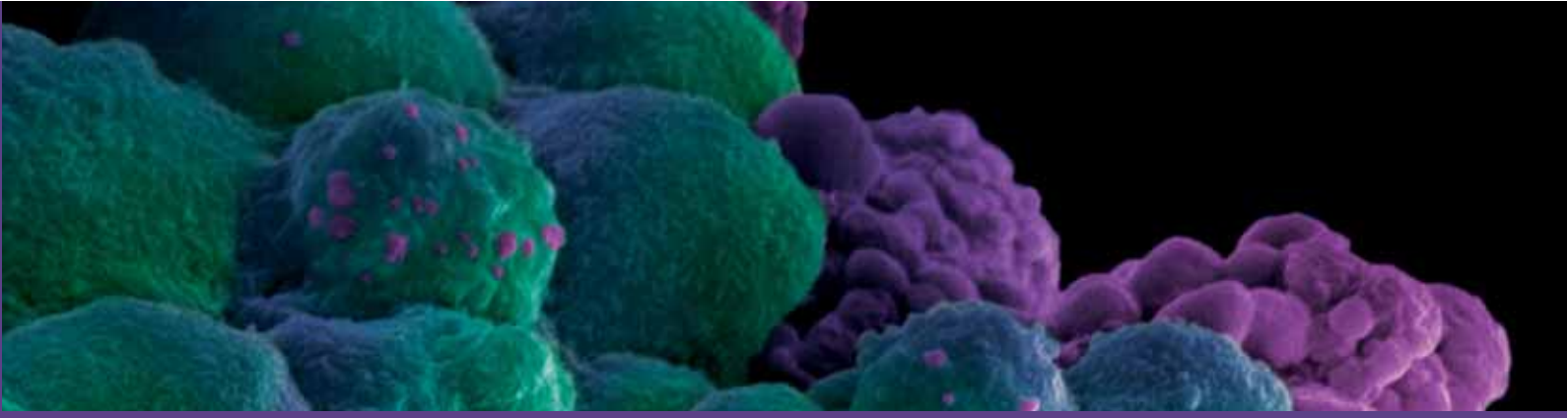


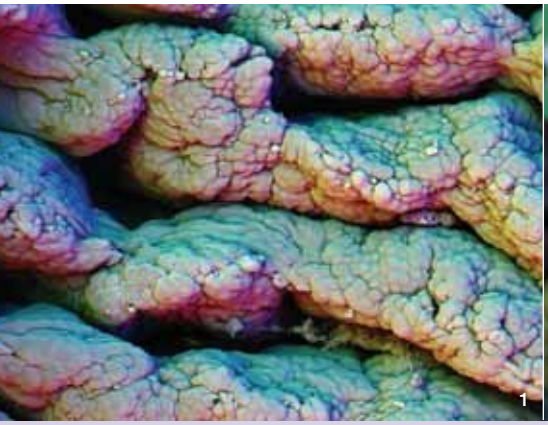
ANNUAL REVIEW

2006

wellcome trust

THE WELLCOME TRUST

The Wellcome Trust is the largest charity in the UK and the second largest medical research charity in the world.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BOARD OF GOVERNORS

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1 Surface of the gut.
2 Young children in Kenya.
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4 A scene from Y Touring's *Every Breath*.
5 Cells in a developing fruit fly.
6 Data management at the Sanger Institute.

This *Annual Review* covers the Wellcome Trust's financial year, from 1 October 2005 to 30 September 2006.


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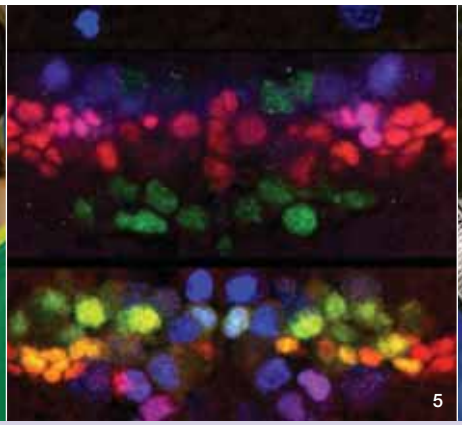
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EXECUTIVE BOARD

Mark Walport
Director

Ted Bianco
Director of Technology Transfer

John Cooper
Director of Resources

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Head of Strategic Planning and Policy

Clare Matterson
Director of Medicine, Society and History

David Phillipps
Director of Finance

Sohaila Rastan
Director of Science Funding

John Stewart
Head of Legal and Company Secretary

Danny Truell
Chief Investment Officer

Other senior management

Allan Bradley
Director of the Wellcome Trust Sanger Institute

Susannah Randall
Head of Communications

As at January 2007

MAKING A DIFFERENCE

The Wellcome Trust's mission is to foster and promote research with the aim of improving human and animal health. During 2005–2010, our aims are:

Advancing knowledge: To support research to increase understanding of health and disease, and its societal context

Using knowledge: To support the development and use of knowledge to create health benefit

Engaging society: To engage with society to foster an informed climate within which biomedical research can flourish

Developing people: To foster a research community and individual researchers who can contribute to the advancement and use of knowledge

Facilitating research: To promote the best conditions for research and the use of knowledge

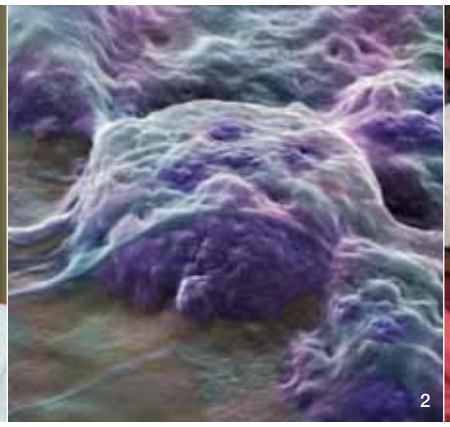
Developing our organisation: To use our resources efficiently and effectively.

Strategic Plan updates, summarising progress in achieving specific objectives during 2005/06, can be found at **www.wellcome.ac.uk/strategicplan**.

WORKING WITH RESEARCHERS

We are working to achieve ever closer relationships with the best researchers to fund work that will have important impacts in improving human and animal health.


1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This *Annual Review* illustrates some of the many ways in which the work we support or carry out ourselves is making a difference.

This year's stories of the discovery and application of new knowledge illustrate how outstanding researchers are gaining insight into biological processes at all scales, from the atomic structure of medically important proteins to the global impact and treatment of malaria. Our understanding of the human genome continues to grow, with yet another surprising discovery from the Wellcome Trust Sanger Institute – that genetic variation between individuals is far higher than previously thought.

Genetics has benefited enormously from high-throughput sequencing and other technologies, which have transformed the way research is carried out. Structural biology is less easy to scale up, but the Structural Genomics Consortium has made excellent progress in its production of structures of medically important proteins, and many valuable discoveries are being made about protein function on the basis of structural information.

Such studies complement research into the threats to health we face in this country and globally. The global impact of malaria, for example, is now much clearer. Wellcome Trust-funded researchers are world leaders in the fight against this insidious disease.

Application of new knowledge has seen trials of new dipstick diagnostic tests for trachoma, trials of new vaccines and diagnostics for tuberculosis, and trials for new treatments for the symptoms of Parkinson's disease. Research we have funded has led to both national and international changes in health policy. The World Health Organization now recommends artemisinin combination therapies for treatment of malaria and the Kenyan Ministry of Health is continuing its Hib immunisation programmes.

Partnerships

We can only achieve this kind of impact through working closely with the research community. Through supporting the best people with the best ideas and providing flexible funding, we hope to support the generation of new knowledge to underpin future discoveries and their subsequent application.

A key issue for all funding agencies is to balance bottom-up and top-down approaches to the support of research. Who drives the process of discovery? Who asks the research questions? Is it the researchers or the funding agencies? We take a flexible approach, and have an open door for the best researchers to bring us their best ideas. However, we also work with the research community to identify areas where there is unmet research need and to provide catalysis to ensure that vital research is not overlooked.

Last year we introduced Strategic Awards to ensure we could support the best ideas wherever they are found. The scope of these awards is really only limited by the imagination of the research community. This year we made our first three awards, providing outstanding research groups with significant and flexible support:

- Professors Austin Smith and Fiona Watt were awarded £7 million to establish an international centre of excellence in fundamental stem cell research. The Wellcome Trust Centre for Stem Cell Research at the University of Cambridge will explore the genetic and biochemical mechanisms that control how stem cells develop into particular types of cells.
- Professors Ray Dolan and Karl Friston, at the Wellcome Trust Centre for Neuroimaging, University College London, received an award of £6.7m. This will enhance their research programme into the neural basis of human cognition, work that is extending our understanding of common neurological and psychiatric diseases, such as schizophrenia and dementia.
- Professor Paul Luzio received a £4m award for the Cambridge Institute for Medical Research. The Institute explores the underlying molecular and cellular mechanisms behind disease and it has led key research into how viruses evade our immune system, genetic susceptibility to diabetes, and progress towards novel treatments for Alzheimer's and Huntington's disease.

Our strategy will continue to create a framework that can support, but not constrain, those that look to us for funding. Our Strategy Committees are key to helping us identify our future research priorities and this year we published an 'à la carte' menu of areas identified as important for future research activity.

To ensure we can support the best people, our portfolio of careers

schemes has been reviewed and a number of new schemes were launched this year. The new Sir Henry Wellcome Postdoctoral Fellowship Awards, worth £250 000 over four years, will allow researchers unprecedented freedom early in their careers to pursue their own research. Our new Flexible Travel Awards will also support collaboration-building and the transfer of ideas and skills through support for sabbaticals and travelling fellowships. Other new initiatives were also launched this year, notably the £91m Seeding Drug Discovery initiative, aiming to provide funding for the early stages of drug discovery, which often struggle to attract funding for commercial development. We hope this initiative will create a stronger synergy between academia and industry and capitalise on the powerful resources that are spread across the academic, biotechnology and pharmaceutical sectors.

In areas of unmet research need, such as drug discovery, a key role for the Trust is acting as a catalyst, bringing together partners to help tackle pressing research problems. Public–private partnerships are an effective model for developing new drugs for important but hitherto neglected diseases and we have formed a number this year.

We have formed an alliance with the Novartis Institute for Tropical Diseases, the Economic Development Board of Singapore and the Medicines for Malaria Venture to jointly initiate research on malaria drug discovery. Malaria continues to kill millions of people around the world and this new partnership will investigate the potential for development of new treatments from existing compounds that have already shown antimalarial activity, and from novel compounds. I hope this initiative will produce the next generation of drugs to treat malaria.

A new alliance was also formed between the Wellcome Trust, The Institute of Cancer Research and GlaxoSmithKline to discover, develop and commercialise novel small-molecule inhibitors of BRAF, a key signal transduction enzyme, for use as anticancer agents. Creative approaches to the discovery of new medicines like this are vital to help society address the growing burden of disease.

Improving healthcare for patients was the aim of a further consortium formed this year. This consortium, led by the Wellcome Trust, provided £84m to boost experimental medicine in the UK and the Republic of Ireland. This major investment aims to develop and strengthen Clinical Research Facilities, which bring together laboratory and clinical patient-based research in order to answer important questions about health and disease. Under the umbrella of the UK Clinical Research Collaboration, this initiative brought together the major health research charities, the government funding bodies and health departments.

A research funder's work does not end with the award of a grant. What matters is what is discovered and that knowledge about these discoveries can be freely accessed around the world.

This year we led a major new initiative, with a nine-strong group of UK research funders, to establish an online digital archive of peer-reviewed research papers in the medical and life sciences. UK PubMed Central, a partnership between the British Library, the European Bioinformatics Institute and the University of Manchester, will allow everyone with access to the internet to access a vast collection of biomedical research at the touch of a button, promoting the free transfer of ideas in a bid to speed up scientific discovery.

I hope that this *Annual Review* illustrates our excitement about the outcomes and impacts of the work that we support. Our doors are open to excellent researchers with excellent ideas.

Mark Walport
Director

January 2007

Images

1 Dr Mark Walport.

2 Embryonic stem cells.

3 Trachoma treatment in Tanzania.

HIGHLIGHTS OF THE YEAR

- Whole-genome map uncovers unexpectedly high levels of copy number variation.
- Functional imaging reveals brain centres involved in decision-making.
- Nanog identified as key pluripotency factor in stem cells.
- Impaired innate immunity revealed as potential cause of Crohn's disease.
- Structures of several important human proteins determined by Structural Genomics Consortium and others.
- UK Biobank successfully completes pilot phase.
- Studies in India highlight depression as a serious health issue for women.
- Research in Kenya demonstrates value of Hib immunisation and informs Government health policy.
- Artemisinin combination therapies recommended by WHO and adopted globally.
- National Science Learning Centre formally opened.

ADVANCING KNOWLEDGE

Supporting research to increase understanding of health and disease, and its societal context.

DECISIONS, DECISIONS

The balancing of emotion and reason can now be followed through the labyrinthine anatomy of the brain.

1

2

What is happening in our brains when we decide on a course of action? Using functional imaging, Professor Ray Dolan's group at the Wellcome Trust Centre for Neuroimaging at University College London (UCL) is unpicking the neural circuitry underlying different contributions to decision-making.

One important influence comes from 'reward': the benefits we expect from an action. In theory, decisions are affected by experience – whether, previously, a reward was more or less than we expected. In animals, dopamine pathways have been implicated in reward learning, and Professor Dolan and colleagues have now shown the same is true in people. Agents that alter dopamine signalling also affect subjects' ability to choose the most rewarding option.

A striking feature of human decision-making is its susceptibility to the context in which choices are presented: the so-called framing effect. This is a challenge to assumptions of 'rational' human behaviour, such as those used in economics. Functional imaging has revealed a central role for the amygdala in framing effects, emphasising the importance of emotional processing.

Finally, we often face a dilemma between acting on what we already know and trying something new that might be better for us. In a collaboration with the UCL Gatsby Computational Neuroscience Unit, which integrated computational models of decision-making with neuroimaging data, the group discovered that different brain areas are active in these two situations. This suggests that harvesting a safe option involves distinct neural processing systems from those associated with trying a less certain alternative.

This work emphasises how complex human decision-making is. There is not one 'analytical centre' that determines choice but a host of interconnected systems influencing the way we think – and the way we act.

Pessiglione M et al. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006;442(7106):1042–5.

De Martino B et al. Frames, biases, and rational decision-making in the human brain. Science 2006;313(5787):684–7.

Daw ND et al. Cortical substrates for exploratory decisions in humans. Nature 2006;441(7095):876–9.

ON REPEAT

Humans are genetically more diverse than previously thought.

3

Genetically speaking, humans are almost identical. But those differences that do exist can affect our health. With the sequencing of the human genome and global efforts to map genetic variation, many surprising findings have emerged – not least the importance of copy number variation.

Copy number variation refers to blocks of DNA throughout the genome, which can be anything from 1000 to 5 million nucleotides long; the number of copies at a given location in the genome can vary from zero to tens or even hundreds. These variations have been implicated in several human genetic diseases, and are known to affect susceptibility to HIV and malaria infection.

Now, a multinational team, including Dr Matthew Hurles and colleagues from the Wellcome Trust Sanger Institute, has constructed the first map of copy number variation across the entire human genome. Surprisingly, it affects 12 per cent of the genome – much more than suspected. Affected areas spanned known genes and disease loci, emphasising the importance of copy number variation in both disease and genetic diversity.

Images

1 Professor Ray Dolan.
2 Functional magnetic resonance imaging of the brain in action.
3 Young children.
4 An early embryo broken open to reveal stem cells.
5 Three-dimensional reconstruction of mouse blastocyst.

MORE POTENT RESEARCH

What makes an embryonic stem cell pluripotent – able to create all types of cell?


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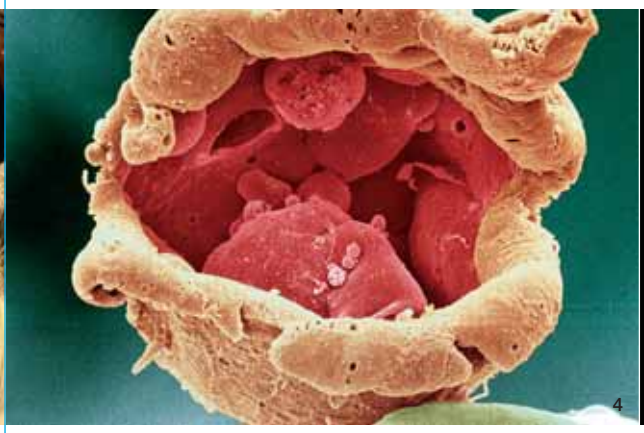
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Dr Nigel Carter's group, also at the Sanger Institute, is one of several teams that have identified specific copy number variations on chromosome 17 as causes of a mental retardation syndrome. The deletion affects two genes, *CRHR1* and *MAPT*, which are likely candidates for the syndrome, as they are active in the brain and known to be involved in degenerative disorders.

In other research (funded by the Wellcome Trust and others), Professor Tim Aitman of Imperial College and others discovered that a low copy number of the *Fcgr3* gene increased susceptibility to a kidney disease, glomerulonephritis, in rats and humans.

Copy number variations are mutations that are likely to have a profound impact on phenotypic differences between individuals. The whole-genome map will greatly aid studies exploring the impact of genetic variation on health.

Redon R et al. Global variation in copy number in the human genome. Nature [in press].

Shaw-Smith C et al. Microdeletion encompassing MAPT at chromosome 17q21.3 is associated with developmental delay and learning disability. Nat Genet 2006;38(9):1032–7.

Aitman TJ et al. Copy number polymorphism in Fcgr3 predisposes to glomerulonephritis in rats and humans. Nature 2006;439(7078):851–5.

The embryonic stem (ES) cell is special. If we knew what gave it the power to create all the cell types of the body (pluripotency), we might be able to create new ES cells and use them to repair damaged tissues. Two lines of research have added significantly to our understanding of the molecular basis of pluripotency.

Dr Magdalena Zernicka-Goetz and colleagues at the Wellcome Trust/Cancer Research UK Gurdon Institute of Cancer and Developmental Biology in Cambridge have located a master switch that controls one of the earliest choices a cell can make. They identified a crucial molecular difference between cells in the four-cell mouse embryo, much earlier than expected.

This difference is a chemical tag (a methyl group) added to the histone proteins, which package DNA in the chromosomes. Tagging just one amino acid in a particular histone (H3) switches on genes that establish and maintain pluripotency. When this modification was introduced into embryonic cells, their daughter cells were pluripotent – showing dramatic activation of pluripotency-associated genes, such as *Nanog*.

Research from Professor Austin Smith[1] and colleagues at the Institute for Stem Cell Research in Edinburgh suggests that *Nanog* has a central role in pluripotency.

When ES cells are fused with other cells, the resulting cell may be converted to a pluripotent state. Broadly speaking, the more differentiated the cell, the less likely it is to become pluripotent after fusion. When ES cells containing higher than normal levels of *Nanog* were used, however, the efficiency of conversion of part-differentiated cells was greatly increased.

So, although not the only player, *Nanog* is clearly a powerful driver of pluripotency.

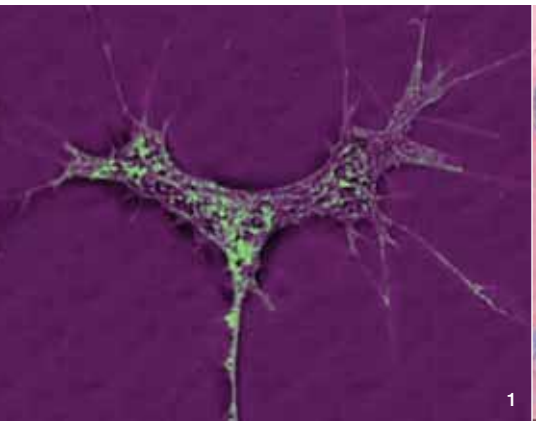
Torres-Padilla ME et al. Histone arginine methylation directs cells towards pluripotency in the early mouse embryo. Nature [in press].

