Connecting science, health and society

Highlights of the Wellcome Trust's work in 2012, a year in which we helped to bring together researchers, teams and centres to better tackle the complex challenges of health research.

wellcome trust

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As at December 2012

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As at December 2012

Wellcome Trust

We are a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health by supporting the brightest minds in biomedical research and the medical humanities.

Our ten-year Strategic Plan for 2010–20 provides the framework for how we intend to evolve our support to be even more effective in achieving this aim.

Our funding focuses on:

1. Supporting outstanding researchers
2. Accelerating the application of research
3. Exploring medicine in historical and cultural contexts.

Our five major challenges are:

1. Maximising the health benefits of genetics and genomics
2. Understanding the brain
3. Combating infectious disease
4. Investigating development, ageing and chronic disease
5. Connecting environment, nutrition and health.

This *Annual Review* covers the period 1 October 2011–30 September 2012.

Contents

An overview of some of our activities in 2011/12, from research successes and public engagement campaigns to the grants we have awarded and the performance of our investments.

Mitochondrial research
A new centre at Newcastle is developing ways to stop children inheriting mitochondrial diseases.

Research leaders of the future
The first ten Sir Henry Dale Fellows – early-career researchers with the potential to become world leaders – have been named.

Stevenage Bioscience Catalyst
The UK's first open innovation bioscience campus has received its first tenants from industry and academia.

In the Zone
Inspired by the London 2012 Games, the Wellcome Trust combined sport and physiology in a touring exhibition and experiment kits for schools.

Tracking MRSA
Rapid whole-genome sequencing shows success in identifying, tracking and stopping hospital outbreaks of MRSA.

Urbanisation and health
An Indian study is revealing the full implications for health when people migrate to cities.

Brains exhibition
Wellcome Collection's most popular exhibition to date explored the history of human efforts to understand the brain's mysteries.

Stem Cell Institute
As pioneering stem cell research wins a Nobel Prize, a new institute is launched to advance our understanding of stem cells and their potential use in medicine.

UK Biobank opens
Researchers can now apply to use the UK Biobank database, with health information and samples from 500 000 volunteers.

Gene therapy successes
Research teams have made striking progress in developing gene therapies – including, for the first time ever, treating a genetic eye disease.

Funding and achievements

970
Total grants awarded

28
Countries receiving funding

492 053
Wellcome Collection visits

12 600
Items of media coverage relating to the Wellcome Trust

£185m
Venture capital finance secured by grantholders for commercialisation of R&D

4433
Scientific research papers associated with the Wellcome Trust
(Published in calendar year 2011, indexed on PubMed and in Thomson Reuters databases)

Online content

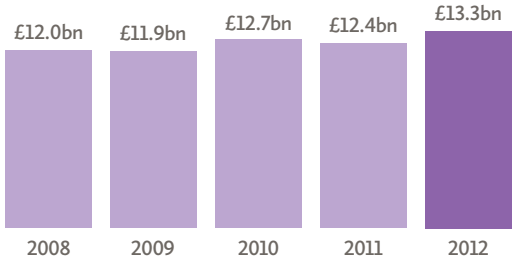
For more content related to the stories featured in the *Annual Review*, see **www.wellcome.ac.uk/annualreview**.

Key financials at a glance

Net asset value

£13.3bn

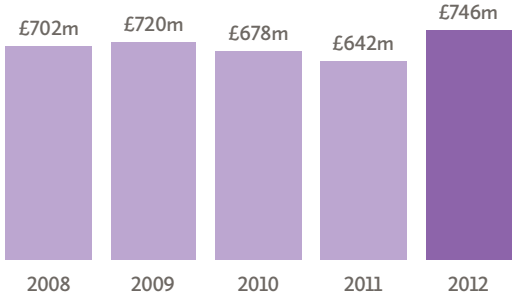
As at 30 September.



Charitable funding committed in year

£746m

For the year ended 30 September.



For more details, see our *Annual Report and Financial Statements* at **www.wellcome.ac.uk/annualreport**.

Financial summary
Our ability to support research and other charitable activities depends on the success of our investment portfolio. We invest globally across a very broad range of assets and strategies. In 2011/12, we were pleased that our investment portfolio recorded a total return of 12%.

We have returned a total of 27% (annualised 8%) over three years and 145% (annualised 9%) over ten years to September 2012. Since the inception of our investment portfolio in 1985, it has provided a total return averaging almost 14% a year.

Our annual grant-making budget is set by reference to a three-year weighted average of our portfolio's value in order to smooth the effects of short-term volatility. Over the next five years we aim to commit in excess of £3 billion for charitable activities, but this will depend on our investment performance.

This year, we have created more opportunities for researchers to build connections with each other and across all parts of society – vital for improving health in the future.

Making connections

Researchers do not work in isolation: productive collaborations, strong leadership and a supportive infrastructure are vital parts of any researcher's success. Similarly, science does not operate in a vacuum. The Wellcome Trust works across many sectors to connect science, health and society so that the fruits of biomedical research are fully able to contribute to better health for all.

In October 2012, the Nobel Prize in Physiology or Medicine was awarded to Professor Sir John Gurdon and Professor Shinya Yamanaka. Their work, 50 years apart, showed that mature cells can be reprogrammed and used to generate so-called induced pluripotent stem cells. John's experiments in the late 1950s overturned theories of cell development and opened up new possibilities in biological research and medicine. Since then, he has continued a highly successful research career, was a co-founder and the first director of the Wellcome Trust/ Cancer Research UK Gurdon Institute, and has also served as a Governor of the Wellcome Trust.

This year's *Annual Review* is all about connecting science, health and society. John's story reflects this theme in many ways: the connections from his original discovery to the development today of new stem cell therapies; the connections he fostered between scientists at the Gurdon Institute; and, through the influence of his work on cloning and stem cell technologies, the wider connections that exist between science and society. These connections resonate with the stories of the Trust's work over the past year, which you can read about in this *Review*.

Connecting science and health

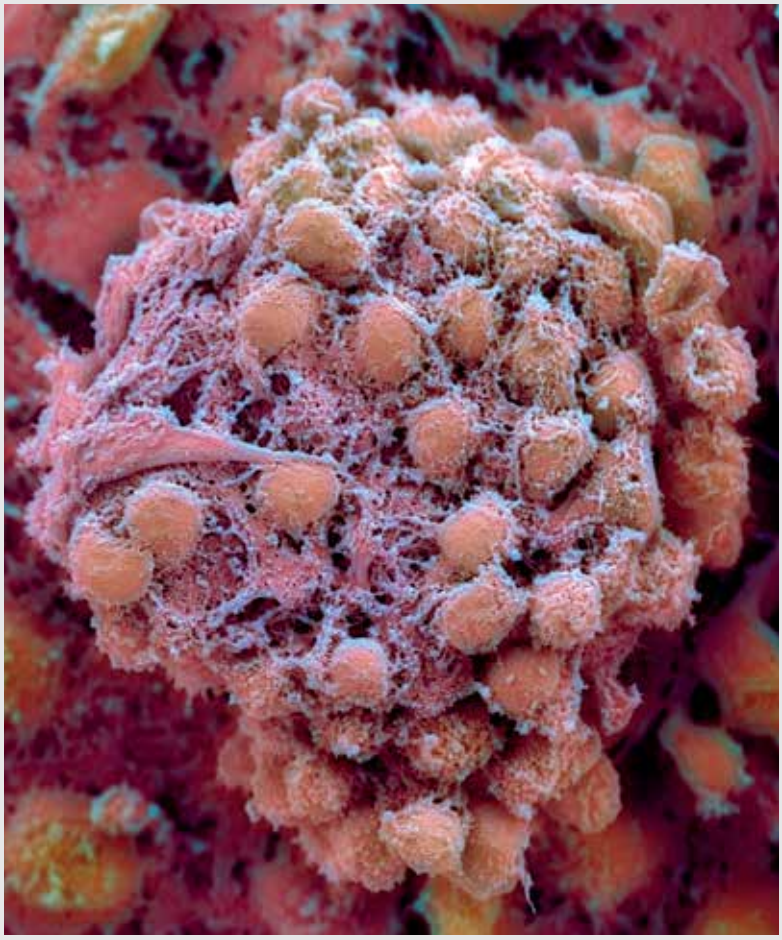
John's experiments showed that an animal's mature, specialised cells all retain its entire genetic code. The genetic information in any one cell could be used to create a new, fully formed organism. This finding sparked interest in the potential for cloning animals, and raised the prospect of reprogramming cells into the same immature state as our natural stem cells and using them for regenerative medicine. Professor Yamanaka's share of the Nobel Prize was for his work published in 2006, which honed an innovative yet practicable technique for genetically engineering mature cells into induced pluripotent stem cells.

Building on this pioneering research, we announced a new centre in Cambridge this year: the Wellcome Trust–Medical Research Council Cambridge Stem Cell Institute. It draws on our existing strengths in the field, uniting many world-class research groups in their efforts to advance our understanding of stem cells and how we can use these to treat a range of human illnesses.

One example of such an application was published this year by a team at the University of Cambridge and the nearby Wellcome Trust Sanger Institute, who combined stem cell biology and gene therapy to correct a faulty gene that can cause cirrhosis of the liver and emphysema in the lungs. They took skin cells from patients, reprogrammed the cells into stem cells and replaced the gene. Then they used the corrected stem cells to generate healthy liver cells. Such techniques – almost unimaginable just a few decades ago – bring us closer to safe and effective treatments based on our growing understanding of genetics and stem cells.

Connecting researchers

The Gurdon Institute celebrated its 21st anniversary this year. Established by a small group of researchers led by John, it adopted his name in 2004,



Scanning electron micrograph of human embryonic stem cells. *Professor Miodrag Stojkovic/SPL*

after he had stepped down from the position of director, recognising his guiding influence in developing a creative and productive environment for developmental biology and cancer research. From the start, his leadership style was inclusive, open and democratic, and this philosophy continues there today. It helped to forge strong links between Gurdon researchers and has inspired similar approaches at other research centres.

Such leadership can sometimes be overlooked in research – it is certainly not something that can be recognised by Nobel Prizes. While we need scientists to be able to do science, they cannot do it in isolation. Most modern biomedical research requires a team of scientists, with a number of international collaborations, the right infrastructure to support them, and someone providing a unifying vision and direction to the research.

With this in mind, many of our fellowship schemes are designed to help develop leadership skills, including a new scheme launched this year in partnership with the Royal Society. Sir Henry Dale Fellowships are named after one of the most eminent neuroscientists of the 20th century, who also served as Chairman of the Wellcome Trust and President of the Royal Society. The Fellowships are for researchers at an early stage of their careers who already show exceptional potential. The fellows receive generous resources to focus on exciting and important research questions while developing the skills, networks and collaborations necessary to become world leaders in their fields.

The rapid development of communications technology in recent years has made the world smaller and extended the range of collaborations available to researchers. However, we must not forget that strong relationships form more readily when people work near each other. This is particularly important for creating an environment that promotes innovation, which often arises when people make unpredictable connections.

