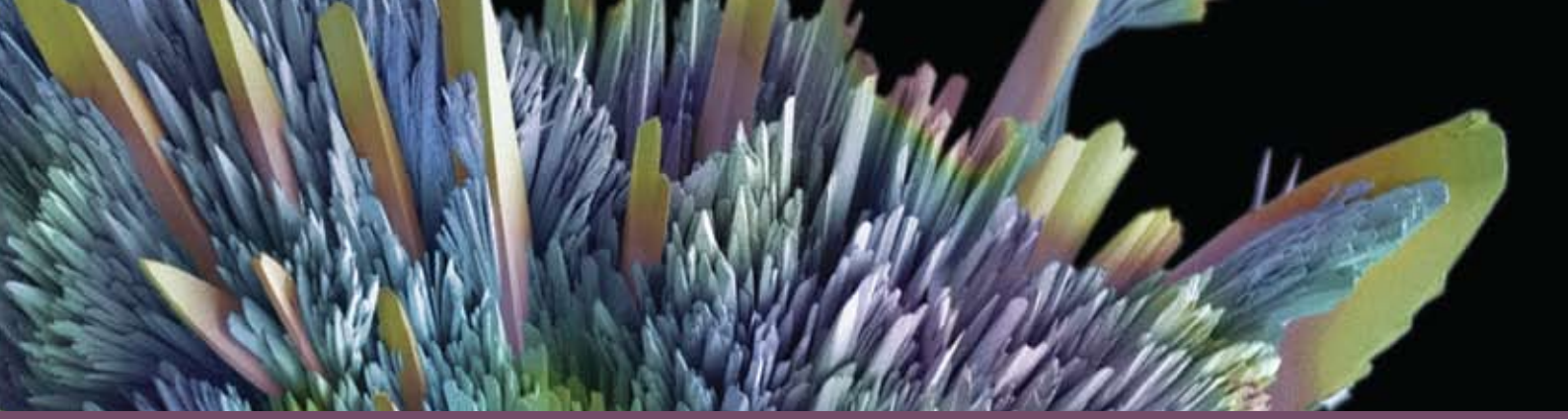

ANNUAL REVIEW

2008

www.wellcome.ac.uk

wellcome trust

THE WELLCOME TRUST

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


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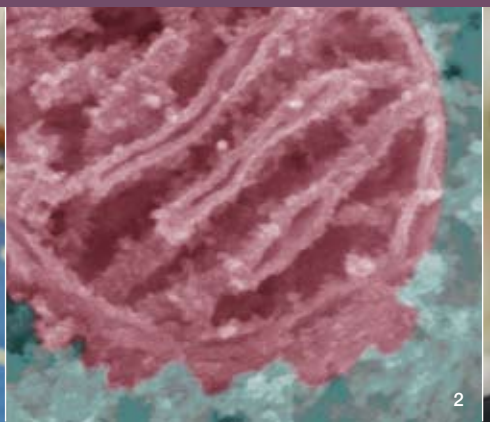
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CONTENTS

BOARD OF GOVERNORS

This *Annual Review* covers the Wellcome Trust's financial year, from 1 October 2007 to 30 September 2008.

Cover image
Salbutamol crystals.

Images
1 Practical science at the launch of Project Enthuse.
2 Electron micrograph of a mitochondrion.
3 Principal Research Fellow Professor Anke Ehlers.
4 Equipment from the lab of Dr Thomas Down.
5 Community engagement in Malawi.
6 Lung cancer cells.


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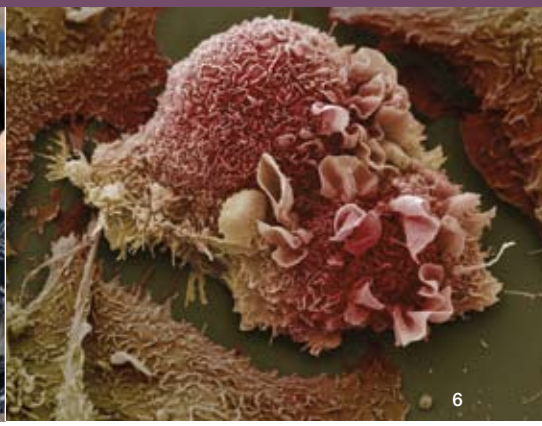
5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EXECUTIVE BOARD

Mark Walport
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Director of Technology Transfer

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Director of Resources

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Head of Strategic Planning and Policy

Clare Matterson
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Head of Molecular and Physiological Sciences

John Stewart
Head of Legal and Company Secretary

Danny Truell
Chief Investment Officer

As at January 2009

MAKING A DIFFERENCE

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

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

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

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

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

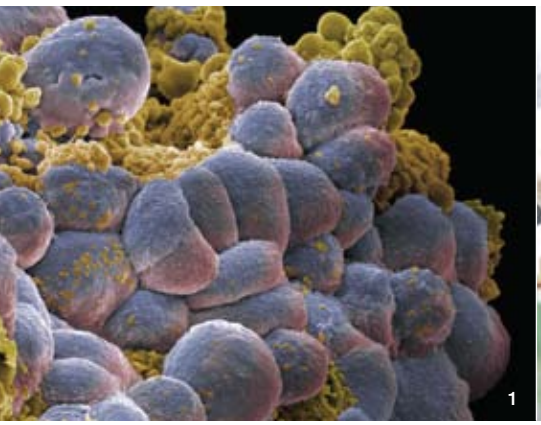
Facilitating research: To promote the best conditions for research and the use of knowledge

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

Strategic Plan updates, summarising progress in achieving specific objectives during 2007/08, can be found at **www.wellcome.ac.uk/strategicplan**.

THE POWER OF PARTNERSHIP

Much can be achieved by working together in effective collaborations.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Collaboration has always been central to research, with much to be gained from pooling expertise, experience and materials. Effective working partnerships are a key foundation for the Wellcome Trust's work and this year we can pride ourselves on a diverse range of initiatives with a wide variety of partners.

One of the most exciting developments of the year was the announcement in December 2007 of a partnership between the Trust, the Medical Research Council, Cancer Research UK and University College London to establish a world-leading medical research institute in London. The UK Centre for Medical Research and Innovation will provide superb facilities for scientists working in partnership with UK universities, industry and other scientists from around the world.

It is vital that discoveries about the causes of disease are effectively translated into new medicines; this will require increased numbers of clinical scientists who understand the complex interplay between drugs and human physiology in health and disease. Working together with academic and industrial partners, including GlaxoSmithKline and Wyeth, we have launched Interdisciplinary Training Programmes for Clinicians in Translational Medicine and Therapeutics, which provide support for clinicians from across the UK to pursue MSc, PhD and postdoctoral research in a range of specialities. We hope that the scheme will create a cadre of clinicians with the expertise to design and conduct studies on novel human therapies.

Industrial partners have also joined us in the new Project Enthuse, which offers bursaries to help to train the UK's science teachers in the latest scientific discoveries. We are delighted to fund this much-needed initiative, run by the National Science Learning Centre, alongside the UK Government and business partners including AstraZeneca, BAE Systems, BP, General Electric, GlaxoSmithKline and Rolls-Royce.

Many of our projects are undertaken with partners from outside of the UK and we continue to support scientific capacity building around the world. One highlight from this year is the Wellcome Trust–DBT India Alliance, launched together with India's Department of Biotechnology. The Alliance will run fellowships, providing support and training for Indian research scientists – from newly qualified postdocs through to senior researchers – enabling them to pursue excellent career paths and continue working in their home country.

In Africa, our Major Overseas Programmes in Kenya, Malawi and South Africa continue to go from strength to strength, and we have made a number of other major investments to enhance the continent's capacity to undertake research. The African Institutions Initiative, for example, is funding the establishment of consortia of universities and research institutions; the Initiative will include institutions both in Africa and in developed countries but, crucially, will be African-led. It will support both well-established institutions and promising ones, and aims to develop research leaders who can act as role models to enthuse young scientists.

Meanwhile, several of our Strategic Awards were given to projects providing training fellowship opportunities for the brightest young African scientists. We are working with African universities and research institutions to build sustainable research programmes initiated and led by Africans, and provide the infrastructure essential for a thriving research environment.

In Asia, we are proud to have helped to establish the first ever centre for the diagnosis and treatment of infectious diseases in Laos, together with the University of Oxford and Mahosot Hospital, Vientiane. This centre will not only improve diagnosis and treatment but also raise the capacity for medical research and training in the country.

But while efforts against infectious disease continue, chronic disease is increasingly recognised as a problem for the whole world. The UK Biobank project will follow

Images

1 Breast cancer cells.

2 Staff and pupils at Simon Langton Grammar School, Canterbury.

3 Researcher at the Trust's Major Overseas Programme in Malawi.

4 MRI scan of the head, showing the brain.

the health of a cohort of 500 000 people, aged between 40 and 69 at entry to the study. In 2008, this project recruited its 100 000th participant, and is on track to complete recruitment by the end of 2010. Cancer is one of the most important of the chronic diseases; to help to combat this, the Trust and the Wellcome Trust Sanger Institute committed support to the International Cancer Genome Consortium, a global collaboration of researchers that will fully sequence thousands of cancer genomes to identify the key mutations involved in up to 50 types of cancer. Acting in the spirit of open collaboration, the Consortium will facilitate and encourage the rapid and free exchange of information to ensure that the global research community avoids any duplication of effort while building this body of knowledge.

The Sanger Institute is playing a leading role in another international collaboration, the 1000 Genomes Project, an effort to sequence the genomes of more than 1000 people from all over the world. This will create a more detailed and medically useful catalogue of human genetic variation than is currently available, which will be of critical importance for future studies of the genetic basis of variation in health and disease.

Genetic variations are also the subject of another large international project. In a follow-up to the Wellcome Trust Case Control Consortium – one of the highlights of the 2006/07 *Annual Review* – we launched the largest ever study of the genetics of common diseases. These genome-wide association studies will involve researchers from at least 60 international institutions, analysing DNA samples from 120 000 people – a larger sample than any previously studied. This will provide greater sensitivity to uncover subtle yet medically important genetic variations involved in 25 diseases.

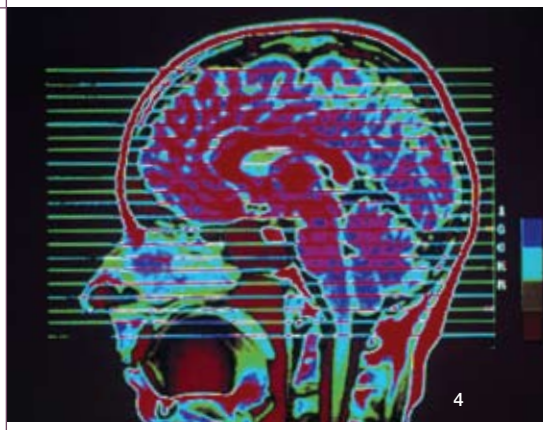
Genomics continues to capture the public's imagination. *Inside DNA: A genomic revolution* is a five-year travelling exhibition that launched in Bristol and is moving to Newcastle, Glasgow and Liverpool. The partnership between Ecsite-uk, the UK Network of Science Centres and Museums, the At-Bristol science centre and the Sanger Institute will enable the public to engage with the science and scientists involved in genomics research, and challenge their perceptions of the subject.

Such public engagement initiatives seek to form a common understanding and bring together people from different backgrounds. Another of our successful projects this year was Science in Film, which brought eight film makers and eight scientists together to plan, shoot and edit short films inspired by science. The resulting films can be seen on our website at **www.wellcome.ac.uk/broadcast**.

Meanwhile, Wellcome Collection continues to go from strength to strength, producing a programme of fascinating and often challenging exhibitions and events. The exhibition that, to my mind, brought home the changing nature of human disease was *Skeletons: London's buried bones* (see **www.wellcomecollection.org/skeletons**), produced in collaboration with the Museum of London's Centre for Human Bioarchaeology. Seeing 26 skeletons from Roman, early medieval and late medieval London gave a glimpse at the wide array of illnesses people have suffered and died from over the last 2000 years. Some of these diseases – notably smallpox – have been consigned to history, while others are now rare or readily treated with modern antibiotics. But tuberculosis was one of the great dangers of the past, just as it is today in many countries. We hope that through medical research, this and many other diseases can join smallpox as historical footnotes.

Mark Walport
Director
January 2009

HIGHLIGHTS OF THE YEAR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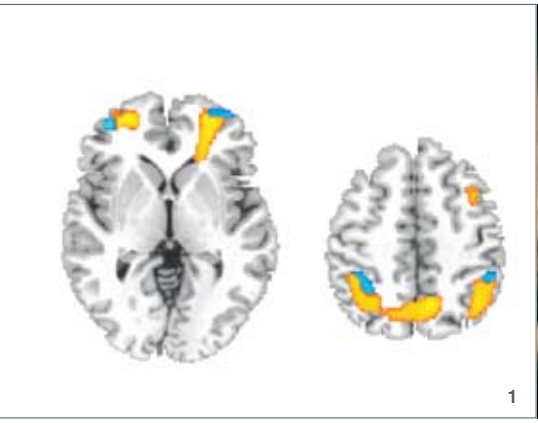
- Self-renewal is found to be the 'default setting' for embryonic stem cells.
- Genome-wide association studies shed light on conditions such as Crohn's disease and schizophrenia.
- Brain imaging reveals distinctive brain activity in people with mental disorders.
- Dementia is found to be much more common than thought in low- and middle-income countries.
- Malaria researchers help INTERPOL to track down drug counterfeiters in South-east Asia.
- A new TB vaccine generates powerful immune responses in African clinical trials.
- Survivors of the 7/7 London bombings benefit from psychological treatments for post-traumatic stress disorder.
- Wellcome Collection attracts 300 000 visits in its first year of opening.
- Project Enthuse is launched to provide UK science teachers with even more continuing professional development opportunities.
- Trust promotes informed debate during updating of the Human Fertilisation and Embryology Act.

ADVANCING KNOWLEDGE

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

BRAIN WAVES

Brain imaging is revealing distinctive brain activity in people with psychological disorders.



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Abnormal behaviour is seen in many mental conditions and presumably reflects disruptions to normal brain function. Insight into these abnormalities is being gathered by brain imaging – increasing understanding and raising hopes of better diagnosis and treatment.

The basis of conditions such as obsessive–compulsive disorder (OCD) has been difficult to trace, in part because human behaviours are tricky to categorise in a way that makes them amenable to study. A productive way forward, being taken by Sam Chamberlain and colleagues in Cambridge, is to identify patterns of brain activity that can act as robust proxies of behavioural traits.

To this end, they looked at brain activity in people with OCD and their unaffected relatives, who might be expected to show similar but less marked abnormalities. Indeed, compared with controls, activity in areas within the frontal lobes – known to be involved in decision-making – were lower in both people with OCD and their relatives.

Neural correlates of another mental disorder, depression, have been uncovered by Cynthia Fu and colleagues from the Institute of Psychiatry, London. Ultimately, this may lead to more objective diagnosis of depression.

Responses were recorded to faces manipulated digitally to show varying degrees of sadness. By analysing activity across the whole brain, Dr Fu was able to identify patterns consistently seen in people with depression but not controls.

Finally, Senior Research Fellow Paul Fletcher and colleagues in Cambridge have used brain imaging to explore susceptibility to schizophrenia, using ketamine to induce a state of psychosis in healthy volunteers.

Brain activity was monitored in volunteers before and after a dose of ketamine. Some distinctive brain activations seen before ketamine was administered were significantly more common in those reporting psychotic symptoms. Moreover, activation at certain sites seemed to predict which types of symptom an individual experienced.

It may therefore be possible to use brain imaging to identify vulnerabilities to particular psychotic symptoms, before they become clinically apparent.

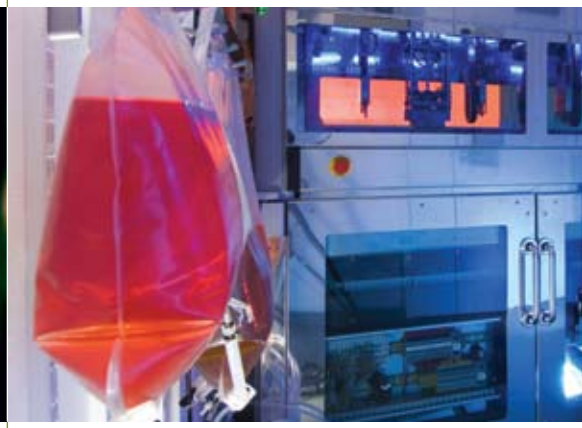
Chamberlain SR et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science 2008;321(5887):421–2.

Fu CH et al. Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. Biol Psychiatry 2008;63(7):656–62.

Honey GD et al. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J Neurosci 2008;28(25):6295–303.

SHAKING THE HAYSTACK

It's bonanza time for genome-wide analyses.



Last year saw a significant advance in the genetic analysis of common diseases, with a flood of papers from the Wellcome Trust Case Control Consortium. A further outpouring of findings has followed this year, as other groups and consortia have applied whole-genome approaches to a range of conditions.

Genome-wide association studies are taking advantage of high-throughput genotyping techniques to screen the entire genome of large numbers of individuals, to identify sites in the genome that may be contributing to a disease. This year saw a whole host of studies published dissecting conditions as varied as osteoporosis, ankylosing spondylitis, psoriasis, Crohn's disease and type 2 diabetes.

The latest Crohn's research identified 21 new risk genes, bringing the total to more than 30 – though collectively they explain only about a fifth of the total genetic risk. This suggests that many additional genes contribute to Crohn's, and also illustrates how complex the condition is. The studies also picked up unexpected connections between diseases – one gene increases susceptibility to both Crohn's and psoriasis, another contributes to both Crohn's and asthma.

As well as disease, genome-wide studies have also shed light on other biological

Images

1 Areas of abnormal brain activity (blue) in people with OCD or their relatives undertaking a cognitive task.

2 Clinical depression may be associated with specific patterns of brain activity.

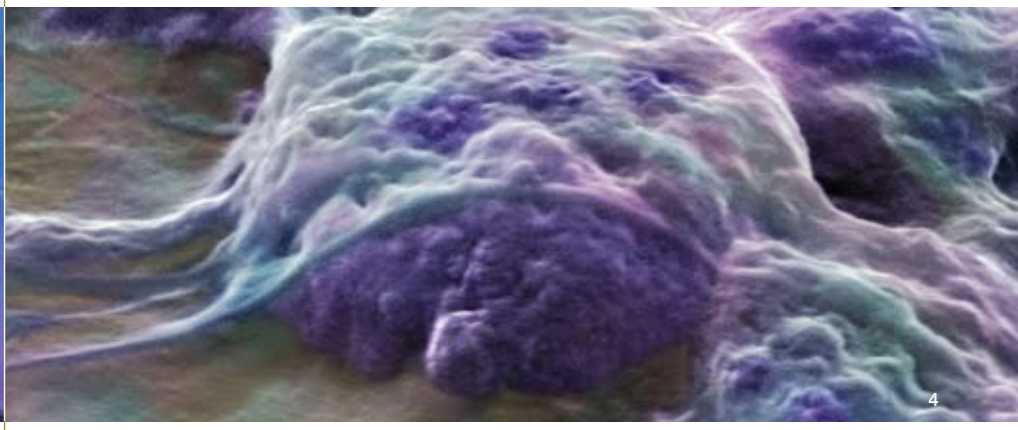
3 Large numbers of people can be genotyped in high-throughput facilities.

4 Embryonic stem cells.

THE UPS AND DOWNS OF STEM CELL FATE

Pluripotency may be the default setting for embryonic stem cells.

3



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characteristics, such as height. A further 20 genes affecting height were identified by an Anglo-Swiss consortium, bringing the total number to more than 100.

Particularly exciting has been the use of genome association studies in schizophrenia – which has been extremely hard to dissect genetically. A genome-wide analysis involving nearly 500 cases identified a number of potential genetic candidates, three of which were strongly confirmed in a follow-up in nearly 17 000 affected individuals.

Wellcome Trust-funded researchers also contributed to a major international collaboration looking for links between schizophrenia and copy number variation – deletion or duplication of small chunks of DNA. The presence of copy number variation was associated with an increased risk of schizophrenia, as was loss of specific sites on chromosomes 1 and 15.

The picture that is emerging is that variation at a great number of genes contributes to disease. Most are rare and most are non-deterministic – only a subset of people with a risk gene end up with the condition, possibly because of interactions with other risk genes or with environmental factors.

References for this article can be found at www.wellcome.ac.uk/annualreview.

Embryonic stem (ES) cells have the remarkable ability to both self-renew and create all of the other cell types of the body. A crucial question is how they manage to maintain this pluripotency. Research from Austin Smith at the Wellcome Trust Centre for Stem Cell Research in Cambridge and Ian Chambers in Edinburgh is revealing how a gene called *Nanog* may play a crucial role.

Nanog is known to be important in the ES cell state, but its exact role has been unclear. Now, Dr Chambers, Professor Smith and colleagues have found that levels of Nanog protein fluctuate in ES cells. Cells with low levels – or lacking Nanog entirely – can still self-renew but are more prone to differentiate. This suggests that Nanog is not absolutely required for self-renewal, but acts as a generic inhibitor of differentiation.

In fact, with colleagues in the USA and Canada, Professor Smith has found that self-renewal may be an innate property of ES cells. It had been thought that external signals were needed to keep ES cells self-renewing, but when all external signals were eliminated, ES cells endlessly self-renewed without differentiating.

The emerging picture suggests that Nanog contributes to ES cells' intrinsic self-renewal capacity, by blocking differentiation. But fluctuating levels mean that occasionally cells have a 'window of opportunity' in which they can escape Nanog control and begin differentiating.

An insight into the possible mechanisms of Nanog action has come from Dr Chambers's work linking pluripotency to X inactivation – the epigenetic silencing of one X chromosome in female (XX) cells. In ES cells, unlike most other cells, both X chromosomes are active. When they begin to differentiate, X inactivation is re-established.

