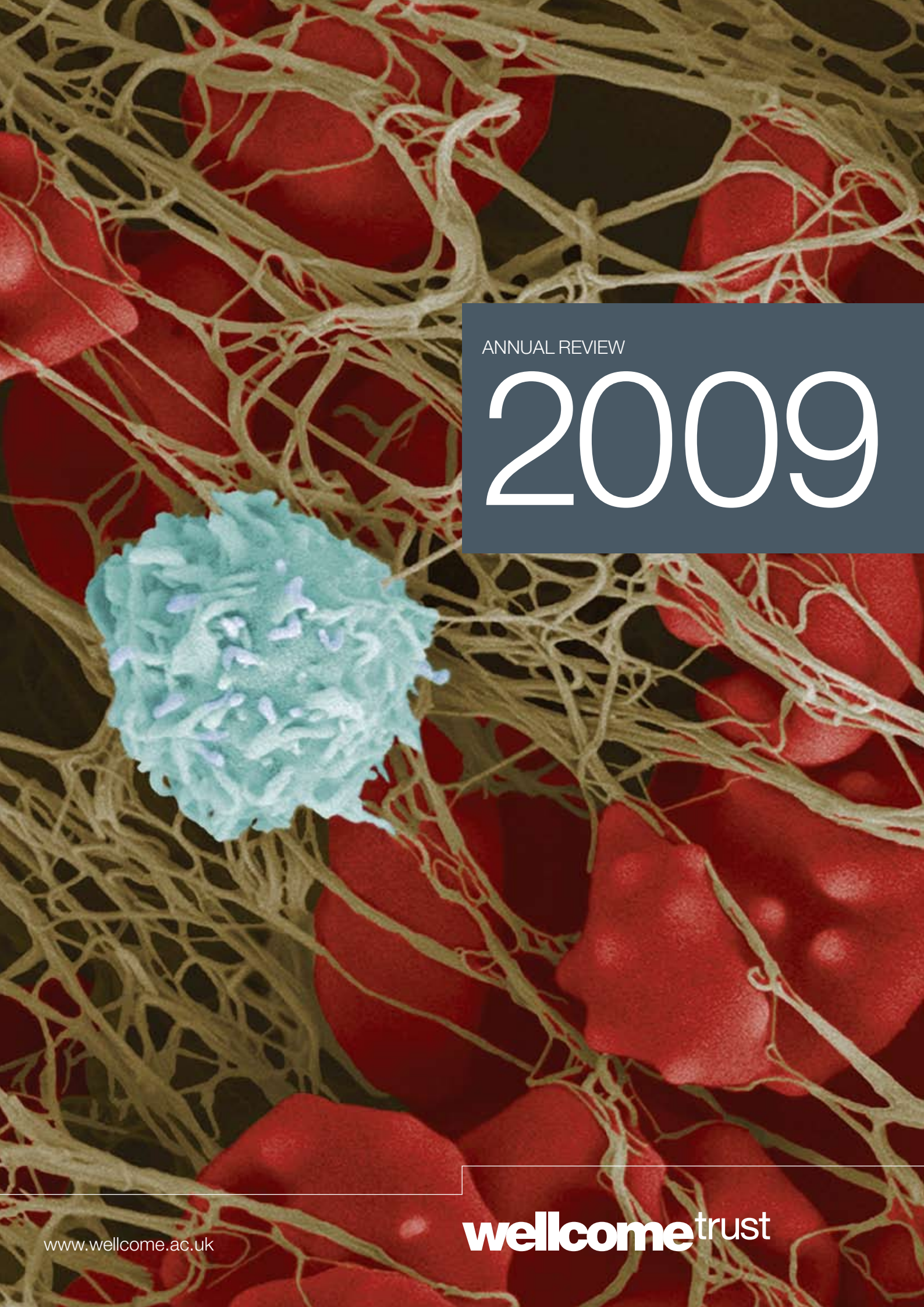

ANNUAL REVIEW

# 2009

wellcome trust

www.wellcome.ac.uk

# The Wellcome Trust

## 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.

**www.wellcome.ac.uk/strategicplan**.


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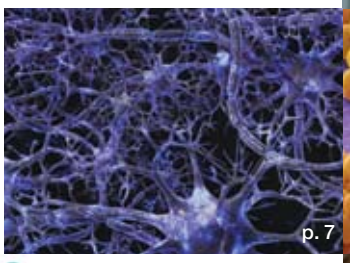
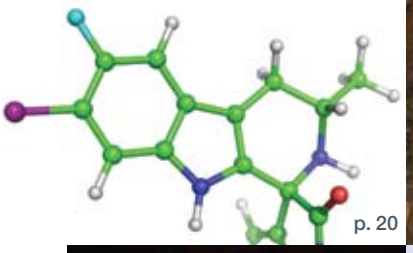
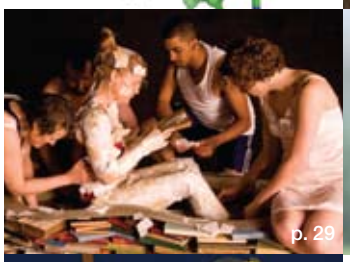
**COVER IMAGE**
Colour-enhanced image of a blood clot, showing many red blood cells and a single white blood cell in a mesh of fibrin. The red blood cells are crenated – spiky – because they are dehydrated.
*Anne Weston*













## THE YEAR IN REVIEW

# Five years of progress

**As we reach the end of our five-year Strategic Plan, we can celebrate much success and look forward to exciting new directions.**

The end of 2009 sees not only the end of a year's activities but also the fruition of a five-year Strategic Plan that began in 2005. In that Plan, we set out that we wanted our funding to lead to increased understanding of health and disease, and its societal context, and to use that knowledge to develop improved health benefits. I feel that we have met those aims. The last five years have seen our funding contribute to some vital breakthroughs in biology and medicine and the pursuit of much inspirational science.

One of our biggest areas of success continues to be in genetics and genomics. As DNA-sequencing technology continues to improve at a remarkable rate, we have seen studies take advantage of the Human Genome Project since the completion of the first whole-genome draft in 2000. Chief among these is the advent of genome-wide association studies, in particular the work of the Wellcome Trust Case Control Consortium. By examining the whole genomes of thousands of patients, the Consortium has been able to identify genetic variants associated with common diseases, including heart disease, diabetes and rheumatoid arthritis, as well as other characteristics such as weight and height. These are providing insights into the mechanisms of disease, opening up new avenues of research into their causes and possible treatments.

Crucial to our understanding of biological mechanisms is knowing the shape of a protein and how this affects its function. Over the last four years, the Structural Genomics Consortium has determined the three-dimensional structures of over 450 proteins with relevance to human health and disease – including diabetes, cancer and malaria – exceeding its target of 375 structures. In 2007, we committed £16 million to enable the Consortium to solve an additional 600 structures. This will further our understanding of these proteins and supply new targets for therapeutic intervention.

Advances in genomics have also made possible projects such as the Cancer Genome Project, an ambitious initiative to map the individual mutations involved in many different types of cancer. An early success was the discovery of *BRAF* as an important gene involved in malignant melanoma and a high proportion of other cancers. The Project has also made significant progress in distinguishing the 'driver' mutations that cause cancer from the 'passenger' mutations that are a result of it.

The Wellcome Trust Sanger Institute plays a key role in many of these projects and continues to be a leading light in the genomics field. In addition to its work in human genetics, it has completed a number of important genome sequences, notably the parasites *Trypanosoma brucei* and *Leishmania*, which cause two of the major diseases in low-income countries, sleeping sickness (human african trypanosomiasis) and leishmaniasis.

These sequences are among the important breakthroughs our funded scientists have made in infectious disease research. We are particularly proud of the work of our Major Overseas Programmes, which have pioneered many life-saving treatments for major diseases in low- and middle-income countries. Our Major Overseas Programme in Thailand, for example, established the use of artemisinin combination therapies for the treatment of malaria. In 2006, these were recommended by the World Health Organization as the frontline treatment for the disease and adopted globally. In Vietnam, meanwhile, researchers have completed an important phase II clinical trial of a new typhoid fever vaccine, developed with funding from our Technology Transfer division. The vaccine proved both safe and effective in eliciting good immune responses in children, encouraging results that can pave the way for larger phase III clinical trials.

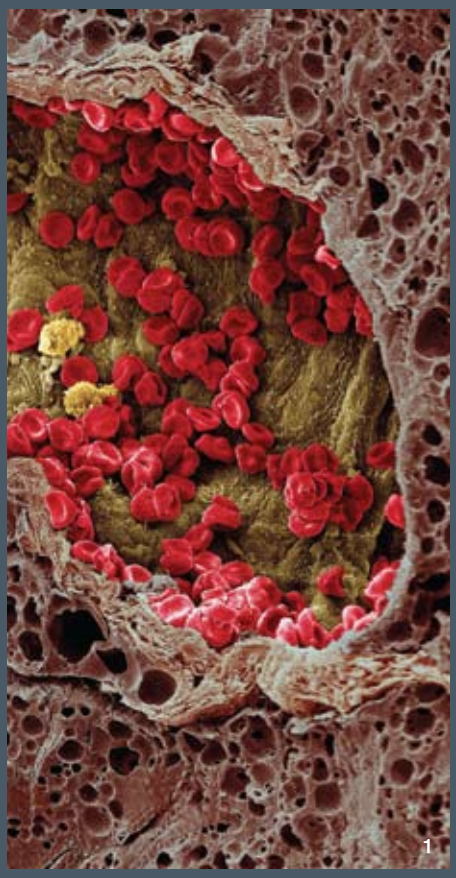
In Kenya, researchers at the KEMRI–Wellcome Trust Research Programme found that invasive bacterial infections, most of which could be prevented with existing vaccines, were the leading cause of death among children at a rural Kenyan hospital. The findings highlighted the neglected threat of bacterial disease to public health and the need to overcome the political and financial barriers to widespread use of vaccines. Researchers at the Programme have also demonstrated that vaccinating against *Haemophilus influenzae* serotype b (Hib), which can lead to meningitis and pneumonia and causes 400 000 deaths per year globally, reduces the number of cases of Hib disease by 88 per cent. The Kenyan Ministry of Health subsequently committed to funding an ongoing nationwide immunisation programme.

In neuroscience, we have seen some significant breakthroughs in our understanding how the brain functions, which could prove crucial to treating neurological and psychiatric diseases. Professor Ray Dolan's group at the Wellcome Trust Centre for Neuroimaging at University College London, for example, is using functional imaging to reveal the brain centres involved in decision making and other cognitive processes. Other brain imaging research at the University of Cambridge and the Institute of Psychiatry at King's College London has revealed distinctive brain activity in people with psychological conditions

**IMAGES**

**1** Blood vessel grown into a melanoma, to which Trust-supported research has linked the *BRAF* gene.

**2** The Trust ran an event at the House of Commons to promote new Darwin initiatives to MPs and peers.



such as obsessive–compulsive disorder and depression.

In 2007, Trust-funded researchers at the University of Edinburgh successfully reversed the autism-like symptoms of Rett syndrome in mice. This suggested that the effects of Rett are not permanently wired into the brain and raises hopes that a range of human neurodevelopmental disorders may be reversible. In London, researchers at the Institute of Psychiatry have developed a highly effective form of cognitive therapy that has helped individuals suffering from post-traumatic stress disorder, including survivors of the 7/7 London terrorist attacks and the Omagh bombing.

We are proud to have supported some of the biggest science projects in the UK over the last few years. The Diamond synchrotron, the largest scientific infrastructure project in the UK for 40 years, has been open to researchers since 2007, producing beams of very bright light that allow scientists to look at the atomic structures of molecules. Meanwhile, UK Biobank, launched in 2006, is well on the way towards achieving its aim of gathering, storing and protecting the world's largest bank of blood and DNA samples, and health information, collected from 500 000 volunteers in the UK aged between 40 and 69. By following this group over many years, it will provide researchers with a unique resource for studying the roles of genes, lifestyle and environment in disease.

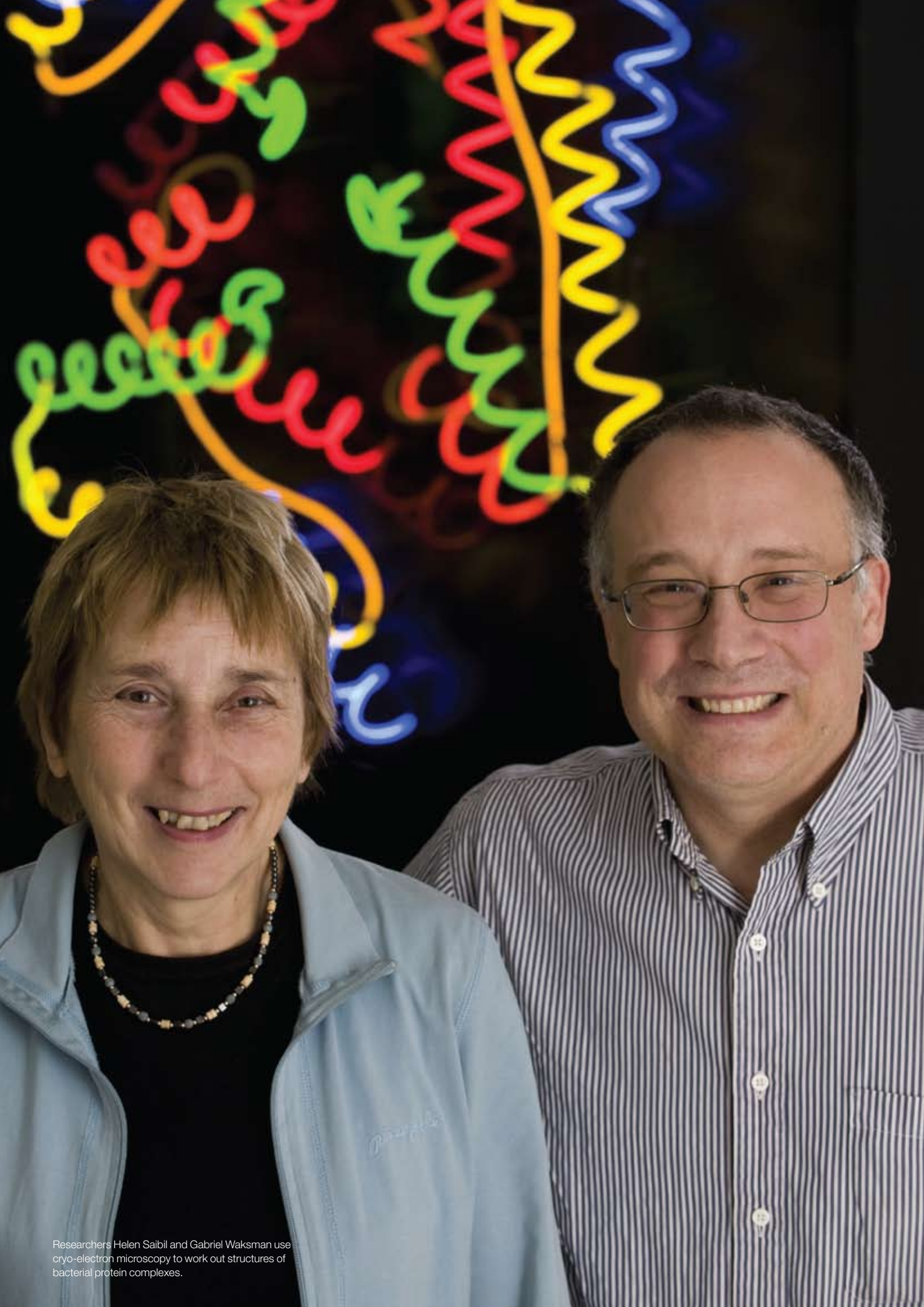
While our Strategic Plan primarily focused on the practical benefits of our advancing knowledge, one of our core goals remains to inspire members of the public, particularly children, with scientific knowledge. Key to this is the development of teachers, who will go on to inspire today's young people, giving them the confidence to understand, debate and question issues surrounding science. In 2006, we helped to establish the National Science Learning Centre to provide teachers and other educators with access to the resources and expertise to get to grips with the complexities of contemporary science. This was taken a step further last year with the launch of Project Enthuse, which offers bursaries to help to train the UK's science teachers in the latest scientific discoveries. In 2007, we were delighted to open the doors to Wellcome Collection, our public venue at 183 Euston Road. In the relatively short time since its opening, Wellcome Collection has garnered critical acclaim and attracted large visitor numbers with its unique mix of science and art. It clearly illustrates the strong appetite of people to explore the connections between science, medicine and wider culture.

Looking forward, we are adding support for the world's best biomedical investigators to take risks and innovate to answer the most challenging research questions. We will also expand our support for translational research to help to bring new medical products and technologies closer to clinical use. And we will outline several strategic 'themes' to identify important global challenges for the research community to respond to. These will link the diverse areas of biomedical science, ethics, history of medicine, public engagement and policy issues that are so important to the Trust. All our work is done in partnership, with governments, with other funders and, most importantly of all, with the universities, research institutes and individual and teams of researchers who enable us to achieve our mission. Many thanks to you all.

**Mark Walport**
Director
January 2010

## HIGHLIGHTS OF THE YEAR

- Genome-wide association studies identify scores of loci involved in common diseases. ▷ p. 6
- Spores found to be critical to spread of *C. difficile*. ▷ p. 10
- New genes causing commonest form of motor neurone disease identified. ▷ p. 11
- Genome of schistosome parasite sequenced. ▷ p. 13
- Promising antimalarial enters drug development pipeline. ▷ p. 20
- Phase I trial confirms safety of neoglycoside antibiotic. ▷ p. 22
- Innovative live surgery broadcast attracts 3.5m viewers. ▷ p. 25
- Darwin-inspired teaching resources supplied to thousands of UK schools. ▷ p. 26
- Structure of membrane transporter protein determined at Diamond synchrotron. ▷ p. 37



Researchers Helen Saibil and Gabriel Waksman use cryo-electron microscopy to work out structures of bacterial protein complexes.

# Advancing knowledge

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

## AN INSIDE JOB

**Advanced imaging techniques are providing a glimpse of important bacterial 'nanomachines'.**

Within the cell, proteins typically operate as part of large multisubunit assemblies – nanomachines capable of performing sophisticated molecular engineering. Researchers at University College London and Birkbeck, University of London have used cryo-electron microscopy to work out the structures and possible mechanisms of action of two important bacterial protein complexes.

Cryo-electron microscopy – electron microscopy at extremely low temperatures – can provide a 'snapshot' of structures within their natural environments. Helen Saibil has used the technique to piece together the structures of the bacterial 'chaperones' GroEL and GroES, which together form a barrel-like chamber within which polypeptides fold up into their correct shapes.

Now, for the first time, Professor Saibil's group has visualised a polypeptide bound to a chaperone complex as it begins to fold, as well as when it has reached its final conformation.

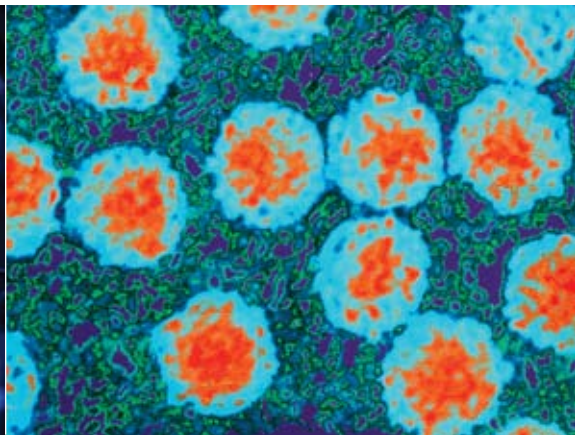
This work exploited a variation of the GroEL–GroES system used by the bacteriophage T4 (a bacterial virus). A key T4 protein (gp23) is too large to fit within the standard GroEL–GroES complex. To accommodate gp23, GroES is replaced by a related but larger protein known as gp31, which is encoded within the T4 genome. The cryo-electron microscopy revealed that, even with this larger chaperone, the folding chamber is strained and deformed by the presence of gp23 within it.

Gabriel Waksman and colleagues, meanwhile, have been tackling a massive protein complex situated in the bacterial membrane – actually spanning the two membranes that make up the surface coat of Gram-negative bacteria. This 'type IV' secretion system is particularly significant as it is the route by which plasmids encoding antibiotic resistance factors and other important molecules are exported from the cell.

The structure reveals how 14 copies of three different proteins come together to form a two-chambered, double-walled channel.[2] It is open on the inside of the cell but squeezed shut on the outside. Importantly, its structure is quite different from other characterised export systems. Ultimately, an understanding of its structure could aid the development of agents to block the spread of antibiotic resistance.

*1 Clare DK et al. Nature 2009;457(7225):107–10.*

*2 Fronzes R et al. Science 2009;323(5911):266–8.*



## COMING UP TRUMPS

**Genome-wide studies have identified hundreds of disease associations.**

Set up in 2007, the Wellcome Trust Case Control Consortium has pioneered a new wave of large-scale, high-throughput genome-wide association studies. These studies have identified several hundred genetic sites influencing ('associated with') common diseases. Looking forward, next-generation sequencing technologies are providing the tools to identify many more.

Genome-wide studies have continued to develop at an astonishing rate. As well as being applied to a wider range of conditions, such as Alzheimer's disease,[1] they are also being used to explore physiological traits relevant to disease, such as blood lipid[2] or blood glucose[3] levels or blood pressure.[4] Extensive international collaborations have enabled data to be pooled, which has enabled even more risk loci to be identified (see page 8).

While each individual association has value, collectively they may shed further light on disease processes. Studies of Crohn's disease, for example, implicated autophagy (breakdown and disposal of cell structures) as an important disease process.[5] Studies of autoimmune conditions have revealed that many risk loci are shared between diseases.[6] In type 1 diabetes, genetic discoveries are shedding light on environmental influences on disease (see right).

The studies also provide clues to the 'genetic architecture' of disease. Most conditions are influenced by a large number of genes, mostly of small individual effect. Indeed, a significant fraction of the genetic contribution to disease remains unaccounted for. Furthermore, only rarely has the precise genetic risk factor (the 'causal variant') been identified. In some cases, a single association may actually be a composite of several genetic variants lying close together (as seen in rheumatoid arthritis).[7]

To winkle out the remaining genetic factors – and to move from an association to a causal variant – a much more detailed view of human genetic variation is needed. This is the goal of the 1000 Genomes Project, which is using next-generation sequencing technologies to provide a high-resolution view of variation. A stepping-stone towards this goal was the sequencing of the first individual African genome, in a collaboration between the Wellcome Trust Sanger Institute and the next-generation sequencing company Illumina.[8]

With new statistical and methodological tools also being developed (see page 33), these resources will continue to drive rapid progress in the genetic dissection of common diseases.

