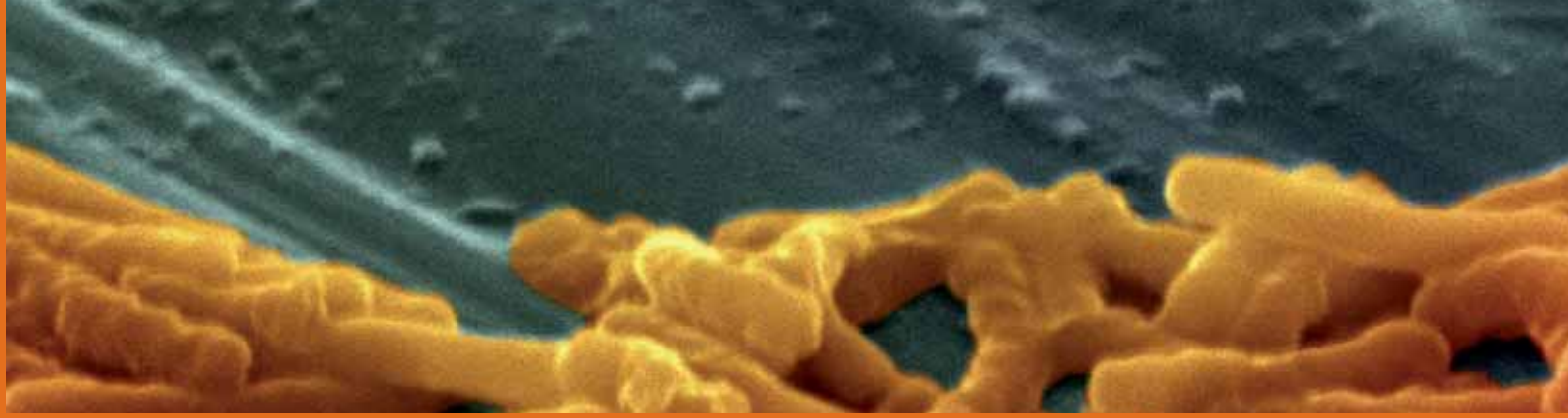
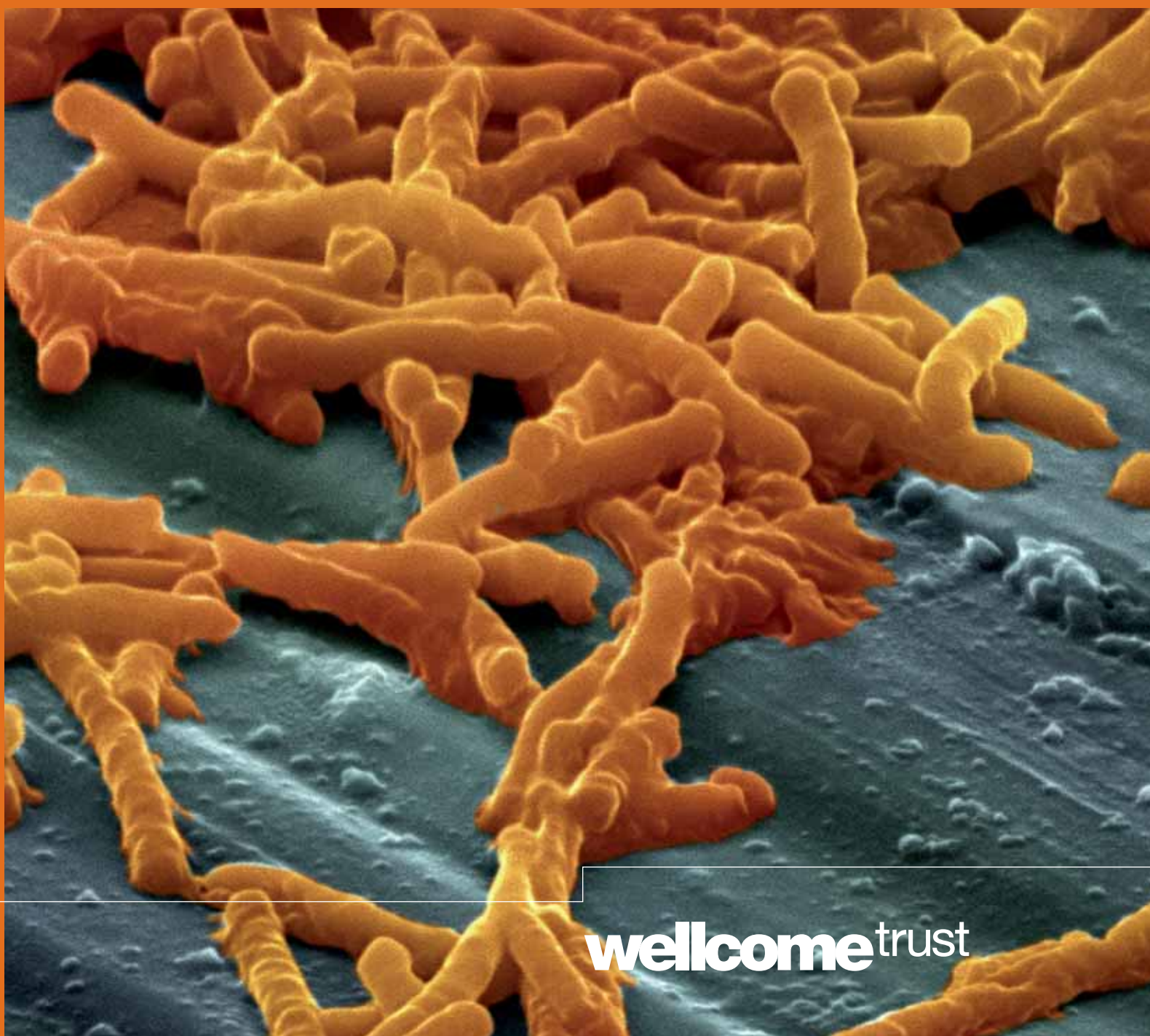


ANNUAL REVIEW

2007

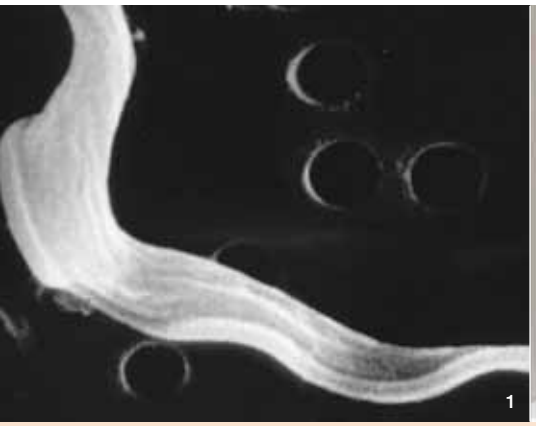


wellcome trust

WELLCOME TRUST ANNUAL REVIEW 1 October 2006–30 September 2007

THE WELLCOME TRUST

The Wellcome Trust is the largest charity in the UK. It funds innovative biomedical research, in the UK and internationally, and supports public debate about biomedical research and its impact on health and wellbeing.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CONTENTS

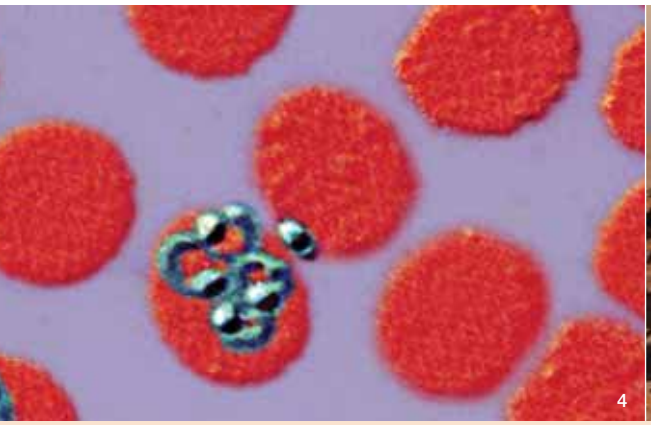
BOARD OF GOVERNORS

*While finalising this publication, we were saddened to learn that Alastair Ross Goobey had died, following a long illness. Alastair was an outstanding Governor and extraordinary friend of the Wellcome Trust. A Governor since 2002, his advice was instrumental in helping to develop the investments of the Trust. He took a great interest in all aspects of our activities and will be sadly missed by those who worked with him.

Images

1 A trypanosome parasite.
2 Stephen Fry in Wellcome Collection.
3 Examining material in the Wellcome Library.
4 Malaria parasites inside red blood cells.
5 The Beagle 2 spacecraft.
6 The Africa Centre for Health and Population Studies.

This *Annual Review* covers the Wellcome Trust's financial year, from 1 October 2006 to 30 September 2007.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EXECUTIVE BOARD

Mark Walport
Director of the Wellcome Trust

Ted Bianco
Director of Technology Transfer

John Cooper
Director of Resources

David Lynn
Head of Strategic Planning and Policy

Clare Matterson
Director of Medicine, Society and History

David Phillipps
Director of Finance

Alan Schafer
Head of Molecular and Physiological Sciences

John Stewart
Head of Legal and Company Secretary

Danny Truell
Chief Investment Officer

As at January 2008

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

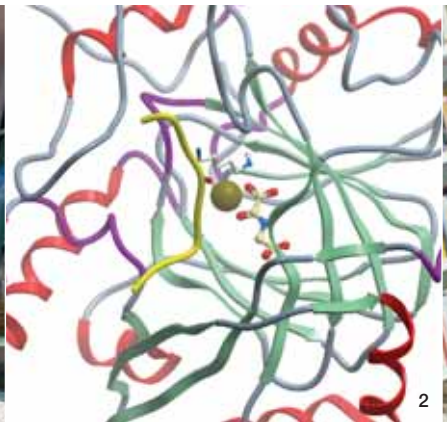
Developing our organisation: To use our resources efficiently and effectively.

Strategic Plan updates, summarising progress in achieving specific objectives during 2006/07, can be found at **www.wellcome.ac.uk/strategicplan**.

BEING BOLD

Sometimes big is definitely better…


1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One of the benefits of having significant sums to award in grants is the opportunity to make major investments – to think big. We have been in the fortunate position of being able to do that while maintaining our core support for curiosity-driven investigator-led proposals. But rather than do 'more of the same' we have consciously set aside large sums to be spent on the truly innovative, large-scale projects that will have enduring impact. This year we can see how this policy has borne fruit magnificently.

The undoubted highlight has been the stream of papers emerging from the Wellcome Trust Case Control Consortium (page 6). Identifying genes associated with common diseases has been a goal of human geneticists for decades, yet with a few notable exceptions progress has been frustratingly slow. It has taken advances in technology, methodology and statistical tools to arrive at a situation where reliable associations can now be identified.

More than 30 genes have been pinpointed by the Consortium using this approach, and others are likely to be confirmed by more detailed follow-up work. They are providing valuable leads for researchers investigating the biology of these conditions, and have opened up a host of new therapeutic targets.

Crucially, this work has only been made possible by the availability of a dense map of genetic markers – an outcome of the Human Genome Project, the sequencing of which identified sites of single-letter variation in the human genetic code (so-called single nucleotide polymorphisms, SNPs). Recognising the value of SNPs as genetic markers, we supported the SNP Consortium, a public–private partnership that mapped hundreds of thousands of SNPs across the genome and made them freely available for use in research.

From the SNP Consortium emerged the International HapMap Project, to which we have also contributed support. The HapMap Project is characterising human genetic variation across different human populations. It is variation between individuals that will underpin differing susceptibilities to disease.

While SNPs still appear to be the main source of human genetic variation, copy number variation is also turning out to be significant (pages 6–7). Blocks of DNA may be missing or present in different numbers of copies in different people. We are now discovering that this feature is more common than we thought, is distinct from SNP variation, and impacts on health. In a new venture funded this year, the Case Control Consortium will be searching for copy number variation as a possible factor in common diseases.

The Consortium was not the only notable 'big science' achievement of the year. January 2007 saw the opening of the Diamond synchrotron, a joint venture with the UK Government (page 37). This initiative, the largest scientific infrastructure project in the UK for 40 years, has been many years in gestation and it gives me great pleasure to see such a world-class facility up and running.

The value of structural approaches, where Diamond will have its biggest biological impact, is amply illustrated by the continuing success of the Structural Genomics Consortium (page 37). Another public–private partnership, and based on an international collaboration involving the UK, Canada and Sweden, the Structural Genomics Consortium has confounded sceptics – easily surpassing its targets. Protein structures, again freely released into the public domain, have given insight into fundamental biological questions and are also of direct practical benefit, stimulating new drug development.

Large-scale high-throughput approaches are one of the strengths of the Wellcome Trust Sanger Institute. It continues to play a key role in unravelling the mysteries of the human genome – an entity that is more complex than anyone had thought when the sequencing project was launched (pages 6–7). The Sanger Institute has also shown how

Images

1 Buildings housing the Wellcome Trust Sanger Institute.

2 Structure of JMJD2A demethylase enzyme, determined by the Structural Genomics Consortium.

3 Dr Mark Walport with Stephen Fry (left) and Trust Deputy Chairman Professor Martin Bobrow (right) at the opening of Wellcome Collection.

4 Lung cancer cells in culture.

much can be gained from comparative genomics – identifying key differences between strains and different but related species (pages 10–11).

The Cancer Genome Project, a partnership between the Sanger Institute and the Institute of Cancer Research, is another ambitious initiative that continues to generate important information (page 7). An early success was its discovery of *BRAF* as a key gene involved in malignant melanoma. It now looks as if *BRAF* may be exceptional in causing such a high proportion of these cancers. An exhaustive trawl of kinase genes in a range of human tumours has revealed great diversity in the mutations present in cancers. Not all the mutations are necessarily contributing to cancer growth, and it is a significant challenge distinguishing the 'drivers' from the 'passengers'.

Another key factor in the success of the Case Control Consortium was the network of collaborating groups across the UK that made it possible. Collaboration has always been central to research but now there is even more to be gained from pooling expertise, experience and materials. Crucially, results in one cohort could be compared with those obtained in others, thus confirming that the observed effects are reproducible – an issue that has dogged human genetics for years.

Collaboration has also been an important feature of our Major Overseas Programmes. It is striking to see how our centres in the Far East have established productive links both within their host countries and with others in the region – and globally (pages 20–21 and 31). Combating threats such as H5N1 avian calls for a coherent joined-up approach – the pathogens concerned are no respecters of national borders. And by sharing results, as has happened with steroid treatment of meningitis, researchers can tackle questions that none alone could possibly have answered.

This trend towards 'big science' is sure to continue. Progress continues on the UK Biobank project, which with data on 500 000 people will provide an unrivalled resource for epidemiological research. This year we have promoted more imaginative thinking around electronic patient records, where the UK's national infrastructure provides a huge opportunity for health research. The technical and logistical challenges are significant but this is an opportunity that must not be let slip away.

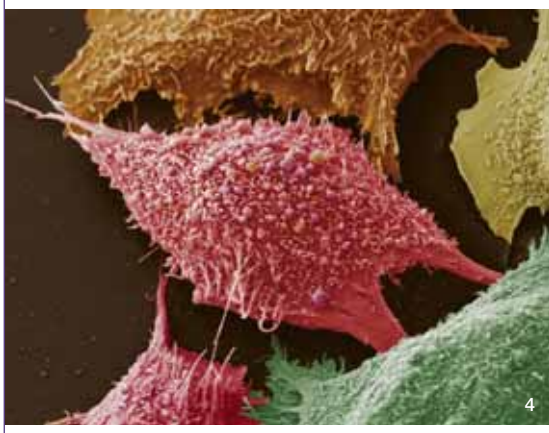
The great advances made by large-scale initiatives should not cause us to lose sight of the high-quality research being carried out by individual research groups. The work of Professor Adrian Bird and colleagues in Edinburgh and researchers at the Behavioural and Clinical Neuroscience Institute in Cambridge shows how studies of animal models can shed light on key biological processes. In elegantly conceived experiments, Professor Bird's group has shown that the autism-like symptoms of a mouse model of Rett syndrome can be reversed through use of agents affecting the methylation state of DNA. The Cambridge group discovered that unusual patterns of dopamine receptor activity in the brain were associated with both impulsive behaviour and susceptibility to cocaine addiction in rats.

Discussion of this year's highlights would not be complete without mention of the opening of Wellcome Collection, our new public venue at 183 Euston Road, London. It has proved a huge success, in terms of both critical acclaim and visitor numbers. Its unique mix of science and art, old and new, clearly illustrates the connections between science, medicine and wider culture. It, too, demonstrates that an imaginative idea, conceived and delivered on a grand scale, can deliver rich rewards.

Dr Mark Walport
Director

January 2008

HIGHLIGHTS OF THE YEAR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- Wellcome Trust Case Control Consortium finds 30 genes associated with common diseases.
- Wellcome Trust Sanger Institute researchers discover further complexity in the human genome.
- Cancer Genome Project identifies 'driver' and 'passenger' mutations in systematic analysis of kinase genes in human cancers.
- Autism-like symptoms reversed in mouse model of Rett syndrome.
- Predisposition to impulsive behaviour and drug addiction linked to pre-existing dopamine receptor abnormalities.
- Key promoter of inflammatory bowel disease identified.
- Diamond synchrotron opens to its first users.
- Risk of mother-to-child transmission of HIV found to be lowest in exclusively breastfed infants.
- Typhoid vaccine successfully completes phase I trial in Vietnam.
- Wellcome Collection opens to the public.

ADVANCING KNOWLEDGE

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

A CASE FOR CELEBRATION

The Wellcome Trust Case Control Consortium has identified genes involved in a host of common diseases.

The past couple of decades have seen enormous efforts made to identify genes increasing our susceptibility to common diseases. Whole-genome scans now enable the entire genome to be screened for possible contributory factors. Unfortunately, the field has been blighted by 'false positives' – statistical associations discovered in one population but not apparent in another. Now, though, an approach spearheaded by the Wellcome Trust Case Control Consortium is finally generating robust data.

The Consortium is making use of the dense map of genetic markers produced by the SNP Consortium and its follow-up, the International HapMap Project. Advances in technology have enabled high-throughput analysis of hundreds of thousands of such markers in large numbers of individuals.

The Consortium also depended on coordination among the UK's leading researchers (and groups abroad). Crucially, genetic associations identified in one population could be tested in other, increasing confidence that an association is real.

In essence, case–control approaches look for genetic variations that are more common in people with a given condition than in matched healthy individuals. The Consortium used the approach on a variety of conditions. This work, and follow-up by individual disease groups and collaborators, has now identified more than 30 genetic factors contributing to diseases including heart disease, type 1 and type 2 diabetes, Crohn's disease, rheumatoid arthritis and ankylosing spondylitis. The number of genes continues to increase with more detailed data analysis and follow-up.

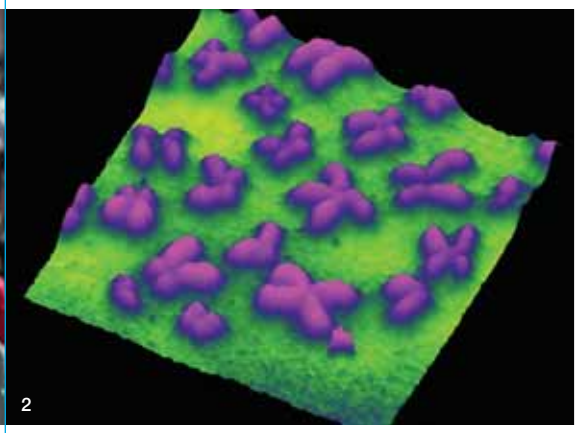
Interestingly, the approach also led to the identification of genes associated with other characteristics, such as weight and height.

Because so many factors affect common diseases, and a single gene will generally have only a small effect, the identification of susceptibility genes will have limited value in the prediction of disease in individuals. Far more important is the insight provided into mechanisms of disease, opening up new avenues of research into causes and possible treatments.

Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447(7145):661–78.

RETHINKING THE GENOME

The more the human genome is studied, the more surprises emerge.



When the first draft of the human genome was completed, Sir John Sulston argued that it was a beginning not an end. The wave of unexpected discoveries that have followed have vindicated that view. And it is fitting that the Wellcome Trust Sanger Institute has been at the forefront of efforts to understand the genome – as illustrated by its work on conserved regions and copy number variation.

The ENCODE (Encyclopedia of DNA Elements) project is an international collaboration analysing in detail 1 per cent of the human genome. This analysis has thrown up a whole host of surprising findings – from the unexpectedly large proportion of the genome copied into RNA to the seemingly almost random distribution of gene control regions. The ENCODE project, to which Sanger Institute researchers Dr Manolis Dermitzakis and Dr Tim Hubbard made key contributions, is challenging received wisdom about how genes and genomes are organised – highlighting how much is still to be learned about genome function and evolution.

Last year, Dr Matt Hurles and colleagues discovered surprisingly high levels of copy number variation – blocks of DNA

Images

1 Human variation: genetic differences influence our susceptibility to disease.

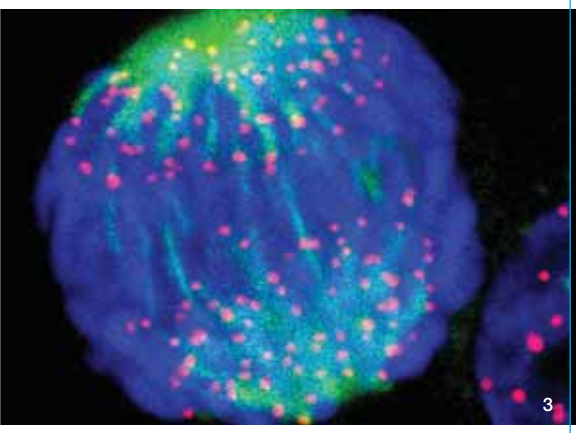
2 Human chromosomes.