Silva J et al. Nanog promotes transfer of pluripotency after cell fusion. Nature 2006;441(7096):997–1001.

1 Now at the Wellcome Trust Centre for Stem Cell Research, University of Cambridge.

TOUCHING A NERVE

We all need help with directions sometimes, and nerve cells are no exception.



The wiring of nerve cells is a complicated process. The cerebral cortex alone contains at least 10 billion neurons, with 60 trillion synapses linking them. Connecting up these cells is thus finely controlled. Gradually, though, research – including that of Professor Christine Holt (University of Cambridge) and colleagues – is identifying key mechanisms in axon guidance.

Axon growth is guided by 'push and pull' mechanisms. The growing tips of axons (growth cones) are repelled from certain areas and attracted towards others.

A protein called Slit2, for example, repels growth cones of frog retinal axons. Professor Holt's group found that Slit2 led to a burst of protein synthesis in the growth cone, increasing levels of an actin regulatory protein, cofilin. This led to the dismantling of actin filaments, suggesting that changes to the internal skeleton of the cell are important in controlling the direction of axon growth.

Other work has focused on links between morphogenesis and axon guidance. For example, a protein known primarily as a gene regulator – Engrailed-2 – was also found to affect growth cones when present outside the cell, again by stimulating new protein synthesis. Interestingly, extracellular Engrailed-2 repels some neurons but attracts others.

Other morphogens, including two members of the Wnt family of proteins, are also known to guide axon growth. With colleagues in Spain, Professor Holt has shown that a probable inhibitor of Wnt signalling, SFRP1 (secreted Frizzled-related protein 1), acting through a receptor known as Frizzled-2 (Fz2), also plays a role in axon guidance.

So, as well as patterning the body, morphogens may also be important in wiring the developing nervous system.

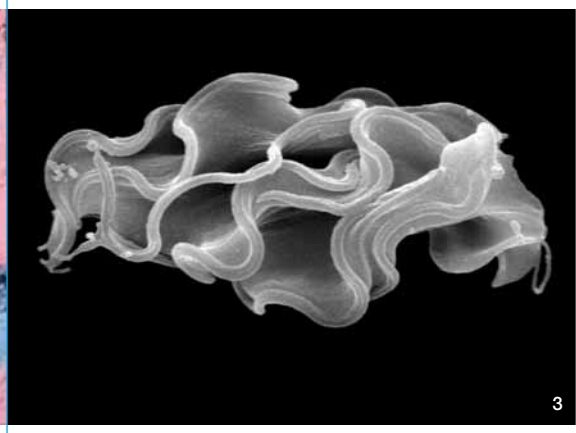
Piper M et al. Signaling mechanisms underlying Slit2-induced collapse of Xenopus retinal growth cones. Neuron 2006;49(2):215–28.

Brunet I et al. The transcription factor Engrailed-2 guides retinal axons. Nature 2005;438(7064):94–8.

Rodriguez J et al. SFRP1 regulates the growth of retinal ganglion cell axons through the Fz2 receptor. Nat Neurosci 2005;8(10):1301–9.

TARGETING THE TRYPANOSOME

Research is revealing weak points in the parasite's defences.



No vaccine exists for human African trypanosomiasis (sleeping sickness), and few drugs are available. But the recent publication of the genome sequence for *Trypanosoma brucei*, the parasite responsible, has increased our understanding of the parasite's biology and has boosted the search for drug targets.

One promising target is the flagellum – the 'tail' that propels the parasite through the bloodstream. Professor Keith Gull at the University of Oxford and colleagues have shown that the flagellum plays a critical role in cell division and is, therefore, essential for parasite survival. They have identified flagellar proteins that, being unique to the trypanosome, have potential as drug targets.

Other studies have revealed further chinks in the trypanosome's armour. Trypanosomes use an unusual mechanism to regulate gene activity, in which messenger RNAs are held by RNA-binding proteins until they are needed. By interfering with this system, Dr Ed Hendriks and Dr Keith Matthews were able to alter a specific step in differentiation – the first time this process has been genetically modified in trypanosomes.

Images

1 Retinal growth cone.

2 Staining of a single retinal ganglion cell, showing its long thread-like axon.

3 A malformed trypanosome after cell division has been disrupted.

4 A normal trypanosome.

5 Key amino acids in the 5-HT3 receptor.

FORM AND FUNCTION

The newly discovered structures of key proteins have revealed valuable insights into their functioning.

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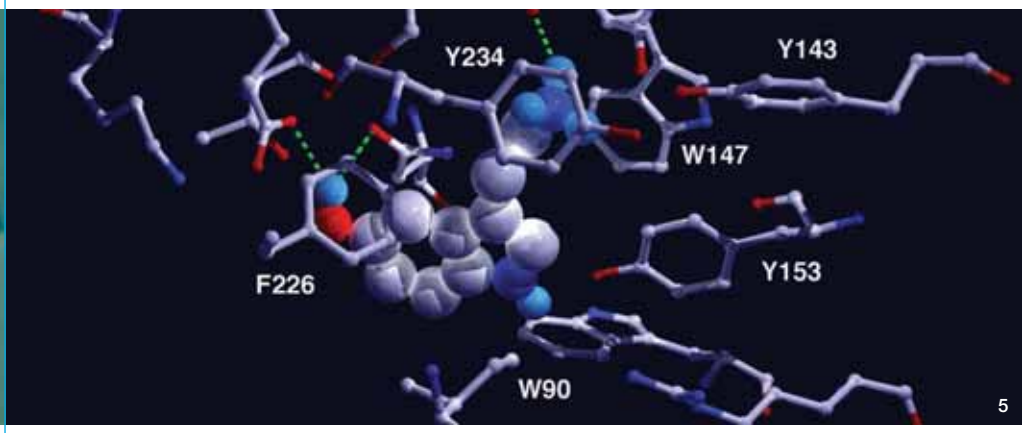

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Exploiting a naturally occurring parasite transporter, Professor Ian Gilbert and colleagues showed that nitroheterocycle compounds attached to melamine were effective against the parasites that give rise to human African trypanosomiasis.

Lastly, Professor Alan Fairlamb, whose Wellcome Trust Principal Research Fellowship was renewed this year, is searching for candidate molecules to screen in a dedicated drug discovery programme at the University of Dundee. He and his team are focusing their search on a molecule called trypanothione – unique to trypanosomes and *Leishmania* parasites – and its associated enzymes.

Broadhead R et al. Flagellar motility is required for the viability of the bloodstream trypanosome. Nature 2006;440(7081):224–7.

Hendriks EF, Matthews KR. Disruption of the developmental programme of Trypanosoma brucei by genetic ablation of TbZFP1, a differentiation-enriched CCCH protein. Mol Microbiol 2005;57(3):706–16.

Baliani A et al. Design and synthesis of a series of melamine-based nitroheterocycles with activity against Trypanosomatid parasites. J Med Chem 2005;48(17):5570–9.

University of Dundee Tropical Disease Initiative. www.drugdiscovery.dundee.ac.uk/tropical/overview/.

To function properly, proteins must adopt particular three-dimensional structures. By elucidating protein structures, or even just the conformation of single amino acids, researchers can often deduce how proteins work in the body – and therefore begin designing or refining drugs to modify protein activity and, hopefully, treat or prevent disease.

Dr Sarah Lummis (University of Cambridge) and colleagues, for example, have discovered how a neurotransmitter receptor (5-HT3), an ion channel, is opened and closed. The mechanism depends on the conformation of a single proline in a 'hinge' region of the receptor. In one conformation the channel is open; in the other it is closed.

Myosin 5 transports material around the cell, by 'walking' along actin fibres. Dr Peter Knight at the University of Leeds and colleagues have found that, without any bound cargo, myosin 5's long tail domains fold up with its motor domains, and this globular form binds weakly to actin. When its cargo binds, the structure unfolds, the motor domains attach to actin, and the myosin 5 begins its walk.

The structure of Hsp90, determined by Professor Laurence Pearl (Institute of Cancer Research) and colleagues, has revealed a complex set of rearrangements that enable Hsp90 to bind and activate its target proteins. Since Hsp90 is needed to activate proteins driving proliferation in many cancer cells, drugs that block Hsp90 hold promise as anticancer therapies.

Finally, among much research facilitated by the Structural Genomics Consortium, Dr Udo Oppermann and colleagues have discovered how anti-osteoporosis drugs, bisphosphonates, bind to their target enzymes – opening up the prospect of more finely tailored drugs.

Ali MM et al. Crystal structure of an Hsp90-nucleotide-p23/Sba1 closed chaperone complex. Nature 2006;440(7087):1013–7.

Lummis SC et al. Cis-trans isomerization at a proline opens the pore of a neurotransmitter-gated ion channel. Nature 2005;438(7065):248–52.

Thirumurugan K et al. The cargo-binding domain regulates structure and activity of myosin 5. Nature 2006;442(7099):212–5.

Kavanagh KL et al. The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. Proc Natl Acad Sci USA 2006;103(20):7829–34.

- The Structural Genomics Consortium is a not-for-profit organisation that aims to determine the three-dimensional structures of proteins of medical relevance, and place them in the public domain without restriction. It is supported by the Wellcome Trust and a range of public and private sources in the UK, Canada and Sweden.

GUT FEELING

Understanding the hormonal control of appetite may be the key to effective anti-obesity treatments.

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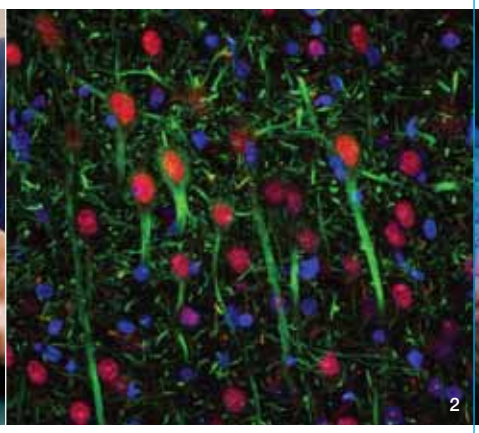

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Obesity is thought to cause 1000 premature deaths a week in the UK. By focusing on the way the body controls appetite, Professor Steve Bloom and colleagues at Imperial College London are investigating anti-obesity therapies based on naturally occurring hormones and neurotransmitters.

All current methods of weight control have significant problems. Surgery can be effective for severe obesity, but carries a 3 per cent mortality rate. Anti-obesity used drugs have unpleasant side-effects. More generally, dieting suffers a high failure rate.

A major challenge is understanding the body's own physiology. The body has homeostatic set points to maintain body weight, but it is more sensitive to weight loss than weight gain. So when we lose weight, we have a powerful drive to eat more to put weight back on.

Control of appetite is therefore likely to be key to weight-control strategies. The Imperial group is investigating the hormonal and neural systems underpinning appetite control – and developing new interventions based upon them.

Control of energy balance, eating, metabolism and physical exercise is complex. Nevertheless, Professor Bloom's group has identified several key players in this system, and shown that gut hormones can influence appetite. Indeed, injections of oxyntomodulin, a hormone released by the small intestine after eating, not only reduced energy intake but also increased subjects' spontaneous activity.

The team is now working on a formulation of the hormone that can be injected once a day or less, as well as investigating the therapeutic potential of other factors, including neuromedin, neuropeptide S and PYY3-36.

Wynne K et al. Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. Int J Obes (Lond) 2006 [Epub ahead of print].

Wynne K et al. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. Diabetes 2005;54(8):2390–5.

INNATE INVOLVEMENT

Two unexpected facets of innate immunity have been identified.

The recent renaissance of interest in innate immunity – a nonspecific form of defence common across the animal kingdom – has yielded a number of interesting findings. Now, research has highlighted the potential significance of innate immunity in two areas: Crohn's disease and breast milk.

Currently, it is thought that Crohn's disease results from an overactive immune system, which treatments are designed to 'damp down'. But Professor Tony Segal and colleagues at University College London have put forward a different hypothesis – that impaired innate immunity is responsible for the disorder.

The team showed that the immune response of people with Crohn's disease was much lower than that of healthy people when challenged by exposure to weakened *E. coli* or trauma to the rectum, ileum or skin.

They suggest that bowel contents that breach the mucosal barrier may not be cleared as effectively in people with an impaired immune response, which could lead to the chronic inflammation characteristic of Crohn's disease.

Images

1 A typical modern Western diet.

2 Cells within the brain's appetite control centre.

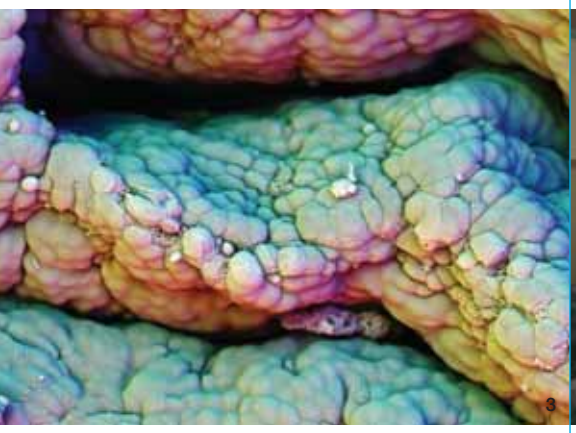
3 Surface of the gut.

4 Examining a premature baby in Kilifi, Kenya.

5 Malaria parasite within red blood cells.

KNOW YOUR ENEMY

New modelling techniques are providing a clearer picture of the extent of malaria across the globe.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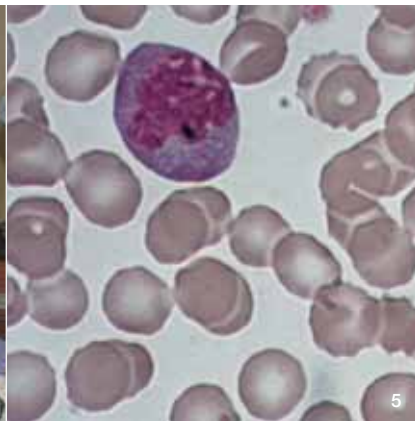
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In separate work, Dr Mario Labéta and colleagues at Cardiff University have shown that breast milk can regulate the activity of the innate immune system in babies.

The team has been investigating the mechanisms controlling the activity of Toll-like receptors (TLRs), which recognise parts of microbial pathogens and activate the innate immune response. They found that as yet unidentified proteins present in early breast milk (but not formula milk) boosted the immune responses triggered by some TLRs, while inhibiting those triggered by others.

As well as demonstrating a novel activity of human milk, the work has also identified a possible new target for modulating innate immune responses.

Marks DJ et al. Defective acute inflammation in Crohn's disease: a clinical investigation. Lancet 2006;367(9511):668–78.

LeBouder E et al. Modulation of neonatal microbial recognition: TLR mediated innate immune responses are specifically and differentially modulated by human milk. J Immunol 2006;176(6):3742–52.

Information on the prevalence, distribution and likely future spread of malaria is vital for a number of reasons: giving affected countries an idea of disease burden, providing a baseline from which to measure the success of intervention programmes, and facilitating effective disease-control planning. In a series of studies, Professor Bob Snow, Dr Simon Hay and colleagues at the Kenya Medical Research Institute–Wellcome Trust Research Programme have developed tools to collect and analyse data on the distribution of malaria in affected regions.

Across the world, malaria scientists collect information on how many people are infected with malaria parasites. This information is sometimes more widely accessible, but not always. To date, such data have never been gathered into a single source and linked to a map of the world. The Malaria Atlas Project (www.map.ox.ac.uk) has so far assembled information from 3126 communities in 79 countries – the single largest repository of contemporary information on malaria risk yet produced.

To create a global map of malaria risk worldwide, the researchers from Kenya and Oxford use information from satellites orbiting the Earth, population censuses and other electronic forms of information on factors that affect the distribution of malaria mosquito vectors and how often they are likely to infect humans. Statistical approaches will be used to fill in the 'gaps', based on comparisons between areas where information exists and those where it is lacking.

Applications of early versions of these models estimate that, in 2002, 515 million people developed a clinical episode of *Plasmodium falciparum* malaria – many more than previously thought.

Hay SI and Snow RW. The Malaria Atlas Project: developing global maps of malaria risk. PLoS Med 2006;3(12):e473.

Snow RW et al. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature 2005;434(7030):214–7.

- In 2005/06 Professor Snow was awarded a Wellcome Trust Principal Research Fellowship and Dr Hay a Senior Research Fellowship.

ALLERGIES AND MODERNITY

An acclaimed social history of allergy highlights dramatic changes in our perceptions of this common condition.

1

Allergy, argues Professor Mark Jackson in his acclaimed new book *Allergy: The history of a modern malady*, is not just a collection of symptoms. Perceptions of allergy have changed markedly over time. Understanding these changes tells us much about the changing face of public health and society more generally.

The term 'allergy' was coined 100 years ago by an Austrian paediatrician, Clemens von Pirquet. Hay fever, though, was first described in 1819 by British physician John Bostock. He suggested it was a disease of the middle and upper classes, and it was soon widely accepted that only 'persons of cultivation' suffered from allergies. Professor Jackson notes that in E M Forster's *Howard's End* (1910), hay fever appears as the "embodiment of innate cultural refinement".

The last century witnessed a surge in allergies. In the inter-war years, just one in 30 people suffered allergic reactions: that figure was one in three by the turn of the century. Allergies now cost the NHS more than £900 million a year.

The reasons for this increase are controversial. The finger of blame has been pointed at environmental pollutants and even an obsession with cleanliness. Indeed, argues Professor Jackson, Director of the Wellcome Trust-funded Centre for Medical History at the University of Exeter, allergy is not just a medical condition but also an "index of cultural anxiety", encapsulating fears about our lifestyles and environment. Allergies have become a powerful and pervasive metaphor for the "pathology of progress". Once seen as exclusive to the ultra-civilised, allergies are now viewed as a by-product of civilisation itself.

The book was positively reviewed in historical, medical and popular press. *Publishers Weekly* described it as "a masterful overview of the evolution of allergy as a public health problem". According to the *Guardian*, "this fascinating study is undoubtedly an important contribution to the social history of medicine". Its first print run sold out within five months.

Jackson M. Allergy: The history of a modern malady. London: Reaktion Books; 2006.

MEET THE CHALLENGE

The UK health system is facing two growing health concerns.


2

The National Health Service in the UK may be regarded as one of the best in the world, but with improvements in diagnosis, treatment and prevention, and altering social circumstances, healthcare priorities are constantly changing. Liver cirrhosis and autism are two conditions that are throwing up significant challenges to public health.

Professor David Leon and Dr Jim McCambridge, a Wellcome Trust Health Services Research Fellow, looked at the rate of cirrhosis mortality in 12 European countries between 1955 and 2001. While a decline in the mortality rate was seen in most countries from the 1970s onwards, the rate in the UK increased, and continues to rise steeply. The problem is most acute in Scotland, where the mortality rate more than doubled between the periods 1987–1991 and 1997–2001. The most likely cause is the UK's rising consumption of alcohol.

Prompted by reports suggesting a rise in the prevalence of autism and autistic spectrum disorders (ASDs), Professor Gillian Baird and colleagues studied nearly 57 000 nine- and ten-year-olds from South Thames, UK.

Images

1 Detail of a poster held in the Wellcome Library.

2 Testing cognitive skills in a boy with autism.

3 Modern drinking culture.

4 Women in India.

WELL WOMEN

Women's mental health is a major but neglected issue for developing countries.

3

4

ASDs were present in around 1 per cent of the children studied, one-third of whom had autism as defined by World Health Organization criteria. It is unclear whether these findings represent an actual increase in autism, better detection of the disorder or changes in the way it is diagnosed.

Accurate data on disease prevalence are vital for effective public health planning and the development of education programmes to try to avert greater problems in the future.

Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. Lancet 2006;367(9504):52–6.

Baird G et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet 2006;368(9531):210–5.

- Professor David Leon received programme grant funding in 2005/06 to study alcohol use and low life expectancy among Russian men.