**This research was supported by the Wellcome Trust and other funders.**

*1 Harold D et al. Nat Genet 2009;41(10):1088–93. Erratum in: Nat Genet 2009;41(10):1156.*

*2 Prokopenko I et al. Nat Genet 2009;41(1):77–81.*

*3 Soranzo N et al. Nat Genet 2009;41(11):1182–90.*

*4 Newton-Cheh C et al. Nat Genet 2009;41(6):666–76.*

*5 Parkes M et al. Nat Genet 2007;39(7):830–2.*

*6 Barton A et al. Hum Mol Genet 2009;18(13):2518–22.*

*7 Orozco G et al. Hum Mol Genet 2009;18(14):2693–9.*

*8 Bentley DR et al. Nature 2008;456(7218):53–9.*

## CLOSE ASSOCIATION

**Follow-up of genome-wide analyses can reveal disease mechanisms – and even possible environmental influences on disease.**

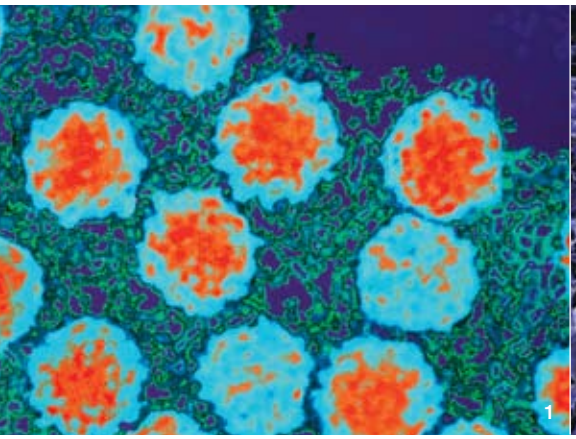
Genome-wide studies identify associations between a disease and a genetic marker, but only rarely is that marker itself the factor affecting risk. More likely, it just happens to be close to (and hence inherited with) the true culprit. At the Cambridge Institute of Medical Research, Linda Wicker and John Todd's groups are homing in on 'causal variants' in type 1 diabetes.

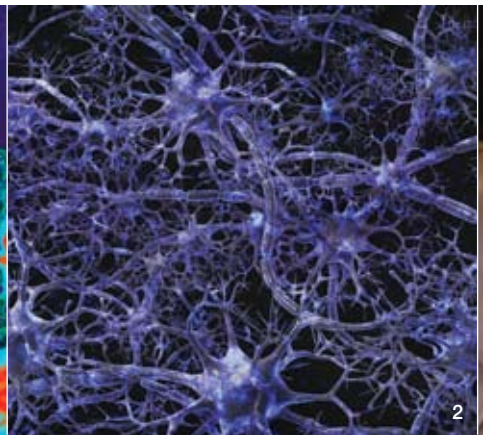
One way to connect the two is to look for nearby genes that could plausibly affect a disease. As type 1 diabetes is caused by a self-directed immune response, Linda Wicker, John Todd and colleagues focused on a likely candidate gene (encoding a protein known as IL2RA or CD25) involved in immune system function.[1]

Genetic variants around the *IL2RA* gene affected how much IL2RA protein was present on the surface of a key set of immune cells. Moreover, the variants previously linked to diabetes had the greatest effect on IL2RA levels. Hence, variation in IL2RA levels affecting the function of these immune cells is likely to underlie the increased risk of diabetes.

Adopting a different strategy, John Todd, Sergey Nejentsev and collaborators at Roche-454 used next-generation techniques to sequence ten genes implicated in type 1 diabetes in nearly 1000 patients and controls.[2]

**IMAGE**
Millions of samples can be genotyped in high-throughput facilities.





## MIND YOUR LANGUAGE

This deep sequencing revealed fine-grained variation that could be tested for its association with disease.

The strongest association was seen with four variants around the *IFIH1* gene, encoding the MDA5 protein, which is involved in the interferon response to enteroviruses – common RNA viruses already suggested as possible environmental factors in some cases of type 1 diabetes. Interestingly, all four lowered the risk of disease (i.e. they were protective) and disrupted the MDA5 protein. This suggests that 'normal' immune responses to enteroviruses may increase the risk of beta cell damage, leading to type 1 diabetes.

In separate work, Professor Todd and David van Heel at Barts and The London School of Medicine and Dentistry have found that some diabetes risk alleles also predispose to coeliac disease (and vice versa), suggesting a strong biological link between the two.[3] Dietary antigens are known to trigger an immune response that affects gut tissue in coeliac disease, but beta cells may also be affected, leading to type 1 diabetes.

**This research was supported by the Wellcome Trust and other funders.**

*1 Dendrou CA et al. Nat Genet 2009;41(9):1011–5.*

*2 Nejentsev S et al. Science 2009;324(5925):387–9.*

*3 Smyth DJ et al. N Engl J Med 2008;359(26):2767–77.*

**Genes affecting reading and language skills may be having a wide impact.**

On rare occasions, a reading or language impairment results from mutation of a single gene. Usually, though, many genes are likely to be involved. As work by Tony Monaco and Simon Fisher at the Wellcome Trust Centre for Human Genetics in Oxford is revealing, both may reflect aberrant wiring of the nervous system.

Dyslexia is common, affecting around 10 per cent of the population. Professor Monaco has obtained compelling evidence that a gene known as *KIAA0319* is a risk factor for the condition. The genetic variant most strongly associated with dyslexia is in the control region of the gene. It contains a binding site for a gene-silencing protein, which significantly reduces *KIAA0319* activity.[1]

Why low levels of *KIAA0319* protein predispose to dyslexia is not clear. The protein is present on the surface of cells and seems to help neurons to migrate to their correct locations in the cerebral cortex during development of the brain.

Interestingly, a study of 6000 seven-to-nine-year-olds from the ALSPAC birth cohort (see page 38) revealed that *KIAA0319* was also associated with poor reading ability – but not other cognitive measures such as IQ – in the general population.[2] As the variant is carried by around 15 per cent of people, it is likely to be having a significant impact, with diagnosed cases of dyslexia representing the extreme end of a spectrum of impairment.

Rather than affecting reading and writing skills, mutations of *FOXP2* – identified by Professor Monaco and Dr Fisher in 2001 – cause a rare severe speech disorder. In a recent investigation of genes regulated by *FOXP2*, Dr Fisher identified a gene, *CNTNAP2*, encoding a protein present in the membranes of neurons, where it mediates interactions with other cells. Variants of *CNTNAP2*, Dr Fisher and Professor Monaco discovered, are associated with common forms of specific language impairment.[3]

*CNTNAP2* has also been implicated in language delay in autism. Possibly, certain variants of *CNTNAP2* increase the risk of language abnormalities, while different genes contribute more to other deficits seen in autism.

As *FOXP2* also affects the development of neuronal pathways, these studies highlight the importance of nervous system wiring to the development of language and reading skills. It remains a significant challenge to identify exactly how gene variation (and environmental factors) influence neural wiring and complex skills such as language and reading.

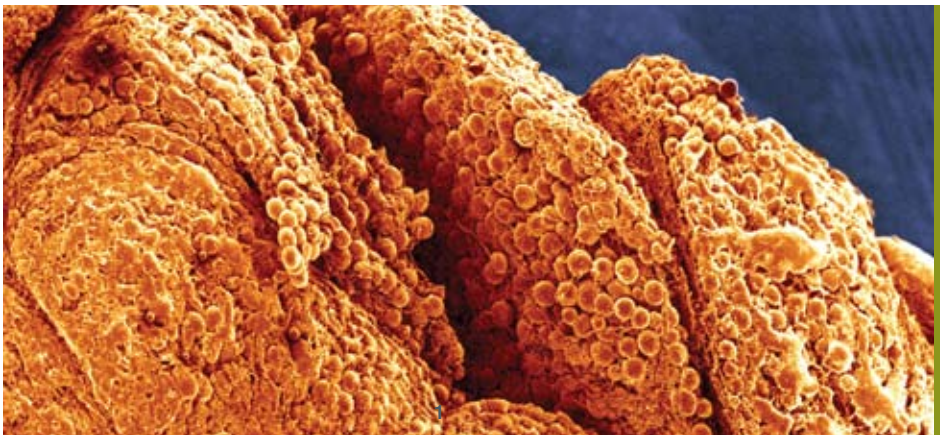
*1 Dennis MY et al. PLoS Genet 2009;5(3):e1000436.*

*2 Paracchini S et al. Am J Psychiatry 2008;165(12):1576–84.*

*3 Vernes SC et al. N Engl J Med 2008;359(22):2337–45.*

IMAGES

**1** Enteroviruses are thought to be involved in some cases of type 1 diabetes.
**2** Abnormal wiring of neurons in the brain may underlie reading and language disorders.
**3** A gene implicated in dyslexia may affect reading skills in the general population.



# GENOMES SHAPE UP

**Genome-wide studies are shedding light on the genetics of human size and shape, while follow-up studies are revealing more about the genes' biological effects.**

Genome-wide studies are revealing the genetic architecture of complex or 'quantitative' traits – where characteristics vary over a range of values rather than in the 'either/or' fashion of classical Mendelian genetics. Human size and shape are both archetypal quantitative traits and of medical significance – not least because of the link between excess weight and type 2 diabetes.

In 2007, the Wellcome Trust Case Control Consortium identified the first gene associated with height variation in the general population, *HMGA2*. More recently, further analysis revealed 20 other loci affecting height, collectively explaining around 3 per cent of height variation (or a 5 cm difference between people with mainly 'short' alleles and those with mainly 'tall' alleles).[1] The loci affect a wide range of pathways, including the well-studied 'hedgehog' signalling pathway, components of the extracellular matrix and pathways implicated in cancer. Ultimately, the number of genes affecting height is likely to run into the hundreds.

One way in which genes can affect height is by influencing skeletal growth. In a study of 20 000 individuals from the UK and the Netherlands, Panos Deloukas at the Wellcome Trust Sanger Institute and colleagues identified genetic variants affecting height and skeletal frame size. Several genes were found to affect traits such as trunk length, hip axis length and femur length.[2]

The height we finally grow to appears to be influenced by multiple independent pathways – trunk size, for example, is controlled independently of leg length (the main factor affecting height). Breakdowns such as this can suggest which processes particular genes may be affecting, and provide insight into bone-related medical conditions such as osteoporosis and arthritis.

Another gene to emerge from the Case Control Consortium's early work was *FTO*, the first gene found to affect body mass index in the general population. This was followed up by the discovery that common variants around the *MC4R* locus, mutation of which causes severe childhood obesity, also have an effect on body weight.[3] Two recent studies have advanced this area considerably.

Pooling of data from 15 studies, including those conducted by the Consortium, confirmed the effects of *FTO* and *MC4R* but also identified six further loci affecting body weight. Strikingly, several of these genes are active in the brain, highlighting the brain's key role in weight control.[4]

In terms of health, weight is not necessarily the best guide to someone's medical prospects – the size and location of fat deposits are of more critical importance. A pooling of data from 16 genome-wide association studies has now identified two loci specifically affecting waist circumference and one affecting waist-to-hip ratio in women.[5] In these cases, it appears that the genetic effects may be on the development and metabolism of fat rather than the brain's energy balance.

*FTO* remains the locus with the greatest impact on weight, and its discovery has opened up a fertile area of research. There are hints that *FTO* may have an effect on appetite. Studies of children's recorded calorie intake in the ALSPAC cohort (see page 38), for example, found a link between the *FTO* risk allele and increased calorie intake.[6]

By contrast, work on a mouse model carrying an *FTO* mutation, developed by Roger Cox, Frances Ashcroft and colleagues at MRC Harwell and the Wellcome Trust-funded OXION initiative, suggests that *FTO* has a metabolic effect. Unlike mice completely lacking *FTO*, these animals do not overeat but are lean and have a high metabolic rate – and hence are constantly burning off more energy.[7] Notably, the work suggests that interfering with *FTO* could offer a way to control obesity.

Collectively, these studies illustrate how complex control of body form is. As all of the genetic variations are of modest effect size (and much of the genetic influence remains undiscovered), the implications for individuals are generally still minor. Crucially, though, they provide a route into the key pathways affecting health-related traits in the general population.

**This research was supported by the Wellcome Trust and other funders.**

*1 Weedon MN et al. Nat Genet 2008;40(5):575–83.*

*2 Soranzo N et al. PLoS Genet 2009;5(4):e1000445.*

*3 Loos RJ et al. Nat Genet 2008;40(6):768–75.*

*4 Willer CJ et al. Nat Genet 2009;41(1):25–34.*

*5 Lindgren CM et al. PLoS Genet 2009;5(6):e1000508.*

*6 Timpson NJ et al. Am J Clin Nutr 2008;88(4):971–8.*

*7 Church C et al. PLoS Genet 2009;5(8):e1000599.*

IMAGE
Adipose tissue, the amount and distribution of which is affected by genetic variants.

# HISTORY IN THE GENOME

**The 'domestication' of sheep retroviruses is revealing the history of sheep domestication.**

Sheep were among the first animals to be domesticated, some 9000 years ago, as a source initially of meat and later of secondary products such as wool. As Charles Darwin appreciated 150 years ago, domestication dramatically alters evolution. More recently, Massimo Palmarini's research into sheep retroviruses at the University of Glasgow is providing a fascinating glimpse of evolution both ancient and modern in this important livestock species.

Like all mammals, sheep can be infected by retroviruses – viruses that have RNA as their genetic material. Their RNA is copied into DNA, which then integrates into the genome, where it directs the production of virus particles. Occasionally a retrovirus genome can become 'trapped' in the host genome: it no longer makes the virus but is passed on from generation to generation in the host DNA. Such elements are known as endogenous retroviruses. They are surprisingly common: the human genome, for example, contains many thousands.

Professor Palmarini is particularly interested in a retrovirus known as Jaagsiekte sheep retrovirus (JSRV) and its endogenous relatives. JSRV causes a form of lung cancer in sheep. As well as having veterinary importance, it is also a valuable model system for understanding the interplay between infectious and endogenous retroviruses.[1]

Remarkably, endogenous retroviruses are not simply carried around as 'junk' but have evolved to play important roles in host cells. In a poacher-turned-gamekeeper twist, one of their roles is to block infection by pathogenic retroviruses. For example, one endogenous relative of JSRV produces a slightly modified envelope protein that intermingles with the protein produced by the invading virus. In doing so, it prevents the virus protein from being processed through the cell's intracellular protein trafficking system, so the cell cannot release new virus particles.[2]

Even more surprisingly, Professor Palmarini and colleagues in Texas have shown that endogenous retroviruses play a key role in sheep reproduction, being essential for the development of the placenta.[3] Viral envelope proteins are very effective at sticking cells together and promoting cell fusion. They may be being put to work in the formation of multinucleate cells in the placenta, which depends on cell fusion. During evolution, it is possible that viral defence was their first role, but they were later co-opted to support reproduction.

Aside from their biological role, endogenous retroviruses are also useful tools for tracking evolutionary changes. Because mutations steadily accumulate in their DNA sequences, it is possible to estimate how long they have been resident in the sheep genome.

Of the 27 endogenous retroviruses related to JSRV, some are very ancient, dating back to the time when sheep and goat lineages were diverging (5–7 million years ago). Two entered the genome around the time different sheep species were appearing, around 3 million years ago. These elements became fixed in the genome when domestication began. And one element seems to have entered the sheep genome within the past two centuries.

Sheep and goats were originally domesticated for their meat, probably on multiple occasions in south-west Asia. After spreading throughout Europe, these animals were largely supplanted by a second wave of animals selected for wool production. Some 'primitive' types clung on at the fringes on expansion or escaped and survived as feral animals.

By looking at the pattern of endogenous retroviruses in 133 breeds of sheep, Professor Palmarini has been able to determine the relatedness of breeds and hence their likely domestication history.[4] Some elements show distinct geographic patterns: enJSRV-18, for example, is found in Soay sheep, now confined mainly to the island of St Kilda, and Mediterranean mouflon. In fact, Soay, mouflon of Sardinia, Corsica and Cyprus, and Scandinavian breeds appear to be the last relics of the first great wave of domesticated sheep, largely displaced by 'modern' breeds.

The work also sheds light on an 'outlier' among UK sheep: the 'Jacob' sheep, named after the Biblical story of Jacob, who was given every "speckled and spotted" sheep from his father-in-law, Laban. One theory is that it was imported from Norse countries; another suggestion is that it was washed up after the sinking of the Spanish Armada. The genetic evidence confirms its status as an oddity, related to Asian breeds.

**This research was supported by the Wellcome Trust and other funders.**

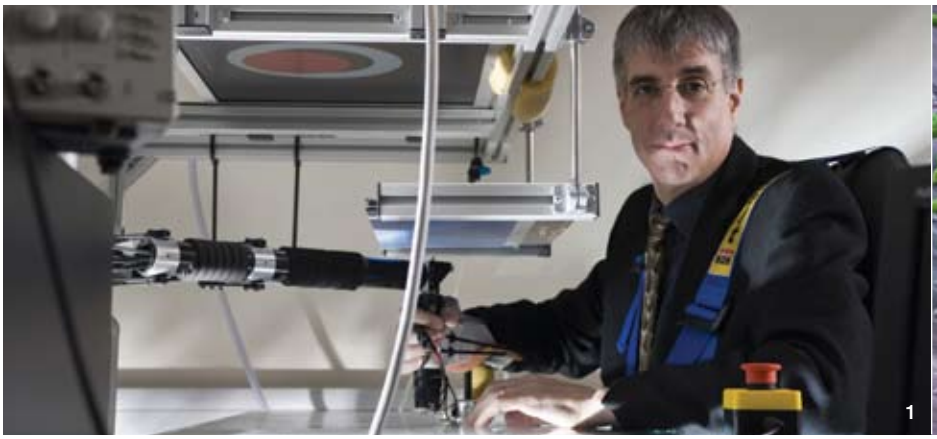
*1 Arnaud F et al. PLoS Pathog 2007;3(11):e170.*

*2 Arnaud F et al. J Virol 2007;81(20):11441–51.*

*3 Dunlap KA et al. Proc Natl Acad Sci USA 2006;103(39):14390–5.*

*4 Chessa B et al. Science 2009;324(5926):532–6.*

**IMAGE**
Retroviruses can be used to study the evolution of domesticated sheep.



## BETTER LATE THAN NEVER

**What happens when the brain changes its mind?**

Controlling movement is central to human life. Although models have come up with good explanations of how movement decisions are made in the brain, none can explain one crucial aspect: how we change our mind. By exploiting ingenious mechanical tools, Daniel Wolpert at the University of Cambridge has come up with a possible solution to this conundrum.

Humans show astonishing motor control skills: although a computer can beat the world's best chess player, none comes close to an average five-year-old's ability to move a pawn. These skills rely on our ability to integrate sensory information from multiple sources.

But sensory information is inherently ambiguous ('noisy'). To cope with this noise, the brain adopts a statistical approach. A decision to move is thought to be based on the rapid accumulation of noisy information until it hits a threshold, triggering action.

This model has stood up well to testing, but has one obvious flaw: it cannot account for changes of mind – once the threshold has been reached, movement is inevitable.

Working with Michael Shadlen from the University of Washington in Seattle, Professor Wolpert has come up with a way round this problem. Because of lags in the motor system, it is possible that the brain is still processing information even as movement is being triggered. Together, the two researchers developed a model that predicts that if this 'late' information contradicts earlier input sufficiently strongly, it is possible that an alternative threshold is reached, leading the brain to send a second signal that countermands the first – resulting in a change of mind.

To test this idea, a system was set up in which volunteers had to decide in which direction a set of spots was moving across a screen – with extra random spots making it difficult to judge.[1] Subjects had to choose left or right, by moving a robotic handle. Crucially, around 10–15 per cent of the time, subjects headed in one direction before veering toward the other – changing their mind.

Significantly, these changes of mind usually corrected a wrong choice – suggesting that additional active processing of information had led to a better decision.

Even though based on an artificial situation with a simple binary choice, the findings may well be broadly applicable. Even though processing is so rapid it happens below the level of conscious awareness, it is plausible that similar mechanisms are at work when we experience the cognitive sensation of changing our mind.

*1 Resulaj A et al. Nature 2009;461(7261):263–6.*

## SPORE DRAW

**The spore is *Clostridium difficile*'s secret weapon – but may also be its Achilles heel.**

*Clostridium difficile* has become one of the most worrisome public health threats of the 21st century. Commonly seen in healthcare settings, cases have leapt tenfold in the last decade. *C. difficile* is both highly infectious and difficult to eradicate – traits that, research at the Wellcome Trust Sanger Institute has revealed, are linked to the durability of its spores.

To get a better picture of *C. difficile* transmission, Trevor Lawley, Gordon Dougan and colleagues have established a model hospital environment with mice as 'patients'. When *C. difficile* was introduced, it colonised the intestines of mice without causing any symptoms. The mice shed spores, but did not infect others living with them. However, when treated with antibiotics, the mice become highly infectious 'supershedders', releasing vast numbers of spores that rapidly spread disease through the mouse community.[1]

The sudden change occurs because antibiotic treatment kills most of the naturally occurring bacteria in the gut, opening up an environment that *C. difficile* can rapidly colonise. When antibiotic treatment is halted, the gut bacteria recover and displace *C. difficile* (although some animals remain supershedders for several months).

The work highlights the importance of non-pathogenic gut bacteria in keeping

IMAGES
**1** Daniel Wolpert at the University of Cambridge.
**2** *Clostridium difficile*.

*C. difficile* under control. In theory, manipulating the gut's microbial ecosystem – promoting the growth of harmless bacteria – could provide a way to manage *C. difficile*. Indeed, the gut bacteria present in mouse faecal material can be used to inoculate animals and suppress *C. difficile*. Although this is not a practical option for people, it may be possible to identify which bacterial species are most effective at suppressing *C. difficile* and use them in a form of 'bacterial therapy'.

The Sanger Institute team has also been able to purify spores, enabling a proteomic analysis to be carried out (in conjunction with Jyoti Choudhary and the Sanger mass spectrometry team). This has revealed hundreds of spore-associated polypeptides, many seen across the *Clostridium* family but some specific to *C. difficile*.[2] Ultimately, a greater understanding of the make-up of the spore will provide leads towards better diagnostics and vaccines.

The team is also looking at how spores are affected by widely used disinfectant techniques. While spores are eradicated by highly oxidising approaches such as vapourised hydrogen peroxide ('deep clean'), many cleansing products have worryingly little effect. Collaborations are now being established with hospitals to identify ways to use the new findings to track and, it is hoped, to block the spread of *C. difficile*.

*1 Lawley TD et al. Infect Immun 2009;77(9):3661–9.*

*2 Lawley TD et al. J Bacteriol 2009;191(17):5377–86.*

## AGGREGATE LEADS

**The genetic basis of amyotrophic lateral sclerosis is gradually being unpicked.**

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neurone disease. It causes a relentlessly progressive muscle paralysis as motor neurones degenerate, and is invariably fatal. Around 10 per cent of cases run in families, with the remainder occurring sporadically. For the past 15 years mutations in just one gene, *SOD1*, have been linked to ALS, but *SOD1* explains only a fraction of cases and the mechanisms of disease remained frustratingly unclear. In the past 18 months, Chris Shaw at King's College London and colleagues have identified two further genes that cause ALS when mutated, shedding more light on this distressing condition.

Inside the motor neurones of people with ALS are characteristic clumps of protein that have been tagged for recycling but have not been broken down. The main constituent of these clumps is a protein known as TDP-43, and in 2008 Professor Shaw's group discovered mutations in the gene encoding TDP-43, *TARDBP*, in a familial case of ALS.[1] Screening for changes in this gene revealed mutations in one large family and two sporadic cases.[2] Follow-up work by many other groups has confirmed that *TARDBP* mutations are a significant cause of ALS.

Although TDP-43 mutations are rare, TDP-43 protein is deposited in 90 per cent of all people with ALS and is the single biggest clue to the cause of motor neurone disease.

The discovery of *TARDBP* also led Professor Shaw's group to consider similar proteins as possible causes of ALS in other families. This hunch proved correct, with the subsequent identification of a mutation in a gene known as *FUS*.[3] Screening other unexplained cases revealed a further seven families with *FUS* mutations.

