The best *research* for better *health*

Highlights of the Wellcome Trust's work in 2012/13, including our support for people to make discoveries and innovations and to promote better health for individuals and society.

wellcome trust

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As at December 2013

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As at December 2013

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 2012–30 September 2013.

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An overview of some of our activities in 2012/13, from research successes and public engagement campaigns to the grants we have awarded and the performance of our investments.

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Infectious genomics
Three teams are using genomic techniques to analyse pathogens, understand outbreaks and inform treatment of infectious diseases.

Codebreakers
Over a million pages of documents from the history of genetics have been digitised and made freely available online.

Our survey said...
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Cancer genetics
Signature patterns of genetic mutation are revealing the specific biological processes that cause cancer.

Wonder season
A month-long season of engaging public events and activities celebrated the wonders of the brain.

Cutting-edge imaging
A new imaging system integrates information from an array of sources to guide epilepsy surgery more safely and accurately.

Combating coronavirus
Researchers are analysing a new, deadly respiratory disease that has appeared in the Middle East.

Death on show
A Wellcome Collection exhibition explored the complex and contradictory subject of death.

Sustaining health
A new funding scheme supports research into the connections between the changing environment and our future health.

Funding and achievements

922
Total grants awarded

30
Countries receiving funding

535 487
Wellcome Collection visits

154
Fellowships awarded or renewed

£218m
Venture capital finance secured by grantholders for commercialisation of R&D

4711
Scientific research papers associated with the Wellcome Trust
(Published in calendar year 2012, indexed on PubMed and in Thomson Reuters databases)

The Trust brings people together, enabling collaboration, excellent research and, ultimately, better health."

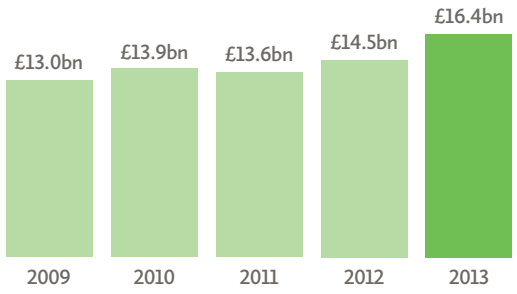
Sir William Castell, Chairman of the Wellcome Trust

Key financials at a glance

Investment assets net of bond liabilities

£16.4bn

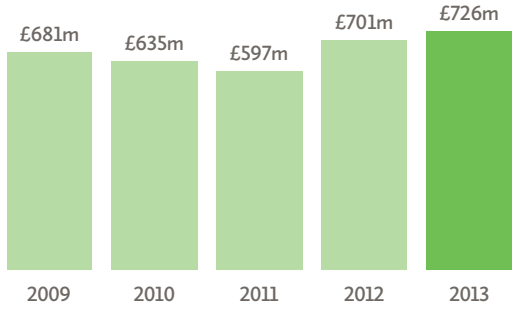
As at 30 September.



Total grant funding and direct charitable activities

£726m

For the year ended 30 September.



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 2012/13, we were pleased that our investment portfolio recorded a total return of 18%.

We have returned a total of 35% (annualised 10%) over three years and 153% (annualised 10%) over ten years to September 2013. 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.

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

The Wellcome Trust's new Director introduces this year's *Annual Review* and looks forward to the opportunities ahead.

Past, present and future

It is a privilege and honour to lead one of the world's outstanding philanthropic institutions, which has contributed so much to science, medicine and society, *writes Jeremy Farrar.*

When I entered the Wellcome Trust's headquarters in London as Director for the first time on 1 October 2013, I felt humbled and inspired. As I've begun to settle in to the role, drawing on the expertise and enthusiasm of my colleagues inside the Trust and listening to the ideas of those in the wider research community, those feelings have only got stronger. I thought I knew a lot about the Trust, having being funded by it for almost 20 years, but the scale of what we are supporting, catalysing and leading is breathtaking. You get a sense of that from reading this year's *Annual Review*, but even these tremendous stories from the past year represent just a fraction of what we do.

The Trust played a vital role in my career as a scientist. It provided generous and flexible support without which it would have been impossible to establish and sustain the South-east Asia Major Overseas Programme as a world-class centre for infectious disease research. But the team in Vietnam was only ever one of thousands of research groups and individuals supported by the Trust and its staff, whose work collectively really does change lives for the better.