The World Health Organization (WHO) estimates that, by 2020, neuropsychiatric disorders will be the second greatest cause of loss of quality of life because of disability or death globally. One in four people attending primary care in developing countries is thought to have a mental illness, yet mental health support is often extremely limited.

Working with women from Goa, India, Dr Vikram Patel from the London School of Hygiene and Tropical Medicine and colleagues found that women with gynaecological symptoms were at an increased risk of depression. Conversely, women who were depressed were more likely to develop gynaecological symptoms.

Both gynaecological symptoms and depression were associated with social issues, including economic problems and 'gender disadvantages' (such as sexual violence, low family support and being widowed).

Current WHO guidelines – which assume that gynaecological symptoms indicate reproductive tract infections – could lead to women with gynaecological problems being incorrectly classified as having a sexually transmitted infection, and could mean that depression and/or social issues affecting them are overlooked. As such, the researchers suggest that treatments for gynaecological problems should target both infection and psychosocial factors.

A separate study showed that mental illness during pregnancy was linked to low-birth-weight babies, who are at an increased risk of neonatal death.

Dr Patel is now leading another Wellcome Trust-funded study to develop an effective, affordable and sustainable healthcare programme that integrates management of depression into routine primary care.

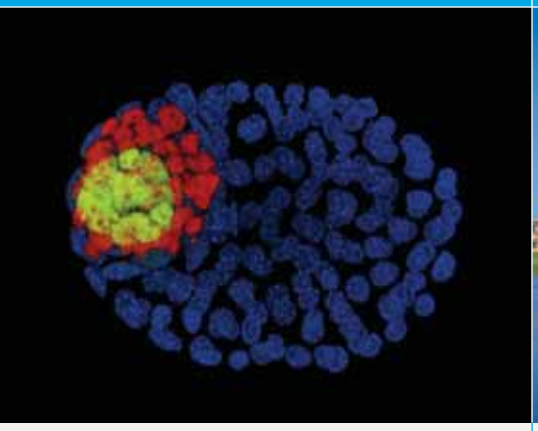
Patel V et al. Gender disadvantage and reproductive health risk factors for common mental disorders in women: a community survey in India. Arch Gen Psychiatry 2006;63(4):404–13.

Patel V et al. The burden and determinants of dysmenorrhoea: a population-based survey of 2262 women in Goa, India. BJOG 2006;113(4):453–63.

Patel V, Prince M. Maternal psychological morbidity and low birth weight in India. Br J Psychiatry 2006;188:536.

NEW FUNDING

Centres and core support



Nearly £20 million has been invested in core support for world-leading research centres in vibrant areas of research.

Strategic Award funding is a mechanism to provide outstanding research groups with significant levels of support.

A new **Wellcome Trust Centre for Stem Cell Research** has been established at the University of Cambridge following a £7.0m Strategic Award to Professor Austin Smith and Professor Fiona Watt. The Centre will also run a new four-year PhD programme dedicated to stem cell biology.

The **Wellcome Trust Centre for Neuroimaging at University College London**, funded through a £6.7m Strategic Award, builds on its earlier success as the Functional Imaging Laboratory. It will be led by Professor Ray Dolan and Professor Karl Friston.

A Strategic Award of £4.0m was made to the **Cambridge Institute for Medical Research** for the renewal of its core support and to establish two new training programmes operating at the interface between clinical and basic research.

An existing Wellcome Trust Centre**, the Wellcome Trust Centre for Cell Biology**, University of Edinburgh, was awarded £3.3m renewal of its core funding.

Wellcome Trust Sanger Institute

The Wellcome Trust Sanger Institute was awarded £340 million for 2006–11, following a review of its achievements over the past five years.

The Wellcome Trust Sanger Institute is the only research centre directly funded by the Wellcome Trust. In October 2005 it was awarded £340m to support its activities over the five-year period 2006–11.

During this period the Sanger Institute will drive forward its revised scientific strategy. Under Professor Allan Bradley, who took over as Director in 2000, its emphasis has shifted from genome sequencing to large-scale studies aimed at understanding the function of genes and their contributions to health and disease.

The new strategy will see a further refinement of this approach, with an enhanced focus on the Sanger Institute's core strengths: large-scale studies of natural and engineered variation in genome sequence, in humans, pathogens and model organisms (see pages 38 and 49).

Underpinning these major programmes will be the Sanger Institute's unique skills in informatics and high-throughput technologies such as sequencing and large-scale engineering of gene knockouts in the mouse.

Influenza research

Two important new projects have been funded on human and avian flu.

The Wellcome Trust's Major Overseas Programme in Vietnam, led by Professor Jeremy Farrar, has been at the forefront of efforts to understand the impact of H5N1 avian flu in people. A new award of £385 000 to Dr Cameron Simmons in Vietnam will support a collaboration with groups in Switzerland and the USA, which aims to investigate whether monoclonal antibodies derived from people who survived H5N1 infection (including Hn, the girl pictured above) can provide protection against this strain of virus.

This grant was 'fast-tracked' through the grant appraisal process, in recognition of the great threat posed by H5N1 influenza.

Support is also being provided for an influenza virus genome-sequencing pipeline. The pipeline, a collaboration between the Medical Research Council's National Institute for Medical Research, the University of Cambridge, the Health Protection Agency, the Veterinary Laboratory Agency and the Wellcome Trust Sanger Institute, will allow researchers to track viruses affecting animal and human populations.

The sequence data will provide valuable information about the spread of different strains of virus and identify strains that need to be targeted by vaccination.

Major awards in the history of medicine

Unpicking the complex political, cultural and environmental forces that have influenced health, disease and medicine over the last 250 years is the goal of two major history of medicine awards.

A Strategic Award in the History of Medicine was made to the Centre for the History of Science, Technology and Medicine at the University of Manchester. This five-year award will strengthen the group's position as one of the UK's leading centres for research into the history of 19th- and 20th-century medicine.

As well as analysing economic data on healthcare, the Manchester group will explore the many NHS changes of the last 30 years. Another strand of research will focus on the impact of the Cold War, as military-derived technologies were deployed in medical research and practice.

A key aim is to provide useful information for patients, medical professionals and policy makers to help inform future healthcare policy-making, as well as to preserve the record of the past.

A five-year Enhancement Award was jointly awarded to the University of Ulster in Northern Ireland and University College Dublin in the Republic of Ireland to enable researchers to work together on common themes. Research will focus particularly on medical developments in Ireland, north and south.

A selection of notable grants awarded in 2005/06.

PROGRAMME GRANTS

MOUSE MODELS
Professor Elizabeth Fisher (Institute of Neurology) and **Dr Victor Tybulewicz** (National Institute for Medical Research) Down's syndrome: identifying the causes of brain and heart defects in an engineered mouse model.

WOUND HEALING
Professor Paul Martin (University of Bristol) Inflammatory response in wound healing: cell biological and genetic analysis in mice and zebrafish.

POPULATION STUDIES
Dr Eliya Zulu (Africa Population and Health Research Centre, Kenya) Impact of urbanisation and poverty on health in sub-Saharan Africa.

CELL BIOLOGY
Professor Kim Nasmyth (University of Oxford) Mechanisms of chromosome segregation in meiosis.

TRANSCRIPTION
Professor Nicholas Proudfoot (University of Oxford) Transcription termination: molecular mechanisms and links to RNA processing.

DIABETES
Professor Stephen O'Rahilly (University of Cambridge) Insulin resistance: identifying patients and analysing potential genetic contributions.

PHYSIOLOGY
Professor Malcolm Parker (Imperial College London) Energy homeostasis and ovulation: function of ligand-dependent nuclear receptor corepressor RIP140.

STATISTICAL GENETICS
Professor Lon Cardon (University of Oxford) Genome association studies: development of new statistical methods focusing on multiple interacting loci in complex human diseases (e.g. Crohn's disease).

INFECTIOUS DISEASE
Dr Neil French (London School of Hygiene and Tropical Medicine) Karonga Prevention Study, Malawi: impact of retroviral rollout on HIV and associated TB and pneumococcal infections in local community.

VETERINARY MEDICINE
Professor Mark Woolhouse (University of Edinburgh) Disease burden in East African cattle: characterising the full range of infections affecting animals in first year of life.

AGEING
Professor Martin Prince (Institute of Psychiatry) Ageing and dementia: identifying the risk factors for dementia in ageing populations in Latin America and China.

PROJECT GRANTS

DEVELOPMENTAL BIOLOGY
Professor Sir John Gurdon (University of Cambridge) Nuclear reprogramming: searching for factors that can revert frog nuclei to early developmental stages.

MALARIA
Dr Balbir Singh (University Malaysia Sarawak) and **Dr David Conway** (London School of Hygiene and Tropical Medicine) Effect of *Plasmodium knowlesi* (seen mainly in monkeys) in humans in the Far East.

MICROBIOLOGY
Dr Marjan van der Woude (University of York) *Salmonella enterica*: understanding how variation in *S. enterica* helps it evade the host response in humans and livestock.

MENTAL HEALTH
Dr Ed Watkins (University of Exeter) Rumination: its role in increasing susceptibility to depression and possible therapeutic approaches.

VISUAL SCIENCE
Dr Joshua Solomon (City University) Effect of context on visual perception (jointly funded with the Biotechnology and Biological Sciences Research Council as part of the the Cognitive Foresight Programme).

NEUROSCIENCE
Dr Patricia C Salinas (University College London) The role of Wnt signalling in synapse formation in the central nevous system.

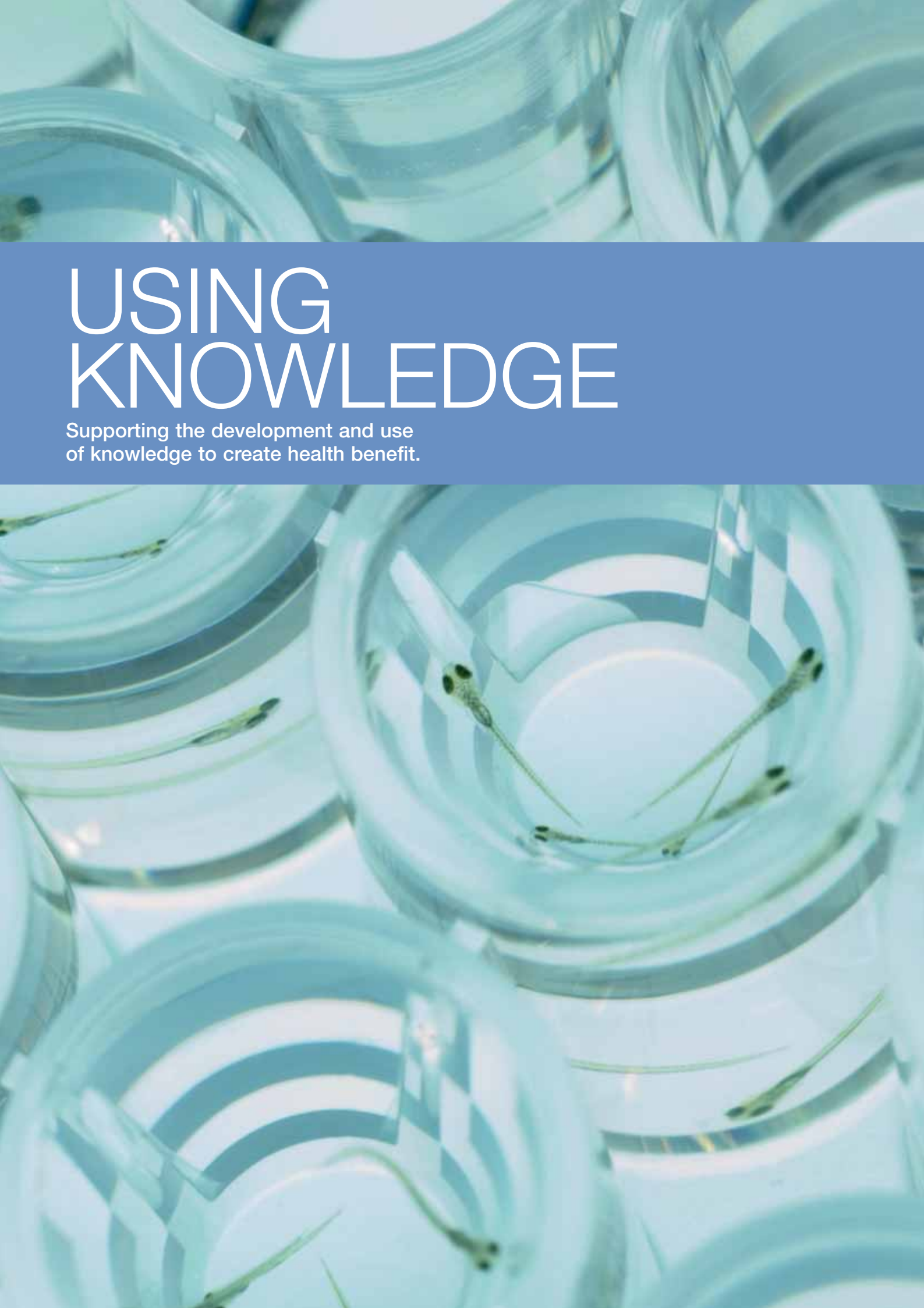
MEDICAL HUMANITIES PROJECT GRANTS

HISTORY OF MEDICINE
Professor Peter Harper (University of Wales) Preserving the history of human and medical genetics.

BIOMEDICAL ETHICS
Dr Paula Saukko (University of Exeter) Nutrigenomics: an analysis of claims made for nutrigenomics products in marketing materials and the media.

HISTORY OF MEDICINE
Dr Vanessa A Harding (Birkbeck College) Health in early modern London, 1550–1750: creating a detailed database of residents to assess the environmental and other factors affecting health.

Details of all grants made can be found in *Grants Awarded 2005/06*, available on the Wellcome Trust website.



USING KNOWLEDGE

Supporting the development and use of knowledge to create health benefit.

LIFE-SAVING NUMBERS

Clinically relevant, practical findings from studies in Kenya are leading directly to health policy changes – and saving children's lives.

Research led by Dr Anthony Scott at the Kenya Medical Research Institute–Wellcome Trust Research Programme in Kilifi, Kenya, has helped ensure that Kenyan children will continue to receive vaccinations against Hib – a disease that causes 400 000 deaths per year globally – as part of standard immunisation programmes.

Hib (*H. influenzae* type b) infection is expensive and difficult to diagnose, and can lead to pneumonia and meningitis. Although a Hib vaccine exists, a lack of available data on its effectiveness and on Hib disease burden means that Hib immunisation is a low priority for many developing countries.

In 2001, a five-year programme (sponsored by the Global Alliance for Vaccines and Immunization) was launched to provide free Hib vaccine to Kenya and 11 other African countries; but from 2007, these countries are being asked to contribute financially to the programme.

To assess the impact of Hib vaccination, researchers at Kilifi examined Hib infection rates in 38 000 under-fives admitted to Kilifi District Hospital between 2000 and 2005. Hib immunisation reduced the number of cases of Hib disease by 88 per cent, on the basis of which the Kenyan Ministry of Health committed itself to funding the ongoing immunisation programme.

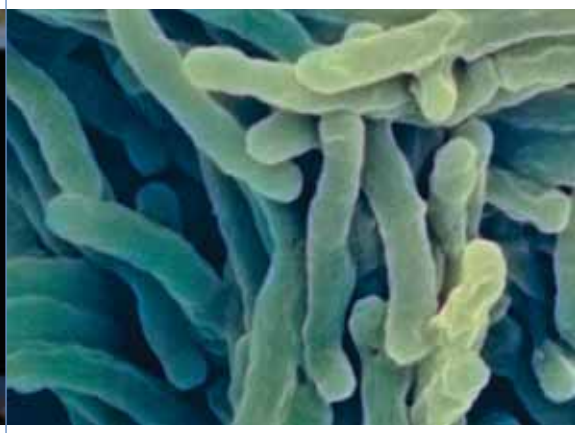
Other work supports the introduction of pneumococcal vaccines into immunisation programmes. In a similar surveillance study of children attending the hospital in Kilifi, the incidence of pneumococcal bacteraemia – blood poisoning caused by bacterial infection – was four times greater than previously estimated from inpatient studies, suggesting that bacterial infections have a much greater impact on child health than had been appreciated.

Cowgill AD et al. Effectiveness of Haemophilus influenzae type b Conjugate vaccine introduction into routine childhood immunization in Kenya. JAMA 2006;296(6):671–8.

Brent AJ et al. Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. Lancet 2006;367(9509):482–8.

TAMING TB

A new vaccine and diagnostics will aid the fight against TB.



About 1.7 million people die from tuberculosis (TB) annually; 500 children die of it every day. As such, new tools to control TB are urgently needed.

Dr Helen McShane of the University of Oxford has been developing and testing a 'prime–boost' vaccine for TB. The existing vaccine, BCG, is not always fully protective against TB disease, particularly in adults. However, it may be more effective when used as a 'prime' in combination with a second 'boost' immunisation based on the new vaccine.

The combination has been shown to be safe and immunogenic in phase I and phase II clinical trials in adults. With recently agreed Technology Transfer funding, further phase II trials, first in adults then in children and infants, are planned for South Africa's Western Cape – where TB is rife.

Professor Ajit Lalvani, whose Senior Research Fellowship in Clinical Science was renewed this year, has identified another possible benefit of BCG. BCG has been thought to work by preventing TB disease rather than by blocking initial infection. Use of a new diagnostic test by Professor Lalvani showed that BCG did seem

Images

1 Young children in Kenya.

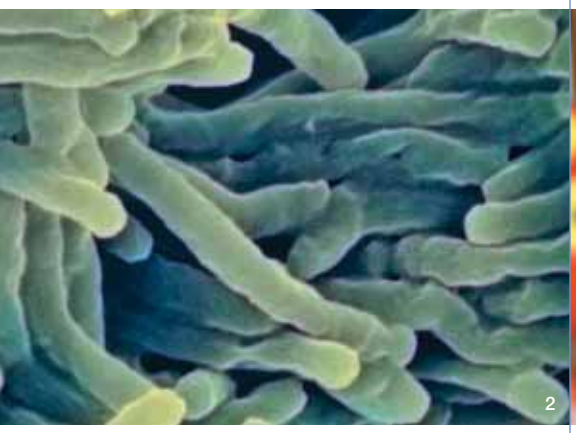
2 *Mycobacterium tuberculosis.*

3 Samples held in the Manchester CRF.

4 Nursing care in the Manchester CRF.

CARE IN THE CLINIC

Fascinating insights into the brain have been obtained thanks to research support and patient care facilities at the Cambridge Clinical Research Facility.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to protect children from infection as well as disease. BCG may therefore be more useful in disease control than once thought.

Sadly, advanced TB diagnostics are not an option for resource-poor countries, while the low-cost methods promoted by the WHO lack sensitivity and give no information about drug resistance. But a new test, the MODS assay (microscopic observation drug susceptibility), developed in Peru by Professor Bob Gilman and evaluated and refined by Dr David Moore and colleagues at Imperial College London and in Lima, Peru, is an affordable, sensitive and rapid test for TB and drug-resistant TB. The speed can save lives – a patient with multidrug-resistant TB may be dead before drug resistance has been identified by conventional methods.

McShane H et al. Recombinant modified vaccinia virus Ankara expressing antigen 85A boosts BCG-primed and naturally acquired antimycobacterial immunity in humans. Nat Med 2004;10(11):1240–4.

Soysal A et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. Lancet 2005;366(9495):1443–51.

Moore DA et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med 2006;355(15):1539–50.

Research on people is a vital part of work to understand human biology and disease processes, and the impact of new medicines. It calls for the highest possible levels of care and support. The Wellcome Trust Clinical Research Facilities (CRFs), the UK's first sites dedicated to research on people, provide an environment uniquely tailored to clinical research.

The Cambridge CRF, based at Addenbrooke's Hospital, has strengths in areas such as nutrition, energy balance and obesity, endocrinology and metabolic defects, and brain function.

With Wellcome Trust support, Professor Barbara Sahakian, Professor Trevor Robbins and colleagues have used the CRF to study cognitive function in healthy volunteers – specifically, their ability to suppress impulsive behaviours and to learn from complex input.