This timing suggested that Nanog and other pluripotency factors could be involved – and sure enough, when they were absent, reversal of X inactivation was disrupted.

Significantly, as well as tying together the processes of X inactivation and pluripotency, these findings link Nanog to epigenetic regulation of gene activity. Thus Nanog may act at least in part by controlling epigenetic programming of cells.

Silva J, Smith A. Capturing pluripotency. Cell 2008;132(4):532–6.

Chambers I et al. Nanog safeguards pluripotency and mediates germline development. Nature 2007;450(7173):1230–4.

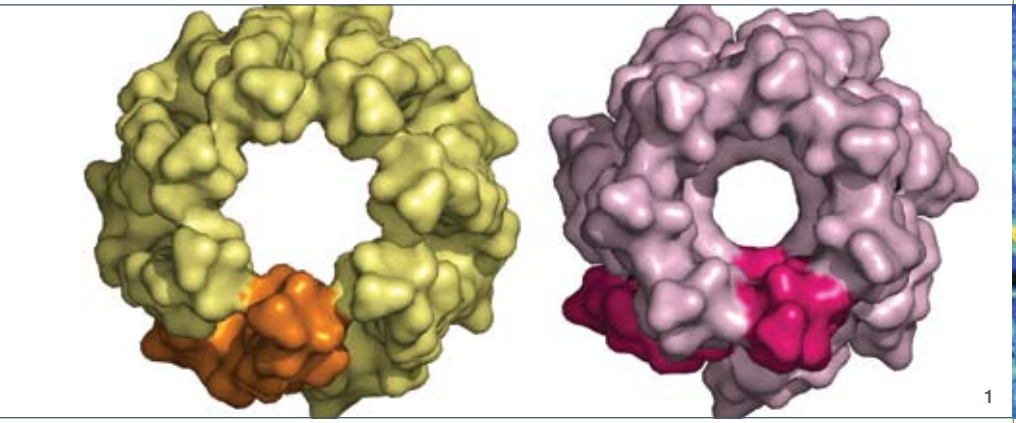
Ying Q-L et al. The ground state of embryonic stem cell self-renewal. Nature 2008;453(7194):519–23.

Navarro P et al. Molecular coupling of Xist regulation and pluripotency. Science 2008;321(5896):1693–5.

This research was supported by a range of funders, including the Wellcome Trust.

OPENING UP

Structural studies have provided new insights into bacterial ion channel opening.



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Ion channels allow cells to transport material across their membranes selectively. How opening and closing is achieved, however, is poorly understood. Two recent studies have shed light on the dynamics of two important bacterial channels – a pressure-sensitive channel and a drug efflux pump.

The MscS channel enables bacteria to survive a sudden osmotic shock. Faced with low osmotic pressure outside, a cell would explode were it not for the opening of pressure-sensitive channels, which allow ions and small solutes to escape, thus relieving pressure.

The ion channel consists of seven MscS molecules arranged in a barrel shape, but its structure is known only in a closed state. Now, James Naismith in St Andrews, Ian Booth in Aberdeen and colleagues have used a combination of structural modelling and electrophysiological analysis of engineered channels to work out the structure of the open state and the mechanism of channel opening.

According to their model, the seven MscS monomers tilt and slide to open and close the channel – much as the diaphragm mechanism controls the iris aperture in a camera.

A similar approach has been adopted by Wellcome Trust Senior Research Fellow Ben Luisi in Cambridge. His group's focus has been a drug efflux pump, which ejects drugs from the cell. The pump consists of an inner membrane channel (AcrB), an outer membrane channel (TolC) and a protein linking the two (AcrA).

TolC is present as a trimer, part of which forms a plug that meshes with the linking component, AcrB. When particular residues in this area were altered, the pump remained partially open, and its structure suggested a mechanism for docking with AcrB.

Opening and closing seems to depend on an initial interaction between TolC and AcrB, which squeezes open the TolC channel slightly and exposes grooves for binding of the third component, AcrA. Once engaged, AcrA docks into TolC, fully opening the channel.

With ion channels playing so many critical biological roles, understanding how their opening and closing is controlled is an important challenge – not least by suggesting routes toward the development of targeted therapeutics.

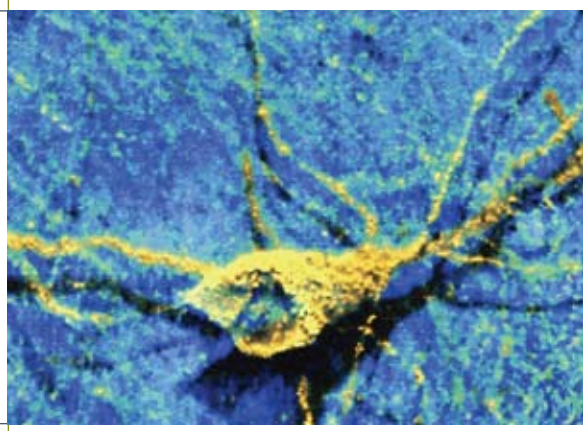
Wang W et al. The structure of an open form of an E. coli mechanosensitive channel at 3.45 Å resolution. Science 2008;321(5893):1179–83.

Bavro VN et al. Assembly and channel opening in a bacterial drug efflux machine. Mol Cell 2008;30(1): 114–21.

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

ATTENTION SEEKING

Attention is in short supply – but can be used more flexibly than once thought.



Faced with a barrage of visual information, our brains concentrate on – or attend to – limited aspects of a scene. According to conventional thinking, only four or five objects can be attended to at a time. Rather than it being a simple numerical capacity, however, Paul Bays and Masud Husain at University College London (UCL) have found that people have a limited supply of attention, which is parcelled out among different parts of a scene. Meanwhile, Alex Thiele and colleagues in Newcastle have found further evidence that the cellular mechanisms of attention depend on the neurotransmitter acetylcholine.

Attending to parts of a scene places demands on short-term or 'working' memory. To test the capacity of working memory, the UCL team briefly showed subjects a screen featuring coloured shapes before changing the position of one of the shapes. As the number of shapes increased, subjects were less able to spot changes. But no sudden change occurred at four or five objects. So working memory seems to have a small capacity, but instead of being limited to a fixed number of items, it can be spread out over a small but variable number.

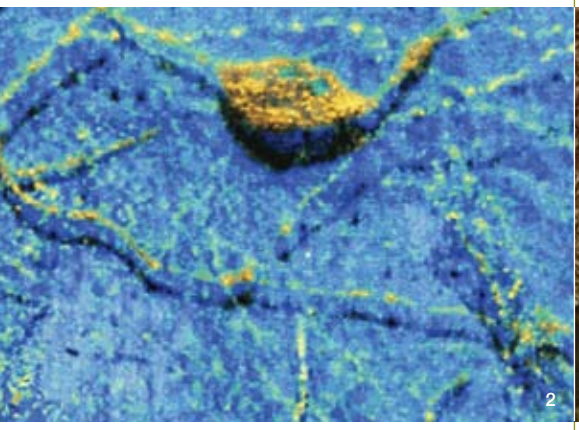
Remarkably, when subjects' eye movements were tracked while they were looking at shapes in a specified

Images

1 Open and closed states of the MscS ion channel.

2 Attention depends on the action of acetylcholine-containing neurons in the brain.

3 Lung cancer cells.



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order, subjects could recall the next shape in the sequence better than ones just focused on. This suggests that the brain has already allocated attention to the forthcoming shape before the eye has actually moved to focus on it.

In separate studies, Alex Thiele in Newcastle and colleagues have shed light on the cellular mechanisms underpinning attention. By recording brain activity in individual neurons in the visual area of the brain in a primate model, they showed that attention is linked to levels of acetylcholine.

As well as illuminating a key attribute of human perception, the two studies have significant clinical relevance. After a stroke, for example, some people struggle to take in information from one side of their visual field (hemispatial neglect). Abnormal attention is also a feature of Alzheimer's disease and attention deficit hyperactivity disorder. A greater understanding of underlying mechanisms could therefore point the way to treatments for these and other conditions.

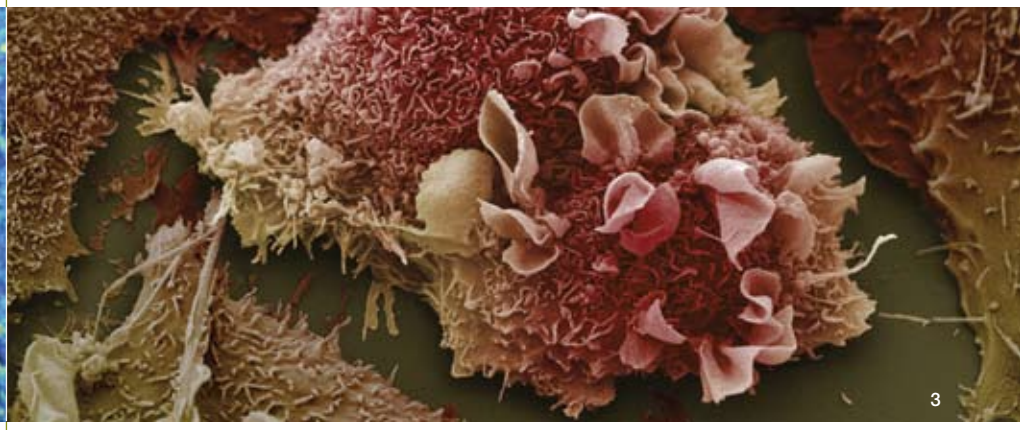
Bays PM, Husain M. Dynamic shifts of limited working memory resources in human vision. Science 2008;321(5890):851–4.

Herrero JL et al. Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. Nature 2008;454(7208):1110–4.

This research was supported by a range of funders, including the Wellcome Trust.

THE EVOLUTION OF CANCER

Thanks to new DNA-sequencing technologies, the evolution of individual cancers can now be pieced together.



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The Cancer Genome Project, based at the Wellcome Trust Sanger Institute, has shown that human cancers are, genetically speaking, highly complex: any one cancer contains many mutations, some directly involved in cancerous growth ('drivers'), others mere bystanders ('passengers'). Using 'next-generation' DNA-sequencing technologies, Mike Stratton, Andy Futreal and colleagues have now been able to look at DNA rearrangements in cancer cells in unprecedented detail and even piece together the evolutionary history of a cancer.

Next-generation sequencing technologies newly introduced at the Sanger Institute are radically increasing the generation of sequence information – the equivalent of around two human genomes is sequenced every day.

As a result, genomic rearrangements can now be analysed faster and in more detail than ever before. A study of two individuals with lung cancer, for example, identified 103 acquired structural changes in cancer cells in a background of 306 inherited genomic rearrangments, all at base-pair resolution – demonstrating the feasibility of systematic searches for cancer-causing rearrangements.

Development of a cancer is a type of evolutionary process. Each human cancer begins with a single aberrant cell. This cell divides, creating progeny that, on occasion, differ from the parent cell. These changes are passed on to future generations, where new changes get introduced. At any particular time, therefore, a cancer will consist of multiple subclones of cells, all descendants of the original founder.

Crucially, some of these subclones will have a selective advantage and will proliferate while others are outcompeted.

By fully characterising the genetic changes seen in blood cells from 22 people with a type of leukaemia, the Cancer Genome Project team was able to piece together the evolutionary history of the subclones seen in each individual. Generally, one subclone dominates in each person – but with cells turning over rapidly, even rare variants have the potential to generate leukaemia.

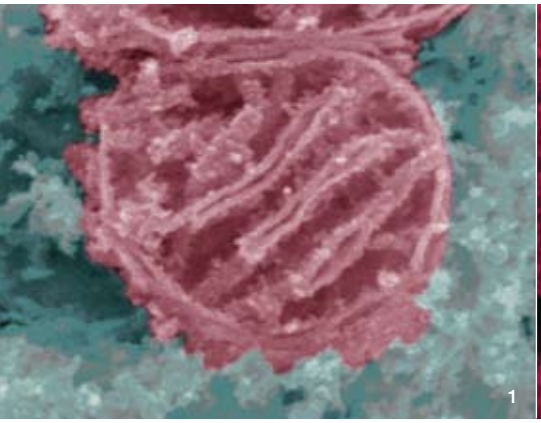
These studies highlight how ultra-high-throughput sequencing can be applied to the analysis of cancers. In the future, one application might be sequencing of cells from different parts of the body, or at different stages of disease, to link particular features of a cancer to its underlying genetic abnormalities.

Campbell PJ et al. Identification of somatically acquired rearrangements in cancer using genome-wide massively parallel paired-end sequencing. Nat Genet 2008;40(6):722–9.

Campbell PJ et al. Subclonal phylogenetic structures in cancer revealed by ultra-deep sequencing. Proc Natl Acad Sci USA 2008;105(35):13081–6.

ENERGY GAP

Mitochondrial DNA mutations are surprisingly common.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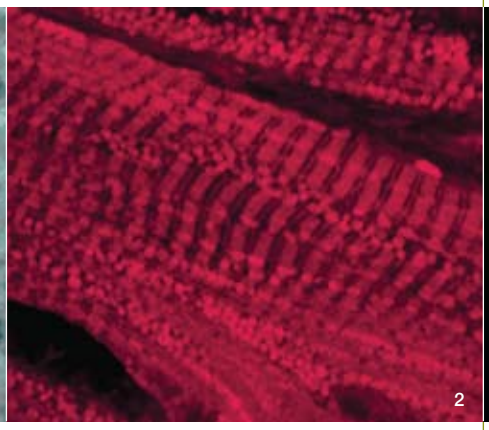
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Mitochondria generate the bulk of the cell's energy. Derived from once-free-living bacteria, they retain the remnants of an ancestral genome, now down to its last 37 genes. Mutations in these genes cause a variety of conditions, typically affecting tissues with high energy needs, yet their full impact has been obscure. Now, Patrick Chinnery, Doug Turnbull and colleagues at Newcastle University have found that they affect significantly more people than previously thought.

The Newcastle group used two approaches to assess the incidence of mitochondrial DNA mutations. One was to assess how many new mutations appeared in a series of more than 3000 live births. One in 200 was found to carry a mutation not seen in their mother.

In a complementary strand of work, the researchers calculated the prevalence of mutations in the working-age population around Newcastle, by analysing all suspected cases of mitochondrial disease seen at a neurology clinic between 1990 and 2004.

By tracing family members, they found that 9.2 in 100 000 people had clinically apparent mitochondrial DNA disease, making it one of the most common inherited neuromuscular disorders. In addition, a further 16.5 in 100 000 children and adults were at risk of mitochondrial DNA disease.

The inheritance of mitochondrial DNA disorders is complex – the severity of symptoms varies widely in the offspring of affected mothers. Offspring get all their mitochondria from their mother, but if she has a mix of normal and mutant mitochondria, what decides whether they receive normal or affected mitochondria or a mix of both?

The answer, it appears, is pure luck. When the Newcastle team looked at the precursors of egg cells created early in development, they discovered that the cells inherited a random selection of mutant and normal mitochondria. What an offspring ends up with simply depends on the fraction of mutant mitochondria in the egg that gets fertilised.

Discovery of this 'mitochondrial genetic bottleneck' may provide an opportunity to screen out eggs with many mutant mitochondria, reducing the risk that a mother has a severely affected child.

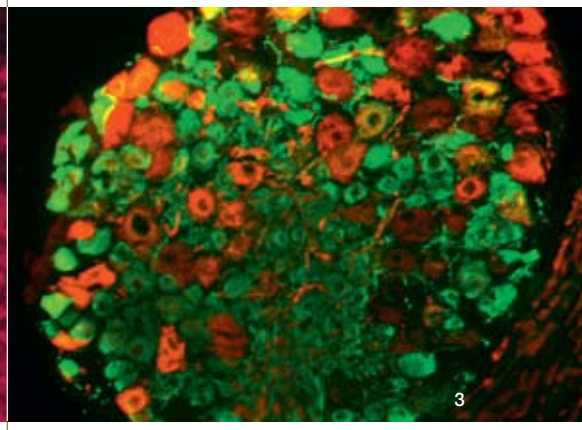
Schaefer AM et al. Prevalence of mitochondrial DNA disease in adults. Ann Neurol 2008;63(1):35–9.

Elliott HR et al. Pathogenic mitochondrial DNA mutations are common in the general population. Am J Hum Genet 2008;83(2):254–60.

Cree LM et al. A reduction of mitochondrial DNA molecules during embryogenesis explains the rapid segregation of genotypes. Nat Genet 2008;40(2): 249–54.

COLD CURES

Not all pain is the same.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Many noxious insults trigger pain, such as heat, cold and tissue damage. All these insults are detected by pain-sensing neurons, nociceptors, which rapidly send messages to the spinal cord and then on to the brain. But there are subtle differences in how they are detected, and John Wood of University College London and colleagues are unpicking the cellular mechanisms that distinguish different types of pain.

Although cold tends to inhibit our sensory and motor systems, pain perception is not affected – it serves a valuable defence function. To explore the mechanisms underlying this effect, Professor Wood's team examined the function of key nociceptor sodium channels, the activation of which triggers a nerve impulse and ultimately leads to the sensation of pain.

While the activity of most types of channel dropped when skin was cooled, that of one specific channel – known as $Na_v1.8$ – was unaffected. Moreover, chilling actually lowered the threshold at which $Na_v1.8$ channels opened. Thus $Na_v1.8$ appears to be the crucial element of cold pain sensing by nociceptors.

But are there specific nociceptors for pain or does each sensory neuron detect a range of stimuli? To address this question, Professor Wood used a toxin to eliminate

Images

1 Mitochondria, the cell's source of energy.

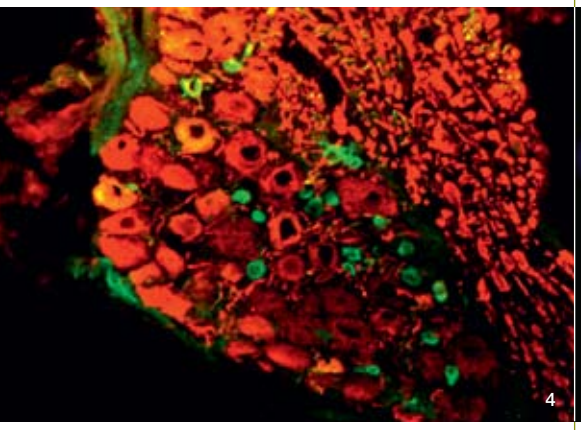
2 Cardiac muscle stained for mitochondria.

3, 4 Toxin-induced elimination of $Na_v1.8$ neurons (green).

5, 6 Chromosomes (blue) are moved in dividing cells by microtubules (red), which attach to kinetochores (green)

LONG DIVISION

The properties of a protein complex key to cell division are gradually being revealed.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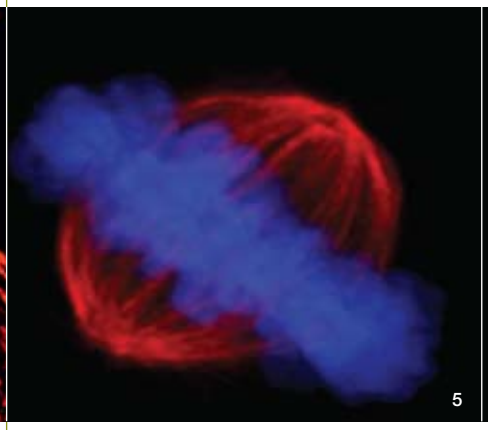
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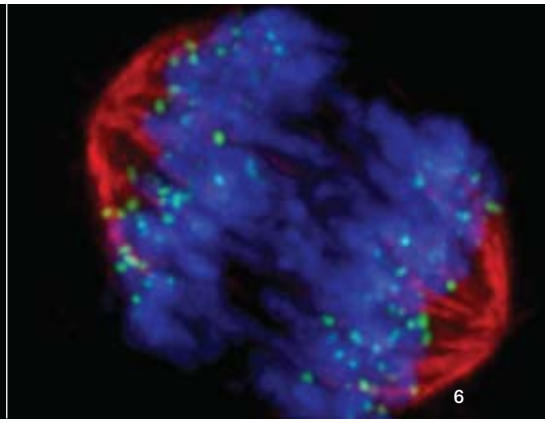
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specifically all sensory neurons carrying the $Na_v1.8$ sodium channel.

As expected, responses to cold stimuli were lost. In addition, responses to mechanical pressure and inflammation were also abolished. On the other hand, responses to heat and nerve damage were unaffected. $Na_v1.8$ neurons thus appear to be selective for mechanical, cold and inflammatory pain but not for sensing of heat or nerve damage.

A greater understanding of the molecular and cellular mechanisms of pain detection will help to identify processes that could be targeted therapeutically. There remains an urgent need for better pain-relieving medicines, particularly for chronic pain.

Zimmermann K et al. Sensory neuron sodium channel $Na_v1.8$ is essential for pain at low temperatures. Nature 2007;447(7146):855–8.

Abrahamsen B et al. The cell and molecular basis of mechanical, cold, and inflammatory pain. Science 2008;321(5889):702–5.

Professor Wood is a member of the London Pain Consortium, which received a £5 million Strategic Award in 2007/08.

Separation of chromosomes during cell division depends on the kinetochore, a protein complex assembled on a specific region of DNA, the centromere. Molecular cables, microtubules, attach themselves to the kinetochore and direct chromosomes to separate ends of the cell. Groups at Wellcome Trust Centres in Edinburgh and Dundee are picking apart the structure and function of this crucial cellular component.

Robin Allshire, a Wellcome Trust Principal Research Fellow at the Wellcome Trust Centre for Cell Biology in Edinburgh, has been studying the mechanisms that ensure that a kinetochore forms at the right location on a chromosome. Centromeres contain an unusual histone protein, CENP-A. Professor Allshire's team has now found that, in fission yeast, incorporation of CENP-A at centromeres is dependent on a distinct form of chromatin (known as heterochromatin) that flanks the region where CENP-A is normally deposited.

Also in Edinburgh, Principal Research Fellow Bill Earnshaw has found more evidence of the importance of chromatin structure. With colleagues in the USA, he has helped to create human artificial chromosomes with a synthetic centromere to which different types of protein can be targeted. Many proteins had no effect, but those that altered the compaction of DNA to make heterochromatin led to a rapid loss of kinetochore function.