Research centres and institutes encourage such interactions, but there are fewer examples when it comes to collaboration in applied research. Stevenage Bioscience Catalyst is a new approach to fostering 'open innovation' between academic researchers and industry scientists. Supported by the Wellcome Trust, GlaxoSmithKline and government agencies, it is a site where researchers from the public, private and charitable sectors can come together and share expertise in early-stage drug discovery and development. The first tenants, a team from a drug and medical device development company, moved in this year, and the University of Cambridge announced that it would establish a centre of innovation for its researchers on the campus. As more tenants move in, opportunities for collaboration and innovation will multiply.

Connecting with the public

At the Trust, we firmly believe that science flourishes most when the public can feel a connection with it, relate it to their own lives, participate in informed debates and share in the delight of scientific discoveries. We support artists, broadcasters and educators who engage people of all ages with biomedical research and the issues around it.

We also hold exhibitions and events at our own venue, Wellcome Collection. For example, *Brains: The mind as matter* examined not what we know about how the brain works, but rather the methods by which researchers through history have tried to find out. It was our most popular exhibition to

date, with more than 1400 visitors a day on average. The success of Wellcome Collection means that, just five years after it opened, we have decided to create new galleries and spaces to meet demand. The development work will take place from summer 2013 to summer 2014, but we plan to keep the building open to the public throughout.

This year, we had a singular opportunity to connect new audiences with science: the London 2012 Olympic and Paralympic Games. As well as entering the spirit of the Games and engaging the public with the physiology and biology of athletic endeavour, it was important to us that science should have a place in the legacy of London 2012 alongside the sports initiatives and urban regeneration projects.

Our contribution, therefore, was In the Zone. Focusing on the science of the body and mind in motion, kits full of ideas for inspirational, practical science experiments were delivered to more than 30 000 schools across the country, as well as to teacher training colleges, science centres and more. An interactive touring exhibition attracted tens of thousands of visitors with high-energy shows and opportunities to test their own physical abilities. It was a fantastic way to harness the world's greatest sporting event and engage people with science.

Science relies on people being not just engaged with it, but willing to participate in it as well. UK Biobank is a major biomedical research resource, drawing on data from half a million volunteers who have had biological samples taken, been weighed and measured, and answered questions about their lifestyle, diet and medical history. UK Biobank is now open to researchers from all over the world – academic and industry scientists alike – who want to investigate how and why some people develop diseases like cancer or heart disease while others do not. It is a prime example of a project that directly connects scientific research with improving health for the good of society.

Future connections

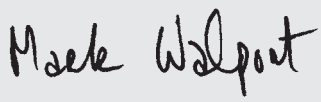
I will be leaving the Trust in 2013 to take up the position of Chief Scientific Adviser to the UK government. I am very proud of what has been achieved in my ten years as Director, but rather than reflecting on that here, I want to look forward.

Whether in stem cell biology, genetics, neuroscience or any number of other fields, these are exciting times in biomedical science. Researchers make astounding leaps forward every year, and yet each discovery seems to confirm that we are barely scratching the surface in terms of understanding our fundamental biology and how to apply these advances. Across medical research, using the tools and knowledge we have accumulated, there is huge potential to make truly extraordinary improvements in health in the years ahead.

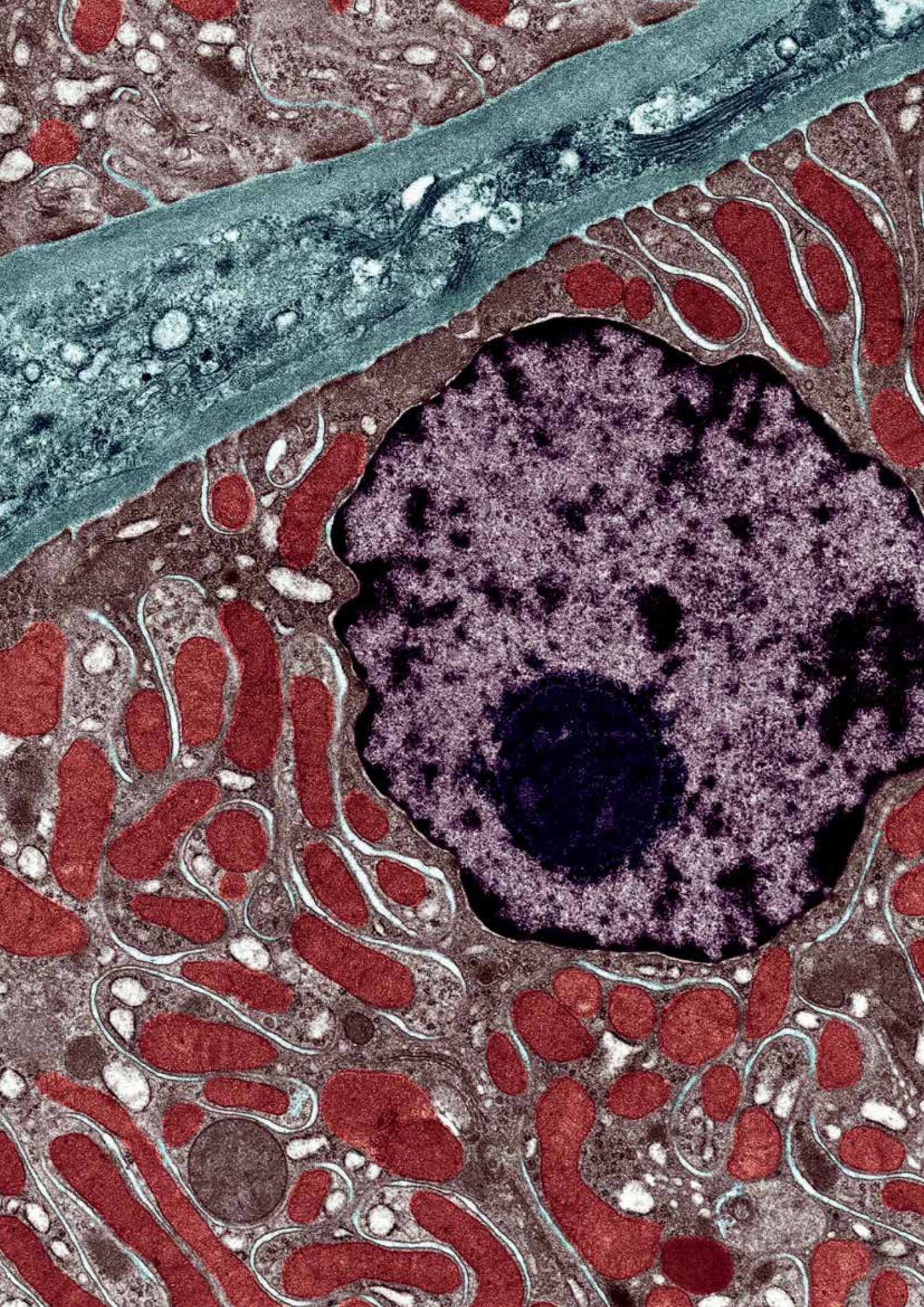
However, we also know that the future will bring new challenges. In the Wellcome Trust's Strategic Plan 2010–20, one of the five broad areas of research we identify as central to our work this decade is the relationship between the environment, nutrition and health. Climate change, population growth and cultural changes such as increasing urbanisation will have a significant impact on health around the world, but it is as yet impossible to make confident predictions about the precise effects.

In this area, as in so much of our work, our focus is to keep making connections. We are increasing our funding of research to characterise the relationships between environment and health, but we are also communicating about these issues, raising them up the scientific agenda, and looking for partners in other sectors whose involvement will be essential for us to make a real difference.

Improving health requires more than excellent science: it also requires the capacity for technological innovation, appropriate regulatory and legal frameworks, readiness within healthcare systems to adopt new approaches, and public acceptance of new treatments and policies. On top of supporting excellent research, therefore, the Wellcome Trust has an important role to play across all these sectors. We help to connect science, health and society so that the fruits of research are accessible and available to contribute to better health for everyone.



Sir Mark Walport
Director of the Wellcome Trust
December 2012



Researchers are developing IVF techniques to stop children inheriting mitochondrial diseases from their mothers.

In January 2012, the Wellcome Trust awarded £4.4 million to Newcastle University, which contributed a further £1.4m, to establish the Wellcome Trust Centre for Mitochondrial Research. The Centre will bring together ground-breaking laboratory researchers, doctors caring for patients with mitochondrial diseases, and the clinical research expertise of the Newcastle Fertility Centre, which has an international reputation in reproductive biology.

The cells in our bodies require energy to function properly. Most of this energy is supplied in chemical form by mitochondria, small parts of the cellular machinery that are thought to be descendants of bacteria that colonised our cells more than 2 billion years ago. Mitochondria are almost like cells within cells, each having its own membrane and its own genes separate from the rest of the genome, which is stored in the cell nucleus. Mutations in mitochondrial genes can lead to devastating diseases, typically affecting tissues that use a lot of energy, such as the heart, muscles and brain.

Mitochondrial genes are passed exclusively down the maternal line. Researchers at the new Centre have already developed two techniques that could prevent the transmission of mitochondrial diseases from mother to child, by using donor eggs with healthy mitochondria. The nuclear DNA, which contains the information for every characteristic and function of the child except their mitochondria, is removed from the donor egg and replaced with the nuclear DNA from one of the mother's eggs. This leaves an egg cell with the mother's nuclear DNA and the donor's healthy mitochondrial DNA.

The team has shown that these techniques work in the laboratory, and is now working on further experiments to assess their safety before they can be used with patients.

Professor Doug Turnbull, director of the Centre, and his colleagues recognise that such work is potentially controversial, so an important focus of their work is to talk to patients, the public and policy makers to make sure their work is transparent and understood, and that people realise these techniques, based on existing *in vitro* fertilisation techniques, are safe and effective.

Mitochondrial abnormalities do not just cause inherited diseases: mitochondrial failure has been seen in conditions such as Parkinson's disease, suggesting that the impact of energy failure might be greater than expected and an important factor in ageing and degenerative diseases. The Centre's work will also investigate this aspect of mitochondrial function, and pave the way for developing new ways to prevent and treat such diseases.

Mitochondria (red) around the nucleus of a kidney cell.
University of Edinburgh/Wellcome Images

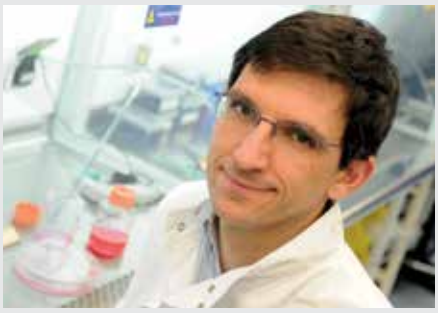
From left:

Data from an MRI scan. *Gabrielle Voinot/ Look at Sciences/SPL*

Dr Venkatraman Ramakrishnan. *Wellcome Images*

Dr Ludovic Vallier. *NC3Rs*

Trypanosoma brucei parasites, the object of Dr Bungo Akiyoshi's research. *Gull Lab, Sir William Dunn School of Pathology/Wellcome Images*



Making MRI more sensitive

Magnetic resonance imaging (MRI) is used more than 1.5 million times a year in the NHS, but there is still a lot of potential for finding new and better ways to apply the technology. Professor Simon Duckett and his team at the University of York received a £3.6 million Strategic Award this year to radically improve the sensitivity of MRI, using a technique called hyperpolarisation.