Normally, TDP-43 and FUS proteins are found in the nucleus. The effects of mutations in their respective genes are strikingly similar, both leading to large protein aggregations. The pathological effects of TDP-43 could be due to the build-up of toxic deposits in the cell, but equally could be due to loss of normal TDP-43 function in the nucleus. The latest discoveries have provided powerful biological tools to explore underlying disease mechanisms and distinguish between these possibilities.

**This research was supported by the Wellcome Trust and other funders.**

*1 Sreedharan J et al. Science 2008;319(5870):1668–72.*

*2 Rutherford NJ et al. PLoS Genet 2008;4(9):e1000193.*

*3 Vance C et al. Science 2009;323(5918):1208–11.*

**IMAGE**
Chris Shaw of King's College London.

## TRACKING CALCIUM

**An understanding of calcium dynamics in the cell may point the way toward new therapeutics.**

Calcium signalling underpins everything from fertilisation to muscle contraction. Several groups' work this year has significantly advanced our understanding of how calcium flows are finely tuned in the cell.

Three small chemical messengers are crucial to calcium signalling: two ($InsP_3$ and cADPR) trigger release from endoplasmic reticulum (ER) stores; a third, NAADP, was discovered only recently but has turned out to be the most potent stimulant of calcium release.

Antony Galione and John Parrington in Oxford, Mark Evans in Edinburgh and colleagues in the USA and China have made an important step forward in understanding the NAADP system, identifying its receptor and the location of the NAADP-sensitive calcium store.[1] Surprisingly, calcium is released from acidic compartments such as lysosomes, not previously known as major calcium stores. This initial burst of calcium can trigger further calcium release through the $InsP_3$ and cADPR systems, amplifying the original signal.

Calcium is a versatile signalling system: a wide range of signals can be generated, from local 'puffs' to global 'waves' spreading across the cell. Colin Taylor in Cambridge and colleagues have found that 'tuning' of $InsP_3$ receptors can generate complex spatiotemporal patterns of calcium release.

Their reseach has shown that $InsP_3$ receptors are initially randomly distributed in the ER membrane. When $InsP_3$ first binds, receptors aggregate into small clusters, which alters their sensitivity to both $InsP_3$ and calcium. The signal generated will therefore depend on levels of $InsP_3$ and calcium (and other inputs). $InsP_3$ can thus generate a hierarchical set of responses – initially from single channels, then puffs from clusters of channels and then waves as multiple puffs coalesce.[2]

Ultimately, modulating calcium signalling could be a way to modify the behaviour of cells involved in disease processes. The receptors that mediate calcium release are obvious targets. Working with Professor Taylor and others, Barry Potter in Bath has developed a range of chemical analogues that mimic or interfere with the triggers of calcium signals; these agents have been used to provide detailed insight into the mechanics of $InsP_3$ receptor activation.[3] Working with groups in Germany, Professor Potter has also designed other agents to block NAADP signalling and modulate the activation of T cells[4] – opening up a possible route to the treatment of autoimmune diseases.

**This research was supported by the Wellcome Trust and other funders.**

*1 Calcraft PJ et al. Nature 2009;459(7246):596–600.*

*2 Taufiq-Ur-Rahman et al. Nature 2009;458(7238): 655–9.*

*3 Rossi AM et al. Nat Chem Biol 2009;5(9):631–9.*

*4 Dammermann W et al. Proc Natl Acad Sci USA 2009;106(26):10678–83.*

## ALL IN THE BRAIN

**Infections can cause a variety of physical symptoms, but they also make us feel bad. How these feelings are triggered in the brain is now becoming clear.**

Ever since the Ancient Greeks, the mind and emotions have been cordoned off from the body. Recently, however, there has been a flourishing of research into the neural correlates of emotions and 'subjective' feelings. In work begun at University College London and continued at the University of Sussex, Hugo Critchley and Neil Harrison are examining how inflammation in the body affects mood and brain function.

We all recognise the sensation of feeling 'under the weather' when laid low by an infection. Yet while the immune system's response to infection receives close scrutiny, much less attention is given to the attendant mental symptoms – collectively known as 'sickness behaviour'.

To get a better handle on the brain's response to systemic infection, Professor Critchley, Dr Harrison and their colleagues have explored the effects of artificially induced inflammation on brain activity, brain function and mood. Volunteers were injected with either typhoid vaccine, to induce inflammation, or a saline placebo, then given a battery of tests while their brain activity was being monitored by functional magnetic resonance imaging.

Participants who received the vaccine suffered a notable deterioration of mood.[1] Functional imaging revealed corresponding changes in brain activity:

IMAGE
'Sickness behaviour' illustrates how systemic infection can affect the brain.

images of emotional faces, for example, triggered abnormally high activity in an area of the brain known to be involved in depression, while connectivity between this area and other regions of the brain was reduced. Such findings could explain why feeling ill has much in common with feeling depressed.

In addition, participants suffered greater fatigue, confusion and impaired concentration when undertaking a cognitively demanding task. Doing the test activated 'interoceptive' brain regions – those implicated in sensations of internal body states.[2] The extent to which these areas were activated was a good match for the levels of fatigue and confusion reported. Those who did well on the test tended to recruit additional prefrontal areas of the cortex.

The results thus provide direct evidence of how an immune response can influence brain activity, performance and subjective feelings. In the long term, an understanding of these processes may suggest ways to overcome the negative impact of infection on our brains and behaviour.

*1 Harrison NA et al. Biol Psychiatry 2009;66(5):407–14.*

*2 Harrison NA et al. Biol Psychiatry 2009;66(5):415–22.*

## FLUKE OF NATURE

**The genome sequence of a schistosome parasite is of interest to medical researchers and evolutionary biologists alike.**

Schistosomes – flukes or parasitic flatworms – are responsible for a huge global health burden. Over 200 million cases of schistosomiasis occur every year, disabling millions and killing hundreds of thousands. The genome sequence of *Schistosoma mansoni*, sequenced by Matt Berriman and colleagues at the Wellcome Trust Sanger Institute,[1] is suggesting new ways to break the transmission cycle but is also providing clues to pivotal stages of evolution: the development of organs and of the bilateral body plan.

The *S. mansoni* genome consists of some 360 million bases, and shows some curious features. Within its 12 000 genes, the gaps in its coding regions (introns) are small near the starts of genes and much larger towards their ends. The genome sequence also revealed families of genes with very small exons (chunks of coding sequence) that seem to be mixed and matched in multiple combinations – possibly a mechanism to increase protein variability and help the parasite to evade the host immune system.

A detailed analysis of the genome has identified many possible avenues for drug development, such as proteins not seen in vertebrates and new members of protein families typically targeted by drugs. Indeed, some *S. mansoni* proteins resemble those for which potential drugs already exist.

Schistosomes are an important evolutionary stepping-stone. Comparisons with more simple organisms such as sea anemones have shed light on the new genetic features that led to anatomical innovations maintained throughout the evolution of higher animals – such as the three-layered body plan and the formation of organs. Similarly, comparisons up the family tree are providing insight into the steps needed to create the complex anatomical structures seen in higher animals.

*1 Berriman M et al. Nature 2009;460(7253):352–8.*

**IMAGE**
The head of the parasitic flatworm *Schistosoma mansoni*.

# New funding

## NEW GENOME-WIDE STUDIES

**Anorexia nervosa, dengue fever and tuberculosis in Russia are among the conditions to be studied in ten new genome-wide association studies receiving a total of £10 million funding.**

David Collier of the Institute of Psychiatry is working with the Wellcome Trust Case Control Consortium and international collaborators to explore the genetic risk factors associated with anorexia nervosa.

Cameron Simmons (University of Oxford) is jointly leading a programme with Martin Hibberd (Genome Institute of Singapore) and Anavaj Sakuntabhai (Pasteur Institute) to identify the genetic basis of dengue shock syndrome, a life-threatening complication of dengue virus infection that particularly affects the young. Studies in Vietnam will test the theory that susceptibility is due to host genetic variation.

Sergey Nejentsev at the University of Cambridge is working with the Wellcome Trust Sanger Institute and the TB-EUROGEN consortium to identify genetic risk factors affecting susceptibility to mycobacterial infection and progression to TB.

Other studies to be carried out under the umbrella of the Wellcome Trust Case Control Consortium will examine host control of HIV, renal transplant failures and pre-eclampsia, while the Sanger Institute has received support for core genotyping facilities.

Other studies will tackle congenital heart disease, complications of pregnancy and childhood kidney cancer.

## PANDEMIC INFLUENZA

**In partnership with other UK agencies, the Wellcome Trust has moved rapidly to support research on pandemic H1N1 swine flu.**

In May 2009, the Trust convened a workshop with the Medical Research Council (MRC), the UK Department of Health and others to identify research priorities and opportunities during an unfolding influenza pandemic.

After 'fast-track' peer review, two programmes were jointly funded by the Trust and the MRC. Led by Andrew Hayward at University College London, the 'FluWatch' programme, awarded £2.1 million, will examine the spread and impact of swine flu in up to 10 000 individuals in 4000 households, providing a detailed view of flu in the community.

The Mechanisms of Severe Acute Influenza Consortium (MOSAIC), led by Peter Openshaw of Imperial College London, has been awarded £2.7m. It will study up to 500 cases to try to unpick both host and viral factors contributing to disease severity.

A second workshop, with the MRC, the Biotechnology and Biological Sciences Research Council and the UK Department for Environment, Food and Rural Affairs, focused on veterinary swine flu. A £1.7m consortium grant was subsequently awarded to fund the COSI (Combating Swine Influenza) initiative. A collaboration led by James Woods at the University of Cambridge will monitor the spread of pandemic H1N1 swine flu in the UK pig industry, while Ian Brown at the Veterinary Laboratories Agency Weybridge and colleagues will examine the virus's effect on pigs.

## NEURODEGENERATIVE DISEASE

**Three research programmes tackling Alzheimer's disease, Parkinson's disease and motor neurone disease have received a total of £17 million Strategic Award funding through a neurodegenerative disease partnership with the Medical Research Council (MRC).**

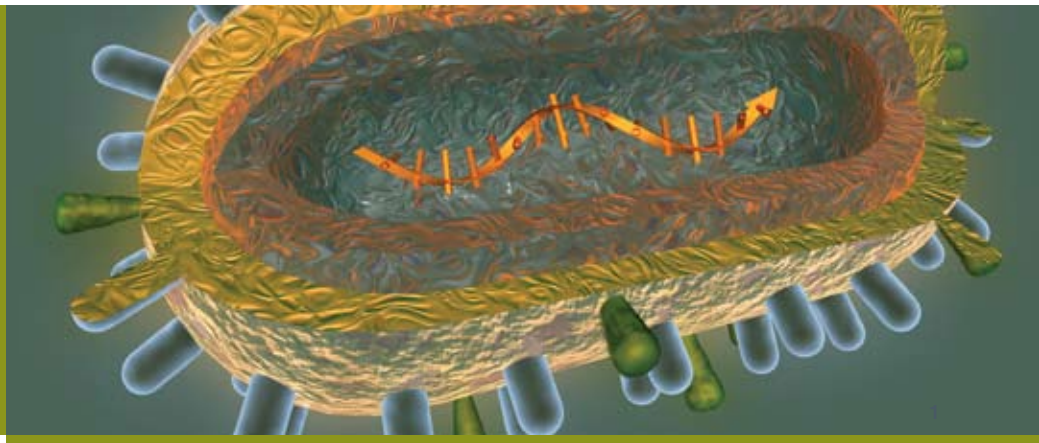
The multidisciplinary collaborations aim to provide a better understanding of the causes and mechanisms of disease, in a bid to improve early diagnosis and identify new therapeutic leads.

The Alzheimer's programme will be led by Peter St George-Hyslop of the Cambridge Institute for Medical Research. Investigators from Cambridge, Bristol, Germany and Canada will use innovative tools from physics, chemistry and biology to investigate how the accumulation of amyloid beta and tau proteins leads to the death of brain cells in Alzheimer's and related neurodegenerative diseases.

Chris Shaw of the MRC Centre for Neurodegeneration Research, King's College London, will head a programme based on recent advances in understanding the genetic causes of motor neurone disease (see page 11). The collaboration includes investigators from King's, University of California San Diego, Cambridge, Dundee and Manchester.

The Parkinson's disease programme will be led by Nicholas Wood, John Hardy and Anthony Schapira of the Institute of Neurology, University College London (UCL), working with researchers from Dundee, Sheffield and UCL. Its goal will be to generate a better understanding of genetic risk factors in Parkinson's disease.

IMAGE
Influenza virus.



## BIOMEDICAL ETHICS

**John Harris and Sir John Sulston of the University of Manchester have been awarded a £0.8 million Strategic Award in Biomedical Ethics to establish a programme of work focused on the human body.**

The work, to be undertaken in collaboration with Sarah Cunningham-Burley at the University of Edinburgh, will cover five main themes: human biomaterials and the uses of human organs and tissues; 'genethics', the ethical issues surrounding human genetics and genome sequencing; reproductive technologies, including current technologies such as pre-implantation genetic diagnosis and emerging techniques such as gamete production from stem cells; enhancement (physical and mental); and bioethical methods, including philosophical enquiry.

John Harris is the Sir David Alliance Professor of Bioethics at the University of Manchester. Sir John Sulston was the founder Director of the Wellcome Trust Sanger Institute and was awarded the 2002 Nobel Prize for Physiology or Medicine. This programme of research will form part of Manchester's Institute for Science, Ethics and Innovation, launched in 2008.

Smaller Biomedical Ethics Enhancement Awards were made to Malcolm Dando at the University of Bradford ('dual-use' applications of biomedical research), Susan Golombok at the University of Cambridge (assisted reproduction and new family make-ups) and Michael Parker at the University of Oxford (ethics of collaborative global health research).

## A SELECTION OF NOTABLE GRANTS AWARDED IN 2008/09

### PROGRAMME GRANTS

**INFLUENZA**
**Professor Wendy Barclay** (Imperial College London): Interferons, innate immune responses and clinical disease during influenza infection.

**ADOLESCENT HEALTH**
**Professor Cesar Victora** (Federal University of Pelotas, Brazil): Using three birth cohorts to explore the impact of early life events on adolescent health and wellbeing.

**PROTEIN TRANSLATION**
**Professor Christopher Proud** (University of Southampton): Control of elongation factors eEF2K and eEF2.

**BIOBANKING**
**Professor Zhengming Chen** (University of Oxford): Support for the Kadoorie Biobank Study of 515 000 Chinese people aged 35–74.

**NEUROSCIENCE**
**Professor Jon Driver** (University College London): How sensory processing is affected by crosstalk with other regions of the brain.

**HUMAN GENETICS**
**Professor Sir Walter Bodmer** (University of Oxford): Identifying genes that affect the structure of faces of people in the British Isles.

### PROJECT GRANTS

**MICROBIOLOGY**
**Professor Gad Frankel** (Imperial College London): How effector proteins enable pathogenic *E. coli* to adhere to mucosal surfaces.

**PSYCHOLOGY**
**Matt Field** (University of Liverpool): Motivational processes and their links with alcohol abuse.

**EPIGENETICS**
**Branwen Hennig** (London School of Hygiene and Tropical Medicine): Diet, malnutrition and the epigenetic status of young babies in the Gambia.

**VASCULAR BIOLOGY**
**Professor Salvador Moncada** (University College London): Nitric oxide and the antioxidant status of vascular endothelial cells.

**STATISTICAL GENETICS**
**Professor Gil McVean** (University of Oxford): Analysis of data from the 1000 Genomes Project.

**CHILD DEVELOPMENT**
**Professor Edward Sonuga-Barke** (University of Southampton): Use of white noise to improve concentration of children with attention problems.

**PHYSIOLOGY**
**Professor Robert Unwin** (University College London) and **Scott Wildman** (Royal Veterinary College): ATP signalling in the kidney.

**HUMAN GENETICS**
**Ed Hollox** (University of Leicester): Population variability of the copy number variable *FGFR3* gene.

**CELL BIOLOGY**
**Peter Lawrence** (University of Cambridge): Planar cell polarity and cell migration in *Drosophila*.

**ENVIRONMENT**
**Melvyn Hillsdon** (University of Bristol): 'Four Hundred Area Study', evaluating the impact of the built environment on physical activity in 400 sites around the UK.

**SCHIZOPHRENIA**
**Professor David Porteous** (University of Edinburgh): Structure and function of the DISC1 schizophrenia susceptibility factor.

**INFLAMMATION**
**Professor Maria Belvisi** (Imperial College London): Theophylline as a possible therapy for chronic cough.

### STRATEGIC AWARD IN THE HISTORY OF MEDICINE

**MODERN HISTORY**
**Nick Hopwood** (University of Cambridge): Health, fertility and reproduction in the 20th century.

### HISTORY OF MEDICINE PROGRAMME GRANT

**ANCIENT HISTORY**
**Professor Philip Van der Eijk** (Newcastle University): English translations of Galen's works.


Gordon Hamilton of Keele University.

# Using knowledge

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

## AN ATTRACTIVE SOLUTION

**Pheromone traps may be a way to control *Leishmania*-transmitting sand flies.**

Among parasites transmitted by insects, single-celled protozoans of the genus *Leishmania* are second only to malaria in terms of their impact on health. In some cases, the parasites cause the potentially fatal visceral leishmaniasis, which affects some half a million people a year. One way to mitigate their effects may be innovative 'pheromone traps' being developed by Gordon Hamilton and colleagues at Keele University and the Fundação Oswaldo Cruz in Brazil.

In South America, *Leishmania infantum chagasi* is transmitted by sand flies (*Lutzomyia longipalpis*). As with mosquitoes and malaria, it is only females that take blood meals and transmit the parasite. If feeding on humans could be reduced, the risk of infection would be decreased.

The strategy adopted by Dr Hamilton and his team has been to exploit the natural communication systems that affect sand fly behaviour – specifically, their reproduction. Male sand flies aggregate on and around host animals, releasing chemical pheromones that attract females and other males to the mating and blood-feeding site ('lek'). With Technology Transfer funding, Dr Hamilton and his colleague Krishnakumari Bandi have been able to synthesise the male sand fly sex pheromone from intermediates that are easily and cheaply obtained from plant sources.

The synthetic pheromone attracted female sand flies in the laboratory, and in a recent field trial, Dr Hamilton, Daniel Bray and Reginaldo Brazil extended this work to show that pheromone-baited traps successfully attracted both female and male sand flies.[1] Dispensers were set up to release the pheromone in similar quantities to those seen around leks in the field, and worked equally well with both mechanical and sticky traps. They also showed that lek sites treated with insecticide attracted and killed significantly greater numbers of females than control sites.

The results suggest that a 'lure-and-kill' strategy centred on synthetic sex pheromone could be an affordable and practical approach to lowering transmission of visceral leishmaniasis, complementing the high-cost, long-term alternatives of potential new drugs and a *Leishmania* vaccine.

*1 Bray DP et al. J Med Entomol 2009;46(3):428–34.*

**IMAGE**
Single-celled *Leishmania* parasites.

1

2

# A SERIOUS DRUG PROBLEM

**Poor-quality antimalarial drugs and artemisinin-resistant parasites are a dangerous combination.**

Artemisinin-based combination therapies are the treatments of choice for uncomplicated malaria. One of the advantages of artemisinins is the speed with which they kill malaria parasites, clearing infections within a couple of days. Unfortunately, following anecdotal reports of a decline in efficacy, Nick White and colleagues at the Wellcome Trust South-east Asia Major Overseas Programme's Tropical Research Network have found clear evidence of reduced parasite sensitivity to artesunate in western Cambodia – a potentially catastrophic development if resistant parasites spread more widely.

Professor White and colleagues compared treatment with either artesunate alone or with mefloquine in western Cambodia – a past hotbed of antimalarial resistance – and north-west Thailand. Disturbingly, it took almost twice as long to clear parasites in Cambodia, and nearly one in three patients receiving artesunate alone suffered a recurrence of infection.[1]

The rise of resistance is probably linked to the extensive use of artesunate alone in this region over several decades. Although Cambodian government policy is to use combination therapies, work carried out with the London School of Hygiene and Tropical Medicine revealed that a worrying 78 per cent of artesunate use was as a monotherapy.[2] In north-western Thailand, by contrast, artesunate remains highly efficacious after 13 years of combination therapy.[3]

Mathematical modelling suggests that high coverage with combination therapies could eliminate resistant parasites and prevent their wider dissemination. However, there is a sting in the tail. Their use would impose further strong selection pressures on parasites, and if the containment programme did not achieve elimination then any remaining parasite, the 'last man standing', would be the most resistant – and malaria could become even more difficult to treat.[4]

Resistance may also derive from the widespread use of poor-quality antimalarial drugs. Often these are the products of a deadly counterfeit drug trade. But even genuine drugs may be low-quality, because of poor manufacturing or storage. The South-east Asia Network's centre in Laos has shown that both genuine but poor-quality and counterfeit drugs are an important cause of unnecessary suffering and even death.[5]

The scale of the problem is of significant concern. A recent random sampling of pharmacies in Laos found that 88 per cent of those stocking artesunate were selling counterfeit versions of the drug.[6] Worryingly, 15 per cent of the fakes included detectable amounts of artemisinin. Meanwhile, in Africa a team including staff from the Wellcome Trust's Major Overseas Programme in Kenya tested more than 1000 antimalarial samples from 21 districts in Tanzania. Overall, an alarming 12 per cent were substandard – a figure that reached 24 per cent for quinine products.[7]

Researchers have called for more attention to be given to pharmaceutical quality monitoring, and a set of guidelines has been proposed that could be applied to obtain objective information through medicine quality surveys and to improve reporting to assess the impact of interventions.[8]

To catalyse action specifically against the trade in counterfeit medicines, the Trust organised a workshop with the American Pharmaceutical Group, bringing together a range of stakeholders and opinion formers to discuss the problem and ways in which it might be tackled.

**This research was supported by the Wellcome Trust and other funders.**

*1 Dondorp AM et al. N Engl J Med 2009;361(5):455–67.*

*2 Yeung S et al. Malar J 2008;7:96.*

*3 Carrara VI et al. PLoS One 2009;4(2):e4551.*

*4 Maude RJ et al. Malar J 2009;8:31.*

*5 Keoluangkhot V et al. Am J Trop Med Hyg 2008;78(4):552–5.*

*6 Sengaloundeth S et al. Malar J 2009;8:172.*

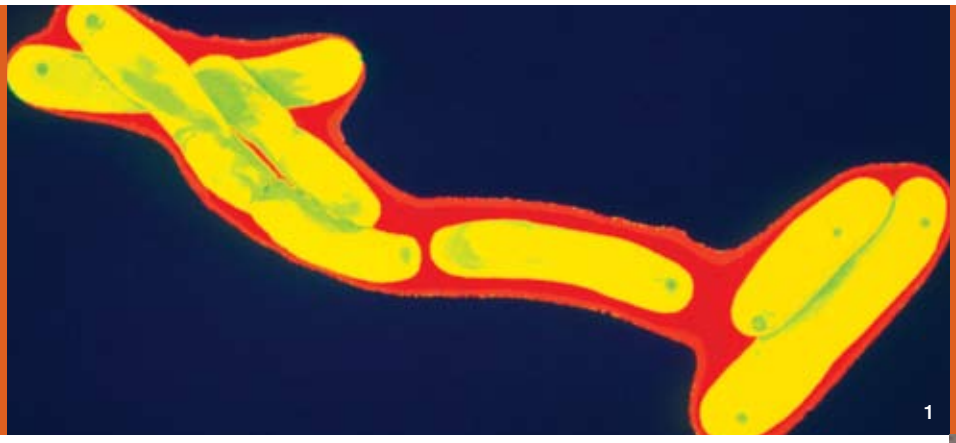
*7 Kaur H et al. PLoS One 2008;3(10):e3403.*

*8 Newton PN et al. PLoS Med 2009;6(3):e52.*

IMAGES

1 Holograms have been used to make it harder to produce fake packaging for antimalarials.

2 Drug sales in rural Africa.



# CLEAN AIR ACTS

**Simple methods may be able to cut drastically the spread of TB in healthcare settings.**

Back in the 1950s, Riley and Wells undertook a classic series of experiments exposing guinea pigs to air from a ward of tuberculosis patients. The animals succumbed to TB, convincingly demonstrating that the disease was spread through airborne particles. With TB undergoing an alarming resurgence, particularly in low-income countries, Rod Escombe (a Research Training Fellow in Clinical Tropical Medicine) and Carlton Evans (a Research Career Development Fellow in Clinical Tropical Medicine) at Imperial College London, with collaborators in Peru and elsewhere, are revisiting these studies and developing practical interventions that could slash the spread of TB.