3 A dividing HeLa cell, with DNA stained blue.

4 Prostate cancer cells.

DRIVING MISREGULATION

Mining the human genome reveals far more 'cancer genes' than expected.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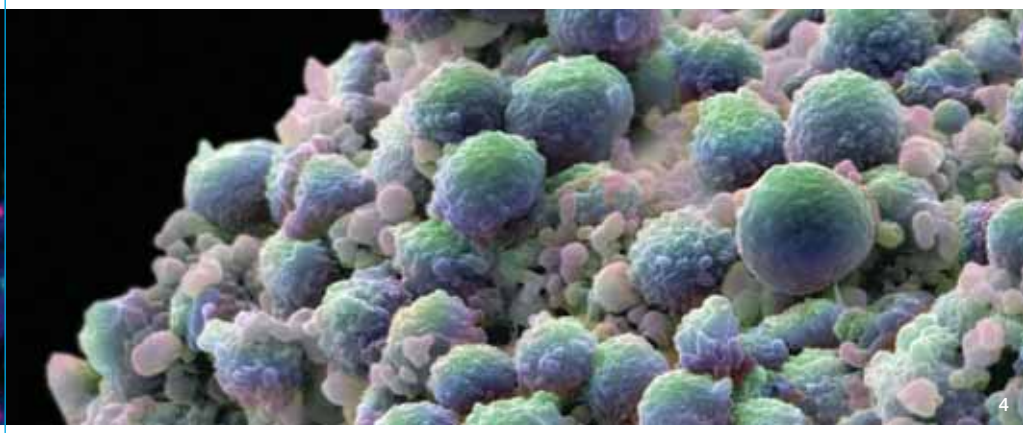
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present in different numbers, or missing entirely, in different people. Further analysis by Dr Dermitzakis, Dr Hurles and colleagues has revealed that copy number variation does not necessarily correlate with another source of human genetic variation, single nucleotide polymorphisms (SNPs). Hence SNP-based searches for disease-linked variants may miss out on predispositions caused by changes in copy number.

And research continues to identify conditions influenced by copy number variation. In one of the few studies to date of its clinical consquences, Professor Tim Aitman and colleagues discovered a link between copy number variation affecting the *FCGR3B* gene and susceptibility to autoimmune diseases – but only those affecting the whole body rather than specific organs.

ENCODE Project Consortium. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 2007;447(7146):799–816.

Stranger BE et al. Relative impact of nucleotide and copy number variation on gene expression phenotypes. Science 2007;315(5813):848–53.

Fanciulli M et al. FCGR3B copy number variation is associated with susceptibility to systemic, but not organ-specific, autoimmunity. Nat Genet 2007;39(6):721–3.

ENCODE is funded by the National Human Genome Research Institute.

All cancers occur due to abnormalities in DNA sequence. The steady accumulation of these abnormalities throughout life ultimately means that one in three people in the Western world develops cancer. This year, the Cancer Genome Project – an international collaboration led by Professor Michael Stratton and colleagues at the Wellcome Trust Sanger Institute – has dramatically expanded the database of known cancer genes, adding significantly to our understanding of cancer biology and fuelling research into the development of new treatments.

The project set about probing the genetic make-up of cells taken from 210 different human cancers. The study focused on the genes encoding all 518 known human protein kinases, enzymes that regulate other proteins through the addition of a phosphate residue. These key molecular players can have a strong influence on cell growth and division and if not working properly can trigger tumour development.

The molecular scrutiny revealed over 1000 different mutations. However, the presence of a mutation does not necessarily mean that it is contributing to uncontrolled cell growth. Indeed, most changes appear to be 'passenger' mutations incidental to tumour development. But the researchers highlighted 158 mutations in 120 kinase genes as possible 'drivers' of disease.

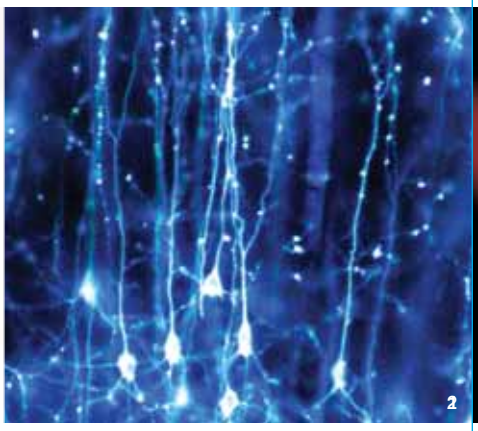
Although it adds considerably to the 350 genes previously implicated in cancer, the study highlights how genetically complex even a single tumour is. And as each tumour type turned out to have a wide range of driver mutations, no obvious drug targets emerged for particular cancers. Nevertheless, the study has opened up a whole host of new molecular pathways to investigate and drug targets to explore.

Greenman C et al. Patterns of somatic mutation in human cancer genomes. Nature 2007;446(7132):153–8.

RETT REVERSAL

Studies in mice suggest that autism-like conditions may be reversible.

1



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Rett syndrome is an autism-like disorder caused by the mutation of a single gene – *MECP2*. Although the function of nerve cells is clearly affected, they do not die as in neurodegenerative conditions such as Alzheimer's. A key question, then, is: can the brain's developmental abnormalities be reversed? Working with a mouse model, Professor Adrian Bird and colleagues at the University of Edinburgh have uncovered remarkable evidence that they can.

Professor Bird's team has been studying the *MECP2* gene for several years. It encodes a protein that regulates the activity of other genes. Mutations in the gene affect around 1 in 10 000 girls, and also causes distressing physical symptoms, including loss of movement, abnormal breathing patterns and difficulty with speech. Many children display an abnormal, stiff-legged gait and some become confined to a wheelchair.

Professor Bird's team created a mouse model of this disease by silencing the expression of *MECP2*. To their surprise, the Rett-like symptoms these mice developed disappeared when the gene was reactivated.

This implies that the effects of the Rett syndrome mutation are not permanently wired into the brain. If this is also true in people, it might be possible to reverse the symptoms of Rett syndrome by reactivating the *MECP2* gene (although the approach used in mice is not one applicable to people).

More generally, the study raises hopes that a range of human neurodevelopmental disorders might be reversible.

Guy J et al. Reversal of neurological defects in a mouse model of Rett syndrome. Science 2007;315(5815):1143–7.

PAIN-FREE LIVING

A rare defect in pain perception points the way to new analgesics.

3

Pain is an important protective mechanism, but there are many occasions when we would prefer not to experience it. Chronic pain, in particular, can make a life a misery and is difficult to control. Studies of families with a total lack of pain sensation, led by Dr Geoffrey Woods of the University of Cambridge, have identified a key mechanism in pain detection and may offer a new route to effective pain relief.

Six children from three related families from northern Pakistan came to the attention of researchers because of their extraordinary abilities to tolerate normally painful experiences. Superficially, there was nothing wrong with their peripheral and central nervous systems and they seemed in good health in spite of a catalogue of cuts, bruises and breaks they had endured throughout childhood.

By studying the affected family network, the researchers were able to home in on the genetic basis for this condition. The disorder was associated with a region of chromosome 2 containing *SCN9A*, a gene that encodes a voltage-gated sodium channel found on pain-responsive neurons. Sequence analysis of this

Images

1 A laboratory mouse: mice are helping to reveal the mysteries of Rett syndrome.

2 A network of neurons in the brain: miswiring may cause conditions such as Rett syndrome.

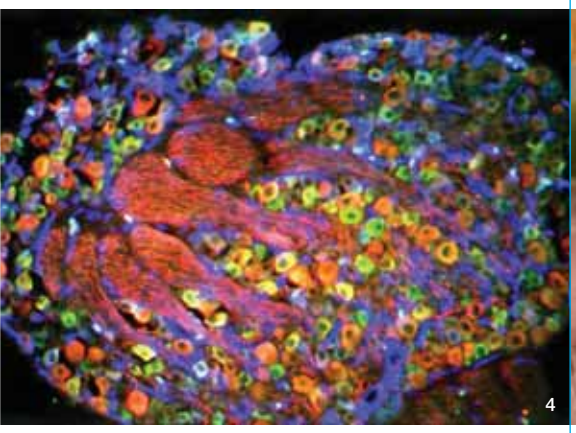
3 Visualising pain: an artwork by Deborah Padfield.

4 A section through pain-sensing neurons.

5 Appetising meals: the hormone leptin may influence the desirability of food.

APPETITE FOR DECONSTRUCTION

How does the brain integrate the factors that control our appetite?



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gene in the affected individuals revealed three distinct mutations. *In vitro* experiments demonstrated that these mutations shut down these sodium channels completely.

This raises the possibility that variation in *SCN9A* might account for differences in pain tolerance between individuals. Furthermore, since the individuals with loss-of-function mutations in this gene are otherwise healthy, a drug that could selectively target this sodium channel has the potential to produce pain relief without affecting other aspects of nervous system function.

Cox JJ et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature 2006;444(7121):894–8.

What controls how much we eat? The regulation of food intake is complex, but it has become clear that a specific brain area, the hypothalamus, plays a key role in integrating hormonal signals from body tissues. But as Dr Sadaf Farooqi, Dr Paul Fletcher and colleagues have discovered, other brain areas are also influenced by hormones.

The hormone leptin is known to be a powerful regulator of feeding – without it, mice (and people) eat voraciously and become morbidly obese. Leptin is produced by fat cells, and is a signal for starvation, as falling levels trigger an increase in food intake.

Leptin acts directly on the hypothalamus but, as the researchers discovered, this is not its only target in the brain. In studies of brain activity in two individuals lacking leptin, before and after leptin therapy, leptin enhanced the response to 'fullness' signals after food, but also had an effect in the brain's reward areas – the pathways associated with pleasurable sensations.

Crucially, in the leptin-deficient state the patients recorded higher activity in reward pathways when shown pictures of food, and they rated them as more desirable. Thus leptin not only enhances 'fullness' signals in the hypothalamus but also influences the desirability of food.

Exactly how leptin acts on brain cells is unclear, but work from Professor Dominic Withers, Professor Mike Ashford and others provides clues to the cellular systems that might respond to leptin and nutrients in the regulation of food intake and energy balance.

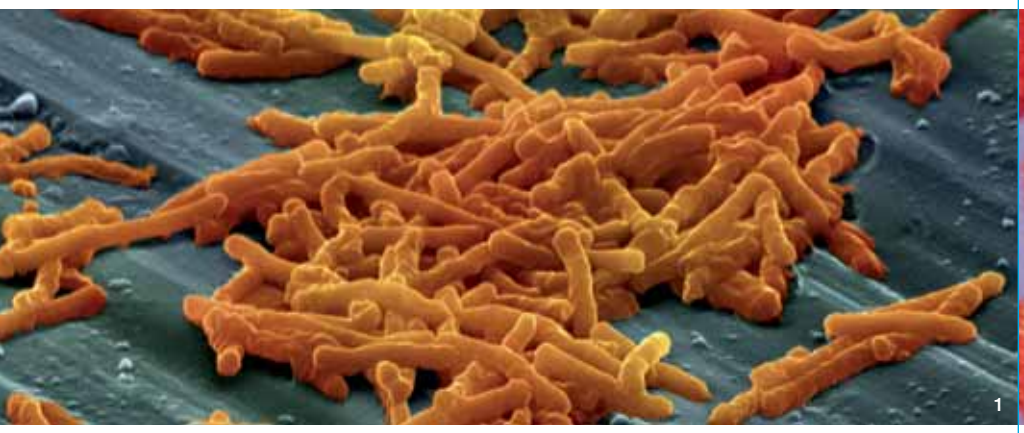
The enzyme AMP-activated protein kinase (AMPK) is thought to be a master 'energy sensor', the body's fuel gauge. Research on two knockout mouse strains lacking AMPK in either of two key cell populations in the hypothalamus suggests a more complicated picture. One strain became obese, but the other remained lean. Both strains remained sensitive to leptin, but showed abnormal glucose sensing by neurons. Therefore, while AMPK is an important sensor of some types of nutrients, it does not appear to be the master regulator of energy homeostasis in the hypothalamus.

Farooqi IS et al. Leptin regulates striatal regions and human eating behavior. Science 2007;317(5843):1355.

Claret M et al. AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. J Clin Invest 2007;117(8):2325–36.

COMPARE AND CONTRAST 1: BACTERIA

Comparisons between genome sequences can reveal why some bacteria are deadlier than others…



While a complete genome sequence often reveals much about an organism, more can be learned from comparisons with close relatives. They can pinpoint genetic features linked to pathogenic properties and shed light on evolution, as illustrated by work from Professor Julian Parkhill and colleagues at the Wellcome Trust Sanger Institute.

Yersinia enterocolitica is a gut-dwelling mild microbial pathogen. Its relatives *Y. pseudotuberculosis* and *Y. pestis* are much nastier, causing gastroenteritis and bubonic plague respectively. A three-way comparison of their genomes has revealed genes associated with life in the gut (unlike its relatives, *Y. pestis* lives in the bloodstream) and with different clinical symptoms. Interestingly, *Y. pseudotuberculosis* lacks clusters of metabolic genes present in *Y. enterocolitica*, suggesting that they occupy distinct niches within the gut. *Y. pestis* is thought to have evolved very recently, and is in the process of shedding genes not needed in its new habitat. As a result, it is becoming more deadly.

Clostridium botulinum produces the world's most lethal toxin (2 kg could kill everyone on the planet). Although it can infect the body, it is primarily an environmental organism, and its genomic characteristics are quite distinct from relatives such as *C. difficile*. It has a very stable genome, unlike *C. difficile*, which seems to have hoovered up DNA from many bacteria. Rather than constantly adapting to a living host, it relies on opportunism – a sudden lethal strike followed by leisurely digestion.

Different strains of *C. botulinum* are only tenuously related. Indeed, the concept of a bacterial species is increasingly hard to nail down. Some bacteria, such as *Streptococcus pneumoniae*, seem to have a 'supragenome' – a large pool of genes only a subset of which are found in any one strain.

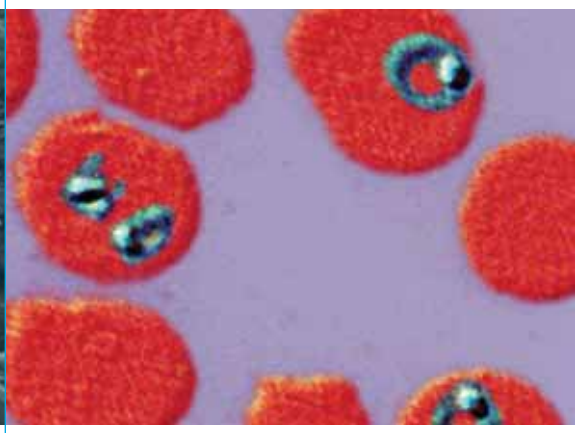
Thomson NR et al. The complete genome sequence and comparative genome analysis of the high pathogenicity Yersinia enterocolitica strain 8081. PLoS Genet 2006;2(12):e206.

Sebaihia M et al. Genome sequence of a proteolytic (Group I) Clostridium botulinum strain Hall A and comparative analysis of the clostridial genomes. Genome Res 2007;17(7):1082–92.

Hiller NL et al. Comparative genomic analyses of seventeen Streptococcus pneumoniae strains: insights into the pneumococcal supragenome. J Bacteriol 2007;189(22):8186–95.

2: PARASITES

…and are providing new insights into parasite biology.



The genome of *Plasmodium falciparum*, the most deadly malaria parasite, was sequenced in 2002. But the laboratory strain sequenced is likely to differ from those present in the wild. Moreover, as with humans, it will be crucial to unpick the impact of genetic variation in natural populations. A first step towards this goal has been taken by Dr Matt Berriman and colleagues at the Wellcome Trust Sanger Institute. In a second project they have used comparisons of related species to investigate another important parasite, *Leishmania*.

The malaria project compiled new sequences for a parasite obtained directly from a patient in Ghana, a laboratory isolate and the chimpanzee parasite *P. reichenowi*. These were compared with the fully sequenced *P. falciparum* reference genome.

In this and two other studies published simultaneously, some 27 000 sites of variation were identified in the genome. Analysis of these sites sheds light on genes involved in the parasite's arms race with the host. Parasite molecules that are exposed to our immune system need to change rapidly for the parasite to avoid detection. Analysing DNA

Images

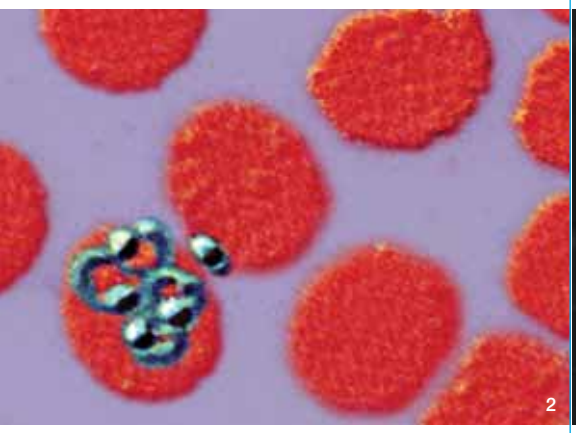
1 *Clostridium difficile*, a microbe with a highly dynamic genome.

2 Malaria parasites inside red blood cells.

3 A bloodstream-stage trypanosome parasite.

A DEADLY MOSAIC

Trypanosomes are adept at changing their surface structures. Their trick is to create a multitude of mosaic genes.



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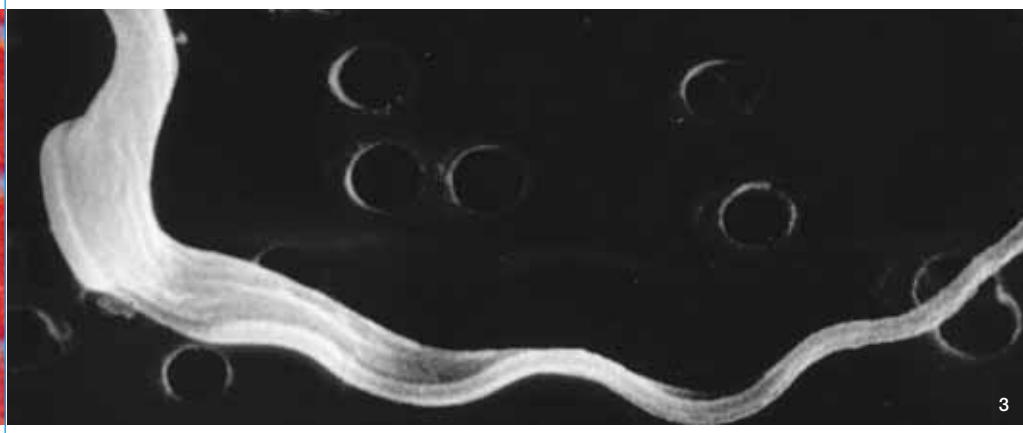

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variation reveals those molecules that are interacting with the immune system and therefore represent possible vaccine targets.

The *Leishmania* project compared new sequences for *L. infantum* and *L. braziliensis* with the published genome of *L. major*. These parasites cause different forms of disease, so the genome comparisons reveal genetic features that may be linked to particular clinical symptoms.

The genomes turn out to have remarkably similar structures – only about 200 genes really differ in their presence or absence between the three genomes. The main genetic changes seem to arise from gene loss or inactivation. Changes in a small number of genes may therefore be having a big impact on the nature of disease, though other effects – such as differences in gene activity or gene copy number – could also be significant.

Jeffares DC et al. Genome variation and evolution of the malaria parasite Plasmodium falciparum. Nat Genet 2007;39(1):120–5. Errata in: Nat Genet 2007;39(4):567, Nat Genet 2007;39(3):422.

Peacock CS et al. Comparative genomic analysis of three Leishmania species that cause diverse human disease. Nat Genet 2007;39(7):839–47.

Trypanosomes, single-celled parasites infecting people and livestock, cause enormous deprivation throughout Africa. Their resilience to host immune responses stems from their extraordinarily variable surface coat – as soon as the immune system has geared up to attack one form, another type appears and proliferates, leading to wave after wave of infection. The sequencing of the trypanosome genome suggested unexpected ways in which the parasite might be generating this diversity, and research from Professor Dave Barry and colleagues at the Wellcome Trust Centre for Molecular Parasitology in Glasgow has revealed new insights into these deadly masters of disguise.

A key finding from the trypanosome genome project was the discovery of many hundreds of damaged genes coding for the main trypanosome surface protein. Professor Barry and colleagues have found that these damaged genes are used as a source of spare parts for functional genes. Small sections are included in active genes, altering the structure of the protein displayed on the cell surface.

This enormous capacity to create mosaic genes theoretically enables the parasite to create far more surface forms than previously thought. New mosaic forms can appear within a few weeks of infection, and they may even enable the parasite to reinfect people who have developed immunity to existing strains.

Other work from the Glasgow group has identified an unusual method of DNA repair, which could contribute to the DNA-shuffling process creating mosaic genes. And a mathematical study suggests that it is the parasite itself, rather than pressures from the immune system, that generates waves of infection in a host. The parasite has thus evolved mechanisms to prolong infections, through a series of mini-infections, rather than immediately overwhelming a host – thereby increasing its chances of transmission.