One of the Trust's great strengths is its independence – we have the freedom to fund anyone we think can improve our understanding of health, disease and medicine. But being independent does not mean working alone. On the contrary: everything we achieve is through partnerships, whether within the research community or with the public. I want people to know that if they come to us with a great idea, whether it is in basic biology, applied research, medical humanities or science communication, we will listen. We are ready to be creative, to take on the big challenges in medicine, and to take risks in our approach if it will catalyse innovation. I particularly want to encourage scientists at an early stage of their career to come and find out what the Trust can offer – by its nature, science is always changing, and who better than the next generation of researchers to identify, embrace and accelerate progress?

As we adapt to the future, it is important to remember our history, and I am extremely grateful to the Board of Governors for trusting me with Sir Henry Wellcome's legacy. I am also grateful to Sir Mark Walport for doing so much to build the Trust's impact and influence over the past decade, and to Ted Bianco and the Executive Board for running the Trust so positively in the interim period.

The Wellcome Trust is an extraordinary, fun and inspiring place with a strong ethos and mission. I very much look forward to working with my colleagues to build on our success in the years to come.

Dr Jeremy Farrar
Director of the Wellcome Trust
December 2013

A still from *Where birds dance their last*, a film made by artist Lêna Bùi while based at the Wellcome Trust's Major Overseas Programme in Vietnam, as one of six Art in Global Health residencies. She explored zoonosis research and travelled to a number of rural areas to examine the human–animal interface. *Lêna Bùi*

The best we can be

There is a team at the heart of every story in our *Annual Review*, working in diverse fields from basic biology to medical technology to public engagement with research, *writes Ted Bianco*. But they are all united by a common goal: to do the best work possible to promote better health for all of us.

Metabolic imbalance – the breakdown of the biological processes that control how our bodies get and use energy from our diet – can lead to serious disorders such as obesity and diabetes. With the prevalence of obesity on the rise, we need a better understanding of metabolism and better treatments for when it falls out of balance. The Trust and the Medical Research Council (MRC) committed £24 million this year to bolster research at the Wellcome Trust–MRC Institute of Metabolic Science in Cambridge, which aims to provide both understanding and treatments.

Professor Stephen O'Rahilly, a Wellcome Trust Senior Investigator and Co-Director of the Institute of Metabolic Science, was awarded a knighthood this summer for services to medical research. He said that the honour was more about the researchers he had worked with over more than 20 years than about himself. It was a modest response, but one that most scientists would recognise because the best research today typically demands skills and experiences beyond the reach of any individual.

As you might expect, therefore, the Institute draws on many areas of biomedical research, including genetics, molecular biology, epidemiology, nutrition and behaviour science. But it also has dedicated space for NHS clinics where doctors, many of them also clinical researchers in the Institute, treat people who have metabolic disorders. Whether you see it as bringing patients into the lab or scientists into the clinic, this confluence is fundamental to the ethos of the Institute. It recognises that there is a vital interplay between researchers, patients and the people who care for them.

There is a team at the heart of every story in our *Annual Review*. Many are international and multidisciplinary. Some, as at the Institute of Metabolic Science, involve patients in research. But all these teams share a common goal: everyone we fund is united by a desire to make something, or someone, better, whether that means a better understanding of the world, our bodies and our minds, or better treatments and strategies to maintain and improve our health.

Healthy environments

Metabolism lies at the interface of the body and the environment. Scale up a level and you can start to consider the way human societies interact with the environment and how this affects us. Growing populations, particularly in cities, coupled with climate change and other environmental factors, will have an enormous effect on our health in the future. We will have to change our behaviour in order to adapt, collectively and individually, but which changes will help and which might harm?

> Working together, we strive to be the best we can be, motivated by our common goal of supporting the best research for better health."

We need evidence. Research in many relevant fields is at a distinctly early stage of development, so how can the Wellcome Trust best support research to bolster the evidence base on health and the environment? This year we launched a scheme, Sustaining Health, that will support pilot studies to assess the existing evidence, determine the kinds of questions we need to start asking, and kick-start research projects that we hope will yield useful answers. What we already know is that these are challenges that will require teams working across national boundaries, across scientific disciplines, and across industry, academia and – crucially – the public.