To get a better handle on TB transmission, air from a TB ward in Lima, Peru was channelled to guinea pig colonies established on the roof of the hospital. Using genetic fingerprinting techniques to trace the origins of each animal infection, the researchers were able to investigate effects of HIV infection and TB drug resistance on TB transmission.

The research revealed striking differences in the transmission of TB from different patients.[1] Nearly all guinea pig infections (98 per cent) could be traced to just 8.5 per cent of the patients. Importantly, the vast majority of transmission was from patients with multidrug-resistant TB inadequately treated with first-line therapy – an all-too-common situation in many low-income countries, where access to diagnostic tests for drug resistance is poor or absent.

The results highlight the importance of early identification of high-risk patients carrying multidrug-resistant TB, treating them appropriately and establishing infection control measures to prevent TB transmission in the first place. Such measures need not necessarily be expensive. Dr Escombe's previous research showed that as simple a measure as increasing natural ventilation – opening doors and windows – can produce high rates of air exchange likely to reduce TB transmission in healthcare settings.

Another possible solution is to sterilise the air in hospital wards and clinics, by placing ultraviolet lights in the upper part of the room. In Peru, upper-room ultraviolet lights were found to cut TB transmission to guinea pigs by 70 per cent – the first demonstration of their effectiveness against TB in a clinical setting.[2] As ultraviolet lights are relatively easy to install and require little maintenance, they are well suited to use in resource-poor settings.

Providing there is adequate mixing of air, they offer an important new tool for preventing the transmission of drug-resistant TB. Their use has now been recommended in World Health Organization policy on TB control in healthcare facilities and other settings.

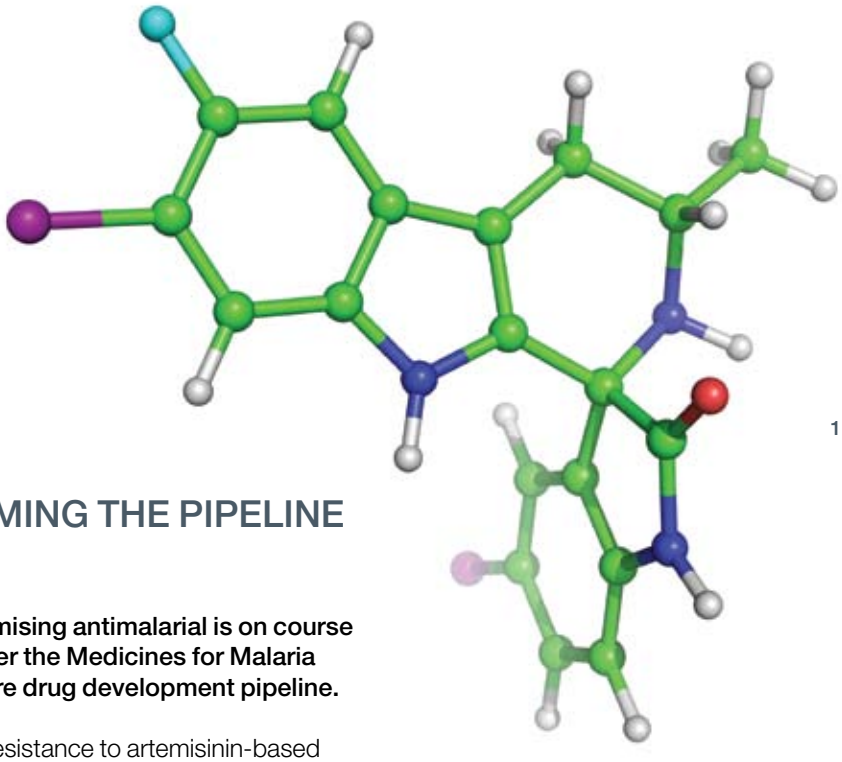
*1 Escombe AR et al. PLoS Med 2008;5(9):e188.*

*2 Escombe AR et al. PLoS Med 2009;6(3):e43.*

**IMAGES**

**1** *Mycobacterium tuberculosis*.

**2** TB is a particular problem in impoverished areas of Peru.



1

2

## PRIMING THE PIPELINE

**A promising antimalarial is on course to enter the Medicines for Malaria Venture drug development pipeline.**

With resistance to artemisinin-based drugs a growing concern (see page 18), there remains a need to pursue new pharmacological leads in the battle against malaria. With Technology Transfer funding, the Novartis Institute for Tropical Diseases in Singapore is testing a range of possible new compounds, with a view to passing on the most promising to the Medicines for Malaria Venture (MMV) – a public–private partnership based in Switzerland that has also received funding from the Wellcome Trust. Encouragingly, the first compound is due to make the transition to the MMV pipeline.

The Novartis Institute for Tropical Diseases (NITD), a public–private partnership between Novartis and the Singapore Economic Development Board, was set up in 2002. Its aim is to develop small-molecule therapeutics for infectious diseases of low-income countries, principally dengue, tuberculosis and malaria. It works on compounds originating within Novartis as well as others identified in academic research.

The NITD concentrates on early stages of drug discovery, identifying and chemically refining potential new agents, and carrying out preclinical studies to test for efficacy and toxicity in animal models.

Its most promising antimalarial compound emerged from a screen of a large library of natural products held by the Novartis parent company. The compound was lethal to cultured parasites, and *in vivo* tests after chemical optimisation have confirmed its potency. Three doses rapidly and completely eliminated malaria parasites in infected mice – far exceeding the 'gold standard' for efficacy at this stage of development.

The next step is to file for 'investigational new drug' status late in 2010, which would enable the compound to be registered for clinical trials. MMV and NITD will jointly manage the clinical development, and phase I clinical trials could start in the first half of 2011.

## STRONGER BONDS

**A simple intervention can strengthen bonds between parent and child even in an impoverished setting.**

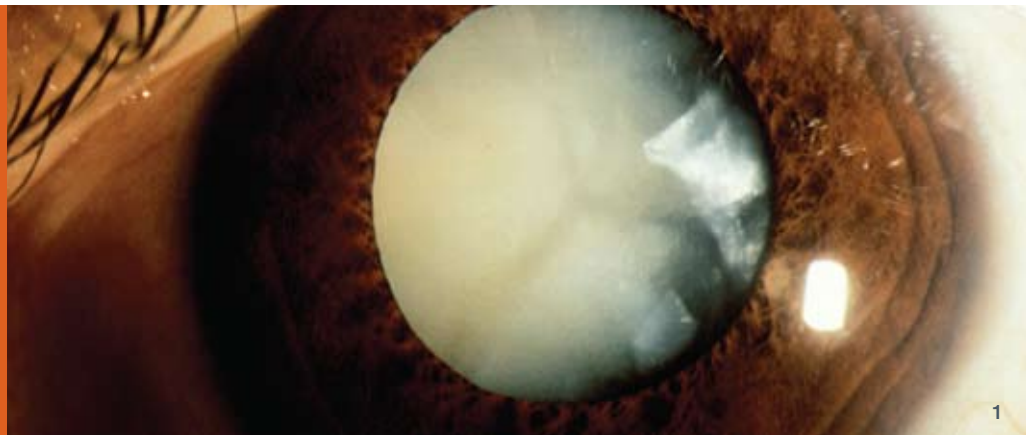
The quality of the relationship between infant and caregiver (usually a mother) in the early years of life can have a long-term impact. If a secure attachment develops, infants are more likely to forge good relationships with their peers and develop as socially and emotionally well-adjusted children, and are less likely to develop mental health problems as they grow older. A clinical trial involving researchers in Reading, Oxford and South Africa has now shown that a simple intervention delivered by local people without medical training can significantly enhance the mother–infant relationship.[1]

The trial was carried out in Khayelitsha, a sprawling township of more than a million inhabitants on the outskirts of Cape Town. In a pilot study, mother–child attachment had been improved when new mothers received professional support and guidance on parenting. In the latest work, a randomised controlled trial tested whether a similar intervention delivered by lay community workers, intended to promote sensitive parenting and foster secure infant attachment to mothers, had a similar beneficial effect.

IMAGES

**1** The chemical structure of the spiroindolone, NITD609, a preclinical candidate for malaria.

**2** A simple intervention can improve mother–child bonding even in impoverished settings.



1

The study involved nearly 450 pregnant mothers, half of whom received support and parenting guidance (based on World Health Organization recommendations) together with specific measures to encourage sensitive, responsive interactions, and half received standard antenatal and postnatal care. Compared with mothers in the standard care condition, those who received the intervention were significantly more sensitive in interactions with their infants at six and 12 months. At 18 months, a significantly greater proportion of infants in the intervention group were rated as 'securely attached' (74 per cent versus 63 per cent). Some benefits to mothers' mental health were seen at six months, but not at later stages.

Although similar interventions have been shown to work in high-income countries, this is the first study to demonstrate benefits in a socioeconomically deprived low-income country. Given its simplicity, it is potentially a sustainable intervention for vulnerable populations even in highly deprived settings.

*1 Cooper PJ et al. BMJ 2009;338:b974.*

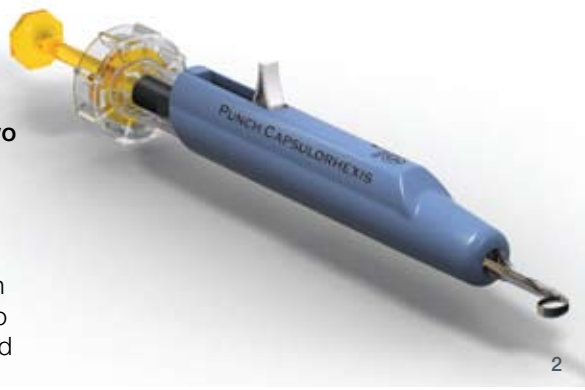
## BETTER BY DESIGN

**Award-winning products could significantly improve treatment of two common medical conditions.**

Cataracts and broken bones are both common medical problems. Two products developed in Nottingham with Technology Transfer support promise to improve their treatment significantly, and have been recognised with prestigious awards for innovation.

An injectable bone scaffold, designed to promote bone healing after fractures, won an Orthopaedic Innovation Award at the national Medical Futures Awards. Developed by RegenTec, a biotechnology spin-off company set up by Kevin Shakesheff from the University of Nottingham, it is a toothpaste-like substance at room temperature. It can be injected into bone fractures, hardening into a matrix that supports the regrowth of bone and associated blood vessels and other tissues.

In time, it may also be possible to integrate factors that encourage the growth of particular types of cell, to boost the regenerative process, and to use the matrix in combination with stem cell therapies. The company hopes to launch a marketable product within 18 months.

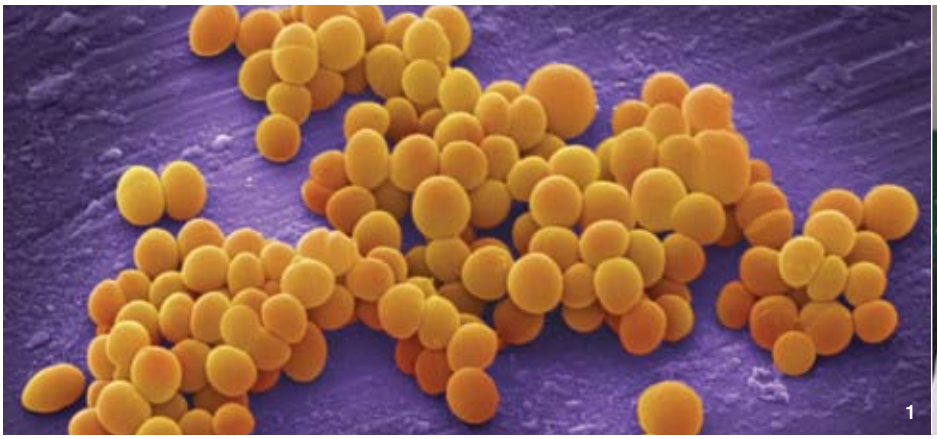



2

Also developed in Nottingham, a new disposable blade designed specifically for cataract surgery could have global application. Although practised thousands of times daily, cataract surgery is a relatively crude procedure in which a circle is cut in the eye's lens capsule with a needle and forceps. John Stokes, a Consultant Ophthalmologist at Nottingham University Hospitals NHS Trust, has worked with Warwick Design Consultants to develop a disposable device with a standardised blade that can make precise circular cuts.

The prototype device was awarded the Medical Devices prize at the National NHS Innovation Awards. As an affordable and simple-to-use device, it may also ultimately benefit the 1.5 million people a year in low-income countries who lose their sight to untreated cataracts.

**IMAGES**
**1** A cataract in an eye.
**2** The device for making precise cuts in the cornea.



## ADAPT AND SURVIVE

**Chemical modification of compromised antibiotics is giving them a new lease of life.**

Aminoglycosides have been used for many years to treat a range of bacterial infections. As with all antibiotics, though, the emergence of drug-resistant strains is a significant and growing problem. Using an understanding of the drugs' structure and the mechanisms of resistance, Achaogen Inc. has been chemically modifying existing aminoglycosides in a systematic manner in order to work round resistance. The first fruits of this endeavour, a 'neoglycoside', recently came through a highly successful phase I trial.

Aminoglycosides are broad-spectrum antibiotics. Achaogen's principal targets are multidrug-resistant Gram-negative bacteria, including intestinal pathogens such as *E. coli, Pseudomonas aeruginosa* and MRSA.

Aminoglycosides are complex organic molecules produced by a range of bacteria. Although highly effective, their use is being curtailed by the development of resistance. To maintain their efficacy, Achaogen has made a range of chemical modifications to the sites on the molecules known to be targeted by resistance mechanisms. Preclinical studies have shown that this is a successful strategy for overcoming resistance while maintaining the agents' antibacterial properties.

In the phase I trial, the safety of the leading candidate was tested in a small randomised placebo-controlled trial. No ill-effects were seen, paving the way for phase II trials in 2010, starting with complicated urinary tract infections.

There is reason to be optimistic that neoglycosides will overcome the hurdles of phase II and III trials. For antibiotics, the jump from animal to human studies is not so great, as the target – the bacterium – is the same in both cases. Moreover, a great deal is already known about the safety and effectiveness of aminoglycosides, which will be relevant to the development of their relatives.

**The results of the phase I trial were released at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Annual Meeting in San Francisco, September 2009 (www.achaogen.com/news).**

## NEWBORN NEED

**Despite antiretroviral rollout programmes, not all young infants in South Africa are getting the treatment they need.**

South Africa is home to one in seven of the world's HIV-infected population. While children under 16 make up just 6 per cent of this total, they account for 12 per cent of new infections and 13 per cent of HIV-related deaths. As Marie-Louise Newell and colleagues' work at the Africa Centre for Health and Population Studies in KwaZulu-Natal has revealed, even when antiretroviral drugs are available they are not always finding their way to the very youngest infants.[1]

The Africa Centre maintains a long-running demographic surveillance system in the subdistrict of Hlabisa, a particularly deprived rural area with a high incidence of HIV. It has been actively involved in South Africa's rollout of antiretroviral drugs, and is thus well-placed to assess how rollout is achieved in practice.

The Africa Centre researchers found that around 350 children under 16 had been started on antiretrovirals by the beginning of 2008; of these, 245 were under ten but just two were under one year of age. Modelling of the population suggested that there were likely to be more than 2500 HIV-infected children under ten in the area, at least 521 of whom would need immediate treatment.

IMAGES
1 MRSA, an important target for neoglycosides.
2 The Africa Centre's Marie-Louise Newell.

# New funding

## A SELECTION OF NOTABLE GRANTS AWARDED IN 2008/09

Furthermore, if antiretrovirals were available to prevent mother-to-child transmission, the annual number of infant infections could be halved.

The group has worked with the local Department of Health to improve the identification of HIV-infected children so treatment can start within the first year of life. Up to June 2008, around 470 children were being treated. Over the following year, the numbers doubled and around 1000 are now receiving antiretrovirals.

*1 Cooke GS et al. PLoS One 2009;4(9):e7101.*

## VACCINE DEVELOPMENT

**The Wellcome Trust and Merck & Co., Inc. have jointly committed £90 million to establish new laboratories to develop affordable vaccines for diseases affecting low-income countries.**

As well as developing new vaccines in areas of unmet need, the MSD–Wellcome Trust Hilleman Laboratories will also optimise existing vaccines, a valuable way of increasing the impact of vaccination in resource-limited settings.

The venture is the first time a research charity and a pharmaceutical company have jointly formed a separate entity with equally shared funding and decision-making rights. The Hilleman Laboratories will operate on a not-for-profit basis but will be run as a business enterprise. The £90m investment will be made over seven years and will support around 60 staff.

The Laboratories will be based in India, providing access to a wide range of expertise in vaccine research, policy and manufacturing. The venture's Chief Executive Officer will be Altaf Lal, who has spent 20 years working at the US Centers for Disease Control and Prevention. Dr Lal is currently based at the US Embassy in India.

The new venture is named in honour of the pioneering vaccine scientist Maurice Hilleman, who is credited with the development of more than 30 licensed vaccines, including products for measles, mumps and hepatitis B, during a career that included nearly 30 years at Merck.

### MEDICAL ENGINEERING

**Professor Ross Ethier** (Imperial College London): Enhanced implants and surgical techniques for osteoarthritis.

**Professor John Fisher** (University of Leeds): Regenerative and replacement technologies for later life.

**Professor Reza Razavi** (King's College London): Improved medical imaging for cardiovascular, psychiatric and other conditions.

**Professor Lionel Tarassenko** (University of Oxford): Technological approaches to more individualised medical treatment.

### TRANSLATION AWARDS

#### TYPHOID FEVER

**Laura Martin** (Novartis Vaccines Institute for Global Health): Conjugate vaccine against typhoid fever.

#### DIARRHOEA

**Professor Chris Probert** (University of Bristol): Development of a diarrhoea diagnostic device.

#### PRE-ECLAMPSIA

**Louise Kenny** (University College Cork): A metabolite biomarker-based screening test for pre-eclampsia.

### SEEDING DRUG DISCOVERY

#### CANCER

**Professor Caroline Springer** (Institute of Cancer Research): Inhibitors of lysyl oxidase and treatment of metastatic cancer.

#### HEPATITIS C VIRUS

**Neil Thompson** (Astex Therapeutics Ltd): Fragment-based drug discovery for hepatitis C.

#### BACTERIAL INFECTION

**Professor Peter Andrew** (University of Leicester): Inhibitors of the pneumococcal toxin, pneumolysin.

**IMAGE**
The Africa Centre is situated in the heart of rural KwaZulu-Natal.

Channel 4's Krishnan Guru-Murthy prepares for *Surgery Live*.

# Engaging society

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

## REALITY SURGERY

**Three-and-a-half million viewers watched surgeons operating on live television.**

Over four evenings in May 2009, 3.5m viewers tuned into Channel 4 to watch *The Operation: Surgery Live*. This pioneering broadcast project took television viewers live into the operating theatre to watch leading surgeons perform life-saving operations, including brain and open-heart surgery. The four surgeons – who routinely talk medical students through procedures during operations – answered questions from the public while they worked.

A live video link from the operating theatre was played to a full house at the Wellcome Collection auditorium each evening. The evenings were hosted by Channel 4's Krishnan Guru-Murthy, with a second surgeon on hand to answer questions when the operating surgeon was too busy.

Funded by a Wellcome Trust People Award, the collaboration between the Wellcome Trust, Channel 4 and Windfall Films, an independent production company, built on the popularity of 'Live Surgery' – two events held at Wellcome Collection in 2007, in which the audience watched open-heart surgery live via a satellite link.

*The Operation: Surgery Live* aimed to expose a wider audience to modern surgery, remove some of the mystique surrounding it, and inspire young people to consider careers in surgery.

A special area on Channel 4's website encouraged visitors to set up discussion groups on Facebook and Twitter. Viewers at home could put questions about the procedures to the surgical team during the broadcasts by phone, email and Twitter.

More than 5000 people joined the Facebook group, while the Twitter group was the leading 'trending topic' by the final night. Users are continuing to debate medical issues, to which clinical practitioners have spontaneously participated.

*The Operation* was just one of the innovative events and exhibitions organised by Wellcome Collection during the year. History, science, medicine and art were juxtaposed in a series of imaginative and critically praised exhibitions, including *War and Medicine* ("historically fascinating, scientifically informative and ethically challenging" – Rachel Campbell-Johnston, the *Times*) and *Exquisite Bodies* ("I greatly enjoyed this exhibition and regret only that it is not twice the size" – Brian Sewell, *Evening Standard*).

**www.channel4.com/explore/surgerylive/**
**www.facebook.com/group.php?gid=91972614803**
**twitter.com/surgerylive**


## 200 NOT OUT

**Every state school in the UK benefited from evolution-based teaching resources during Darwin200 year.**

Darwin200 was a national programme of events that took place during 2009, to celebrate the 200th anniversary of Charles Darwin's birth in February 1809 and the 150th anniversary of the publication of *On the Origin of Species* in November 1859. The Wellcome Trust joined in the celebrations, supporting a range of education and other projects exploring Darwin's theories and their importance for science today.

To give school students an understanding of the long-lasting legacy of Darwin's work, the Trust commissioned a programme of free science activities for school students aged five to 19. In March 2009, every state primary school in the UK was sent a Great Plant Hunt Treasure Chest, produced by the Royal Botanic Gardens, Kew.

Each chest contained a mini seed bank, plant press, plant identikit, books, and exciting classroom and outdoor activities. In May 2009, children took part in Great Plant Hunt Week – a week-long search for ten common species of plants. Participants recorded when and where the plants flowered, learning key scientific skills in the process. To date over 10 000 teachers have signed up to stay updated on the project and 'the hunt goes on' into 2010.

Survival Rivals, a set of free science kits commissioned by the Trust for UK state secondary schools, encourages students to explore the ideas behind Darwin's famous theories and how they continue to underpin biological and medical research today.

*I'm a Worm, Get Me Out of Here* explores natural selection for 11–14-year-olds. *Brine Date* for 14–16-year-olds looks at sexual selection in brine shrimp. And *The X-Bacteria* for post-16 students tracks the development of antibiotic resistance in bacteria. A total of 8570 kits had been sent to schools by October 2009.

The National Centre for Biotechnology Education at the University of Reading was granted a Society Award to develop a resource enabling science teachers to use modern methods of DNA data analysis, so that they can teach 16–19-year-old biology students about the latest molecular evidence for evolution. DNA to Darwin examines links between DNA and evolution in a range of case studies, such as lactose tolerance in humans and antibiotic resistance in MRSA. A course run by the Science Learning Centres enables teachers to get the most from the resource.