They were able to distinguish effects mediated through two key pathways in the brain: noradrenaline and serotonin systems. This work will shed light on conditions in which these behaviours are disrupted, including depression, drug addiction and attention deficit hyperactivity disorder.

The CRFs support high-quality research funded by a range of bodies. A notable example in 2006 was the study of an individual in a persistent vegetative state, who showed specific neural responses to stimuli, suggesting that she retained conscious awareness. This study, funded by the Medical Research Council, depended on both the expertise and equipment at the Wolfson Brain Imaging Centre and the CRF's accommodation and intensive clinical and nursing care.

Chamberlain SR et al. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 2006;311(5762):861–3.

Owen AM et al. Detecting awareness in the vegetative state. Science 2006;313(5792):1402.

IN ON THE ACT

Artemisinin combination therapies are now the recommended World Health Organization treatment for malaria.

1

2

A rare success story in the fight against malaria has been the development and use of therapies based on artemisinin, originally isolated from the sweet wormwood plant. Professor Nick White and colleagues at the Wellcome Trust's South-east Asia Major Overseas Programme have pioneered the use of artemisinin combination therapies (ACTs), which have proved extraordinarily effective at controlling malaria in Vietnam and Thailand. ACTs are now the recommended World Health Organization treatment for malaria.

Artemisinin derivatives are potent, well-tolerated, rapidly acting drugs that carry a low risk of resistance, as long as they are used in combination with other antimalarial drugs. ACTs are, however, more expensive than other treatments. Nearly all countries have now in principle adopted ACTs as their first line of defence against malaria. In practice, however, ACTs do not always reach the people that need them.

The Institute of Medicine, one of the US National Academies, has called for an annual global subsidy to make ACTs more affordable. The Institute estimates that international organisations and developed countries would have to contribute up to US$300–500 million per year to reduce the cost of ACTs to 10 cents per course or less, in line with the price of the cheapest single-drug artemisinin-derived therapy.

Development of a new drug for malaria has been a remarkable scientific and technical achievement. An equally committed and concerted effort is now needed to ensure that all vulnerable people – mostly young children in Africa – can benefit from ACTs.

WHO Guidelines for the Treatment of Malaria. Geneva: World Health Organization; 2006. www.who.int/malaria/docs/TreatmentGuidelines2006.pdf [accessed 23 November 2006].

Institute of Medicine, Board on Global Health. Saving Lives, Buying Time: Economics of malaria drugs in an age of resistance. Washington, DC: National Academies Press; 2004. http://newton.nap.edu/catalog/11017.html?onpi_newsdoc07202004 [accessed 23 November 2006].

TACKLING TRACHOMA

A new dipstick diagnostic test for trachoma has been successfully trialled.

3

Trachoma, eye damage resulting from *Chlamydia trachomatis* infection, is a major cause of blindness across the world. Although the condition can be cured by a single dose of antibiotics, identifying who should be treated has been difficult. Now, a team headed by Professor David Mabey (London School of Hygiene and Tropical Medicine) and Dr Helen Lee (University of Cambridge) has evaluated a cheap, simple and quick diagnostic dipstick for *C. trachomatis*, developed by Dr Lee and colleagues. Following successful trials, the test is being fine-tuned for use in areas of different trachoma prevalence.

In eradication campaigns, whole communities must be treated for trachoma because it is spread extremely easily. Currently, clinical signs are used to diagnose trachoma, so treatment can be targeted effectively – but clinical observation is not an accurate guide to infection.

Dr Lee's laboratory has developed technologies that have been used in a new generation of robust and simple diagnostic tests for a range of

Images

1 Testing for malaria in South-east Asia.

2 Malaria-transmitting mosquito.

3 Using the trachoma diagnostic in Tanzania.

4 Real antimalarial drugs.

COSTS OF COUNTERFEITING

Researchers fear that Africa is next in line for the influx of fake antimalarials.


3


4

infections. Teaming up with Professor Mabey, the group has evaluated a test for trachoma. A trial in Tanzania (where trachoma is rife) showed that the dipstick was more than twice as good as clinical signs at predicting trachoma cases, identifying over 97 per cent of cases correctly. The work was captured in a BBC documentary aired in more than 100 countries.

In new research funded by the Wellcome Trust, the team will test the effectiveness of the dipstick in The Gambia, Senegal and Ethiopia (areas with high, medium and low levels of trachoma, respectively). In addition to evaluating its performance in the field, they will use mathematical modelling to determine the most cost-effective strategies for using the dipstick to identify communities needing treatment.

Michel CE et al. Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study. Lancet 2006;367(9522):1585–90.

The swamping of South-east Asia with fake antimalarials is a massive threat to health that is likely to spread to Africa, says Dr Paul Newton of the Wellcome Trust–Mahosot Hospital–Oxford Tropical Medicine Research Collaboration in Laos. This illegal and pernicious trade could be responsible for thousands of deaths, as fake drugs often contain no active ingredients, subtherapeutic levels of active ingredient and even toxic substances.

Dr Newton has worked with colleagues in South-east Asia, Europe and the USA to raise awareness of this growing threat. At least eight of the 14 main types of antimalarial drug are being counterfeited, including artesunate, a highly efficacious treatment for potentially fatal falciparum malaria and a key component of ACT (artemisinin combination therapy).

Recent studies have found that about half of all ‘artesunate’ packs bought in South-east Asia are fake, with the majority sampled in some research containing no artesunate.

The situation is exacerbated by increasingly sophisticated counterfeits, with highly realistic holograms on the fake packaging. High prices, high demand and a shortage of raw material mean that an epidemic of fake artesunate in Africa is highly likely.

The World Health Organization is set to launch IMPACT (International Medical Products Anti-Counterfeiting Taskforce), which is expected to work with pharmaceutical manufacturers to make drugs harder to fake, and easier to trace from factory to consumer. IMPACT will also tackle the under-reporting of fake drugs by consumers, healthcare providers and pharmaceutical companies.

Dr Newton and colleagues hope to set up a network to detect and analyse counterfeit antimalarials, to assist drug regulatory authorities and to pinpoint where fakes were made.

Newton PN et al. Counterfeit anti-infective drugs. Lancet Infect Dis 2006;6(9):602–13.

Newton PN et al. Manslaughter by fake artesunate in Asia – will Africa be next? PLoS Med 2006;3(6):e197.

WIDE SCREEN

With its first drugs entering clinical trials, DanioLabs is making the transition from small fry to big fish.

1

Two compounds developed by DanioLabs Ltd, a spin-out from the University of Cambridge and the University of California, San Francisco, have entered clinical trials for the treatment of Parkinson's disease symptoms.

The company uses *in vivo* assays in zebrafish to look for new clinical uses of either established drugs or those that dropped out of the research and development pipeline, alone or in combination.

DanioLabs has pioneered the use of zebrafish in compound screening. The fish are vertebrates that model human systems closely; they have transparent embryos, it is possible to work with single cells, and the genome is easy to manipulate and is currently being sequenced.

The company, which developed with Wellcome Trust Technology Transfer funding, focuses on treatments for ophthalmic and neurological disorders. The company operates an in-house drug discovery process that re-screens existing drugs and also offers screening services to pharmaceutical companies.

DanioLabs has continued to grow since its launch in 2002 – attracting £3.2 million in venture capitalist funding in 2005. Currently, two compounds (novel combinations of established drugs) are undergoing phase I trials for the treatment of drooling and excessive sweating in Parkinson's disease. There is also a further compound under investigation for seborrhoea (excessive sebum secretion), an additional feature of Parkinson's disease but also a pathogenic factor in acne and the skin condition seborrhoeic dermatitis.

The company is also researching treatments for several other conditions, with compound screens currently underway for epilepsy, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

www.daniolabs.com

BREATHE EASY

Clinicians and patients will both benefit from a new laryngoscope.

2

Keeping a patient's airways clear is vital during anaesthesia or emergency treatment. Usually doctors use a laryngoscope, to assist placing a flexible tube through the vocal cords and into the windpipe. Laryngoscope design has changed little since the 1940s. Great skill is needed to use them safely and they can damage patients' teeth, vocal cords and soft tissue.

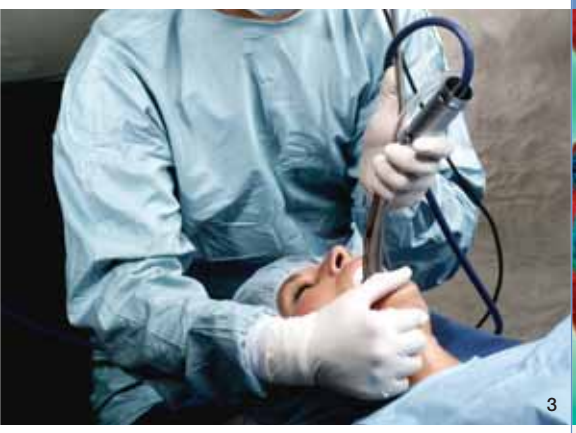
Matt McGrath, a former John Logie Baird Young Innovator of the Year, founded Aircraft Medical Ltd in 2001, having started designing his laryngoscope two years earlier as part of his degree course. With the support of a Wellcome Trust Translation Award, his company developed Mk 4 and Mk 5 prototypes, which led to the 2006 launch of the McGrath® Series 5 laryngoscope.

Thanks to an integrated camera and screen, the portable battery-powered McGrath® Series 5 provides a clearer view of the airway. As a result, it is easier to manoeuvre – good for patient and for doctor. The laryngoscope is size-adjustable and also features disposable blades to prevent cross-infection between patients.

Images

1 Adult zebrafish.
2 Matt McGrath and his laryngoscope.
3 Intubating a patient in the operating theatre.

NEW FUNDING



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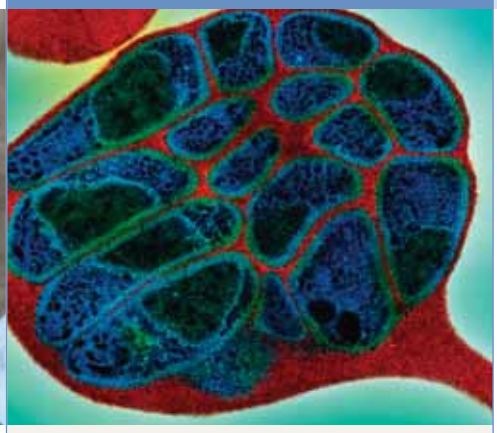
The McGrath® laryngoscope has been described as the "most significant advancement in laryngoscope design since the 1940s" (Dr Gary Enever of the Royal Victoria Infirmary, Newcastle). In a recent study on 150 patients at the Royal Infirmary of Edinburgh, the McGrath® demonstrated 94 per cent grade 1 views, whereas current equipment achieves under 70 per cent.

LMA North America has been appointed exclusive distributor in the USA, in a five-year contract with potential value of US$50 million to Aircraft Medical. With laryngoscopes being used in 60 million anaesthetisations each year, the product has a chance of making a significant impact on health.

Shippey B et al. Rapid sequence intubation using the McGrath videolaryngoscope. Eur J Emerg Med 2006;13(5):A12–13.

New malaria drugs



The Wellcome Trust, the Singapore Economic Development Board and the Medicines for Malaria Venture (MMV) have pledged over £10 million to a new partnership dedicated to malaria drug development.

The new programme, which received £6.4m from the Wellcome Trust, will be led by Professor Alex Matter of the Novartis Institute for Tropical Diseases (NITD) in Singapore – a partnership between Novartis and the Singapore Economic Development Board.

The NITD will conduct research jointly with several institutions, including the Genomics Institute of the Novartis Research Foundation and the Swiss Tropical Institute.

Scientists at the NITD will investigate the potential of existing compounds with some antimalarial activity, as well as exploring novel compounds. The research will focus on two main goals: a one-dose cure for *Plasmodium falciparum*, the most dangerous form of malaria; and new treatments for *P. vivax*, the most widely distributed cause of malaria.

Development of the most promising candidate drugs will be taken forward by MMV.

A selection of notable grants awarded in 2005/06.

TECHNOLOGY TRANSFER AWARDS

Dr Richard Marais and **Dr Caroline Springer** (Institute of Cancer Research) Research into drug-like inhibitors of BRAF kinase for the treatment of malignant melanoma. The Wellcome Trust and the Institute of Cancer Research have also established an alliance with GlaxoSmithKline to discover, develop and commercialise novel small-molecule inhibitors of BRAF.

Dr James Hamilton (University of Keele) Pheromone-based sand-fly traps: sex pheromones will lure disease-transmitting sand flies to insecticide-laden traps.

Dr Andrew Gee (University of Cambridge) Mathematical manipulations to improve ultrasound imaging.

Professor Sir Tom Blundell (University of Cambridge) Fragment-based inhibition of protein interactions.

Professor Paul Addison (CardioDigital Ltd, East Lothian) Software enhancements to predict responsiveness to cardioversion therapy in atrial fibrillation patients.

Professor Paul Sharp (Odontis Ltd) Using stem cells to regrow teeth: moving from animal studies to human application.

Dr Lorenzo Frigerio (University of Warwick) Engineering plants to produce higher yields of secretory IgA than are currently possible.

Details of all grants made can be found in *Grants Awarded 2005/06*, available on the Wellcome Trust website.

ENGAGING SOCIETY

Engaging with society to foster an informed climate within which biomedical research can flourish.

SCHOOL REPORT

Better teachers using a better curriculum: the prospects for UK science education are looking up.

School students have been clamouring for more meaningful science education. Teachers agree and, given training and resources, are keen to deliver it. The opening of the National Science Learning Centre at York and the launch of the Twenty First Century Science curriculum are important steps towards this goal.

The Wellcome Trust has provided £25 million for the National Science Learning Centre, in York, to support teachers' continuing professional development, with the Department for Education and Skills contributing £26m funding for nine regional centres.

In March 2006, the Prime Minister, Tony Blair, opened the National Centre, saying: "At school we all knew the one thing that made a difference was if the teacher felt personal enthusiasm for their subject, then it was communicated to their students." In the first year, more than 1000 teachers and technicians attended courses in York, a figure that will rise to 5000 teachers annually from 2013.

The Twenty First Century Science GCSE, launched in September 2006 following a successful pilot, will help prepare 14–16-year-olds for a rapidly changing world. Its modular approach is designed to cater both for the academically gifted destined for a career in science and for non-specialists who will nonetheless be living in a science-dominated world.

The GCSE aims to give essential factual education while also conveying the nature of science and rooting science in the world experienced by today's young people. It will also challenge science teachers, technicians and teaching assistants to keep themselves updated with a rapidly developing subject and to make use of innovative techniques that engage students – for example, through the national network of Science Learning Centres.

www.sciencelearningcentres.org.uk

AIRING THE ISSUES

'Real' characters can breathe life into ethical debates.

A mum tries to calm the blazing row between her vegetarian animal-loving son and his medical researcher sister. Sonny opposes research on animals, sister Anita believes it is justified, while mum's Buddhist boyfriend provides an interesting commentary. Later, Sonny's principles are tested when asthma puts him into hospital.

Funded by a Wellcome Trust Society Award, *Every Breath*, written by Judith Johnson and produced by Y Touring Theatre Company, is a thought-provoking yet balanced production. It does not attempt to push any particular argument, but helps the audience to see all sides of a complex and emotive issue.

A live debate follows the performances, encouraging students to explore the issues. Y Touring's website has downloadable lesson resources to help teachers and students.

Aimed at 14-year-olds and upwards, the play has been seen by more than 14 000 youngsters this year. Although

Images

1 Trainee teachers at the National Science Learning Centre.

2 A scene from *Every Breath*.

3 A speaker at one of the 'wellbeing' events.

SHARED EXPERIENCE

Members of the public and a range of experts engaged in thoughtful discussions about the nature of wellbeing.


2


3

showing predominantly in schools, Y Touring has taken the production to a young offenders' centre as well as the Edinburgh Fringe Festival, where it won the best production award.

Every Breath is specifically designed for cross-curricular learning. One 14-year-old said: "It was good to see drama and science mixed together like that. It's better than sitting in the classroom and reading about it in a book."

www.ytouring.org.uk

- The *Every Breath* project also received funding from the Association of Medical Research Charities.

Naturally, we all value our health and wellbeing. Scientific discoveries impinge on our sense of 'wellness', but so too do our social circumstances – our relationships, environment, family and so on. A series of public events organised by the Wellcome Trust featured a range of perspectives on a topic close to our hearts.

The first event, 'What Makes us Happy?', brought insights from science, philosophy and gritty street reality to explore the concept of happiness.

Music has always been important in self-expression and scientists are now beginning to understand how it affects us. 'Exploring the Rhythms of Life' combined science and psychology with live performance to demonstrate what happens when music meets mind.

'Full Life, Long Life?' used philosophy and science to explore the choices and consequences of the lives we lead. Faced with an over-60s population boom, could we 'cure' ageing to live a longer life? As lifestyle makes more demands on medicine, we may see a new relationship between medicine and culture developing.

Feeling close to the speakers, audiences raised points easily in a non-academic, friendly environment. More than 200 people attended the three July events, which were oversubscribed several times over. As a result, the events were run again (and were again sold out) later in 2006.

These sell-out events augur well for the opening of Wellcome Collection in 2007 (see page 41), which has a similarly intimate 'forum' space.

THE RHYTHM OF LIFE

How do you get young people interested in a subject as alien as epigenetics? Or psychotherapies? Dance and drama may be the answer.

At first sight, the idea that dance could be used to interpret epigenetics – the chemical modification of DNA or its proteins – seems far-fetched. Yet to see young dancers perform so exuberantly, and to hear how discussion of the dance's fluid choreography led to sophisticated discussion of DNA and inheritance, is to appreciate the power of artistic approaches to engage people with biomedical science.

The intricate moves of the young dancers in IMPACT Danscience's project draw upon both classical Indian dance and the dynamics of cells, nuclei and chromosomes. The project is the result of a series of workshops run by the choreographers Mayuri Boonham and Subathra Subramaniam of ANGIKA Dance Company, and biomedical scientist Dr Sheila Ochugboju.

If dance and epigenetics seems like a strange combination, how about cognitive behavioural therapy (CBT) and frozen peas? Acclaimed performance artist Bobby Baker, who has herself undergone CBT and other psychotherapies, raises important and challenging issues in her 'How to Live' project, which featured at a special event at the European Science Open Forum in Munich in July 2006 and later played at the Barbican.

By helping a frozen pea diagnosed with a personality disorder undergo CBT, Baker manages to be both thought-provoking and entertaining. "Charming, eccentric, thoughtful," said *The Financial Times*; "Farcical and dark, and as Bobby promises at the outset, makes you feel better," thought the *Guardian*.

- A DVD of IMPACT Danscience is available at: **www.impactdanscience.co.uk**.

'How to Live' also received support from Calouste Gulbenkian Foundation and Arts Council England. It is due to tour in 2007 (see **http://bobbybakersdailylife.com** for details).

YOUNG CITIZENS

'Young citizens' have had a chance to have their views heard.

The new world of genetic technology will affect young people more than the older generation. But what do they think about the application of these technologies to reproductive decision-making? Dr Rachel Iredale and colleagues at the University of Glamorgan's Genomics Policy Unit ran a 'citizens' jury' for young people between 16 and 19 years old to find out where they would draw the line with 'designer babies'.

Fourteen young people from Wales were chosen as jurors; they cross-examined experts on topics such as preventing genetic disease, sex selection and 'saviour siblings'. They also heard from non-experts who had personal experience of the issues before reaching their verdict.

The organisers concluded that the first citizens' jury with this age group demonstrated the validity of the method in terms of engaging young people with current issues in science, and that they have important and useful things to say about genetic technologies.