One component of the kinetochore, Kar3, is a molecular motor that helps to move the kinetochore along microtubules in a sliding mechanism. Tomoyuki Tanaka and colleagues in Dundee have discovered that a second mechanism operates at the anchor points at the end of the microtubule. This pulls microtubules, like a rope being hauled in.

Folco HD et al. Heterochromatin and RNAi are required to establish CENP-A chromatin at centromeres. Science 2008;319(5859):94–7.

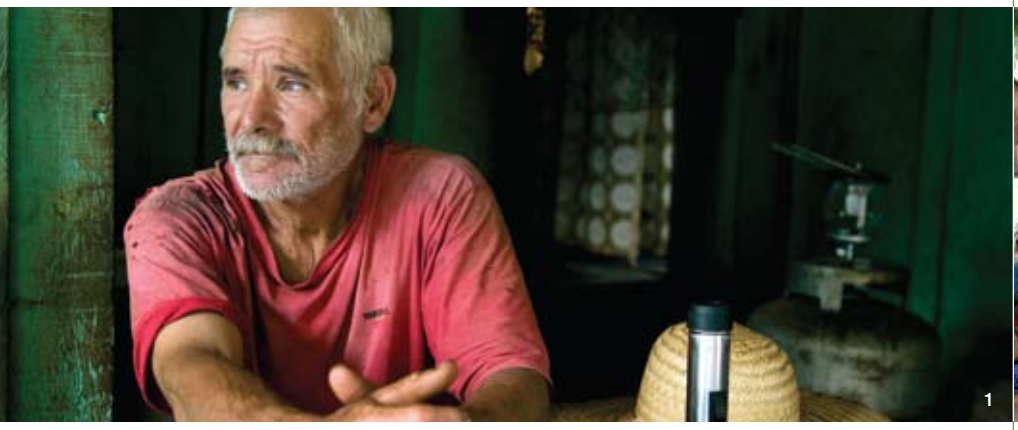
Nakano M et al. Inactivation of a human kinetochore by specific targeting of chromatin modifiers. Dev Cell 2008;14(4):507–22.

Tanaka K et al. Molecular mechanisms of microtubule-dependent kinetochore transport toward spindle poles. J Cell Biol 2007;178(2):269–81.

This research was funded by the Wellcome Trust and others. Tomoyuki Tanaka, formerly a Wellcome Trust Research Career Development Fellow, is now a Cancer Research UK Senior Research Fellow.

MISSING DEMENTIA

Is dementia less common in developing countries? New research suggests not.



The reported prevalence of dementia in developing countries is surprisingly low. Now, an international collaboration led by Martin Prince at the Institute of Psychiatry has found that its prevalence has been substantially underestimated in low- and middle-income countries, and that it is almost as common as in developed countries. Moreover, dementia is imposing a considerable psychological and economic burden on large numbers of carers.

Professor Prince leads the 10/66 Dementia Research Group, an international collaboration assessing the impact of dementia and related conditions in low- and middle-income countries. It derives its name from the fact that less than one-tenth of population-based dementia research has focused on the two-thirds or more of all people with dementia who live in developing countries.

Members of the collaboration assessed almost 15 000 people over the age of 65 in 11 countries, using culturally sensitive tools to factor out different perceptions of ageing and dementia.

The results suggested that there is a 'hidden epidemic' of dementia, its prevalence in urban settings in Latin America comparable to those seen in Europe and the USA. By 2040, the number of people with dementia in Latin America – more than nine million – is likely to match that in North America.

Moreover, as healthcare is generally limited in such regions, patient care usually falls to spouses or other family members. Dementia is the single biggest factor contributing to dependency, creating significant economic and psychological pressures: carers are often forced to cut working hours and are at high risk of depression or other forms of mental distress.

Previous underestimates may reflect the fact that people in lower-income countries are less likely to seek help for elderly relatives showing signs of dementia – it is often seen as a 'natural' part of ageing.

The findings suggest that there is a major health burden going unaddressed in many countries. More positively, intervention studies in Russia and India carried out by the 10/66 Group (funded by the World Health Organization) suggest that simple home-based interventions can provide significant benefits to both carers and patients.

Llibre Rodriguez JJ et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. Lancet 2008;372(9637): 464–74.

Llibre Rodríguez J et al. The prevalence, correlates and impact of dementia in Cuba. A 10/66 Group population-based survey. Neuroepidemiology 2008;31(4):243–51.

CARE AND THE COMMUNITY

The secret to informed consent may lie in community engagement.

Informed consent – ensuring that people who participate in research do so voluntarily and with a full awareness of what is involved – is a thorny ethical issue in developing countries. Research in Kenya and Malawi is revealing how informed consent operates in the field, and emphasising the importance of pro-active community engagement.

Although often discussed, relatively little empirical research into informed consent has been carried out – a deficit being tackled by Joseph Mfutso-Bengo in Malawi and Sassy Molyneux and colleagues in Kenya.

Dr Mfutso-Bengo and Dr Molyneux have explored the reasons why people do or do not volunteer to take part in trials. It is often assumed that participants believe they will benefit from the intervention being tested – the so-called therapeutic misconception. In fact, a broader motivation is a desire to access the better general healthcare often provided to participants. By contrast, discussions with community members suggested several reasons why people decline to take part in trials, including potential volunteers' lack of awareness of health research and investigators adopting culturally insensitive practices.

In Kenya, Dr Molyneux, Vicki Marsh, Dorcas Kamuya and others have focused on strengthening relations between the

Images

1 In Latin American countries such as Cuba, dementia may be more common than thought.

2, 3 Engaging with the local community in Malawi.

4 A young child in a hospital in Malawi.

THE HIDDEN COSTS OF ANAEMIA

Even when treated successfully, severe anaemia increases the risk of death.

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KEMRI–Wellcome Trust Research Programme at Kilifi and its 240 000-strong local community. A malaria vaccine trial (see page 38) provided an opportunity to assess internationally recommended 'best practice' for informed consent – such as community as well as individual consent and formal tests of participants' understanding. Qualitative studies confirmed the value of such practices.

However, a quiz designed to test understanding appeared to fuel misconceptions, and unearthed concerns about blood sampling and vaccine side-effects. This encouraged additional discussions between the research team and potential participants. Overall, the relationships between the two groups were identified as central to community members' perceptions of trials.

Informed consent is thus not simply a matter of providing factual information and testing participants' understanding, which may underplay the significance of pre-existing and evolving relationships and attitudes.

Pro-active community engagement is at the heart of the Wellcome Trust's new international public engagement initiative, which made 15 awards in 2007/08, including several in East Africa.

References for this article can be found at www.wellcome.ac.uk/annualreview.

Severe anaemia is a major problem in Africa. It is responsible for 12–29 per cent of childhood admissions to hospital, and between 4 and 10 per cent of these children are likely to die in hospital. And as Kamija Phiri, Job Calis, Michaël Boele van Hensbroek and Malcolm Molyneux in the Malawi–Liverpool–Wellcome Trust Programme for Research in Tropical Medicine in Blantyre, Malawi, have discovered, an alarming number of those that survive die after discharge from hospital.

Nearly 20 years ago, a group in Kenya reported that children who had been treated for anaemia in hospital continued to die in unexpectedly high numbers after being discharged. As this finding had never been followed up, Dr Boele van Hensbroek and Professor Molyneux set out to see if it was also true of Malawian children.

They compared three groups – children admitted to hospital with anaemia, children admitted for other reasons and a community sample – following them for 18 months after enrolment.

They found the same disturbing pattern – children who had had severe anaemia were far more likely to die (all-cause mortality of 12.6 per cent, compared with 2.9 per cent of the hospital controls and 1.4 per cent of the community controls).

The biggest single factor associated with death after discharge was HIV status.

As anaemia is so common, these figures point to an alarmingly large number of deaths among young African children who have left hospital.

What might be causing anaemia in the first place? The investigators found that admission to hospital with severe anaemia was strongly associated with bacterial infections, malaria, hookworm infections, HIV and vitamin deficiencies, but not iron or folate deficiencies.

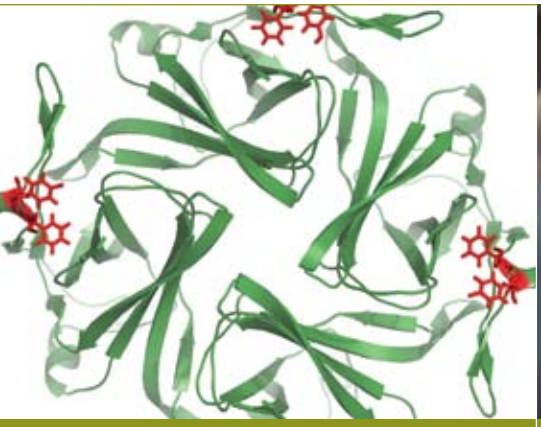
Severe anaemia in children in sub-Saharan Africa has generally been thought to be mainly a result of malaria, but these findings suggest that other infections or dietary deficiencies may also be of importance. Understanding the causes of severe anaemia is an important step towards designing effective treatment and preventative strategies for it, to ensure that the health of vulnerable young children is protected both in hospital and back in the community.

Phiri KS et al. Long term outcome of severe anaemia in Malawian children. PLoS ONE 2008;3(8):e2903.

Calis JC et al. Severe anemia in Malawian children. N Engl J Med 2008;358(9):888–99.

NEW FUNDING

CHANGING CHANNELS



A £6.5 million Strategic Award to the OXION network will support interdisciplinary research on ion channels and their role in disease.

Ion channels (above), pores that control the flow of ions through cell membranes, play important roles in many physiological processes. They have also been implicated in numerous medical conditions – there are more than 60 ion channels in which mutations lead to human diseases. Ion channels are also the targets of many drugs.

OXION, a research and training network encompassing 25 groups mainly but not exclusively based in Oxford, has developed an interdisciplinary approach to ion channels. Led by Professor Frances Ashcroft and Professor Nick Rawlins, its work ranges from molecular and cellular approaches to *in vivo* physiology and behaviour studies, and aims to generate a better understanding of ion channel function in health and disease.

The £6.5m award will provide funds for core infrastructure and support additional collaborations among members of the network. It also includes a training element, enabling researchers to develop a range of multidisciplinary skills.

Finally, it will also help to strengthen links between basic and clinical research, and promote the translation of knowledge into new diagnostics and therapies.

THE NEXT 999

The 1000 Genomes Project will shed light on rare human genetic variation.

While initiatives such as the Wellcome Trust Case Control Consortium have done much to identify common genetic variations increasing disease risks, it is becoming clear that rare variants are also important: although not widely distributed, collectively they account for a significant fraction of disease risk.

To understand rare variation better, detailed genome comparisons are needed over a much larger number of individuals. This is the goal of the 1000 Genomes Project, an international collaboration being led by Richard Durbin at the Wellcome Trust Sanger Institute.

With partners in the USA, China and Germany, the US$50 million (£34m) 1000 Genomes Project will analyse the genomes of at least 1000 individuals from different populations around the world, generating a staggering 6 trillion base pairs of sequence information. It will examine variation affecting single nucleotides as well as larger changes such as deletions or rearrangements.

Currently, the capacity to generate human genome sequence information exceeds the ability to understand what the data actually mean. By clarifying the extent and nature of rare variation, the 1000 Genomes Project will add significant additional meaning to the deluge of sequence data.

A FLOURISHING FIELD

Two new awards will help to establish centres of excellence in medical humanities.

Health is experienced on a profoundly personal level. Individual perceptions of health are often intimately entwined with social and cultural factors, as well as personal experience.

In recognition of the importance of this area, the Wellcome Trust has made two major awards, through its medical humanities programme, to establish centres of excellence at King's College London and the University of Durham.

At King's, which will receive £2 million, Brian Hurwitz and colleagues will study 'The Boundaries of Illness' – personal and cultural representations of health and illness and the boundaries between them.

Martyn Evans and colleagues at the University of Durham, awarded £1.8m, will examine 'Medicine and Human Flourishing' – exploring the human side of medicine, in particular the relationship of health and medicine to wider notions of wellbeing.

Medical humanities research provides an opportunity to reflect upon people's experience medical practice, illness and health – insights that may help to shape the future delivery of medical care.

INDIAN INITIATIVES

Strategic Awards totalling £15 million have been made to support health research in India.

A £5m partnership with the Public Health Foundation of India, supported by a grant to Srinath Reddy, will help to establish new Indian Institutes of Public Health and enhance the capacity of the public health system in India.

In common with other emerging economies, India is facing an increasing burden from chronic diseases. With £4.5m Wellcome Trust funding to Shah Ebrahim of the London School of Hygiene and Tropical Medicine, a South Asia Centre is being set up in India to expand research into the prevention and control of chronic diseases such as diabetes and mental illness.

Maternal and child mortality and morbidity in high-mortality populations in South Asia and sub-Saharan Africa are the focus of a £5.5m award to Anthony Costello of University College London, which will establish a network of researchers and field sites in Bangladesh, India, Nepal and Malawi.

The Trust has also launched a new partnership with the Government of India's Department of Biotechnology to fund biomedical research in India. Both partners have committed £40m to the venture.

A SELECTION OF NOTABLE GRANTS AWARDED IN 2007/08.

STRATEGIC AWARDS

PAIN
Professor Stephen McMahon (King's College London) Core support for the London Pain Consortium.

CENTRE FUNDING

PARASITOLOGY
Professor David Barry (University of Glasgow) Renewal of core support for the Wellcome Trust Centre for Molecular Parasitology.

PROGRAMME GRANTS

NERVE GROWTH
Professor Christine Holt (University of Cambridge) Protein dynamics in the growth cone and long-distance navigation of nerve fibres.

DEVELOPMENTAL BIOLOGY
Professor Elizabeth Robertson (University of Oxford) Control of transcriptional networks by growth factor signalling pathways in the mammalian embryo (Principal Research Fellow programme grant renewal).

MALARIA
Dr Peter Bull (University of Oxford) Malaria variant surface antigens and development of immunity.

HIV/AIDS
Dr Simon Gregson (Imperial College School of Medicine) Evaluating the impact of HIV prevention and treatment programmes in Zimbabwe.

CIRCULATION
Professor David Beech (University of Leeds) TRP ion channel function in vascular smooth muscle cells.

VACCINATION
Professor Vincenzo Cerundolo (University of Oxford) and **Professor Gurdyal Besra** (University of Birmingham) Synthetic small-chemical agonists of natural killer T cells as potential vaccine adjuvants.

SEXUAL BEHAVIOUR
Professor Anne Johnson (University College London) Support for the third British National Survey of Sexual Attitudes and Lifestyles, planned for 2010.

POPULATION STUDIES
Professor Stephen Tollman (University of the Witwatersrand, South Africa) Core support for the Agincourt health and socio-demographic surveillance system in rural South Africa.

CELL BIOLOGY
Professor Mike Tyers (University of Edinburgh) Cellular networks that control cell size in budding yeast.

PROJECT GRANTS

DERMATOLOGY
Professor Jonathan Rees (University of Edinburgh) Development of a digital tool to aid diagnosis of skin lesions.

MENTAL HEALTH
Professor Glyn Lewis (University of Bristol) Exploring the origins of depression at age 17 in the Avon Longitudinal Study of Parents and Children cohort.

INFLUENZA
Professor Ten Feizi (Imperial College London), **Dr Alan Hay** (National Institute for Medical Research) and **Professor Menno de Jong** (Vietnam Major Overseas Programme) Development of a platform for monitoring changes in the receptor-binding characteristics of H5N1 flu virus isolated from human infections.

OPHTHALMOLOGY
Dr Jugnoo Rahi (University College London) A genome-wide association study of refractive error (myopia and hypermetropia).

PSYCHIATRY
Professor Ian Goodyer (University of Cambridge) Brain imaging of adolescents with disruptive behaviour disorders.

DIABETES
Dr Timothy Frayling (University of Exeter) Variation in type 2 diabetes susceptibility genes expressed in pancreatic beta cells.

HISTORY OF MEDICINE ENHANCEMENT AWARD

SOCIAL MEDICINE
Professor John Stewart (Glasgow Caledonian and Strathclyde Universities) The relationship between health and the provision of healthcare in society.

STRATEGIC AWARD IN BIOMEDICAL ETHICS

NEUROETHICS
Professor Julian Savulescu (University of Oxford) Core support for an interdisciplinary neuroethics research centre.

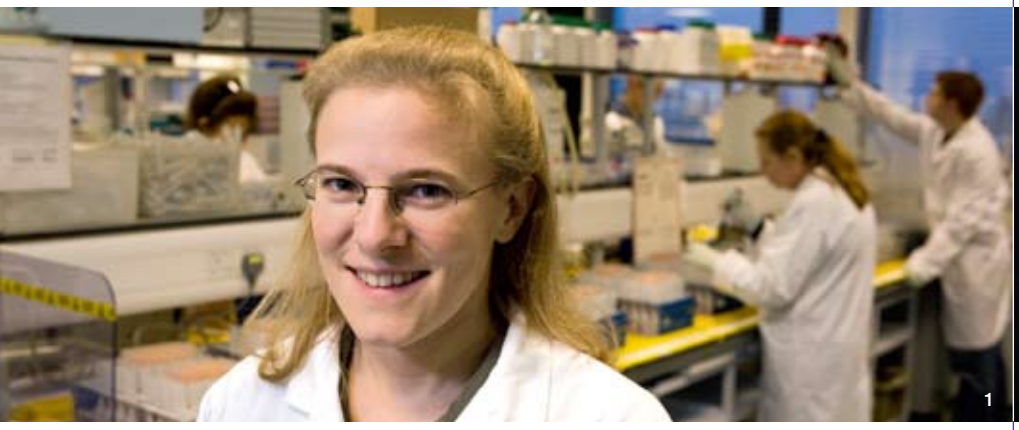
Details of all grants made can be found in *Grants Awarded 2007/08*, available on the Wellcome Trust website.

USING KNOWLEDGE

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

BETTER BY DESIGN

A better understanding of drug–receptor interactions may lead to improved beta-blockers.



Beta-blockers, drugs used to treat various heart conditions, act on β-adrenoceptors – cellular receptors for adrenaline and noradrenaline. These receptors come in several forms with different biological roles. Thanks to a growing understanding of the key factors underpinning ligand binding specificity, Jillian Baker, a Wellcome Trust Clinician Scientist Fellow in Nottingham, is developing more precisely targeted beta-blockers.

Although in use for decades, beta-blockers have a range of side-effects. In particular, they tend to exacerbate the symptoms of asthma or other respiratory conditions – so some 300 000 people are denied their benefits. In part this is because the drugs that act on β1-adrenoceptors, found in heart tissue, also interact with β2-adrenoceptors, which predominate in the respiratory system.

The nature of the interaction between drug and receptor is incompletely understood, limiting the scope to devise strategies to improve drug selection. For example, the amino acid residues in the ligand-binding region of β1 and β2 receptors are very similar, even though several compounds differ markedly in how well they bind to each protein.

Structural and mutagenesis studies of β-adrenoceptors might resolve these issues. The structure of a β2-adrenoceptor was worked out in 2007 and that of a turkey β1-adrenoceptor was mapped out in 2008, by a team at the Laboratory of Molecular Biology in Cambridge.

Structural comparisons are beginning to reveal the basis for specificity in ligand binding. The situation may be even more complicated, however, as the β1-adrenoceptor appears to have two distinct but overlapping ligand-binding sites.

Dr Baker's team has identified a compound selective for the β1-adrenoceptor. With a £2.9 million Seeding Drug Discovery award from Technology Transfer, the Nottingham team aims to improve selectivity further, to develop compounds suitable even for those with respiratory complaints.

Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. Br J Pharmacol 2005;144(3):317–22.

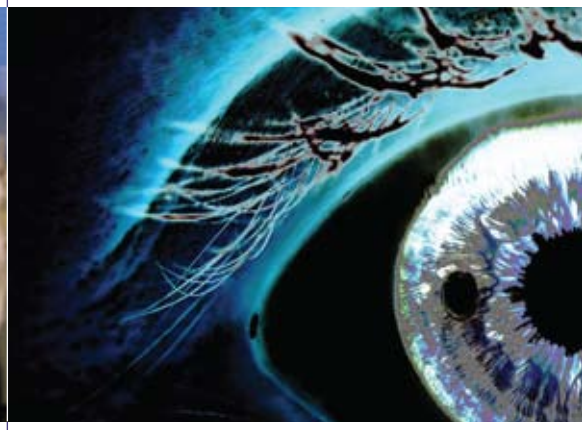
Baker JG et al. Role of key transmembrane residues in agonist and antagonist actions at the two conformations of the human beta1-adrenoceptor. Mol Pharmacol 2008;74(5):1246–60.

Warne T et al. Structure of a beta1-adrenergic G-protein-coupled receptor. Nature 2008;454(7203):486–91.

The β1-adrenoceptor structure research was supported principally by a joint grant from Pfizer and Medical Research Council Technology; ligand-binding studies were supported by the Biotechnology and Biological Sciences Research Council.

FUTURE SIGHT

Gene therapy may provide a new option for young people with a rare form of blindness.



Although rare, blindness due to Leber's congenital amaurosis (LCA) strikes early and no effective treatment is available. Pioneering gene therapy at Moorfields Eye Hospital – involving James Bainbridge, an eye surgeon and Advanced Training Fellow at the Institute of Ophthalmology, and Adrian Thrasher, a Wellcome Trust Senior Clinical Fellow at the Institute of Child Health – has shown that the technique is safe and in at least one case restored some level of vision.

First described around 150 years ago by Theodor Leber, LCA appears at birth or in the first few months of life and causes progressive deterioration of the retina and loss of vision. In the 1990s several genes were identified that caused the condition, including *RPE65*.

Significantly, the structure of the retina seems relatively unaffected in young people with *RPE65* mutations, which raised hope that gene therapy could restore some level of vision. Support for this idea came from studies in mice and on Briard dogs, which also suffer from LCA.