The Trust also commissioned a five-minute animation that formed the centrepiece of Sir David Attenborough's award-winning BBC1 documentary, *Charles Darwin and the Tree of Life*, broadcast in February 2009 and watched by 6.3 million viewers. The animation is featured on the Wellcome Trust's *Tree of Life* microsite, along with an interactive fly-through explaining the evolutionary links between living things and activities encouraging secondary school students to explore these concepts.

*Routes*, developed by Oil Productions for the Trust and Channel 4 Education, was a ground-breaking eight-week exploration of genetics and bioethics using a variety of platforms – including an online documentary, minigames and puzzles, a murder-mystery drama, discussion forums, video blogs, mobile updates and live events.

The *Routes* drama was serialised in Channel 4's '3-minute wonder' primetime slot. As of October 2009, the *Routes* website had been visited by over 132 000 people, and the *Sneeze* minigame had been played a staggering 20m times. *Routes* was nominated for a Children's BAFTA award and four British Interactive Media Awards.

As part of Darwin200, the Trust part-funded an exhibition at the Fitzwilliam Museum in Cambridge exploring the cultural resonance of Darwin's theories. *Endless Forms: Charles Darwin, natural science and the visual arts*, held from June to October 2009, brought together nearly 200 exhibits from around the world, highlighting artistic responses to Darwin's work, including imaginings of prehistoric Earth and evocations of a troubled life dominated by the struggle for existence.

Fittingly, the Natural History Museum's £78m Darwin Centre, to which the Trust contributed £10m, was opened during Darwin200. The dramatic eight-storey cocoon-shaped building encased in glass has doubled the size of the Museum's laboratory areas, and holds 17m entomology specimens and 3m botany specimens. Museum visitors can now watch scientists in action, and even ask them about the work they are doing.

**www.wellcometreeoflife.org**
**www.nhm.ac.uk/visit-us/galleries/orange-zone/darwin-centre**
**www.darwinendlessforms.org.**
**www.greatplanthunt.org**
**www.survivalrivals.org**
**www.dnadarwin.org**
**www.routesgame.com**

IMAGES
1 Inside the Natural History Museum's Darwin Centre.
2 Sir David Attenborough helps to launch the Wellcome Trust's Darwin200 schools materials.

1

## RUN FOR YOUR LIFE

**The televised race for survival between millions of human-sized sperm cells attracted 1.5 million viewers.**

In *The Great Sperm Race*, a documentary part-funded by a Wellcome Trust Broadcast Award and screened on Channel 4 in March 2009, the microscopic world of sperm and egg was scaled up 34 000 times to human size.

Using computer graphics and actors representing sperm cells, the programme portrayed the huge challenges sperm face in the hostile environment of the female reproductive tract, assaulted on every side by powerful acids, white blood cells and other 'hostile combatants'.

Millions of human-sized contenders raced to fertilise an egg, negotiating some of the world's most striking landscapes, including a valley in the Canadian Rockies and buildings on London's South Bank.

Leading reproductive scientists helped to develop the programme, and the Channel 4 website published a peer-reviewed document of the science behind the programme – the first time a television programme treatment has been through a scientific peer-review process.

The website also features *The Great Sperm Race* game, funded by a Wellcome Trust People Award. The game was widely distributed on gaming websites and social media networks, and had been played more than 3.5m times by October 2009.

Another notable Broadcast Development Award was made to Nigel Wattis of Mindful Films, for a film based on choreographer Wayne McGregor's three-week residence at the University of California San Diego. McGregor worked intensively with cognitive scientists, exploring the mental processes associated with creativity. The resulting new work was staged at Sadler's Wells in London in October 2009 as part of the centenary celebrations of the Ballets Russes.

2

The film explores the genesis of this piece, and of another new work by McGregor for the Royal Ballet premiered at Covent Garden three weeks later. The film was screened on ITV's *South Bank Show* in January 2010.

**www.channel4.com/programmes/the-great-sperm-race**

**www.randomdance.org/wayne_mcgregor**

**IMAGES**

**1, 2** Actors took on the role of sperm in *The Great Sperm Race*.

## HOME WIN

**A public engagement project in Kenya has helped to dispel some of the myths surrounding medical research.**

The KEMRI–Wellcome Trust Research Programme in Kenya includes a major site at the coastal town of Kilifi, carrying out research into malaria and other infectious diseases affecting children. Researchers at Kilifi were keen to give local students an insight into their work, and into the process and goals of biomedical research more generally. Thanks to an International Engagement Award, they were able to develop and pilot school activities that have helped to forge better links with the local community and even encouraged students to consider a career in medical research.

The Kenya Programme is an international institute, including a number of researchers from Kenya and East Africa. Local residents participate in much of its research, the fruits of which have influenced healthcare in Kenya and throughout Africa. However, local awareness of its work is limited.

In an initial survey, the project team, led by Alun Iwan Davies, discovered that many students were unsure about the purpose of the Programme. Some thought its main role was to treat the sick. Others mentioned rumours circulating in the community that revealed significant misconceptions (and even bizarre suggestions that researchers were devil worshippers).

In March 2009, the team held a participatory planning workshop attended by local science teachers, scientists and a representative from the District Education Office to plan school activities. Suggested activities included school trips to the Programme, visits by scientists to schools, a football game pitting scientists against students, and an inter-school science competition. As not all students could visit, students from three schools filmed Kilifi's research facilities and produced a 'virtual tour' to be shown in schools.

The activities ran for six months, and a follow-up survey found significant changes in knowledge and attitudes. The intervention with the biggest impact was the school visits by Kenyan scientists, with whom students could identify most closely. Their support and enthusiasm significantly motivated students to take an interest in science – and in some cases consider scientific careers.

## THE BEST OF TIMES, THE WORST OF TIMES

**A play telling the stories of children on dialysis has won a prestigious national award.**

*For the Best* was based on the physical entrapment and vivid imaginative travels experienced by children on dialysis. It was developed by artist Mark Storor, in collaboration with Anna Ledgard, from the stories, pictures, songs and poems created by children attending the dialysis unit at Evelina Children's Hospital and children at two primary schools.

Funded by a Wellcome Trust Arts Award, *For the Best* won the 2009 Theatre Management Association Theatre Award for Best Show for Children and Young People, placing it alongside the work of major national theatre institutions. It was seen by 1800 people during its run at the Unicorn Theatre in London during June 2009.

The play received almost universal critical acclaim. The *Guardian* described it as a "devastating theatrical journey that throws dazzling light on the idea of illness as metaphor" and an "extraordinary, fierce and moving show". In *Time Out*'s words, it was "as magical as the circus and as epic as Greek tragedy". And Whatsonstage.com deemed it "possibly the most extraordinary show currently playing in London".

IMAGES
1 'Home-grown' researchers can act as role models for African children.
2 Primary school children helped to develop *For the Best*.

# New funding

## A SELECTION OF NOTABLE GRANTS AWARDED IN 2008/09

Some of the children were also involved in the performance, leading the audience in small groups through a series of installations to the theatre's main arena. There, six professional performers acted out the children's descriptions of their illness and its impact on their families.

A family of four are supported by a nurse, who moves in with them, underscoring the omnipresence of the illness: a black-eyed creature stalks them, the dark shadow that lives with them permanently. Children on dialysis are living with the real possibility of dying, if donor organs are not available. Death, suggests one, is simply "a door in a room that we have not yet noticed and won't until our eyes adjust to the dark". The play does not shy away from this stark fact – any more than do the stories and pictures of the children for whom it is an everyday part of life.

## CHELTENHAM FESTIVALS

**A Society Award will see biomedical science embedded across the full range of Cheltenham Festival events.**

The Cheltenham Music Festival was launched in 1945 and a Literature Festival in 1949. Its Jazz Festival began in 1996 and the Cheltenham Science Festival in 2002. Collectively, the Festivals now attract some 150 000 visitors each year. Informal links between the Festivals were solidified in 2006, when they collectively came together under the 'Cheltenham Festivals' umbrella.

One of the strengths of this arrangement has been the mixing of participants from a wide range of backgrounds. To build on this interdisciplinarity, Cheltenham Festivals have been awarded a £200 000 Society Award, which will support efforts to embed biomedical themes across the full range of Festivals.

A Biosciences Project Manager will be appointed to coordinate planning across the Festivals, and to turn the many creative ideas generated during planning into reality. The support will also enhance audience reach by touring and education/outreach projects, better use of technology, and additional work with media and broadcast partners.

The long-term aim of the three-year project is to embed planning practices so that scientific themes become a permanent feature across all Cheltenham Festivals.

### ENGAGING SCIENCE CAPITAL AWARDS

**Caroline Worthington** (Florence Nightingale Museum): Reinvigorating the Museum for the centenary of Florence Nightingale's death in 2010.

**John Lippiett** (Mary Rose Trust): Reconstructing the Barber Surgeon's cabin and the secondary collection of the *Mary Rose* in its new museum.

**Pamela Willis** (Museum of the Order of St John): Enhancing the visitor experience and highlighting the Order's contribution to the history of medicine.

### INTERNATIONAL ENGAGEMENT AWARDS

**Paul Nampala** (Makerere University, Uganda): Pairing Ugandan MPs with health researchers.

**Gabriel Harp** (Srishti School of Art, Design and Technology, India): Using cultural artefacts to catalyse discussions among public health researchers and policy makers.

### SOCIETY AWARD

**HUMAN GENETICS**
**Peter Finegold** (Nowgen: A Centre for Genetics in Healthcare): Bringing modern genetic methods such as genome-wide association studies into the classroom.

### PEOPLE AWARD

**REPRODUCTION**
**Jen Topping** (Channel 4): Flash-based game for *Great Sperm Race* website.

### LARGE ARTS AWARD

**DEMENTIA**
**Sherry Neyhus** (Opera Group): *The Lion's Face*, an opera exploring social, emotional and physical aspects of dementia.

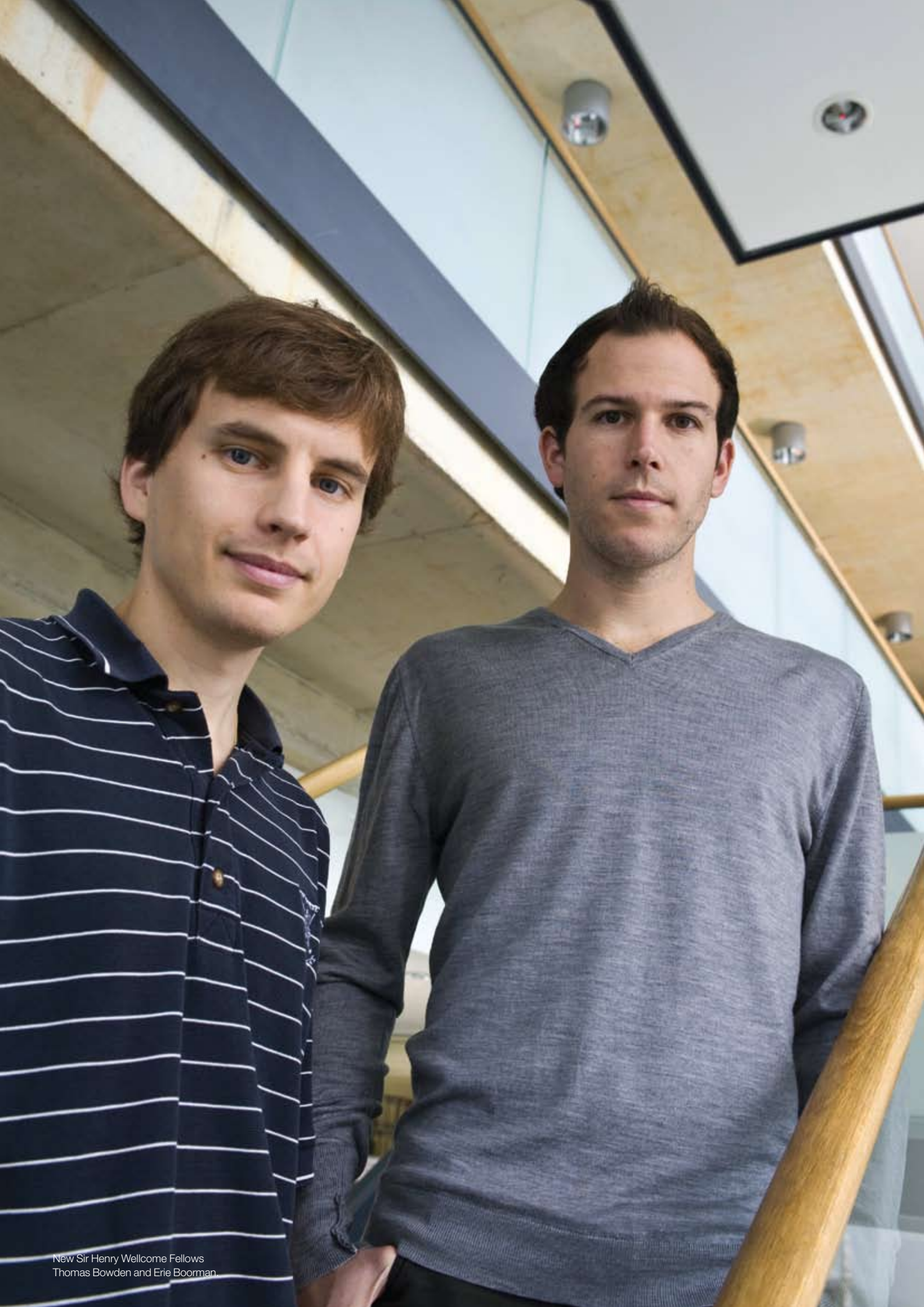
### SMALL ARTS AWARD

**FORENSIC SCIENCE**
**Adrian Jackson** (Cardboard Citizens): *Mincemeat*, a play and coroner's inquests inspired by the use of the corpse of a homeless man during World War II.

### HISTORY OF MEDICINE PUBLIC ENGAGEMENT

**SMALLPOX**
**Andrew Chater** and **Sanjoy Bhattacharya** (Wellcome Trust Centre for the History of Medicine at UCL): A video-rich web resource on the history of smallpox, to be hosted on Timelines TV.

**IMAGE**
A scene from *For the Best*.



New Sir Henry Wellcome Fellows
Thomas Bowden and Erie Boorman

# Developing people

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

## GIANT STEPS

**Two Wellcome Trust-funded students from Oxford have secured prestigious Sir Henry Wellcome Fellowships.**

Wellcome Trust Four-year PhD Programmes have proved highly popular, and competition for places is intense. Launched in 2006, Sir Henry Wellcome Fellowships are likewise highly competitive, providing newly qualified postdoctoral researchers with unprecedented freedom and funds to establish their research. Making the transition from four-year student to fellow, two researchers from Oxford are taking advantage of their Fellowships to establish international networks and develop their skills base.

After a Master's in chemistry at the University of St Andrews, Thomas Bowden joined the Trust-funded Four-year PhD Programme in Structural Biology at the University of Oxford, undertaking his thesis work in the labs of Dave Stuart and Yvonne Jones in the Wellcome Trust Centre for Human Genetics. Here, he has specialised in the binding of viruses to host cells[1,2] – an area he is taking forward in his Fellowship. His focus will be bunyaviruses such as Crimean–Congo haemorrhagic fever virus, which have extremely high mortality rates.

While an undergraduate, Dr Bowden spent time in labs at the Scripps Research Institute at La Jolla, California, which will also be his base for part of his Fellowship. He has also established collaborations with teams at St Andrews and the Max Planck Institute of Biochemistry in Martinsried, Germany.

Uniquely, his Fellowship will allow him the flexibility to network between these sites, developing a set of multidisciplinary skills that will complete his conversion from chemist to molecular virologist.

By contrast, Erie Boorman is establishing a niche in the field of decision making and cognitive neuroscience. After his degree at Stanford, Dr Boorman studied for a Master's under Matthew Rushworth and Heidi Johansen-Berg as part of his four-year PhD in Oxford.

Dr Boorman has applied functional imaging techniques to study brain activity during decision making, as well as new anatomical methods to image cortical circuits.[3,4] Such work is providing a fascinating picture of activity in the brain as it weighs up different options. His goal now is to add to this portfolio of skills, such as machine learning and neuro-economics, to integrate computational and psychological perspectives. International collaborations will again be important, with his Fellowship split between Oxford and the California Institute of Technology.

*1 Bowden TA et al. J Virol 2008;82(23):11628–36.*

*2 Bowden TA et al. Nat Struct Mol Biol 2008;15(6):567–72.*

*3 Boorman ED et al. Neuron 2009;62(5):733–43.*

*4 Boorman ED et al. Curr Biol 2007;17(16):1426–31.*

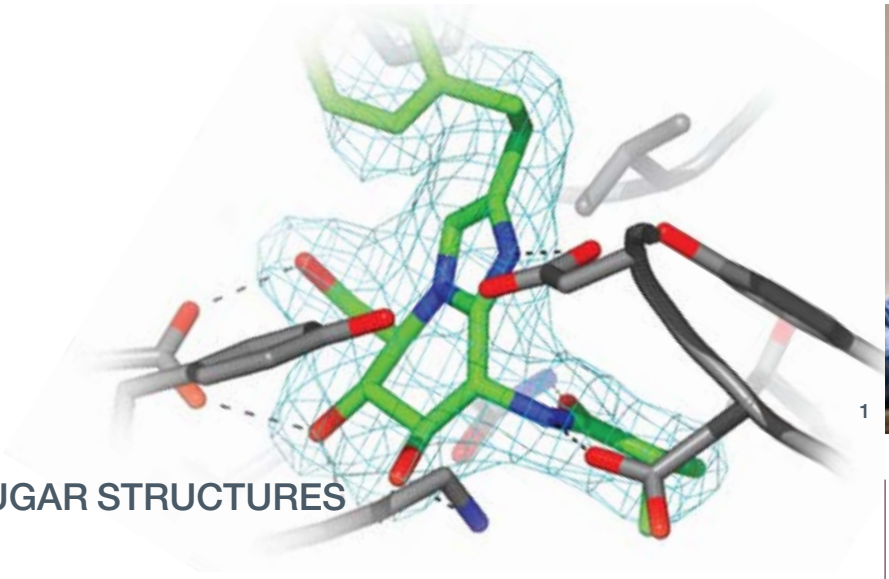
## MIND, BODY, MEDICINE

**Wellcome Trust grantholder Philip van der Eijk has been awarded a prestigious Alexander von Humboldt Professorship.**

Professor van der Eijk was formerly Director of the Wellcome Trust-funded Northern Centre for the History of Medicine, a partnership between Newcastle and Durham Universities. He has received many grants from the Trust, including a University Award in 1994, after which he took up a personal Chair of Greek at Newcastle.

The Humboldt Professorship, worth €3.5 million (around £3.1m), is awarded to scientists and scholars outside Germany, enabling them to carry out a large-scale research project at a German university. One of the most prestigious European academic prizes, it is awarded to up to ten researchers each year, usually in the fields of natural sciences, medicine and mathematics. Professor van der Eijk is the first recipient from the humanities.

Professor van der Eijk's field of interest is the dialogue between medicine and philosophy, the mind–body interface, the transfer of medical knowledge, and the relationship between medicine, moral values and religion. An expert in Ancient Greece and classical antiquity, in 2009 he was awarded a History of Medicine programme grant, which is supporting an ambitious project to provide scholarly translations of Galen's writings. Despite Galen's seminal position in medical history, much of his work has never been satisfactorily translated.



1

## SUGAR STRUCTURES

**The sugars attached to proteins are surprisingly important across many areas of biology.**

Daan van Aalten, whose Senior Research Fellowship was renewed this year, has established himself as a leading figure in 'glycobiology' – studies of sugar molecules and the polymers made from them. From the protective coats of yeast and bacteria, he has moved on to processes happening within the cell – where addition of sugar molecules to proteins is playing an unexpectedly important role in the life of the cell.

Professor van Aalten began work on chitin, possibly the most common natural product on Earth. A long polymer of a single sugar (*N*-acetylglucosamine), chitin makes up the shells of a multitude of animals, from lobsters to locusts. More importantly, from a medical point of view, chitin is also found in the cell wall of fungi that infect people.

In the first five years of his Fellowship, Professor van Aalten has worked out the structures of key enzymes in chitin metabolism, identified natural products that inhibit these enzymes and developed small chemical molecules with similar inhibitory properties.[1] Spectacular progress in this area is being taken forward through Technology Transfer Seeding Drug Discovery funding.

The work funded through the Fellowship renewal will build on what was initially a side project in his laboratory. As well as being used to make polymers, *N*-acetylglucosamine is also added to proteins, modifying their activities. Most excitingly, it appears that *N*-acetylglucosamine is added to the same sites as phosphate groups (serine and threonine residues), a modification used to control the activity of many cellular proteins. *N*-acetylglucosamine appears to be an additional part of this control system, competing for the same target sites. *N*-acetylglucosamine modification may therefore figure in many key cellular processes, from cell division and cancer to control of insulin secretion.

Having worked out the structures of the enzymes that carry out this reversible modification,[2,3] Professor van Aalten has designed highly specific small-molecule inhibitors that are being used to dissect the role of this sugar modification in a range of cellular processes.

*1 Dorfmueller HC et al. J Am Chem Soc 2006;128(51):16484–5.*

*2 Rao FV et al. EMBO J 2006;25(7):1569–78.*

*3 Clarke AJ et al. EMBO J 2008;27(20):2780–8.*

## DATA DETECTIVE

**With the right methods, electronic health records can establish the true impact of adverse drug reactions.**

Despite their benefits, all drugs have side-effects and their use always reflects a balance between benefits and drawbacks. At the London School of Hygiene and Tropical Medicine, Liam Smeeth, a Wellcome Trust Senior Research Fellow in Clinical Science, is analysing data from electronic health records to gain a clearer picture of adverse reactions to a range of widely used medications.

Clinical trials are designed to assess drug efficacy and safety. However, no clinical trial can include all possible patient types or pick up very rare (but serious) reactions. Thus even once a drug is in widespread use, ongoing assessment of its effects is needed. One way in which this can be done is through use of computerised health records. Of particular value is the General Practice Research Database (GPRD), which includes completely anonymous medical records for over 3.6 million patients registered at almost 500 general practice surgeries.

Even with this amount of data on tap, there is a need to be cautious about associations. To minimise confounding factors, Professor Smeeth has adopted an approach in which people act as their own controls, comparing periods before and after the initiation of drug use (while controlling for factors such as the resulting age difference).

His analyses have explained some otherwise puzzling findings. For example, some diabetes medicines appeared to

**IMAGE**
Structure of 'GlcNAcstatin', a highly specific enzyme inhibitor.

## DO THE MATH

increase the risk of fractures, but only in women and only of certain bones – patterns that were difficult to explain. Professor Smeeth's much larger analysis (more than 1800 patients who used the drugs and also had fractures) confirmed the association was present for both sexes and that a wide range of bones were affected.[1]

A similar approach revealed that antipsychotics, usually used to treat schizophrenia, were associated with an increased risk of stroke – particularly in patients with dementia.[2]

Such studies are not always purveyors of bad news, however. Analysis of GPRD data found no evidence that women given new bisphosphonate drugs for osteoporosis were at higher risk of abnormal heart rhythms.[3] And a mammoth analysis of nearly 130 000 patients and 600 000 controls cleared statins of involvement in a range of serious conditions (such as cancer), as some high-profile studies had alleged.[4]

Professor Smeeth's studies illustrate how analysis of data held in electronic patient records can improve patient care. As well as posing technical and confidentiality challenges, though, there is also a need for rigorous statistical and methodological approaches to ensure that data analyses do actually provide meaningful results.