As well as writing their report, the young jurors presented their conclusions to the Human Genetics

Images

1 Epigenetics dancers.

2 The group who sat on the citizens' jury.

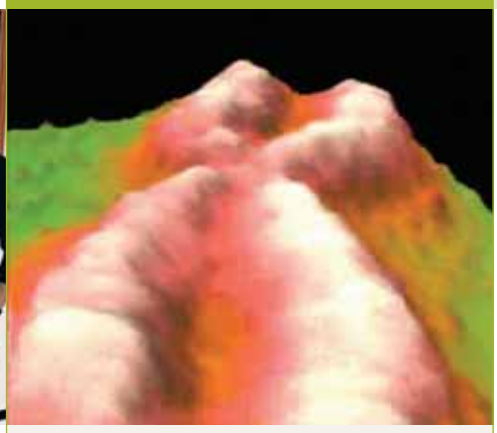
Commission, the Human Fertilisation and Embryology Authority, and the Health and Social Services Committee of the Welsh Assembly Government. They included agreement that it is acceptable to use genetic technology to prevent genetic disorders being passed on, or to save a sibling. But the jury opposed sex selection for social reasons.

They also declared that 'designer babies' is not a useful term – and that the Human Fertilisation and Embryology Authority should have some members under 20.

Iredale R et al. What choices should we be able to make about designer babies? A Citizens' Jury of young people in South Wales. Health Expect 2006;9(3):207–17.

NEW FUNDING

Generation Genome



At-Bristol has been awarded a £1.5 million Capital Award to produce a five-year national touring exhibition on genomics.

At the heart of the *Generation Genome* project is a vast 350 m^2 travelling exhibition aimed at 14-year-olds and above, to engage them in the science of the human genome, genomics research, and related social and ethical issues. It will be hosted by science centres and museums in the UK.

The travelling exhibition will feature a continuously updated News and Views area and a Dialogue Zone, as well as multiple opportunities for visitors to engage with topical ideas and ethical issues at 'opinion stations'.

Six smaller replicable 'exhiblets' – satellite mini-exhibitions, featuring basic introductory material, the updated News and Views area and opinion stations – will visit smaller museums and shopping centres.

The project also includes an education dimension, such as teachers' resources and workshops, as well as informal engagement events, including debates and meet-the-scientists opportunities. *Generation Genome* is being produced by At-Bristol on behalf of Ecsite-UK, the UK's network of science centres and museums.

A selection of notable grants awarded in 2005/06.

PUBLIC ENGAGEMENT

INTERNATIONAL PUBLIC ENGAGEMENT
Seven projects were awarded a total of £933 000 through the Livestock for Life initiative, which aimed to forge closer links between researchers, policy makers and livestock owners in developing countries.

WEBSITE
Dr Sue Ziebland (University of Oxford) Living with autism: establishing a web resource combining factual information with video and audio material from affected families; part of the ongoing DIPEx (Database of Individual Patient Experiences) project.

VISUAL COMMUNICATION
Shirley Wheeler (University of Sunderland) Visual design: discussions with scientists, designers and the public about ways to portray molecular biology and science information visually.

INTERACTIVE EXHIBITS
Martin J Freeth (Windfall Digital Ltd) Development of interactive genetics exhibits.

SCIENCE AND ART
Cambridgeshire County Council
Genetics-inspired art on the Great Shelford to Addenbrooke's Hospital cycle path. The path features 10 000 stripes representing the genetic code for the *BRCA2* gene, which was sequenced at the nearby Wellcome Trust Sanger Institute, and celebrates the 10 000th mile of the National Cycle Network.

HISTORY OF MEDICINE
Dr Tilli Tansey (Wellcome Centre for the History of Medicine, University College London) Dr Tansey and Professor Les Iversen will video interviews with 12 leading neuroscientists.

HISTORY OF MEDICINE
Justin Hardy (Hardy & Sons Ltd)
A docudrama based on the medical relief operations at the liberated Belsen concentration camp. The same team made the award-winning drama *Trafalgar Battle Surgeon.*

RESEARCH
Professor Sarah Franklin (London School of Economics and Political Science) How new approaches in public engagement have impacted on biomedical scientists.

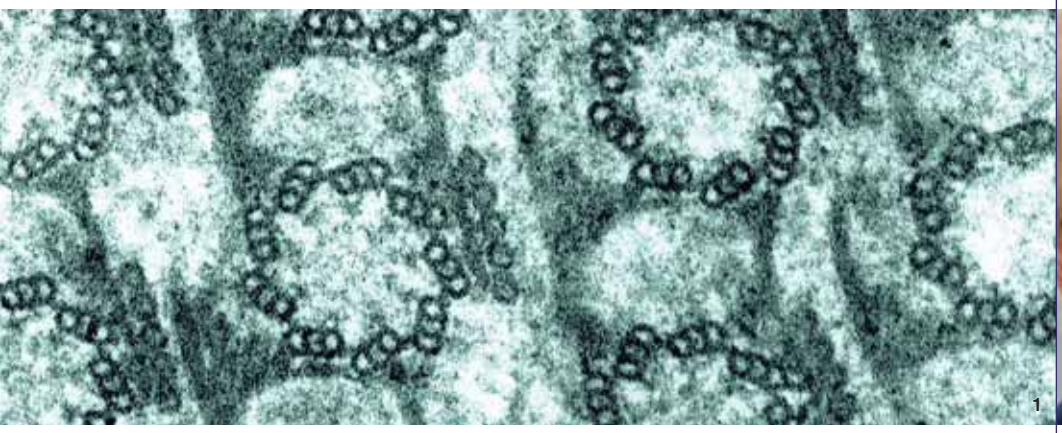
Details of all grants made can be found in *Grants Awarded 2005/06*, available on the Wellcome Trust website.

DEVELOPING PEOPLE

Fostering a research community and individual researchers who can contribute to the advancement and use of knowledge.

SECRETS OF THE CILIA

Studies of a rare genetic condition are revealing unexpectedly important roles for cilia in development.



1

Wellcome Trust Senior Research Fellow Professor Philip Beales (Institute of Child Health) and colleagues have discovered that cilia – tiny hair-like structures on the surface of cells – may be involved in a range of fundamental developmental pathways. The researchers have identified several genes causing a rare genetic condition, Bardet–Biedl syndrome (BBS), and discovered that these can interact with each other to influence disease severity. Each appears to affect the function of cilia.

BBS is an inherited complex disorder, causing obesity, vision defects, cognitive impairment, kidney failure and other problems. Several genes mutated in the condition have been discovered; one of the latest is *BBS10*, identified in studies of families from an isolated Lebanese village particularly affected by the condition.

In a separate study, Professor Beales and colleagues showed that a single nucleotide polymorphism in an interacting gene, *MGC1203*, does not itself cause BBS, but can have a novel effect on its severity. The *MGC1203* protein was found at the base of cilia and interacts with most BBS proteins. Symptoms thus depend not only on which BBS gene is affected, but also on any other BBS gene alterations present, and on the effects exerted by mutations within other, non-disease (so-called 'modifier') genes, such as *MGC1203*.

The group also uncovered a connection with 'planar cell polarity', which controls aspects of cell function such as cell orientation and polarity. In mice, mutations in BBS genes disrupt cell polarity. Furthermore, BBS genes were shown to interact with cell polarity genes, suggesting a novel role for cilia in this process.

Other aspects of the syndrome, such as obesity and extra digits, cannot be readily explained by dysfunctional cilia but it is likely that further study of the BBS genes will eventually explain these links.

Ross AJ et al. Disruption of Bardet–Biedl syndrome ciliary proteins perturbs planar cell polarity in vertebrates. Nat Genet 2005;37(10):1135–40.

Badano JL et al. Dissection of epistasis in oligogenic Bardet–Biedl syndrome. Nature 2006;439(7074):326–30.

Stoetzel C et al. BBS10 encodes a vertebrate-specific chaperonin-like protein and is a major BBS locus. Nat Genet 2006;38(5):521–4.

Images

1 Cross-section through cilia showing their distinctive microtubule rings.

2 Professor Nick White.

Left:
Professor Philip Goulder, a Senior Research Fellow at the University of Oxford.

ROYAL SOCIETY FELLOWSHIPS

Royal Society recognition for Wellcome Trust-funded scientists.

2

Professor Nick White, Chairman of the Wellcome Trust's Major Overseas Programme in South-east Asia, was elected a Fellow of the Royal Society in 2006.

Two researchers associated with new Wellcome Trust Centres – **Professor Austin Smith** (Wellcome Trust Centre for Stem Cell Biology, University of Cambridge) and Principal Research Fellow **Professor Karl Friston** (Wellcome Trust Centre for Neuroimaging, University College London) – were made Fellows of the Royal Society this year.

Several researchers with major Wellcome Trust grants were also recognised: **Professor Peter Donnelly** (University of Oxford), **Professor Richard Jackson** (University of Cambridge), **Professor Malik Peiris** (University of Hong Kong) and **Professor Helen Saibil** (Birkbeck College London).

- A list of other researchers receiving notable awards this year can be found at **www.wellcome.ac.uk/annualreview06**.

AVATAR AID

Virtual reality could unlock the secrets of paranoia.

Paranoid thoughts, arising from an exaggerated or unfounded distrust of others, regularly affect one in three people in the UK, but are particularly problematic in psychotic conditions such as schizophrenia. A team from the Institute of Psychiatry has developed a virtual reality system to investigate the processes behind this kind of thinking, and to develop treatments for it.

In a Wellcome Trust-funded pilot study, the group pioneered the use of virtual reality – already shown to help people to overcome phobias – to develop an understanding of paranoid thoughts. Now, one of the original researchers, Dr Daniel Freeman, has been awarded a Research Career Development Fellowship to continue this work.

Paranoia arises from abnormalities in social cognition – understanding how people interact with one another and interpreting interpersonal behaviour in particular social situations. People with paranoid thinking patterns interpret social signals abnormally – believing that everyone on a bus is looking at them, for example.

As well as undertaking various studies exploring these aberrant ways of thinking, Dr Freeman is also using the virtual reality system to assess patients' responses and behaviour in a fully immersive but totally controlled environment. For example, it will be possible to compare the responses of patients with those of non-clinical individuals in the general population, to identify behaviours characteristic of paranoid thinking.

It is hoped that in the future, this system could be adapted to become part of cognitive behavioural therapy, a form of psychotherapy.

Freeman D et al. The psychology of persecutory ideation II: a virtual reality experimental study. J Nerv Ment Dis 2005;193(5):309–15.

Freeman D et al. Acting on persecutory delusions: the importance of safety seeking. Behav Res Ther 2007;45(1):89–99 [Epub ahead of print].

Freeman D et al. Psychological investigation of the structure of paranoia in a non-clinical population. Br J Psychiatry 2005;186:427–35.

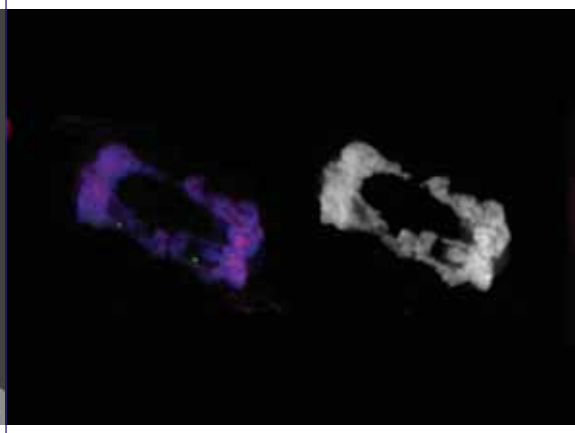
Freeman D. et al. Can virtual reality be used to investigate persecutory ideation? J Nerv Ment Dis 2003;191(8):509–514.

Freeman D. Suspicious minds: the psychology of persecutory delusions. Clin Psychol Rev [in press].

The group has also produced a self-help book, *Overcoming Paranoid and Suspicious Thoughts*. See **www.paranoidthoughts.com**.

CONDENSATION REACTION

A key component of chromosome condensation has been discovered.



Every human cell contains nearly 2 m of DNA crammed into a nucleus just 6 µm across. The pinnacle of this extraordinary feat of packaging is the winding of chromatin into the chromosomes visible during cell division. Now, work by Wellcome Trust Principal Research Fellow Professor Bill Earnshaw at the Wellcome Trust Centre for Cell Biology in Edinburgh has revealed a key player in this process of condensation.

Two protein complexes, condensin I and II, contribute to chromosome condensation, but are not the complete picture – in some types of cell, chromosomes can condense without them. So Professor Earnshaw and a team led by Dr Paola Vagnarelli looked for factors that were needed for chromosome condensation in the absence of condensins, using genetically modified chicken cells.

They identified an activity – probably a protein or protein complex – that could maintain chromosomes in a condensed form during mitosis. This activity, which they named 'regulator of chromosome architecture' (RCA), only functioned when a protein called Repo-Man (discovered in the lab of

Images

1 An image from a virtual reality underground tube environment used in studying paranoid and suspicious thinking.

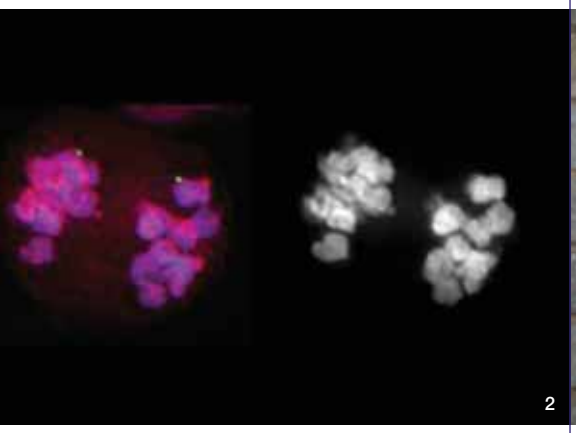
2 Left pair: 'bridged' chromosomes, where chromatin has not remained condensed. Right: normal condensed chromosomes.

3 Dr Sumantra Chattarji.

4 Effects of stress on a pyramidal amygdala neuron.

STRESSFUL MEMORIES

After severe stress or trauma, we may remember things we would prefer to forget. Stress-induced changes to the amygdala could explain why.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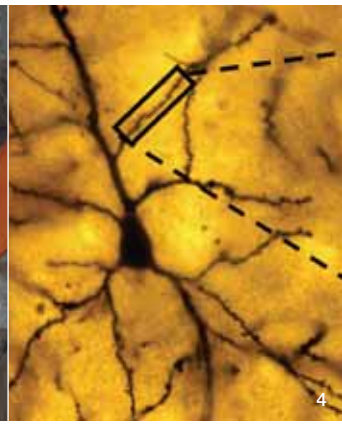

4

Professor Angus Lamond, another Wellcome Trust Principal Research Fellow) was inhibited. Blocking Repo-Man probably prevents an associated enzyme, protein phosphatase 1 (PP1, which is involved in many cell processes), from removing key phosphate groups needed for RCA activity.

RCA and condensins probably act together to condense chromosomes, suggests Professor Earnshaw. One interesting possibility is that RCA drives condensation and condensin stabilises the compacted forms.

Vagnarelli P et al. Condensin and Repo-Man-PP1 co-operate in the regulation of chromosome architecture during mitosis. Nat Cell Biol 2006;8(10):1133–42.

Wellcome Trust International Senior Research Fellow Dr Sumantra Chattarji and his team at the National Centre for Biological Sciences in Bangalore, India, are studying how the wiring of the brain changes under stress. A better understanding of the cellular mechanisms that imprint emotional memories in our brains could lead to better treatments for severe anxiety or post-traumatic stress disorder.

Stress intrigues memory researchers because of its contrasting impact on different types of memory, and opposite effects on different parts of the brain. Prolonged stress impairs recollection of facts and events, by causing damage to the hippocampus. By contrast, it greatly amplifies emotional memories, by enhancing the wiring of neuronal circuitry in the amygdala.

With collaborators in the USA, Dr Chattarji has begun to identify the biochemical and electrophysiological changes in single neurons that affect the hippocampus and amygdala – and, through them, mouse behaviour. Raising levels of the signalling chemical brain-derived neurotrophic factor, for example, can simultaneously heighten anxiety by strengthening connections in the amygdala, but reduce depressive symptoms by protecting the hippocampus.

The amygdala has received less attention than the hippocampus, but Dr Chattarji's research has identified stress-induced changes in the amygdala that underlie sensitivity to emotional experience. Ultimately, this work will provide a clearer picture of the neural changes that leave people susceptible to flashbacks of highly stressful events, and lead to new approaches to understanding and treating conditions such as stress-induced depression and chronic anxiety.

Mitra R et al. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci USA 2005;102(26):9371–6.

Vyas A et al. Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. Neuroscience 2006 [Epub ahead of print].

Govindarajan A et al. Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. Proc Natl Acad Sci USA 2006;103(35):13208–13.

THE BILINGUAL BRAIN

A small area of the brain helps to control choice of language in bilingual people.

1

2

The ability of bilingual people to read or hear a particular language, and respond using that language alone, suggests some kind of language-specific system in the brain. But the same areas of the brain are active no matter what language someone is using. Now, though, Wellcome Trust Senior Research Fellow Professor Cathy Price and colleagues at the Institute of Neurology have identified an area of the brain that is active when a person switches from one language to another.

In the group's study, 25 German–English speakers and ten Japanese–English speakers were shown pairs of words and told to ignore the first one (the primer). The words were either related (e.g. bathtub–SHOWER) or not (e.g. bathtub–SPOON). When the words were related, brain activity in language areas was typically lowered, as the brain had been 'primed' to be thinking about that subject.

Sometimes the related pairs were in the same language (e.g. trout–SALMON) and sometimes in different languages (e.g. forelle–SALMON). The researchers could thus identify whether areas of the brain were responding just to the meaning of the words or were also sensitive to a change in language in which they were presented.

Using functional imaging techniques, the team detected one area that responded to both the switch in language and the meaning of the words – the head of the left caudate. Researchers think that this area could be important in telling the brain which language to respond in.

Interestingly, bilingual people with damage to this area of the brain are known to have problems switching between languages. The team will now to try to piece together this language-sensitive circuit in the brain by examining individuals with damage in this and other brain areas.

Crinion J et al. Language control in the bilingual brain. Science 2006;312(5779):1537–40.

CITATION STARS

Wellcome Trust-funded scientists are highly influential in malaria.

3

Thomson Scientific's *Essential Science Indicators* tracked more than 14 500 authors in 134 countries to identify the most influential malaria researchers – those whose work (published during 1995–2005) was cited most often by their peers. Wellcome Trust-funded researchers occupied five of the top ten places in their independent citation 'league table'.

The Wellcome Trust has historically been a major supporter of research in developing countries generally and on malaria specifically. It has established programmes in South-east Asia and sub-Saharan Africa, and has identified and supported leading individuals to drive their research forward. This long-term commitment to excellence is reflected in the malaria research indicators.

Professor Kevin Marsh, Director of the KEMRI (Kenya Medical Research Institute)–Wellcome Trust Research Programme in Kenya, made second place. As well as leading the Research Programme, Professor Marsh has made major contributions to our understanding of the host immune response to the malaria parasite.

Images

1 An English–French dictionary.

2 Professor Cathy Price.

3 Professor Kevin Marsh.

4 Malaria studies in Kenya.

NEW FUNDING

In third spot was Professor Nick White, Chairman of the Wellcome Trust's South-east Asia Major Overseas Programme in Thailand and Vietnam. Professor White has pioneered the use of artemisinin combination treatments for malaria (see page 20). He was recently awarded an OBE and made a Fellow of the Royal Society.

Professor Marsh's colleague Professor Bob Snow also made the top five. Professor Snow has carried out a series of landmark studies on global disease burden and risk of malaria (see page 11 and right), and promoted the use of research findings to drive policy making.

Two other Trust-funded researchers made the top ten: Professor François Nosten, Director of the Shoklo Malaria Research Unit in Mae-Sot, Thailand, who has overseen some of the largest drug trials ever undertaken in malaria; and Professor Adrian Hill at the Wellcome Trust Centre for Human Genetics, University of Oxford, who is developing and testing malaria vaccines.

Principal Research Fellows

Four Principal Research Fellowships, the most senior of the Wellcome Trust's personal support schemes, were awarded or renewed this year.

Professor Chris Fairburn, University of Oxford, has pioneered the use of cognitive behavioural therapies for eating disorders. He is now attempting to adapt a successful treatment for bulimia nervosa for use in other eating disorders.