Launched in February 2007, a trial led by Robin Ali involved three young adults with LCA. Intact copies of the *RPE65* gene were inserted into the cells of the retina, using a virus vector. None of the three suffered any adverse effects. The

Images

1 Jillian Baker, a Clinician Scientist Fellow at the University of Nottingham.

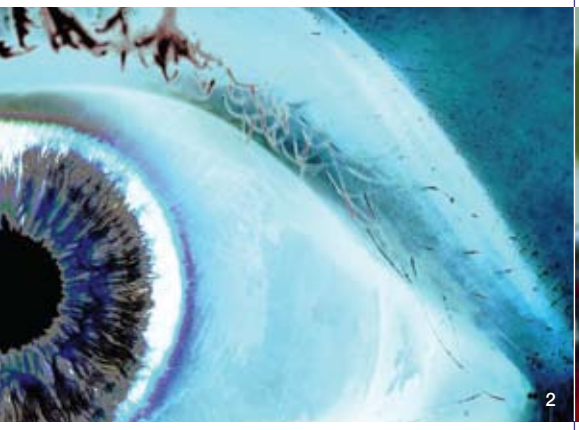
2 Gene therapy may be an option for people with some inherited eye conditions.

3 A young child with Williams syndrome.

4 Nigel Carter of the Wellcome Trust Sanger Institute.

DECIPHERING GENETIC DISEASE

The DECIPHER database is benefiting patients, clinicians and researchers.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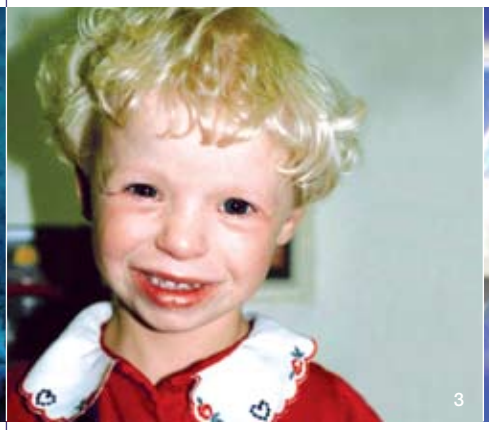
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vision of two remained stable while that of the third improved significantly – possibly because the disease was at an earlier stage of progression.

Though preliminary, these findings – along with those from a similar trial carried out in the USA – justify trials in children with less advanced degeneration and greater potential for benefit.

Bainbridge JW et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med 2008;358(21):2231–9.

The gene therapy trial was funded by the Department of Health, the National Institute of Health Research Biomedical Research Centre for Ophthalmology and the British Retinitis Pigmentosa Society.

Chromosomal rearrangements are a common cause of developmental conditions in young infants. The DECIPHER database, set up by Nigel Carter at the Wellcome Trust Sanger Institute and Helen Firth in Cambridge, enables clinicians and researchers worldwide to pool knowledge about the causes and consequences of these conditions.

Dr Carter has pioneered the development of tools that can search the entire human genome for copy number variation – regions that have been duplicated or lost. These alterations are a common cause of developmental conditions. Traditional methods of diagnosis rely on microscopic analysis of chromosomes, but cannot spot subtle changes.

Dr Carter teamed up with Dr Firth, a clinical geneticist at Addenbrooke's Hospital in Cambridge, to develop the DECIPHER database so new findings emerging from the use of genomic tools could be shared globally. As conditions may be extremely rare, the global reach can be particularly valuable. For example, the database enabled researchers to identify a syndrome caused by a small deletion on chromosome 17. A similar cluster of cases – two from Vancouver, Canada, and one from Cambridge – revealed a new syndrome linked to loss of part of chromosome 14.

Connecting cases this way can reassure clinicians that the genetic change detected is directly linked to the condition – everyone has some shuffled DNA, most of it harmless. Information can also be shared on the progression of disease. Researchers can use the information to investigate genes in the affected regions and how their loss or duplication might cause the condition.

Parents also benefit from a diagnosis. As well as being able to guide clinical care, a diagnosis can be comforting – parents at last have an explanation for their child's condition and can be reassured that they were not in any way to blame. It may also reveal whether they are at risk of having another affected child.

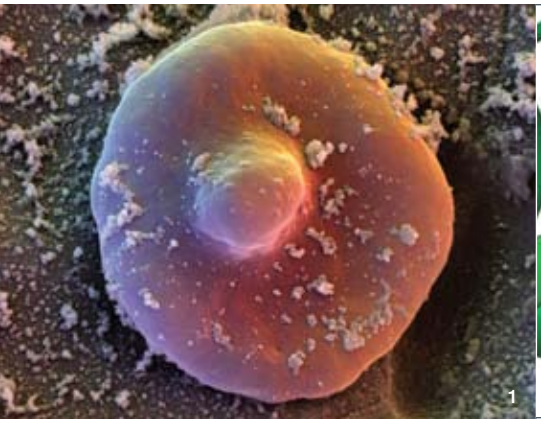
Since it was set up in 2004, more than 100 centres have registered with DECIPHER. More generally, genomic analysis has been taken up by many medical genetic centres as an adjunct to conventional methods. And at least one centre has already abandoned the microscope in favour of DNA-based tools.

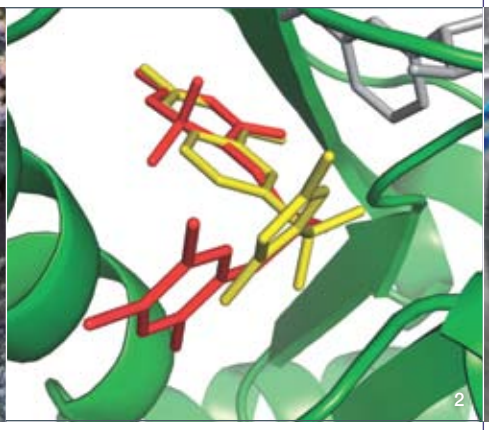
Zahir F et al. Novel deletions of 14q11.2 associated with developmental delay, cognitive impairment and similar minor anomalies in three children. J Med Genet 2007;44;556–61.

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

BOOSTING THE PIPELINE

High-throughput screens are identifying new compounds with antimalarial activity.





As part of an international programme of work on *Plasmodium falciparum* and *P. vivax* malaria parasites, Elizabeth Winzeler and colleagues at the Genomics Institute of the Novartis Research Foundation in San Diego have been using high-throughput screening techniques to identify compounds that could form the basis of a new generation of antimalarial drugs.

Conventional screening approaches identify compounds that interfere with target proteins. Often, though, these compounds have little impact on living systems – possibly because they cannot gain access to their targets in the cell. Cell-based assays overcome this problem but replace it with another: it is hard to tell what the compound is targeting and hence the mechanism of action.

The San Diego team has used computational methods to tackle this problem. A high-throughput cell-based screen of 1.7 million compounds identified 6000 able to inhibit growth of *P. falciparum* in red blood cells. Reassuringly, the 6000 included most known antimalarials.

To work out what these compounds might be doing, the team turned to 'activity profiling' – assessing their effects on a barrage of cell-based assays. The effects of each compound were then compared with those seen when chemicals with known targets were used. This matching – or 'guilt by association' – gives clues to the possible mechanisms of action of test compounds.

As the *P. falciparum* genome has been sequenced, high-throughput approaches can be used to identify possible drug targets. The function of many *P. falciparum* genes is not known, which hampers their use as possible targets. To work round this problem, the San Diego team measured gene activity at various developmental stages and in two malaria parasite species, to identify distinctive patterns of activity. The role of nearly 1000 genes of unknown function could then be predicted on the basis of shared activity patterns.

Although at an early stage, this work is identifying possible lead compounds for antimalarial drug development. The most promising candidates will be passed onto the Medicines for Malaria Venture public–private partnership for further development.

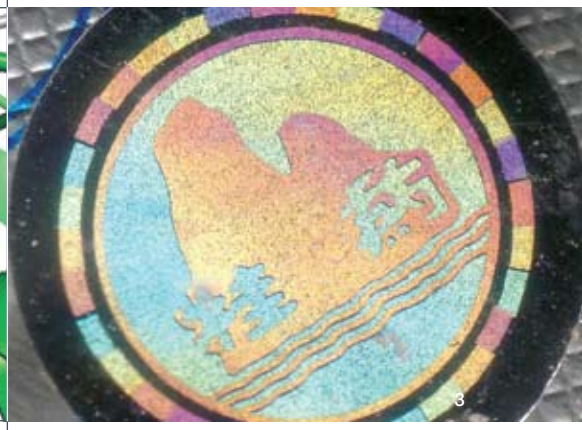
Plouffe D et al. In silico activity profiling reveals the mechanism of action of antimalarials discovered in a high-throughput screen. Proc Natl Acad Sci USA 2008;105(26):9059–64.

Zhou Y et al. Evidence-based annotation of the malaria parasite's genome using comparative expression profiling. PLoS ONE 2008;3(2):e1570.

This work was supported through a Strategic Award to the Novartis Institute of Tropical Diseases, with additional funding from the Medicines for Malaria Venture and the Singapore Economic Development Board.

BY JUPITER

Malaria researchers have helped to track down drug counterfeiters.



The trade in fake antimalarial drugs harms many patients and increases the risk that drug resistance will develop. Working with INTERPOL, the WHO and a team of forensic scientists in 'Operation Jupiter', Paul Newton from the Wellcome Trust's South-east Asia Programme has helped to locate and shut down a distribution network of fake antimalarials in China.

Artesunate, used in many artemisinin-based combination therapies, is a vital weapon in the battle against malaria. But in countries with a large burden of malaria, such as Myanmar, Laos, Cambodia, Vietnam and Thailand (on the Thai–Myanmar border), as many as half of all artesunate tablets are fake.

Dr Newton has done much to publicise the scale and impact of the trade in counterfeit drugs. Recently, he teamed up with investigators from INTERPOL, representatives of the WHO and Chinese law enforcement agencies to analyse and trace the origins of fake artesunate.

In a unique 'forensic pharmacological' collaboration, six laboratories undertook a barrage of tests to analyse the composition of the fake drugs – and identify their possible origins – by assessing their chemical composition, gases around the tablets in blister packs and even the pollen embedded in the tablets during manufacture.

Images

1 Malaria-infected red blood cell.

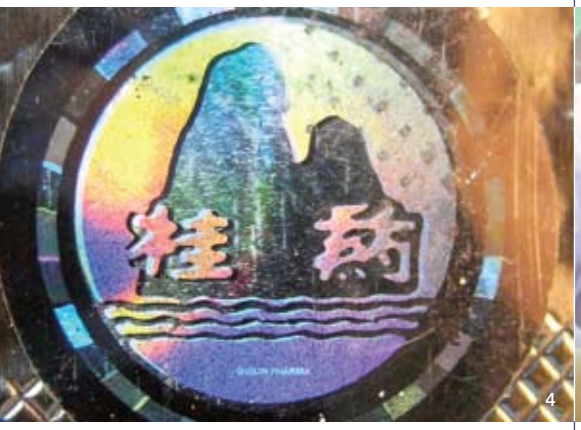
2 Small chemical inhibitors bound to a parasite target enzyme.

3, 4 Holograms on the packaging of fake antimalarials.

5, 6 Helen McShane at the University of Oxford.

A BOOST FOR BCG

A vaccine designed to boost BCG's anti-TB immunity has generated powerful immune responses in clinical trials.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Many counterfeits were hard to differentiate from the genuine product, while others were poor copies (one managed to misspell 'tablet' on its packaging). Most of the fakes contained no artesunate, and some contained potentially toxic ingredients. Even more worryingly, some included sub-therapeutic amounts of artesunate or artemisinin – which, if consumed, could promote the spread of drug-resistant parasites.

The presence of a particular type of calcite and pollen flora in the tablets suggested that at least some of the counterfeits were made in southern China. Armed by INTERPOL with these findings, Chinese authorities made arrests in China's Yunnan Province in 2006. The suspects are alleged to have traded 240 000 blister packs of counterfeit artesunate.

Operation Jupiter depended on effective international collaboration and analytical techniques rarely available in South-east Asia. Without considerable extra resourcing it will be difficult to tackle the trade in counterfeit drugs, which are now also spreading across Africa. A partial solution may lie with portable detectors that can reliably determine whether medicines in shops and pharmacies do contain their stated active ingredient.

Newton PN et al. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. PLoS Med 2008;5(2):e32.

Some 2 billion people are infected with *Mycobacterium tuberculosis*, the cause of tuberculosis, and 2 million die of it every year. For more than 80 years, the BCG vaccine has provided some protection, but it has many drawbacks, including its inability to protect adults from infection. A new vaccine being developed by Helen McShane, a Senior Research Fellow in Clinical Science at the University of Oxford, has been shown to boost immune responses dramatically in clinical trials in South Africa and The Gambia.

The vaccine, MVA85A, is based on a modified form of vaccinia virus displaying a TB antigen on its surface. It has been designed as a booster vaccine – stimulating a heightened response by re-stimulating the immune response initially generated by a 'priming' vaccine such as BCG. Following successful trials in the UK, the vaccine has undergone clinical trials in Africa to assess its safety and ability to stimulate immune responses.

In both South Africa and The Gambia, MVA85A had no significant side-effects. Most encouragingly, in both settings it generated powerful T-cell immune responses – those thought most likely to protect against *M. tuberculosis*. Detailed analysis suggests that a wide range of responses is being stimulated.

Moreover, a trial in the UK has shown that the immune boost provided by MVA85A does not depend on the length of time since BCG was given – responses were the same whether it was given weeks or years later.

These highly promising findings support rapid progress towards phase IIb clinical efficacy trials, which would test the ability of MVA85A to protect against infection with TB.

With a £4m award from Technology Transfer and £4m from the Aeras Global TB Vaccine Foundation, Dr McShane has begun a phase IIb clinical trial of the vaccine in South African children. In addition, Isis Innovation Ltd, the technology transfer arm of the University of Oxford, has announced a new joint venture with biopharmaceutical company Emergent BioSolutions Inc. to develop the vaccine.

Brookes RH et al. Safety and immunogenicity of the candidate tuberculosis vaccine MVA85A in West Africa. PLoS ONE 2008;3(8):e2921.

Hawkridge T et al. Safety and immunogenicity of a new tuberculosis vaccine, MVA85A, in healthy adults in South Africa. J Infect Dis 2008;198(4):544–52.

Pathan AA et al. Boosting BCG with recombinant modified vaccinia ankara expressing antigen 85A: different boosting intervals and implications for efficacy trials. PLoS ONE 2007;2(10):e1052.

Beveridge NE et al. Immunisation with BCG and recombinant MVA85A induces long-lasting, polyfunctional Mycobacterium tuberculosis-specific CD4+ memory T lymphocyte populations. Eur J Immunol 2007;37(11):3089–100.

WHAT DOCTORS DO

Ensuring that doctors follow good medical practice could make a big difference to healthcare delivery.

The past few decades have seen an emphasis on evidence-based medicine and ensuring that doctors use treatments known to work. Research suggests that this approach could provide healthcare benefits if it were adopted more widely in low- and middle-income countries.

Doctors can draw upon a huge body of knowledge, generally in 'quality-assured' forms such as clinical guidelines and WHO recommendations. Ensuring that the medical profession follows 'good practice' is particularly important in low- and middle-income countries, which face strong pressures to use scarce health funds effectively.

SEA-ORCHID (South-East Asia Optimising Reproductive and Child Health in Developing Countries), an international collaboration funded by the Wellcome Trust and the Australian Health and Medical Research Council, has been systematically evaluating whether the health of mothers and babies in four South-east Asian countries – Indonesia, Malaysia, The Philippines and Thailand – could be improved by better assimilation of emerging medical knowledge.

An audit of current practice suggested that some aspects of maternal and child care, such as treatment of pre-eclampsia, follow recommended practice. But significant deviations were seen: appropriate prophylactic antibiotic use during caesarean sections, for example, was observed in fewer than 5 per cent of cases in most hospitals. Rates of episiotomy, which should be used sparingly, ranged from 31 per cent to 95 per cent.

On the basis of these findings, the SEA-ORCHID team has developed interventions to help build capacity in the skills needed to carry out and assimilate research findings.

Independently, Tazeen Jafar at the Aga Khan University, Karachi, Pakistan, and colleagues looked at the role of the doctor–patient relationship – and of patients themselves – in the management of chronic conditions.

They discovered that one-third of heart attack patients were slow to go to hospital, mostly because they were unaware of the need to respond rapidly to the symptoms of heart attacks. They also found that training for physicians, emphasising the value of doctor–patient communication, significantly increased patients' adherence to medication for high blood pressure. With heart conditions a growing problem in countries such as Pakistan, it is vital that people get the right treatment when they need it.

References for this article can be found at www.wellcome.ac.uk/annualreview.

GUT FEELING

Adding starch to oral rehydration solutions significantly reduces diarrhoea in adults with cholera.

Oral rehydration solutions are effective treatments for diarrhoea, a common and potentially fatal consequence of many infections. Nevertheless, while they stabilise a person's health, these solutions do not actually stop the diarrhoea, so individuals are still in discomfort and may be discouraged from using them. A study in Vellore, India, based on a partnership between researchers from India, the UK and the USA, has now shown that addition of a complex carbohydrate can markedly reduce diarrhoea.

More than 4.5 million cases of diarrhoea occur every year, most of them in resource-poor countries. Patients are typically given oral rehydration solutions, which help to replace lost fluids.

Although effective, early formulations did not halt diarrhoea, leading the people taking them to wonder whether they were actually working. More recent products have included additives to lower the osmolarity of solutions, to reduce the osmotically driven flow of water from body tissues into the gut lumen. Although these solutions reduce diarrhoea by about 20 per cent, B S Ramakrishna at the Christian Medical College, Vellore, and colleagues in the UK and USA, were convinced that this figure could be lowered still further.

In laboratory studies they had shown that

Images

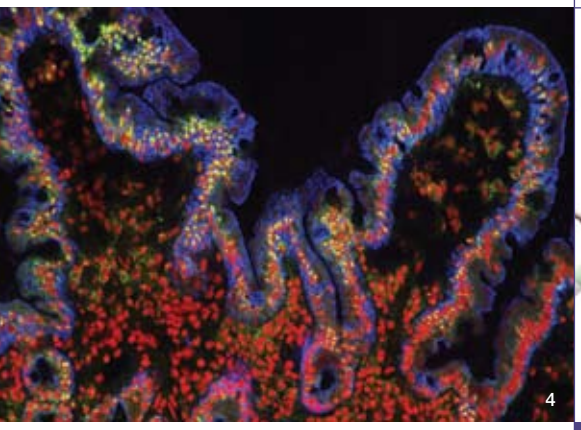
1 Men in Pakistan are at increasing risk of heart disease.

2 Adherence to guidelines could improve maternal health in South-east Asia.

3 Contaminated water supplies can lead to the spread of cholera.

4 Stimulating water uptake in the gut reduces the symptoms of diarrhoea.

NEW FUNDING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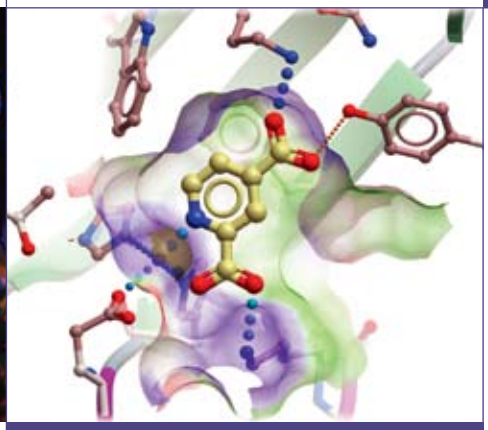
some complex carbohydrates can be metabolised in the gut into short-chain fatty acids, which stimulate sodium and water uptake from the gut lumen. In particular, a type of high-amylose maize starch is partly broken down in the small intestine, releasing glucose, but an undigested 'core' survives to the large intestine, where it is metabolised to short-chain fatty acids.

To test its potential, a clinical trial of an oral rehydration solution fortified with this high-amylose maize starch was run in Vellore. In people with severe diarrhoea, mainly due to cholera, the enhanced solution more than halved the duration of diarrhoea and significantly reduced faecal weight after the first 12 hours of therapy.

As well as providing physical benefits to individual patients, shortening the length of diarrhoea episodes would help to prevent the spread of disease and reduce hospitalisation time and costs. With climate change predicted to increase the burden of diarrhoeal disease still further, such benefits could have a huge impact worldwide.

Ramakrishna BS et al. A randomized controlled trial of glucose versus amylase resistant starch hypo-osmolar oral rehydration solution for adult acute dehydrating diarrhea. PLoS ONE 2008;3(2):e1587.

PUBLIC PROBES



A Strategic Award will fund the development, and release into the public domain, of a set of chemical probes targeting key enzymes controlling gene activity.

The Structural Genomics Consortium (SGC) has determined the structures of many proteins of medical interest (above). As well as benefiting basic research, such information can be used in drug development, aiding the design of small molecules that interfere with protein function. Structures are considered pre-competitive and structural data are freely released into the public domain.

This new award, to Chas Bountra and colleagues at the SGC's Oxford site, takes data release one step further. Chemical probes against three important classes of protein will be developed by an academia–industry partnership and made available for use without restriction.

Academic researchers will benefit from new tools that can be used to investigate biological function; industry will have access to a set of materials and data that could form the basis of new therapeutics.

The proteins targeted are all involved in epigenetic processes – modifications of DNA or associated proteins that affect gene activity. Epigenetic modification has been implicated in a wide range of biological processes and diseases.

A SELECTION OF NOTABLE GRANTS AWARDED IN 2007/08.

STRATEGIC TRANSLATION AWARD

ANTIBIOTICS
Mike Dawson (Novacta Biosystems) Optimising lantibiotic compounds specific for *C. difficile*.

TRANSLATION AWARDS

BIOMEDICAL ENGINEERING
Chris Toumazou (Imperial College London) Development of a wireless implantable sensor to monitor pressure changes in heart chambers continuously after surgery for heart failure.