**This research was supported by the Wellcome Trust and other funders.**

*1 Douglas IJ et al. PLoS Med 2009;6(9):e1000154.*

*2 Smeeth L et al. Br J Clin Pharmacol 2009;67(1):99–109.*

*3 Douglas IJ, Smeeth L. BMJ 2008;337:a1227.*

*4 Grosso A et al. PLoS One 2009;4(3):e4720.*

**Sophisticated statistical analyses are extracting even more information from genome-wide data.**

Genome-wide association studies generate an avalanche of data – but the 'wet experiments' are only half of the story. Perhaps the greatest challenge is in processing the data and extracting as much information of biological relevance as possible. Two Wellcome Trust fellows are playing important roles in this analysis.

Simply put, association studies identify genetic variants that are more common in study populations than in controls. This statistical association requires very careful scrutiny. If the bar of statistical significance is set too high, important loci might be omitted. Set the bar too low and all key loci will be captured – but so too will many irrelevant markers that show an unequal distribution just by chance. Unfortunately, most loci have small effects, so distinguishing 'real' and spurious signals is a challenging task.

At Newcastle University, Heather Cordell, whose Senior Research Fellowship was renewed this year, is working with statisticians and geneticists to develop new statistical techniques for genome-wide data analysis. As well as pooling data to increase sample size, it is also possible to take account of factors such as underlying population structure, the nature of the controls, family relationships and inheritance patterns at particular loci.[1,2]

Statistical tools also come into play after an association has been confirmed. Individual loci may actually encompass several independent genetic influences, or may exert their effects in combination with other loci or with environmental factors.

Cecilia Lindgren, awarded a Research Career Development Fellowship this year, is applying statistical analyses to obtain a better understanding of biological processes involved in the development of type 2 diabetes and obesity. Based at the Wellcome Trust Centre for Human Genetics in Oxford, Dr Lindgren has played a major part in the Wellcome Trust Case Control Consortium's studies.[3,4,5]

This work has highlighted genetic effects on overall obesity (as defined by body mass index) as well as risk factors for diabetes. However, it is not just body weight *per se* that is the problem – it is how and where excess fat is stored. Dr Lindgren now aims to use genome-wide data to identify more of the factors influencing the distribution of fat in the body, particularly in the abdomen (central obesity). She also intends to follow up the most interesting leads to see how they affect body physiology and ultimately disease processes.

**This research was supported by the Wellcome Trust and other funders.**

*1 Cordell HJ. Genomics 2009;93(1):5–9.*

*2 Biernacka JM, Cordell HJ. Eur J Hum Genet 2009;17(5):644–50.*

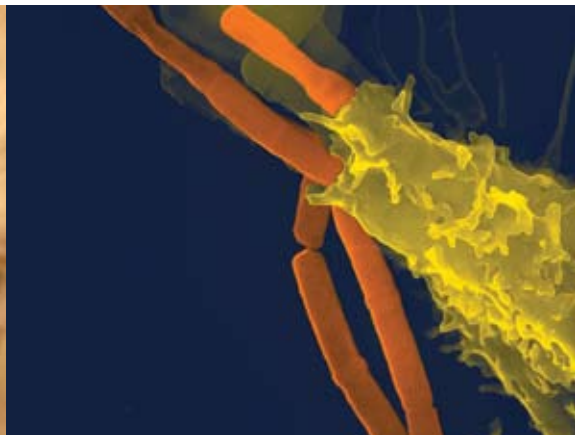
*3 Lindgren CM et al. PLoS Genet 2009;5(6):e1000508.*

*4 Timpson NJ et al. Diabetes 2009;58(2):505–10.*

*5 Loos RJ et al. Nat Genet 2008;40(6):768–75.*

**IMAGES**

**1** Liam Smeeth of the London School of Hygiene and Tropical Medicine.
**2** Cecilia Lindgren, a new Research Career Development Fellow.



## ANIMAL FLU

**A new veterinary fellow is looking at the transmission of influenza viruses in livestock.**

The H1N1 swine flu pandemic and persistent fears of an H5N1 avian flu outbreak have brought influenza A viruses into sharp focus. These viruses affect a range of animals, and as part of the Wellcome Trust's new veterinary initiative, Pablo Murcia will be using a postdoctoral fellowship to investigate genetic variation in influenza viruses and its effects on virus transmission.

Originally from Buenos Aires, Argentina, Dr Murcia trained as a vet, graduating in 1998. A research project during his degree ignited an interest in virology and he went on to undertake an MSc in animal health while attached to the Department of Virology at the University of Buenos Aires.

During this time, he encountered an outbreak of pulmonary tumours in sheep in Patagonia. Curious to know more about the cause of the tumours, Jaagsiekte sheep retrovirus, Dr Murcia got in touch with Massimo Palmarini at the University of Glasgow (see page 9). A fellowship from the American Society for Microbiology enabled him to join Professor Palmarini's lab, where he worked on the sheep virus and endogenous retroviruses.[1,2]

In 2007, he moved to the Cambridge Veterinary School, working under the umbrella of the Cambridge Infectious Diseases Consortium, led by James Wood. Here, Dr Murcia has switched his attention to influenza viruses, collaborating with the Wellcome Trust Sanger Institute to establish an influenza virus genome-sequencing pipeline (part of a programme funded by the Trust).

As well as having veterinary importance, this work is also relevant to human influenza. It is not yet clear how viral genetic variation within an individual host affects the spread of influenza through a population. Working on horses and pigs, Dr Murcia will monitor the spread of infections and investigate this variation within individual animals by sequencing virus isolates in collaboration with the Sanger Institute. He also plans to map this genetic variation to the antigenic variation seen in viral proteins. In addition, collaborations with world-leading researchers at Penn State University in the USA will integrate these findings into models of flu transmission.

**This research was supported by the Wellcome Trust and other funders.**

*1 Mura M et al. Proc Natl Acad Sci USA 2004;101(30):11117–22.*

*2 Murcia PR et al. J Virol 2007;81(4):1762–72.*

## VOLUME CONTROL

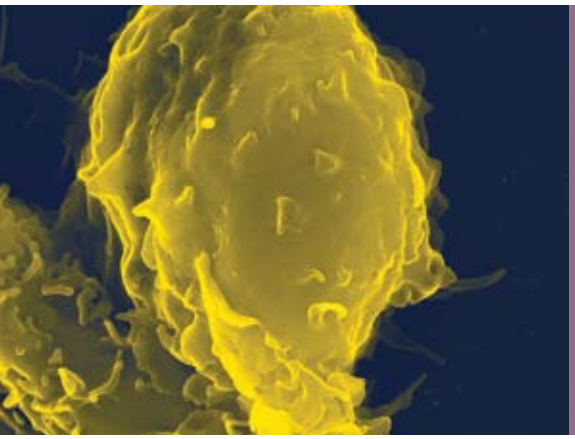
**An understanding of the pathways of immune cell activation will provide opportunities to boost – or block – immune responses.**

Immune responses depend on the activation of certain key defence cells, such as dendritic cells, macrophages and neutrophils. Sometimes – after vaccination, for example – immune responses need to be boosted; if inflammatory conditions develop, though, they need to be suppressed. At the Semmelweis University in Hungary, International Senior Research Fellow Attila Mócsai is unpicking the pathways of immune cell activation – work that may provide methods to fine-tune the strength of immune responses.

One way in which neutrophils are activated is through a family of cell-surface receptors that recognise antibody–antigen complexes. As well as identifying which family members are important in both mouse and human neutrophil activation,[1] Dr Mócsai has explored the intracellular events that follow activation.

Several triggers of neutrophils act through an important signalling pathway controlled by the Syk tyrosine kinase. Downstream steps in this pathway, however, are not well understood. Dr Mócsai has found that one form of phospholipase C (PLCγ2) is specifically involved in neutrophil activation triggered by immune complexes.[2] Blocking PLCγ2 inhibited neutrophil activation – and also completely protected mice from inflammatory arthritis.

**IMAGE**
H1N1 'swine flu' may be transmitted from humans to pigs.



# New funding

## A SELECTION OF NOTABLE GRANTS AWARDED IN 2008/09

With collaborators in Germany, Dr Mócsai has examined signalling downstream of Syk in other situations. In macrophages and dendritic cells, for example, activation of the Card9 adapter through Syk has turned out to be the crucial route by which adjuvants boost immune responses to vaccines based on *Mycobacterium tuberculosis* antigens.[3]

Inflammatory responses to fungal infections also involve Syk, but in this case it has two distinct roles. Acting through Card9, Syk is needed to initiate synthesis of a precursor of interleukin 1β, an essential trigger of inflammatory responses. Syk is also needed to activate the intracellular complex (the 'inflammasome') that processes this precursor into active interleukin 1β, but this role is independent of Card9.[4]

**This research was supported by the Wellcome Trust and other funders.**

*1 Jakus Z et al. J Immunol 2008;180(1):618–29.*

*2 Jakus Z et al. J Exp Med 2009;206(3):577–93.*

*3 Werninghaus K et al. J Exp Med 2009;206(1):89–97.*

*4 Gross O et al. Nature 2009;459(7245):433–6.*

## PRINCIPAL RESEARCH FELLOWS

**Three leading figures in UK science have had their Principal Research Fellowships renewed.**

Principal Research Fellowships (PRFs) are the most senior of the Wellcome Trust's personal support schemes, providing seven years' initial support and a further five years' funding after renewal. This year, the PRFs of Karl Friston, Margaret ('Scottie') Robinson and Brian Spratt were all renewed.

Professor Friston is Scientific Director of the Wellcome Trust Centre for Neuroimaging at University College London. His work focuses on computational models of brain function. In 2003 he was awarded the Minerva 'Golden Brain' award and is one of world's top ten most cited neuroscientists.

A former Senior Research Fellow, Professor Robinson is based at the University of Cambridge. She is a world leader in research into the trafficking of material through the cell in clathrin-coated vesicles.

Professor Spratt was among the first researchers to be awarded a PRF by the Wellcome Trust. His research at Imperial College London focuses on bacterial evolution, population genetics and molecular epidemiology.

### SENIOR RESEARCH FELLOWSHIPS

**ASTHMA**
**Professor Clare Lloyd** (Imperial College London): Allergic airway inflammation and remodelling (renewal).

**STEM CELLS**
**Anton Wutz** (University of Cambridge): Epigenetics and stable cell identity in mammalian stem cells.

### WELLCOME TRUST–NIH FOUR-YEAR PHD STUDENTSHIP

**NEUROSCIENCE**
**Alexander Domanski** (University of Edinburgh): SynGAP regulation of circuit formation in the somatosensory cortex.

### RESEARCH TRAINING FELLOWSHIPS IN PUBLIC HEALTH AND TROPICAL MEDICINE

**MALARIA**
**Emelda Aluoch Okiro** (KEMRI–Wellcome Trust Research Programme, Kenya): Changes in paediatric malaria hospitalisation in East Africa.

**VETERINARY MEDICINE**
**Helen Higgins**: Assessing veterinary surgeons' clinical beliefs in dairy cow preventive medicine.

### SENIOR RESEARCH FELLOWSHIP IN CLINICAL SCIENCE

**ANAESTHESIOLOGY**
**Anthony Pickering** (University of Bristol): Modulation of pain pathways by noradrenaline.

### SIR HENRY POSTDOCTORAL WELLCOME FELLOWSHIP

**DNA DAMAGE**
**Hannah Mischo** (CRUK London Research Institute): Sen1 and prevention of DNA damage.

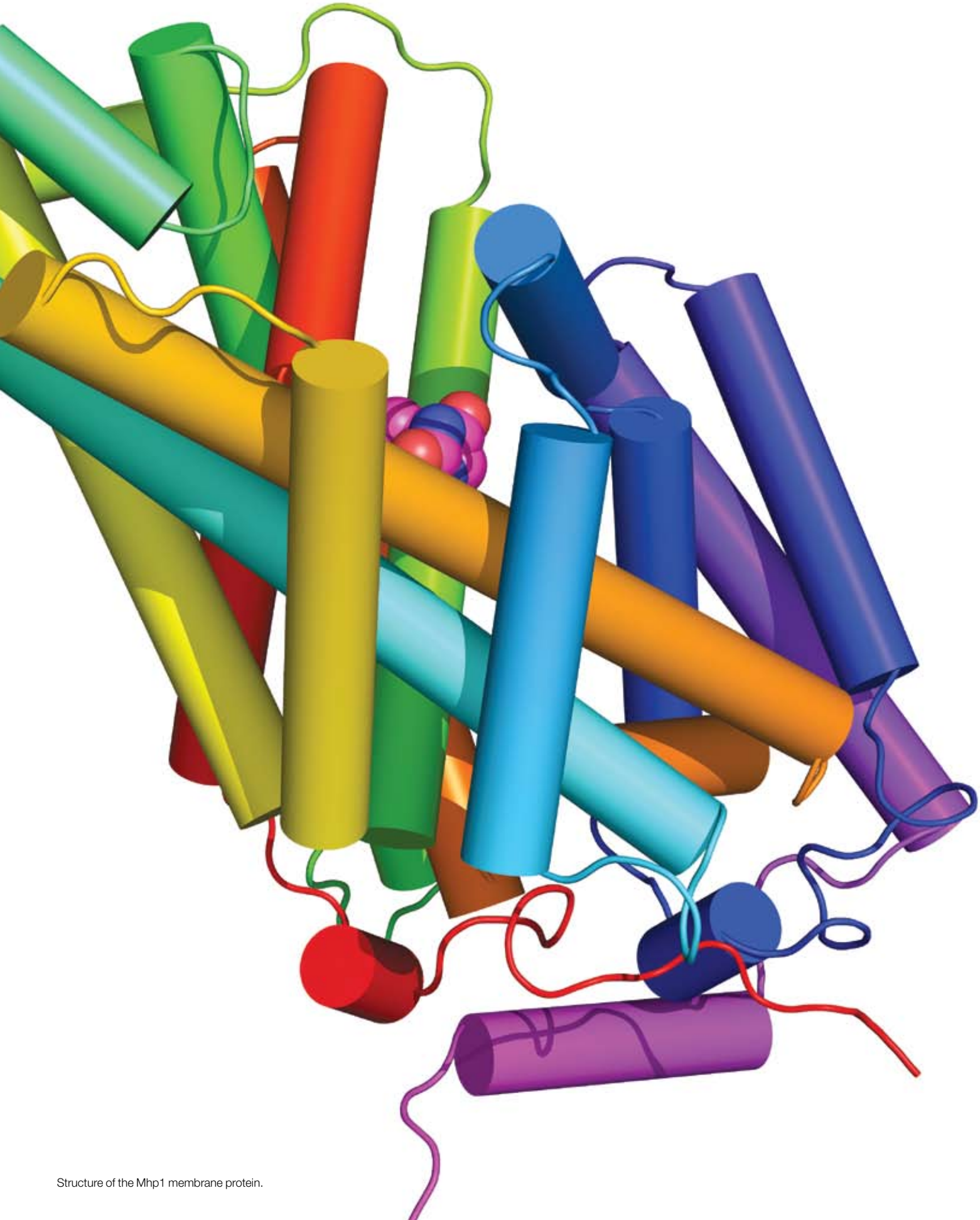
### HISTORY OF MEDICINE FELLOWSHIP

**MUSIC**
**James Kennaway** (Durham University): Music as a cause of ill-health.

### BIOMEDICAL ETHICS FELLOWSHIP

**CLINICAL TRIALS**
**Neema Sofaer** (King's College London): Post-trial access to trial drugs, healthcare and information.

**IMAGE**
A neutrophil, a key player in innate immune responses.



Structure of the Mhp1 membrane protein.

# Facilitating research

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

## INSIDE STORY

**The structure of a bacterial membrane protein has revealed an elegant mechanism of cross-membrane transport.**

Membrane proteins make up around 25 per cent of all proteins (and 40 per cent of drug targets). Yet, because membrane proteins are so hard to work with, relatively few structural studies have been carried out on them. A dedicated Membrane Protein Laboratory, led by Imperial College London's So Iwata, has been set up with Wellcome Trust funding at the Diamond synchrotron, to act as a resource to support structural studies of membrane proteins. Work on a bacterial transporter illustrates the kind of insights that structural studies can provide.

Mhp1, a membrane protein from *Microbacterium liquifaciens*, has a 'metabolic salvage' function. It imports derivatives of the organic molecule hydantoin, which are used to make a variety of amino acids. It is an important 'model' structure as it is one of a large class of similar transporters: more than 800 are known in total, from all classes of life. Its structure was worked out at the Membrane Protein Laboratory by Professor Iwata in collaboration with Peter Henderson from the University of Leeds and others.[1]

Of greatest interest, the structure suggests a mechanism for the specific transport of its substrate – confirming the 'alternating access' model proposed many years ago for the action of membrane transporters.

Without substrate, a central chamber is exposed to the outside environment. When hydantoin engages, it triggers a conformational change that in effect closes the door to the entry of further molecules. A second shift in structure exposes hydantoin to the inside of the cell, where it is ejected and the transporter reverts to its original structure.

The structure is likely to have relevance beyond the world of bacteria. Many membrane transporters, in all kinds of organisms, are thought to operate through the alternating access mechanism. This work should therefore aid understanding of other structures that move molecules across membranes.

**This research was supported by the Wellcome Trust and other funders.**

*1 Weyand S et al. Science 2008;322(5902):709–13.*

## EUROPEAN ENGAGEMENT

**Engagement with the EU has helped to keep key research alive.**

European legislation can significantly affect research in UK institutions. By working with partners with similar interests and by providing evidence on the likely impact of two EU directives – on medical imaging and the use of animals – the Trust has helped to ensure that the needs of medical research are taken into account in the EU legislative process.

The Physical Agents Directive aimed to protect the health of workers exposed to electromagnetic fields. As originally drafted, however, it would have had serious consequences for both clinical and research use of magnetic resonance imaging equipment. Following input from the Trust and others, the Directive was postponed for four years and the process of revision is now underway.

The Use of Animals in Research Directive would have significantly hindered the use of non-human primates and re-use of animals in research, stifling vital research, hindering medical progress and undermining Europe's commercial and scientific competitiveness. Unnecessary bureaucratic requirements would make research in Europe prohibitively expensive, and potentially drive studies abroad to countries with lower standards of animal welfare.

The Trust worked with a large coalition of bodies to collate evidence for the European Parliament and Home Office and House of Lords reviews of the Directive. It is hoped the important revisions made to date will remain intact.

## GROWING UP

**Studies on the ALSPAC birth cohort are revealing a host of factors affecting children's mental development.**

Set up in 1991, the Avon Longitudinal Study of Parents and Children (ALSPAC) is one of the world's largest and longest-running birth cohorts. It covers some 14 000 children and their parents, providing researchers with a treasure trove of data on many aspects of childhood health and development. Several recent studies have made important discoveries about environmental, family and genetic influences on children's mental health and development.

Stan Zammit and colleagues in Bristol have looked at a range of factors that might be associated with subclinical psychotic episodes – possible warning signs of increased risk of schizophrenia in adulthood. They identified links with impaired fetal growth,[1] trauma at or around the time of birth,[2] maternal smoking[3] and events in childhood itself, such as bullying.[4]

Alan Emond and colleagues found an association between binge drinking in mothers and behavioural problems such as hyperactivity at age four (in girls) and at age seven (in both sexes).[5] They also identified a link between lead levels in blood at 30 months and a range of indicators at age seven to eight, including reading and writing ability, SATs results and antisocial behaviour measures, even at lead levels well below the generally recognised risk level.[6]

David Odd (a Wellcome Trust Training Fellow) and colleagues have looked at links between resuscitation at birth and cognition at age eight. As expected, infants with diagnosed brain damage were at risk of lower IQ, but so too were those who had been resuscitated but not identified as affected.[7] Although the IQ differential was smaller, they are a much larger group overall.

Paul Ramchandani and colleagues have found that paternal depression can affect children's wellbeing.[8] A comparison of the effects of prenatal and postnatal depression suggested that 'environmental' influences may be more significant than 'biological' factors.

Cohorts such as ALSPAC are particularly useful for studying the interaction between genes and environment, as a wide variety of 'lifestyle' data are collected and samples are available for DNA analysis. Two studies looking for links between behaviour and genetic variants affecting serotonin metabolism have generated contrasting results. Early life stress and MAOA-LPR interact to increase the risk of hyperactivity,[9] but no effects were seen for a second variant, HTTLPR.[10]

**This research was supported by the Wellcome Trust and other funders.**

*1 Thomas K et al. Br J Psychiatry 2009;194(6):521–6.*

*2 Zammit S et al. Br J Psychiatry 2009;195(4):294–300.*

*3 Zammit S et al. Psychol Med 2009;39(9):1457–67.*

*4 Schreier A et al. Arch Gen Psychiatry 2009;66(5):527–36.*

*5 Sayal K et al. Pediatrics 2009;123(2):e289–96.*

*6 Chandramouli L et al. Arch Dis Child 2009;94(11):844–8.*

*7 Odd DE et al. Lancet 2009;373(9675):1615–22.*

*8 Ramchandani PG et al. J Child Psychol Psychiatry 2008;49(10):1069–78.*

*9 Enoch MA et al. Genes Brain Behav 2009 9 Sep [Epub ahead of print].*

*10 Araya R et al. Am J Med Genet B Neuropsychiatr Genet 2009;150B(5):670–82.*

## TAMING THE 'BEASTLY SCIENCE'

**Sir Bernard Spilsbury almost single-handedly created the field of forensic medicine. His story is inspirational but also a timely warning.**

Educated at Oxford and St Mary's Hospital, London, Spilsbury specialised in the emerging science of forensic medicine – the 'beastly science', as it was then known. He became a nationally recognised figure following the Dr Crippen case in 1910, in which he testified that the remains of a body buried in lime in Crippen's basement belonged to his wife, on the basis of a scar-bearing fragment of skin. Crippen was hanged and Spilsbury became a national celebrity.

Spilsbury was a prolific worker. He undertook more than 25 000 post mortems – up to a 1000 a year. Although best known for lurid high-profile cases – Crippen, the 'Brides in the Bath' trial, the Brighton trunk murders and others that transfixed the British public – his work actually illustrated how mundane sudden death usually was.

He studiously recorded notes on index cards, nearly 4000 of which were purchased by the Wellcome Library in 2008, while a further 3000 were donated in 2009. Together, the cards provide a fascinating insight into death and its forensic investigation from 1905 to 1946 (with the odd gap).

The cards tell of tragic suicide, failed abortions and medical mysteries that stumped Spilsbury (such as likely cases of cot death). Each card tells of a life brought to an untimely end in sad,

# New funding

## A SELECTION OF NOTABLE GRANTS AWARDED IN 2008/09

pathetic or sometimes downright bizarre ways: 42-year-old Ada Farnden took quinine to induce an abortion: "Laundress, four children in six years. Took quinine in port wine at 11am. Taken ill soon afterwards"; five-year-old Louisa Messenger was a victim of "death from poisoning by rhubarb".

The notes may have been intended for a textbook on forensic medicine, which Spilsbury never got round to writing. Instead, his life – professional and personal – headed into inexorable decline. He was badly affected by the death of two sons, in World War II and from TB. Always strong-willed, he became increasingly dogmatic.