Professor Bob Snow (above), who works at the KEMRI–Wellcome Trust Research Programme, will be taking forward his work on mapping malaria risk to predict its likely distribution in ten and 25 years' time. A complementary programme of research will identify the best approaches for national malaria control programmes.

Infectious disease is also the focus of **Professor Alan Fairlamb's** research at the University of Dundee. He is searching for weak points in the defences of trypanosome parasites and developing drugs targeted against them.

At the Wellcome Trust Centre for Cell Biology, University of Edinburgh, **Professor David Tollervey** is studying the function of two large multiprotein cellular structures, the exosome and the ribosome.

A selection of notable grants awarded in 2005/06.

SENIOR RESEARCH FELLOWSHIPS

GENETIC DISEASE
Professor David Rubinsztein (University of Cambridge) Possible therapies for codon repeat diseases such as Huntington's disease.

METABOLISM
Dr Alexander Gourine (University College London) Cardiorespiratory control: chemosensing and the role of brain plasticity.

TROPICAL MEDICINE
Dr Alison Elliott (London School of Hygiene and Tropical Medicine) Helminth infection: effects on immunisation and disease in Ugandan children.

NEUROSCIENCE
Professor Michael Hausser (University College London) Understanding network dynamics and plasticity in the cerebellar cortex.

Professor Angus Silver (University College London) The links between vesicle dynamics and synapse behaviour.

INTERNATIONAL SENIOR RESEARCH FELLOWSHIP

MOLECULAR MOTORS
Dr Roop Mallik (Tata Institute of Fundamental Research, Mumbai, India) Using optical trap technology to study individual molecular motors.

RESEARCH CAREER DEVELOPMENT FELLOWSHIPS

NEUROANATOMY
Dr Heidi Johansen-Berg (University of Oxford) Premotor networks in the human brain: their anatomy, physiology and modulation in disease. Dr Johansen-Berg was formerly a Wellcome Trust Four-year PhD Student and a Research Training Fellow in Mathematical Biology.

BIOMEDICAL ETHICS FELLOWSHIPS

STEM CELL BANKING
Dr Helen Busby (University of Nottingham) Cord blood stem cell banking: ethical aspects of its commercial application.

HISTORY OF MEDICINE RESEARCH LEAVE AWARD

MILITARY MEDICINE
Dr Mark Harrison (University of Oxford) British military medicine in the First World War. Dr Harrison's last book was the award-wining *Medicine and Victory: British military medicine in World War Two*.

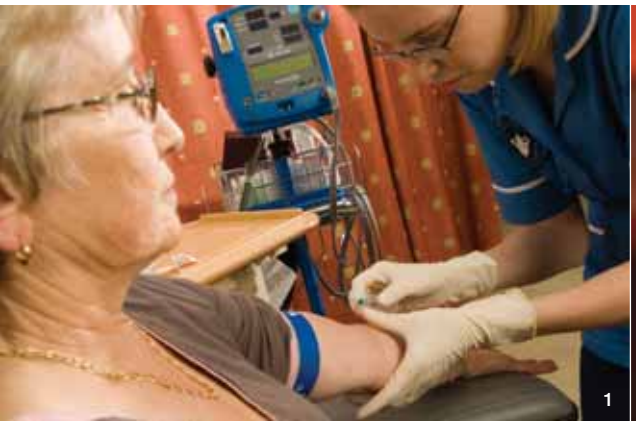
Details of all grants made can be found in *Grants Awarded 2005/06*, available on the Wellcome Trust website.

FACILITATING RESEARCH

Promoting the best conditions for research and the use of knowledge.

ALL SYSTEMS ARE GO

After a successful pilot study, UK Biobank got the green light to roll out nationally.



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UK Biobank will gather, store and protect the world's largest bank of blood and DNA samples, and health information, collected from 500 000 volunteers in the UK aged between 40 and 69. People in this age group are at risk of developing a wide range of fatal and disabling illnesses such as heart disease, diabetes, cancer, mental illness and joint diseases. By following this group over many years, UK Biobank will provide researchers with a unique resource for studying the roles of genes, lifestyle and environment in disease.

To test procedures, a three-month pilot study was held from March to May 2006 in the Altrincham district of Manchester. Some 3800 men and women were recruited in the pilot phase. They each spent about 90 minutes at an assessment centre, answering questions about their health and lifestyles, and giving blood and urine samples. All agreed to allow their health to be followed by UK Biobank for many years, through routine medical and other health-related records.

An independent review panel judged proposals for UK Biobank to be excellent, praising its planning and handling of potential ethical problems, as well as its ability to recruit enough volunteers and assess them extensively within budget. As a result, in August 2006, the funders announced that the study will be rolled out nationally.

Over the next four years, UK Biobank will start recruiting 500 000 adults – nearly 1 per cent of the UK population – who will attend one of a network of 35 assessment centres across the UK, each open for about six months.

www.ukbiobank.ac.uk

- The £61 million UK Biobank project is funded by the Wellcome Trust, the Medical Research Council, the Department of Health, the Scottish Executive and the North West Regional Development Agency.

Images

1 Taking blood during the pilot phase of UK Biobank.

2 Stored biological samples.

3 Robert Hooke's notebook.

RIGHT HOOKE

The Royal Society has regained Robert Hooke's notebook.

3

Study of the past relies heavily on historical documents. This means ensuring that important documents and other materials are in repositories where they can easily be accessed and are protected for future generations. Wellcome Trust funding helps to achieve both these aims.

Robert Hooke is a neglected figure in science history – partly because of a feud with Isaac Newton, who downplayed his achievements. But Hooke did become secretary of the Royal Society.

Strangely, his records of Royal Society meetings went missing – but turned up this year, having lain in a dusty Hampshire attic for half a century. Donations from the Wellcome Trust and others enabled the Royal Society to buy the manuscript.

The donation to the Royal Society was a one-off, in recognition of the huge importance of the material to the nation's scientific heritage. The ongoing Research Resources in Medical History scheme helps to preserve and open up key resources.

Some 90 projects have been funded to date, covering material such as the archives of Broadmoor Hospital, the papers of R D Laing and César Milstein, and records at Great Ormond Street Hospital.

BRED FOR SUCCESS

When it comes to modelling human biology, the mouse remains the organism of choice. A host of shared resources is accelerating mouse research.

The sequencing and annotation of the mouse genome, by the Wellcome Trust Sanger Institute and others, created a powerful resource for researchers exploring mouse biology. Now new biological tools and the results of genetic experiments are offering even more help to mouse researchers.

A major challenge in biomedical research is to disentangle the effects of multiple genes on complex biological traits, including common diseases. Mice have similar biology to humans but can be bred and analysed in ways impossible in humans.

Professor Jonathan Flint, Dr Richard Mott and colleagues at the Wellcome Trust Centre for Human Genetics in Oxford have been carrying out genome-wide analyses of complex traits in genetically mixed mice (as opposed to the 'pure' inbred strains usually used). As well as shedding light on the environmental and genetic influences on these traits, the results are also being made freely available on the web for researchers to explore particular traits in more detail (see http://gscan.well.ox.ac.uk). The methods also illustrate the potential for high-throughput genetic analysis in mice.

Meanwhile, the Sanger Institute continues to develop its mouse resources. Mouse sequence data, extensively annotated, are available through the Ensembl Mouse website (www.ensembl.org/Mus_musculus). Biological tools include MICER and 'gene-trap' resources, which provide the means to generate genetically altered mice.

The Sanger Institute has also been awarded major funding from the US National Institutes of Health and the EU to generate a resource of mouse knockouts of 13 500 genes, as part of two international collaborations (KOMP and EUCOMM) aiming to mutate 95 per cent of mouse genes by 2011. As many as 2500 of these will be converted into mice to examine the role of single genes. All of these resources will be available to the scientific community.

Valdar W et al. Genome-wide genetic association of complex traits in heterogeneous stock mice. Nat Genet 2006;38(8):879–87.

Valdar W et al. Genetic and environmental effects on complex traits in mice. Genetics 2006;174(2):959–84.

Cunningham F et al. TranscriptSNPView: a genome-wide catalog of mouse coding variation. Nat Genet 2006;38(8):853.

BUILDING SIGHTS

Several new biomedical research facilities opened in 2005/06.

The Joint Infrastructure Fund (JIF) and the Science Research Investment Fund (SRIF), run in partnership with the UK Government between 1998 and 2003, saw substantial sums invested in the UK research infrastructure. Recently, several facilities funded through these schemes have opened.

JIF and SRIF funding was restricted to the UK, but the Wellcome Trust has also funded facilities outside the UK to support research at its Major Overseas Programmes. This year saw the opening of new labs at Kilifi General Hospital, Kenya, housing research carried out at the KEMRI–Wellcome Trust Research Programme (see pages 11 and 18).

In the UK, the excellent science base in Scotland has been reflected in a range of infrastructure awards. This year saw the opening of the Sir Graeme Davies Biomedical Research Building, to which the Trust contributed £8 million. The building will house the Glasgow Biomedical Research Centre. In Edinburgh, the Ashworth Building Extension, funded in part by a £4.7m grant from the Trust, was opened in November 2005.

Images

1 Labs at the Wellcome Trust Sanger Institute.

2 Data storage at the Sanger Institute.

3 New laboratories at Kilifi, Kenya.

NEW FUNDING

London saw several new and refurbished facilities opened, including the University College London Centre for Auditory Research (£9m grant), the Department of Medical and Molecular Genetics at Guy's Hospital campus (£6.4m) and the Department of Optometry and Visual Science, City University (£1.5m).

Some 78 buildings in 29 institutions received JIF/SRIF funding from the Trust, whose total investment exceeded £500m. The University of Sheffield received several awards, including funding for the Wellcome Trust and the Wolfson Foundation Facility for Molecular Life Sciences (£16.3m from the Trust), which opened in November 2005.

The University of Cambridge was also successful with several applications, and opened its Henry Wellcome Building, housing the Leverhulme Centre for Human Evolutionary Studies (and 18 000 skeletons), in 2006.

Following these substantial cash injections, the Trust does not routinely support new building projects. Clearly, though, facilities are important to the research enterprise and requests for such support will be considered under exceptional circumstances.

Clinical research facilities

Some £84 million has been committed by ten UK funding agencies to strengthen and extend the UK's Clinical Research Facility (CRF) network. The initiative is founded on the success of the first five CRFs, funded by the Wellcome Trust.

CRFs provide sites for patient-oriented research in a hospital setting. Specialised facilities and staff make CRFs ideal sites for research on people, and they act as local beacons of good clinical research practice.

With Wellcome Trust support, CRFs have been established in Birmingham, Cambridge, Edinburgh, Manchester and Southampton. In an unprecedented joint venture, ten UK funding agencies joined forces to fund eight new bench-to-bedside initiatives – in London (Imperial College, King's College London, the Institute of Cancer Research and University College London), Oxford, Belfast and Newcastle in the UK, and Dublin in the Republic of Ireland.

Four existing CRFs will also receive support for further development. The final sums to be awarded to each centre are currently being negotiated.

- The competition was managed by the Wellcome Trust on behalf of the UK Clinical Research Collaboration. Funders included the Wolfson Foundation, the Medical Research Council, the British Heart Foundation, Cancer Research UK and various health departments.

A selection of notable grants awarded in 2005/06.

RESOURCES

DEVELOPMENTAL BIOLOGY

Dr Mathew Guille (University of Portsmouth) Xenopus Stock Centre: a central repository storing and distributing genetically modified *Xenopus*.

STRUCTURAL BIOLOGY

Professor So Iwata (Imperial College London) Establishing a membrane protein laboratory at the Diamond synchrotron.

EQUIPMENT

DEVELOPMENTAL BIOLOGY

Dr Stephen Wilson (University College London) New aquarium and other equipment for the UCL zebrafish facility.

BONE AND JOINT DISEASE

Professor Stuart Ralston (University of Edinburgh) A variety of equipment for analysing animal models of human bone and joint disease.

MASS SPECTROMETRY

Dr Kevin Brindle (University of Cambridge) A 500 MHz NMR spectrometer for high-throughput metabolomics to examine multifactorial diseases in animal models.

Dr Catherine H Botting (University of St Andrews) A MALDI-TOF mass spectrometer and associated equipment to support several groups studying infectious diseases.

CRYO-EM

Professor Helen R Saibil (Birkbeck College) Cryo-electron microscopy equipment to determine the structure of various large assemblies within the cell.

CONFOCAL AND OTHER IMAGING

Dr Andrew M Fry (University of Leicester)
Dr Craig A McArdle (University of Bristol)
Dr Eric C Schirmer (University of Edinburgh)
Dr Helen le Breton Skaer (University of Cambridge)

RESEARCH RESOURCES IN MEDICAL HISTORY

ARCHIVES

Dr Knight (Royal College of Surgeons of England) Conservation of the College's manuscripts and archives.

Peter Harper (National Cataloguing Unit for the Archives of Contemporary Scientists) Cataloguing the medical physics papers of Sir Joseph Rotblat FRS.

Details of all grants made can be found in *Grants Awarded 2005/06*, available on the Wellcome Trust website.

DEVELOPING OUR ORGANISATION

Using our resources efficiently and effectively.

BOND ISSUE

An innovative bond issue has enhanced the Wellcome Trust's investment portfolio.

The Wellcome Trust derives the vast majority of its income from a diverse portfolio of investments, valued at £13.9 billion (as at 30 September 2006). An innovative bond issue launched in 2006 will add to the Wellcome Trust's funding power over the coming years.

In effect, the Wellcome Trust is using the bond to borrow money from other financial institutions. It undertakes to pay a fixed amount of interest to the lender over the period of the bond and reinvests the sums borrowed. As the interest rate is relatively low, investment returns should comfortably exceed the interest paid.

Because of the Trust's strong financial basis and long-term perspective it is judged to be a low-risk option for investors. The Trust received the highest possible bond credit ratings, Aaa from Moody's and AAA from Standard & Poor's.

The bond issue proved highly popular, enabling the Trust to increase the value of the bonds issued to £550m.

GRANTS ONLINE

An upgraded version of the Wellcome Trust's 'eGrants' online grants application system has been launched – and an enhanced successor is in the pipeline.

A review of the eGrants system in 2005/06 revealed high levels of satisfaction – 93 per cent of respondents declared themselves 'very satisfied' or 'fairly satisfied'. Some 79 per cent preferred the eGrants approach to Word templates. Useful feedback was obtained from respondents, and several new features were introduced as a result.

Meanwhile, development work began on an ambitious new web-based system that will handle not just the grant application process but also refereeing and ongoing management of awarded grants.

This new system will provide convenient online access for grant applicants, grantholders and referees, helping to streamline both the application and review process and the financial management of grants. It is due to launch in late 2007.

Communication with grantholders and potential grantholders remains a high priority. A revised version of the *Wellcome News* newsletter has been launched and a periodic e-bulletin introduced for grantholders. These and other methods will be used to keep the research community up to date with the status of the new grants system.

FINANCIAL PLANNING

Good financial management has enabled the Wellcome Trust to increase its spending projections.

The Wellcome Trust's expenditure is linked to the size of its investment base. It has a long-term target rate of return for its investments of 6 per cent a year in real terms, and aims to distribute, on average, about 4 per cent of its assets each year. To smooth annual fluctuations, expenditure is based on a weighted rolling average spanning several years. With its investments performing strongly, it has been able to increase significantly the funding it plans to make available over the next five years.

Charitable expenditure in 2005/06 was £484 million. The total expenditure budget available for 2006/07 has been increased to £540m. Levels of funding are anticipated to increase in future years, dependent on continuing good performance of the investment portfolio.

The additional funds will be used to support major new initiatives, and are unlikely to impact on funding rates for existing grant schemes.

WELLCOME TRUST 2005/06

A brief overview of corporate activities over the year.

Governors and senior staff

Sir William ('Bill') Castell took over as Chairman of the Wellcome Trust's Board of Governors in May 2006, succeeding Sir Dominic Cadbury, who retired from the Board. Bill was formerly President and CEO of GE Healthcare, the medical diagnostics and biosciences business of the General Electric Company of the USA, and also a Vice-Chairman at General Electric. Before that, he was Chief Executive of Amersham plc. He has a wealth of experience in global healthcare and has also been involved in many not-for-profit activities.

Professor Sir Leszek Borysiewicz, Deputy Rector of Imperial College London and an expert in immunology and viral infections, joined the Board of Governors in January 2006.

In January 2006, Susannah Randall was appointed the Trust's Head of Communications.

Contributions to policy-making

The Trust continued to play an active role in the drive towards open access models of science publishing. A nine-strong group of UK research funders, including the Trust, awarded a contract to run UK PubMed Central (UKPMC) to a partnership of the British Library, the University of Manchester and the European Bioinformatics Institute. UKPMC will provide free online access to the digital archive of published articles resulting from research paid for by any of the funding consortium.

The Trust also reached agreement with a range of science publishers, ensuring that material can be deposited in UKPMC by authors according to the Trust's Grant Conditions without infringing publishers' copyright.

Several submissions to Government consultations were made during the year, including responses to the Department for Education and Skills's consultation on the reform of higher education research assessment and funding, and to the Department of Health's consultation on the regulations to be made under the Mental Capacity Act 2005. The Trust also contributed to the Cooksey Review, which has been considering the nature of the UK's unified health research fund.

With the Academy of Medical Sciences, the Royal Society and the Medical Research Council (MRC), the Trust supported an in-depth study, by an independent committee chaired by Sir David Weatherall, on the use of non-human primates in research. The Trust and the MRC have jointly published an informational booklet on non-human primate use.

Buildings

New research facilities at the Wellcome Trust Genome Campus, Cambridge, were opened by HRH The Princess Royal in October 2005.

Significant work was undertaken during the year to convert the Wellcome Building, the Trust's former headquarters, into a public space. The venue, to be known as Wellcome Collection, is due to open in 2007 and will house a range of permanent and temporary exhibitions, a forum space, a Conference Centre, a bookshop and café, as well as the Wellcome Library and researchers from the Wellcome Trust Centre for the History of Medicine at UCL.

The Trust's current headquarters, the Gibbs Building, 215 Euston Road, London, was again a major attraction during Open House weekend in September 2006. Its eclectic window displays are a talking point for passers-by, while guided tours are given for visitors keen to see Thomas Heatherwick's sculpture 'Bleigiessen', a 30-metre installation composed of 150 000 specially processed glass spheres.

Images

1 The new Chairman.
2 Thomas Heatherwick Studio's 'Bleigiessen'.
3 Sanger Institute buildings.

FINANCIAL SUMMARY 2005/06

In the year ending 30 September 2006, the Wellcome Trust's total charitable expenditure was £484.1m.

Total charitable expenditure, £484.1 million, was broadly in line with 2004/05's figure (£485.9m).

Grants expenditure dipped slightly, while support for direct activities rose by a small amount, reflecting additional work at the Wellcome Trust Sanger Institute and preparation for the opening of the new public venue, Wellcome Collection, in 2007. Support costs increased slightly, principally due to planned expansion at the Sanger Institute, which now employs more than 800 people.

Careers support

Total expenditure on careers support across all funding areas amounted to £100m in 2005/06, an increase on last year's figure (£92m). The bulk of this support is for Principal, Senior and intermediate-level fellowships, along with Four-year PhD Programmes and Research Training Fellowships for medically qualified researchers.

International support

Some £26.3m was awarded directly to researchers at overseas institutions. A further £46.2m was awarded to researchers at UK locations for research overseas. Most international support is targeted at developing and restructuring countries. The total figure of £72.5m includes some funding in developed countries, such as the Structural Genomics Consortium, which carries out research in Canada.

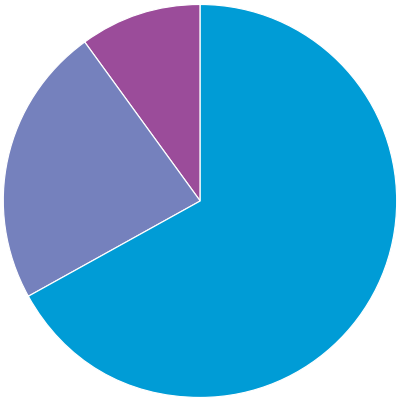
Infrastructure

Awards for buildings, refurbishment and equipment amounted to £15.7m. This figure does not include infrastructure costs awarded as part of project, programme or fellowship grants.