Current MRI technology is based on detecting signals from the hydrogen in water and fat throughout the body. This often involves injecting contrast agents – usually heavy metals – to distinguish more clearly what these signals mean. At York's Centre for Hyperpolarisation in MRI, part-funded by the Wellcome Trust, a new technology called SABRE (signal amplification by reversible exchange) has been used to impart the distinctive magnetic properties to molecules other than hydrogen, so that they can now be detected directly in the scanner. For example, a drug hyperpolarised in this way could be tracked as it was absorbed and metabolised in a patient's body.

As well as expanding the possible applications of MRI and increasing its sensitivity by several orders of magnitude, this technology could also lead to the development of smaller, cheaper scanners.

Expanding investigations

Now in its second year, the Wellcome Trust's Investigator Awards scheme is building a growing body of exceptional researchers. Across four rounds of funding in biomedical science this year, 45 Senior Investigators and 10 New Investigators were announced. The successful researchers included Dr Venkatraman Ramakrishnan of the Medical Research Council Laboratory of Molecular Biology in Cambridge, who received a Senior Investigator award. Dr Ramakrishnan shared the 2009 Nobel Prize in Chemistry for his work in revealing the structure of ribosomes, the components within our cells that translate genetic instructions to make proteins.

Also funded this year was Professor Derek Jones, a New Investigator based at Cardiff University, who is developing an imaging technique to study the connections between brain cells. Five joint awards were made this year, accounting for one New and nine Senior Investigators: among them were Professors William Cookson and Miriam Moffatt, who work together at Imperial College London, looking at the genetics underlying asthma with the aim of developing new treatments.

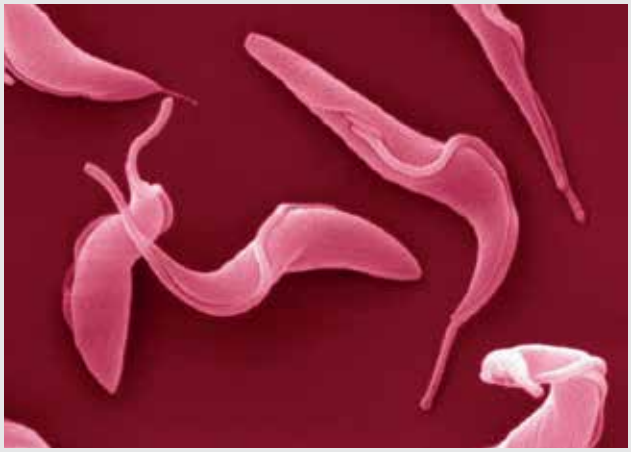
For Investigator Awards in medical history and humanities, see page 18.

Reducing animal use

Wellcome Trust-funded researchers from several institutions won prizes this year for their work in reducing the use of animals in research. The annual prizes are awarded by the National Centre for the Replacement, Refinement and Reduction of Animals in Research. They honour research that makes an original contribution to scientific and technological advances in the '3Rs'.

The overall winner, Dr Ludovic Vallier from the University of Cambridge, published a method of using human skin cells to produce liver cells that are a model for inherited liver diseases. This could help to replace the use of animals in early drug tests.

At the University of Edinburgh, Dr Anna Williams and colleagues produced a cell culture model of repair mechanisms in multiple sclerosis, while Dr Stephen Pettitt of the Institute of Cancer Research and colleagues from the Wellcome Trust Sanger Institute described a new way of developing genetically modified mice. Their innovative methods were both highly commended for their potential to considerably reduce the number of mice used in research.



> These extremely prestigious fellowships will give a vital boost to our most talented researchers, putting them well on the way to a highly successful career."
>
> **David Willetts, UK Minister for Universities and Science**

Research leaders of the future

Ten outstanding researchers received the inaugural Sir Henry Dale Fellowships this year. Run jointly by the Wellcome Trust and the Royal Society, the scheme was introduced in October 2011 to identify and support scientists at an early stage of their careers who have the potential to become world leaders in biomedical research. The fellowships provide generous resources to enable these researchers to pursue exciting research questions, develop new skills, forge collaborations and become internationally competitive.

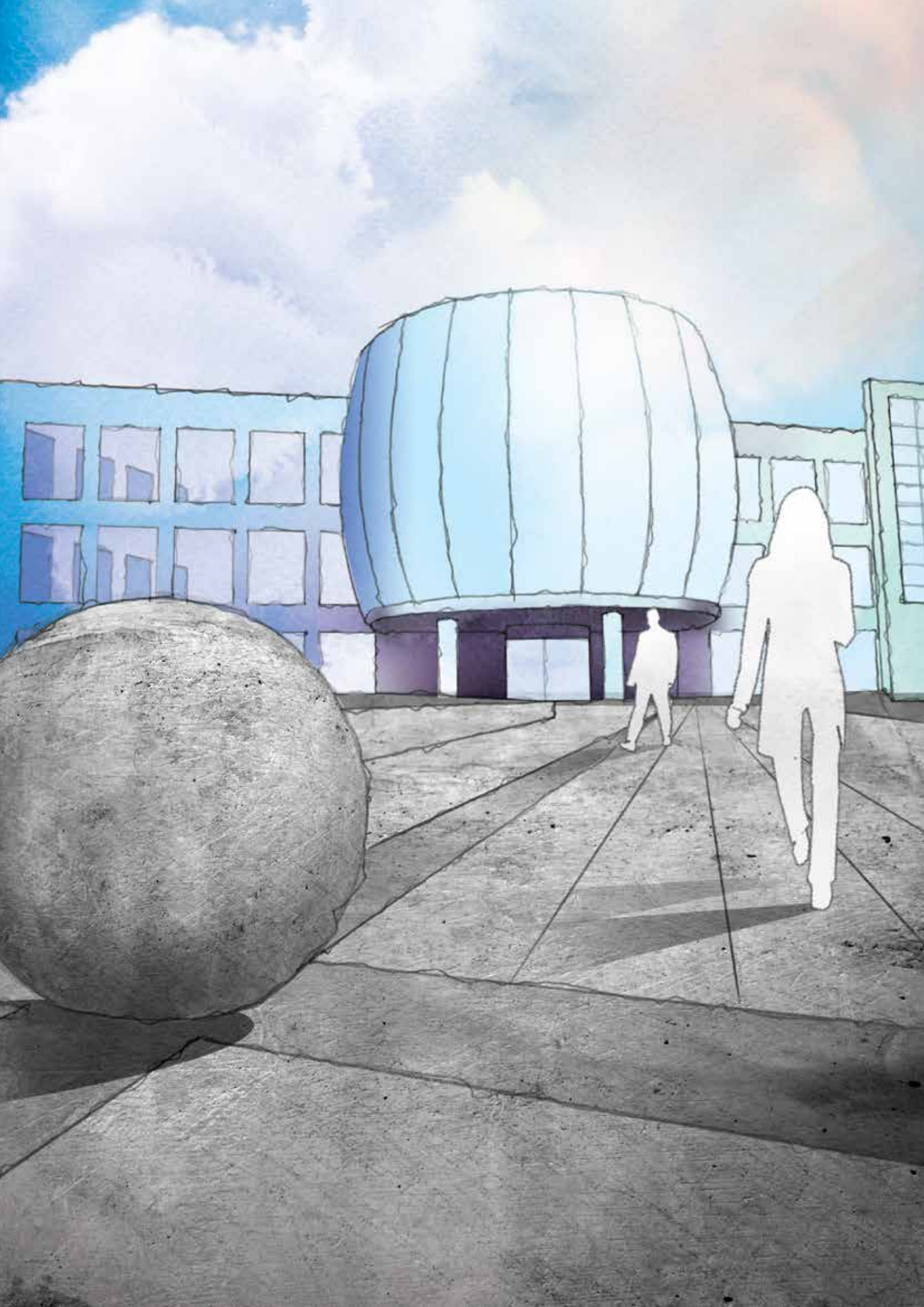
Sir Henry Hallett Dale was one of the most eminent biomedical scientists of the 20th century. Together with Professor Otto Loewi, he was awarded the 1936 Nobel Prize in Physiology or Medicine for the discovery of acetylcholine and its actions in the body. This work revolutionised our understanding of the nervous system.

Dale was the Chairman of the Wellcome Trust from 1938 until 1960, and President of the Royal Society between 1940 and 1945. Today, combining the expertise, experience and influence of these two organisations makes the scheme named after him one of the most prestigious fellowships available to scientists early in their careers.

Among the first recipients was Dr Jennifer Bizley, a former Wellcome Trust-funded PhD student and currently a Royal Society Dorothy Hodgkin Fellow. Based at University College London's Ear Institute, Dr Bizley is looking at how we combine visual and audio information in the brain. She was one of the first people to demonstrate that what we see affects the way our brain cells respond to sound. Her research will determine how this phenomenon helps us to listen in an increasingly noisy world and might lead to better ways of helping people adjust to wearing hearing aids.

With his fellowship at the University of Oxford, Dr Bungo Akiyoshi will study chromosome segregation, a mechanism that cells use to ensure genetic material is passed on accurately during cell division. When chromosome segregation goes wrong, it can cause birth defects or cancer. Dr Akiyoshi will be using a parasite called *Trypanosoma brucei* to learn more about this mechanism and how it might be exploited by drugs in order to help treat human diseases such as cancer.

Dr Maciej Boni also has a fellowship with the University of Oxford, although he is based at the Wellcome Trust's Major Overseas Programme in Vietnam. Dr Boni uses mathematical biology to understand human health and infectious diseases. He will focus on determining the prevalence and severity of influenza in the region, and whether conditions could potentially give rise to another pandemic. Dr Boni will use his findings to advise on the best type of influenza vaccination policy for Vietnam.



The first tenants have moved in to Stevenage Bioscience Catalyst, a life sciences facility that aims to stimulate open innovation across all sectors of biomedical research.

The UK's first open innovation bioscience campus welcomed its first tenants from both industry and academia in 2012. The campus, called Stevenage Bioscience Catalyst, is backed by a £38 million investment from its founding stakeholders: GlaxoSmithKline, the Wellcome Trust, the Department for Business, Innovation and Skills, the Technology Strategy Board and the East of England Development Agency.

Based at GlaxoSmithKline's Stevenage facilities, Stevenage Bioscience Catalyst aims to help rejuvenate the UK's pharmaceutical and biotechnology sector. Focusing on early-stage drug discovery and development, it provides a collaborative environment for researchers from the public, private and charitable sectors. The idea is to bring together people who have shared goals in order to capitalise on what each partner does best. Industry can benefit from the breadth of comprehensive basic research conducted in academia, which has an edge in identifying new biological targets and developing assays. Publicly funded researchers will have access to industry's compound libraries, its expertise in optimising drugs and clinical trial design, and its infrastructure and state-of-the-art facilities.

The first tenants moved in on 23 February 2012. They are the Translational and Medical Sciences Consultancy division of Aptiv Solutions, a company providing drug and medical device development services, with expertise in adaptive clinical trial design, simulation and execution.

Later in the year, the University of Cambridge announced that it is establishing a centre of innovation on the campus. The proximity of Cambridge and Stevenage means that the University's researchers will have access to the expertise, networks and scientific facilities more often associated with multinational pharmaceutical companies, and will be able to share their knowledge of biology and biological systems with their neighbours from industry.