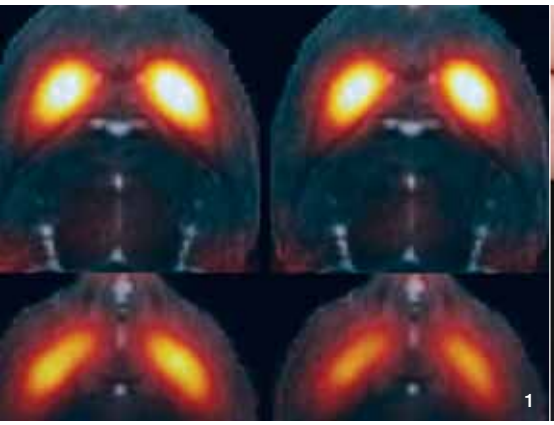
Marcello L, Barry JD. Analysis of the VSG gene silent archive in Trypanosoma brucei reveals that mosaic gene expression is prominent in antigenic variation and is favored by archive substructure. Genome Res 2007;17(9):1344–52.

Burton P et al. Ku-independent end-joining in Trypanosoma brucei cell extracts relies upon sequence microhomology. Eukaryot Cell 2007;6(10):1773–81.

Lythgoe KA et al. Parasite-intrinsic factors can explain ordered progression of trypanosome antigenic variation. Proc Natl Acad Sci USA 2007;104(19):8095–100.

ADDICTION PREDICTION

A study with rats suggests that some individuals are more likely to become hooked on drugs than others.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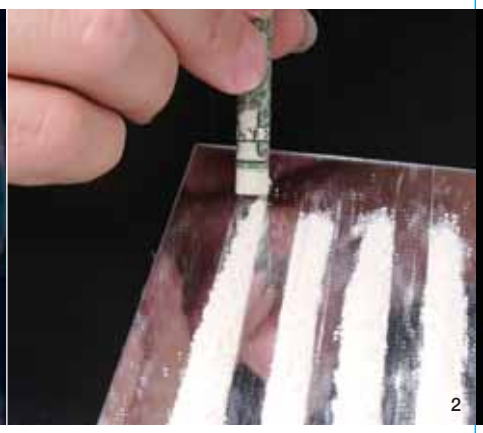
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A long-running debate has focused on the possible predisposition of people to drug addiction. Genetic studies are not clear-cut, and although particular types of behaviour and brain activity are seen in addiction, these could be a consequence rather than a cause of drug taking. A neat experiment in rats, however, provides strong evidence that susceptibility to addiction has a biological component.

The dopamine or 'reward' brain system is well known to be involved in addiction. It is also implicated in certain behaviours, including impulsivity, the tendency to respond prematurely without adequate reflection. Potentially, then, individual variations affecting the dopamine system could predispose to addiction through their effects on behaviour.

To test this idea, a group including Professor Trevor Robbins, Dr Jeffrey Dalley and Professor Barry Everitt in Cambridge monitored drug consumption in rats provided with access to the addictive drug cocaine. Before exposure, they measured the animals' tendency to impulsive behaviour and used brain-imaging techniques to quantify levels of particular dopamine receptors. They then looked to see which factors were associated with high drug consumption.

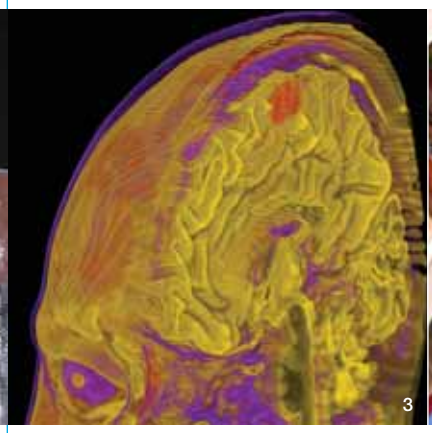
Since the rats had not previously been exposed to the drug, any associations would be a potential cause rather than consequence of drug taking.

The studies revealed that addiction correlated with both impulsive behaviour and low availability of dopamine receptors in key areas of the brain. A defect in dopamine receptor activity in the brain could therefore be a risk factor for drug consumption – in humans as well as rats.

Dalley JW et al. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 2007;315(5816): 1267–70.

SEEING THE UNCONSCIOUS

The unconscious brain may be guiding our actions more than we think.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Non-invasive imaging techniques are revealing the brain in action, and how brain activity maps to conscious awareness (or lack of it). And research is revealing some unnerving aspects of conscious and unconscious thought.

It is already known that visual images can be registered in the brain even when observers are not aware of them. Now Professor Geraint Rees and colleagues at the Wellcome Trust Centre for Neuroimaging have shown that the processing of such unconsciously recognised images is strongly affected by attention.

When subjects engaged in a demanding task were also presented with images that were rendered invisible (by use of a masking technique), brain responses to these images changed according to the attentional demands of the task. So the allocation of attention to a visual stimulus does not depend on its conscious detection.

As well as handling inputs – sensory perceptions of the world – consciousness also shapes our actions. But perhaps not as much as we might think. The frontal lobes of the brain are considered to be critical for initiating voluntary actions.

Images

1 Visualising dopamine D2/D3 receptor density in regions of the brain.

2 Cocaine: susceptibility to addiction may lie, in part, in our genes.

3 Part of the frontal lobe (red) involved in automatic suppression of reflex responses.

4 Decisions, decisions: does the subconscious influence us more than we think?

5 Dutch art flourished in the 17th century, alongside commerce and science. Engraving by C de Passe after M de Vos.

GOING DUTCH

Did Dutch trade kick-start the scientific revolution?

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Yet when Dr Petroc Sumner, Professor Masud Husain and colleagues studied two individuals with localised lesions in key regions of the prefrontal cortex, they found that automatic, unconscious responses that normally suppress unwanted actions were impaired as well.

Similarly, Dr Hakwan Lau and Professor Richard Passingham have found that the prefrontal cortex can also engage in subconscious processing. In their studies, volunteers were subconsciously primed before undertaking a task requiring conscious thought, the prime being either compatible or incompatible with the task. Even though subjects had no conscious knowledge of the prime, incompatible primes disrupted their thinking. Furthermore, brain imaging revealed activity in the prefrontal cortex when an incompatible prime was presented, implying that it is engaged in subconscious processing of information.

Bahrami B et al. Attentional load modulates responses of human primary visual cortex to invisible stimuli. Curr Biol 2007;17(6):509–13.

Sumner P et al. Human medial frontal cortex mediates unconscious inhibition of voluntary action. Neuron 2007;54(5):697–711.

Lau HC, Passingham RE. Unconscious activation of the cognitive control system in the human prefrontal cortex. J Neurosci 2007;27(21):5805–11.

Something resembling modern science first emerged in Europe four-and-a-half centuries ago. The new emphasis on observation and experiment is often portrayed as part of the wider intellectual flowering of the European Renaissance, yet that movement's adherence to classical knowledge was antithetical to the empiricism at the heart of the new thinking. Now, Professor Hal Cook, Director of the Wellcome Trust Centre for the History of Medicine at UCL, has proposed a radical new interpretation: it was commerce that really powered the scientific revolution.

Until now, historians have linked the birth of modern science to religion – a retreat from superstition and the rise of Protestantism, with its more direct, humanistic interpretation of religious texts – alongside the emergence of a natural philosophy emphasising knowledge gained by experiment. The rise of the international trading economy during the same period has generally been seen as independent.

In *Matters of Exchange*, Professor Cook argues that, far from being merely coincidental, the new global commercial culture – seen most clearly in the Dutch Republic during its golden age of 1581–1695 – was the key driver of the scientific revolution.

At the time, Professor Cook suggests, the factors driving Dutch expansionism were seen as precisely those underpinning the new science. The knowledge economy of the day placed a high value on objective description and accumulation of knowledge, through observation and experiment. And they went hand in hand with a scientific methodology that sought rational explanations for observable phenomena.

Indeed, Professor Cook argues, this pragmatism became firmly instilled in Dutch culture and thinking. Its medicine focused not on arcane theories of causes but on careful description and treatment. The result was an explosion in science, botany, medicine, natural history and the arts.

At least some reviewers were convinced: "Cook is deeply persuasive that science and commerce are epistemologically linked through materialist necessity in this magisterial scholarly analysis," said the *Journal of the American Medical Association*. "Altogether an enriching tome," added the *New England Journal of Medicine*.

NEW FUNDING

Africa Centre

A £16.8 million award to the Africa Centre for Health and Population Studies will see it continue its critical research on HIV.

The Africa Centre, based in KwaZulu-Natal in South Africa, is one of the leading African HIV research institutes. Led by Professor Marie-Louise Newell, it has established one of the continent's most comprehensive demographic surveillance systems, covering 90 000 people in mainly rural locations, and has done much to document the extent and impact of HIV and AIDS on South African people (see page 19).

The population is particularly badly affected by HIV – around one in four people in the local community is HIV positive. The infection's impact is compounded by poverty, migration and lack of access to effective treatments.

With renewed five-year core funding, the Africa Centre is well placed to focus on monitoring and evaluating the Anti-Retroviral Treatment Programme for HIV, which is currently being rolled out, and assessing the impact of simultaneous epidemics of HIV, sexually transmitted infections and tuberculosis. The Africa Centre also aims to identify the best ways to deliver HIV-related healthcare in a low-income rural setting.

Opened in 1997, the Africa Centre is a collaboration between the University of KwaZulu-Natal, the South African Medical Research Council and the Wellcome Trust.

The brain of the beholder

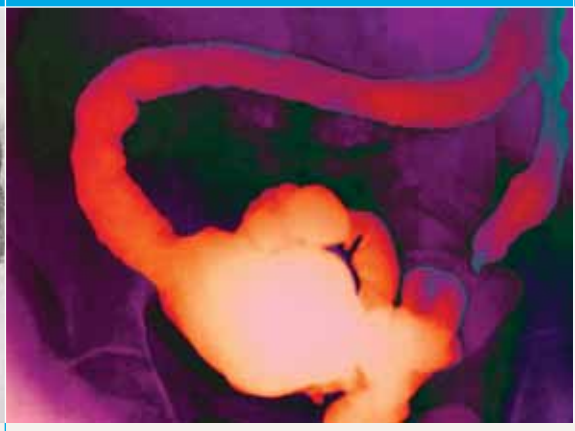
A £1 million Strategic Award is supporting an innovative multidisciplinary programme in 'neuroaesthetics'.

Professor Semir Zeki from University College London (UCL) aims to bring neuroscience into areas normally seen as the territory of artists and philosophers. Can we measure beauty objectively? How are beauty and love related? What does it mean to be happy? What is creativity?

With this new funding, Professor Zeki hopes to attract students and researchers from the sciences, arts and humanities into taking up truly interdisciplinary research. Their work will be overseen by an advisory board that includes author Dame Antonia Byatt, doctor, broadcaster and opera director Sir Jonathan Miller, and the Director of the Courtauld Institute of Art, Dr Deborah Swallow.

With Professor Ray Dolan, Director of the Wellcome Trust Centre for Neuroimaging at UCL, Professor Zeki will bring an experimental neurobiological approach to profound issues that have taxed thinkers for centuries. The results not only will increase our knowledge about the workings of the human brain but also should offer fascinating insights into human nature and how we view ourselves.

Copybook project



The Wellcome Trust Case Control Consortium is turning its attention to copy number variation.

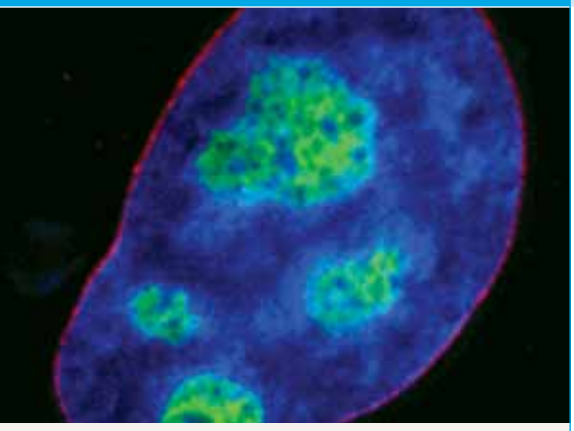
The Wellcome Trust Case Control Consortium demonstrated the value of coordinated efforts to scan entire genomes for disease susceptibility genes (see page 6). It focused on simple variation – single nucleotide polymorphisms (SNPs) – but copy number variation also affects health (see pages 6–7). With £7.7 million follow-up funding from the Wellcome Trust, the Consortium is now sweeping the genome for disease-associated copy number variation.

Copy number variation is much less well understood than SNPs, but understanding is developing rapidly. The Consortium is using newly developed tools to carry out high-throughput analyses of 19 000 samples from eight diseases (the seven diseases from the main study, plus breast cancer), to search for changes in copy number associated with disease.

It will also be dissecting in more detail some of the genomic regions identified in the first phase, which appear to include more than one genetic factor influencing health.

As in phase 1, data and software tools will be made freely available to the research community – emphasising the value of not only the Consortium's scientific discoveries but also its 'pathfinder' role, developing tools and techniques to accelerate research.

A new view of cells



A new Wellcome Trust Centre for Gene Regulation and Expression is being established at the University of Dundee.

The discovery that humans have a surprisingly small number of genes highlighted how important control of gene activity is in human biology. An exquisitely complex set of interactions ensures that genes are only active in the right cells and at the right times.

The Dundee Centre, funded by a £5 million Strategic Award to Principal Research Fellow Professor Angus Lamond and colleagues, will build on the expertise of a number of groups working on different aspects of gene control, including transcription, splicing and chromosome dynamics.

It aims to pioneer a new approach in cell biology by bringing together advanced imaging and proteomics technologies, combined with enhanced data analysis tools, to provide a quantitative understanding of gene regulation and chromosome biology at the single-cell level.

It also plans to establish a collaborative, multidisciplinary environment in which to train young scientists.

A selection of notable grants awarded in 2006/07.

STRATEGIC AWARD

AGEING
Professor Linda Partridge (University College London) The biological mechanisms of cellular and bodily ageing.

PROGRAMME GRANTS

FAT DISTRIBUTION
Professor Keith Frayn (University of Oxford) The impact of fat deposition in different parts of the body and its harmful (or beneficial) effects on metabolic disease.

GERM CELLS
Professor Azim Surani (University of Cambridge) The epigenetic mechanisms of germ cell specification in mice.

GONADOTROPHINS
Professor Ilpo Huhtaniemi (Imperial College London) Further studies of luteinising hormone's action on gonadal and other tissues.

METABOLISM
Professor Paul Stewart (University of Birmingham) Novel regulators of corticosteroid hormone metabolism and possible links to polycystic ovary syndrome and metabolic conditions.

Professor Jonathan Seckl (University of Edinburgh) 11beta hydroxysteroid dehydrogenase type 1 and atherosclerosis risk.

BACTERIAL SECRETION
Professor Gabriel Waksman (Birkbeck, University of London) Structural studies of bacterial type IV secretion systems.

INTRACELLULAR TRANSPORT
Dr Murray Stewart (MRC Laboratory of Molecular Biology, Cambridge) Structural studies of factors needed for import and export of material into and out of the nucleus.

PROJECT GRANTS

PAIN
Professor John N Wood (University College London) Regulation of Nav1.7, an ion channel recently found to have a role in pain detection (see pages 8–9).

LUNG DEVELOPMENT
Dr John Owers-Bradley (University of Nottingham) and **Professor Michael Silverman** (University of Leicester) Measuring alveolar growth and development in childhood by helium-3 magnetic resonance.

DEVELOPMENTAL BIOLOGY
Dr James Briscoe (National Institute for Medical Research) and **Dr Karen Page** (University College London) Mathematical models of Sonic Hedgehog signalling in the neural tube.

ORGAN DEVELOPMENT
Professor Elizabeth A Jones (University of Warwick) Purinergic (ATP-based) and lipid signalling in *Xenopus* kidney development.

RECOMBINATION
Professor Sir Alec Jeffreys (University of Leicester) Analysing recombination hotspots using single-molecule methods in individual sperm.

MALARIA
Professor John M Kelly (London School of Hygiene and Tropical Medicine) *Plasmodium falciparum* centromere function.

INNATE IMMUNITY
Professor Anthony Segal (University College London) Innate immunity and inflammatory bowel disease.

EPIDEMIOLOGY
Professor Sarah Cleaveland (University of Edinburgh) Zoonotic pathogens in linked human and animal populations in rural Kenya.

PROJECT GRANTS (COGNITIVE SYSTEMS FORESIGHT AWARDS)

ATTENTION
Professor Tom Troscianko (University of Bristol) and **Professor David Hogg** (University of Leeds) Developing a computer algorithm modelling attention by studying human attention in a realistic setting (in partnership with the EPSRC).

SPATIAL NAVIGATION
Professor Lars Chittka (Queen Mary, University of London) Studying bee foraging to gain insight into navigation strategies (in partnership with the BBSRC and the EPSRC).

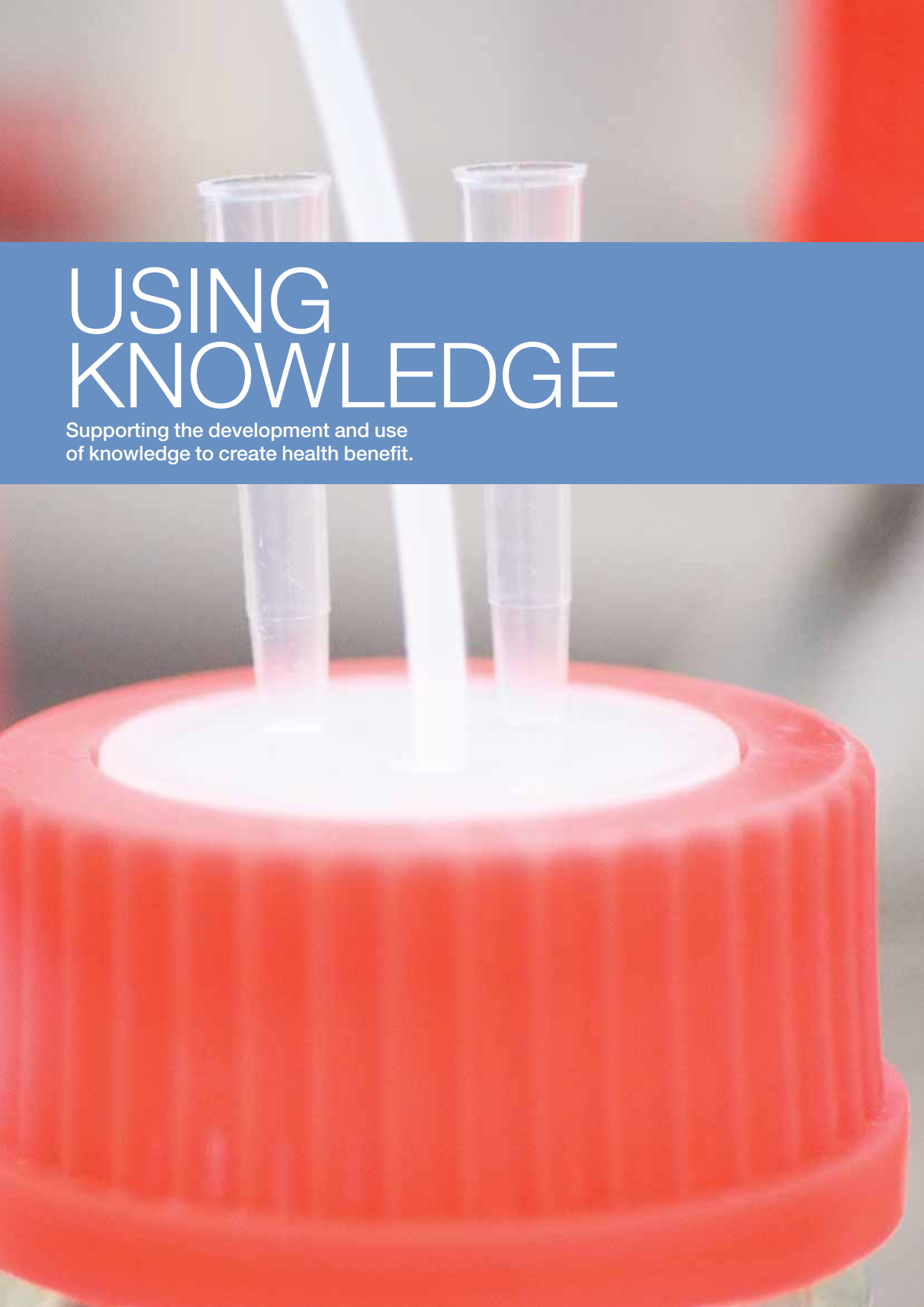
HISTORY OF MEDICINE PROGRAMME GRANT

HISTORY OF MEDICINE
Professor Mark Jackson (University of Exeter) The history of stress.

BIOMEDICAL ETHICS PROJECT GRANT

BIOMEDICAL ETHICS
Professor Stefan Priebe (Queen Mary, University of London) The ethics of financial incentives to promote medicine taking.

Details of all grants made can be found in *Grants Awarded 2006/07*, available on the Wellcome Trust website.



USING KNOWLEDGE

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

BLOOD TIES

A better understanding of blood disorders is leading to improved diagnosis and targeted therapies.