Science is a social endeavour and a fundamental part of our lives. It can change our lives. As we know very well from the Trust's international activities in different societies around the world, understanding the context is vital for engaging the public with research. However, we do all need to be able to engage with science, to celebrate it and to question it.

At the Trust, we delight in bringing scientists and the public together. When the British Neuroscience Association (BNA) asked us for help with public engagement at their 2013 conference, for example, we leapt at the chance. Working with the BNA and their venue, the Barbican Centre in London, we assembled a season of events and activities to fill the halls in the weeks leading up to the conference and all the while it was on. 'Wonder: Art and science on the brain' brought the public into the same space as the researchers and, in turn, it gave the neuroscientists access to people eager to learn about their work and ask thought-provoking questions about brains. It was an inspiring example of public engagement.

Change at the top

In March 2013, we bade farewell to Sir Mark Walport, Director of the Wellcome Trust for ten years, as he set off to become the UK government's Chief Scientific Adviser. Before Dr Jeremy Farrar arrived in October to lead the Trust in the next phase of its journey, it was my honour to serve as interim Director.

Those six months taught me a great deal about the Trust. I was left with more than an admiration for the many talented and conscientious colleagues with whom I have the privilege to work. I was reminded, above all, about the importance of teams. Teamwork can harness the value of each individual, yet be enriched by the diversity of backgrounds and outlook that all of us bring. The Wellcome Trust is a team that has to integrate many different functions: supporting our grantholders in basic and applied biomedical research, the medical humanities and public engagement; making shrewd investments to sustain the resources available to provide that support; and running the whole operation effectively and efficiently to keep everything on track.

Working together, we strive to be the best we can be, motivated by our common goal of supporting the best research for better health.

Dr Ted Bianco
Director of Technology Transfer at the Wellcome Trust
December 2013

The Institute of Metabolic Science is leading efforts to understand and tackle obesity, diabetes and related diseases.

Almost a quarter of adults and one in five children in the UK are obese. This raises their risk of serious conditions such as type 2 diabetes, bone and joint problems, and cardiovascular, gastrointestinal and reproductive diseases. With levels of obesity set to rise ever higher over coming decades, the burden of these conditions on health services is predicted to increase.

In May 2013, the Wellcome Trust and the Medical Research Council (MRC) committed £24 million to the Wellcome Trust–MRC Institute of Metabolic Science in Cambridge. Led by Professor Sir Stephen O'Rahilly and Professor Nick Wareham, the Institute will focus its efforts on research, education, prevention and clinical care in the areas of obesity, diabetes and related diseases. Of the Trust's contribution, £10m has been earmarked for new clinical research facilities, to enhance the infrastructure supporting basic science, and to support joint working with the nearby Wellcome Trust Sanger Institute.

Two floors of the Institute of Metabolic Science house the University of Cambridge Metabolic Research Laboratories and the MRC Centre for Translational Research in Obesity and Related Metabolic Diseases, both directed by Professor O'Rahilly. Laboratory and clinical research is conducted on a range of metabolic and endocrine diseases. A further floor houses the MRC Epidemiology Unit, directed by Professor Wareham, where scientists study the causes of obesity and type 2 diabetes, and potential ways to prevent them.

Bringing doctors, laboratory and clinical scientists, and epidemiologists together will forge multidisciplinary links to aid research. Being located near to Cambridge Science Park – the largest concentration of biotechnology companies in Europe – also creates opportunities for collaboration with industry.

In addition to laboratory space, the Institute has purpose-built clinics that provide outpatient care for children and adults with metabolic and endocrine disorders. This close relationship with patients is an important part of the Institute's ethos and is intended to ensure that advances in basic science are relevant to patients' needs and can be rapidly applied to improve care and the prevention of disease.

This new investment reflects the quality of research already being done at Cambridge, and will boost its potential to help tackle one of this century's most worrying health trends.