The founders expect that the arrival of the first two sets of tenants in Stevenage will create momentum that attracts other academic, pharmaceutical and biotechnology partners.

Illustration of Stevenage Bioscience Catalyst. *Bret Syfert*

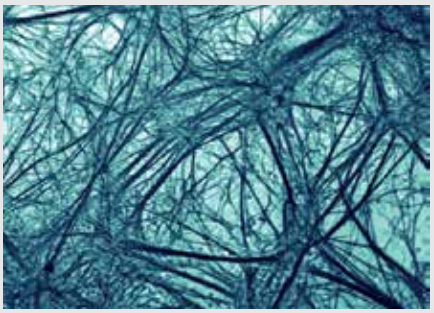
From left:

Neural network derived from embryonic stem cells. *Q-L Ying & A Smith/Wellcome Images*

Illustration of hearing voices in schizophrenia. *Adrian Cousins/Wellcome Images*

Syncona will help healthcare businesses develop their advances. *DNY59/iStockphoto*

A man giving himself an insulin injection. *Ocean Photography/Veer*



Pathfinders

The Wellcome Trust launched Pathfinder Awards in February 2012. These support partnerships between academic and industry scientists to conduct early research and development projects related to rare or neglected diseases. Neglected diseases disproportionately affect people in low-income countries, and – as is true for many rare diseases – there is little financial incentive for private companies to invest in research. This contributes to a lack of options for prevention and treatment.

Pathfinder Awards are designed to help not-for-profit teams run pilot research projects that could generate credible potential products. Further development could then be done either by the industrial partner or through other funding schemes, such as the Trust's Translation Fund.

The first two projects to receive Pathfinder Awards were announced in September 2012. Researchers at Lilly and University College London are developing a line of human stem cells to study a rare group of severe neurological disorders that affect children and young adults. In the other project, a team at Pfizer is working with scientists in the Structural Genomics Consortium at the University of Oxford to study the enzyme affected in a rare hereditary metabolic disorder called homocystinuria.

Avatar therapy

Many people with schizophrenia experience auditory hallucinations. They hear voices that abuse them or command them to harm themselves or other people. Even with drug treatment, about 25 per cent of people with schizophrenia continue to be tormented by such hallucinations.

At University College London, Professor Julian Leff and colleagues are developing an unusual and innovative therapy for use in conjunction with antipsychotic drugs to tackle this problem. In the therapy, patients are invited to create an avatar to represent their hallucination. Voice-morphing software makes the avatar sound the way the patient hears the voice, while computer graphics give it a face. The patient is then encouraged to enter into dialogue with the avatar, stand up to it and tell it to go away. A therapist modifies the avatar's responses so that it comes to agree to stop abusing the patient.

In early tests, avatar therapy reduced the frequency of hallucinations and how threatening they seemed, saving the patients a significant amount of distress. Professor Leff now has a Wellcome Trust Translation Award to refine the technology and evaluate it in a randomised controlled trial. If successful, avatar therapy could be a relatively low-cost way to help people with schizophrenia take control of this aspect of their condition.

Investing in new business

In March 2012, the Wellcome Trust established a £200 million fund to invest in promising healthcare businesses. Syncona, a directly owned and managed investment firm, combines the Trust's experience in the health and biotechnology sectors with its investment expertise. Syncona will identify and invest in new opportunities with the aim of delivering returns to the Trust while supporting advances in health.

Syncona offers a new source of finance and guidance for healthcare businesses at an early stage of their development. The company has already begun making investments, helping businesses turn advances in the life sciences into therapies that will improve patient care.

“

This knowledge will be used in the future to help us predict who might get the disease and also to develop new approaches to prevent it.”

Professor Mark Peakman, King’s College London

Immunotherapy for type 1 diabetes

People who are diagnosed with type 1 diabetes – usually in childhood – take daily injections of insulin to control the condition. This is a lifelong treatment that does not cure the underlying disease or reduce all of the risks associated with it. A new therapy to cure or prevent type 1 diabetes, which is on the rise around the world, would free individuals from the difficulty of managing the disease and would remove significant healthcare costs.

Insulin is produced by beta cells in the pancreas, and its role is to remove excess glucose from the blood. But if a person’s immune system mistakenly attacks and kills these beta cells, this deprives the body of its natural insulin supply. The resulting build-up of glucose has effects such as weight loss and increased hunger and thirst – symptoms of type 1 diabetes, an inflammatory autoimmune disease.

Professor Mark Peakman, a clinical immunologist at King’s College London, began work this year on a Wellcome Trust-funded project to develop a therapy that ‘resets’ the immune system so that it no longer attacks beta cells.

The immune system operates by recognising specific peptides – small proteins or parts of proteins – and attacking any cells that have these peptides on their surface. In autoimmune diseases, the immune system attacks the wrong targets and, as a result, can kill cells that are vital for our health. Professor Peakman and his colleagues are identifying which peptides are wrongly targeted in type 1 diabetes, so that they can investigate whether the immune system could be taught to tolerate these peptides. This approach is called peptide immunotherapy, and it is already being developed for other inflammatory diseases including allergies and multiple sclerosis.

The advantage of using this kind of peptide immunotherapy is that many people with type 1 diabetes have certain genetic similarities in the immune cells that control the recognition and targeting of peptides. This suggests that a therapy using a relatively small number of peptides would be effective in a large proportion of patients. It could even be used to prevent type 1 diabetes developing in people known to be at risk of it because of their family history, for example.

In people who have already have type 1 diabetes, the therapy would stop any further loss of beta cells, and the remaining beta cells should, in many cases, be able to produce enough insulin to control glucose levels. This should help to prevent associated complications, including cardiovascular disease, loss of vision and damage to the nerves and kidneys.

Professor Peakman’s team aims to develop a peptide combination that is suitable for testing in early clinical trials in people with type 1 diabetes.

In the Zone reached 90 000 members of the public, as well as pupils at thousands of schools and colleges, creating a lasting legacy from the London 2012 Games.

The Wellcome Trust's In the Zone project inspired people to take an active interest in the science behind the record-breaking performances at the Olympic and Paralympic Games. Sir Steve Redgrave, winner of five Olympic gold medals, launched the project at the Association for Science Education conference in Liverpool in January 2012, and delivered the first of the In the Zone experiment kits to St Paul's Way Trust School in east London a month later.

Almost 31 000 free experiment kits went to pupils aged four to 18 at schools and colleges across the UK. Developed in collaboration with Pearson Education, the kits were linked to the UK curricula and designed to be fun. They contained equipment and activities for students to carry out hands-on experiments exploring their physiology.

The primary-school kits helped pupils to investigate balance, test how quick off the mark they are and find out whether people with longer legs can jump further. The secondary-school kits included experiments for students to find out how exercise affects breathing rate, test their own muscle strength and explore how the cardiovascular system adapts during different kinds of exercise.

As well as winning an exceptionally positive response from teachers and pupils alike, the kits have inspired further uses. The British Council is adapting them as an English Teaching Resource overseas, and the Brazilian government wants to adapt them for Brazilian schools in the lead-up to the Rio 2016 Games.

An interactive family exhibition also formed part of In the Zone. Created by At-Bristol, the exhibition toured England, Scotland, Wales and Northern Ireland from March to September. Its high-tech, immersive experience allowed visitors of all ages to test their own physical abilities, finding out how high they could jump (and how softly they could land), viewing their veins, sharpening their reaction times and sprinting for gold along a racing track.

Accompanied by high-energy, action-packed live science shows, the exhibition reached around 90 000 people at 21 community open-air events, including county agricultural shows, music festivals, and balloon and airshows. It arrived in east London as part of BT London Live from 27 July to 12 August before continuing its UK tour.

In the Zone was part of the practical learning strand of Get Set – the official London 2012 reward and recognition scheme for schools and colleges demonstrating a commitment to living the Olympic and Paralympic values – and was awarded the Inspire Mark by the London Organising Committee of the Olympic Games.

The In the Zone touring exhibition at the Olympic Park in Stratford. *Wellcome Images*

From left:

Sixteenth-century doctor William Gilbert. Professor Jonathan Barry is compiling a historical database of physicians. *Wellcome Library*

Francis Crick's original pencil sketch of a DNA spiral. *Wellcome Library*

Students at Simon Langton Grammar School in Canterbury. *Wellcome Images*

The *Superhuman* exhibition explored human enhancements of all kinds. *Wellcome Images*

Investigating medical humanities

Following the successful introduction of Investigator Awards in biomedical science (see page 10), the Wellcome Trust has extended the scheme to researchers who are exploring questions at the interface of science, medicine, society and the humanities. The same principle applies: supporting world-class scholars in established academic posts.

Professor Mary Dixon-Woods was among the first group of researchers to receive a Medical History and Humanities Investigator Award. She leads a large programme of research at the University of Leicester on patient safety, healthcare ethics and methodological innovation. With her Senior Investigator Award, she aims to develop principles to guide analysis and resolution of moral dilemmas that arise in the effort to provide safe, good-quality healthcare.

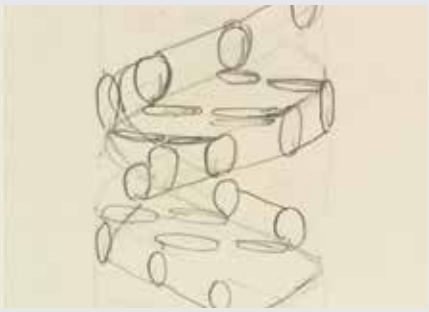
While several physicians are prominent historical figures, there are many others whose contributions to science and medicine are less well known. Professor Jonathan Barry at the University of Exeter has been given a Senior Investigator Award to compile a database of all medical practitioners active in England, Wales and Ireland from around 1500 to 1715. He will document their education, careers and medical practice, as well as including any major contributions to Britain's early modern history.

Dr Sanjoy Bhattacharya at the University of York will use his Senior Investigator Award to study in detail the global movement for primary healthcare in the 1970s and 1980s. This was one of the most ambitious efforts to expand health coverage equitably around the world, and advocacy for primary healthcare is once again rising up the World Health Organization's agenda. Dr Bhattacharya's previous work on the history of smallpox and its eradication in India has shown that implementing global policies can be subject to complex local influences. Understanding the detailed history of such movements is vital to achieving future progress in global health.

One New Investigator Award was made in medical history and humanities this year. Dr Jessica Reinisch of Birkbeck, University of London, has studied the history of international organisations in 20th-century Europe and the role of public health crises and humanitarian disasters in their development. She will now look at the short-lived United Nations Relief and Rehabilitation Administration and its influence on ideas of nationalism and international collaboration in Europe.

"In a society that constantly strives for better, faster and smarter, how much freedom should we have to take advantage of new ways to improve our mental and physical performance?"

Emily Sargent, curator of Wellcome Collection's *Superhuman* exhibition



Opening up geneticists' archives

The Wellcome Library is bringing the papers of the pioneers of modern genetics together for the first time. This is the first phase of a major digitisation programme that will create an unparalleled online repository of books, papers, films, photographs and audio, covering every aspect of the history of medicine and biomedical science.

Foundations of Modern Genetics draws on material from six world-class libraries and archives in the USA, Scotland and England, including the Wellcome Library's own holdings. These collections contain tens of thousands of research notes, letters, sketches, lectures, essays and photographs from the key players in the discovery of the structure of DNA and the subsequent development of genetics – including Francis Crick, James Watson, Sydney Brenner and Lionel Penrose. All the material will be freely available online.