INFLUENZA
Daniel Henderson (PaxVax, Inc.) An oral adenovirus-based vaccine against influenza for pandemic protection.

BIOMATERIALS
Dr Morgan Alexander (University of Nottingham) Using high-throughput microarrays to identify polymers resistant to bacterial colonisation.

ADJUVANT IDENTIFICATION AND DEVELOPMENT

Professor Willem van Eden (University of Utrecht) and **Professor Paul Lehner** (University of Cambridge) Heat shock proteins as adjuvants.

Professor Allan Mowat (University of Glasgow) The mode of action of immunostimulating complexes.

James Brewer (University of Strathclyde) Antigen-presenting-cell and T-cell responses to two classes of adjuvant.

Professor Paul Kaye (University of York) Impact of glycosylation of small-molecule immune enhancers.

Professor Mark Baird (University College of Bangor) Synthetic mycolic acids as potential adjuvants.

SEEDING DRUG DISCOVERY

ANTIBIOTICS
Kevin Judice (Achaogen, Inc.) Aminoglycosides for multidrug-resistant Gram-negative pathogens and MRSA.

METABOLIC DISORDERS
Professor Brian Walker (University of Edinburgh) Optimising lead compounds targeting 11β-hydroxysteroid dehydrogenase for use in metabolic syndrome and cognitive decline in ageing.

Details of all grants made can be found in *Grants Awarded 2007/08*, available on the Wellcome Trust website.

ENGAGING SCIENCE

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

HAPPY ANNIVERSARY

Wellcome Collection attracted more than 300 000 visits in its first year of opening.

Wellcome Collection, opened in June 2007, offers visitors a unique chance to explore different cultural fields inspired by science, and to debate and discuss wider social issues. An eventful year saw innovative exhibitions on sleeping and crystallography-inspired design, as well as a deeply moving photographic exhibition of terminally ill people. The visitor numbers far exceeded expectations and, combined with a string of plaudits from critics, amounted to a highly successful first year of operations.

The first new temporary exhibition of the year, *Sleeping & Dreaming*, a partnership with the Deutsches Hygiene-Museum, Dresden, brought together works from artists, scientists, film makers and historians, illuminating a ubiquitous but mysterious aspect of human behaviour.

Life Before Death, a series of 24 sets of photographs taken of terminally ill people before and after their deaths, resulted from a collaboration between journalist Beate Lakotta and photographer Walter Schels. Featured on the *Guardian* website, it broke the newspaper's record for the highest number of hits in a 24-hour period.

By complete contrast, *From Atoms to Patterns* included 'insulin wallpaper' and other intriguing designs from the 1951 Festival of Britain, all inspired by X-ray crystallography. The final exhibition of the year, *Skeletons: London's buried bones*, featured 26 skeletons from the Museum of London's Centre for Human Bioarchaeology, collectively uncovering 2000 years of London's history.

The temporary exhibitions were complemented by a lively events programme, which included debates about organ donation, obesity and genetic tests, performances of a play exploring chronic fatigue syndrome and a festival to launch The Big Draw 2008.

The exhibitions and events met with wide-reaching critical attention from national and international media. As a contributor to the *Rough Guide* website put it: "Wellcome Collection is a small, eclectic, imaginative, humane, humorous exhibition of objects related, sometimes in the loosest sense, to medicine. It is WONDERFUL."

Wellcome Collection was also one of only four venues shortlisted for this year's prestigious Art Fund Prize, a national award given to a public venue whose project demonstrates the most originality, imagination and excellence.

CUT AND THRUST

Neurosurgery and the sinking of the *Mary Rose* have been the focus of two acclaimed documentaries.

They are two compelling stories. *The English Surgeon* documents the attempts of a leading brain surgeon struggling to save lives in Ukraine. In complete contrast, *The Ghosts of the Mary Rose: Revealed* describes how forensic analysis of sailors' remains may explain the dramatic sinking of the *Mary Rose* in 1545.

Henry Marsh first visited Kiev in 1992, and was horrified by the conditions endured by both patients and doctors. Since then he has made at least two trips a year – taking time off as a consultant at St George's Hospital – to work with Ukrainian neurosurgeon Igor Petrovich.

The English Surgeon, funded by a Wellcome Trust People Award, was produced by Geoffrey Smith and screened on BBC2 in April 2008 to critical acclaim. *Time Out* called it "a life-affirming, unforgettable portrait of a true humanitarian", and the *Guardian* described it as "a lovely, lovely film". It won Best International Feature Documentary at HotDocs 2008.

Shot over two chaotic weeks in the 2007 Ukrainian winter, the film shows Marsh agonising over whom he can and cannot save – and struggling with local logistical and political constraints. At one point he has to use a £30 cordless drill to bore into a patient's skull. Remarkably, the operation is a success.

Images

1 The *Life Before Death* exhibition.

2 The *From Atoms to Patterns* exhibition.

3 Hugh Montgomery, examining the remains of a *Mary Rose* sailor.

4 Professor John Holman, Director of the National Science Learning Centre.

5 A practical demonstration at the launch of Project Enthuse.

ENTHUSING TEACHERS

A £30m initiative will ensure that UK science teachers enjoy even more continuing professional development opportunities.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Not every story has a happy ending. At the emotional climax of the film, he visits the cemetery where Tanya, a patient he was unable to save, is buried, and confronts what it means to fail.

The Ghosts of the Mary Rose – part-funded by the Trust and shown on Five in August 2008 – may have solved one of the biggest mysteries in British naval history.

In 1545, the *Mary Rose*, flagship of the English navy, sank off Portsmouth during the Battle of the Solent. While the French claimed that their cannons took down the vessel, when the ship was raised in 1982 no cannon damage was found.

In the film, Hugh Montgomery – scientist, consultant and one of the volunteer divers who collected remains in 1982 – enlists the aid of forensic scientists to unlock the secrets of the ship's demise.

Their findings are surprising: some 60 per cent of the men appeared to be of southern European origin – most likely mercenaries or Spanish prisoners of war. The warship probably sank when it attempted a sharp turn, causing water to flood through open gun ports. Conceivably, foreign crew members did not understand an order to close the gun ports – so the loss of the *Mary Rose* may have been the result of a simple communication error.

In 2008 the Wellcome Trust joined forces with the UK Government and leading UK businesses to establish Project Enthuse, a £30 million initiative to enable science teaching staff to benefit from continuing professional development courses at the National Science Learning Centre in York.

With science and technology widely seen as crucial to the UK's economic future, science education is of enormous importance. High-quality education is fundamentally dependent on teachers, and it is essential that teaching staff have access to new scientific knowledge and teaching approaches. Launched in November 2005, the National Science Learning Centre aims to provide innovative professional development for science teachers and technicians – inspiring teachers to deliver inspiring lessons.

To promote the uptake of courses at the Centre, the Wellcome Trust teamed up with the UK Government's Department for Children, Schools and Families (DCSF) and a range of UK businesses – BP, BAE Systems, GlaxoSmithKline, Rolls-Royce, AstraZeneca, AstraZeneca Science Teaching Trust, General Electric Foundation, Vodafone and Vodafone Group Foundation – to establish Project Enthuse.

The initiative will provide generous bursaries covering not only fees and travel for individual teachers but also the cost to schools of providing teaching cover and extra funds to help teachers share what they learn with colleagues. As a result, every school in the country will be able to send their science teachers on cutting-edge courses.

The Centre has been involved in two further important developments this year. It successfully bid for an £18m government contract to operate the network of regional Science Learning Centres, on behalf of the DCSF, and also received a £4.4m award from the Gatsby Charitable Foundation to establish a National STEM (science, technology, engineering and maths) Centre.

Since October 2006, John Holman, Director of the National Science Learning Centre, has also been the National STEM Director, charged with developing a coordinated strategy to support STEM teaching. The Gatsby award will further strengthen links between the two areas. The National STEM Centre will contain the most extensive collection of STEM resources ever housed together – an ideal complement to the extensive range of courses on offer at the adjacent National Science Learning Centre.

UNMASKING MENTAL HEALTH

Several projects are helping to foster a more informed and compassionate view of mental health issues.

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Mental health conditions are common but plagued by stereotyping and stigmatisation. Raising awareness of the realities of such conditions lies at the heart of a series of projects using film, drama and the web to communicate the life experiences of people and families affected by autism, schizophrenia and epilepsy.

Sue Ziebland at the University of Oxford and colleagues have launched two new sections of the award-winning website **www.healthtalkonline.org**. 'Life on the Autism Spectrum' features video and audio clips of interviews recounting the experiences of 20 adults with autism, while 'Parents of Children with Autism' features 45 such parents.

The interviews are supplemented with evidence-based information about the conditions, their management and available treatments. The aim is to give people with mental health conditions and their families an understanding of the experiences, difficulties – and joys – they are likely to encounter, and to help them to make informed choices about treatment.

Cardboard Citizens – the UK's only homeless people's professional theatre company – received funding to develop the famous Georg Büchner play *Woyzeck* as an interactive forum theatre production. The play – a vehicle for exploring schizophrenia – was performed for three weeks at the Southwark Playhouse in London, reaching an audience of more than 1500 people over 18 performances.

The theatre company, with Adrian Jackson as Artistic Director, worked with a team of mental health specialists to ensure that mental health issues were portrayed accurately. More than 100 audience members got on the stage and experimented with strategies for confronting and helping someone with schizophrenia throughout the run.

At the Institute of Psychiatry, Elizabeth Kuipers and colleagues at the South London and Maudsley NHS Trust and Rethink are expanding their website dedicated to supporting people with mental illness. The aim is to involve carers more in the research process, and disseminate research findings to patients, carers and the wider public.

Finally, Media Trust Productions have produced five 30-minute films exploring the impact of living with chronic conditions such as cystic fibrosis, autism, Crohn's disease, rheumatoid arthritis and multiple sclerosis. The series, *What Can Science Do For Me?*, was broadcast on the Community Channel early in 2008, attracting 325 000 viewers, while another 40 000 users accessed the films on the Community Channel's website. The films can be viewed on the Community Channel's broadband player.

BARE TO BE DIFFERENT

'Naked Scientist' nabs Royal Society award for science communication.

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Chris Smith, Clinical Lecturer and Specialist Registrar in virology at the University of Cambridge, is better known for his radio show *Naked Scientists* (part-funded by a Wellcome Trust Society Award in 2005), and accompanying podcasts and books. Dr Smith's pioneering show makes complex scientific material accessible to non-scientific audiences worldwide. In August 2008, he was awarded the Royal Society's prestigious Kohn Award for his work.

The *Naked Scientists* show is a light-hearted look at what is happening each week in the world of science, technology and medicine, interspersed with popular chart music. Guest interviewees have included Sir Martin Rees, astronomer and President of the Royal Society, Sir Alec Jeffreys, inventor of DNA fingerprinting, and James Watson, co-discoverer of the DNA double helix.

Dr Smith's informal approach, stripping science down to its bare essentials, has captured the imagination of the listening public. To encourage debate and add a practical, visual aspect to the medium of radio, he has tested out new ideas such as the weekly 'kitchen science' experiments. Listeners can take part in simple home experiments alongside the broadcast and compete to be the first

Images

1 A scene from the Cardboard Citizens version of *Woyzeck*.

2 A scene from the *What Can Science Do For Me?* programme on cystic fibrosis.

3 Chris Smith, the Naked Scientist.

4 Soundtrack to a *Naked Scientists* radio show.

through on the phones with their findings and interpretations.

According to figures for BBC radio, *Naked Scientists* is the most 'listened to again' on every station on which it is broadcast. It is also top of the US science charts for downloads and in the top 20 science podcasts in the iTunes Music Stores of most countries. This provides good evidence that there is a significant appetite for science – if it is presented in ways that appeal to consumers.

Dr Smith received a silver gilt medal, a gift of £2500 and a grant of £7500 for science communication activities. The Kohn Award was established by the Royal Society, with financial support from the Kohn Foundation.

NEW FUNDING

SCIENCE CENTRE REVAMPS

Two existing galleries – and one brand new venture – have received substantial awards to develop innovative visitor experiences.

The *Who Am I?* gallery in the Science Museum's Wellcome Wing and *Your Amazing Brain* at the At-Bristol science centre will benefit from a major overhaul and the chance to reflect the significant developments in science that have taken place over recent years.

The Science Museum has been awarded £2.5 million to redevelop *Who Am I?*, and an associated website and programme of events at the nearby Dana Centre. It will focus on genetics and neuroscience, celebrating recent advances and fostering debate about their social, economic and other implications.

Your Amazing Brain, a flagship gallery at At-Bristol, has received a £1.4m award. The gallery will be renamed *All About Us*, expanding its scope to other parts of the body and their links with the brain.

A new centre, the Science Gallery at Trinity College Dublin (above), which received a £1m award, aims to be "the coolest science club on the planet". Housed in a landmark building, the £10m centre is adopting a cross-disciplinary thematic approach and aims to build an active community of visitors who help to shape the exhibits and events programme.

A SELECTION OF NOTABLE GRANTS AWARDED IN 2007/08.

SOCIETY AWARDS

DEBATING SCIENCE
Tom Shakespeare (Café Scientifique) Rollout of Junior Café Scientifique and launch of a community website.

SCIENCE AND RISK
Professor David Pratt (Institute of Education) Use of new technological tools to support teaching of risk in socio-scientific issues.

LARGE ARTS AWARD

IDENTITY
Anna Ledgard (Artsadmin) A participatory arts project exploring identity, working with young people at the Evelina Children's Hospital Renal Unit.

PEOPLE AWARDS

YEAST BIOLOGY
David Colthurst (Simon Langton Grammar School for Boys) A yeast molecular biology research project being carried out by sixth-formers.

YOUNG DEBATERS
Danielle Nicholson (National University of Ireland) A debating competition for 15-to-18-year-olds, focusing on biomedical science and its social implications.

SMALL ARTS AWARDS

DARWIN FILMS
Judith Knight (Artsadmin) *Darwin Originals*: four short films providing an unorthodox and humorous perspective on Charles Darwin and his legacy.

MEMORY
Shona Illingworth 'Balnakiel': an installation exploring individual and collective memory, based on work with remote Scottish communities.

E-HEALTH PUBLIC ENGAGEMENT

Perry Walker (New Economics Foundation) Discussions with the public and young people on the use of patient records in healthcare research.

HISTORY OF MEDICINE PUBLIC ENGAGEMENT

MEDICINE AND LITERATURE
Clair Greenaway (Cheltenham Festival) 'Writers and Remedies': Bringing writers and historians together at the Cheltenham Literature Festival to discuss medicine in the lives of 18th- and 19th-century authors.

Details of all grants made can be found in *Grants Awarded 2007/08*, available on the Wellcome Trust website.

DEVELOPING PEOPLE

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

OVERCOMING TRAUMA

Survivors of the 7/7 London terrorist bombings have benefited from psychological treatments for post-traumatic stress disorder.

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Distressing sensations such as flashbacks, sleep problems and strong emotions including anxiety, shame, guilt or anger are common after any traumatic event. Most people recover within a few weeks but a significant proportion – around a quarter – continue to experience disturbing and disabling symptoms collectively known as post-traumatic stress disorder (PTSD). Anke Ehlers's team at the Institute of Psychiatry and the University of Oxford has developed a highly effective form of cognitive therapy that has helped survivors of terrorist attacks and other traumatic experiences.

With David Clark, Professor Ehlers has proposed a model of PTSD based on the notion that PTSD develops when trauma survivors continue to perceive the past trauma as a current threat. This leads to a variety of ways thinking (and behaving) that, although intended as coping strategies, actually serve to maintain the condition.

In several studies, cognitive factors specified in this model have been found to be the strongest predictors of chronic PTSD symptoms. The validity of this model has underpinned a PTSD-specific form of cognitive therapy shown to be highly effective in several clinical trials. It is superior to alternative psychotherapies and achieves better outcomes than drug treatments.

One group to benefit significantly has been survivors of terrorist attacks, including survivors of the Omagh bombing. This led to the creation of the Northern Ireland Centre for Trauma and Transformation, which has achieved positive results even in patients with severe terrorism-related PTSD.

Tragically, the London bombings of 7 July 2005 provided another opportunity to apply trauma-focused cognitive therapies. Professor Ehlers has been part of a collaborative effort to identify and treat people directly exposed to the bombings. About 150 people have been treated to date and, encouragingly, the treatment effects have been as great as those seen after Omagh.

Ehring T et al. Do cognitive models help in predicting the severity of posttraumatic stress disorder, phobia and depression after motor vehicle accidents? A prospective longitudinal study. J Consult Clin Psychol 2008:76(2);219–30.

Bisson JI et al. Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis. Br J Psychiatry 2007;190:97–104.

Brewin CR et al. Promoting mental health following the London bombings: a screen and treat approach. J Trauma Stress 2008;21(1):3–8.

Professor Ehlers's Principal Research Fellowship was renewed in 2008.

MATERNAL GAIN

François Nosten's groundbreaking malaria research is recognised by the Institut de France.

3

In June 2008 François Nosten, Director of the Wellcome Trust-funded Shoklo Malaria Research Unit in Thailand, received the Christophe & Rodolphe Merieux Foundation Prize, a €400 000 (£366 000) honour bestowed by the Institut de France on a researcher or team studying infectious diseases in developing countries.

Although malaria therapies exist, until recently little was known about how to treat pregnant women. Ironically, pregnant women are routinely excluded from clinical trials because of the fear of harming an unborn baby. In a deadly 'catch-22' scenario, pregnant women may then not be given the best available treatment because little is known about how they or their child might be affected.

Working with Nick White, Chairman of the Wellcome Trust's South-east Asia Programme, Professor Nosten's work on maternal malaria on the Thai–Myanmar border cut the number of pregnant women dying from malaria from one per hundred live births to zero.

Clinical trials showed that pregnancy alters the efficacy of antimalarials and that the doses of medicines given to pregnant women were too low – findings that led to a revision of WHO guidelines.

Images

Left Participant in a study of brain activity relating to sign language use. See page 33.

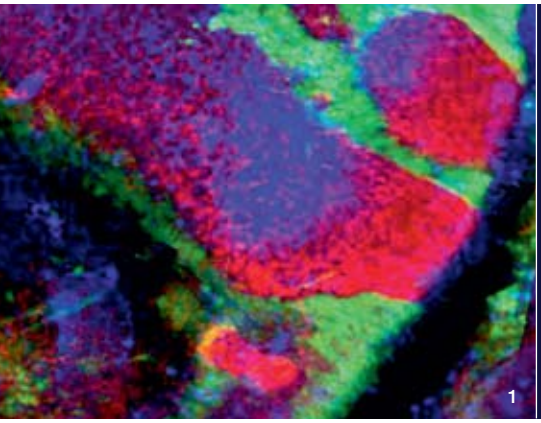
1 The aftermath of the 2005 London terrorist bombings.

2 Professor Anke Ehlers of the Institute of Psychiatry.

3 Professor François Nosten.

BRAIN POWER

What links tadpoles, flies' wings, seahorses and the human brain? A remarkable protein called Lhx2.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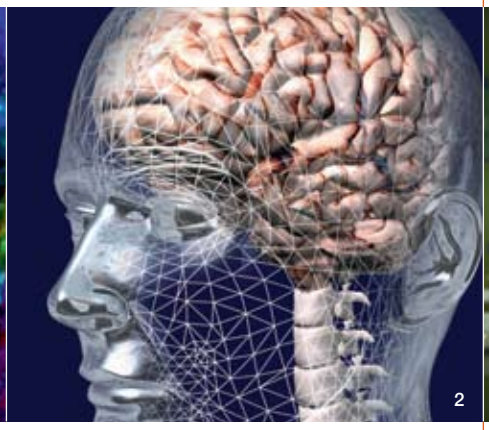
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How do cells form integrated structures during development? Since Hans Spemann's classic work on tadpoles in the 1920s it has been known that certain cells can direct the fate of those around them, organising them into a specific structure. Now, former International Senior Research Fellow Shubha Tole and colleagues have identified a key gene, *Lhx2*, that controls development of the cerebral cortex and the hippocampus – a seahorse-shaped structure crucial to memory formation.

Lhx2 is a relative of a protein involved in fruit-fly wing development. Rather than wings, in mammals Lhx2 has been thought to be a key specifier of cerebral cortex. During development, it is found in cells that become the cerebral cortex but not in an adjacent strip, known as the hem, present at the edge of the cortex.

By clever genetic engineering of mice, Dr Tole and colleagues were able to turn *Lhx2* gene activity on and off in particular regions of the brain and at particular times of development. They discovered that *Lhx2* is essential for specification of the cerebral cortex. It also prevents these cells from turning into hem cells – thereby ensuring that the hem is formed only at the very edge of the cortex.

When *Lhx2* was turned off in patches of cortical cells, however, these cells became hem cells even though they were in the middle of the cortex. And next to each extra hem, a new hippocampus was formed from cells that would have otherwise become part of other cortical regions. This implies that the hem is an organiser that directs adjacent cortical cells to form the hippocampus.

This role of *Lhx2* is not the only trick in its book. Dr Tole's group has found that it is also involved in the early growth of nerves carrying sensory information to the cortex. In fact, it is also needed for development of the olfactory bulb, a key structure in rodents' sense of smell.

It is also active in a stream of cells that helps to build the amygdala, a structure central to the processing of emotional information. This stream of cells originates from the same region that also gives rise to the cerebral cortex, revealing an unsuspected link between development of the amygdala and the cortex.

Mangale VS et al. Lhx2 selector activity specifies cortical identity and suppresses hippocampal organizer fate. Science 2008;319(5861):304–9.

Saha B et al. Dual role for LIM-homeodomain gene Lhx2 in the formation of the lateral olfactory tract. J Neurosci 2007;27(9):2290–7.

Remedios R et al. A stream of cells migrating from the caudal telencephalon reveals a link between the amygdala and neocortex. Nat Neurosci 2007;10(9):1141–50.

INNER SECRETS

Computer analysis can reveal key regulatory features in the genome.