During his life, Spilsbury encountered many suicide victims. His own life ended the same way. In December 1947 he went to his laboratory in University College London, turned on a Bunsen burner and gassed himself to death.

Spilsbury undoubtedly transformed the field of forensic medicine. Yet perhaps he has a second legacy: a warning of the dangers of depending on personal opinion, no matter how authoritative, when the stakes are so high.

**All of the Spilsbury cards have been catalogued and can be accessed through the Wellcome Library's Archives and Manuscripts catalogue (library.wellcome.ac.uk); see www.timesonline.co.uk/tol/news/science/article5429780.ece for more on the Spilsbury papers.**

## AFRICAN CONSORTIA

**More than 50 institutions from 18 African countries are participating in international consortia under a £28 million initiative aimed at strengthening research capacity across Africa.**

The African Institutions Initiative is supporting seven new international and pan-African consortia. The partnerships – each led by an African institution – aim to develop the capacity of institutions to support and conduct health-related research to enhance people's health, lives and livelihoods. The consortia are led by researchers in academic centres in Côte d'Ivoire, Ghana (two), Kenya, Malawi, Tanzania and Uganda.

Although the consortia include partners from high-income countries, the agenda for each has been set by the African centres' needs and priorities. Each consortium operates independently and sets its own priorities, for example investment in leadership training and professional development, support for PhD and postdoctoral fellowships, improved infrastructure, competitive grant schemes and purchase of up-to-date equipment.

Ultimately, the main aim is to build sustainable local research capacity across Africa, by strengthening universities and research institutions and enabling them to develop research networks. In this way, more African universities can become platforms for internationally competitive research tackling locally relevant health challenges.

### BIOMEDICAL RESOURCES

**NEURAL NETWORKS**
**Professor Angus Silver** (University College London): An open source database for biologically realistic neural network models.

**YEAST BIOLOGY**
**Carol Munro** (University of Aberdeen): Novel tools for functional genomics of *Candida albicans*.

### TECHNOLOGY DEVELOPMENT GRANTS

***IN VIVO* IMAGING**
**Alessandro Sardini** (Imperial College): Instrumentation for fluorescent imaging in living animals.

**MUTATION DETECTION**
**Professor Sir Alec Jeffreys** (University of Leicester): High-throughput screening for *de novo* point mutations in human genomic DNA.

### EQUIPMENT

**RADIOTHERAPY**
**Stewart Martin** (University of Nottingham): Experimental radiation biology irradiation facility.

**EMBRYOLOGY**
**Timothy Mohun** (National Institute for Medical Research): An imaging pipeline for screening mouse embryos.

**CELL BIOLOGY**
**Adrien Kissenpfennig** (Queen's University Belfast): A flow cytometry cell sorter.

**BRAIN IMAGING**
**Professor Paul Furlong** (Aston University): A magnetoencephalography system for infants.

**Professor Ray Dolan** (University College London): An upgrade of MRI scanners at the Wellcome Trust Centre for Neuroimaging at UCL.

**DATABASE**
**Gerrit Kleijwegt** (European Bioinformatics Institute): A European Protein Data Bank.

### RESEARCH RESOURCES IN MEDICAL HISTORY

**MEDICAL RECORDS**
**Mike Barfoot** (University of Edinburgh): Preservation of 20th-century case notes relating to tuberculosis and World War II injuries.

**IMAGE**
Spilsbury's index cards in the Wellcome Library.

# Developing our organisation

**Using our resources efficiently and effectively**

## OPERATIONS AND EDUCATION

**Two senior staff with a wealth of experience in contrasting domains have joined the Wellcome Trust.**

Simon Jeffreys, the Wellcome Trust's new Chief Operating Officer, is charged with ensuring that the organisation is run as efficiently and effectively as possible. Having joined the Trust in March 2009, he has assumed responsibility for key business operations, including finance, grants management, facilities management, IT, human resources and legal affairs. He has absorbed many of the responsibilities previously held by John Cooper, who has taken on the role of Chief Operating Officer and Interim Chief Executive of the UK Centre for Medical Research and Innovation.

Simon Jeffreys has spent most of his professional life at PricewaterhouseCoopers and its predecessor firms, latterly as chairman of its global investment management practice and part of the firm's global financial services leadership team.

Derek Bell, former Chief Executive of the Association for Science Education, took over as the Wellcome Trust's Head of Education in January 2009.

Professor Bell will have responsibility for the Trust's education strategy and further developing the Trust's leading role in UK science education. This work will focus on increasing opportunities and strengthening the culture for continuing professional development for science teachers. In addition, Professor Bell will look at how research can best be used to support education policy making and teaching practice.

## ENGAGING COMMUNICATIONS

**Video, tweets and blogs are all being used to communicate the Trust's work.**

The internet has opened up many new ways in which organisations can communicate with different audiences, and the Wellcome Trust has moved to adopt these new approaches.

For example, the news and features posted on the Trust's main website can now be obtained by RSS feeds or by signing up to an e-newsletter. This year has also seen a rapid growth in the use of video features, available on the main websites and on dedicated Wellcome Trust and Wellcome Collection YouTube channels, which both launched in January 2009. The Trust also uses Twitter to provide brief up-to-the-minute information, and has accumulated more than 2000 followers. The audience for Wellcome Trust print publications such as *Wellcome News* and *Big Picture* has also significantly increased both in terms of print circulation numbers and online usage following their inclusion in 'online libraries' such as Yudu, Scribd and Issuu.

Other new developments include a Facebook page for Wellcome Collection, which has attracted more than 1200 members, while the Wellcome Library has launched a blog that provides an informative guide to the Library's activities, purchases and holdings. The Library's fascinating Moving Image and Sound Collection also has its own 'Wellcome Film' YouTube channel.

**www.twitter.com/wellcometrust**
**www.youtube.com/wellcometrust**
**www.scribd.com/Wellcome Trust**
**issuu.com/wellcome-trust**
**www.twitter.com/explorewellcome**

## FAIR SHARES

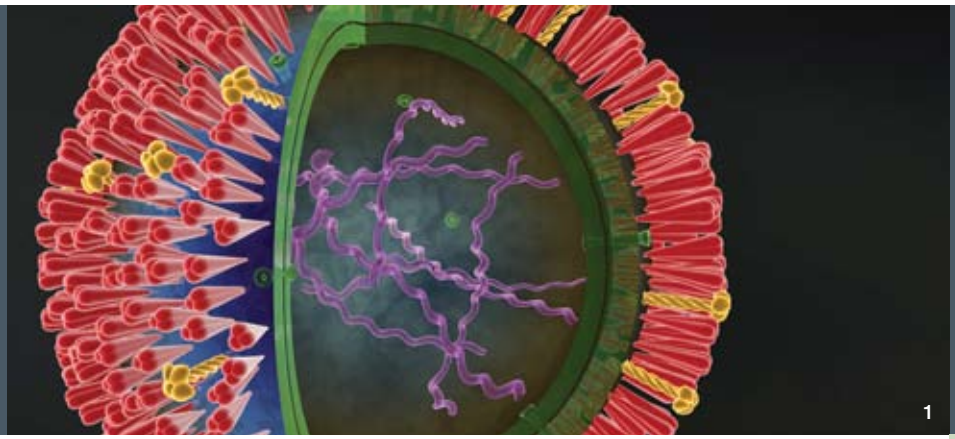
**A £1.2 billion investment in large multinational companies had increased in value by 25 per cent by the end of the year.**

Despite a challenging year, the Wellcome Trust's investments achieved gains of £580 million (5 per cent) during 2008/09, and were valued at £13.0bn at 30 September 2009.

A significant contribution to this strong performance came from investment in late 2008 and early 2009, when stock markets were very weak, of £1.2bn in shares of 32 global companies. Such companies, each valued at a minimum of US$50bn, typically deliver strong returns during difficult economic times, and after the stock market decline, their shares represented very good value. By the end of the year, the value of these investments had already risen to £1.6bn, an increase of 25 per cent.

The fall in stock market prices also enabled the Trust to acquire a range of other shares at favourable prices, including 3 per cent of the shares of Marks & Spencer plc.

Shares now account for around 38 per cent of the Trust's investment portfolio, with holdings geographically well diversified. A growing proportion are managed from within the Trust itself. The ability of the Trust to invest directly in equity markets has been enhanced by the establishment of a Public Securities Execution team led by Tim Johnston, previously at Goldman Sachs and a number of hedge funds.



# CORPORATE ACTIVITIES 2008/09

### Governors and senior staff

The Wellcome Trust's Director, Mark Walport, received a knighthood in the 2009 New Year's Honours List for services to medical research. Sir Mark was appointed chair of the Science and Learning Expert Group established by the UK Department of Business, Innovation and Skills as part of its science and society strategy.

Peter Davies, a senior limited partner at Lansdowne Partners, joined the Board of Governors in September 2009. Simon Jeffreys was recruited to run the Trust's business operations, Derek Bell assumed responsibility for the Trust's education work and Tim Johnston joined the Investment team (see left).

### Research environment

The Human Fertilisation and Embryology (HFE) Act was granted Royal Assent in November 2008. The Trust had worked with a range of partners to ensure that discussions of potentially contentious issues such as hybrid embryos were balanced and factual, and that due consideration was given to the potential medical benefits of research covered by the legislation.

Following a series of meetings with key stakeholders, in June 2009 the Trust published a set of guidelines on the use of medical records in research. *Towards Consensus for Best Practice: Use of patient records from general practice for research* was endorsed by the British Medical Association and the Royal College of General Practitioners.

In November 2008, the Trust published *Medical Research: What's it worth?*, the results of a year-long study commissioned by the Trust, the Medical Research Council and the Academy of Medical Sciences that assessed the returns achieved from investment in research into cardiovascular disease and mental health.

Internally, work began on a new Strategic Plan, to follow the Trust's previous *Strategic Plan 2005–2010: Making a difference*.

### Priority areas

The Trust reacted swiftly in response to the H1N1 swine flu epidemic. An ongoing programme of work on global influenza in human and animal health was rapidly refocused on pandemic H1N1 after the outbreak was detected in February 2009. In spring 2009, a series of workshops were held with key UK funding and public health bodies, leading to the rapid appraisal and funding of a series of collaborative programmes (see page 14). Scientific advisory meetings on seasonal, avian and pandemic influenza were organised to identify gaps in knowledge and research priorities. This work, including vaccine, drug development and epidemiology, is feeding into the World Health Organization's public health research agenda for influenza. The Trust hosted a joint meeting with the WHO on novel influenza vaccines and continues to play an active role in the development of international policy.

The Trust is also supporting the South East Asia Infectious Disease Clinical Research Network, which aims to enhance regional capacity in clinical research and patient management. The Network's activities cover pandemic H1N1 and H5N1 influenza.

With support from the Trust and other bodies in the UK and USA, Professor Sir Andrew Haines from the London School of Hygiene and Tropical Medicine led a study investigating the potential health benefits of reducing greenhouse gas emissions to help combat climate change. Its findings informed discussions at the UN Climate Change Conference in Copenhagen, December 2009.

The Trust also brought together leading researchers and other groups to discuss issues arising from genomic and cohort-based studies. Oxford's Ethox Centre has been commissioned to conduct a literature review in this area.

In collaboration with the Bill and Melinda Gates Foundation, the Trust is supporting a scoping exercise to explore the potential for an 'international index for nutrition', which would assess how well companies were meeting their corporate and social responsibilities, in high-, middle- and low-income countries. The Global Alliance for Improved Nutrition in Geneva is exploring approaches that might encourage food and beverage industries to adopt best practice with regard to the nutritional value of their products.

**IMAGES**
**1** H1N1 influenza virus.
**2** Simon Jeffreys, the Trust's new Chief Operating Officer.

# Financial summary 2008/09

**Total charitable expenditure for the year increased to £720 million (2007/08: £702m). This rise is principally due to a number of large Strategic Awards and new initiatives launched during the year, such as in medical engineering.**

### Careers
Expenditure on careers support totalled £135.2m (2007/08: £147.3m); in addition, a significant proportion of funds committed through the African Institutions Initiative is likely to be used to provide careers support.

### International
Funding to Major Overseas Programmes and to institutions outside the UK totalled £103.2m.

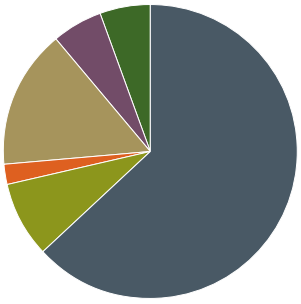
### Infrastructure
Expenditure on buildings, refurbishment, equipment and resources amounted to £20.2m in 2008/09. This figure does not include the significant expenditure on equipment or infrastructure provided as part of other Trust grants, nor the likely expenditure on infrastructure through the African Institutions Initiative.

**NB: These categories are not exclusive: some grants (e.g. international fellowships and capital awards) fall into more than one category. In these cases, sums awarded have been included in all relevant categories, to give a more realistic indication of expenditure in each area.**

## BREAKDOWN OF WELLCOME TRUST CHARITABLE EXPENDITURE 2008/09

Total: £720m

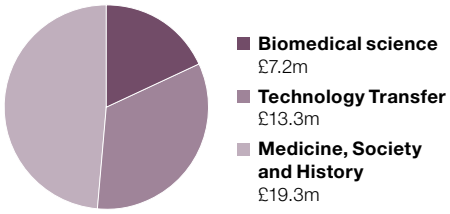
- **BIOMEDICAL SCIENCE GRANTS** £454.5m
- **TECHNOLOGY TRANSFER GRANTS** £60.2m
- **MEDICINE, SOCIETY AND HISTORY GRANTS** [1] £16.5m
- **WELLCOME TRUST GENOME CAMPUS** £109.6m[2]
- **DIRECT ACTIVITIES** £39.8m
- **SUPPORT COSTS** £39.8m



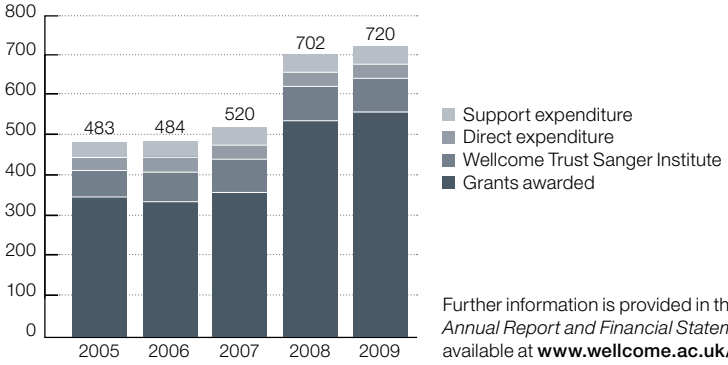
**1 History of medicine, biomedical ethics and public engagement with science.**
**2 This consists of: Wellcome Trust Sanger Institute £97.4m (including £18.1m from other funders); other Genome Campus activities £12.2m.**

### DIRECT ACTIVITIES: £39.8M

Direct activities are those managed by the Wellcome Trust itself or in partnership with others. These include:
- Wellcome Collection
- directly managed public engagement activities
- scientific conferences.




### CHARITABLE EXPENDITURE 2005–09 (£M)




Further information is provided in the Wellcome Trust's *Annual Report and Financial Statements 2009*, available at **www.wellcome.ac.uk/publications**.

## FUNDING HIGHLIGHTS

£49m
**Core support for South-east Asia Major Overseas Programme**

£45m
**Sainsbury–Wellcome Centre for Neural Circuits and Behaviour at UCL**

£28m
**African Institutions Initiative**

£26.9m
**Medical engineering centres of excellence[1]**

£22.8m
**Research Career Development Fellowship funding**

£19.7m
**Seeding Dug Discovery initiative awards**

£15m
**New Senior Research Fellowship funding**

£11.3m
**Neurodegenerative Diseases Initiative[2]**

£10m
**Genome-wide association studies[3]**

£7.7m
**Clinical PhD Programmes**

£7.2m
**Principal Research Fellowship renewals**

£5m
**Oxford Centre for Neural Circuits and Behaviour**

£4.8m
**Novartis Vaccines Institute for Global Health: typhoid fever vaccine**

£3.7m
**Core funding Wellcome Trust Centre for Cell-Matrix Research**

£3.4m
**Flu research consortia grants[4]**

£2.9m
**Joint Basic and Clinical PhD Programmes**

£2.5m
**Kadoorie Biobank Study**

£2.4m
**South-east Asia Major Overseas Programme: primaquine use in vivax malaria**

£2.3m
**Karonga Prevention Study, Malawi**

£1.8m
**Medicine, Society and History Capital Awards**

£1.1m
**Enhancement Awards in Biomedical Ethics**

[1] Plus £13.5m from Engineering and Physical Sciences Research Council.
[2] Plus £5.7m from Medical Research Council.
[3] Including £4.8m support for the Wellcome Trust Sanger Institute.
[4] Plus contributions from Biotechnology and Biological Sciences Research Council, Department for Environment, Food and Rural Affairs and Medical Research Council.

## INVESTMENTS

**The Trust's asset base was £13.0 billion at 30 September 2009, representing a return of £580 million or 5 per cent over the year.**

During a year of volatile global markets, the Trust's flexible and active management of its investment portfolio ensured that its asset base remained intact. The year was marked by significant acquisition of equities including a 3 per cent stake in Marks & Spencer (see page 40). Strong performance of these assets added more than £400m to the Trust's asset base. Performance is well ahead of world markets over three-, five- and ten-year timeframes.

Management of risk continued to be a key focus amid uncertain market conditions. Aided by a variety of defensive strategies, the Trust's exposure to risk has risen only slightly, and is significantly below that seen in global equity markets.

A key factor in the success of the portfolio is its global diversification. UK-based assets now represent just 13 per cent of the total portfolio, the largest constituent being long-term holdings of £0.9bn in residential property in London and South-east England. These prime real estate holdings have held their value well even during the UK's recent house price decline.

To avoid the need to dispose of assets at low prices during volatile periods, the Trust maintains high levels of liquidity in order to meet its annual cash expenditure of over £600m. A second AAA/Aaa bond issue in May 2009 contributed to holdings in cash and short-term bonds of £1.8bn at year-end.

Average annual returns since Wellcome plc was floated in October 1985 have been 14.5 per cent, well ahead of inflation and global equity returns.

# Funding developments 2008/09

**The Wellcome Trust reserves a significant part of its funding for major initiatives and projects of international significance. These are generally supported through Strategic Awards, which, along with some other large or unusual awards, are considered by a Strategic Awards Committee.**

Ongoing funding programmes are 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. 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 support is primarily through the Engaging Science programme, which includes Society Awards, People Awards, International Engagement Awards and Small and Large Arts Awards.

Occasional large capital awards are made to support nationally or internationally important developments.

## NEW FUNDING INITIATIVES

### ADVANCING KNOWLEDGE

- **Insect Pollinators Initiative**
- **Genome-wide association studies**

The Wellcome Trust, the Biotechnology and Biological Sciences Research Council, the Department for Environment, Food and Rural Affairs, the Natural Environment Research Council and the Scottish Government launched an Insect Pollinators Initiative to fund research into the threats to bees and other insect pollinators and possible mitigation strategies.

A further round of funding was provided for genome-wide association studies. Projects could be carried out in collaboration with the Wellcome Trust Case Control Consortium or independently (see page 6).

### USING KNOWLEDGE

- **Health Innovation Challenge Fund themed call**
- **Research and Development for Affordable Healthcare in India**

The Department of Health and the Wellcome Trust invited the first funding proposals under the Health Innovation Challenge Fund, launched to further the development of innovative healthcare products. Through the provision of 'gap-bridging' funding, this five-year, £100 million initiative will stimulate the delivery of technologies, products and interventions having clinical applicability in and beyond the NHS within three to five years. The first themed call, providing total funding of up to £20m, focused on the clinical application of genetic discoveries.

The Research and Development for Affordable Healthcare in India initiative will fund translational projects that deliver safe and effective healthcare products for India, and potentially other markets, at affordable costs. The five-year, £30m initiative will support all areas of technology development, including diagnostics, therapeutics, vaccines, medical devices and regenerative medicine. A significant proportion of the programme should be conducted in India, although international collaborations may be eligible for support. Companies, universities and not-for-profit institutions are eligible to apply.

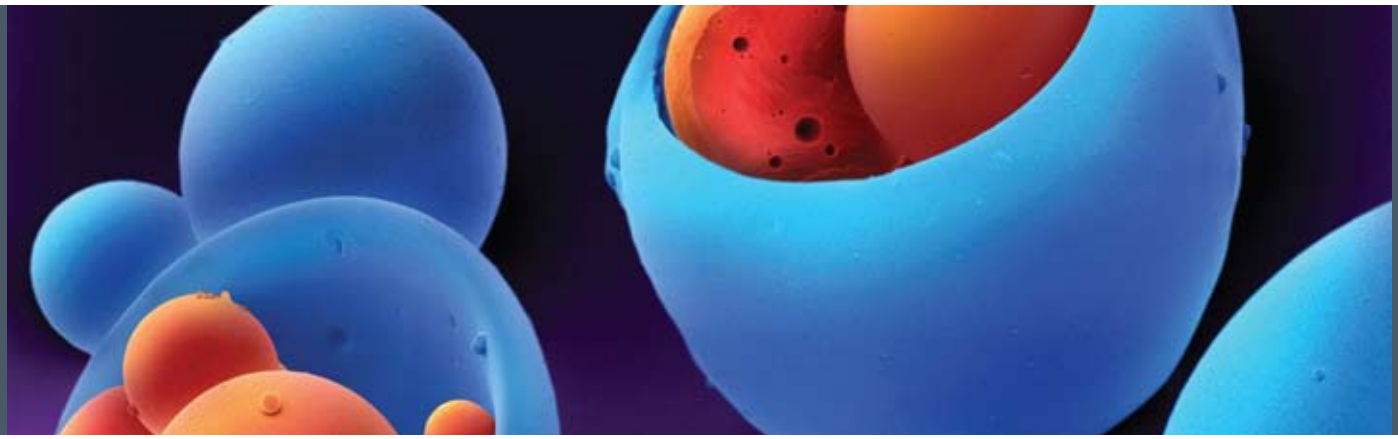
### ENGAGING SCIENCE

- **Science Media Production studentships**

The Wellcome Trust and Imperial College London are launching studentships to support biomedical students interested in a career in science broadcasting. The 18-month studentships will enable two students to undertake a postgraduate course in Science Media Production at Imperial, including a six-month placement in the broadcast industry.

### DEVELOPING PEOPLE

- **Starter Grants for Clinical Lecturers**
- **Wellcome Trust Postdoctoral Training Fellowships for MB/PhD Graduates**
- **Wellcome–Beit Prize Fellowships**
- **Wellcome Trust–MIT Postdoctoral Fellowships**
- **Wellcome Trust–DBT India Alliance fellowships**



The Trust and the Academy of Medical Sciences launched a Starter Grants for Clinical Lecturers scheme, providing up to £30 000 over two years, to support clinicians' research early in their careers.

New Postdoctoral Training Fellowships for MB/PhD Graduates provide up to four years' support, and enable fellows to undertake a period of postdoctoral research and continue their clinical training.

New Wellcome–Beit Prize Fellowships have been launched. The £25 000 awards, which replace the Beit Memorial Fellowships for Medical Research, will be made annually to each of four selected scientists awarded a Research Career Development Fellowship or Intermediate Clinical Fellowship. Each prize will be made in addition to the fellowship support and can be used flexibly in support of fellows' research.