Crick is also the focus of the Wellcome Trust's first Library Fellow, Dr Christine Aicardi. She began her two-year fellowship in October 2011, pursuing a project on Crick's scientific career. This is part of her wider interest in how scientists work, collaborate and interact, and her work will make extensive use of content in the Foundations of Modern Genetics project.

Spreading school success

At Simon Langton Grammar School for Boys in Canterbury, nearly 100 A-level students (girls and boys) are using biochemistry and molecular biology research techniques to explore the chemical nature of myelin basic protein, which is responsible for the development of some cases of multiple sclerosis. The project, a collaboration with the University of Kent, was funded by a People Award from the Wellcome Trust in 2008 and it has proved so successful that the teachers behind it want to encourage more schools to try something similar.

This year, Dr David Colthurst and his fellow teachers at the school received a £250 000 Society Award to extend the approach to four more schools in Sheffield, London, Winchester and Bristol. Each school has picked an area of medical research, and students and teachers will work with researchers at a local partner university to learn the necessary techniques and gain first-hand experience of working on original scientific research.

Superhuman

Inspired by this year's Olympic and Paralympic Games, the *Superhuman* exhibition explored ways in which people have sought to improve on nature and become something 'more'. It ran at Wellcome Collection from July to October 2012, attracting over 1000 visitors a day. The questions it raised – about what is 'normal', where we should draw the line between correction and enhancement, and whether we ought to 'play God' like this at all – prompted enthusiastic reviews, and thoughtful debate and analysis.

The *Lancet* called it "an uncompromising, intelligent exhibition that will put you in the right frame of mind to handle it". Many reviewers were struck by the inclusion of items we take for granted, such as spectacles, smartphones and the contraceptive pill, with *New Scientist* commenting that "the exhibition reminds us that enhancement is already a part of our daily lives". However, visitors were warned against hubris with the very first exhibit they encountered – a small winged statue of Icarus, the boy who flew too close to the Sun.

Two Wellcome Trust-funded projects tested world-first gene therapies this year, for diseases of the eye and the liver.

Researchers at the University of Oxford and Imperial College London are making the first ever attempt to treat choroideraemia, a genetic disease causing blindness, in human patients. Choroideraemia, currently incurable, results from a deficiency of the *REP1* gene on the X chromosome, which leads to the degeneration of the light-sensitive cells of the retina. Men who have the deficient gene lose their sight gradually until they are inoperably blind, usually by their 40s.

The trial involved injecting a virus into one eye of each of 12 men with choroideraemia. The virus carried a segment of DNA that included a healthy copy of the *REP1* gene, and had been engineered to infect the light-sensitive photoreceptor cells in the retina. Once it had 'broken into' the cells, the *REP1* gene inserted itself into the existing cell genome and became active.

The researchers believe the gene will remain in the retinal cells indefinitely, preventing any further degeneration in sight. Funded through the Health Innovation Challenge Fund, a partnership between the Wellcome Trust and the Department of Health, trials began in autumn 2011. While the initial signs are promising, it will take two years to know for sure whether the treatment is successful. If so, the team will then treat the second eye (currently acting as a control) of each of the 12 volunteers.

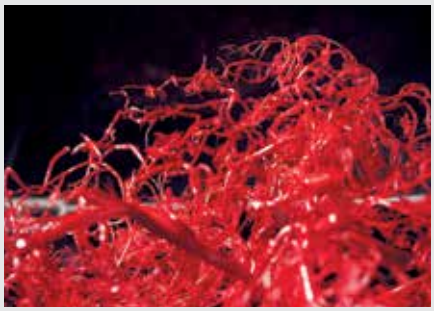
Another group of researchers, at the Wellcome Trust Sanger Institute and the University of Cambridge, have developed a technique to correct a defective gene causing liver and lung disease. A mutation in the alpha1-antitrypsin gene means the protein it codes for is not able to leave the cell in which it is made, causing inflammation that can lead to cirrhosis of the liver and emphysema in the lungs.

In *Nature* in October 2011, the scientists described how they took human induced pluripotent stem cells (hIPSCs) containing the defective gene and used 'molecular scissors' to cut the genome at precisely the right place. They inserted a correct version of the alpha1-antitrypsin gene, then removed all trace of the genetic manipulations except for the corrected gene.

Next, they converted the treated hIPSCs into liver cells and showed that the corrected gene was working normally and producing normal alpha1-antitrypsin protein. Finally, they took stem cells directly from a patient with the alpha1-antitrypsin deficiency and successfully corrected the mutation using the same method.

Combining the potential of gene therapy and stem cells in this way brings us a step closer to the possibility of making treatments specific to individual patients.

Photograph of an eye. *Alloy Photography/Veer*

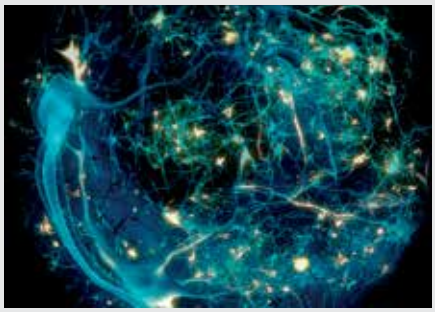


Gene linked to stroke

A genetic variant that increases the risk of a common type of stroke was discovered in a study funded by the Wellcome Trust and published in February 2012. It is one of very few genetic variants that have been found to be associated with stroke, so it could have implications for future treatments.

More than a third of strokes are caused by a blockage to one of the large arteries that supply blood to the brain (large artery ischaemic stroke). Scientists at St George's, University of London, and the Wellcome Trust Centre for Human Genetics at the University of Oxford, together with collaborators around the globe, compared 10 000 stroke patients' genetic make-up with that of 40 000 healthy people.

They found that an alteration in a gene called *HDAC9* increased the risk of stroke: people with two copies of the variant gene were almost twice as likely to suffer large artery ischaemic stroke as those with two normal copies. The mechanism by which *HDAC9* affects stroke risk is not yet clear, but the discovery could lead to new methods of screening and new treatments to prevent some of the 6 million deaths caused by stroke around the world each year.



Cellular celebration

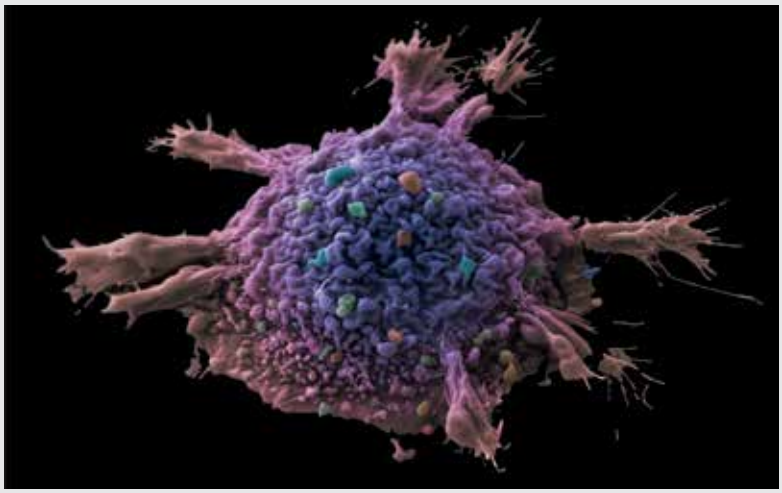
Cell! Cell! Cell! showcased the innermost workings of our bodies on a grand scale over summer 2012. Developed for 360-degree planetariums, the film tells the story of the trillions of cells that make up our bodies and the genes that control them. With funding from the Wellcome Trust, it was created by Intech Science Centre in Winchester, in collaboration with the Wellcome Trust Centre for Human Genetics in Oxford and NSC Creative at the National Space Centre in Leicester.

The show launched in June 2012, taking children and adults on a journey through DNA, exploring its role in determining the fate of all our cells and how these cells make us who we are. Colourful 3D graphics capture the incredible detail of the molecular machinery within our bodies. *Cell! Cell! Cell!* has been shown in digital planetariums across the UK, and there are also related online resources that explore genetic inheritance, the DNA double helix and other important cell structures.

Ancient viruses in our genomes

Our genomes are riddled with ancient viral DNA, and, in April 2012, a Wellcome Trust-funded study shed light on how it got there. Researchers from the University of Oxford, the Aaron Diamond AIDS Research Center in New York and the Rega Institute in Belgium compared the genomes of humans and 37 other species of mammal, including mice and elephants, and collected information about the viral DNA they contained.

They found that millions of years ago, one group of viruses had lost the ability to infect new cells but adapted to surviving in just one cell, replicating and spreading viral genetic material throughout the host animal's genome. DNA from these viruses was much more abundant in mammalian genomes than that of other viruses. The scientists think that these viruses were forced to choose between spreading among animals and spreading throughout a single genome. In opting for the latter, they effectively became 'epidemics' that have been running in our genomes for 100 million years.



> “I look forward to the day whenever I stop treating cancer patients as if they’re all the same, and begin dividing patients into groups which are going to be treated more effectively.”
>
> **Dr Ultan McDermott, Wellcome Trust Sanger Institute**

Genetic clues to new cancer treatments

Not all patients with a particular type of cancer respond to the same drugs in the same way. By examining the effectiveness of drugs on large numbers of cancer cells with different genetic mutations, we might be able to explain why patients’ responses to these drugs differ, and to find ways to determine the best treatment for an individual patient.

Cancer is a genetic disease: it is caused by mutations in genes that control the behaviour of a cell, causing it to grow, multiply or move around the body in a dangerous way. A study published in the *New England Journal of Medicine* in March 2012, by scientists at the Wellcome Trust Sanger Institute and Cancer Research UK, found extraordinary variation in the patterns of genetic mutations in cancer cells, even within a single tumour. Only by understanding these mutations and their effects on drug sensitivity or resistance can we begin to develop ‘personalised medicine’, tailored to each patient based on the specific characteristics of their illness.

The genetic make-up of a cancer cell determines how it responds to cancer drugs that target certain genes or the proteins they regulate. The Cancer Cell Line Screening Project is a five-year collaboration between the Cancer Genome Project at the Sanger Institute and researchers at the Massachusetts General Hospital Cancer Center. They are cataloguing how more than 600 distinct cancer cell lines – derived from cells taken from real tumours and cultivated in the laboratory – respond to 130 established and experimental drugs. The work draws on high-throughput screening and next-generation genome-sequencing techniques developed at the Sanger Institute.

Initial results, published in *Nature* in April 2012, were promising. For example, the analysis suggested that a class of drugs called PARP inhibitors, currently used to treat breast and ovarian cancers, might also be effective as a therapy for a bone cancer called Ewing’s sarcoma. This will be tested in clinical trials and could lead to a new treatment for Ewing’s sarcoma, which affects children and young people.

Such pronounced sensitivity of a type of cancer to a drug used for other purposes is unlikely to be common, but the project is shedding light on the many factors that determine how sensitive cancer cells are to particular drugs. This information will help to guide future drug development, and especially the use of biological markers to identify which drugs are most likely to help which patients.