Obesity is predicted to increase across the world.
Martin Parr/Magnum Photos

From left:

The Trust aims to develop new research leaders. *Alberto Ruggieri/Getty Images*

Construction work on the Francis Crick Institute. *Wellcome Images*

Killer T cells (dark) attacking a tumour cell. *JC Stinchcombe, laboratory of Prof. Gillian Griffiths, University of Cambridge/Wellcome Images*

The H3Africa project is supporting genomics research across Africa. *Sasha Andrews/Wellcome Images*

Leading research

Researchers' careers tend to follow a relatively linear path from PhD, through postdoctoral positions, lectureships and finally, in some cases, to senior managerial positions in research centres or institutes. Young scientists naturally focus on developing their research skills and publishing academic papers, often at the expense of building leadership skills.

As a result, senior researchers can find themselves thrust into prestigious positions with opportunities to shape the direction of science and influence the culture of the wider research community, but without any specific training to prepare them. In many cases, people excel in these roles, yet in the rapidly advancing world of biomedical research, it is becoming increasingly vital to hone skills such as the ability to develop and articulate a strategic vision, solve problems and lead others.

The Wellcome Trust's ten-year Strategic Plan made a commitment to developing outstanding individuals as a key part of support for scientists. The Trust's Research Leadership Development Programme, which began this year with the help of Monitor Deloitte, aims to enhance the leadership style, impact and resilience of researchers. The goal is to build the capabilities of people within research teams and institutional leadership, and to broaden the talent pool from which to recruit future research leaders.

The programme will put individuals in stimulating, unfamiliar environments in order to provoke new ways of thinking. The experience may lead to significant shifts in how they see the world, and to applying their new insights to important challenges. Through interactive discussions and activities with host partners from academia and industry, the programme will increase the participants' awareness of how to define and achieve their vision and to think strategically within biomedical science. It is designed to stretch perceptions of leadership and explore the challenges scientists face.

In its first year, the programme will focus on people who already hold senior positions, such as the directors of Wellcome Trust Centres and Major Overseas Programmes, as well as those who are considering a senior leadership position in academia, industry or a major research centre as their next career move.

There has already been considerable interest in the programme from within Trust-funded institutions. If successful, the scheme will continue and expand in scope, supporting a broader range of participants to increase their leadership skills for the benefit of the whole scientific community.

"What's exciting is working within a melting pot of young scientists… and bringing up their research capabilities to actually become the future research leaders, from wherever they come."

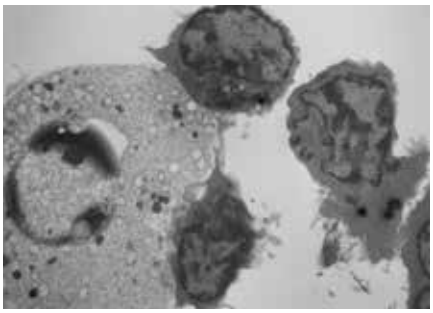
Professor Robert Heyderman, Director of the Wellcome Trust's Major Overseas Programme in Malawi

Crick and mortar

In June 2013, the construction of the Francis Crick Institute passed a significant point as the building reached its full height. A traditional 'topping out' ceremony was held alongside the unveiling of the Crick's strategy by its director, Sir Paul Nurse.

Sir Paul restated the Crick's ambition to become a leading interdisciplinary medical research institute, working to understand why diseases develop and finding new ways to prevent and treat illnesses such as cancer, heart disease and stroke, infections and dementia. He also named public engagement and translational research as top priorities in the years to come.

The new building is scheduled to open in 2015, when it will begin to welcome 1500 leading researchers and support staff. It will bring to fruition a landmark partnership between the Medical Research Council, Cancer Research UK, the Wellcome Trust, University College London, Imperial College London and King's College London.



Killer immune cells

Professor Michael Dustin was awarded a Wellcome Trust Principal Research Fellowship this year, facilitating his move from the New York University School of Medicine to the University of Oxford. Professor Dustin will be head of immunology at the Kennedy Institute, where research focuses on degenerative and inflammatory diseases.