For over a century, clinicians have recognised a number of diseases, now termed the myeloproliferative disorders (MPDs), in which the bone marrow goes into overdrive and produces too many red blood cells, white blood cells or platelets. Work from the group of Professor Tony Green, at the University of Cambridge, is now revealing the molecular defects underlying these disorders, and laying the foundation for more rational diagnosis and treatment.

All the various types of blood cell originate from blood stem cells. Mutations affecting blood stem cells are thought to result in a number of blood disorders, including the MPD.

However, the origins of the MPDs (polycythaemia vera, essential thrombocythaemia and idiopathic myelofibrosis) remained obscure until 2005, when several groups, including Professor Green's, reported mutations in a gene called *JAK2*. Surprisingly a single *JAK2* mutation was found in the majority of people with polycythaemia vera and in around half of those with essential thrombocythaemia or idiopathic myelofibrosis. By analysing patient samples from a large clinical trial, Professor Green's group was also able to identify previously unrecognised disease variants and produce a new molecular classification of the MPDs. Gradually, other genetic causes are being unpicked. In 2007, for example, Professor Green's group found a new set of *JAK2* mutations and identified a novel variant of polycythaemia vera.

Together, these findings have made a dramatic impact on clinical management. A widely used molecular test is already allowing simple and more accurate diagnosis. The identification of molecular lesions not only provides a more logical basis for grouping patients, but also provides targets for novel therapies. Several *JAK2* inhibitors are being developed and the results of initial clinical studies are eagerly awaited.

Baxter EJ et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 2005;365(9464):1054–61. Erratum in: Lancet 2005;366(9480):122.

Campbell PJ et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet 2005;366(9501):1945–53.

Scott LM et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med 2007;356(5):459–68.

NET BENEFITS

Making bednets available for free has greatly increased their use in Kenya.

More than a million children die of malaria in Africa each year. This number could be dramatically slashed if more children slept beneath insecticide-treated bednets. Take-up has been limited, however. Now, Professor Bob Snow and colleagues at the Kenya Medical Research Institute–Wellcome Trust Research Programme in Kenya have shown that free supply of bednets can make a huge impact on coverage – particularly among the poor.

Although the benefits of treated bednets are well-established, how best to encourage their use is less clear. As well as the cost implications, there have been concerns that free bednets will not be valued or used. A common compromise is for bednets to be made by local suppliers and sold at a subsidised price.

But even low-cost bednets may be out of reach of many. Dr Abdisalan Noor (a Wellcome Trust Research Training Fellow) and Professor Snow therefore set out to examine how coverage was affected by cost in Kenya. In 2004, nets were available only through the commercial sector. By 2005, a campaign was making subsidised nets available.

Images

1 Cross-section of a small blood vessel containing red blood cells and a white blood cell.

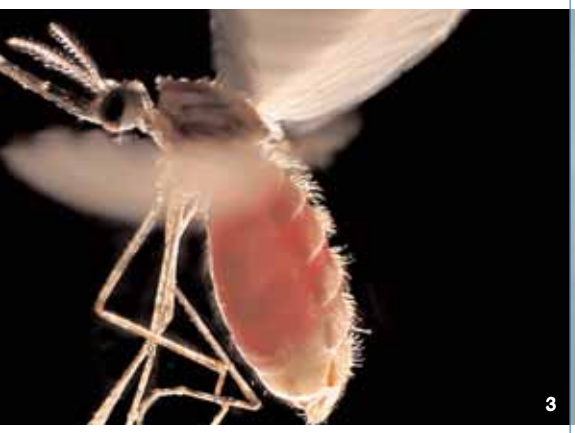
2 Bednets: free distribution greatly increases their use.

3 A malaria-transmitting mosquito after a meal of blood.

4 Mothers breastfeeding young infants in sub-Saharan Africa.

BREAST IS DEFINITELY BEST

Exclusive breastfeeding could significantly reduce the risk of HIV transmission in Africa.



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And in 2006, a mass free distribution programme began.

In 2004, bednet use was just 7 per cent. By 2005, this had risen to 24 per cent. But in 2006, it had leapt to 66 per cent. And while bednet use in 2004 was dominated by richer families, almost no difference between socioeconomic groups was seen in 2006.

Another study has stressed the benefits of providing bednets to older children and adults too. Using the latest models of mosquito behaviour and mortality, Research Career Development Fellow Dr Gerry Killeen and colleagues argue that this would kill adult mosquitoes directly or force them to undertake longer, more hazardous foraging expeditions in search of their next feed.

Noor AM et al. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS Med 2007;4(8):e255.

Killeen G et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS Med 2007;4(7):e229.

In developing countries, where most babies depend on breast milk for their survival, HIV transmission from mother to child during breastfeeding is common. Intriguingly, however, researchers at the Africa Centre for Health and Population Studies in South Africa have found that HIV transmission is far lower if mothers feed their children exclusively with breast milk for the first six months than if they also introduce formula milk or solids at this early stage.

In a study of more than 2000 new mothers in rural and urban areas, Professor Hoosen Coovadia and colleagues found that there was a 4 per cent risk of postnatal HIV transmission between the ages of six weeks and six months to babies fed on breast milk alone. Infants who received a mixture of breast milk and formula were nearly twice as likely to be infected as those receiving breast milk only. Alarmingly, those given both breast milk and solids were almost 11 times likelier than the breast-only group to acquire infection.

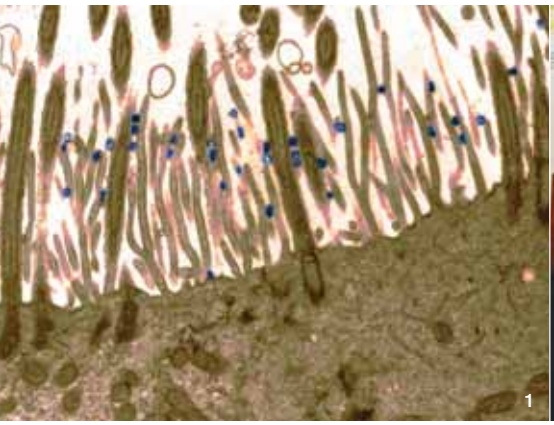
This unexpected benefit of breast milk may come about because it strengthens the baby's gut lining. The larger, more complex proteins found in formula, animal milk and solids, by contrast, may damage the intestine, allowing HIV to pass into the bloodstream more effectively.

UNICEF, the World Health Organization and UNAIDS have already revised their guidelines on infant feeding to reflect these findings. This could dramatically reduce the vertical transmission of HIV from mother to child on the African continent and beyond.

Coovadia HM et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. Lancet 2007;369(9567):1107–16.

KILL OR CURE

Survivors of H5N1 infection may hold the secret to others' survival.



The Spanish flu epidemic of 1918 killed millions. Doctors had no treatments to offer, but among the remedies tried was blood transfusion from survivors to patients. This may well have reduced mortality – and researchers at the Hospital for Tropical Diseases and the Wellcome Trust's South-east Asia Programme in Vietnam have found that an updated approach might offer protection from H5N1 avian flu.

H5N1 kills a high proportion of people it infects. But some survive, and in their bloodstream are antibodies that may prevent the virus infecting cells. To test this idea, Dr Tran Tinh Hien, Dr Cameron Simmons, Professor Jeremy Farrar and colleagues in Vietnam took blood samples from H5N1 survivors and, in collaboration with Professor Antonio Lanzavecchia in Switzerland and Dr Kanta Subbarao in the USA, developed monoclonal antibody cell lines making anti-H5N1 antibody.

A well as binding tightly to H5N1 in biochemical assays, some of these monoclonal antibodies were able to protect mice from infection and kept mice alive after exposure to a lethal dose of virus. Antibodies protected well against the strain of H5N1 people had been exposed to, but also offered protection against other H5N1 strains. A set of monoclonal antibodies of varying specificity might therefore offer an additional weapon against avian flu. Or, in an emergency, transfusions from flu survivors might enhance survival, as in the Spanish flu pandemic.

The Vietnam group is also studying the body's response to H5N1, to find out why the virus is so deadly. Animal studies have suggested that severe disease is linked to rapid virus multiplication (high viral load) and excessive release of cytokines, molecules that signal between immune cells. A comparison of patients with H5N1 and human flu conducted by Dr Menno de Jong, Dr Simmons and Dr Hien confirmed that human H5N1 infection is associated with very high viral loads and a massive cytokine response.

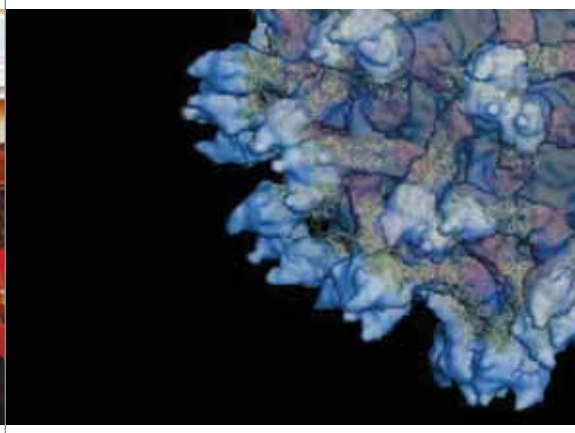
This suggests that early prevention of viral multiplication, and possibly management of the cytokine response, should be priorities in treatment of H5N1.

Simmons CP et al. Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. PLoS Med 2007;4(5):e178.

de Jong MD et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat Med 2006;12(10):1203–7.

FEVERISH ACTIVITY

Dengue is beginning to receive the attention it deserves.



Symptoms of dengue vary from mild fever through to life-threatening dengue shock syndrome or severe dengue. A resurgence of dengue in tropical regions is reawakening interest in the disease. In Vietnam, researchers are dissecting the clinical syndrome and the body's response to the virus to identify possible links to severe disease. They are also part of international collaborations tackling this growing menace.

Over the past 30 years, dengue has emerged as a major threat to health in tropical regions. It affects around 100 million people a year, with several hundred thousand experiencing the more severe form of dengue.

Several distinct strains of dengue virus exist, but the immune response to the virus is complex and poorly understood. In infants, for example, Dr Cameron Simmons and colleagues at the Wellcome Trust's South-east Asia Programme in Vietnam have found that low levels of maternal antibodies correlate reasonably (but not absolutely) with disease severity but, surprisingly, the link between viral load and disease is weak at best. These results could have significant implications for vaccine development.

Images

1 Influenza virus particles on cells lining the airways of the lung.

2 Hn, an 11-year-old girl who survived avian flu infection, with her parents.

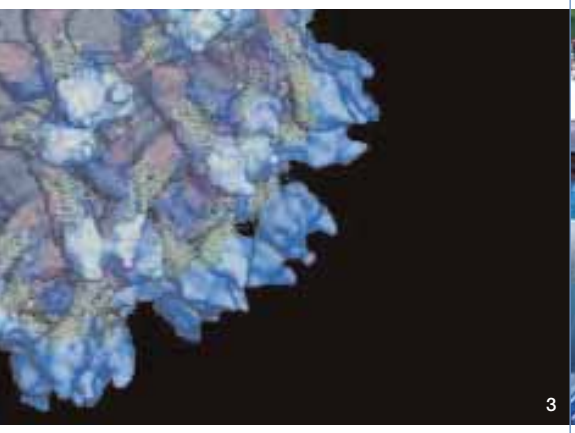
3 Dengue virus.

4 Slum conditions in Vietnam: tainted water supplies promote the spread of typhoid fever.

5 Public water supply in Bangladesh.

TYPHOID TRIAL

A vaccine for typhoid fever has completed a phase II trial.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Similarly, collaborative studies with Dr Kerstin Luhn and others in Oxford have found unusual patterns of regulatory T cell activity in dengue. As in avian flu (see left), disease seems to be triggered by excessive cytokine release. One possibility is that this over-reaction arises from defective regulatory T cell activity. Yet regulatory T cells turned out to be present and active in dengue – but seemed to be overwhelmed by the strength of the response triggered by the virus.

Emphasis is also being placed on coordinated global responses. Professor Jeremy Farrar is playing an active role in DENCO, a global dengue clinical research network, supported by the European Commission and the Wellcome Trust, which brings together clinical aspects with basic science, epidemiology and public health, spanning countries in South-east Asia, South America and Europe, and with close links to the World Health Organization.

Simmons CP et al. Maternal antibody and viral factors in the pathogenesis of dengue virus in infants. J Infect Dis 2007;196(3):416–24.

Lühn K et al. Increased frequencies of CD4+ CD25(high) regulatory T cells in acute dengue infection. J Exp Med 2007;204(5):979–85.

Farrar J et al. Towards a global dengue research agenda. Trop Med Int Health 2007;12(6):695–9.

Responsible for around 200 000 deaths a year, typhoid fever is a major global health problem. A new vaccine developed with Wellcome Trust Technology Transfer funding has recently completed a phase II clinical trial, involving children aged between five and 14 in Vietnam. Encouragingly, the vaccine was both safe and elicited good immune responses in the vaccinated children.

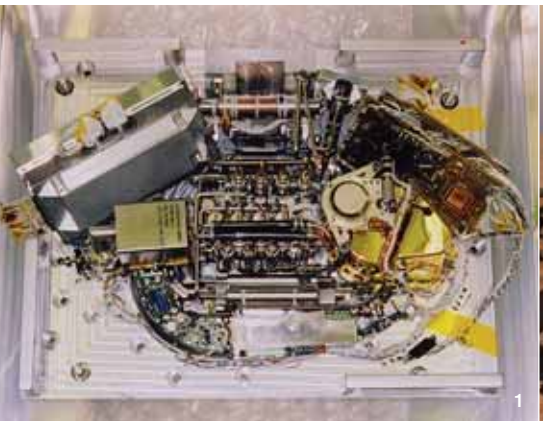
The vaccine has been developed by Emergent Biosolutions Inc., a US-based vaccine and therapeutic company. It is a single-dose drinkable vaccine based on a live attenuated strain of *Salmonella typhi*, the bacterium that causes typhoid fever. The strain has two genes deleted, which abolishes its ability to cause disease. Early development of the vaccine was carried out by Reading-based company Microscience, which later became part of Emergent Biosolutions.

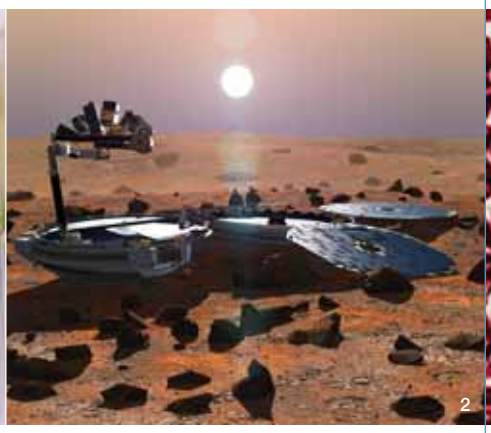
The latest trial was carried out in Vietnam, with support from Professor Jeremy Farrar and colleagues at the Wellcome Trust's Major Overseas Programme. In a double-blind randomised control trial, 101 children received vaccine and 50 placebo. There were no serious adverse events in the treated group, who showed significantly higher antibody responses to bacterial antigens. Previous trials in the UK, USA and in adults in Vietnam have also shown that the vaccine is safe and immunogenic.

Although a phase II trial does not necessarily mean that the vaccine will protect against infection, the better-than-expected results boost confidence that the vaccine will be effective in the field and pave the way for larger phase III trials.

BEAGLE BONUS

Like a phoenix from the flames, Beagle 2 lives again – or at least its technology does.





Among the instruments on board the Beagle 2 spacecraft was a prototype miniaturised mass spectrometer, the development of which was sponsored by the Wellcome Trust. The new technology, it was thought, would also filter through to other lab equipment. Indeed, it now has a potentially life-saving terrestrial application – as a new tool to diagnose TB.

Mass spectrometry is a popular laboratory technique for analysing chemical structures. Mass spec equipment, though, is large and bulky – wholly impractical for a space mission. With Trust support, Professor Colin Pillinger and Dr Geraint 'Taff' Morgan at the Open University set about miniaturising the technology so that it was suitable for interplanetary travel.

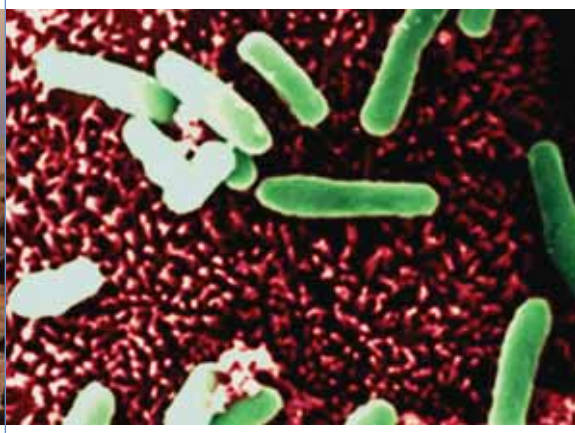
While the equipment never got to search for Martian microbes, the Open University team has adapted the technology to identify chemical products characteristic of *Mycobacterium tuberculosis*, the cause of TB. Now, with £1.34 million Technology Transfer funding, they have teamed up with Wellcome Trust Senior Clinical Fellow in Tropical Medicine Dr Liz Corbett, at the London School of Hygiene and Tropical Medicine, to develop and evaluate the technology in a resource-poor setting.

TB kills around two million people every year, mainly in developing countries. Globally, one person in three is thought to be infected with *M. tuberculosis*. But widely used methods for detecting infection, based on culture of sputum samples, are neither quick nor particularly reliable. Speed is a crucial factor. Conventional methods of diagnosis take weeks – by which time patients with TB may be gravely ill, if not dead, particularly if they are also infected with HIV.

The new device will provide results within hours, so treatment can begin immediately. It will detect the presence of a complex lipid specific for *M. tuberculosis*; integrated software, being developed by the Bioinformatics Group at Cranfield University, will analyse results and determine disease status. When the device has been shown to work under laboratory conditions, it will be trialled in Zimbabwe, where Dr Corbett is based and TB is rife.

SUPER-ANTIBIOTICS

Engineering new antibiotics may create a new tool against *C. difficile*.



MRSA and *Clostridium difficile* are major headaches for the UK public health system, and bacteria are emerging that tolerate the few effective antibiotics still available. New approaches are urgently needed, and the engineered lantibiotics being developed by Novacta Biosystems with Wellcome Trust Technology Transfer funding may provide agents that not only kill bacteria but also are less vulnerable to resistance.

Lantibiotics (lanthionine-containing peptide antibiotics) are produced by certain Gram-positive bacteria and kill other Gram-positive bacteria. They act on lipid II, a precursor needed for bacterial cell wall biosynthesis. Resistance is less likely to arise because lipid II consists of several components, and depends on the coordinated activity of several genes.

The Gram-positive bacterium *C. difficile* causes serious gastrointestinal symptoms that are potentially deadly in weak and elderly people. Although it remains sensitive to drugs such as vancomycin, infections return in up to a quarter of cases, through either reinfection or incomplete eradication.

Images

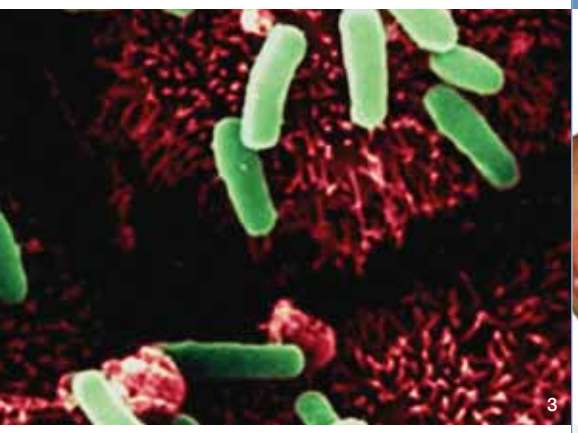
1 The miniaturised mass spectrometer.

2 The Beagle 2 spacecraft.

3 *Clostridium difficile*, a growing problem in the UK.

4 A mock-up of the i-Snake next to a model heart.

NEW FUNDING



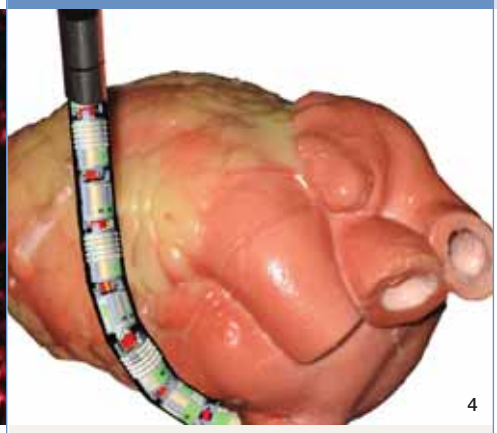
3

One reason why reinfection is so common is that vancomycin is a non-specific antibiotic that eliminates whole swathes of gut bacteria, including harmless bystanders. The gut is thus free territory for recolonisation.

Lantibiotics, by contrast, are potentially more specific. Moreover, because they are peptides made by a commonly used strain of bacteria, it is possible to engineer new peptides using genetic techniques. Through this approach, Novacta, a spin-off from the John Innes Centre in Norwich, has produced a series of lead compounds highly specific for *C. difficile* and with good pharmacological properties both in cells and in animals.

With initial Technology Transfer funding, Novacta has analysed several hundred compounds and assessed their effects on different strains of *C. difficile* and in different infected animals. The success of this research has led to £3.5 million follow-on funding to develop lead compounds by testing for safety and toxicity, with the eventual aim of testing a selected lead compound in a phase I clinical trial.