From left:

A cast of blood vessels in the brain.
Gordon Museum, King’s College London

A still from the *Cell! Cell! Cell!* planetarium show.
NSC Creative

Mammalian genomes contain ancient viral DNA.
dra_schwartz/iStockphoto

A lung cancer cell.
Anne Weston, LRI, CRUK/Wellcome Images

This year, basic research into deafness was recognised with an international neuroscience prize, while a stem cell treatment restored hearing in gerbils, raising the prospect of a new therapy for some forms of human hearing loss.

Impaired hearing is a common condition, with a wide range of possible causes including infections, noise and drugs. There is also a strong hereditary component to hearing loss: several hundred genes may be involved, but we are only just beginning to understand which they are and what role they play.

Professor Karen Steel, working with Professor Steve Brown (currently director of the Medical Research Council Mammalian Genetics Unit), identified the first mouse gene involved in deafness, *Myo7a*, in 1995. It is one of many genes she has worked on that have also been found to underlie deafness in human. Since 2003, Professor Steel has worked at the Wellcome Trust Sanger Institute, studying mice with single-gene mutations that have caused loss of hearing. Her team examines what has changed in these mice by measuring the function of the cochlea and other hearing structures in the ear and brain.

This year, Professor Steel was awarded the Brain Prize, sharing it with French scientist Professor Christine Petit for their contributions to our understanding of the ear and the causes of inherited deafness. The €1 million prize is given each year by a Danish charity, the Grete Lundbeck European Brain Research Foundation, and Queen Margrethe II of Denmark presented the awards at a ceremony in Copenhagen in May 2012.

In September 2012, research published in *Nature* described how scientists led by Dr Marcelo Rivolta at the Centre for Stem Cell Biology, University of Sheffield, used a form of stem cell therapy to restore hearing in deaf gerbils.

The study, funded by Action on Hearing Loss, Deafness Research UK, the Wellcome Trust, the Medical Research Council and the Royal Society, was the first time stem cells had been differentiated into the necessary types of progenitor cell and successfully transplanted into animals. Their hearing improved within weeks.

The gerbils' deafness was the result of damage to the nerves that carry signals from the ear to the brain. This is a model of auditory neuropathy, a human condition that accounts for up to 15 per cent of people with profound hearing loss. Unlike deafness caused by the loss of sound-detecting hair cells in the inner ear, auditory neuropathy cannot be helped by cochlear implants. So this stem cell therapy may have the potential to repair damaged hearing in humans, although it will be many years until such a treatment is ready.

A growing body of research in genetics, neuroscience, stem cells and other fields of science has expanded our understanding of hearing and deafness, suggesting new ways to help people who lose their hearing, whether from birth or later in life.

Professor Karen Steel. *Wellcome Images*

Brains: The mind as matter

Over 100 000 people came to see *Brains: The mind as matter*, which ran from 29 March to 17 June 2012 at Wellcome Collection. The exhibition explored human attempts to unravel the mysteries incorporated in the organ that governs our body, mind and soul.

Famous and infamous brain specimens – including those of Albert Einstein, Charles Babbage and William Burke – were on display alongside works by contemporary artists offering personal responses to the physical form and matter of the brain, and reflections on its nature and meaning from famous thinkers.

The exhibition's aim was to explore what we have done to the brain in the name of medicine, science and culture, as opposed to what it does for us. Exhibits explored historical concepts such as phrenology – the idea that the shape of the skull reflected a person's brain and therefore their character – and trepanning, drilling holes in the skull to relieve pressure on the brain. There were anatomical models of the brain and a film of a modern brain dissection.

Brains garnered five-star reviews and glowing plaudits. *Time Out* called it a "must-see"; *Metro* said that "much of it [was] jaw-dropping…some of it breathtaking". The *New Statesman*, *Guardian* and *New Scientist* called the exhibition "incredibly moving", "exquisite" and "compelling" respectively. Hundreds of articles appeared online across the world, and there was extensive international broadcast coverage.

A free online game exploring the brain's structure was launched on the Wellcome Collection website to complement the *Brains* exhibition. Developed by BAFTA-winning games studio Preloaded, *Axon* set players the task of making as many of the brain's 100 trillion connections as they could by clicking on protein targets. It was played over 4 million times in its first three months and continues to attract gamers.

A wide programme of events accompanied the exhibition, including *Mind Over Matter*, a ground-breaking show at Shoreditch Town Hall featuring photographs and audio narratives from 12 people who had elected to donate their brains after death for research. At Wellcome Collection, visitors could watch 'Brains on Film', a programme of short films and features, including the classic B-movie *Donovan's Brain*, and a series of 'Brain Matters' talks explored the impact of how we understand the brain on issues of identity and ethics.

"

Brains goes beyond just a visual feast, and quietly adds to the sense of gravitas with which we approach our most mysterious organ."

Claire Ramtuhul, *New Statesman*

From left:

A still from the 'Dissecting Brains' film shown at Wellcome Collection. *Martha Henson*

A zebrafish. *Wellcome Images*

Symptoms of psychological distress have been linked to lower life expectancy. *Fancy Photography/Veer*

Professor Daniel Pick. *Matchbox Video*

High-resolution brain activity

A technique for measuring the activity of thousands of individual brain cells simultaneously was reported in *Nature* in May 2012. Dr Misha Ahrens, a Sir Henry Wellcome Postdoctoral Fellow based at Harvard University and the University of Cambridge, developed the technique with colleagues and used it to study the role of different cells when a zebrafish adapts its movement in response to external stimuli. The findings offer an insight into how human brains might work when we adapt our movements to cope with a change in conditions, such as walking on a slippery surface.

Zebrafish are naturally transparent during the larval stage of development, so the researchers introduced a protein that fluoresces if a brain cell is active. Using a laser-scanning microscope, they could see which cells were active, looking at up to 2000 cells at the same time. The zebrafish were paralysed but given visual feedback corresponding to how their brains thought they were swimming. While neural activity can be studied in other animals, such as rats, their brains are larger – and not transparent – so only a small number of brain cells can be observed. The zebrafish model creates new opportunities for studying complete brain circuits.

Mental health and life expectancy

A link between mental health and life expectancy has been found in research led by Wellcome Trust Fellow Dr David Batty. The study, published in the *British Medical Journal* in July 2012, analysed ten years of data from the Health Survey for England, covering more than 68 000 individuals. It showed that people with symptoms of psychological distress were about 20 per cent more likely to die over a given period than people of the same age and sex who reported no such symptoms. There was an effect even when the distress symptoms were relatively mild, but it became more marked as the severity increased.

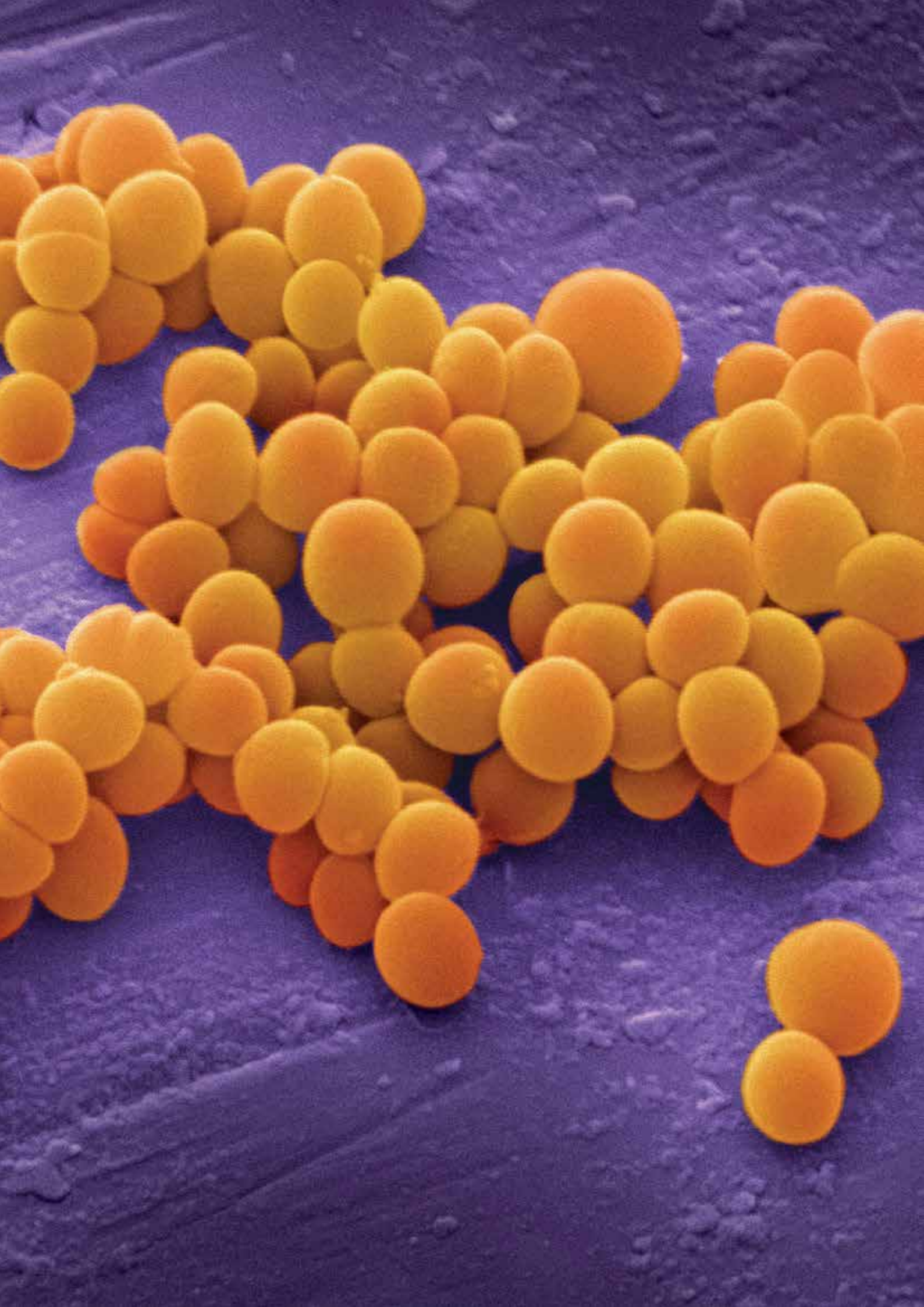
The mechanism underlying this relationship between mental health and life expectancy is not clear. It is possible that even mild mental health problems produce biological changes in the body that increase the risk of certain diseases, such as heart disease. More research will be needed to see whether treating mild mental health problems reduces these risks.

Analysing the Nazi mind

The Allied Forces' deployment of psychological techniques in World War II is not widely appreciated. However, the British and Americans made extensive use of psychoanalysis and psychiatry to probe the Nazi state of mind as part of an urgent mission to understand more about the enemy.

Professor Daniel Pick of Birkbeck, University of London, was supported by the Wellcome Trust to investigate this episode of history, leading to the publication this year of *The Pursuit of the Nazi Mind: Hitler, Hess and the analysts*. The book includes discussion of the British Army's attempts to understand the behaviour and mental state of the Deputy Führer, Rudolf Hess, who was captured in Scotland in 1941.

Professor Pick believes that many of the psychological themes examined during the War are still relevant today, despite the very different context.