3

With ever more genome sequence being generated, a major challenge is to identify biologically important regions. These include the regulatory sequences that control the activity of genes. Thomas Down, a new Research Career Development Fellow at the Gurdon Institute in Cambridge, is developing software tools that trawl genomic data and identify possible control regions.

A major surprise emerging from the Human Genome Project was the relatively small number of genes encoded within the genome. The biological complexity of humans is thus down to not just the number of components from which we are made but also how those components are used. While 1.5 per cent of the genome codes for genes, around 5 per cent appears to be under strong selective pressure, and many of these conserved sequences are likely to be regulatory elements that control where and when genes are active.

As a PhD student at the Wellcome Trust Sanger Institute at Hinxton, Dr Down combined his interests in biology and computing to develop software tools to aid the analysis of genome sequence data. These have included tools to identify distinctive sequence motifs associated with promoters – the primary regions driving gene activity. Testing one

Images

1 Tracking gene activity in populations of cells in the brains of *Lhx2* mutant mice.

2 The *Lhx2* gene plays a key role in building the mammalian cortex.

3 Thomas Down of the Gurdon Institute.

4 Drops of water on the pins of a liquid-handling device.

5 Mairead MacSweeney of University College London.

6 Identifying areas of the brain responding to sign language.

SIGNS OF COMMUNICATION

Studies of sign language are shedding light on communication in people with full hearing as well as in deaf people.


4


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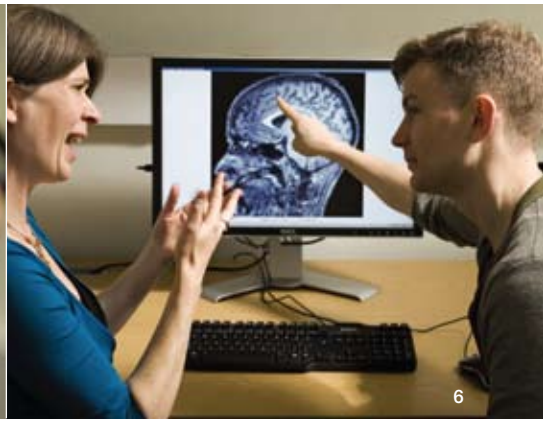
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of these tools in the fruit-fly genome identified 120 motifs, 87 of them novel. For the vast majority, biological evidence suggests that they do indeed function as components of promoters.

At the Gurdon Institute, Dr Down will continue to develop tools to produce a comprehensive directory of regulatory elements in a range of genomes. In addition, he aims to extend this work to work out how these elements function collectively, creating regulatory circuits that control the development of complex organisms.

An ambitious long-term aim is to develop a full enough understanding of these systems that new complex regulatory elements and circuits could be designed from scratch.

Dogruel M et al. NestedMICA as an ab initio protein motif discovery tool. BMC Bioinformatics 2008;9:19.

Down TA. Large-scale discovery of promoter motifs in Drosophila melanogaster. PLoS Comput Biol 2007;3(1):e7.

An understanding of the brain's processing of language has come mainly from studies of spoken languages. But as Research Career Development Fellow Mairead MacSweeney of University College London has discovered, sign language use in deaf people shows similarities with but also differences to spoken language that provide a unique perspective on language processing in the brain.

British Sign Language uses a set of hand/arm gestures and facial articulations to convey meaning. As well as conveying basic linguistic information, intonation, emotion and so on can all be communicated non-verbally. Sign language thus has many of the same characteristics of spoken language but obviously involves a different sense – vision rather than hearing. How does this affect language processing in the brain?

To address this question, Dr MacSweeney and colleagues have been using brain scanning and other techniques to explore brain activity in people perceiving audiovisual speech, silent speech (lip reading) or British Sign Language.

It appears that comprehension of silent speech and sign language share many features with that of audiovisual speech. All activate particular brain regions predominantly in the left hemisphere.

Interestingly, this even appears to be the case for the brain's response to rhyming – the equivalent in sign language being gestures with similar structural properties such as hand location.

There are subtle differences. Areas active in lip reading, for example, depend on both hearing status and lip reading skill, while sign language activates parts of the brain involved in processing motion more than silent speech. In addition, there appears to be growing evidence for a special role for one particular region, the left parietal lobe, in sign language processing. However, its precise role is unclear.

Additional factors can also affect this basic pattern – for example whether the individual is deaf or hearing and at what age they learned sign language. Research with these groups can inform our understanding of how the brain is shaped by experience.

MacSweeney M et al. The signing brain: the neurobiology of sign language. Trends Cogn Sci 2008;12(11):432–40.

Capek CM et al. Hand and mouth: cortical correlates of lexical processing in British Sign Language and speechreading English. J Cogn Neurosci 2008;20(7):1220–34.

MacSweeney M et al. Phonological processing in deaf signers and the impact of age of first language acquisition. Neuroimage 2008;40(3):1369–79.

Capek CM et al. Cortical circuits for silent speechreading in deaf and hearing people. Neuropsychologia 2008;46(5):1233–41.

A NEGLECTED MALARIA

Once considered benign, vivax malaria is actually far from innocuous.

As well as *P. falciparum*, other *Plasmodium* species can cause malaria, including *P. vivax*. Vivax malaria has been considered relatively harmless, but as Career Development Fellow Ric Price has discovered, it is common, serious and, with drug-resistant forms appearing, a growing threat to health in South-east Asia.

Malaria remains a serious problem in South-east Asia, accounting for 40 per cent of the world's cases. Unlike Africa, where falciparum malaria predominates, South-east Asia faces infections from both *P. falciparum* and *P. vivax*.

To test whether *P. vivax* really is 'benign', Dr Price at the Menzies School of Health Research in Australia, working with the Wellcome Trust's South-east Asia Programme, set out to assess the impact of the two malarias in Papua, Indonesia.

An analysis of hospital admissions over a four-year period revealed that 64 per cent of patients with malaria had *P. falciparum*, 24 per cent *P. vivax* and 10.5 per cent mixed infections. In children under one, however, *P. vivax* accounted for nearly half of all malaria admissions. Across all ages, the death rate for *P. vivax*, 1.6 per cent, was comparable to the overall death rate from malaria (2 per cent).

A community study revealed similar patterns. More than half of the population can expect to experience falciparum malaria each year and nearly a third vivax malaria. Again, the prevalence of vivax malaria was higher in young children.

Moreover, vivax can also be harmful during pregnancy. In a separate study, Dr Price found that the fever and anaemia associated with vivax as well as falciparum malaria raised the risk of premature labour and stillbirth in pregnant women.

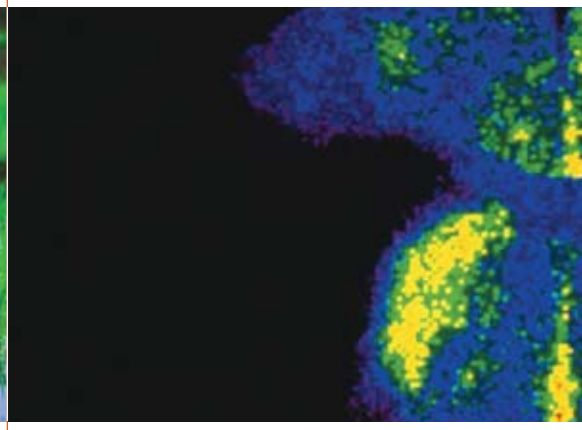
In part, *P. vivax* has been neglected because drug resistance has been less of a problem – it first appeared as recently as 1989. Now, though, drug-resistant forms of *P. vivax* are spreading across much of South-east Asia and more recently in South America. Cure rates for standard treatments have fallen below half for both *P. falciparum* and *P. vivax*.

On the brighter side, effective treatments are available for multidrug-resistant malaria. Indeed, a clinical trial of two artemisinin combination therapies (ACT) confirmed that they were clinically effective for treating multidrug-resistant falciparum and vivax malaria in Papua. A study of the impact of widespread deployment of ACT on *P. vivax* is now underway.

References for this article can be found at www.wellcome.ac.uk/annualreview.

GO WITH THE FLOW

Blood flow to the brain is carefully controlled – but in a surprising way.



The brain is a major consumer of energy, and the harder it works the more energy it needs. As a result, brain activity is tightly coupled to blood flow, which delivers the glucose and oxygen needed to generate energy. But as new Sir Henry Wellcome Postdoctoral Fellow Clare Howarth has discovered, this well-known phenomenon is controlled in an unexpected way.

After a course on magnetic resonance imaging (MRI) fired her interest during a physics degree at Imperial College London, Dr Howarth was accepted onto University College London's highly competitive Wellcome Trust-funded Four-year PhD Programme. There her focus turned to energy consumption by the brain.

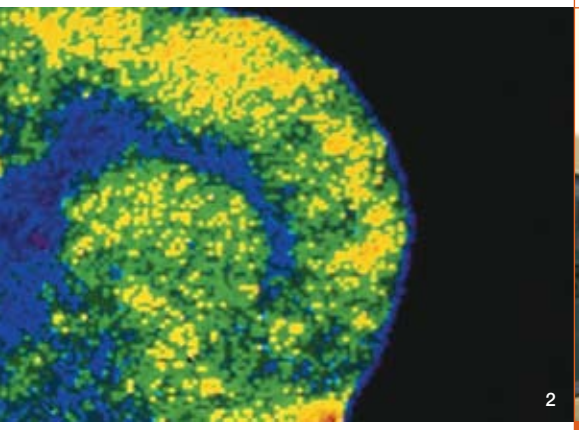
Standard brain imaging techniques, such as functional MRI, make use of the fact that regions of brain activity are marked by increased blood flow. This blood flow was thought to be regulated by smooth muscle surrounding arterioles carrying blood to areas of the brain, but Dr Howarth discovered that although smaller vessels, capillaries, lack smooth muscle, they are sheathed in contractile cells known as pericytes. And it is contraction of these cells that controls capillary diameter and regulates regional blood flow in the brain.

Images

1 In South-east Asia, *Plasmodium vivax* as well as *P. falciparum* causes serious malaria.

2 Colour-coded image of blood flow in the brain.

NEW FUNDING



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As well as making this notable discovery, Dr Howarth has also developed theoretical models for energy consumption by the cerebellar cortex. The actual pattern of blood vessels in the cerebellum is a good match for that predicted on the basis of regional energy needs.

She has also helped to estimate the amount of energy used by conscious perception of stimuli – rather surprisingly, there is a less than 10 per cent increase in energy use associated with conscious perception.

Looking ahead, Dr Howarth will spend her fellowship partly in the lab of Brian MacVicar in Vancouver, an expert on glial cells, and partly in Nicola Sibson's team in Oxford. Her main focus will be on trying to understand the cellular mechanisms that link neuronal activity to control of blood flow.

Peppiatt CM et al. Bidirectional control of CNS capillary diameter by pericytes. Nature 2006;443(7112):700–4.

Schölvinck ML. The cortical energy needed for conscious perception. Neuroimage 2008; 40(4):1460–8.

TRANSLATIONAL PARTNERSHIPS

Four academia–industry partnerships have been awarded £22 million to support training of clinicians in translational research.

Despite the remarkable pace of change in biomedical research, translation into patient benefits has been less rapid. To tackle this bottleneck, the Wellcome Trust has teamed up with industry to support new Interdisciplinary Training Programmes for Clinicians in Translational Medicine and Therapeutics.

The aim of the initiative is to create a pool of researchers, fluent in human physiology, medicine and clinical pharmacology, who have the knowledge and skills to develop and evaluate new therapies. The Trust has provided £11m, with matching funding from industry.

Funding has been awarded to:

- Newcastle University in partnership with Roche, AstraZeneca, Sanofi-Aventis, Sirtris Pharmaceuticals, PTC Therapeutics and GlaxoSmithKline
- the University of Cambridge and GlaxoSmithKline
- the Universities of Edinburgh, Aberdeen, Dundee and Glasgow, and Wyeth Research
- Imperial College London and GlaxoSmithKline.

A SELECTION OF NOTABLE GRANTS AWARDED IN 2007/08.

PRINCIPAL RESEARCH FELLOWSHIPS

LANGUAGE DEVELOPMENT
Professor Dorothy Bishop (University of Oxford)[1] The causes and impact of specific language impairment and links to other neurodevelopmental conditions.

STRUCTURAL BIOLOGY
Professor Randy Read (University of Cambridge)[1] Development of new methods for protein crystallography.

MALARIA
Professor Andy Waters (moving from Leiden to the Wellcome Trust Centre for Molecular Parasitology in Glasgow) Gene expression in the malaria parasite.

SENIOR RESEARCH FELLOW IN CLINCIAL SCIENCE

IMMUNOLOGY
Rodrigo Floto (University of Cambridge) Control of antigen processing by Fc receptors.

SENIOR RESEARCH FELLOW IN BASIC BIOMEDICAL SCIENCE

NEUROSCIENCE
Professor Dmitri Rusakov (University College London)[1] Cellular mechanisms of fast signalling at single synapses in the hippocampus.

CELL BIOLOGY
Dr Ewald Hettema (University of Sheffield) Endoplasmic reticulum and peroxisome multiplication.

INFECTIOUS DISEASE
Dr Cameron Simmons (University of Oxford) Dengue pathogenesis and vaccine design.

SIR HENRY WELLCOME POSTDOCTORAL RESEARCH FELLOWSHIP

NEUROSCIENCE
Misha Ahrens (University of Cambridge) Theoretical frameworks for representation of time in the brain.

INTERMEDIATE CLINICAL RESEARCH FELLOWSHIP

NEUROSCIENCE
Dr Dharshan Kumaran (University College London) The neural mechanisms underlying knowledge acquisition in the human brain.

RESEARCH TRAINING FELLOWSHIP

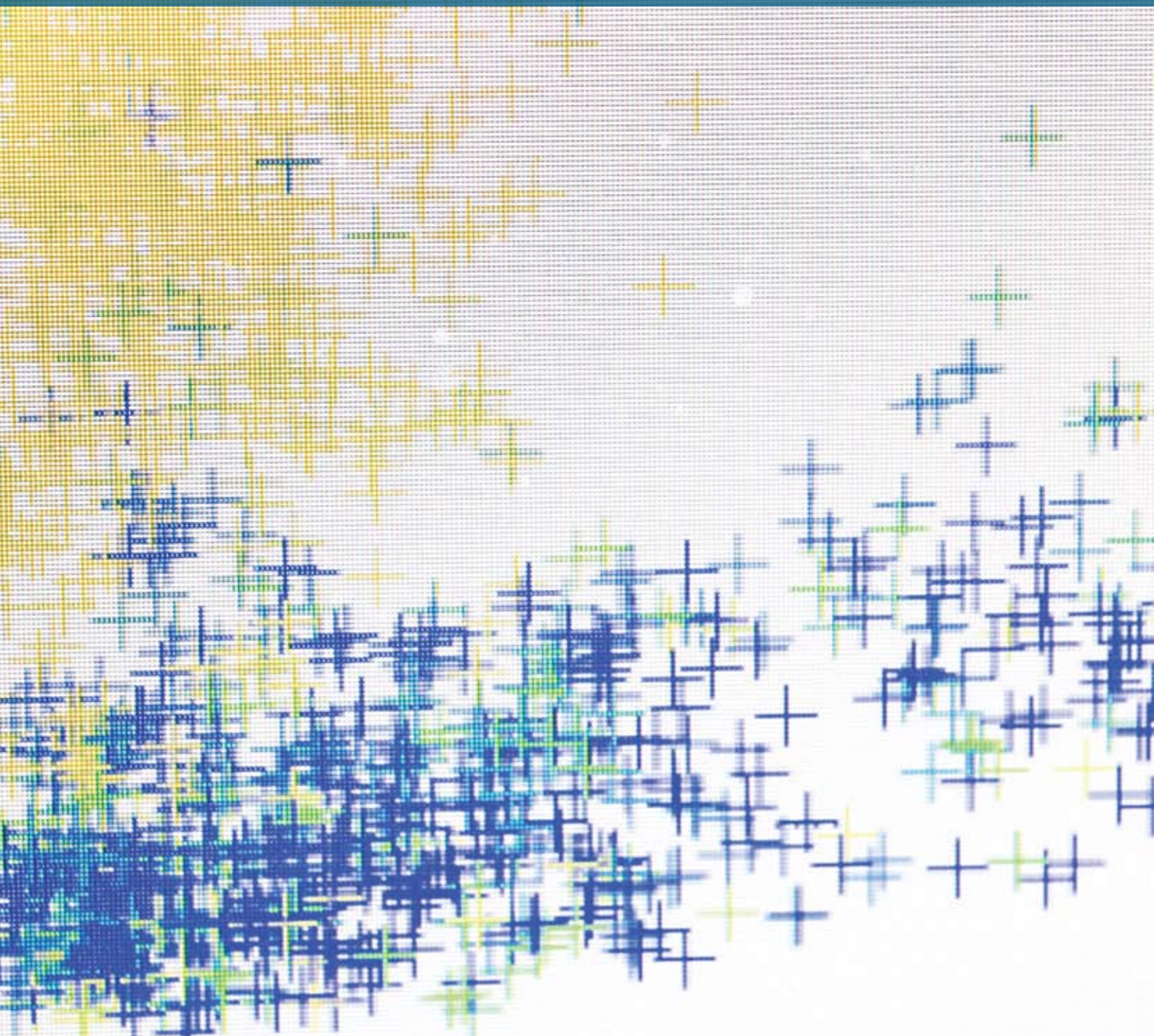
NEUROENDOCRINOLOGY
Seyed Sam (Imperial College London) The action of kisspeptin, a neuropeptide linked to puberty, in the hypothalamus.

[1] Fellowship renewals.

Details of all grants made can be found in *Grants Awarded 2007/08*, available on the Wellcome Trust website.

FACILITATING RESEARCH

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



DEALING WITH DATA

The Wellcome Trust has been working to enhance researchers' access to patient data.

Personal information, such as that held in patient records and large-scale databases, offers huge potential for health research. The Wellcome Trust has been working to ensure that these resources can be used more widely in research, with due safeguards to maintain data confidentiality and security.

Sir Mark Walport, the Trust's Director, and the Information Commissioner, Richard Thomas, conducted a Data Sharing Review, publishing a report in July 2008, which looked at the use and sharing of personal data in the public and private sectors. One of their conclusions was that greater use could be made of personal data in research, with principles of data confidentiality extending to researchers as well as health professionals.

The Trust emphasised the potential public benefits of greater data access in its input to the draft NHS Constitution, published in June 2008. The Trust was also involved in discussions with the UK Department of Health on the 2008 revision to the Health and Social Care Act. The updated Act allows for patient information to be shared for medical research when there are significant potential public benefits.

In May 2008, the Trust hosted a national consensus meeting involving GPs, researchers and patient groups, aiming to develop guidance for best practice in the use of patient records for research. As well as agreeing on the importance of patient confidentiality, delegates supported a number of principles, including the need for transparency, clearly defined processes for the use of data, and improved public awareness of patient record use in research. A consensus document, endorsed by the Royal College of General Practitioners, will be published in 2009.

The Trust also responded to several consultations, including the General Medical Council's consultation on consent and confidentiality and the NHS Connecting for Health consultation on the wider use of patient information.

Finally, a new e-health funding partnership with three Research Councils has sought to stimulate and support the use of electronic databases in health research. A total of £10.6 million was awarded to 17 projects, with the Trust contributing £9.3m. The awards, announced in July 2008, included three public engagement projects exploring the issues surrounding use of personal information in health research.

Spotlight on personal information:
www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Personal-information/

Images

1 Health records contain a wealth of information that could be used in research.

2 Tobacco smoke has serious harmful effects.

STOP AND START

Clinical Research Facilities are helping to improve clinical practice.

Studies at Wellcome Trust Clinical Research Facilities (CRFs) have revealed the benefits of smoking bans and led to fewer complications after abdominal surgery.

The Edinburgh CRF provided support for the STOPIT (Study of Public Place Intervention on Tobacco Exposure) study, funded by NHS Health Scotland, which provided dramatic evidence of the health impact of passive smoking. Smoking in public places was banned in Scotland a year before the English ban. During this time, admissions for acute coronary syndrome dropped by 17 per cent in Scotland but only 4 per cent in England.

The Cambridge CRF has been used in a large, Trust-funded pilot study evaluating a stepwise primary-care-based screening programme for type 2 diabetes, generating valuable information for healthcare planners.

Studies at the Manchester CRF have dramatically reduced complications arising from surgery on abdominal aortic aneurysms. Jane Eddleston's studies showed that exercise testing of patients – who often have other cardiovascular conditions – could be used to identify those most at risk.

References for this article can be found at www.wellcome.ac.uk/annualreview.

CLINICAL APPROACH

A clinical trial facility in Kenya has hosted groundbreaking work on a malaria vaccine.

One of the factors holding back medical research in Africa is a dearth of centres and staff able to carry out clinical trials. A facility established at the KEMRI–Wellcome Trust Research Programme at Kilifi, Kenya, has not only hosted a highly successful clinical trial of the world's leading malaria vaccine but is also providing a base to test locally important interventions and develop a skilled local workforce.

Malaria kills around a million people a year, most of them young children in sub-Saharan Africa. Progress towards an effective vaccine has been painfully slow, but there are encouraging signs that some have a significant (albeit not complete) protective effect.

Of these, the RTS,S vaccine developed by GlaxoSmithKline is the most promising, typically achieving protection rates of about 30 per cent. Even more positively, a phase II trial, organised by the Malaria Vaccine Initiative and run in Kilifi and a second site in Tanzania, upped this figure to 53 per cent, thanks to a new immune-boosting adjuvant.

These exciting findings have justified a much larger phase III trial involving 15 000 children across several sites in Africa, including Kilifi and the Trust-funded facilities in Malawi.

The Kilifi facility occupies a building funded by the Trust and the Malaria Clinical Trials Alliance, and complements the main laboratory and administrative block funded by the Trust. Kilifi now has all the facilities needed to run major international trials, and has trained local staff to design and run their own studies to equally high standards. Moreover, by concentrating the physical infrastructure and specialist support staff, the facility can offer a high-quality environment for all kinds of intervention – vaccine, drug trials or other clinical studies.