BREAKDOWN OF WELLCOME TRUST CHARITABLE EXPENDITURE 2005/06

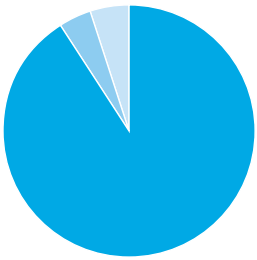
Total: £484.1m

- **GRANTS** £324.7M
- **DIRECT ACTIVITIES** £119.3M
- **SUPPORT COSTS** £40.1M



GRANTS: £324.7M

Competitive grant schemes are run in the Wellcome Trust's areas of interest: biomedical science; Technology Transfer; and Medicine, Society and History (history of medicine, biomedical ethics and public engagement with science).

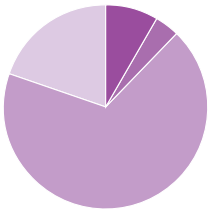


- **Biomedical science** £295.7m
- **Technology Transfer** £13m
- **Medicine, Society and History** £16m

DIRECT ACTIVITIES: £119.3M

Direct activities are those managed by the Wellcome Trust itself or in partnership with others. These include:

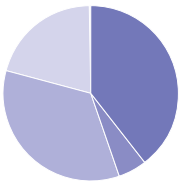
- Wellcome Trust Genome Campus (including Sanger Institute)
- Wellcome Library
- Directly managed public engagement activities
- Scientific conferences.



- **Biomedical science** £9.5m
- **Technology Transfer** £4.2m
- **Genome Campus** £83.8m
- **Medicine, Society and History** £21.8m

SUPPORT COSTS: £40.1M

Support costs include expenditure required to run the Wellcome Trust and Genome Campus. These include costs associated with administering grants and the wide range of other activities carried out by the Trust.



- **Biomedical science** £18.9m
- **Technology Transfer** £2.5m
- **Genome Campus** £8.9m
- **Medicine, Society and History** £9.8m

The expenditure values used here are audited figures taken from the Wellcome Trust's *Annual Report and Financial Statements*, which include a detailed breakdown of the Trust's expenditure and investments during the year. The *Annual Report* is available at **www.wellcome.ac.uk**.

FUNDING HIGHLIGHTS

£19.4m
Rollout of UK Biobank.

£18.4m
New and renewed Principal Research Fellowships.

£16m
Phase 2 Structural Genomics Consortium funding.

£7.0m
Wellcome Trust Centre for Stem Cell Research, University of Cambridge.

£6.7m
Wellcome Trust Centre for Neuroimaging at UCL.

£6.4m
Malaria drug discovery programme at the Novartis Institute for Tropical Diseases.

£4.1m
Ensembl genome browser (European Informatics Institute).

£4.0m
Cambridge Institute for Medical Research core support.

£3.3m
Renewal of core support for Wellcome Trust Centre for Cell Biology, University of Edinburgh.

£3.0m
Renewal of core support for Karonga Prevention Study, Malawi.

£1.5m
Generation Genome touring exhibition.

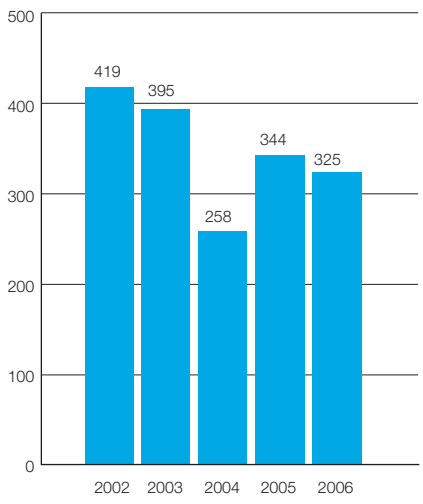
INVESTMENTS 2005/06

The value of the Trust's investment portfolio ended the year at £13.9 billion. This figure included £539m raised through the bond issue (see page 40). The net value of £13.4bn represents an increase of £1.1bn on last year.

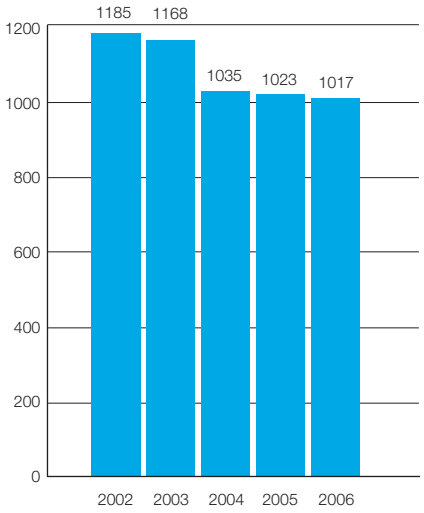
The Trust maintains a diversified portfolio of investments, encompassing equities (stocks and shares) in UK and other markets, cash and bonds, venture capital investments, and property investments. All sectors performed well during the year, particularly private equity, with buyout funds benefiting from strong market conditions. In property, the South Kensington estate made significant gains on the back of strong demand for premium properties in London.

The Trust took advantage of equity market strength in the first half of the year to sell £1bn of equities, which was used to fund increased investment in hedge funds and active currency strategies. This should serve to enhance returns and to diversify risk further. The Trust also instigated a passive currency hedging strategy at the start of 2006, which helped to mitigate the impact of the strongest year for sterling since 1990.

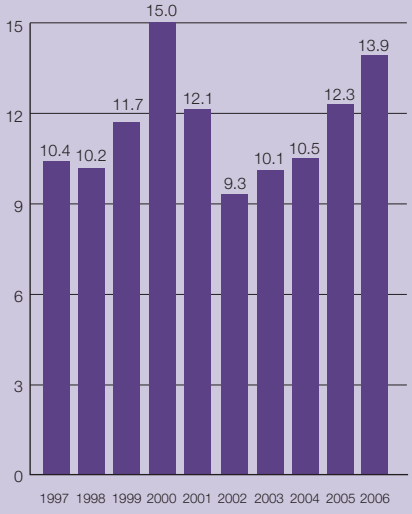
Grants awarded 2002–06 (£m)



Grant liabilities 2002–06 (£m)



Market value of total portfolio at 30 September (£bn)



FUNDING DEVELOPMENTS 2005/06

An overview of strategy development, new initiatives, significant changes to funding policies, and an analysis of the year's funding.

The Wellcome Trust's funding is based around funding streams, covering core areas of biomedical science and the medical humanities. Cutting across these streams are funding programmes in Technology Transfer and Public Engagement (see below).

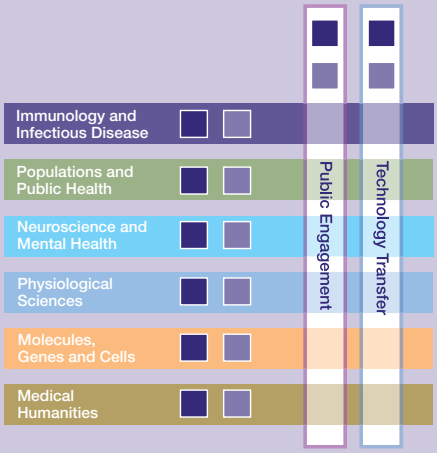
Each funding stream has associated with it one or more Funding Committees, responsible for most funding decisions, and a Strategy Committee, which advises the Trust on the needs and opportunities within its area of interest.

The funding streams offer a variety of forms of support, such as project and programme grants, and career development awards.

Technology Transfer funding comprises Translation Awards and Strategic Translation Awards. A special initiative, Strategic Translation Awards in Drug Discovery, was launched in 2005.

Public Engagement is supported primarily through the Engaging Science programme, which includes Society Awards and People Awards. Occasional large Capital Awards are made to support nationally or internationally important developments.

Strategic Awards and some other large or unusual awards are considered by a Strategic Awards Committee, comprising Governors, senior staff and other representatives, on a one-off basis.



Wellcome Trust funding streams.

STRATEGIC AWARD PRIORITY AREAS

The following areas were identified by Strategy Committees as priorities for Strategic Award applications:

- mathematical biology/statistical methods – training and capacity building
- public health research – training and capacity building
- *'in vivo'* physiology – training and capacity building
- neuroimaging – interdisciplinary networks/programmes
- emerging diseases – interdisciplinary networks/programmes
- promotion of interactions at the clinical–basic science interface.

PRIORITY AREAS

Mathematical biology/statistical methods: all the Strategy Committees highlighted the need to build expertise in statistics, study design, data analysis and mathematical biology.

The Populations and Public Health Strategy Committee identified a need to address training of and interactions between clinicians, basic scientists and practitioners in **public health research**.

The Physiological Sciences Strategy Committee expressed concern about a potential skills gap in ***in vivo* research**.

To take full advantage of the UK's strengths in **neuroimaging**, the Neurosciences Strategy Committee identified a need for increased networking between major imaging centres, and interdisciplinary programmes involving mathematicians, physicists and engineers.

The Immunology and Infectious Disease Strategy Committee saw research into rapid, accurate diagnosis and response to **emerging diseases** as crucial. Networks of epidemiologists, molecular biologists, clinicians and veterinarians, and linking surveillance data with research, are a priority.

Several Strategy Committees highlighted the need for more **interactions between basic and clinical science**.

STRATEGY DEVELOPMENT

At its annual strategy meeting in June 2006, the Board of Governors outlined 'vision statements' for the future.

More focus on the best people

While support has always been focused on individuals with the best ideas, there will be a greater emphasis on identifying the most successful researchers, or those with the greatest potential, and encouraging them to come up with bold applications for support.

Larger, longer, braver awards

Huge medical challenges remain. At the same time, new technological opportunities are emerging. To achieve more in the future, ambitious plans are needed, which may call for imaginative funding solutions.

An enhanced international funding and advocacy profile

The priority will be to build upon the Major Overseas Programmes, in the context of the new international strategy (see right). The potential for an increased presence in India and in continental Europe will also be explored.

Reputation as a trusted and important partner of choice

Highly successful partnerships have been forged with governments, other funding agencies and charities. Possible collaboration in areas such as clinical research, public health and interdisciplinary research will be explored.

STRATEGIC INITIATIVES

Funding opportunities

Following strategic reviews, funding opportunities were overhauled, or new or revised schemes were launched, in the following areas:

- careers support
- global health research
- drug discovery research.

Funding policies

Significant changes to funding policy were implemented in the following areas:

- eligibility (UK and Europe)
- international eligibility
- open access publication.

CAREERS SUPPORT

The suite of Wellcome Trust personal support schemes was overhauled during the year. A significant introduction was the Sir Henry Wellcome Postdoctoral Fellowship scheme, with awards worth £250 000 over four years, providing fellows with unprecedented freedom early in their career to pursue their own research.

Among other innovations, Research Career Development Fellowships were extended to five years and competitions were launched for new Four-year PhD Programmes and Clinical Research Training Programmes. Finally, new Flexible Travel Awards will support collaboration-building and skills transfer, through sabbaticals and travelling fellowships.

GLOBAL HEALTH RESEARCH

The Wellcome Trust's new global health research strategy builds on its long-standing commitment to research in developing countries.

The Trust plans to increase its support in this area, building on the Major Overseas Programmes in South-east Asia and Africa. The priority will be to identify key people to take forward research in high-quality and supportive environments, tackling important local medical issues. Capacity-strengthening and putting research into practice will be central to future activities.

Technology Transfer funding will also be available to tackle neglected diseases. Funding is also provided for research into the ethical issues raised by studies in developing countries, and the potential for more international public engagement is being explored.

DRUG DISCOVERY RESEARCH

A Technology Transfer initiative, Seeding Drug Discovery, was launched in October 2005. It provides funding for the early stages of drug discovery, which struggle to attract funding for commercial development. The £91 million, five-year initiative is open to researchers at public or private institutions, including commercial companies, in the UK and the Republic of Ireland.

FUNDING POLICIES

Eligibility rules for researchers in the UK were relaxed during the year, enabling scientists employed at Research Council units or charity-funded institutions to apply for funding. Internationally, current or past International Senior Research Fellows, or other overseas researchers in receipt of major Trust grants, can now apply for support through most funding schemes.

As part of the Trust's drive to promote open access publishing, submission of published papers to repositories such as PubMed Central was made mandatory during the year. Initially, this grant condition applied to newly awarded grants. From 1 October 2006, it has applied to all grants.

FUNDING ANALYSIS

Total no. of grant applications: 2666

Total no. of grants awarded: 790

Value of applications considered: £923.6m

Value of grants awarded: £333.9m

No. of programme grants awarded: 64

No. of PRFs awarded/renewed[1]: 8

No. of SRFs awarded/renewed: 27

No. of intermediate fellowships awarded: 63

No. of training (junior) fellowships awarded: 26

No. of PhD studentships supported: 133

FUNDING RATES

	By no.	By amount
Project grants	24%	22%
Programme grants	41%	43%
New PRF (full app.)	40%	45%
SRF (full app. basic)	11%	10%
SRF (full app. clinical)	17%	16%
SRF (full app. tropical)	60%	60%
SRF (full app. international)	11%	11%
Intermediate fellows	19%	19%
Training (junior) fellows	14%	16%
Biomedical Ethics	50%	27%
History of Medicine	46%	29%
Livestock for Life	19%	18%
Research Resources in the History of Medicine	62%	41%
Small public engagement awards (< £30 000)	19%	26%
Large public engagement awards (> £30 000)	9%	10%

Total no. of institutions receiving funding in 2005/06 (UK): 84

Total no. of institutions receiving funding in 2005/06 (non-UK): 74

ONGOING LIABILITIES[2]

Total grants liabilities: £1.017bn

No. of countries receiving funding: 54

Fellows currently supported: 825

Researchers currently supported: 3493

Total no. of institutions receiving funding (UK): 92

Total no. of institutions receiving funding (non-UK): 123

[1] Includes PRF programme grant renewals.
[2] As at 30 September 2006.

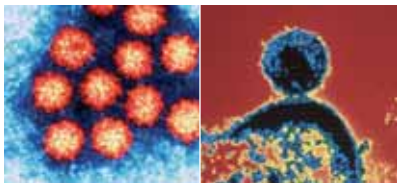
PRF: Principal Research Fellowship
SRF: Senior Research Fellowship

STREAMS FUNDING 2005/06

1 October 2005 to 30 September 2006.

IMMUNOLOGY AND INFECTIOUS DISEASE

The Immunology and Infectious Disease stream supports research that will further our knowledge and understanding of the infectious organisms that cause disease in humans and animals, and of the immune systems that fight these organisms.



Total number of grants awarded	115
Total value of grants awarded	£54m
Number of programme grants awarded	13
Value of programme grants awarded	£14m

MAJOR PERSONAL SUPPORT AWARDS

- 2 renewal Principal Research Fellowships
- 2 renewal Senior Research Fellowships in Clinical Science
- 3 new (and 1 renewal) Senior Research Fellowships in Basic Biomedical Science

OTHER NON-FUNDING/INTERVIEW COMMITTEE ACTIVITIES DURING YEAR

- £0.7m to establish a consortium to sequence genomes of influenza strains
- Frontiers Meeting on 'Emerging Zoonotic Infections: Integrating research, diagnosis and surveillance'
- Vaccinology Frontiers Meeting on 'Bringing Industry and Academia Together for the Next Generation of Vaccines'

POPULATIONS AND PUBLIC HEALTH

The Populations and Public Health stream supports research to improve understanding of the determinants of disease and quality of life in populations, and to provide a sound evidence base to inform decisions in public health and healthcare delivery.

Total number of grants awarded	50
Total value of grants awarded	£19m
Number of programme grants awarded	5
Value of programme grants awarded	£7m

MAJOR PERSONAL SUPPORT AWARDS

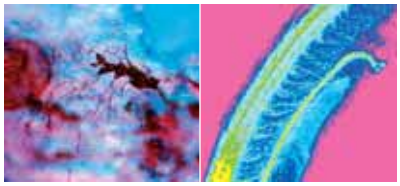
- 1 new Principal Research Fellowship
- 1 new Senior Research Fellowship in Basic Biomedical Science

OTHER NON-FUNDING/INTERVIEW COMMITTEE ACTIVITIES DURING YEAR

- £19.4m for UK Biobank project
- £3.0m core funding for the Karonga Prevention Study in Malawi (focusing on HIV and antiretroviral therapy roll-out with population-based epidemiological and demographic studies)
- Joint meeting with the European Commission: 'From Biobanks to Biomarkers'

NEUROSCIENCE AND MENTAL HEALTH

The Neuroscience and Mental Health stream supports high-quality research into the function of the nervous system in health and disease.



Total number of grants awarded	85
Total value of grants awarded	£40m
Number of programme grants awarded	7
Value of programme grants awarded	£8m

MAJOR PERSONAL SUPPORT AWARDS

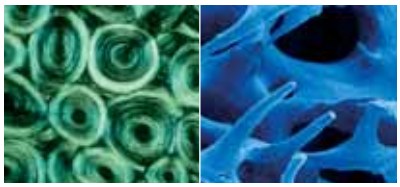
- 1 renewal Principal Research Fellowship
- 2 renewal Senior Research Fellowships in Clinical Science
- 2 renewal Senior Research Fellowships in Basic Biomedical Science

OTHER NON-FUNDING/INTERVIEW COMMITTEE ACTIVITIES DURING YEAR

- £6.7m Strategic Award for core support for Wellcome Trust Centre for Neuroimaging at University College London
- Pilot scheme supporting Masterclasses in Clinical Neuroscience to catalyse collaboration between basic and clinical neuroscientists

PHYSIOLOGICAL SCIENCES

The Physiological Sciences stream supports high-quality basic and clinical research relevant to the understanding of biological processes at the cell, organ, system and whole-animal levels in health and disease.



Total number of grants awarded	66
Total value of grants awarded	£23m
Number of programme grants awarded	5
Value of programme grants awarded	£6m

MAJOR PERSONAL SUPPORT AWARDS

- 1 new Senior Research Fellowship in Clinical Science
- 1 new Senior Research Fellowship in Basic Biomedical Science

MOLECULES, GENES AND CELLS

The Molecules, Genes and Cells stream supports high-quality research that will further our understanding of the fundamental biology and specialist functions of molecular, cellular and genetic processes, and their role in health and disease.

Total number of grants awarded	102
Total value of grants awarded	£72m
Number of programme grants awarded	15
Value of programme grants awarded	£24m

MAJOR PERSONAL SUPPORT AWARDS

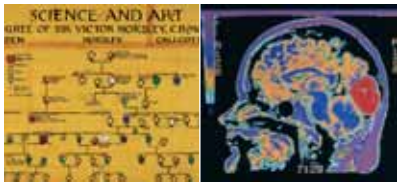
- 1 new (and 3 renewal) Principal Research Fellowships
- 4 renewal Senior Research Fellowships in Basic Biomedical Science
- 4 new International Senior Research Fellowships

OTHER NON-FUNDING/INTERVIEW COMMITTEE ACTIVITIES DURING YEAR

- £7.0m Strategic Award to establish Wellcome Trust Centre for Stem Cell Research
- £4.0m Strategic Award for renewal of core support to Cambridge Institute for Medical Research (and to establish two new training programmes at the interface between clinical and basic research)
- £3.3m renewal of core support for Wellcome Trust Centre for Cell Biology, University of Edinburgh
- £16m for phase 2 funding of Structural Genomics Consortium (conditional on additional funding being secured)

MEDICAL HUMANITIES

The Medical Humanities stream aims to enhance understanding of the historical and social context of medicine and biomedical science. It supports research in history of medicine and biomedical ethics, and encourages use of findings, for example to inform public policy making.