Rapid whole-genome sequencing could be used to identify infectious outbreaks earlier, potentially ending them more quickly.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major public health problem, with people often becoming infected while in hospital for other reasons. Its antibiotic resistance makes MRSA slower and more expensive to treat than other infections. Genome sequencing could help to reduce the spread of MRSA by identifying outbreaks more quickly, and by helping to understand how an outbreak is being transmitted and how it can be effectively controlled.

To test this approach, researchers at the Wellcome Trust Sanger Institute, the University of Cambridge and biotechnology company Illumina used whole-genome-sequencing techniques to retrospectively analyse an outbreak of MRSA in a Cambridge hospital. They obtained samples and sequenced them as if the outbreak were happening right then, in real time. The project was supported by the Wellcome Trust and other funders, including the UK Clinical Research Collaboration, which itself is Trust-funded.

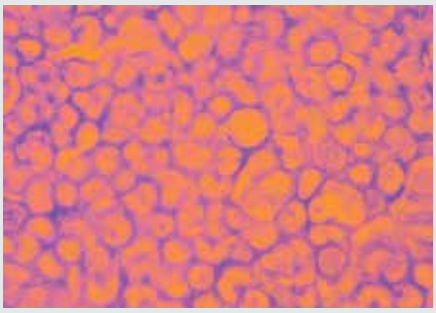
The researchers showed that, unlike current laboratory techniques, sequencing technology could distinguish between people whose MRSA infection was part of the larger outbreak and those who had been infected by an unrelated strain. This is critical because it can help to identify how a specific strain is spreading between people. They also found that they could have identified the outbreak at an earlier stage than current clinical testing – an advantage that could have helped to end the outbreak sooner.

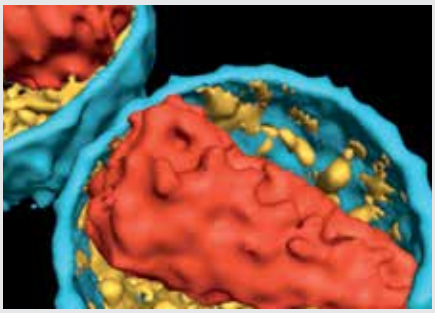
In addition, the team was able to compare the genome of the outbreak MRSA strain with MRSA genes that are known to confer resistance to antibiotics. This would have allowed them to say which antibiotics were most likely to work in treating the infection during the outbreak. As well as guiding treatment for individual patients, this sort of analysis – published in the *New England Journal of Medicine* in June 2012 – could help to discover new mechanisms of drug resistance as they evolve in the bacteria.

The approach was verified when the infection control team at another hospital in Cambridge identified 12 patients with MRSA infections. Sequencing demonstrated that the bacteria in all 12 cases were closely related and that this was an outbreak. It also revealed that the outbreak covered more than twice as many people as previously realised.

While this work was still underway, a new case was identified in a different unit of the hospital. Despite there being no apparent links between the previous patients and this unit, sequencing showed that this case was also part of the outbreak. Hospital workers were screened and one was found to be carrying MRSA. Again, sequencing confirmed the bacteria were related to those in the outbreak. The member of staff was treated, preventing further transmission of the infection. This episode, described in the *Lancet* in November 2012, clearly shows the potential of advanced genome sequencing to identify and control infectious outbreaks more effectively than is currently possible.

Methicillin-resistant *Staphylococcus aureus* bacteria.
Annie Cavanagh/Wellcome Images





Flu severity depends on host genes too

People who have a particular variant of a gene called *IFITM3* are significantly more likely to require a stay in hospital when they get influenza. The finding, reported in *Nature* in March 2012, helps explain why flu can be life-threatening for some people but has only mild effects in others.

A team of scientists at the Wellcome Trust Sanger Institute led work on the *IFITM3* gene after it was implicated in mechanisms of resistance to influenza A and other viruses. They discovered that disrupting the gene in mice led to more serious and prolonged illness in response to relatively mild strains of influenza. In humans, the researchers found that some patients admitted to hospital in 2009–10 – with either seasonal flu or the pandemic H5N1 strain – had rare variant forms of *IFITM3* that made them more susceptible.

Knowing more about the interactions between viruses and the human immune system will help us prevent infections in the future.

Vitamin D and TB

South Africa has the third-highest burden of tuberculosis (TB) in the world, and infection rates are highest in Cape Town, where there are greater seasonal variations in people's vitamin D levels than in other parts of the country. In a paper published in *Proceedings of the National Academy of Sciences* in November 2011, Wellcome Trust Senior Research Fellow Professor Robert Wilkinson and colleagues showed that black people in Cape Town were about five times more likely to be infected with TB if they had low levels of vitamin D. The number of new TB cases in Cape Town is highest in the months following winter and lowest after summer, suggesting that low vitamin D levels are directly responsible for the increased susceptibility.

In a paper published in the same journal in September 2012, Professor Wilkinson and colleagues also described how giving vitamin D supplements to people with TB affected the response of their immune systems to the infection. Overall, vitamin D reduced the time it took for inflammation to clear, suggesting it might be a useful addition to standard TB treatments.

Key to HIV infection

Scientists have found the 'key' that HIV uses to enter the nucleus of an infected cell and integrate itself into the cell's DNA. This is how HIV replicates and spreads through the body, but how it passes through the nuclear pore complex – a gateway into the nucleus – has been unclear. In December 2011, a team led by Professor Greg Towers, a Wellcome Trust Senior Research Fellow, published research showing that a specific part of the virus called the capsid protein binds to a component of the nuclear pore complex, opening the gateway and letting HIV in.

The finding provides a potential new target for drugs to combat HIV infection. HIV evolves rapidly and so it quickly develops resistance to drugs that target the virus itself. Treatments targeting the human nuclear pore complex – in effect, changing the locks – might be harder for the virus to beat.

From left:

Influenza B virus particles. *R Dourmashkin/Wellcome Images*

Cape Town. *Joseph Ferris III on Flickr*

Internal structure of HIV, showing the capsid protein in red. *Stephen Fuller/Wellcome Images*

Work at the Shoklo Malaria Research Unit in Mae Sot, Thailand. *Mads Monsen*

“

Malaria already kills hundreds of thousands of people a year – if our drugs become ineffective, this figure will rise dramatically.”

Professor François Nosten, Shoklo Malaria Research Unit

Antimalarial resistance

The spectre of untreatable malaria loomed this year as researchers published evidence that resistance to artemisinin, the recommended treatment, has spread across Thailand.

Over the last two decades, clinical trials by researchers at the Wellcome Trust Major Overseas Programmes in Thailand and Vietnam have shown that therapies based on artemisinin, an ancient Chinese herbal remedy for fevers, are more effective than other antimalarials. As a result, in 2006 the World Health Organization recommended artemisinin-based combination therapies (ACTs) as first-line treatments for the most deadly species of malaria parasite, *Plasmodium falciparum*.

In 2009, there were unsettling reports that artemisinin-resistant malaria parasites had emerged in western Cambodia, near the southern border of Thailand. Researchers at the Trust’s Thailand Programme had hoped it would be possible to prevent the spread of resistance by eliminating *P. falciparum* from that region. But a study published in the *Lancet* in April 2012 suggests that, while that approach may well help, containing the spread of resistance will be harder than originally thought.

And, 800 km away on Thailand’s northern broder with Myanmar, researchers at the Trust’s Shoklo Malaria Research Unit have also reported cases of resistance to artemisinin. They found that the average time it took ACT to clear parasites from patients’ bloodstream had increased between 2001 and 2010. This rise in cases of slow-clearing infections is a clear sign that the drugs are becoming less effective.

In another study published on the same day in *Science*, in collaboration with scientists at the Texas Biomedical Research Institute, San Antonio, the same researchers provided compelling evidence that the decline in the parasite clearance rates was due to genetic changes in a region on chromosome 13 of the *P. falciparum* genome.

Fears about resistance to ACT have been fuelled by the findings of another study, by Trust-funded researchers who have been examining the ingredients of antimalarials on sale in Africa. In January 2012, they reported in *Malaria Journal* that some of those medicines contained active pharmaceutical ingredients that would not cure malaria but could cause serious side-effects. Others contained small amounts of artemisinin derivatives – enough to pass simple authenticity tests but not enough to rid the body of malaria parasites, creating ideal circumstances for the parasite to develop resistance to the drug.

The research confirms that we are in a race against time to prevent the spread of drug-resistant malaria. Urgent coordinated action by scientists, medics, public health organisations and policy makers is needed to prevent one of the world’s major killers from becoming much more dangerous.

We are beginning to realise the potential of stem cells for use in therapies, as recognised by the 2012 Nobel Prize in Physiology or Medicine, shared by Sir John Gurdon and Shinya Yamanaka.

In August 2012, the Wellcome Trust and the Medical Research Council announced a new institute for stem cell biology and medicine at the University of Cambridge. The £8 million centre will build on existing investment by the two funders in stem cell research, uniting 25 leading research teams working across the three main types of stem cell: embryonic, adult and induced pluripotent cells. The teams' work will advance our understanding of the roles stem cells play in our bodies and their potential to treat a range of life-threatening conditions.

It was 50 years ago that Professor Sir John Gurdon first proved that mature, specialised cells could be reprogrammed to become immature cells capable of developing into all tissues of the body. This achievement was recognised in October 2012, when it was announced that he had won the Nobel Prize in Physiology or Medicine would. Sir John, also a former Wellcome Trust Governor, shared the Prize with Professor Shinya Yamanaka, who transformed skin cells back into stem cells using genetic engineering. This work, published in 2006, opened the way to using a patient's own tissue to create stem cells that can be used to replace damaged or faulty cells. For example, in October 2011, researchers used human induced pluripotent stem cells to correct a gene mutation responsible for a type of liver disease (see page 21).

As well as innovative forms of treatment, stem cells offer us new ways to understand the basic biology of disease. In February 2012, scientists at the Wellcome Trust/Cancer Research UK Gurdon Institute – named in honour of Sir John – took donated skin cells, reprogrammed them into stem cells and used them to generate large numbers of nerve cells that behave just like the cells in the human brain. These populations of nerve cells are being used to model the progression of Alzheimer's disease and could also be used to test potential new treatments for the disease when they are in the early stages of development.

The UK is recognised as one of the best places in the world for stem cell research and the new Wellcome Trust–MRC Cambridge Stem Cell Institute is intended to make sure that this continues, attracting the best international researchers in stem cell biology and regenerative medicine.

Professor Sir John Gurdon. *Wellcome Images*

From left:

UK Biobank gives a picture of health and disease across the British population. *Ocean Photography/Veer*

A fibroblast, involved in wound healing. *Matthew Daniels, University of Oxford/Wellcome Images*

Respiration monitor. *Covidien plc*

Richard Tyrone Jones holding a model heart. *Andrew Crowe*

UK Biobank opens

After spending six years amassing a unique repository of health information and samples from 500 000 volunteers, UK Biobank opened to researchers on 30 March 2012. Funded by the UK Department of Health, the Medical Research Council, the Scottish Government and the Wellcome Trust, and based in Stockport, UK Biobank is a valuable scientific resource. Studies using data from people's biological samples, medical histories and lifestyle questionnaires will help to unravel genetic and environmental contributions to the development of many diseases.