A flexible friend



4

The 'i-Snake' surgical robot will take keyhole surgery into previously unexplored territory.

Keyhole surgery was one of the great medical advances of the 20th century. Sophisticated surgical operations could be carried out with comparatively little trauma, and patients could rapidly return to normal life.

But there are limits to the procedures that can be carried out this way. The 'i-Snake', the brainchild of Professor Lord Darzi and Professor Guang-Zhong Yang of Imperial College London, will be designed to take keyhole surgery into previously inaccessible new territories. With £2.1 million of Technology Transfer funding, the multidisciplinary team is drawing inspiration from the world of herpetology, by developing a flexibly jointed robot that will navigate its way through body spaces to hard-to-reach locations.

As well as novel locomotory functions, the i-Snake's pioneering engineering will also provide multiple sensing mechanisms and imaging tools at its 'head', so it will be manoeuvrable with a high degree of precision. Therefore the surgeon will be able to visualise the i-Snake's journey and use a suite surgical tools, located within its core, when it arrives at the site of the disease.

Among many possible applications are clinical investigation of the alimentary tract or complex multi-vessel coronary bypass surgery.

A selection of notable grants awarded in 2006/07.

SEEDING DRUG DISCOVERY TRANSLATION AWARDS

OBESITY
Professor Stephen Bloom (Imperial College School of Medicine) Novel analogues of pancreatic polypeptide Y4 as antiobesity agents.

ANTIBIOTICS
Dr David Payne (GlaxoSmithKline) Novel antibacterials for Gram-negative pathogens.

ANTIBIOTICS
Dr Lloyd Czaplewski (Prolysis Limited) Novel compounds to treat life-threatening, drug-resistant staphylococcal infections.

MULTIPLE SCLEROSIS
Dr Roland Kozlowski (Lectus Therapeutics Ltd) Novel Kv1.3 ion channel inhibitors for the treatment of multiple sclerosis.

INFLAMMATION
Professor David Ray (University of Manchester) Refining glucocorticoid receptor agonists for the treatment of inflammatory conditions.

CANCER
Professor Ashok Venkitaraman (Sentinel Ltd) Refining cytotoxic compounds activated in hypoxic environments for use in glioblastoma treatment.

OTHER TRANSLATION AWARDS

VACCINE DEVELOPMENT
Dr Andrew J Pollard (University of Oxford) A recombinant Opa protein vaccine for meningococci.

PRF PROGRAMME GRANT RENEWAL

DEPRESSION
Professor Mark Williams (University of Oxford) Developing and testing cognitive behavioural therapies for people at risk of suicide.

PROJECT GRANTS

TUBERCULOSIS
Professor Juraj Ivanyi (King's College London) and **Dr Jenny Woof** (University of Dundee) Evaluating an engineered human IgA antibody specific for the alpha-crystallin antigen of *M. tuberculosis*.

MALIGNANT HYPERTHERMIA
Professor Philip Hopkins (University of Leeds) A blood-based screening test for malignant hyperthermia, an inherited abnormality of muscle metabolism.

DEPRESSION
Professor Ricardo Araya (University of Bristol) A trial of a psychological intervention for adolescent depression in poor areas of Santiago, Uruguay.

Details of all grants made can be found in *Grants Awarded 2006/07*, available on the Wellcome Trust website.

ENGAGING SOCIETY

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

A TASTY TREAT

Some 70 000 members of the public visited Wellcome Collection in its first three months.

1

2

Wellcome Collection, the new £30 million visitor attraction from the Wellcome Trust, was opened at an evening gala reception on 20 July 2007 by James Watson and Stephen Fry – who enthused: "One of the most remarkable collections of medical and physiological items ever assembled is united with three intelligent, inspiring and intriguing exhibitions to make as compelling a visit as London has to offer."

Wellcome Collection is the transformation of the Wellcome Building, the former headquarters of the Wellcome Trust, at 183 Euston Road, London. It provides stimulating insight into the human condition, combining cultural, scientific and artistic frames of reference.

"A new museum that is unashamedly 'braining up'," applauded Nigel Richardson in the *Daily Telegraph*. "You will spill back on to the Euston Road feeling both exhilarated and ever so slightly more intelligent."

"A treasure," agreed the Londonist website: "London's best new galleries in years." Writing in the *Independent*, Janet Street-Porter called it: "One of the most thought-provoking exhibitions I've been to in years." Even the *Sun*, not usually known for its coverage of either art or science, devoted a double-page spread to its delights.

The nine-storey building houses three galleries. The largest of these, on the ground floor, hosts temporary themed exhibitions, opening with *The Heart* (see right).

The other two galleries house two permanent exhibitions. *Medicine Man*, previously shown at the British Museum, contains more than 500 artefacts from Sir Henry Wellcome's original collection, including a lock of George III's hair and Napoleon's toothbrush. And *Medicine Now* explores contemporary medical topics such as obesity and genomes through the eyes of scientists, artists and popular culture.

The exhibitions are supplemented by a lively programme of public events, where audiences can explore and debate current issues and ancient mysteries of human wellbeing.

All the visitor attractions have been positively received. Even the Peyton and Byrne café gained rave reviews: "This cheerful spot is welcome indeed," concluded Jenni Muir in *Time Out*.

HEART STARTING

A Wellcome Collection exhibition explored the many meanings of the heart.


3

***The Heart* – the opening temporary exhibition in the new £30 million Wellcome Collection – explored the medical and cultural significance of the heart, through attractions as diverse as drawings of an ox heart by Leonardo da Vinci, prints by Andy Warhol and (for the non-squeamish) live heart surgery.**

Curated by James Peto and Emily Jo Sargent, the exhibition encouraged audiences to contemplate the heart's anatomical and symbolic power through the ages.

Medical understanding of the heart has developed considerably over time. Drawings by Leonardo da Vinci and mid-17th-century anatomical tables onto which entire human blood vessels were varnished illustrate early attempts to understand its function. A modern perfusion machine is a reminder that we now know enough to mimic the heart.

But the heart also has powerful cultural symbolism. The ancient Egyptian Book of the Dead shows the heart being weighed against the 'feather of truth' in order to determine the deceased's suitability for the afterlife. Hearts also appear on poignant 19th-century playing cards. They are cut in half – one half accompanied a child going to a

Images

1 Stephen Fry in the *Medicine Now* gallery in Wellcome Collection.

2 Infant identification kit, in Wellcome Collection's *Medicine Man* exhibition.

3 'Our Lady of the Seven Sorrows', an exhibit in *The Heart* exhibition.

4 Modern heart surgery, inside *The Heart*.

5 Continuing the debate (L–R): James Munro, Andy Davis and Gunes Taylor from Weston College at the Debating Matters national final.

MOTION CARRIED

Through Debating Matters, sixth formers rigorously debate contemporary real-world issues hitting the headlines.


4


5

Foundling Hospital while the child's mother retained the other half so that she might be able to reclaim her child in later life.

That the heart continues to fascinate was evident from the 35 000 visitors who came specifically to see the exhibition. Some 200 attended the live broadcast of heart surgery from Papworth Hospital in July 2007 – tickets for which sold out within a day.

A notable visitor was Jennifer Sutton, 23, from Ringwood, Hampshire – who underwent a heart transplant at Papworth in June 2007 and lent her original heart to Wellcome Collection. Within weeks, she came to view the organ that nearly killed her.

The multifaceted view of the heart was carried through to a successful symposium, 'Matters of the Heart', and a book edited by James Peto, *The Heart*, published by Yale University Press. "In an age when research is increasingly sophisticated, and often seemingly inaccessible," said the *Lancet* in its review, "an intelligent impression of the cultural and social implications of these marvellous achievements is uplifting and most uniquely welcome."

More than 200 schools – 85 per cent from the state sector – and 2000 students have participated in the Debating Matters competition since 2004, when the Wellcome Trust provided funding to the Institute of Ideas through an Engaging Science Society Award. More than a third of the schools had never previously been involved with debate.

The Institute of Ideas and Pfizer Debating Matters competition was piloted in 2003 and is now well established as the country's leading schools debating competition. Sixth-form students in eight UK regions debate issues that impact on the world, and the way in which we understand and shape it. Many of these issues have a scientific strand to them.

In their preparation, students are expressly asked to find the evidence they need to support their case. During the competition, judges from a range of professional backgrounds pose questions and prompt students to develop and defend their arguments. At the end, they offer critical but constructive feedback.

The focus is on the quality of the arguments and response to questions from the judges, the opposing team and the audience. Students need not only to make a convincing case, but also to think on their feet. Time and time again, students have shown that they can rise to the challenge.

The National Final 2006/07 took place at King's College London and the National Portrait Gallery, with Mark Walport, Director of the Wellcome Trust, as one of the judges. Queen Elizabeth's Sixth Form College from the North East won the first prize, after a close-fought round on human genetics, with Elfed High School from north Wales as runners-up.

Students taking part have been enthusiastic. Ryan Devlin from Winstanley College, Wigan, said: "School life completely changed when we got involved with Debating Matters. Suddenly we were sitting around talking about huge global issues. It was revelatory."

ACTION AND INFLUENCE

New courses, a move into new areas and an expanded remit marked a successful year for the National Science Learning Centre.

In its second operational year, the National Science Learning Centre in York delivered nearly 4000 training days to more than 1500 teaching staff, over 90 per cent of whom scored their experience as good or excellent.

As well as this practical support, the Centre also fed into education policy making, with its Director, Professor John Holman, being appointed the UK Government's National STEM Director in October 2006, with a remit to coordinate the UK's science, technology, engineering and mathematics (STEM) activities across schools and other centres of learning.

The National Science Learning Centre opened in 2005, part of a £51 million partnership with the Department for Children, Schools and Families to provide high-quality continuing professional development opportunities for science teachers and technicians.

As well as more training days, the Centre also added 44 new courses, and now offers 76 in total. These range from a summer school for newly qualified teachers through to 'Leadership for Impact: New and aspiring heads of science', which will form one third of a new MA in Science Education and Leadership being offered by the University of York.

A Network Projects Director was appointed in December 2006 to coordinate activities across the ten Science Learning Centres. The National Centre also began developing a bid, with the regional Centres, to create a united network of Science Learning Centres across England.

The Centre has also worked closely with other key bodies in education, such as the Qualifications and Curriculum Authority, with which the Centre ran a series of workshops on curriculum development, and the Training and Development Agency for Schools.

Professor Holman's appointment as National STEM Director will help to ensure that Science Learning Centres are integral to initiatives promoting STEM education. The STEM programme is underpinned by the STEM High Level Strategy Group, which offers advice to ministers on national priorities and includes a representative from the Wellcome Trust.

HEROES OF WAR

A new docu-drama recounts a remarkable mercy mission.

***The Relief of Belsen*, a feature-length drama-documentary telling one of the most extraordinary stories to emerge from World War II, premiered on 15 October 2007 on Channel 4.**

On 17 April 1945, a British ambulance unit accompanying the drive to Berlin was ordered instead to a newly liberated prison camp in northern Germany to handle an outbreak of typhus. That camp was Bergen-Belsen.

The arriving British unit found 40 000 prisoners starving and living in squalor, including, in one hut designed for 100, 1346 people – not counting the dead.

Over the next few weeks, an international team of doctors, nurses, former inmates, soldiers and local Germans, led by the medical corps of the British Army, worked to try to save the dying prisoners of Belsen, while the war continued to rage throughout Europe. In the process, they created the biggest hospital in Europe.

The Relief of Belsen tells this story, using scripted drama, testimony and extensive news footage from the 'horror camp'. It received a Wellcome Trust Public Engagement Award in the History of Medicine to ensure its medical and historical authenticity.

Images

1 A practical demonstration at the National Science Learning Centre in York.

2 Teachers share thoughts during the course at York.

3 Treating one of the patients at Belsen.

4 A scene from *The Relief of Belsen*, screened on Channel 4.

5 Part of the Centre of the Cell visitor attraction.

NEW FUNDING


4

It was made by the producers of the award-winning film *Trafalgar Battle Surgeon*, also part-funded by the Trust, which was watched by some 1.4 million viewers on Channel 4 in August 2005. The critically acclaimed film, which garnered a 2005 Royal Television Society Award, examined the role of Sir William Beatty, surgeon on *HMS Victory*, and Navy doctors in the Battle of Trafalgar.

Film-making can play an important role raising awareness and interest in science and medicine. As well as these high-profile projects, the Trust has funded many others that engage a variety of audiences. This area is poised to become a bigger part of the Trust's public engagement activities over the coming years.

Nuclear medicine


5

An innovative visitor centre situated in a medical school will provide young people with an exciting insight into medical science.

The Centre of the Cell, recipient of a £600 000 Public Engagement grant from the Wellcome Trust, is sited within the research laboratories of Barts and The London, Queen Mary's School of Medicine and Dentistry. It aims to inspire and engage young people, and show more clearly how modern science is underpinning today's medical advances.

The attraction, masterminded by Professor Fran Balkwill, a renowned cancer researcher and author of several highly illustrated science books for children, has attracted funding from several sources. The Trust's contribution is for the nucleus of the cell, fittingly its central focus. It will feature a mix of interactive games and audiovisual shows, all highlighting the central place of the cell in life, health and disease.

The Centre of the Cell aims to attract school visits from schools in the local area, one of the poorest parts of London. The hope is that the inspiring experience on offer will encourage young children to consider a career in science and to think more deeply about the place of science in modern life.

A selection of notable grants awarded in 2006/07.

SOCIETY AWARDS

FILM
Jane Stephenson (Media Trust)
'My Illness': a series of 30-minute films on patients' experiences of different illnesses.

EDUCATION
Dean Madden (University of Reading)
'From DNA to Darwin': education activities illustrating molecular evidence for evolution.

PEOPLE AWARDS

NEW MEDIA EDUCATION
Kam Memarzia (PlayGen Ltd)
An interactive video game for 12- to 16-year-olds about biomedical science at the nanoscale.

THEATRE
Mark Sands (Deafinitely Theatre)
Playing God: a play about the ethical issues surrounding cochlear implants for deaf children.

THE FACE
Helen Middleton-Price (Nowgen)
A programme of events at the Manchester Science Festival themed around the face.

ARTS AWARDS

THE BRAIN
Tina Gonsalves, **Chris Frith** and **Hugo Critchley**
'Chameleon': an interactive, audiovisual installation, developed jointly by an artist, neuroscientists and computer scientists, exploring the communication of emotional states.

INFECTIOUS DISEASE
Steve Ball (Birmingham Repertory Theatre)
The Speckled Monster: a site-specific, interactive theatre production and science education programme for young people, based on a historical local smallpox outbreak.

HISTORY OF MEDICINE PUBLIC ENGAGEMENT

MENTAL ILLNESS
Joe Matthews (Seneca Productions)
A drama-documentary based on Bethlem Hospital.

Details of all grants made can be found in *Grants Awarded 2006/07*, available on the Wellcome Trust website.

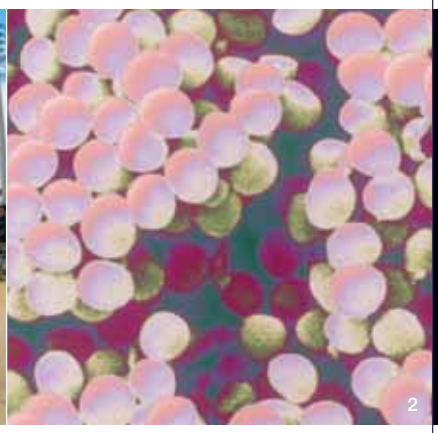
DEVELOPING PEOPLE

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

OF TYPHOID AND TOADS

A research programme in Thailand and Laos is helping to enhance regional research capacity.

1


2

The South-east Asia Major Overseas Programme is based in Bangkok, Thailand, and Ho Chi Minh City, Vietnam. Satellite units exist in these countries, with collaborations in several nearby countries, including a long-standing partnership with Laos.

Sandwiched between Vietnam and Thailand, Laos is a predominantly rural country of around 6.5 million people. Since 1999, the Thai unit has been collaborating with researchers at Mahosot Hospital, Vientiane. The research, which is led by clinicians Dr Paul Newton, Dr Mayfong Mayxay (a former Wellcome Trust fellow) and Dr Rattanaphone Phetsouvanh in Vientiane, concentrates on infectious diseases, to support evidence-based clinical practice and health policy.

Malaria has been a key priority. An analysis of malarial parasites, and cure rates in malaria patients, has revealed high levels of resistance to chloroquine and sulphadoxine-pyrimethamine. This, and other evidence, has led to the government of Laos changing treatment policy to artemisinin-based combination therapy.

Bacterial infections have also been an important focus. As in much of Asia, the causes of fever in Laos are poorly understood. Studies have uncovered a surprisingly high incidence of typhoid fever, identified *Staphylococcus aureus* as the main cause of septicaemia in the under-ones, and revealed unexpectedly high incidences of scrub typhus, murine typhus and leptospirosis. Such information is important as it has guided changes in the use of suitable antibiotics. Although Laos does not yet have a serious problem with drug-resistant bacteria, nearby countries do and there is a risk that such strains will be introduced or arise *de novo*.

But research extends beyond infectious diseases: the Laos team recently came across cases of fatal heart damage in children who had eaten the skin and eggs of a common toad, *Bufo melanostictus*. Interviews suggested that toad poisoning may be relatively common and a significant public health issue.

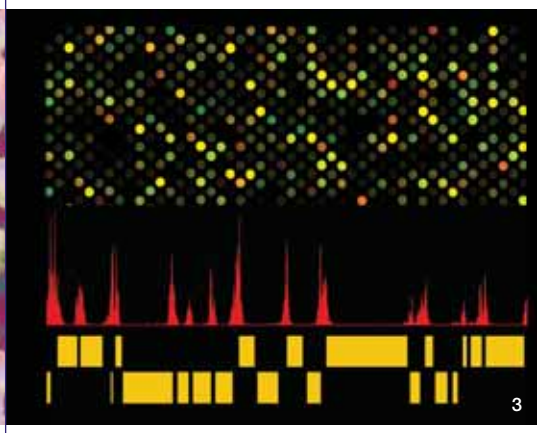
Mayxay M et al. Combined molecular and clinical assessment of Plasmodium falciparum antimalarial drug resistance in the Lao People's Democratic Republic (Laos). Am J Trop Med Hyg 2007;77(1):36–43.

Phetsouvanh R et al. Causes of community-acquired bacteremia and patterns of antimicrobial resistance in Vientiane, Laos. Am J Trop Med Hyg 2006;75(5):978–85.

Keomany S et al. Toad poisoning in Laos. Am J Trop Med Hyg 2007;77(5):850–3.

MODIFIED BY ASCENT

Fruitful studies of DNA–protein interactions are helping a young researcher up the career ladder.


3

How do histone proteins control gene activity? Dr Catherine Millar, a Wellcome Trust International Prize Travelling Fellow awarded a Research Career Development Fellowship this year, is using yeast to understand some of the intricacies of gene control.

Dr Millar studied for her PhD in Professor Adrian Bird's laboratory in Edinburgh, focusing on a protein known as MBD4.

From Edinburgh, she moved to the laboratory of Professor Michael Grunstein at the University of California, Los Angeles. Her work there shifted to the modification of histones and their possible role in controlling gene activity.

Dr Millar's focus has been a variant of histone H2A known as Htz1 in yeast. Although Htz1 is found mainly at inactive genes, acetylation at one particular point is associated with active genes. Now in Manchester, Dr Millar is using her Fellowship to establish a group to probe more deeply into Htz1 function.

Millar CB et al. Enhanced CpG mutability and tumorigenesis in MBD4-deficient mice. Science 2002;297(5580):403–5.

Millar CB et al. Acetylation of H2AZ Lys 14 is associated with genome-wide gene activity in yeast. Genes Dev 2006;20(6):711–22.

Images

1 Hmong farming women in Laos.

2 *Staphylococcus aureus*, the main cause of septicaemia in under-ones in Laos.

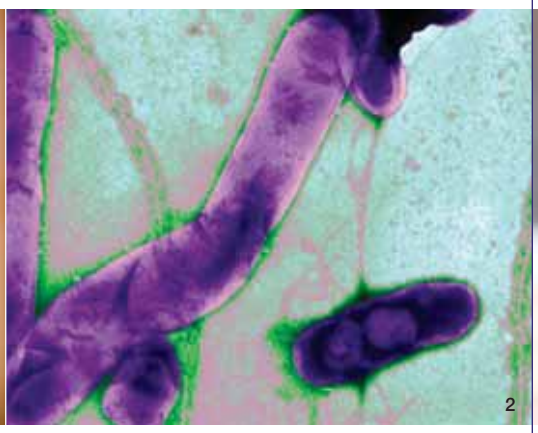
3 Htz1 binding sites mapped using whole-genome microarrays.

Left:
Dr Catherine Millar, a new Research Career Development Fellow at Manchester.

GUT REACTION

How regulatory T cells orchestrate immune responses in the gut is gradually being revealed.

1



2

The cells in the intestinal wall have a tricky balancing act to perform. They must generate an immune response to defend the body against pathogens in the gut but must not react to dietary antigens or the symbiotic microbes that have made it their home. Research led by Professor Fiona Powrie, Wellcome Trust Senior Research Fellow at the University of Oxford, is piecing together the complex web of interactions that maintain this delicate balance.

It is becoming increasingly clear that the gut's immune mechanisms play a key role in our defence – but also contribute to common medical complaints. Around 1 in 1000 people in developed countries endures inflammatory bowel disease (IBD), where an overactive immune system ends up damaging the body's own tissues.