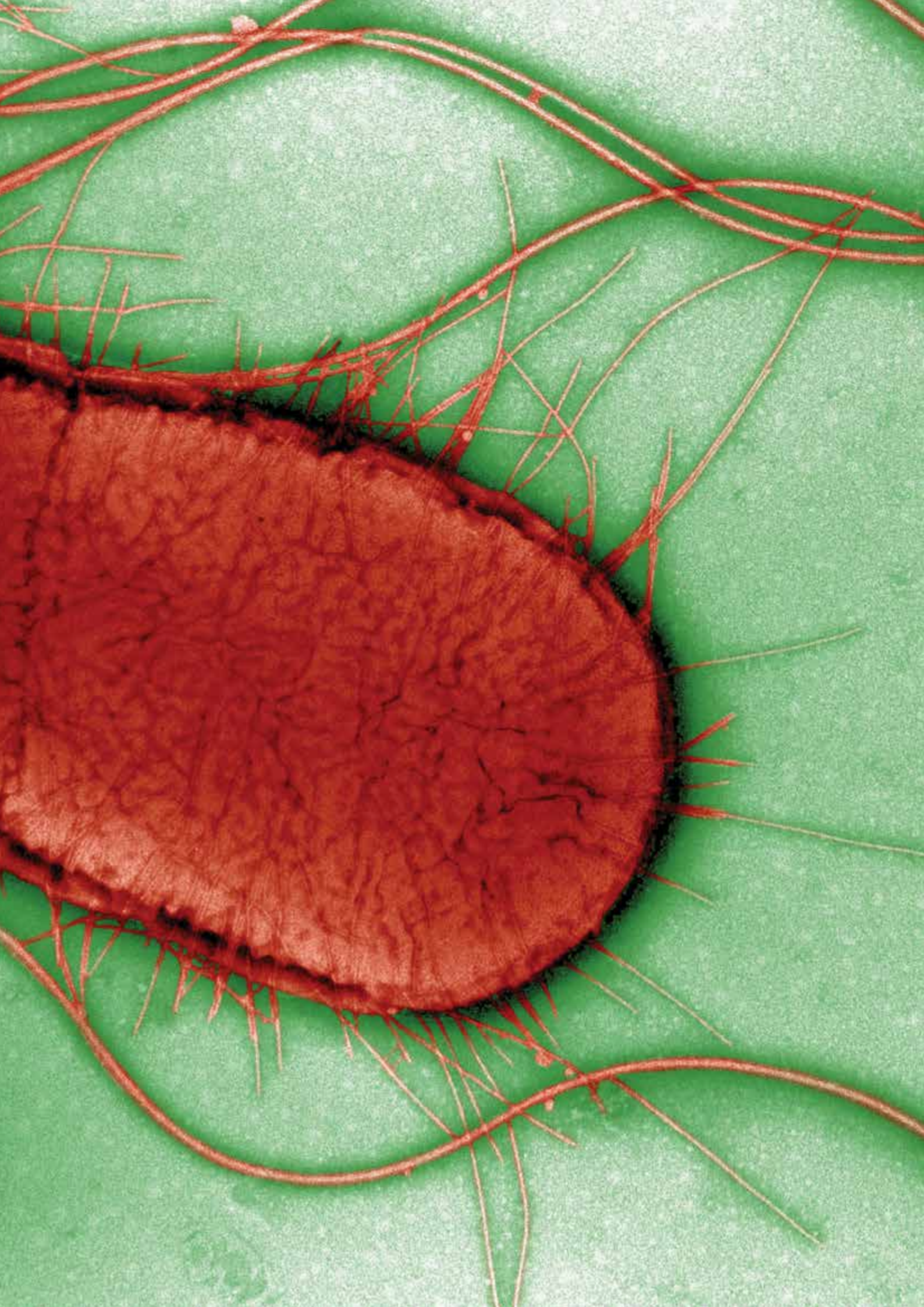
In New York, he investigated the 'immunological synapse', the interface between the attacking immune cells and their prey. The killer cells of the immune system identify their targets by detecting proteins on the membranes of cells harbouring viruses or bacteria. In autoimmune diseases, however, the killer cells mistakenly attack uninfected healthy cells.

Professor Dustin will recruit a team of biologists, engineers, mathematicians and medical scientists to exploit the latest high-throughput and bioinformatics technology. With their help, and the expertise in super-resolution microscopy at Oxford, he will continue his analysis of the immunological synapse, particularly its significance in the development of autoimmune diseases.

African genetics

The first projects to be funded through the Human Heredity and Health in Africa initiative (H3Africa) were announced in October 2012. Supported by the US National Institutes of Health and the Wellcome Trust, H3Africa aims to improve the health of people in Africa through genomic research. Among the first round of funded projects were genetic studies of rheumatic heart disease and type 2 diabetes.