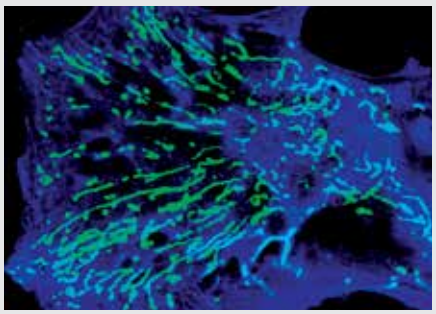
Half a million volunteers aged between 40 and 69 were recruited from Scotland, England and Wales over four years from 2006. They were invited to assessment centres, where they completed a questionnaire and were interviewed about their lifestyle, medical history and diet. Memory, early life factors and psychosocial events, such as how often people see family and friends, were also recorded.

Researchers took measures of height, weight, body fat, hand grip strength, bone density, lung function and blood pressure. Blood and urine samples were also taken and preserved so that it will later be possible to extract DNA and measure other biologically important substances. The final 100 000 participants to be recruited also had hearing, fitness and eye tests. As a result of this initial data collection phase, UK Biobank now holds more than 1000 separate pieces of information on each of its 500 000 volunteers. They include 26 000 people with diabetes and 50 000 with joint disorders, 41 000 teetotallers and 11 000 survivors of heart attacks.

This information will grow as the participants' stored samples are analysed and their health is followed over the next 25 years. In this time, all changes in their health, medical tests, drug prescriptions and deaths will be added to the database, taking advantage of the UK's centralised NHS and electronic records such as cancer and death registries.

Researchers can now able to apply to use the database. They are not given access to the volunteers, who will remain strictly anonymous; only information that does not identify participants is provided to researchers. Scientists from the UK and overseas, from academia and industry, will be able to use the resource to find out why some people develop particular conditions and others do not, paving the way for new ways to prevent and treat diseases.

> "Even if I can't benefit from the results personally, I know my children, my children's children and perfect strangers will."
>
> **Barbara Collins, a UK Biobank volunteer from London**



Helping wounds heal

Recovering from an injury, illness or surgery involves the repairing of damaged tissue. In October 2011, researchers at the University of Bristol and the Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester described how cells detect and respond to tissue damage, which could open up new opportunities for improving the healing of wounds.

When blood vessels are broken, plasma leaks out of them and causes fibroblast cells to migrate to the damaged tissue, where they make the wound contract and plug it with collagen and other structural molecules. Every step of the healing process requires cells to repeatedly stick to and unstick from other cells. Using atomic force microscopy, the scientists revealed the signalling pathway that controls the 'stickiness' of fibroblasts in response to changes outside the cells. Blocking these signals stopped tissue from repairing properly, suggesting that modulating them with drugs or other therapies could help to improve the way our wounds heal.

Monitoring respiration

In 2003, the Wellcome Trust and the Scottish Government invested £1 million in CardioDigital Ltd, a Scottish company developing electronic medical devices. The company had found that a pulse oximeter – a sensor placed on a patient's finger to measure oxygen levels in the blood – could be used to measure breathing rate as well.

The Trust supplemented the funding in 2005 and 2006, as CardioDigital developed software that could turn pulse oximeter data into accurate clinical information about respiration. CardioDigital's assets were acquired in 2008 by Covidien plc, a leading global healthcare products company, which integrated the respiration rate software with its own leading pulse oximetry products.

In March 2012, Covidien announced that the technology had received regulatory appproval to be used in the USA and the European Economic Area. The sensor can make several measurements simultaneously, freeing clinicians from having to count the rise and fall of a patient's chest to measure breathing rate. The system also provides data about trends, to help clinicians detect and respond to dangerous respiratory events more quickly.

Living with heart failure

'Richard Tyrone Jones's Big Heart' is a solo show of poetry and comedy all based around the fact that, at the age of just 30, Jones found out he had heart failure. Funded through a Wellcome Trust People Award, the show covers the poet's attempts to educate himself and others on the body's 'engine room'. He discusses how and why he was diagnosed with the condition at such a young age, and talks about the experience of his heart stopping for four seconds.

Jones performed the show at the Edinburgh Fringe Festival, Liverpool's Dadafest and around the UK in autumn 2012. It was both poetic and scientifically accurate, while maintaining a sense of humour throughout. It even included a biomedical cover of Tom Lehrer's 'The Elements' song, using 48 tongue-twisting genetic conditions.

Not only is the global population continuing to increase, but also the way we live is changing, which could have a considerable effect on our health.

More than half the world's population now lives in cities or other urban environments. This is mostly driven by migration – people want to live where there are jobs, resources and other opportunities. But moving to the city brings pressures on the way we live, which can significantly affect our health.

In 2005, the Wellcome Trust-funded Indian Migration Study began recruiting workers in four urban factories who had moved to the city from the countryside and still had a brother or sister living in their home village. The factories were in four different cities around India but the pairs of siblings were from 20 of the 29 states in the country, reflecting how far people are willing to move to find work. The researchers measured the nearly 7000 participants' cardiovascular risk factors, recorded whether they were obese or had diabetes, assessed their diet and levels of physical activity, determined their socioeconomic position, and performed several laboratory tests.

Initial results from the study, published in 2010, showed that migration to cities was associated with increases in obesity within ten years, which drove other changes that also raised the risk of cardiovascular disease. Further analysis in 2011 showed that the urban environment might affect the way a gene called *FTO* contributed to the likelihood of obesity in India. The researchers' conclusion was that rural migrants rapidly adopt lifestyles that put them at the same risk of disease as the indigenous urban population.
The strength of the Indian Migration Study is that, by using pairs of siblings, it accounts as far as is feasible for confounding factors such as genetics or early life experiences. It reveals the likely impact of increasing migration on the health of individuals and the healthcare systems that support them.

More research from the Indian Migration Study was published this year, including a paper in *PLoS ONE* in October 2011 showing that the migrants quickly adapted to urban levels of physical activity. Rural men had the highest levels of physical activity, whereas those born in the city and those who moved there had similar but lower levels. The pattern was the same in women but with slightly lower levels of activity overall. Another paper, published in early 2012 in the *National Medical Journal of India*, looked at diet. The researchers were able to identify a number of specific foods that obese people ate more of than their normal-weight neighbours.

These studies may point the way towards methods of encouraging people to change their physical activity and food consumption, which would help to slow the rise in diabetes and obesity in Indian cities.

Indian city illustration. *Bret Syfert*

From left:

A gray wolf. *US Fish and Wildlife Service (Midwest Region) on Flickr*

Sir David Attenborough in conversation.

Leishmaniasis is moving into cities in Brazil. *Ocean Photography/Veer*

Artworks from the *Dekha Undekha* exhibition.

Modelling population change

Environmental changes can have profound effects on a species, influencing population numbers and physical characteristics – even the frequencies of certain genetic variants within the species. These effects can be documented when they occur, but it is difficult to predict what impact a specific change in environment will have because there are so many interacting variables.

Professor Tim Coulson of Imperial College London seeks to understand the consequences of environmental change on the characteristics of a whole population. In a Wellcome Trust-funded project, he used data from a population of wolves in Yellowstone National Park, Wyoming, to construct a model of environmental change. Changes in the depth of snow in winter, the availability of prey and the occurrence of disease, for example, can all affect the wolves' survival, reproduction, growth and even the colour of their coats. Information about all these variables has been rigorously recorded in Yellowstone since the wolves were reintroduced to the habitat in the mid-1990s.

In a paper published in *Science* in December 2011, Professor Coulson described a model that allows researchers to test how changes in environment would affect the size of the wolf population and, through changes to the gene pool, factors such as the frequency of black or grey coats over centuries. The model treats the population as a collection of individuals, each with many attributes. Distributions of these attributes can then be constructed that change over time according to their association with survival, development and reproduction. One interesting finding was that changes in the average value of an environmental factor had a greater impact across the population than increased variability in that factor. For example, an increase in the average temperature in Yellowstone would be more significant to the wolves than larger swings in temperature around the same annual average.

The wide range of population responses to environmental changes makes accurate prediction challenging. It may be that the best we can do with our current information and technology is to explore possible consequences of different scenarios of environmental change, using models such as this one. The framework used to develop the model can naturally be applied to any species, and Professor Coulson's colleagues have already begun applying it to insect and plant populations. Meanwhile, he is collaborating with a team at Stanford University, using data from the Framingham Heart Study, to apply the model to human populations. Such work means researchers will be able to start asking questions such as what the long-term effects on life expectancy might be if obesity rates continue to rise.

> "The biggest impact I've seen on human health is slums…Huge areas occupied by people living, whole families, in tiny little apartments with no sanitation – and no future."
>
> **Sir David Attenborough**

Man of the (natural) world

Environmental change can manifest itself in different ways in different parts of the globe, but the naturalist and broadcaster Sir David Attenborough, who has seen more of the globe than most people, is adamant that the major issues affect us all. These include the challenge of producing enough power to support the ever-increasing population and ensuring that everyone has access to clean water and sanitation to prevent the spread of infectious diseases.

Sir David says the fundamental source of the environmental problems we face is the rapid growth of the human population. In an interview filmed this year by the Wellcome Trust, he says that the number of people in the world has tripled in his lifetime and that many of our problems would be made more manageable if we could slow that rate of growth. But another critical aspect of solving these problems is to persuade politicians and the people who elect them that action is required. The Trust is expanding its activities in areas where health intersects with issues of the environment and nutrition, and a large part of this work will be to communicate the problems and the potential solutions.

Sex pheromones in the city

Before the 1980s, leishmaniasis was a rural disease in Brazil. A potentially fatal parasitic infection transmitted by female sand flies, it was a risk for people in the countryside, particularly the forests. But as people have migrated to the cities, so the disease has followed. For example, there is evidence that leishmaniasis is spreading from the south-west state of Mato Grosso do Sul, moving along the highways towards the east, threatening in particular São Paolo, the largest city in the southern hemisphere and the seventh most populous city in the world. Another factor in the spread of the disease is the environmental degradation of the forests, which has led to the insects that carry the parasite becoming the dominant species in their habitats.

This year, field trials of a new approach to controlling sand flies began in Brazil with the support of a Wellcome Trust Translation Award. The project uses a combination of a synthetic sand-fly sex pheromone and a pesticide to lure and then kill female sand flies. The scientists hope to demonstrate that this strategy can reduce the transmission of leishmaniasis to humans.

Art and health in the slums

In February 2012, an ambitious art exhibition funded by the Wellcome Trust opened in Dharavi, one of the most disadvantaged areas of Mumbai. *Dekha Undekha* (Seen Unseen) brought together residents, artists and health professionals to express concerns affecting many of Dharavi's million inhabitants. Together, they explored issues such as sanitation, personal hygiene, domestic violence, maternal health and superstitions.

The project aimed to help local residents develop skills in photography, ceramics and textile art, and discuss urban health issues more openly – informed by input from health experts. Through a series of workshops over a year, participants created a joint exhibition at a Dharavi primary school, including cushions reflecting female health conditions, a street play on safe sex, and dreams moulded on ceramic slippers. These activities brought visitors into the urban slum and encouraged them to engage with the reality of the residents' lives.

We are indebted to the researchers and experts who give up their time to sit on our advisory committees or review our grant applications.

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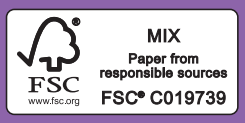

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