to identify complementary areas and opportunities for added value, as well as any gaps.

The MRC’s population health research strategy also needs to complement two other key initiatives: the National Prevention Research Initiative (NPRI) and the UK Clinical Research Collaboration (UKCRC) Strategic Planning Group in Public Health. Both of these have highlighted the importance of studying behaviour that affects people’s health. The combination of a broad MRC strategy across the whole population health research landscape, the topic-specific strategies of the NPRI and the emerging UKCRC plans will enable a matrix of research support to be developed to benefit public health. The PHROG’s next step, therefore, is to hold discussions with key stakeholders. It aims to agree the MRC’s strategy for delivering its vision in winter 2006, and to finalise and publish the strategy early in 2007.
Seven former and current MRC scientists have been named Fellows of the Royal Society in recognition of their achievements in biomedical science. They are Professor David Barton of the Institute of Cancer Research, Professor Stephen Barnett of the University of Strathclyde, Professor Valerie Beral of the University of Oxford, Professor Peter Donnelly, also of the University of Oxford, Dr Matthew Freeman of the MRC Laboratory of Molecular Biology, Professor Richard Jackson of the University of Cambridge and Professor Austin Smith of the Institute of Stem Cell Research at the University of Edinburgh.

Dr Anatoli Kamali, head of the Masaki Station at the MRC/Ugandan Virus Research Institute, was named ‘Best African Scientist’ at the Microbicides 2006 conference in Capetown. The award was given for his expertise in clinical studies and trials in Africa, and for having attracted funding from partners in the North of the continent.

The 2006 Dr H.P. Heineken Prize for Biochemistry and Biophysics has been awarded to Sir Alec Jeffreys, Royal Society Wolfson Professor at the University of Leicester, for his ‘discovery of the genetic fingerprint’. Sir Alec will be presented with the biennial award at a ceremony in Amsterdam on 28 September.

Professor Chris Higgins, director of the MRC Clinical Sciences Centre in London, has been appointed Vice-Chancellor of the University of Durham. Professor Higgins, who graduated from Durham with a PhD in 1979 and went on to have an illustrious career in biomedical science, will replace former Chief Medical Officer Professor Sir Kenneth Calman when he retires in 2007.

Four MRC scientists received awards in the honours list for the Queen’s eightieth birthday this year: Professor Sally MacIntyre, director of the MRC Social and Public Health Sciences Unit in Glasgow, received a CBE for her work on socio-economic, gender and geographical inequalities in health and wellbeing, as did Professor Nick Hastie, director of the MRC Human Genetics Unit, who has studied viral replication, gene expression and development genetics. Meanwhile Dr Ann Prentice, director of the MRC Human Nutrition Unit in Cambridge, was awarded an OBE, alongside Dr David Spiegelhalter of the MRC’s Biostatistics Unit, also in Cambridge. Dr Prentice has been instrumental in addressing the nutrient requirements for bone health, encompassing nutritional issues in affluent and developing societies. Dr Spiegelhalter is best known for his ground-breaking work on statistical methods of analysing and interpreting data, best known as Bayesian analysis.

Natalie Zhang, former student at the National Institute for Medical Research’s summer school for research, was awarded two prizes at the Intel International Science and Engineering Fair held in May. She won second prize from the American Association for Clinical Chemistry and fourth prize in biochemistry presented by Agilent Technologies. Her project looked into X-ray crystallography of RNA ‘pseudo-knots’, as a mechanism for developing new antiviral agents.

Vintage papers from The Lancet

Compiled by Ruth Richardson with a foreword by Richard Horton, editor of The Lancet, this anthology includes articles of scientific and historical importance published in the journal since its first issue in 1823. It includes landmark examples of MRC research, such as testing treatments for patients with tuberculosis, vaccines for polio, whooping cough and smallpox, and the Magpie trial of magnesium sulphate to treat pre-eclampsia. The papers are presented in their original form, alongside snippets of contemporary news and comment which appeared in the journal at the time of publication.

Ruth Richardson (Ed), Elsevier, 2006
£32.99 ISBN 0080446833