A possible answer to the miseries of IBD may lie with regulatory T cells: immune cells exciting great interest because of the ability to turn off unwanted immune responses. Professor Powrie's research has revealed much about how these cells operate, both in normal health and in inflammatory conditions such as IBD.

Of particular interest has been the discovery that, unlike most tissues, the gut does not depend only on regulatory T cells from the thymus – it produces its own. This production is dependent on a classical regulatory T cell stimulus, TGF-ß, and the vitamin A metabolite retinoic acid. It also appears that regulatory T cells occupy a distinct location in the gut tissue.

Professor Powrie's group has also identified factors that may tip the intestinal balance towards over-reaction. The cytokine IL-23, for example, seems to be specifically involved in promoting inflammatory reactions in the gut – and is thus an exciting new target for IBD therapies.

Coombes JL et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. J Exp Med 2007;204(8):1757–64.

Uhlig HH et al. Characterization of Foxp3+CD4+CD25+ and IL-10-secreting CD4+CD25+ T cells during cure of colitis. J Immunol 2007;177(9):5852–60.

Hue S et al. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. J Exp Med 2006;203(11):2473–83.

Kullberg MC et al. IL-23 plays a key role in Helicobacter hepaticus-induced T cell-dependent colitis. J Exp Med 2006;203(11):2485–94.

ONE, TWO, MANY

A single-gene disorder has proven more tractable than a complex condition.

Genetic studies can identify the factors underlying behavioural conditions, providing clues to underlying biological mechanisms. In a recent example, a team led by Professor Jonathan Flint (recently awarded a Principal Research Fellowship) identified a mutation causing lissencephaly, a rare condition in which the migration of neurons through the brain is disrupted during early development. But unlike single-gene disorders, genetic analysis of complex behavioural traits remains challenging.

The lissencephaly story begins with a large-scale mutagenic study of mice, and a search for animals with unusual behavioural traits. One such animal showed abnormalities in brain structure and neuron migration similar to those seen in other strains with lissencephaly-like features. The animal had acquired a mutation in a tubulin gene, which affected its ability to make microtubules, components of the cell's internal skeleton.

The similarity between the mouse mutants led the team to screen for tubulin mutations in people with lissencephaly of unknown cause. Two such individuals had mutations

Images

1 Professor Fiona Powrie, a Senior Research Fellow at the University of Oxford.

2 Intestinal bacteria.

3 Professor Jonathan Flint, a new Principal Research Fellow at the University of Oxford.

4 A typical site of schistosome transmission, Lake Victoria in Uganda.

5 The head of a schistosome parasite.

A FLUKE OF NATURE

Wide-scale programmes are underway to tackle schistosome parasites in Africa. But is the impact of such interventions fully understood?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affecting the human version of the mouse tubulin gene. Follow-up studies identified tubulin mutations in six more people with a range of neuro-developmental conditions.

But unlike single-gene abnormalities, genetic dissection of behavioural traits or neuropsychiatric conditions remains difficult. For example, a large-scale whole-genome scan for factors associated with neuroticism failed to identify genes clearly associated with the trait, even though twin studies imply that genes are important. Possibly, many rare interacting factors underlie such traits – and hence very large studies will be needed to identify them unambiguously.

Keays DA et al. Mutations in alpha-tubulin cause abnormal neuronal migration in mice and lissencephaly in humans. Cell 2007;128(1):45–57.

Poirier K et al. Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (TUBA1A). Hum Mutat 2007;28(11):1055–64.

Shifman S et al. A whole genome association study of neuroticism using DNA pooling. Mol Psychiatry 2007 [Epub ahead of print].

In Uganda, two Wellcome Trust-funded fellows – Dr Simon Brooker and Dr Alison Elliott – are aiming to find out more about the impact of schistosomes and their control.

Control of infections calls for a good understanding of where they occur. Transmission will vary across a country, and information is rarely available for every region. Nonetheless, by combining field data with climate data acquired from remote sensing systems, spatial patterns can be modelled, helping to fill gaps in survey data.

Using this approach, Dr Brooker, a newly appointed Career Development Fellow at the London School of Hygiene and Tropical Medicine (LSHTM), and colleagues have developed a predictive map of infection risk. By reducing the need for expensive field surveys, the approach has made national control efforts economically feasible, and has helped to guide control in Uganda, as part of the Gates Foundation-financed Schistosome Control Initiative. Other work has evaluated the health impact and cost-effectiveness of control.

On the other hand, schistosome infections are so common that they frequently overlap with other infections, such as HIV/AIDS or TB. HIV is known to accelerate TB disease, and Dr Elliott, who holds a Career Post in Clinical Tropical Medicine at the LSHTM, has discovered that schistosomes further accelerate TB progression in HIV-infected individuals.

Nevertheless, most helminth infections go unnoticed, as the parasite blocks the host's immune response. And while this might promote other infections, or interfere with BCG vaccination, it may actually have benefits – protecting against severe malaria or allergic conditions. Dr Elliott is therefore leading a clinical trial in Uganda examining the effects of de-worming treatments of pregnant mothers and children on infection and responses to vaccination.

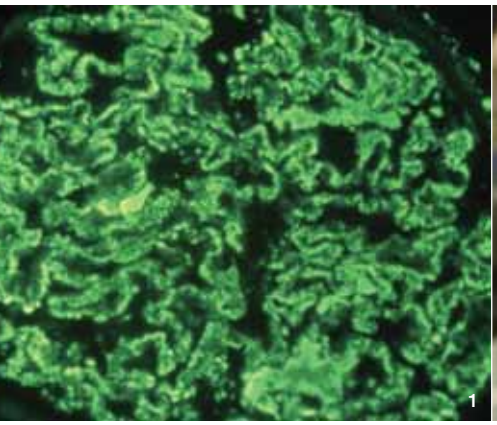
Clements AC et al. Bayesian geostatistical prediction of the intensity of infection with Schistosoma mansoni in East Africa. Parasitology 2006;133(Pt 6):711–9.

Kabatereine NB et al. Impact of a national helminth control programme on infection and morbidity in Ugandan schoolchildren. Bull World Health Organ 2007;85(2):91–9.

Brown M et al. Schistosoma mansoni, nematode infections, and progression to active tuberculosis among HIV-1-infected Ugandans. Am J Trop Med Hyg 2006;74(5):819–25.

THE H FACTOR

The complex role of factor H in kidney disease is gradually being unravelled.



The complement system is an important part of the body's defences against infection. It is based on a complex cascade of reactions that ultimately generates a protein superstructure that destroys invading cells. Given this firepower, complement must be kept under tight control. The bloodstream protein factor H plays a crucial role in this control, and deficiencies in its activity have been linked to several diseases. At Imperial College London, new Wellcome Trust Senior Research Fellow Dr Matthew Pickering has been clarifying the role of factor H in kidney disease.

Exactly how factor H contributes to disease processes is not always clear. Using transgenic mice lacking factor H, Dr Pickering has been teasing these processes apart.

Complement activation has been implicated in an inflammatory kidney disease, membranoproliferative glomerulonephritis type 2, also known as dense deposit disease. The disease develops spontaneously in mice lacking factor H. However, its severity is reduced in the absence of complement protein C5. In addition, antibody-triggered kidney disease is prevented when animals lacking factor H are given anti-C5 antibody. As well as implicating C5 in the disease, these findings identify C5 as a potentially important drug target.

Factor H has also been linked to retinal degeneration and a rare kidney disease of children, atypical haemolytic uraemic syndrome (aHUS). The genetic factors driving the nephritis seen in mice lacking factor H appear distinct from those linked to aHUS. This appears to reflect the impact of different mutations in the factor H gene. Indeed, when transgenic mice were created with the aHUS version of the factor H gene, the animals developed signs of aHUS.

These mice are important as they represent the first animal model of aHUS. They pinpoint complement activation on kidney endothelial cells as the key site of damage and open up the prospect of testing targeted therapies.

Pickering MC et al. Prevention of C5 activation ameliorates spontaneous and experimental glomerulonephritis in factor H-deficient mice. Proc Natl Acad Sci USA 2006;103(25):9649–54.

Pickering MC et al. Spontaneous hemolytic uremic syndrome triggered by complement factor H lacking surface recognition domains. J Exp Med 2007;204(6):1249–56.

ASSEMBLING A CAREER

How proteins aggregate is the focus of a new Sir Henry Wellcome Fellow.

Sir Henry Wellcome Fellowships were introduced in 2006 to provide researchers early in their careers with a unique opportunity to develop their research. Among the first batch of successful applicants was Dr Thomas Jahn, whose interests lie in the mechanisms driving abnormal folding of proteins implicated in neurodegenerative disorders such as Parkinson's and Alzheimer's disease.

Dr Jahn studied biochemistry at the University of Halle, before being awarded a place on the Four-year PhD Programme at the University of Leeds. Under the supervision of Professors Sheena Radford and Steve Homans, he used a variety of biophysical techniques to study the folding of beta-2-microglobulin.

This protein shows a natural tendency to aggregate into fibrils similar to those seen in Alzheimer's disease (amyloid fibrils), resulting in the disorder dialysis-related amyloidosis. The structural studies showed that beta-2-microglobulin first converts into a partially unfolded intermediate form that has a high propensity to bind further copies, polymerising into a fibril.

Images

1 Membranous glomerulonephritis.

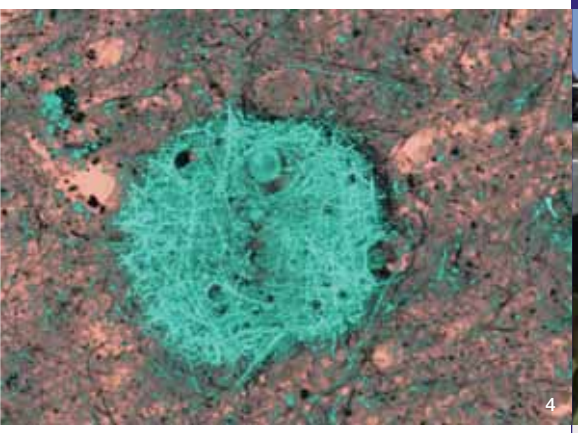
2 Dr Matthew Pickering, a new Senior Research Fellow at Imperial College London.

3 Dr Thomas Jahn, one of the first Sir Henry Wellcome Fellows.

4 An amyloid plaque, as seen in Alzheimer's disease.

5 Dairy cows.

NEW FUNDING



With his new Fellowship providing £250 000 support over four years, Dr Jahn is moving to the University of Cambridge to study variants of alpha-synuclein, a protein implicated in Parkinson's disease. He plans to combine biophysical analysis with studies of accumulation in the brain of living fruit fly, to try to identify biochemical features that are predictive of protein aggregation in living cells. The move to Cambridge will also facilitate collaboration with the groups of Dr Michele Vendruscolo and Professor Christopher Dobson in the Department of Chemistry.

Jahn TR, Radford SE. Folding versus aggregation: polypeptide conformations on competing pathways. Arch Biochem Biophys 2007;469(1):100–17.

Smith AM et al. Direct observation of oligomeric species formed in the early stages of amyloid fibril formation using electrospray ionisation mass spectrometry. J Mol Biol 2006;364(1):9–19.

Jahn TR et al. Amyloid formation under physiological conditions proceeds via a native-like folding intermediate. Nat Struct Mol Biol 2006;13(3):195–201.

Animal insights

Clinical veterinary research will benefit from a new £10.7 million initiative.

Veterinary research is important not just to the future health of animals. Diseases that jump species from animals to humans are a constant threat to human health – SARS and H5N1 avian flu being just two recent examples.

The Wellcome Trust's new clinical veterinary initiative, being run in partnership with the seven UK veterinary schools and coordinated by Professor Sandy Trees from the University of Liverpool, aims to create a community of 'clinically literate researchers and research-literate clinicians'.

Funding of £7m will be used to create three types of fellowship for different career stages: one-year Research Entry Fellowships, Integrated Training Fellowships towards a PhD, and Postdoctoral Fellowships. These awards will be administered by the Trust.

The remaining £3.7m of funding will be available for small grants such as laboratory animals training, vacation scholarships, intercalated awards and summer schools.

A selection of notable grants awarded in 2006/07.

PRINCIPAL RESEARCH FELLOWSHIPS

T CELLS
Professor Gillian Griffiths (University of Cambridge) Secretion mechanisms of cytotoxic T lymphocytes.

ALZHEIMER'S DISEASE
Professor Peter St George-Hyslop (University of Cambridge) Molecular and cellular studies of presenilins in Alzheimer's and other diseases.

SENIOR RESEARCH FELLOWSHIP IN CLINICAL SCIENCE

EPIDEMIOLOGY
Professor Liam Smeeth (London School of Hygiene and Tropical Medicine) Making better use of computerised clinical data for epidemiological research.

SENIOR RESEARCH FELLOWSHIPS IN BASIC BIOMEDICAL SCIENCE

CELL BIOLOGY
Dr Blanche Schwappach (University of Manchester) Assembly-dependent transport of multimeric membrane proteins to the cell surface.

VIROLOGY
Dr Ian Goodfellow (Imperial College London) Mechanisms of norovirus replication.

INTERNATIONAL SENIOR RESEARCH FELLOWSHIP

CELL SIGNALLING
Dr Attila Remenyi (Eotvos Lorand University, Hungary) Protein scaffolds organising MAP-kinase-mediated signal transduction.

RESEARCH CAREER DEVELOPMENT FELLOWSHIP

NEUROSCIENCE
Dr James Kilner (University College London) Applying statistical approaches to the mirror neuron system.

SIR HENRY WELLCOME POSTDOCTORAL FELLOWSHIP

EMERGING INFECTION
Dr Shelly Cook (Natural History Museum) Vector and host biology and genetic diversity of flaviviruses.

RESEARCH TRAINING FELLOWSHIPS

CHILD PSYCHOLOGY
Dr Helen J Baker-Henningham (University of the West Indies, Jamaica) Young children's social and emotional competence.

HISTORY OF MEDICINE FELLOWSHIP

WOMEN'S HEALTH
Dr Elizabeth Toon (University of Manchester) Screening and women's health in the UK, 1960–2000.

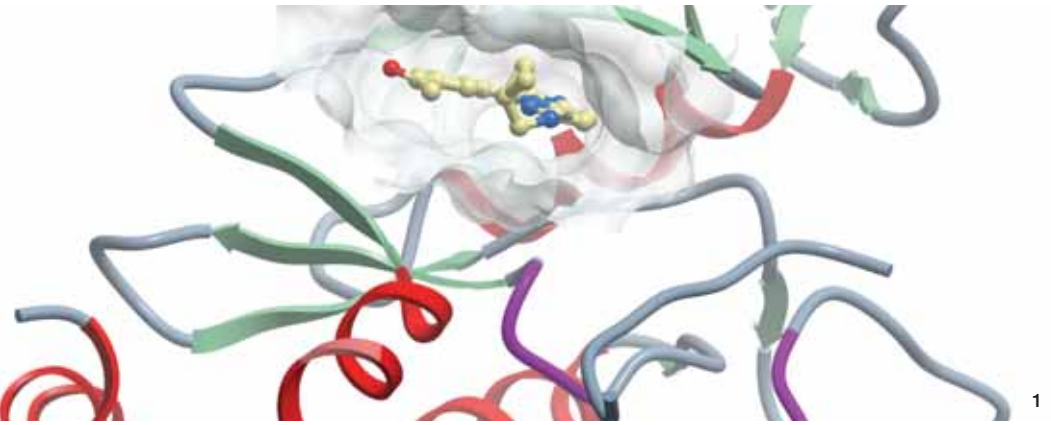
Details of all grants made can be found in *Grants Awarded 2006/07*, available on the Wellcome Trust website.

FACILITATING RESEARCH

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

STRUCTURAL SUCCESS

The Structural Genomics Consortium is generating new drug leads as well as new knowledge.



1

The Structural Genomics Consortium (SGC), operating out of labs in Oxford, Toronto and Stockholm, is bringing a high-throughput approach to protein structure determination. The SGC has significantly boosted the numbers of structures being released, and is responsible for almost one in four of all protein structures going into public databases. And the freely released information is of value in both fundamental research and targeted drug development.

Modification of histones has emerged as an important mechanism controlling gene activity. Accordingly, much attention has been focused on the enzymes that add or remove these modifications. Of particular importance is how the exquisite specificity of these enzymes is achieved.

A structural study of the JMJD2A demethylase, which removes methyl groups from a pair of lysine residues on histone H3, provides some answers. Stanley Ng, a graduate student at the SGC and the University of Oxford, determined the structure of the enzyme bound to histones with different forms of methylated lysines.

This structural analysis will help to clarify the molecular basis of histone modification, and may also be a starting-point for the development of chemical inhibitors.

New chemical leads are also arising from work on PIM kinases, a class of enzymes involved in cell signalling. Structural studies revealed an unusual binding site for a particular class of inhibitors (imidazo[1,2-b]pyridazines). Unlike similar inhibitors, they block access of ATP to the enzyme's active site rather than competing directly at the actual binding site. They are thus more selective inhibitors. One of the more active inhibitors suppressed the growth of a variety of leukaemic cell lines, illustrating their promise as targets for therapeutic intervention.

Ng SS et al. Crystal structures of histone demethylase JMJD2A reveal basis for substrate specificity. Nature 2007;448(7149):87–91.

Pogacic V et al. Structural analysis identifies imidazo[1,2-b]pyridazines as PIM kinase inhibitors with in vitro antileukemic activity. Cancer Res 2007;67(14):6916–24.

LIGHT FANTASTIC

The Diamond synchrotron is up and running.

2

Welcoming its first users in January 2007, Diamond is the result of a decade-long £263 million collaboration between the Wellcome Trust and the UK Government. In phase 1, seven beamlines were established. Phase 2 will provide for another 15. Demand is already high – when active, beamlines are running 24 hours a day.

Professor Dave Stuart at the Wellcome Trust Centre for Human Genetics in Oxford was the first to use the macromolecular structure beamline. Professor Stuart is visualising the structure of ephrin receptors – proteins found on the surface of cells that guide migrating cells to their correct location. Abnormal ephrin signalling has been implicated in several cancers.

Diamond is also home to the Trust-funded Membrane Protein Laboratory, run by Diamond Fellow Professor So Iwata, which is providing support for researchers working with membrane proteins. Such proteins are central to many biological processes but are difficult to crystallise, making structural studies problematic.

Outside biology, Diamond is being used to study materials ranging from meteorites to ancient manuscripts.

Images

1 Structure of PIM1, with substrate, produced by the Structural Genomics Consortium.

2 An aerial view of the Diamond synchrotron.

TESTING TOMORROW'S MEDICINES

Clinical Research Facilities are being used to test a variety of innovative therapies.

The explosive growth of biomedical research over the past decades is generating huge potential for the development of new treatments. Ensuring that this potential is realised will call for concerted efforts in translational research and experimental medicine. A key step in this process will be early testing of new therapies, and Clinical Research Facilities are ideal sites in which to carry out this research.

Many kinds of approach are being explored. Gene-based therapies have yet to realise the benefits initially hoped for, but research continues on possible strategies, particularly in the promising area of DNA vaccines. In Birmingham, for example, a phase I study is being carried out of a cancer treatment based on an engineered herpes simplex virus producing granulocyte–macrophage colony-stimulating factor, which enhances the immune response against cancer cells.

Meanwhile, in Southampton, highly promising results have been obtained in a prostate cancer treatment, in which an electroporation technique is used to deliver immune-stimulating DNA vaccines.

Preliminary results suggest that the technique is safe and feasible for use in people and stimulates strong immune responses.

Gene-based studies demand specially trained support staff, found only in Clinical Research Facilities. The same is true of the challenging neurosurgery research being carried out in Birmingham. A pioneering neurosurgical study is examining the potential of deep-brain stimulation to reduce long-term dependence on levodopa in Parkinson's disease. This technique is also a possible treatment for Tourette syndrome.

One of Manchester's specialist areas is magnetic resonance imaging, which has many possible applications. For example, a study is using the technique to optimise monoclonal antibody therapy, seeking to improve the treatment of people with colorectal cancer.

CHANGING PRACTICE

Research at Clinical Research Facilities can feed directly into healthcare delivery.

Studies hosted at Clinical Research Facilities (CRFs) reveal disease mechanisms and test experimental new therapies. Such work takes time to influence practice, but some studies have more immediate impact.

The Southampton CRF has been contributing to a multicentre trial assessing the value of early antibiotic use in people with severe, acute necrotising pancreatitis. The trial found no evidence of benefit in preventing infection or improving survival. The results have led to changes in local practice – helping to reduce antibiotic usage and lessen the risks of hospital-acquired infections.

Other work has led to validation of biomarkers of liver fibrosis identified at the CRF. A non-invasive blood test, the Enhanced Liver Fibrosis (ELF) Test, can detect early stages of liver fibrosis – of value, as the condition is potentially reversible if caught early. The test is cheaper than a liver biopsy. It received regulatory approval in May 2007.

Southampton has also become involved in substance abuse in sport. A growth hormone doping test, developed from work carried out in the CRF, has entered the validation process prior to commercial release.

Images

1 Studies in the Manchester Clinical Research Facility.

2 Liver tissue affected by fibrosis.

3 Cycling, a sport that has struggled to control drug use.

4 The newly opened building at the European Bioinformatics Institute.

NEW FUNDING

In Birmingham, research on a possible blood test for bowel cancer has had spin-off benefits in colonoscopy. Traditional colonoscopy is unpleasant and carries risks of gut damage. More sophisticated technologies were thus introduced for research studies and shown to be significantly safer. They are now gradually being implemented across the NHS.