The Wellcome Trust and the Massachusetts Institute of Technology (MIT) launched a new fellowship scheme to promote interdisciplinary science. The Wellcome Trust–MIT Postdoctoral Fellowship scheme provides four years' support for research at the interface of biology/medicine and mathematics, engineering, or computer, physical or chemical sciences. Fellows will spend two to three years at MIT and one to two years in the UK.

Three fellowship schemes have been launched by the Wellcome Trust–DBT India Alliance, an £80m partnership between the government of India and the Wellcome Trust. Funding is available for Early Career Fellowships, Intermediate Fellowships and Senior Fellowships. The first awards have been made to successful applicants in each scheme.

### FACILITATING RESEARCH

- **Health Research Capacity Strengthening initiative**

The Health Research Capacity Strengthening initiative, a partnership between the Trust and the UK Department for International Development, is supporting two bodies awarding grants in Kenya and Malawi. The Consortium for National Health Research in Kenya and the National Research Council of Malawi have received £10m each over five years to make awards according to their national research and training priorities. Schemes have been launched for Centres of Research Excellence, Research Group Leaders, Research Training Fellows and Research Placements.

## FUNDING ANALYSIS

| | |
|---|---|
| Total no. of grant applications | **3138** |
| Total no. of grants awarded | **1104** |
| Total value of applications considered | **£1.4bn** |
| Total value of grants awarded | **£531m** |
| No. of programme grants awarded | **38** |
| No. of PRFs awarded/renewed[1] | **3** |
| No. of SRFs awarded/renewed | **22** |
| No. of intermediate fellowships awarded | **8** |
| No. of training (junior) fellowships awarded | **44** |
| No. of PhD studentships awarded | **184** |

| FUNDING RATES | Number | Value |
|---|---|---|
| Project grants | 23% | 21% |
| Programme grants | 46% | 42% |
| New PRFs (full app.) | 0% | 0% |
| SRFs (full app. Basic) | 16% | 20% |
| SRFs (full app. Clinical) | 30% | 29% |
| SRFs (full app. Tropical) | 0% | 0% |
| SRFs (full app. International) | 9% | 8% |
| Intermediate fellowships | 11% | 9% |
| Training (junior) fellowships | 26% | 26% |
| History of Medicine Strategic and Enhancement Awards | 100% | 69% |
| History of Medicine ad hoc | 40% | 24% |
| History of Medicine outreach | 33% | 15% |
| Research Resources in Medical History | 48% | 20% |
| Biomedical Ethics | 39% | 29% |
| People Awards | 22% | 21% |
| Society Awards | 50% | 54% |
| Arts Large Awards | 13% | 13% |
| Arts Small Awards | 14% | 13% |
| Total no. of institutions receiving funding in 2008/09 (UK) | | **88** |
| Total no. of institutions receiving funding in 2008/09 (non-UK) | | **73** |

| OUTSTANDING LIABILITIES | |
|---|---|
| Total grants commitments[2] | **£1.41bn** |
| No. of countries receiving funding | **74** |
| Fellows currently supported | **802** |
| Researchers currently supported | **3459** |
| Total no. of institutions receiving funding (UK) | **106** |
| Total no. of institutions receiving funding (non-UK) | **125** |

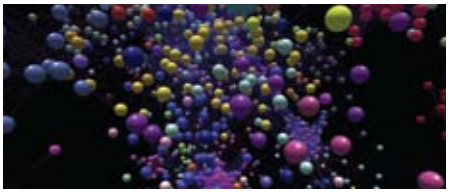
**[1] Includes PRF programme grant renewals.**

**[2] As at 30 September 2009.**

**PRF: Principal Research Fellowship**
**SRF: Senior Research Fellowship**

IMAGE
Microparticle drug delivery.

# Streams funding 2008/09



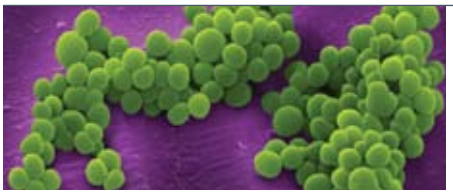
## MOLECULES, GENES AND CELLS

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.

| | |
|---|---|
| Number of grants awarded | 185 |
| Value of grants awarded | £82.5m |
| Number of programme grants awarded | 12 |
| Value of programme grants awarded | £14.8m |
| New and renewed Principal and Senior Research Fellowships | 8 |

### OTHER MAJOR AWARDS

- £5.7m Core support for Wellcome Trust Centres for Cell-Matrix Research and Stem Cell Research, and Gurdon Institute
- £5.2m Genome-wide association studies
- £2.6m Strategic Award (type 2 diabetes; Mark McCarthy)
- £2.5m Strategic Award (enzyme regulation; Ashok Venkitaraman)
- £2.5m Capital Award to UK Health Protection Agency for pilot manufacturing facility



## 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.

| | |
|---|---|
| Number of grants awarded | 173 |
| Value of grants awarded | £64.3m |
| Number of programme grants awarded | 9 |
| Value of programme grants awarded | £11.8m |
| New and renewed Principal and Senior Research Fellowships | 7 |

### OTHER MAJOR AWARDS

- £49.2m Core support for South-east Asia Major Overseas Programme
- £3.4m H1N1 influenza fast-track funding
- £2.8m UK Centres for Clinical Tropical Medicine

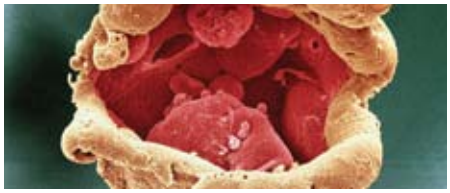
## NEUROSCIENCE AND MENTAL HEALTH

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

| | |
|---|---|
| Number of grants awarded | 121 |
| Value of grants awarded | £53.3m |
| Number of programme grants awarded | 8 |
| Value of programme grants awarded | £11.3m |
| New and renewed Principal and Senior Research Fellowships | 6 |

### OTHER MAJOR AWARDS

- £45m Sainsbury–Wellcome Centre for Neural Circuits and Behaviour at UCL
- £11.3m Strategic Awards in Neurodegenerative Diseases
- £7.7m Clinical PhD Programmes
- £5m Oxford Centre for Neural Circuits and Behaviour
- £2.9m Joint Basic and Clinical PhD Programmes



## 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.

| | |
|---|---|
| Number of grants awarded | 80 |
| Value of grants awarded | £26.9m |
| Number of programme grants awarded | 4 |
| Value of programme grants awarded | £4.7m |
| New and renewed Principal and Senior Research Fellowships | 4 |

## 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.

| | |
|---|---|
| Number of grants awarded | 45 |
| Value of grants awarded | £23.4m |
| Number of programme grants awarded | 4 |
| Value of programme grants awarded | £9.0m |
| New and renewed Principal and Senior Research Fellowships | 0 |

### OTHER MAJOR AWARDS

- £27.7m African Institutions Initiative
- £5m DfID Health Research Capacity Strengthening Initiative in Malawi, Kenya
- £1.8m UK Biobank

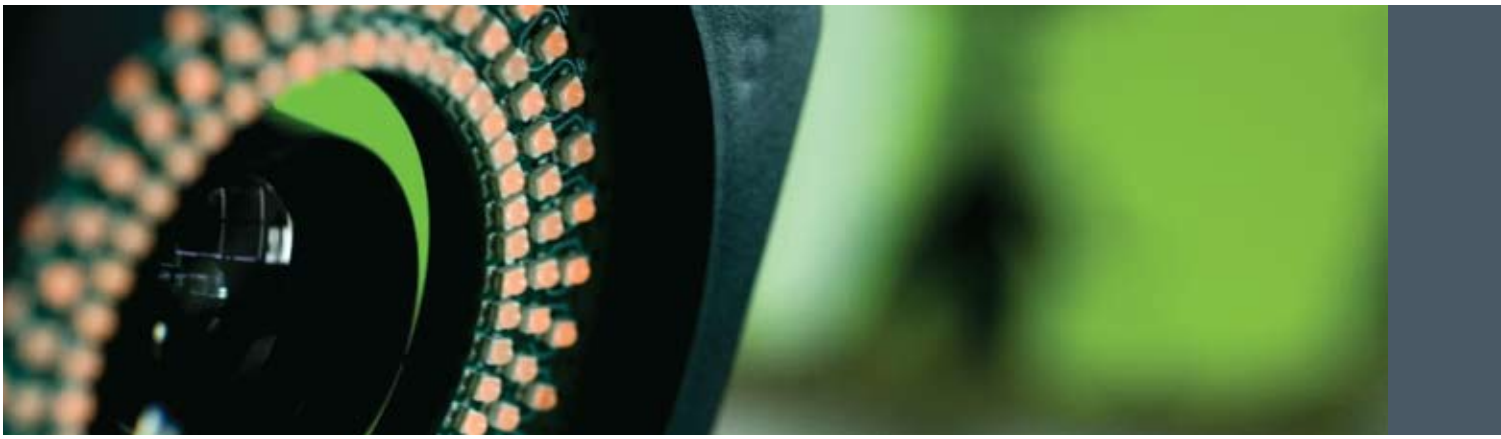
## MEDICAL HUMANITIES

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.

| | |
|---|---|
| Number of grants awarded | 151 |
| Value of grants awarded | £10.4m |
| Number of programme grants awarded | 1 |
| Value of programme grants awarded | £0.4m |

### OTHER MAJOR AWARDS

- £0.8m Strategic Award in Biomedical Ethics



# TECHNOLOGY TRANSFER

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

Unmet medical needs in low- and middle-income countries were a major focus of the year, with the launch of a vaccine development venture in partnership with Merck and an affordable healthcare initiative in India. In the UK, four medical engineering centres of excellence were funded, alongside translational projects in a range of areas including cancer, infectious disease and prosthetics.

Vaccines represent one of the most cost-effective ways to relieve the health burden imposed by infectious diseases. Yet for many diseases affecting low- and middle-income countries, no vaccines exist or they are not optimised for locally prevalent strains. To address this need, the Trust has launched a new vaccine development initiative in partnership with Merck, to be run as an independent not-for-profit enterprise in India (see page 23).

The Medical Engineering Initiative, launched in 2008 in partnership with the Engineering and Physical Sciences Research Council, made four awards totalling £40.4 million, to Imperial College London, King's College London, the University of Leeds and the University of Oxford.

The Imperial centre, led by Ross Ethier and colleagues, aims to develop better implants and surgical techniques for people with osteoarthritis. At King's College, Reza Razavi and colleagues are refining imaging technologies, to improve diagnosis and treatment of a range of cardiovascular and psychiatric conditions.

With a motto of '50 more years after 50', John Fisher and colleagues at Leeds are working on a range of regenerative and replacement technologies to mitigate the effects of ageing. Finally, Lionel Tarassenko in Oxford is leading a varied programme of work using technological solutions to provide more individualised healthcare.

Medical engineering was also a theme of several Translation Awards made during the year. Mihailo Ristic from Imperial, for example, is developing an MRI-guided endoscope, while Chris Toumazou is designing a bio-artificial pancreas for type 1 diabetes.

In the Seeding Drug Discovery initiative, several awards went to projects tackling infectious diseases. Peter Andrew of the University of Leicester is developing drugs against pneumolysin, a toxin responsible for much of the tissue damage seen in pneumococcal infections. Johan Neyts of the Rega Institute for Medical Research, Leuven, Belgium, is working on agents to combat dengue virus, while Neil Thompson and colleagues at Astex Therapeutics Ltd are using an innovative fragment-based drug discovery approach to identify inhibitors of hepatitis C virus.

Seeding Drug Discovery awards were also made in other areas of medical need. Clive Robinson of St George's, University of London, is developing a new class of drugs that target the root cause of asthma and allergic diseases. Caroline Springer of the Institute of Cancer Research is developing inhibitors of lysyl oxidase, an enzyme associated with metastatic growth of cancers. And David Madge and colleagues at Xention Ltd are developing small-molecule inhibitors of cardiac ion currents to treat atrial fibrillation.

In diagnostics, Louise Kenny of University College Cork received a Translation Award to support early research aimed as developing a biomarker-based assay for pre-eclampsia, the most common serious complication of pregnancy. At the University of Bristol, Chris Probert is refining a device for diagnosing the causes of diarrhoea to enable its routine use in clinical settings.

Among other notable awards, Lisbeth Illum and colleagues at Critical Pharmaceuticals Ltd are developing a human growth hormone nasal spray for children with growth hormone deficiency, and Julian Yates and colleagues at the University of Sheffield are designing a rapid manufacturing system for facial soft tissue prostheses.

In all, Strategic Translation Awards worth £8m were made to four projects, and Translation Awards totalling £13m were made to 16 projects. Initial applications were considered in the Affordable Healthcare Initiative, while the first call for proposals was made in the £20m Health Innovation Challenge Fund, a partnership with the UK Department of Health. The first awards under these initiatives are expected in 2010.

**IMAGE**
Optical motion tracking in Ross Ethier's lab at Imperial College London.

# 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.**

Appropriately for the 150th anniversary of Darwin's *On the Origin of Species*, evolutionary processes were a strong theme of the Sanger Institute's research in 2009. The strengths of the Institute's research were also reflected in the scientific conferences and courses organised at the Genome Campus.

This year, Sanger Institute researchers directly measured the rate of mutation – the driving force of evolution – in the human genome. Strikingly, other discoveries raised interesting evolutionary questions, such as why 4 per cent of people from the Indian subcontinent carry a mutation that appeared 30 000 years ago and significantly increases the risk of heart disease, and why more than 200 human genes can apparently be inactivated without any effect on health.

Studies of variation in the human genome – the legacy of our evolution – aim to identify loci involved in disease. As well as co-leading the 1000 Genomes Project and the project generating the first sequence of an African genome (page 6), Sanger Institute researchers played leadership roles in a new map of structural variation and a host of studies linking human genetic variants to disease (page 6). In cancer genetics, the first risk genes involved in testicular cancer were identified.

Work on *Clostridium difficile* (page 10) and *Schistosoma mansoni* (page 13) reflects two facets of the Sanger Institute's commitment to infectious disease. Interactions with pathogens – natural selection in action – were also explored in work on *Chlamydia* and *Candida*. Each shows extensive gene loss, but with very different outcomes: spread of undetectable *Chlamydia* and loss of virulence for *Candida*.

The platforms to knock out genes in the mouse genome and to characterise their effects have ramped up significantly this year. Sanger Institute researchers have produced more than 5000 mutant mouse embryonic stem cell lines, as part of major international programmes. More than 300 mutant mice are being extensively characterised. Consistent with the Sanger philosophy of sharing biological resources, these cells and mice are made freely available to the academic community. They have also been used by Institute researchers, leading to the discovery of the first microRNA mutation causing deafness in the mouse (a change also implicated in human hearing loss).

Several Sanger Institute scientists have been formally recognised this year. Karen Steel was elected a Fellow of the Royal Society, Gordon Dougan was made a Fellow of the American Academy of Microbiology, Julian Parkhill has been elected to the Fellowship of the UK Academy of Medical Sciences, and both Richard Durbin and Mike Stratton have been elected as members of the European Molecular Biology Organisation.

### Conference Centre

In 2008/09 the Conference Centre generated sales of just under £2.4 million. Approximately 80 per cent of events related to scientific research, with the remainder being run for commercial purposes.

### Advanced Courses and Scientific Conferences

The Advanced Courses and Scientific Conferences programmes have been combined into one department.

The Advanced Courses programme ran 22 courses in Hinxton, Thailand, Malawi, Uruguay and Kenya. New courses teaching practical laboratory skills were held, including 'Genetic Manipulation of ES Cells'. A new IT-based course was developed, 'Genomic Epidemiology of Malaria', which will be run in Bangkok in 2010.

Of particular note was the 'Molecular Approaches to Clinical Microbiology' course, held at the Malawi–Liverpool–Wellcome Trust Clinical Research Programme, which attracted participants from clinical diagnostics and research departments all over Africa. This course will be further developed and held in other African countries.

The Scientific Conferences programme held 26 events ranging from large-scale conferences to summer schools, workshops and invitation-only retreats. The annual 'Genomic Disorders' meeting continues to grow in popularity, while the largest event during the year was the 'Genomics of Common Diseases' conference. The '2nd Summer School of Human Genomics' was also very popular, with international tutors providing intensive tuition to promising PhD students.

Future plans are to expand the number of conferences held in Hinxton, creating an internationally renowned scientific programme fostering discussion, debate and collaboration in the latest cutting-edge areas of research, innovation and ideas.

**IMAGE**
Genome Campus by night.

# PUBLIC ENGAGEMENT

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

A more thematic approach was adopted during the year, starting with a themed Society Awards call for proposals on genetic variation and health. Darwin celebrations were a major theme of the year (see page 26), and the experience gained in this work and other large-scale ventures such as Wellcome Collection is feeding into further initiatives integrating commissioned work and response-mode funding, starting with a six-month season of activity exploring the theme of identity.

### Grants

A total of 98 grants were awarded under the £3.3 million Engaging Science initiative, and 41 grants under the broadcast and international engagement schemes.

**Society Awards:** Ten of these large awards (over £30 000) were made for a range of important activities. Support was provided to the Cheltenham Festivals (see page 29), the Naked Scientists and a partnership aiming to integrate human genomics into the school curriculum.

**People Awards:** There were 45 awards (up to £30 000) made to support a diverse range of activities, including performances, exhibitions, talks, conferences, debates and documentaries.

**Arts Awards:** 38 small grants (up to £30 000) and two large grants (over £30 000) were awarded.

**Broadcast Development Awards:** 21 awards (up to £10 000) were made to support the development of broadcast proposals with a link to biomedical science.

**International Engagement Awards**: 17 small awards (up to £30 000) were made under the new International Engagement Awards programme. In addition to this, one large award was made to the Wellcome Trust Major Overseas Programme in South Africa to support the development of its in-country programme.

**Capital Awards:** Three major capital awards were made, to the Florence Nightingale Museum, the Mary Rose Trust and the Museum of the Order of St John.

### Education

The Trust's nationally significant role in science education was reflected in the appointment of Sir Mark Walport as chair of the UK government's Science and Learning Expert Group. Derek Bell joined the Trust from the Association for Science Education to lead the Trust's education work, the centrepiece of which is an ambitious project to identify options for the future shape of UK science education.

The National Science Learning Centre had another successful year, providing 6519 training days, while the now formal network of regional Science Learning Centres contributed to almost 20 000 training days. In all, 73 per cent of UK secondary schools and 17 per cent of primary schools have had participants attending training at a centre.

Two issues of the *Big Picture* schools resource were published during the year – *Health and Climate Change* and *Music, Mind and Medicine* – while a special issue on influenza was published in September 2009.

### Supporting researchers and broadcast

Six training workshops on narrative skills were run for UK Trust-funded researchers, in addition to a refresher event for previous attendees. An international engagement workshop was held in South Africa, principally for international engagement grantholders but also to help to develop an international community of practitioners in low-income countries.

A bursary scheme was launched to enable practising biomedical scientists to undertake a postgraduate qualification in Science Media Production at Imperial College London, along with a six-month industry placement.

A number of projects supported by broadcast awards won prizes during the year, most notably *Here's Johnny* (Kat Mansoor), which won two Grierson Awards (Best Documentary on the Arts and the Bloomberg Award For Best Newcomer), and *The English Surgeon*, which won nine awards, including the Best International Feature Documentary at Hotdocs in 2008.

### Book Prize

The £25 000 Wellcome Trust Book Prize was launched in October 2008. The annual Prize will be awarded to the year's outstanding work of fiction or non-fiction on a theme linked to health, illness or medicine. Comedian and writer Jo Brand chaired the judging panel for the 2009 award.

IMAGE
Henry Marsh, who features in the award-winning documentary *The English Surgeon*.

# 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 space, a bookshop and a café.**

Wellcome Collection attracted over 335 000 visits during 2008/09, exceeding last year's figures. In October 2009, it reached a total of 750 000 visits since its opening in June 2007, and is expecting its millionth visit in the summer of 2010. This steady increase is encouraging, particularly as visitor numbers to new museums typically decline after initial interest.

## Temporary exhibitions

Wellcome Collection's four temporary exhibitions during 2008/09 attracted almost 122 000 visits. *War and Medicine* considered the constantly evolving relationship between warfare and medicine; *Madness & Modernity* looked at how madness and art interacted in Vienna at the turn of the 20th century; *Bobby Baker's Diary Drawings* charted the artist's struggle with mental illness; and *Exquisite Bodies* explored anatomical wax models from the Victorian era. The exhibitions received widespread press coverage. *Guardian* critic Stuart Jeffries, visiting *War and Medicine* in November 2008, noted: "Thanks to the Wellcome Collection, I am once more in serious danger of learning something."

## Events

June 2009 saw two lunchtime 'Packed Lunch' pilot events, where visitors bring their own lunch and listen to stimulating talks by scientists, medics, artists and others. Packed Lunches will now become a regular part of the Wellcome Collection programme, and the two pilots have been released as podcasts.

Some 1800 visitors attended a 'Quacks and Cures' evening in July 2009. Attractions included a re-creation of a Victorian medical show, diagnoses by 19th-, 20th- and 21st-century doctors, as well as Ben Goldacre, the *Guardian*'s 'Bad Science' columnist, talking about the placebo effect.

On Saturday 20 June 2009, Wellcome Collection held a Midsummer Picnic on the theme of collecting and collectors at Cumberland Market in Somers Town, in partnership with West Euston Time Bank, a local community volunteer group. Some 300 people participated in the event, part of the Trust's community engagement programme.

## Wellcome Collection Club

The Wellcome Collection Club, which offers a stylish, comfortable room with refreshment facilities for members to relax in, along with monthly Club socials and private exhibition views, now has around 500 members.

## Wellcome Library

The Library received over 38 000 visits – a 15 per cent increase on last year. The 'Insights' visits continued to flourish, with new themes 'Caricatures and Cartoons', 'Fascinating Faces', 'Medi-cinema' and 'Native Americans' joining the programme during the year. Another new theme, 'Anatomies of London', was chosen by *Time Out* as one of the ten best events taking place during the 'Story of London' festival in June 2009.

The Wellcome Library blog was launched in October 2008, and attracted 24 000 visits from some 139 countries.

The most eye-catching addition to the Library's collections was 'Acts of Mercy', a series of four large paintings by Frederick Cayley Robinson, previously hung in the Middlesex Hospital. Two of the paintings now grace the Library's entrance hall.

Over 100 hours of medical films were digitised during the year and can be viewed at **www.youtube.com/wellcomefilm**.

## Wellcome Images

The Wellcome Image Awards – which recognise the most informative, striking and technically excellent recent acquisitions by Wellcome Images – celebrated their tenth round. The winners were featured on national TV news and in many newspapers.

An exhibition of 150 photographs of China taken by Victorian photographer John Thomson, part of the Wellcome Images collections, opened in April 2009 in Beijing and will tour other venues in China.

## Conference Centre

The Conference Centre continues to thrive, bringing in a revenue of £1.45 million for the year and generating a trading surplus of £0.7m.

## Business

Blackwell bookshop was named by *Time Out as* one of its top five museum bookshops of the year. Both the bookshop and Peyton and Byrne café have continued to be popular destinations for visitors.

IMAGES
1 Wellcome Collection's Midsummer Picnic at Cumberland Market, London.
2 Anatomical wax Venus from the *Exquisite Bodies* exhibition.

# Advisory committees

The Wellcome Trust is indebted to the many researchers who gave up their time to sit on our advisory committees, and to the thousands of scientific referees, in the UK and overseas, who provide comments on grant applications. The following pages list the external members of our advisory committees during 2008/09.

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