Total number of grants awarded	171
Total value of grants awarded	£8m
Number of programme grants awarded	0
Value of programme grants awarded	–

MAJOR PERSONAL SUPPORT AWARDS

- History of Medicine Strategic Award to University of Manchester
- History of Medicine: 2 University Awards
- Biomedical Ethics: 1 University Award

OTHER MAJOR AWARDS

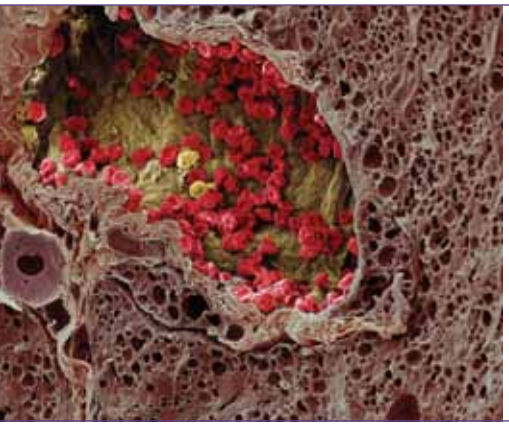
- First University Award in Biomedical Ethics
- £1.2m award for core support of Nuffield Council on Bioethics

OTHER ACTIVITIES DURING THE YEAR

- Biomedical Ethics Summer School, September 2006
- 'Practices and Representations of Health' conference at Warwick University, June 2006

TECHNOLOGY TRANSFER

Technology Transfer at the Wellcome Trust seeks to maximise the impact of research innovations on health by facilitating the development of early-stage technologies to a point at which they can be further developed by the market.



The major award of the year was the £6.4 million grant to Professor Alex Matter at the Novartis Institute for Tropical Diseases in Singapore, for a programme of drug discovery research in malaria. This complements last year's £8.1m award to Professor Michael Ferguson and colleagues, who are establishing a neglected disease drug discovery programme at the University of Dundee. With the £91m Seeding Drug Discovery Initiative launched in 2005, the Trust has developed a range of ways of supporting the early stages of drug development in tropical and other diseases.

Technology Transfer funding concentrates on projects that are too early either to attract venture capital or to be seen by industry as credible in-licensing opportunities. Two forms of translational research support are available: Translation Awards and Strategic Translation Awards.

Translation Awards are a response-mode form of support, used to support a diverse array of technologies from the physical sciences and mathematics as well as biology. They are open to academic institutions and early-stage companies.

In the third full year of funding, 44 applications were received from 29 institutions; 20 per cent were awarded. The mean value of awards has been £445 545 (ranging from £74 000 to £1 022 854). The average time from application to decision is around three to four months.

The projects address a wide range of potential applications, including therapeutics, vaccines, diagnostics and medical devices. Others are in support of new platform technologies, such as: fragment-based drug design with a focus on protein–protein interactions; T-cell therapy for immunodepressed patients; ultrasonic elasticity imaging for tumour detection; and pheromone-baited traps for vector control in visceral leishmaniasis.

One award was made to support workshops on intellectual property in sub-Saharan Africa. Additional workshops were supported on vaccine research, including a frontier meeting to facilitate greater integration between industry and academia.

Strategic Translation Awards support translational research in areas of key importance to the Wellcome Trust. Nine applications have been considered to date, in diagnostics, vaccination, regenerative medicine, genotyping technology and drug discovery. The mean value of awards has been £3 million (ranging from £1.1m to £8.1m). New awards were made to: Professor Paul Sharpe for work on the development of natural replacement teeth using stem cell technology; Dr Helen McShane for work on a new tuberculosis vaccine (see page 18); and Professors Richard Marais and Caroline Springer for research into the discovery of drug-like inhibitors of BRAF kinase for the treatment of malignant melanoma.

An award of £6.4m was made to Professor Alex Matter at the Novartis Institute for Tropical Diseases in Singapore for drug discovery research into malaria. The research consortium includes investigators from across the Novartis Foundation institutes, together with the Swiss Tropical Institute and the Biomedical Primate Research Centre. The five-year programme aims to discover compounds for use in a single-dose treatment for falciparum malaria and a new therapeutic option for vivax malaria. Promising compounds will be channelled into the Medicines for Malaria Venture for further development.

The **Seeding Drug Discovery** initiative, launched in November 2005, received 86 applications for funding, of which eight were taken to the final application stage. Shortlisted applicants from academic institutions were awarded small grants to engage industry experts to advise on project design and outsourcing options. The first awards will be made in financial year 2006/07. Based on the quality of the first wave of applications, Seeding Drug Discovery has been rolled out as a five-year initiative with a grants budget of £91m.

Several projects supported through Technology Transfer funding have made encouraging progress (see page 22). In addition, several small companies that received support during early validation of their technology have raised further funds. These include: the University of Leeds spin-out, Syntopix Ltd, which floated on the Alternative Investments Market (AIM); Paradigm Therapeutics Ltd, which successfully completed a fourth professional funding raising round; Celltran Ltd, which raised further finances to extend its business operations; and CardioDigital Ltd, which received the first down-payment on a future investment round.

WELLCOME TRUST GENOME CAMPUS

The Wellcome Trust Genome Campus at Hinxton, near Cambridge, is home to the Wellcome Trust Sanger Institute, the Wellcome Trust Conference Centre and Wellcome Trust Advanced Courses.

The official opening of the new laboratory space for the Wellcome Trust Sanger Institute in October 2005 symbolised its shift into new scientific territories. It is now a centre driven by the need to understand biological function, underpinned by unique high-throughput sequencing and genetic manipulation techniques. Other parts of the Genome Campus continue to develop their programmes of activities, and building work began on the £8.6 million extension to the European Bioinformatics Institute.

Wellcome Trust Sanger Institute

The Sanger Institute passed three major milestones in 2005/06: in October 2005, the extension to the Genome Campus was opened by HRH The Princess Royal; in December 2005, the Wellcome Trust announced the award of £340 million funding for 2006–11; and, in September 2006, the Sanger Institute proposed a new strategic focus on natural and experimental genetics.

The Genome Campus extension includes new laboratory space for 140 staff, accommodation for model organisms and a Data Centre housing some of the UK's most powerful computers. These new facilities underpin a major drive to make data and resources available to scientists around the world.

The funding award will enable the Sanger Institute to drive forward its new strategic focus, based on large-scale studies of the effects of variation in DNA sequence in humans, model organisms such as mice and zebrafish, and pathogens.

The Sanger Institute has also attracted major awards from the European Union and the US National Institutes of Health (see page 38).

The Sanger Institute led the sequencing of the first human chromosome sequence – chromosome 22 – and, fittingly, it was also behind the final report, on chromosome 1, published in May 2006. Study of human genetic variation was enriched by the completion of the first phase of the International HapMap Project, in which the Sanger Institute was a major participant. It has also led efforts to map copy number variation (see page 7).

In pathogen research, significant results include the genome sequences of *Clostridium difficile* and the capsule genes of the pneumococcus bacterium, both current issues for healthcare. The Sanger Institute is also involved in a project analysing the spread of influenza virus (see page 14).

The Sanger Institute produces more DNA sequence than at any time in its history, but its outputs are now focused on the medical and biological context of sequence data.

Wellcome Trust Advanced Courses

The programme expanded significantly in 2005/06, doubling the number of courses run for PhD students and postdoctoral scientists. New courses included 'The Molecular Basis of Infection: Basic and applied research approaches', a laboratory-based course on new molecular techniques used to study bacterial infection.

A new initiative this year has been the expansion of courses overseas. Two human bioinformatics workshops were held in Mexico and Brazil, and an IT suite has been set up in the Institute of Hygiene in Uruguay, as a base for the Advanced Courses training programme in South America.

Extra courses are planned for 2006/07, both at the Genome Campus and overseas, starting with a workshop at the KEMRI–Wellcome Trust Research Programme in Kenya in December 2006.

Wellcome Trust Conference Centre and Meetings Programme

A total of 14 scientific meetings were held as part of the Wellcome Trust Meetings Programme at Hinxton this year. These included two meetings held jointly with University of California San Diego and *Cell*, several in partnership with Cold Spring Harbor Laboratory, and a conference on vaccine adjuvants held jointly with the World Health Organization and the Malaria Vaccines Initiative.

A review of the Meetings Programme was carried out in conjunction with Keystone Symposia. The results were positive. Overall, 98 per cent of respondents said that the meeting they had attended had been good for them.

The Wellcome Trust Conference Centre operates as a semi-commercial entity. It completed its first three-year business plan in 2005/06, meeting its efficiency, quality and standards targets. Over 60 major scientific meetings and courses were held at the Conference Centre, generating revenue of £1.7m. Most meetings were scientific and research-focused, so qualified for extensive discounts.

PUBLIC ENGAGEMENT

The Wellcome Trust's Public Engagement activities aim to raise awareness and understanding of biomedical science, its social and ethical implications, and its historical context.

This year saw the official opening of the National Science Learning Centre at York and the first widespread use of the innovative new Twenty First Century Science GCSE curriculum, the development of which was part-funded by the Wellcome Trust. Educationalists were among the groups represented at the Trust's Engaging Science conference, which highlighted the stimulating diversity of individuals and groups involved in public engagement in its broadest sense, who collectively are helping to ensure science is integrated into and respected within wider society.

Grants

A total of 59 grants were awarded under the £3 million Engaging Science funding scheme.

Society Awards: Seven of these large awards (over £30 000) were made for a range of nationally important activities. A notable award was to Professor Keith Roberts at the John Innes Research Centre, for the installation of a city exhibition entitled 'Making Faces' as part of the British Association Festival of Science in Norwich. Two awards were made to support academic research about public engagement.

People Awards: Ever popular, 26 of these small, flexible, rapid-turnaround awards were made to a variety of organisations, supporting diverse activities including performances, exhibitions, talks, conferences, debates and documentaries.

Arts awards: In the Sciart strand of funding, nine grants were made for small Research and Production Awards, as well as three Production Awards (of up to £120 000). One award was for film-maker Ian Knox, producer Rebecca O'Brien and neuropsychologist Paul Broks to make a documentary film based on the experience of jazz guitarist Pat Martino, who lost his memory following brain surgery for an aneurysm. The Pulse scheme (performing arts for young people) also received record numbers of applications, with 12 being awarded.

Grants worth £2.2m for public engagement were made through the Wellcome Trust's Strategic Awards Committee to At-Bristol to develop a touring exhibition, *Generation Genome* (see page 29), and to the Science Museum to digitise parts of Henry Wellcome's collection (the Science Museum has many of Wellcome's collection of objects on indefinite loan).

Livestock for Life, a one-off grant scheme to strengthen links between livestock keepers, researchers and policy makers in developing countries, made 19 awards. Fifteen exhibitions opened across the UK thanks to ReDiscover funding – a joint initiative with the Millennium Commission and the Wolfson Foundation.

The Wellcome Trust held a two-day conference in April to mark the past five years of its public engagement funding. This was followed by the publication *Engaging Science: Thoughts, deeds, analysis and action*, setting out Wellcome Trust funding highlights over ten years with essays from experts on the state of public engagement in the UK.

Education

The National Science Learning Centre at the University of York opened to teachers in October 2005 with a formal opening by the Prime Minister, Tony Blair, in March 2006 (see page 26).

Two issues in the *Big Picture* series, a publication for teachers and post-16 students, were published, on *Sex and Gender* and *Thinking*. Full text and classroom facilities are available online.

Supporting researchers

The Wellcome Trust hosted two events designed to facilitate interaction between broadcasters and senior Trust-funded researchers. In addition, pilot training sessions were run by the National Science Learning Centre to provide an introduction for researchers wanting to work in schools. The Wellcome Trust renewed its partnership with the UK Research Councils to run the Researchers in Residence scheme, with the contract awarded to the University of Edinburgh.

Public participation

The Wellcome Trust organised several events to offer a foretaste of the public programme in Wellcome Collection opening in 2007. These included 'wellbeing' discussion events (see page 27) and a one-day extravaganza in the British Library Piazza showcasing nine talented young UK designers, who created remedies for modern-day ailments and peddled them to the public in the style of a Wild West medicine show.

In February 2006, the Wellcome Trust hosted a discussion evening to mark the publication of *Better Humans? The politics of human enhancement and life extension* in partnership with the think-tank Demos. The publication received extensive media coverage.

LIBRARY AND INFORMATION RESOURCES

The Wellcome Library provides free public access to more than a million items related to the history of health, disease and medicine. The Wellcome Trust also works to enhance access to key information resources and publishes material in a range of formats for a variety of audiences.

This year's award of the contract to run UK PubMed Central, to a partnership between the British Library, the University of Manchester and the European Bioinformatics Institute, reflects the central place of the web in providing access to information. Use of the Wellcome Library website continues to grow and considerable resource material is now published on the Wellcome Trust's main site. The major exception is developing countries, where, for the time being at least, there is still a role for alternative resources such as CD-ROMs.

The Wellcome Library

In October 2005, the Wellcome Library collections were awarded 'Designation' status by the Museums, Libraries and Archives Council (MLA), in recognition of their outstanding national and international importance.

Among many notable acquisitions was a portrait of an 18th-century Dorset farmer, Benjamin Jesty, who, in 1774, used cowpox inoculations to protect his wife and children against smallpox – 20 years before Edward Jenner's famous 'first' vaccination.

In January 2006, the Wellcome Library co-organised (with the Digital Curation Centre) and hosted a two-day workshop on future-proofing institutional websites. Websites are key repositories of information, but their transience may mean important material is lost, without suitable archiving procedures – such as the Wellcome Library's web-archiving programme.

Two INSET training days for teachers were held in 2006, to encourage teachers to use historical approaches (and Wellcome Library materials) in their teaching.

The winning images in the Wellcome Trust Biomedical Image Awards 2006 went online and on show at the Wellcome Library foyer in July 2006. An additional display opened at the National Science Learning Centre in York.

Biomedical Information

On 27 July 2006, the contract to run UK PubMed Central (UKPMC) was awarded (see page 41). As part of the drive towards open access, the Medical Journals Backfiles Digitisation project was launched in May 2006. Through the project, complete back issues of significant biomedical journals – eventually some three million pages covering nearly 200 years – are being made freely available online.

The £1.3 million initiative is jointly funded by the Wellcome Trust and the Joint Information Systems Committee (JISC), and was developed through a partnership between the Trust, JISC, the US National Library of Medicine and medical journal publishers.

In April 2006, the Wellcome Trust won the first Scholarly Publishing and Academic Resources Coalition (SPARC) Europe Award for its work on open access publishing.

Publishing

The second and third issues of *Wellcome Science* were published, showcasing notable Wellcome Trust-funded projects and providing insight into the latest scientific discoveries. Subjects covered included the placebo effect, clinical use of stem cells, body clocks and the neuroscience of social interactions. *Wellcome Focus on Ageing* summarised scientific, medical and social developments in ageing.

Full text for *Wellcome Science* and *Wellcome Focus* is now available online, along with all articles from the Trust's quarterly magazine, *Wellcome News*.

The Trust's Human Genome website was relaunched with: an updated design; in-depth sections on topics such as diabetes, cancer and gene therapy; and new articles on the science of the human genome, its role in health and medicine, and the broader social impact of genetic knowledge.

The Publishing Group – International Health underwent an extensive evaluation of its educational and training CD-ROMs, which are now in use by more than 50 000 people in over 80 countries worldwide. The evaluation revealed very high levels of user satisfaction; nearly half of all users reported improvements in professional or clinical practice, or improved healthcare delivery. A third edition of the best-selling CD-ROM on malaria was published during the year.

A collaboration with Fiocruz, the Brazilian national research organisation, will see Topics in International Health CD-ROMs translated into Portuguese for the Brazilian and Portuguese-speaking African markets. The project promises to bring the CD-ROMs to countries with a combined population of over 200 million.

ADVISORY COMMITTEES

Basic Immunology and Infectious Disease Funding Committee

Professor A C Hayday
(Chair) Guy's, King's and St Thomas' School of Medicine, King's College London

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University of Birmingham

Professor M Duszenko
University of Tübingen, Germany

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Trinity College Dublin, Ireland

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University of Aberdeen

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Imperial College of Science, Technology and Medicine, London

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Professor D Soldati-Favre
University of Geneva, Switzerland

Professor J A Vazquez-Boland
University of Bristol

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Professor N J Buckley
University of Leeds

Professor T J Elliott
Southampton General Hospital

Professor P W Ingham
(in abeyance 2005/06) University of Sheffield

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Institute of Cancer Research, London

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University of Cambridge

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University of York

Professor C M R Turner
University of Glasgow

Professor M J Whitaker
University of Newcastle upon Tyne

Professor M Yaniv
Pasteur Institute, Paris, France

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(Chair) St George's Hospital Medical School, University of London

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(from June 2006) Queen Mary College, University of London

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Professor A V Campbell
(to May 2006) Centre for Ethics in Medicine

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European Commission, Brussels, Belgium

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University of Manitoba, Canada

Dr P Martin
University of Nottingham

Professor S McLean
University of Glasgow

Professor N Nevin
Queen's University Belfast

Professor D Wassenaar
University of KwaZulu-Natal, Pietermaritzburg, South Africa

Professor S Wilkinson
Keele University

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University of Oxford

Professor R Franklin
University of Cambridge

Professor J A Franklyn
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Trinity College Dublin, Ireland

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University of Manchester

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Cardiff University

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Professor P A Garety
Institute of Psychiatry, King's College London

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Immunology and Infectious Disease Strategy Committee

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(from February 2006) Governor, Wellcome Trust

Professor P Smith
Governor, Wellcome Trust

Professor J O Thomas
Governor, Wellcome Trust

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International Centre for Genetic Engineering and Biotechnology, New Delhi, India

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University of Edinburgh

Professor A B Rickinson
University of Birmingham

Professor M E J Woolhouse
University of Edinburgh

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Mr E Walker-Arnott
Governor, Wellcome Trust

Dr P Ayris
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Ms A Fleming

Mr N Hopwood
(from April 2006) University of Cambridge

Mr N Kingsley
(to April 2006) The National Archives, Kew

The Wellcome Trust is committed to the principles of peer review. We are indebted to the many researchers who gave up their time to sit on our advisory committees, and to the thousands of scientific referees, in the UK and overseas, who provide comments on grant applications. The following pages list the membership of our advisory committees during 2005/06.

Livestock for Life Awards Funding Committee

Professor H R P Miller
(Chair) University of Edinburgh

Dr J Claxton
European Commission, Brussels, Belgium

Professor J R Gillespie
University of California, Davis, USA

Dr C Heffernan
University of Reading

Professor K Homewood
University College London

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ANTHRA, Andhra Pradesh, India

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African Development Bank, Tunis, Tunisia

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GlaxoSmithKline

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University of Leeds

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Cancer Research UK, London Research Institute

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National Institute for Medical Research, London

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Molecules, Genes and Cells Funding Committee

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(Chair) University of Manchester

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University of Manchester

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University of Nottingham

Professor P R Avner
Pasteur Institute, Paris, France

Professor L R Cardon
University of Oxford

Dr R M Cooke
GlaxoSmithKline

Dr A J Greenfield
Medical Research Council Mammalian Genetics Unit

Professor A I Lamond
University of Dundee

Professor C L Mummery
Netherlands Institute for Developmental Biology, The Netherlands

Professor G Murphy
Cambridge Institute for Medical Research

Professor S Neidle
University of London

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University of Kent, Canterbury

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Professor R J White
University of Glasgow

Professor D I Wilson
University of Southampton

Molecules, Genes and Cells Strategy Committee

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(Chair) University of California, San Francisco, USA

Professor A P Bird
Governor, Wellcome Trust

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Scanning electron micrograph of breast cancer cells (Annie Cavanagh).

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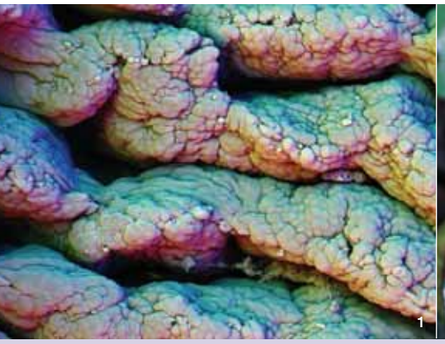
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