Thus, as well as globally important trials, the facility also hosts studies addressing local public health questions. For example, Jay Berkley has begun a Trust-funded trial of prophylactic antibiotic use in malnourished children. After being discharged from hospital, such children often die when they return home. Dr Berkley is testing whether a year's use of antibiotics after discharge can protect vulnerable children during this critical period.

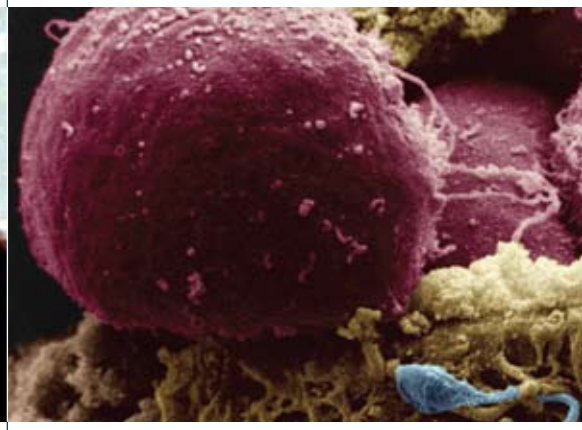
Bejon P et al. Efficacy of RTS,S/AS01E: clinical malaria in 5 to 17 month old children. N Engl J Med 2008;359:2512–32.

Abdulla S et al. Safety and immunogenicity of RTS, S/AS02D malaria vaccine in infants. N Engl J Med 2008;359:2533–44.

The Malaria Vaccine Initiative is funded by the Bill and Melinda Gates Foundation and operated by the not-for-profit organisation PATH.

HYBRID VIGOUR

Accurate information helped to ensure a mature debate about mixed-species embryos.



In 2007, the Government introduced draft legislation to update the 1990 Human Fertilisation and Embryology Act. Perhaps the most contentious change was a provision to allow the creation of human–animal hybrid embryos – seen by scientists as vital in embryonic stem cell research but of ethical concern to some groups. To encourage informed discussion about a potentially highly emotive subject, the Wellcome Trust organised a range of briefings and other activities to communicate the scientific, medical and ethical context of the new Act.

The UK has a well-established regulatory framework for research on human embryos, rooted in the 1990 Human Fertilisation and Embryology Act. The new legislation was designed to take account of the rapid pace of change since 1990, including the use of human–animal hybrid embryos, a potential source of human embryonic stem cells.

Although of great medical potential, research on such cells is held back by a lack of human material. To overcome this difficulty, human DNA can be inserted into non-human eggs and early-stage embryos grown to the point at which embryonic stem cells can be isolated.

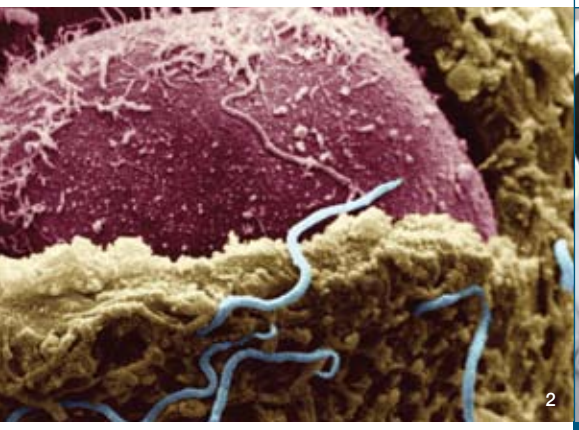
To promote a reasoned debate, the Trust developed briefing material on the key issues for members of the House of

Images

1 Staff at the Clinical Trial Facility in Kilifi.

2 An early human embryo.

NEW FUNDING



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Lords and the House of Commons. The Trust also helped to arrange meetings between scientists and MPs, to explain the science contained in the legislation and the potential medical benefits of research.

Thanks to these efforts, and those of scientists, other organisations and patient groups, the UK Government was persuaded that the creation of human–animal hybrid embryos in medical research was justified.

In addition to its work with politicians, the Trust also organised public engagement activities to encourage broader informed debate. These included a leaflet about human–animal hybrid embryos and their value in research, a supplement in *The Times* on stem cells, a web spotlight including interviews with stem cell scientists, and a Radio 4 debate chaired by Ed Stourton from the *Today* programme.

The work has helped to ensure that research in the UK can continue within a transparent and ethically robust regulatory framework. The Human Fertilisation and Embryology Authority has recently granted licences to three research groups to create human–animal hybrid embryos for research in areas including muscular dystrophy and heart disease.

INTO AFRICA

Medical research and training in Africa have received a £20 million boost.

A sustainable research base requires high-quality research facilities but also training and career opportunities for home-grown researchers. Four Strategic Awards announced in 2008 are intended to provide training and infrastructure support for the brightest young African researchers – the potential scientific leaders of tomorrow.

The KEMRI–Wellcome Trust Research Programme, Kenya, received an award of almost £9m. Funding will be used to develop capacity in translational research, social science and clinical trials.

Brian Greenwood from the London School of Hygiene and Tropical Medicine has been awarded over £7m to support training of African scientists to undertake high-quality malaria research in African universities.

Also receiving funding are two Wellcome Trust Senior Research Fellows. Robert Wilkinson at the University of Cape Town, South Africa, has received £3m to establish a Clinical Infectious Disease Centre focusing on HIV and TB.

Alison Elliott from the London School of Hygiene and Tropical Medicine has received £1m to develop infection and immunity research and training within Uganda.

A SELECTION OF NOTABLE GRANTS AWARDED IN 2007/08.

CAPITAL AWARDS

MOLECULAR MEDICINE
Professor Irene Leigh (University of Dundee) A Centre for Molecular Medicine bringing together basic and clinical research groups.

TROPICAL MEDICINE
Professor Janet Hemingway (Liverpool School of Tropical Medicine) A facility for multidisciplinary and translational tropical medicine research.

DENTAL RESEARCH
Professor Jennifer Kirkham (University of Leeds) A Dental Clinical and Translational Research Unit.

MICROBIOLOGY
Professor Jeff Errington (Newcastle University) A Centre for Bacterial Cell Biology.

STRATEGIC AWARDS

BIOINFORMATICS
Professor Janet Thornton (European Bioinformatics Institute) Bringing a commercially developed high-quality chemogenomic database into the public domain.

HIV
Professor Jonathan Weber (Imperial College London) Core support for an HIV vaccine testing facility.

E-HEALTH

Professor Andrew Morris (University of Dundee) Developing a Scotland-wide interdisciplinary centre for work linked to electronic patient records.

Professor John Danesh (University of Cambridge) A pilot study linking blood donations to electronic patient records.

BIOMEDICAL RESOURCES

VIROLOGY
Dr David Lewis (Health Protection Agency) Securing the future of the National Collection of Pathogenic Viruses.

HUMAN GENETICS
Dr Willem Ouwehand (University of Cambridge) Storing material from controls used in Wellcome Trust Case Control Consortium genome-wide analyses.

RESEARCH RESOURCES IN MEDICAL HISTORY

ARCHIVES
Peter Harper (University of Bath) Cataloguing of the papers of Nobel laureate Sir Bernard Katz.

Details of all grants made can be found in *Grants Awarded 2007/08*, available on the Wellcome Trust website.

DEVELOPING OUR ORGANISATION

Using our resources efficiently and effectively.

TAKING STOCK

A rapid response minimised the impact of the global financial crisis on the Wellcome Trust's asset base.

With financial markets looking vulnerable, in 2008 the Trust moved swiftly to protect the value of its investment portfolio. It expanded its equity sale programme from £3 billion to a total of over £4.5bn and disposed of certain other assets, generating record levels of cash holdings.

While this provided considerable protection from the year's turmoil, the depth of the financial crisis led to a net fall in the Trust's investment asset base to £13.1bn at 30 September 2008, a drop of 10.8 per cent over the year. This compares favourably with the falls in global and UK equities of 16 per cent and 21 per cent, respectively.

Ten-year returns for equities have reached their lowest levels since the US War of Independence in the 1770s. With equities now offering relatively good value, the Trust has begun to reinvest, while maintaining sufficient reserves of cash to support charitable activities without having to dispose of assets at distressed prices.

Overall, the Trust's financial position remains strong. Since the flotation of Wellcome plc in October 1985, returns have averaged 14.9 per cent a year, considerably exceeding both the global equity index and the Trust's targeted return (6 per cent real returns).

A HIGHER PROFILE

The Wellcome Trust has been a keen participant in global health discussions.

Although UK-based, the Wellcome Trust has an international agenda. It funds considerable research in developing countries and has played a pivotal role in numerous international consortia. Human health is an international issue.

This year, the Trust has been involved in multilateral discussions to develop a road map for avian influenza research, spanning vaccine and drug development, surveillance and epidemiology. Fred Hayden, seconded from the University of Virginia, has been appointed to coordinate this work and is spending one week a month at the Trust's offices.

The Trust is also in discussion with the WHO about a coordinated distribution policy for vaccines and drugs, should an avian influenza pandemic break out.

ACTIVE ENGAGEMENT

More efforts are being made to engage with the scientific community.

While response-mode funding remains core to the Trust's work, more proactive strategies are also being developed.

Central to this approach has been the recruitment of senior scientific figures. Recent years have seen the arrival of Professor Richard Morris, a leading neuroscientist from the University of Edinburgh, and Dr Alan Schafer, a geneticist and former head of GlaxoSmithKline's Technology Development Department.

With other senior scientific staff, Pat Goodwin and Jimmy Whitworth, they have set out to build stronger links with the research community and other key groups. The aim has been to gather input on the possible ways in which the Trust can act catalytically to drive forward fields of research and application of new knowledge into practical benefits.

The Trust has been active in organising Frontiers Meetings, bringing together key individuals to discuss emerging and important areas, including, in 2007/08, autism research and the ethics of genome-wide analyses.

With a diverse portfolio of funding schemes, including response-mode grants, Strategic Awards and special initiative funding, the Trust is well placed to take these new ideas forward.

CORPORATE ACTIVITIES 2007/08

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


1


2


3

Governors

In January 2008, Professor Dame Kay Davies and Professor Christopher Fairburn from the University of Oxford and Professor Peter Rigby, Chief Executive of the Institute of Cancer Research, London, joined the Board of Governors.

Two lay Governors also joined the Board in 2008: Rod Kent and Baroness Manningham-Buller, former Director-General of the Security Service.

Policy

In 2008 the Trust has played an active role in parliamentary and public discussions about the possible use of human–animal embryos in research (see pages 38–39).

With the Medical Research Council (MRC) and the Academy of Medical Sciences, the Trust commissioned a study to quantify the economic benefits of medical research (report available at **www.wellcome.ac.uk/economicbenefits**). The work is an experimental approach to the assessment of economic returns, using cardiovascular disease and mental health as case studies.

The Trust has continued to promote open access. In 2007, the UK PubMed Central Publishers Panel – comprising research funders and publisher trade associations – agreed a set of principles for the re-use of documents for which open access fees have been paid. By February 2008, more than a quarter of Trust-funded papers were freely available through PubMed Central and UK PubMed Central.

The Director of the Wellcome Trust, Sir Mark Walport, coauthored a report on sharing of personal data with Information Commissioner Richard Thomas (see page 37).

Peers and partners

As well as its work with the World Health Organization (see left), the Trust has been in discussion with the Bill and Melinda Gates Foundation about joint initiatives in international settings. A particular focus has been food companies' activities in developing countries and emerging economies, faced with both widespread malnutrition and a growing epidemic of obesity.

In the UK, the Trust has launched a number of initiatives with UK Research Councils, including the MRC (neurodegenerative disease), the Engineering and Physical Sciences Research Council (EPSRC; medical engineering) and the Economic and Social Research Council ('e-health', with the MRC and EPSRC). It has also been engaged in extensive discussions with the UK Government, the MRC and Cancer Research UK about the £500 million UK Centre for Medical Research and Innovation (see page 44).

The Trust is also a partner in the UK Clinical Research Collaboration, which has been undertaking numerous activities to promote clinical research in the UK. It is also a founder member of the Association of Medical Research Charities, which celebrated its 21st anniversary by publishing a booklet and website, *A Very Public Benefit*, outlining medical benefits derived from charitable funding of research.

Sir Mark Walport is a non-executive board member of the Office of Strategic Coordination of Health Research, a government body set up to develop and implement a national strategy for translational medicine research. A key focus this year has been on translational medicine, e-health and public health.

Several high-level meetings have been held during the year to discuss climate change and its impact on health. Human health and wellbeing are under serious threat from climate change, particularly in developing countries.

Wellcome Collection

The Trust's innovative public venue, Wellcome Collection, celebrated its first birthday in July 2008. It has been hugely successful, attracting 300 000 visitors and many positive reviews.

Wellcome Collection was also shortlisted for the prestigious Art Fund Prize – a national award recognising originality, imagination and excellence in public venues.

Images

1 Professor Dame Kay Davies.

2 Jugglers at Wellcome Collection's first birthday celebrations.

3 Clinical research, a priority area in the UK.

FINANCIAL SUMMARY 2007/08

In the year ending 30 September 2008, the Wellcome Trust's total charitable expenditure was £701.6m.

Total charitable expenditure for the year increased significantly to £702 million (2006/07: £520m). This rise principally reflected a number of large Strategic Awards and new initiatives launched during the year. These were made possible by a one-off budget supplement of £500m, likely to be committed over the next five years.

Careers

Expenditure on careers support totalled £147.3m (2006/07: £125.5m). Six Principal Research Fellowships were awarded or renewed during the year.

International

Some £52.3m was awarded to researchers at institutions outside the UK and Republic of Ireland, including those at the Wellcome Trust's Major Overseas Programmes. This represents a 26 per cent increase over 2006/07 (£41.4m). A further £18.4m was awarded to researchers at UK institutions for research to be carried out overseas. Total international expenditure was £70.7m.

Infrastructure

Support specifically for buildings, refurbishment, equipment and resources amounted to £121.8m, a substantial increase over 2006/07 (£13.4m). This increase mainly reflects several large capital awards in the UK and overseas. This figure does not include the significant expenditure on equipment or infrastructure provided as part of other Trust grants.

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 2007/08

Total: £701.6m

GRANTS

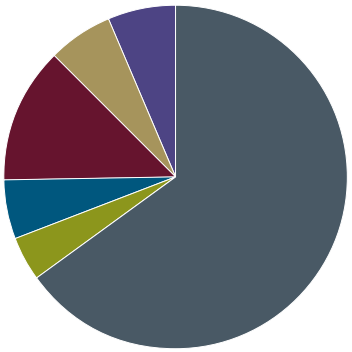
- **BIOMEDICAL SCIENCE** £456.8m
- **TECHNOLOGY TRANSFER** £30.2m
- **MEDICINE, SOCIETY AND HISTORY**[1] £38.3m
- **WELLCOME TRUST SANGER INSTITUTE** £89.9m[2]

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

[2] Including £14.3m from other funders.

OTHER EXPENDITURE

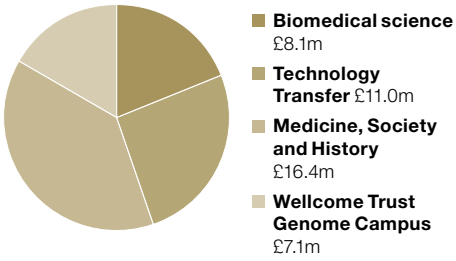
- **DIRECT ACTIVITIES** £42.6m
- **SUPPORT COSTS** £43.8m



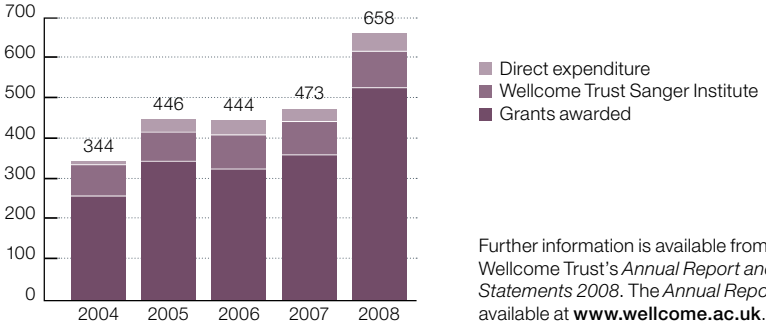
DIRECT ACTIVITIES: £42.6M

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

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



CHARITABLE EXPENDITURE 2004–08 (£M)



Further information is available from the Wellcome Trust's *Annual Report and Financial Statements 2008*. The *Annual Report* is available at **www.wellcome.ac.uk**.

FUNDING HIGHLIGHTS

£30.5m[1]
Wellcome Trust Case Control Consortium phase 2 funding

£29.3m
Capital Awards in the UK

£26m
Principal Research Fellowship support

£20m
Research and training support in Africa

£16m
Support for Kenya Major Overseas Programme

£15m
Strategic Awards to India

£10m
Project Enthuse

£8.8m
Renewal of core funding, Malawi Major Overseas Programme

£8.7m
HIV vaccine testing facility, Imperial College London

£8.6m[2]
Cancer Genome Project: identifying drug-sensitising genotypes

£6.5m
OXION ion channel research network

£5.8m
1000 Genomes Project

£5m
London Pain Consortium

£5m
PaxVax: pandemic flu vaccine development

£4.9m
Transferring chemogenomic databases to the European Bioinformatics Institute

£4.9m
Capital Awards to science centres

£4.5m
South-east Asia Major Overseas Programme: clinical trial of artesunate in children with severe malaria

£4.1m
Achaogen: new aminoglycosides for drug-resistant bacteria

£4m
Clinical trial of TB vaccine

£4m
Structural Genomics Consortium: chemical probes for epigenetic control proteins

£3.9m
Strategic Awards in Medical Humanities

£3.5m
Novacta Biosystems Ltd: development of lantibiotics for *C. difficile*

£2.8m
Renewal of core funding, Wellcome Trust Centre for Molecular Parasitology, Glasgow

£2.5m
Strategic Awards in Biomedical Ethics

£2m
Adjuvant identification and development initiative

[1] Includes £7.7m awarded to the Wellcome Trust Sanger Institute.

[2] Includes £4.6m awarded to the Wellcome Trust Sanger Institute.

INVESTMENTS 2007/08

A challenging year saw the value of the Wellcome Trust's investment portfolio fall by 10.8 per cent to £13.1 billion.

The global financial crisis has presented significant challenges to the management of the Trust's investment portfolio. Active restructuring of investments across classes, however, helped to mitigate some of the more extreme fluctuations. Between March 2006 and May 2008, the Trust sold more than £4.5bn of equities, reducing its equity holdings from 69 per cent of its portfolio in September 2005 to 38 per cent in September 2008. More than 80 per cent of UK equities have been sold, reducing their contribution from 32 per cent to 6 per cent of the total portfolio.

The Trust also reduced its holdings of commercial property and sold a US$250m portfolio of mature private equity buyout fund interests in early 2008.

Holdings of short-term cash and bonds were increased from 5 per cent to 9 per cent of the portfolio, reaching record levels of £1.3bn by the end of the year. These holdings should provide sufficient liquidity to support the Trust's activities during the undoubtedly turbulent times ahead.

The value of the Trust's hedge fund portfolio remained steady at £3.2bn. As these are largely US dollar-denominated assets, the dollar's 13 per cent increase in value against sterling proved beneficial. The strength of the dollar also contributed to a 2 per cent appreciation in the value of the buyout portfolio.

The Trust's portfolio of venture funds delivered a creditable 11 per cent return in 2007/08, despite limited opportunities for companies to be floated in public markets.

With equities now looking more attractive for long-term investors, the Trust is looking to expand its holdings, particularly in large global companies.

FUNDING DEVELOPMENTS 2007/08

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

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 and Small and Large Arts Awards.

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

NEW FUNDING INITIATIVES

ADVANCING KNOWLEDGE

- **UK Centre for Medical Research and Innovation**
- **Research centre in neural circuits and behaviour, UCL**
- **Neurodegenerative diseases initiative**
- **Genome-wide analyses**

The Wellcome Trust, with the UK Government, the Medical Research Council (MRC), Cancer Research UK and University College London (UCL), is creating a £500 million UK Centre for Medical Research and Innovation (UKCMRI). The Centre, due to open by the end of 2013, will be located next to the British Library and the Eurostar terminal at St Pancras. The Trust has committed £100m to the project.

The UKCMRI will bring together groups from the MRC's National Institute for Medical Research, the Cancer Research UK Research Institute and UCL, and will forge links with researchers in nearby universities and hospitals. Sir Paul Nurse, President of Rockefeller University in New York, will head an independent science planning committee to determine the new Centre's scientific mission and the facilities needed to achieve it.

In partnership with the Gatsby Charitable Foundation, the Trust is developing a new research centre. It will be known as the Sainsbury–Wellcome Centre for Neural Circuits and Behaviour and will be hosted by UCL.

The Trust and the MRC have launched a £30m initiative to support interdisciplinary consortia studying the mechanisms underlying neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis and Parkinson's disease.

Building on the success of the Wellcome Trust Case Control Consortium, a scheme has been launched to support further genome-wide analyses.

USING KNOWLEDGE

- **Medical Engineering initiative**
- **Using health research evidence in policy making**

The Trust and the Engineering and Physical Sciences Research Council (EPSRC) have launched a joint £45m initiative to boost innovation in medical engineering within the UK.

With the Alliance for Health Policy and Systems Research, the Trust has launched an initiative to strengthen the capacity of policy makers to use health research evidence in policy making.

ENGAGING SOCIETY

- **International Public Engagement**
- **Genetic variation and health**

An International Public Engagement initiative has been launched to support projects strengthening links between research and the public in developing countries.

A focused call for Society Award proposals related to genetic variation and health was launched in spring 2008.

Public engagement activities were also supported through the electronic patient record initiative (see right).