The CRF in Cambridge has been used to look after patients in a persistent vegetative state (PVS) following brain injury, who have been undergoing brain-imaging studies. The patients' responses to specific stimuli suggest that they retain conscious awareness – findings that could have significant implications for PVS diagnosis.

Dellinger EP et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245(5):674–83.

Parkes J et al. European liver fibrosis (ELF) markers accurately distinguish fibrosis severity in chronic hepatitis C (CHC); an external validation study in a population-based cohort. Hepatology 2006;44(4) Suppl. 1:283A.

Erotokritou-Mulligan I et al. Validation of the growth hormone (GH)-dependent marker method of detecting GH abuse in sport through the use of independent data sets. Growth Horm IGF Res 2007;17(5):416–23.

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

Name that gene

The challenging task of formalising human gene nomenclature is being taken on by the European Bioinformatics Institute.

The Human Genome Organisation's Gene Nomenclature Committee (HGNC) is the only authority worldwide providing unique, standardised nomenclature for human genes – essential housekeeping to avoid confusion and promote data sharing. This year, Dr Ewan Birney of the European Bioinformatics Institute (EBI) and Dr Elspeth Bruford of University College London were awarded a biomedical resources grant to take on the task of assigning nomenclature to human genes, with the HGNC moving to the EBI.

Based at the Wellcome Trust Genome Campus at Hinxton, near Cambridge, the EBI is a leading centre for analysis and annotation of the human genome. This year also saw the completion of the Wellcome Trust-funded extension to the EBI building, the 'East Wing'. The Trust funds other work at the EBI, including the Ensembl genome browser and Macromolecular Structure Database.

Professor Janet Thornton of the EBI is also involved in a £5.9 million Strategic Award on ageing and age-related disease, led by Professor Linda Partridge and colleagues at UCL.

A selection of notable grants awarded in 2006/07.

STRATEGIC AWARDS

TROPICAL MEDICINE
Thailand Major Overseas Programme Re-housing the Programme's offices and laboratories.

MOUSE MODELS
Immunity and Infection Genomics Consortium ENU mouse mutagenesis facility at the Australian National University, Canberra.

CAPITAL AWARD

CHROMOSOME BIOLOGY
Professor Kim Nasmyth (University of Oxford) A contribution towards the building costs of the Institute of Chromosome Biology.

TECHNOLOGY DEVELOPMENT GRANT

SOFTWARE
Professor Peter Green (University of Bristol) Development of ClonalFrame software for analysis of bacterial sequence data and association mapping.

EQUIPMENT GRANTS

RNAi
Professor Andrew Sharrocks (University of Manchester) Establishing an RNAi facility.

PROTEIN ANALYSIS
Professor Peter Tompa (Institute of Enzymology, Hungary) An AKTA protein purification system.

BIOMEDICAL RESOURCES GRANT

DEVELOPMENTAL BIOLOGY
Professor Susan Lindsay (University of Newcastle upon Tyne) and **Professor Andrew Copp** (Institute of Child Health, London) Human Developmental Biology Resource.

RESEARCH RESOURCES IN MEDICAL HISTORY GRANT

ARCHIVES
Dr Andrew Grout (Edinburgh University Library) Widening access to University of Edinburgh MD theses, 1726–1930.

HISTORY OF MEDICINE PROJECT GRANT

ARCHIVES
Dr John Lagnado (Biochemical Society) Cataloguing the Biochemical Society archives, including items belonging to Fred Sanger.

Details of all grants made can be found in *Grants Awarded 2006/07*, available on the Wellcome Trust website.

DEVELOPING OUR ORGANISATION

Using our resources efficiently and effectively.

GROWTH PATTERNS

Wellcome Trust assets grew to more than £15 billion during the year.

Active management of a diversified investment portfolio led to further excellent growth in the Trust's assets, even during the credit squeeze in autumn 2007. During the year, the Trust's investment base rose by £1.7bn, from £13.4bn to £15.1bn.

The success of this year's asset management – a return of 17 per cent – continues a period of excellent performance. Returns over the past three years have averaged 17.6 per cent, and over the past five years 15.7 per cent, against a net target of 6 per cent. Over each of the past five years, investment returns have exceeded £1bn; cumulative gains in the period have been more than £8bn.

Over the longer term, since the flotation of Wellcome plc in 1986, annual returns have been 16.2 per cent, significantly higher than global equity total returns and the Trust's targets.

At the same time, the Trust has been developing a number of sophisticated tools to monitor and manage risks in its investment portfolio. This has significantly reduced volatility of investment values over time.

Returns quoted are nominal figures (i.e. before adjustment for inflation).

TAKING THE TEMPERATURE

An independent survey of opinion leaders and grantholders revealed positive views, along with some suggestions for improvement.

During 2007, the Trust commissioned Ipsos MORI to undertake an independent opinion audit of important Trust stakeholders, to find out about their perceptions of the Trust and its work. Ipsos MORI interviewed 51 opinion formers (such as representatives from academia, government, other funding organisations and the media) and received over 1200 responses to an online survey of grantholders.

The findings were extremely positive. Familiarity with the Trust's core activities was high, and stakeholders associated values such as 'excellence', 'professional conduct' and 'dynamism' with the Trust. Most said that they would speak very favourably about the Trust and its activities.

There was a lower awareness of the Trust's work outside biomedical research; some felt the Trust could do more to communicate its international activities.

In terms of the future, there was a desire to see more communication on the Trust's strategic direction and funding opportunities. Opinion leaders also suggested that the Trust should consider its niche in the light of the opportunities and challenges arising from the changing biomedical research landscape, both in the UK and internationally.

NEW FACES

The Wellcome Trust has been reorganising – bringing in more scientific expertise and gearing up for a new grants management system.

This year saw a new senior scientific team put together, with considerable experience in basic science and translational medicine.

Professor Richard Morris joined the Trust to take up a role as Head of Neuroscience and Mental Health, while maintaining his group in Edinburgh. Alan Schafer, new Head of Molecular and Physiological Sciences, co-founded the biotech company Hexagen, and has led GlaxoSmithKline's Technology Development Department.

Pat Goodwin remains Head of Pathogens, Immunology and Population Studies and Jimmy Whitworth Head of International Activities. Completing the senior team, Catherine Quinn, previously at the University of Oxford, is heading up a new Grants Management department.

The new Grant System being launched in 2008 will provide grantholders with more scope to manage grants and applications electronically. Nevertheless, applicants and grantholders clearly appreciate personal interactions with Trust staff, and the new structure is designed to provide a service better tailored to their needs.

The reorganisation is part of an ongoing scrutiny of operating costs to ensure that the Trust is run efficiently while continuing to provide a high-quality service.

CORPORATE ACTIVITIES 2006/07

A brief overview of the Wellcome Trust's corporate activities over the year.

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Governors and senior staff

Professor Richard Hynes, a Howard Hughes Medical Institute Investigator at the Massachusetts Institute of Technology, was appointed a Governor in January 2007. Professor Adrian Bird was appointed Deputy Chairman, for a three-year term until 31 March 2010. Professor Ron Plasterk left the Board of Governors, having taken up a new role as the Dutch minister of research and universities. Professor Martin Bobrow, Professor Sir Leszek Borysiewicz and Professor Dame Jean Thomas also left the Board.

Dr Mark Walport's position as Director of the Wellcome Trust was extended for a second term to 2013. Dr Walport and the Chairman of the Wellcome Trust, Sir William Castell, were invited by the UK Government to join the Health Innovation Council. Chaired by Lord Darzi, the Council is charged with promoting innovation, from discovery to take-up by health systems.
Dr Walport was also appointed to the board of the new Office for Strategic Coordination of Health Research (OSCHR). Established after the 2006 Cooksey Report, OSCHR is charged with developing a single integrated Health Research Strategy for England covering all areas of health research.

Several senior staff joined during the year (see left).

Wellcome Collection

This year saw the opening of Wellcome Collection, a major new public venue located in the Trust's former headquarters building at 183 Euston Road (see pages 26 and 51). As well as exhibition and events space, it houses the Wellcome Library, the Wellcome Trust Centre for the History of Medicine at UCL, and a new Conference Centre.

Contributions to policy making

The Trust has worked with a range of partners to draw attention to the threats to research posed by the EU Physical Agents (Electromagnetic Fields) Directive. Approved by the European Commission in 2004, the Directive was intended to protect workers exposed to electromagnetic fields. However, the legislation could also limit the use of magnetic resonance imaging (MRI) for research, diagnosis and treatment. Unusually, in light of the evidence presented, the EC announced in October 2007 that implementation of the Directive would be delayed, to allow further discussion.

The Trust also provided MEPs with access to information about the use of non-human primates in medical research. This followed a proposal that a timetable be set to phase out primate use across the EU.

The Trust contributed to the debate on animal–human hybrid embryos. A UK Government White Paper revealed plans to outlaw such hybrids, a move that would have denied scientists a valuable research tool. Following input from the Trust and others, and a public consultation that found general public support for hybrid use in medical research, plans for a ban were dropped.

The potential to use electronic patient records in research, through the Connecting for Health initiative, has been a major focus during the year. Use of patients' medical information could prove invaluable in research, and is an area in which the UK, with its nationwide National Health Service, has a distinct advantage. A public consultation commissioned by the Trust revealed that the public are positive about participating in research and sharing personal data if effective systems are in place to ensure informed consent, anonymity and security of their data.

Data sharing and release remained a priority. This year saw the launch of UK PubMed Central, set up by the Trust, as part of a group of leading UK research funders in partnership with the British Library. From 1 October 2006, it became a formal condition that all research papers funded in whole or in part by the Trust must be made freely accessible. The Trust also announced a new data management and sharing policy.

Images

1 Professor Adrian Bird, the Trust's new Deputy Chairman.

2 Outside Wellcome Collection.

3 Functional magnetic resonance imaging, an important research and medical technology.

FINANCIAL SUMMARY 2006/07

In the year ending 30 September 2007, the Wellcome Trust's total charitable expenditure was £519.8m.

Total charitable expenditure for the year grew slightly to £520 million (2006: £484m), mainly due to higher Science Funding and Technology Transfer grants expenditure.

The total grants awarded increased by £34m, owing to a small rise in funding rates and the number of grants funded.

Expenditure on activities managed directly by the Trust was similar to last year's figure. Support costs increased slightly, mainly as a result of expenditure on a new grants management system and associated restructuring costs (see page 40).

Careers

Expenditure on careers support totalled £125.5m, an increase of £25m over 2005/06. Seven Principal Research Fellowships were awarded or renewed over the year. Funding for Senior Research Fellowships also increased, and this was the first year of funding of Sir Henry Wellcome Fellowships for outstanding researchers at the beginning of their careers.

International

Some £41.4m was awarded directly to researchers at overseas institutions. Of this, £21.6m was for the support of research at the Trust's Major Overseas Programmes in South-east Asia (Thailand and Vietnam) and Africa (Kenya, Malawi and South Africa). A further £33.3m was awarded to researchers at UK institutions for research to be carried out overseas. Total international funding, £74.7m, was slightly higher than in 2005/06.

Infrastructure

Support specifically for buildings, refurbishment, equipment and resources amounted to £13.4m. This figure does not include the significant expenditure on equipment or infrastructure provided as part of other Trust grants.

BREAKDOWN OF WELLCOME TRUST CHARITABLE EXPENDITURE 2006/07

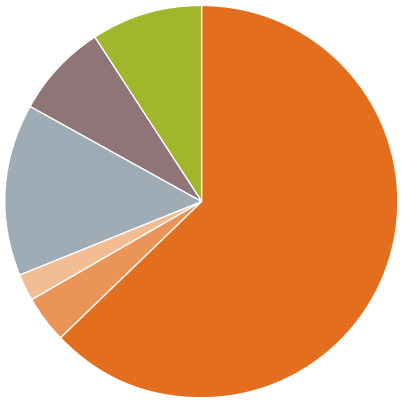
Total: £519.8m

GRANTS AWARDED

- **BIOMEDICAL SCIENCE** £327.1m
- **TECHNOLOGY TRANSFER** £20.1m
- **MEDICINE, SOCIETY AND HISTORY**[1] £12.0m
- **WELLCOME TRUST SANGER INSTITUTE** £72.9m

OTHER EXPENDITURE

- **DIRECT ACTIVITIES** £40.6m
- **SUPPORT COSTS** £47.1m

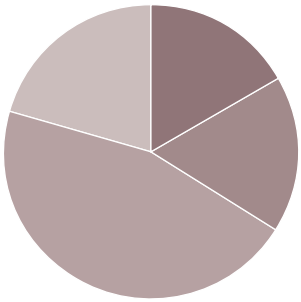


1 History of medicine, biomedical ethics and public engagement with science funding.

DIRECT ACTIVITIES: £40.6M

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

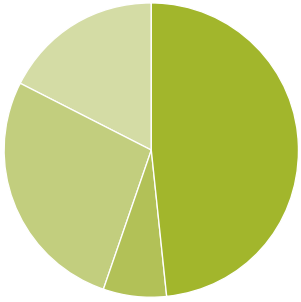
- Wellcome Trust Genome Campus, excluding the Sanger Institute
- Wellcome Library
- Directly managed public engagement activities
- Scientific conferences.



- **Biomedical science** £6.6m
- **Technology Transfer** £6.8m
- **Medicine, Society and History** £18.0m
- **Wellcome Trust Genome Campus** £9.2m

SUPPORT COSTS: £47.1M

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



- **Biomedical science** £22.9m
- **Technology Transfer** £3.2m
- **Medicine, Society and History** £12.8m
- **Wellcome Trust Genome Campus** £8.2m

The expenditure values used here are extracted from the Wellcome Trust's *Annual Report and Financial Statements 2007*, 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

£30m
New and renewed Principal Research Fellowships and programme support.

£16.8m
Renewal of funding for Africa Centre.

£7.7m[1]
Case Control Consortium phase 2 funding.

£6.3m
Capital Award for Institute of Chromosome Biology, University of Oxford.

£5.9m
Strategic Award for research on ageing and age-related disease.

£5m
Funding for first Sir Henry Wellcome Fellows.

£5m
Centre for Gene Regulation and Expression, University of Dundee.

£3.7m[2]
Clinical veterinary research initiative.

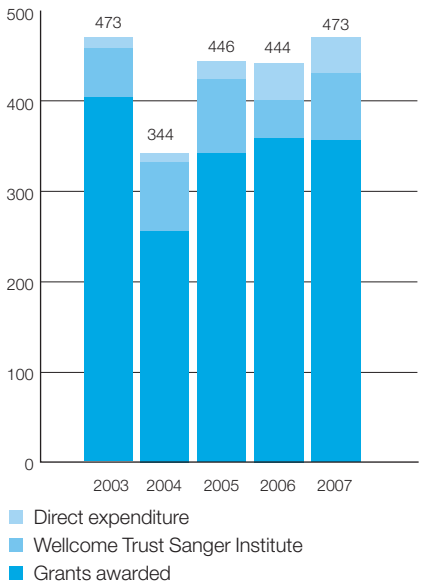
£7.6m
Diagnostics for the Real World, for point-of-care diagnostics.

£2.1m
i-Snake robotic surgical tool.

£0.6m
Centre of the Cell.

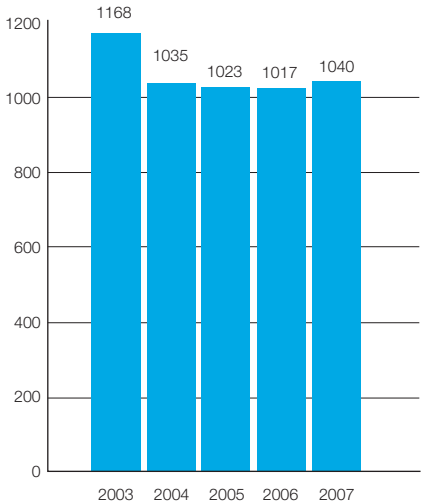
1 Includes funds awarded to the Wellcome Trust Sanger Institute.
2 Plus £7m in future financial years.

Charitable expenditure 2003–07 (£m)*



*Excluding support costs.

Grant liabilities 2003–07 (£m)



INVESTMENTS 2006/07

The Trust's asset base grew to £15.1 billion during the year, with particularly strong returns from Asian and emerging markets, private equity and UK residential property assets.

The Trust holds a world-class portfolio of investments widely diversified across asset type and geographical region. Rather than restrictive strategic benchmarks, the Trust's approach to asset management is a flexible and dynamic approach, based on the identification of the best investment opportunities wherever and in whatever form they may arise. A return of 17.0 per cent in 2006/07 reflects the success of this commitment to excellence and focus on absolute return.

Public equities enjoyed another strong year, with gains in excess of 40 per cent in Asian and emerging markets. Holdings in UK equities were again reduced, to 14.7 per cent of total assets. More than half of the Trust's portfolio is now held in 'alternative' assets (hedge funds, buyout funds, venture, property and emerging market equities).

The Trust's commitment to hedge funds rose to £3.1bn. The Trust is also seeding up to US$550m in funds, principally hedge funds, managed by New Smith Capital Partners, and is taking a financial interest in the group.

The Trust remains a major investor in private equity, with investments in over 500 partnerships and total commitments in excess of £3.8bn. Net annual returns have exceeded 21 per cent.

The Trust's property portfolio continued to prosper, the 36 per cent gain in the value of residential property also reflecting the benefits of active portfolio management.

Returns quoted are nominal figures (i.e. before adjustment for inflation).

FUNDING DEVELOPMENTS 2006/07

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

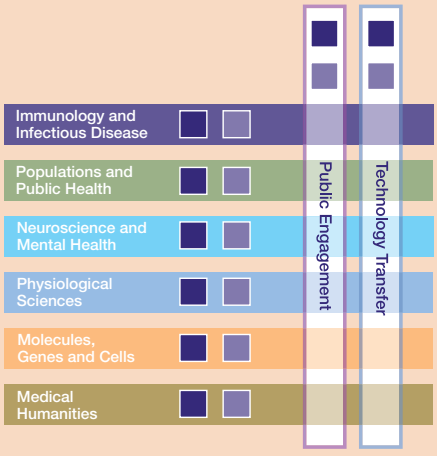
The Wellcome Trust's funding is based around funding streams, covering core areas of biomedical science and the medical humanities. Cutting across these streams are funding programmes in Technology Transfer and Public Engagement (see below).

Each funding stream has associated with it one or more Funding Committees, responsible for most funding decisions. Strategy Committees advise the Trust on needs and opportunities within specific areas: (1) Neuroscience and Mental Health; (2) Molecular and Physiological Sciences; (3) Pathogens, Immunology and Public Health; (4) Medical Humanities; (5) Technology Transfer; and (6) Public Engagement.

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, as well as Strategic Translation Awards in Seeding Drug Discovery. Public Engagement is supported primarily through the Engaging Science programme, which includes Society Awards, People Awards and Arts 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.



Wellcome Trust funding streams.

NEW FUNDING INITIATIVES

DEVELOPING PEOPLE

- US–UK funding partnerships
- Translational medicine and therapeutics programme
- Clinical veterinary research training initiative

GLOBAL HEALTH RESEARCH

- Research capacity strengthening in African institutions
- Malawi and Kenya capacity development

A new partnership between the Wellcome Trust and the US National Institutes of Health (NIH) enables postgraduate students to undertake four-year PhD training in centres in the UK or Republic of Ireland and the NIH at Bethesda, Maryland.

Through a new programme run in partnership with the Howard Hughes Medical Institute (HHMI), postdoctoral researchers working with a major Trust award holder can join the laboratory of an HHMI investigator for up to one year (and vice versa).

A new initiative will support interdisciplinary research training programmes for clinicians in translational medicine and therapeutics. Programmes will enable clinicians to combine a rigorous grounding in the principles of translational medicine with research opportunities that apply the latest approaches to important clinical problems. Programmes will be underpinned by partnerships between UK academic institutions and industry.

A £10.7 million initiative in clinical veterinary research was launched, in partnership with the seven UK veterinary schools. Funding of £7m will be used to create fellowships at different career stages. The remaining £3.7m will be available for small grants such as vacation scholarships.

GLOBAL HEALTH RESEARCH

A major new initiative was launched in 2007 to strengthen the institutional research base in Africa, particularly in universities. Funding will be provided to enhance research facilities in African research centres that are part of consortia or networks linked to leading higher education institutions in the UK or elsewhere.

Some £10m was also committed to health research capacity development in Kenya and Malawi, with matching funds from the UK Government's Department for International Development and £1m from the International Development Research Centre, Canada. Funding through this initiative will become available in 2008 and, unusually, local funding schemes will be established and administered directly by national bodies.

The Trust also expanded its global health fellowship schemes. The new Fellowships in Public Health and Tropical Medicine provide a complete career ladder for researchers at academic institutions in developing countries.

FACILITATING RESEARCH

A new funding initiative was launched in 2007 to support the development and use of electronic patient record resources in health research, in partnership with the Economic and Social Research Council, the Engineering and Physical Sciences Research Council and the Medical

FACILITATING RESEARCH
- Electronic patient records initiative
- Capital funding initiative

USING KNOWLEDGE
- Health Innovation Challenge Fund
- Adjuvants

PUBLIC ENGAGEMENT
- Arts funding
- Broadcast Development Awards
- Public engagement 'beacons'

Research Council. Proposals were sought in three areas: health research using electronic patient records and cohort databases, training programmes and workshops, and public engagement activities.