DEVELOPING PEOPLE

- **Indian Biomedical Research Careers Programme**
- **Expanding the International Senior Research Fellowship scheme**

The Trust and the Indian Government are jointly funding a Biomedical Research Careers Programme, to be delivered by the Wellcome Trust–DBT India Alliance, a new independent, public charitable trust. Each year, the Alliance is expected to award around 40 Early Career Fellowships, 20 Intermediate Fellowships and 15 Senior Research Fellowships.

The Trust's International Senior Research Fellowship scheme has expanded to include Croatia, Slovenia and the Slovak Republic. The scheme is intended to build countries' capacity to carry out high-quality science, providing future generations of scientists with opportunities to develop careers in their home countries.

FACILITATING RESEARCH

- **African institutions initiative**
- **Electronic patient record initiative**

The Trust has launched a new initiative to strengthen institutional research capacity in Africa. Funding will be provided to support the creation of consortia among institutions in Africa as well as between African institutions and those in the UK or other developed countries. The centre of gravity for funding will be in the host African institutions.

In partnership with the Economic and Social Research Council, the EPSRC and the MRC, the Trust ran a one-off competition to support programmes based on the use of electronic patient records in health research.

RESEARCH POLICY AND PRACTICE

- **Concordat to Support the Career Development of Researchers**
- **Guidelines for application of the 3Rs in research**
- **An Integrated Research Application System**

The Trust has signed up to the Concordat to Support the Career Development of Researchers, which provides guidelines on the employment of contract research staff in the UK higher education sector.

The Trust, the MRC, the Biotechnology and Biological Sciences Research Council, the Natural Environment Research Council and the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) have collaborated to produce a common set of principles covering the use of animals in research and application of the 3Rs. Compliance with the guidelines will be a condition of funding for new grants involving the use of animals. The guidelines also cover research in laboratories outside the UK.

The Trust has also fed into the development of an Integrated Research Application System (IRAS), which was introduced in 2008. IRAS captures information required for applications to a number of review bodies and ethics committees across the health and social care sector. It should streamline administration and save time for researchers seeking permission to conduct research within the UK National Health Service.

FUNDING ANALYSIS

Total no. of grant applications:	**2999**
Total no. of grants awarded:	**1131**
Value of applications considered:	**£1.291bn**
Value of grants awarded:	**£525m**
No. of Strategic Awards awarded:	**38**
No. of programme grants awarded:	**44**
No. of PRFs awarded/renewed:[1]	**6**
No. of SRFs awarded/renewed:	**22**
No. of intermediate fellowships awarded:	**34**
No. of training (junior) fellowships awarded:	**69**
No. of PhD training studentships supported:	**184**

FUNDING RATES

	By no.	By amount
Project grants	27%	26%
Programme grants	53%	50%
New PRFs (full app.)	100%	100%
SRFs (full app. Basic)	26%	30%
SRFs (full app. Clinical)	13%	14%
SRFs (full app. Tropical)	–	–
SRFs (full app. International)	12%	13%
Intermediate fellowships	21%	23%
Training (junior) fellowships	24%	24%
History of Medicine Strategic & Enhancement	50%	58%
History of Medicine ad hoc	24%	20%
History of Medicine outreach	50%	12%
Research Resources in Medical History	48%	41%
Biomedical Ethics	33%	30%
People Awards	23%	23%
Society Awards: Activities	21%	14%
Large Arts Awards	21%	16%
Small Arts Awards	16%	16%

Total no. of institutions receiving funding in 2007/08 (UK):	**71**
Total no. of institutions receiving funding in 2007/08 (non-UK):	**34**

OUTSTANDING LIABILITIES[2]

Total grants liabilities:	**£1.26bn**
No. of countries receiving funding:	**35**
Fellows currently supported:	**758**
Researchers currently supported:	**4324**
Total no. of institutions (UK):	**102**
Total no. of institutions (non-UK):	**112**

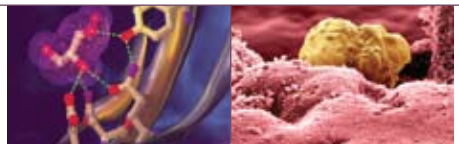
[1] Includes PRF programme grant renewals.

[2] As at 30 September 2008.

PRF: Principal Research Fellowship
SRF: Senior Research Fellowship

STREAMS FUNDING 2007/08

1 October 2007 to 30 September 2008.



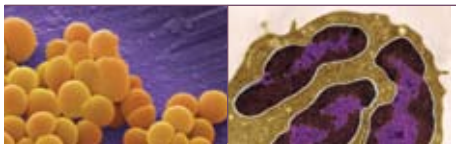
MOLECULES, GENES AND CELLS

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

Total number of grants awarded	211
Value of grants awarded	£93.6m
New and renewed Principal and Senior Research Fellowships	14
Number of programme grants awarded	13
Value of programme grants awarded	£16.1m

OTHER MAJOR AWARDS:

- £30.5m Wellcome Trust Case Control Consortium phase 2
- £5.8m Strategic Award for 1000 Genomes Project
- £4.9m Strategic Award for chemogenomic databases
- £4m Strategic Award for public domain epigenetic probes



IMMUNOLOGY AND INFECTIOUS DISEASE

The Immunology and Infectious Disease stream aims to increase our knowledge and understanding of the infectious organisms that cause disease in humans and animals, and of the immune systems that fight these organisms.

Total number of grants awarded	191
Value of grants awarded	£65.3m
New and renewed Principal and Senior Research Fellowships	5
Number of programme grants awarded	13
Value of programme grants awarded	£18.5m

OTHER MAJOR AWARDS:

- £20.4m African training and infrastructure awards
- £8.8m renewal of core funding for Malawi Major Overseas Programme
- £8.7m Strategic Award for HIV testing facility
- £3.4m Strategic Award for respiratory medicine centre, Imperial College London
- £3.4m Strategic Award to Jenner Institute
- £2.8m renewal of core funding for Wellcome Trust Centre for Molecular Parasitology
- £2m Adjuvant Identification and Development initiative

NEUROSCIENCE AND MENTAL HEALTH

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

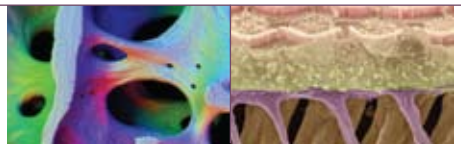
Total number of grants awarded	226 (inc. 68 electives)
Value of grants awarded	£51.8m
New and renewed Principal and Senior Research Fellowships	5
Number of programme grants awarded	6
Value of programme grants awarded	£8.2m

OTHER MAJOR AWARDS:

- £6.5m Strategic Award for OXION network
- £5m Strategic Award for London Pain Consortium

OTHER ACTIVITIES DURING YEAR:

- £5.5m 'pump priming' initiative for young clinicians with Academy of Medical Sciences



PHYSIOLOGICAL SCIENCES

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

Total number of grants awarded	89
Value of grants awarded	£31.9m
New and renewed Principal and Senior Research Fellowships	3
Number of programme grants awarded	6
Value of programme grants awarded	£7.1m

POPULATIONS AND PUBLIC HEALTH

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

Total number of grants awarded	62
Value of grants awarded	£26.8m
New and renewed Principal and Senior Research Fellowships	1
Number of programme grants awarded	5
Value of programme grants awarded	£10.6m

OTHER MAJOR AWARDS:

- £15m Strategic Awards in India
- £9.3m e-health initiative

OTHER ACTIVITIES DURING YEAR:

- £4.7m UK Centres for Excellence in Public Health under the UKCRC

MEDICAL HUMANITIES

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

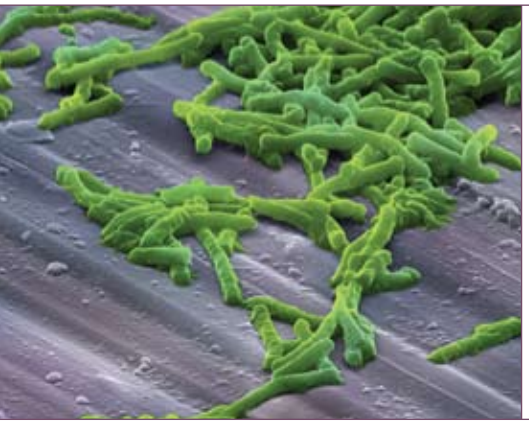
Total number of grants awarded	145
Value of grants awarded	£9.3m
Number of programme grants awarded	0
Value of programme grants awarded	£0

OTHER MAJOR AWARDS:

- £3.9m Strategic Awards in medical humanities
- £2.5m Strategic Awards 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.



Development work on vaccines for pandemic flu, tuberculosis and leishmaniasis was supported this year, alongside innovative research on biocompatible materials for cartilage repair and production of blood substitutes from human stem cells. In addition, a £45 million initiative in medical engineering was launched to drive forward the development of new products.

Translation Awards support a diverse array of technologies, covering the physical sciences and mathematics as well as biology; they are available to both academic institutions and early-stage companies. Of 43 full applications received during 2007/08, 37 per cent were successful. The mean value of awards was £608 000 (range £25 000–1.6m) and the average duration was 30 months (range 9–42 months). Funding decisions are generally made within three to four months.

Projects funded address a wide range of potential applications, including therapeutics, vaccines, diagnostics, medical devices and enabling technologies.

CellMedica Ltd received funding to develop a virus-specific T-cell therapy for immunosuppressed patients. In surgery, an award to Orthox Ltd is supporting work on a novel approach for repair of cartilage tears within knee joints using a bioresorbable, load-bearing cartilage implant, while Morgan Alexander and colleagues at the University of Nottingham are using high-throughput microarrays to identify polymers resistant to bacterial colonisation, to prevent biofilm formation.

In veterinary medicine, Andrew Waller and colleagues at the Animal Health Trust were awarded funding to develop a point-of-care test for horses infected with *Streptococcus equi* (the cause of 'strangles').

Several awards reflected the needs of developing countries. Paul Kaye and colleagues at the University of York, for example, are developing a therapeutic T-cell-based vaccine for human visceral leishmaniasis, while Cambridge Optronics Ltd is working on a low-cost compact microscope for routine diagnostic use in resource-poor settings.

Strategic Translation Awards are designed to support translational research in areas of key importance to the Wellcome Trust. Twenty-two applications have been considered to date (mean value £3.3m, range £1m–8.6m), in diagnostics, vaccines, regenerative medicine, genotyping technology, medical engineering and drug discovery.

Seven new projects in academic institutions and companies were taken forward this year. These included research on vaccines against tuberculosis (Helen McShane, University of Oxford) and pandemic influenza (Dan Henderson, PaxVax, Inc.), as well as antiviral drugs for dengue fever (Alex Matter, Novartis Institute for Tropical Diseases). Mike Stratton and Andy Futreal, leaders of the Cancer Genome Project at the Wellcome Trust Sanger Institute, are working with colleagues in the USA on high-throughput screening and genotyping techniques to identify drug-sensitising genotypes in human cancer cells.

Other notable awards covered the possible use of human embryonic stem cells to generate red blood cell concentrates for blood transfusion and an innovative bacteriophage-based approach to treat *Staphylococcus aureus* and MRSA.

The £91m **Seeding Drug Discovery** initiative, launched in 2005, has so far made 17 awards over four rounds of funding (mean value £3m; range £1.3m–5.0m). In 2007/08, seven awards were made for drug discovery programmes in therapeutic areas spanning sepsis, malaria, bacterial infections, cardiovascular disease and degenerative central nervous system disorders.

During the year, a new £45m initiative in medical engineering was launched in partnership with the Engineering and Physical Sciences Research Council. It aims to support the development of centres of excellence integrating medicine with the physical sciences, mathematics and engineering to foster a culture of innovation and product development in areas of unmet medical need. Final funding decisions will be made in 2008/09.

Several companies that received support through Translation Awards for validation of their technologies have had success in raising further funds, including the start-up companies Population Genetics Technologies Ltd, Aircraft Medical Ltd, Achaogen, Inc. and CardioDigital Ltd. Overall, companies and projects funded through Technology Transfer have raised over £273m in third-party support to date.

WELLCOME TRUST GENOME CAMPUS

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

The Wellcome Trust Sanger Institute's investment in new DNA-sequencing technology has radically increased its output of genome sequence data. It continues to be a major player in numerous international consortia and collaborations. Meanwhile, the Wellcome Trust Advanced Courses programme and Meetings Programme are continuing to expand their portfolio of courses, conferences and workshops.

Wellcome Trust Sanger Institute

This year marked the 15th anniversary of the Sanger Institute, which has grown into one of the world's outstanding biomedical institutions. The Institute's remit is to understand gene function in health and disease; its projects range from cancer to cognition, diabetes to development, embryology to evolution. It also provides valuable free scientific resources to the scientific community.

Reflecting the huge influence of its work, an analysis by ScienceWatch ranked the Sanger Institute the number one UK institution for citation impact during 2003–07. Richard Durbin headed the list of UK-based individuals.

This year the Sanger Institute invested in 'next-generation' technologies to build on its world-leading position in genome sequencing. The output is staggering: whereas the first human genome took 13 years to complete, the Institute generated the equivalent of 300 human genomes in just six months.

The success in sequencing and associated bioinformatics platforms has been recognised by a grant from the Medical Research Council to sequence 17 strains of laboratory mouse. This work complements the Sanger Institute's international mouse gene knockout projects (KOMP and EUCOMM), which reached a major milestone this year by producing 1000 knockout alleles in mouse embryonic stem cells.

The Sanger Institute will play a major role in the second phase of the Wellcome Trust Case Control Consortium (see pages 6–7). DNA samples from 120 000 people are being analysed – the largest ever genetic study of common diseases. Sanger Institute researchers are part of several consortia unpicking the genetic underpinning of common human disease, and recent findings include genes implicated in obesity and susceptibility to infection. The Institute also provides specialist resources to clinicians, such as the DECIPHER database (see page 19).

This year the Institute has been instrumental in establishing two international consortia: the 1000 Genomes Project (see page 14); and the International Cancer Genome Project, led by Mike Stratton, which will identify the key mutations in 50 cancer types – creating a valuable resource and ultimately promising better ways of diagnosing, treating and preventing cancer.

Wellcome Trust Advanced Courses

The Advanced Courses programme ran 18 courses including four new courses at Hinxton: Genome-wide Approaches with Fission Yeast, the Joint Wellcome Trust–European Bioinformatics Institute Proteomics Bioinformatics Workshop, Genomics and Molecular Virology, and Practical Aspects of Small Molecule Drug Discovery.

Its overseas programme has also been progressing. In addition to the pathogen and human bioinformatics workshops held in Uruguay and Kenya, additional IT rooms were set up at Wellcome Trust Major Overseas Programmes in Vietnam and Malawi, and both drew participants from a range of countries within their regions.

In 2008/09 the programme will expand to 22 courses – 14 Advanced Courses and eight workshops. These include workshops in India and Thailand, and an advanced microbiology laboratory course in Malawi, as well as a Genomic Epidemiology of Malaria course at Hinxton.

Wellcome Trust Conference Centre and Meetings Programme

In 2007/08, 2040 delegates participated in 23 events held at Hinxton as part of the Wellcome Trust Meetings Programme. External sponsorship deals were used to fund bursaries and additional invited speakers. Highlights included pilots of new events, such as the Wellcome Trust School of Human Genomics and Fundamentals of Clinical Genetics, which were both well received and will be repeated.

Conference facilities at Hinxton enjoyed another busy year, generating more than £2 million of business (80 per cent to like-minded organisations charged at subsidised rates). The remaining business filled gaps in the conference diary and generated income to subsidise scientific events.

A feasibility study is currently underway to determine the options for expanding the conference facilities.

PUBLIC ENGAGEMENT

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

As well as grants for UK activities, this year the Wellcome Trust made its first awards for projects in developing countries. Education and film making remained priorities, while a major new initiative was launched to document and track public attitudes to science in the UK.

Grants

Society Awards: Ten large awards (over £30 000) were made. Two significant projects, building on previous successful funding, involve young people. Tom Shakespeare in Newcastle is expanding the Junior Café Scientifique programme, while Tony Gilland and the Institute of Ideas are continuing the nationwide Debating Matters schools debating competition.

People Awards: There were 34 awards (up to £30 000) made to support a diverse range of activities, including performances, exhibitions, talks, conferences, debates and documentaries.

Arts Awards: Three large (over £30 000) and 36 small grants were awarded.

Broadcast Development Awards: Some 18 awards (up to £10 000) were made to support the development of early-stage ideas for TV, radio or new media into compelling proposals that can be pitched to the broadcast industry. One large grant was made to Dan Chambers at Blink Productions to co-produce with Channel 4 a feature-length programme, *The Great Sperm Race,* on the journey from testicle to conception. In addition, Jonathan Hall and Hannah Robinson won the Grand Prize at the American Screenwriters Association International Screenplay Competition for *Fireworks*.

International Engagement Awards: There were 15 awards (up to £30 000) made under the new International Engagement Awards programme.

A notable award was made to Marie-Louise Newell and the Africa Centre, aiming to place youth at the forefront of community engagement in research in South Africa.

Capital funding: Three major capital awards were made to the Science Museum, the science centre At-Bristol and the Science Gallery Dublin (see page 29).

Education

In September 2008 *Primary Science*, the first in a new series of *Perspectives on Education*, was published. The series will provide commentaries from researchers and policy makers on key issues in science education. The first volume was well received and, alongside other work in education research, reinforces the Trust's commitment to science education policy.

A review of the first five years of the National Science Learning Centre conducted in April 2008 confirmed that the Centre has made a significant impact. Its core funding was renewed, while £27 million additional funding has been secured through Project Enthuse (see page 27).

In May 2008 the Trust brought together educational researchers and users of research to consider how 'experimental approaches', including randomised controlled trials, might be applied in educational research.

Two issues of *Big Picture* were published this year, on drug development and 'how we look'.

Darwin200

To commemorate the 200th anniversary of the birth of Charles Darwin, a wide range of projects are being developed under the 'Darwin200' banner. The most ambitious is to provide new Darwin-inspired experiments for every state school in the UK. Teachers will be supported by continuing professional development resources, programmes on Teachers TV and access to an online library of evolution-related clips from the BBC archives.

The Trust is als developing multimedia projects, including an animated version of the Tree of Life, a website showcasing the best Darwin resources and an online game for teenagers.

Supporting researchers and broadcast

Training workshops on narrative techniques were run for Trust-funded researchers. Among those benefiting was Hugo Spiers from University College London, who delivered the BA Award Lecture at the Annual Festival of Science in Liverpool.

Through the Science on Film scheme, scientists were able to partner with documentary makers to create films for the Soho Short Film Festival.

Public attitudes

The National Centre for Social Research was commissioned to conduct the first phase of Wellcome Monitor – a survey of people's knowledge about and attitudes towards biomedical science.

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 was officially opened in June 2007. During its first full year of operation, it attracted more than 300 000 visits (almost twice as many as originally forecast). The exhibitions and live events programmes recorded almost 170 000 visits. A further quarter of a million people visited the Wellcome Collection website.

During its first year, Wellcome Collection proved popular with public and critics alike. An external evaluation found that 98 per cent of those surveyed rated their visit as excellent or good. Nearly 67 per cent felt that they had learned more about health, medicine and science as a result of their visit.

Temporary exhibitions

Exhibitions spanned a range of topics, from sleep to archaeology (see page 26). Almost 6500 visitors attended a gallery tour over the year. A family activity pack was introduced a few months after opening to enable younger visitors to navigate the galleries.

Events

An ongoing programme of live public events supports the exhibitions. At 'Flesh', for example, held in November 2007, visitors could take a suturing session with a plastic surgeon and find out about mummification and plastination.

In May 2008, *Nobody Lives Forever*, a play written by Judith Johnson and performed by Y Touring Theatre Company, explored the questions raised by stem cell research. Performances were held while the Human Fertilisation and Embryology Bill was going through Parliament.

On the weekend of 26–28 September 2008, 'Drawing on Life', the national launch of The Big Draw, attracted more than 5000 visits – Wellcome Collection's busiest weekend since opening. The event was a collaboration between Wellcome Collection, the Campaign for Drawing, University College London and the Bow Arts Trust.

Wellcome Collection Club

Currently, the Wellcome Collection Club has around 400 members. As well as the comfortable facilities of the Club, there are opportunities to meet and relax at Club socials, and specially organised events run on a monthly basis.

Wellcome Library

With over 33 000 visits, the Library had its busiest year yet. In the first user satisfaction survey since its return to 183 Euston Road, responses to the newly refurbished spaces were overwhelmingly positive: "it is a total joy and pleasure to have access to the Wellcome Library"; "your amazing collection refreshes my scholarly enthusiasm".

Library hours were extended to include all-day Saturday opening, while the successful public 'Insights' programme of visits included a variety of themes such as The Body in History and Healing Herbs. These one-hour sessions enable visitors to see collections first hand and meet the staff who curate them.

Notable additions to the collections included casenotes by celebrated forensic pathologist Sir Bernard Spilsbury, whose career encompassed the Crippen case and the 'Brighton Trunk Murders', a portrait of Lili Elbe, one of the first to undergo gender reassignment surgery (in 1929–30), and the notebooks of general practitioner Robert Storrs (1801–1847), an early adopter of the stethoscope.

Wellcome Images

With nearly 3500 images published during the year and more than 100 000 images freely available on its new website, Wellcome Images continues to grow and to disseminate the Library's collections. The Wellcome Image Awards, a celebration of the best images added during the year, attracted widespread publicity. An exhibition of the award-winning images toured Japan.

Conference Centre

Over 27 000 delegates attended 495 events throughout the year. User feedback was highly positive.

Business

Blackwell bookshop has proved to be a popular destination for book launches. Wellcome Collection's café, run by Peyton and Byrne, won the Theme Bar and Restaurant Awards prize for Best Café Bar 2008.

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Cover image:
Salbutamol crystals. Salbutamol is used in inhalers for conditions where there is a narrowing of the airways, such as bronchitis, asthma and emphysema. The cluster of crystals is about 600 µm in diameter. *Annie Cavanagh*

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