A new capital funding scheme, to be run every two years, will provide funds for new buildings or refurbishment of existing laboratories. Up to £30m is available for the first round of funding.

A one-off call for proposals was launched for genome-wide association studies in common, complex disease, using DNA samples from existing disease collections or cohorts. A scheme was launched to provide access to commercially produced gene knockout mouse strains. This resource will be coordinated by the European Mutant Mouse Archive.

USING KNOWLEDGE

The Trust committed £50m over five years to a new Health Innovation Challenge Fund, with matching funding from the UK Department of Health. The £100m fund will be used to support the translation of research into new products and approaches to treat disease.

A specific initiative was launched to promote research on vaccine adjuvants, agents that improve the body's response to vaccines. This initiative was open to researchers outside the UK and scientists in industry as well as academia.

MEDICAL HUMANITIES

A call for Strategic Award proposals in the medical humanities was launched, to provide support for major ventures exploring the human experience of medicine.

The Trust's Biomedical Ethics Programme was substantially revised, with an immediate priority of building capacity and quality by supporting centres or collaborations. After this initial phase, attention will shift to fellowship and other support.

Capital funding is also available in these areas (see above).

PUBLIC ENGAGEMENT

A new Arts Awards scheme was launched in 2007, building on the success of previous Pulse and Sciart funding. Broadcast Development Awards were launched to enable early-stage ideas for media projects to be developed into full proposals that can be used to secure further funding or a broadcasting platform.

The Trust also supported the £8m initiative launched by the UK higher education funding councils and Research Councils UK to develop a network of public engagement 'beacons'.

FUNDING ANALYSIS

Total no. of grant applications: 2603

Total no. of grants awarded: 893

Value of applications considered: £963m

Value of grants awarded: £370m

No. of programme grants awarded: 51

No. of PRFs awarded/renewed:[1] 9

No. of SRFs awarded/renewed: 27

No. of intermediate fellowships awarded: 34

No. of training (junior) fellowships awarded: 66

No. of PhD studentships supported: 98

FUNDING RATES

	By no.	By amount
Project grants	26%	26%
Programme grants	59%	52%
New PRFs (full app.)	47%	57%
SRFs (full app. Basic)	17%	17%
SRFs (full app. Clinical)	33%	32%
SRFs (full app. Tropical)	67%	75%
SRFs (full app. International)	19%	26%
Intermediate fellows	10%	10%
Training (junior) fellows	19%	19%
Biomedical Ethics	23%	24%
History of Medicine	27%	21%
Research Resources in Medical History	45%	49%
Society Awards: Activities	12%	10%
Society Awards: Research	25%	19%
Large Arts Awards	7%	4%
Small Arts Awards	20%	23%

Total no. of institutions receiving funding in 2006/07 (UK): 73

Total no. of institutions receiving funding in 2006/07 (non-UK): 51

ONGOING LIABILITIES[2]

Total grants liabilities: £1.040bn

No. of countries receiving funding: 35

Fellows currently supported: 754

Researchers currently supported: 3228

Total no. of institutions receiving funding (UK): 87

Total no. of institutions receiving funding (non-UK): 138

1 Includes PRF programme grant renewals.

2 Excludes supplementations and grants no longer required.

PRF: Principal Research Fellowship
SRF: Senior Research Fellowship

STREAMS FUNDING 2006/07

1 October 2006 to 30 September 2007.

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	173
Value of grants awarded	£90.1m
Number of programme grants awarded	16
Value of programme grants awarded	£19.3m

OTHER MAJOR AWARDS:

- Follow-on funding for Wellcome Trust Case Control Consortium
- £5m Strategic Award to the Centre for Gene Regulation and Expression, University of Dundee
- £5.9m Strategic Award for the genomic and biochemical analysis of ageing, University College London
- £6.3m Capital Award to the University of Oxford for Institute of Chromosome Biology

MAJOR PERSONAL SUPPORT AWARDS:

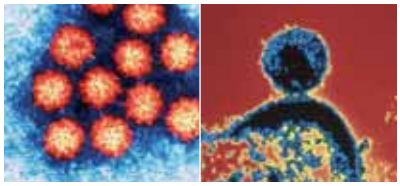
- 2 new (plus 1 renewed) Principal Research Fellowships
- 4 new (plus 5 renewed) Senior Research Fellowships
- 5 new International Senior Research Fellowships

OTHER ACTIVITIES DURING YEAR:

- Call for proposals for genome-wide association studies
- Two calls for proposals for acquisition of mouse knockout lines

IMMUNOLOGY AND INFECTIOUS DISEASE

The Immunology and Infectious Disease stream aims to increase 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	161
Value of grants awarded	£73.9m
Number of programme grants awarded	12
Value of programme grants awarded	£15.2m

OTHER MAJOR AWARDS:

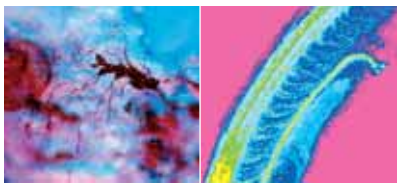
- £1.6m Strategic Award to the Centre for Immunity, Infection and Evolution, University of Edinburgh
- £2.1m Strategic Award to the Immunity and Infection Genomics Consortium
- £1.2m Strategic Award to the Centre for Drug Discovery, Dundee

MAJOR PERSONAL SUPPORT AWARDS:

- 1 new Principal Research Fellowship (plus 2 renewals of programme grants associated with PRFs)
- 3 new (plus 3 renewed) Senior Research Fellowships

NEUROSCIENCE AND MENTAL HEALTH

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



Total number of grants awarded	122
Value of grants awarded	£43.5m
Number of programme grants awarded	6
Value of programme grants awarded	£7.3m

OTHER MAJOR AWARDS:

- £1.1m Strategic Award in neuroaesthetics

MAJOR PERSONAL SUPPORT AWARDS:

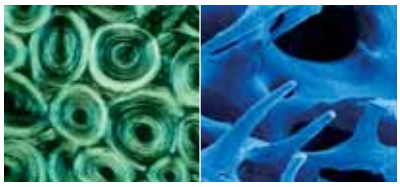
- 1 new Principal Research Fellowship (plus 2 renewals of programme grants associated with PRFs)
- 1 new (plus 2 renewed) Senior Research Fellowships

OTHER ACTIVITIES DURING YEAR:

- 3 Masterclasses in Clinical Neuroscience
- 2 Cognitive Foresight project grants awarded in partnership with the Research Councils

PHYSIOLOGICAL SCIENCES

The Physiological Sciences funding stream aims to support 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	97
Value of grants awarded	£38.4m
Number of programme grants awarded	12
Value of programme grants awarded	£12.7m

MAJOR PERSONAL SUPPORT AWARDS:
- 3 new Senior Research Fellowships

OTHER ACTIVITIES DURING YEAR:
- *In vivo* physiology and pharmacology techniques: acting to increase awareness and understanding

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	46
Value of grants awarded	£16.3m
Number of programme grants awarded	4
Value of programme grants awarded	£6.6m

OTHER MAJOR AWARDS:
- £3.7m Strategic Award for clinical veterinary research
- £1.6m Strategic Award to SPARTAC antiretroviral trial

MAJOR PERSONAL SUPPORT AWARDS:
- 2 new Senior Research Fellowships

OTHER ACTIVITIES DURING YEAR:
- £16.8m Africa Centre renewal
- £7m commitment for future fellowships in clinical veterinary medicine

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	143
Value of grants awarded	£12.0m
Number of programme grants awarded	1
Value of programme grants awarded	£0.5m

OTHER MAJOR AWARDS:
- 2 Enhancement Awards and 1 Strategic Award

MAJOR PERSONAL SUPPORT AWARDS
- 3 University Awards

OTHER ACTIVITIES DURING YEAR:
- Biomedical Ethics Summer School

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.

Over the past nine years, around 120 translational research projects from 50 institutions have been funded under Development Fund and Translation Award schemes. Many of these have raised additional investment and a number have already developed products. This year saw the first awards made in the Seeding Drug Discovery initiative. Support was also provided for development of a range of new technologies, in diagnostics, surgery and other areas.

Translation Awards support a diverse array of technologies, not only from biology but also from the physical sciences and mathematics; they are available to both academic institutions and early-stage companies. Of 27 applications received from 17 institutions during 2006/07, 26 per cent were awarded. The mean value of these awards has been £646 000 (range £240 000–1.0 million) and the average duration 25 months (range 10–36 months). 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, medical devices and enabling technologies. Examples include the development and evaluation of an injectable scaffold for reconstructive surgery, preclinical and clinical studies of a novel meningococcal vaccine, clinical studies into the therapeutic management of inflammatory bowel disease, and research to improve the reliability and safety of medicinal infusions outside a clinical environment.

Other awards were for the development of a drug delivery system for the treatment of brain tumours, research into a cell-based bandage for the treatment of meniscal cartilage injuries, and DNA sequencing using single molecule tunnelling techniques.

Strategic Translation Awards are designed to support translational research in areas of key importance to the Wellcome Trust. Twelve applications have been considered to date, in diagnostics, vaccination, regenerative medicine, genotyping technology and drug discovery. The mean value of awards has been £3.2m (range £1.3–8.1m). New awards were made this year to two multidisciplinary teams working at the interface between engineering and medicine, tackling two important medical issues: diagnosis of tuberculosis (page 22) and minimal invasive surgery (page 23).

An award of £7.6m was made to Dr Helen Lee to support research and development into rapid diagnostics for infectious diseases. The programme, based at the University of Cambridge and within Diagnostics for the Real World Ltd, builds on earlier work on a rapid test for chlamydia infection, later applied to other sexually transmitted infections and to trachoma. Dr Lee's team is also working on proof-of-concept studies of a new DNA amplification technology that could offer an alternative to polymerase chain reaction chemistry for DNA detection assays.

The £91m Seeding Drug Discovery initiative, launched in 2005, made ten awards in its first two rounds of funding. Eight awards were for full drug discovery programmes in therapeutic areas spanning bacterial infections, cancer, amyloidosis, obesity, multiple sclerosis and inflammation.

The mean value of these awards has been £2.8m (range £1.3–4.0m) and the average duration is 30 months (range 24–36 months). Two smaller awards were made to explore the feasibility of novel approaches to the treatment of aspergillosis and management of allergy. The scheme has continued to attract considerable interest from the academic community and companies alike, and the competition has been expanded to two rounds a year.

Several companies that received support during early validation of their technology have had success in raising further funds. These include the start-up companies Celltran Ltd, Senexsis Ltd, Polytherics Ltd and Population Genetics Technologies Ltd. Another group of companies successfully concluded terms under which they were acquired by public companies, including Paradigm Therapeutics Ltd, DanioLabs Ltd and Oxxon Therapeutics Ltd. Emergent Biosolutions floated on the New York Stock Exchange. Overall, Trust-funded companies have raised over £155m to date.

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 Wellcome Trust Sanger Institute continues to be highly productive, in terms of both genome sequencing and published outputs. The Advanced Courses programme has been expanding both its UK-based and international activities, while the Wellcome Trust Conference Centre has attracted leading speakers to a series of high-profile scientific events.

Wellcome Trust Sanger Institute

The Sanger Institute has been further developing its emphasis on human genetics over the last 12 months, culminating in the appointment of Professor Leena Peltonen as Head of Human Genetics. Professor Peltonen is an acknowledged leader in studies of the molecular basis of both single-gene disorders and more common complex diseases. Professor Aarno Palotie also joined the Sanger Institute, and these appointments strengthen the Institute's research into human disease.

The Sanger Institute's new strategy, developed in 2006, sets out ways to capitalise on the major contributions previously made to genome sequencing and high-throughput projects, with a special emphasis on genetic variation and its impact on health. Sanger researchers continued to publish in high-impact scientific journals, appearing as authors on more than 260 original research papers – an increase of 20 per cent over 2005/06 – including 38 in *Nature, Nature Genetics, Science* or *Proceedings of the National Academy of Sciences (USA)*. These articles include many of the discoveries of the Cancer Genome Project (see page 7), the ENCODE Consortium (pages 6–7) and pathogen sequencing projects (pages 10–11).

The Sanger Institute's work with the Wellcome Trust Case Control Consortium has resulted in major publications (page 6). The Institute has received a major award to undertake a second phase of the project to refine mapping of variants and to study copy number variation, an area where the Institute is a world leader (pages 6–7). Other papers described genes involved in X-linked deficits in mental development, diabetes and other common diseases.

As part of the development in Genome Campus conferences, Sanger Institute staff organised international conferences on hearing, mouse molecular genetics and DECIPHER, a database of sub-microscopic chromosomal anomalies implicated in disease or abnormal development. This will be an area of growth in coming years.

The Sanger Institute's Public Engagement Programme opened its new visitor space during the year and relaunched **www.yourgenome.org**. It also made a major contribution to the national travelling exhibition project *Inside DNA: A genomic revolution*, while continuing to develop resources and experiences for age 14+ students, for teachers and for adult groups.

Wellcome Trust Advanced Courses

The Wellcome Trust Advanced Courses programme organised nine Advanced Courses and six workshops at the Wellcome Trust Genome Campus, and three workshops overseas. Two bioinformatics workshops were held at the IT training room previously set up at the Institute of Hygiene in Montevideo, Uruguay. With the support of Sanger Institute instructors, previous participants are being encouraged to become the trainers of the future.

An IT training room was set up in Kilifi, Kenya, at the Kenya Medical Research Institute–Wellcome Trust Research Programme and a workshop, 'Working with Pathogen Genomes', was held in December 2006, with scientists attending from all over Africa.

Next year will see new Advanced Courses in Hinxton on molecular virology, global analysis of fission yeast gene function, and small molecule drug discovery, as well as the development of IT training rooms at the Wellcome Trust Major Overseas Programmes in Vietnam and Malawi.

Meetings Programme and Conference Centre

A total of 16 meetings were held at Hinxton as part of the Wellcome Trust Meetings Programme in 2006/07. Highlights included the 'Genomics of Common Diseases' conference held in July 2007 jointly with *Nature Genetics*. This event showcased many of the research projects funded by the Case Control Consortium, with the auditorium at full capacity.

Over £2 million of business was run through the Conference Centre, almost three-quarters being aligned with the Trust's mission and hence charged at subsidised rates. The remaining business filled gaps in the conference diary and generated sufficient profit to subsidise the scientific events.

A study is currently underway to determine the options and cost plans for expanding the conference facilities.

PUBLIC ENGAGEMENT

The Wellcome Trust's Public Engagement activities aim to engage with society to foster a climate within which biomedical science can flourish.

While the opening of Wellcome Collection was the highlight of the year in public engagement, grant-giving continued to be an area of significant activity. Planning began for work associated with Darwin anniversaries in 2009, and the year also saw the development of new strategies for education and broadcast.

Grants

A total of 86 grants were awarded under the £3 million Engaging Science funding programme and one capital grant of £600 000 was made.

Society Awards: Six large awards (over £30 000) were made for a range of important activities. One award was made to Dean Madden at the National Centre for Biotechnology Education in Reading to provide practical bioinformatics activities enabling biology students aged 16–19 to explore modern evidence for evolution. In addition, four awards were made to support academic research about public engagement.

People Awards: Some 48 awards (up to £30 000) were made to support a diverse range of activities, including performances, exhibitions, talks, conferences, debates and documentaries. A notable award was to Deafinitely Theatre (above), the UK's only deaf-led professional theatre company, to develop a production that explored issues surrounding cochlear implants in a deaf child.

Arts Awards: In February 2007, the Wellcome Trust launched its new Arts Awards funding scheme to build on the work of the Sciart and Pulse schemes. Since its launch, 25 small grants (up to £30 000) and three large grants have been awarded. One award was to Samantha Moore to produce *An Eyeful of Sound*, a short animated documentary film that explores synaesthesia, incorporating conversations with synaesthetes as well as visual interpretations of their synaesthetic reactions to everyday sounds.

Capital Award: A grant of £600 000 was awarded to Professor Fran Balkwill to develop Centre of the Cell – a new interactive exhibition for children located in east London (see page 29).

Education

In June 2007, the Trust approved a new Education Strategy. Central to this is the desire to establish the Trust as a major influence on school-focused education from primary stages onwards.

In September 2007, the Trust and the US National Science Foundation hosted an international conference examining 'the national value of science education'. The Trust is also supporting a project examining the impact of assessment on science education at the end of Key Stage 2 (10–11-year-olds). This work is being undertaken by the Institute of Education and Ipsos MORI. The study will also compare pupils' and teachers' attitudes and learning outcomes in England with those in Wales, which recently withdrew end of Key Stage 2 assessment.

Two issues of the *Big Picture* series, a publication for post-16 students and teachers, were published – on epidemics and evolution. Both publications are available online.

New developments

The Trust has initiated a programme to mark the bicentenary in 2009 of the birth of Charles Darwin and 150 years since the publication of *On the Origin of Species*. Activities will include a series of Darwin-inspired biomedical experiments available to every schoolchild in the UK, a number of broadcast and web projects, and a cultural initiative.

The Trust has also begun to implement its new broadcast strategy, which will combine training and development activities for scientists and broadcasters and provide a small amount of highly targeted funding.

In conjunction with the development of a Trust-wide international strategy, a public engagement strand has been developed with a focus on developing countries.

Supporting researchers

Support for Wellcome Trust-funded researchers expanded in 2007 with the provision of a web resource, responsive support and training sessions. The Trust hosted two events for young researchers explaining how to engage with different audiences, while Fellows were able to attend a session on engaging and influencing people through use of narrative techniques.

The Trust has sought to improve institutional support for researcher engagement through the Beacons for Public Engagement scheme, in partnership with the UK Funding Councils and RCUK (UK Research Councils). The Trust also continues its support of the Researchers in Residence scheme, in partnership with the RCUK.

WELLCOME COLLECTION

Wellcome Collection is a free public venue hosting events and permanent and temporary exhibitions. It also houses the Wellcome Library, the Wellcome Trust Centre for the History of Medicine at UCL, a Conference Centre, a forum and events spaces, a bookshop and a café.

Wellcome Collection opened to the public on 21 June 2007. Formerly the headquarters of the Wellcome Trust, 183 Euston Road now houses more than 1300 medical, cultural and historical artefacts, including works by Antony Gormley, Marc Quinn and Pablo Picasso – all designed to stimulate dialogue between art, science, history and the public.

Exhibitions

Wellcome Collection contains two permanent galleries charting the evolution of our cultural responses to health, sickness and discovery. *Medicine Man*, first hosted in the British Museum in 2003, exhibits objects from Sir Henry Wellcome's original collection. *Medicine Now* explores issues in contemporary medicine, including malaria, obesity, genomics and cloning.

A large gallery on the ground floor hosts an ongoing programme of thematic temporary exhibitions. It opened with *The Heart* (see pages 26–27). Works by artists such as Spencer Tunick, Mauro Perucchetti, Gunther von Hagens, Antony Gormley and Marc Quinn are displayed around the building.

Events

The exhibitions are supported by an ongoing programme of public events. 'Heartfelt Emotions', a weekend symposium held on 7–8 September 2007, brought together neuroscientific, clinical, behavioural, social, epidemiological, historical and literary expertise to explore the physical and metaphorical role of the heart in our emotions.

'Medicine and Literature', a series of four free evening events, began in September 2007, exploring different forms of writing about medicine. Speakers included Michael Blastland, author of a book, *Joe*, about his severely autistic son, and Jonathan Cole, who described the lives of people with spinal cord injuries in his book *Still Lives*.

Wellcome Library

Wellcome Collection is also home to the Wellcome Library. With around 2.5 million items, including 600 000 books and journals, an extensive range of manuscripts, and more than 100 000 paintings, prints and drawings, it is one of the world's major resources for the study of the history of medicine.

Following the move the Library began a programme of events and talks, including twice-monthly Insights visits, covering topics such as the life and work of Henry Wellcome, the body in history, Hinduism, Buddhism and Jainism, and the preservation and conservation of books and manuscripts.

In the first six months after reopening (April–September 2007) the Library registered more than 2000 new readers – up 88 per cent from the previous year. In all, nearly 11 000 visitors used the Library – an increase of 32 per cent over 2005/06.

'Uncover', the touch-screen interactive in Wellcome Collection, proved popular, with visitors viewing some 38 000 Library images. Further insight into its remarkable holdings appeared in *Cures and Curiosities: Inside the Wellcome Library*, a lavishly illustrated book edited by Tony Gould and with a foreword by Sebastian Faulks, which was published by Profile Books to commemorate the Library's reopening.

Wellcome Images

Formerly known as the Medical Photographic Library, Wellcome Images provides access to more than 100 000 items, from stunning modern images to the fascinating historical works held in the Wellcome Library. The new Wellcome Images website includes much improved functionality. Images are now freely available for download for personal, academic teaching or study use, under Creative Commons licences.

Members' Club

Wellcome Collection also includes a Club. Members can take advantage of a stylish Club Room (offering WiFi and refreshments), where they can meet other members and swap ideas, read, bring guests or simply relax.

Conference Centre

The Conference Centre – offering four meeting rooms and a tiered 154-seat auditorium for corporate and private events – hosted 125 events. Initial user feedback has been highly positive.

Business

The booksellers Blackwell opened a branch in Wellcome Collection in May 2007. It stocks a wide variety of books on subjects including medicine, science, history and art, along with Wellcome Collection merchandise.

Wellcome Collection's café, run by Peyton and Byrne, opened in June 2007, and has enjoyed a number of favourable reviews.

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