This is the first funding scheme to support genomic studies in Africa. It will help to build research capacity across the continent in order to understand the local genetic and environmental causes of illness. H3Africa will help to develop expertise among African scientists, foster increased collaboration, enhance the infrastructure for genomics research in Africa, and contribute to training the next generation of African researchers in the use of contemporary genomic approaches for studying important health problems.



Researchers are working together to incorporate the latest genomic technology into the UK's response to infectious diseases.

In the UK, approximately 10 per cent of deaths and 4 per cent of hospital admissions are caused by infectious diseases. The Health Innovation Challenge Fund, which is supported equally by the Wellcome Trust and the UK's Department of Health, this year awarded a total of £11 million to three leading research groups to develop technologies that can help diagnose, monitor and control infections.

Professor Derrick Crook of the University of Oxford will lead a team using whole-genome sequencing to analyse disease-causing bacteria such as *Clostridium difficile*, *Staphylococcus aureus* and *Mycobacterium tuberculosis*. At regional centres in Oxford, Brighton, Leeds and Birmingham, thousands of clinical samples will be rapidly sequenced to determine the most important characteristics of the bacteria. The work will help to identify which species are involved, whether they have developed resistance to any antibiotics, and how patients can best be treated.

At the University of Cambridge, Professor Sharon Peacock will lead a complementary programme to further develop the use of whole-genome sequencing technology for important microbial threats. This work will help to support the active surveillance of infectious diseases, and to investigate outbreaks and respond to emergencies. The overall aim is to understand how to apply genomics to controlling infections at local, regional and national levels, and how to integrate this technology into practice. The team will study numerous bacteria, including species of *Salmonella*, *Shigella* and *E. coli*. As well as this, the project will provide an emergency response service to deal with outbreaks in the East of England.

Significant genomic variation is also seen in viruses; this determines how quickly they spread, the severity of illness they cause and their resistance to drugs. Professor Paul Kellam of University College London and the Wellcome Trust Sanger Institute will lead a team using whole-genome sequencing to identify virus genomes in clinical samples. They will develop the systems, facilities and capacity needed to routinely capture such viral genetic sequences, to monitor drug resistance and guide treatment, to identify the source of viral infections, and to track emerging epidemics. The project will target HIV, hepatitis C, norovirus, measles, influenza and other viruses.

All three initiatives involve collaborations between academic institutions, the private sector, the NHS and Public Health England (the Department of Health agency responsible for public health). The three teams will standardise their sequencing data and deposit it in a single online repository linked to national epidemiology databases. Working together, they will lay the foundations for a single, integrated national strategy for detecting, preventing and stopping these diseases, making a significant contribution to the nation's health.

Electron micrograph of *Escherichia coli*.
David Gregory and Debbie Marshall/Wellcome Images

From left:

Mosquito heads. *Derric Nimmo and Paul Eggleston/ Wellcome Images*

Dublin's new Clinical Research Facility already has many projects underway. *Wellcome Images*

A portable ventilator. *OneBreath, Inc.*

New research aims to treat the causes of Alzheimer's disease. *Anthea Sieveking/Wellcome Images*

Dengue drug

There are over 50 million cases of dengue fever every year; estimates range up to 390m. The disease, often referred to as breakbone fever, can have life-threatening complications and has become endemic in the tropics and subtropics. It is spreading rapidly and there are no treatments available.

As a result of Wellcome Trust funding, Professor Johan Neyts and colleagues, from the Rega Institute and the Centre for Drug Design and Discovery at KU Leuven in Belgium, have identified compounds that stop all four types of the dengue virus replicating.

In August 2013, Janssen Pharmaceuticals, Inc. entered into a research collaboration with the Trust and KU Leuven to further develop these compounds so they are suitable for clinical development. The involvement of a leading industry virology group will accelerate this work, aiming to produce the first drug for treating dengue fever.

Clinical support

Dublin gained a new Clinical Research Facility this year, thanks to a joint initiative between Trinity College Dublin and St James's Hospital, with funding from the Wellcome Trust and the Health Research Board of Ireland. The €7 million centre was opened in June 2013 by the Taoiseach, Enda Kenny.

The facility will support studies in biomedical research and experimental medicine, as well as clinical trials of potential new therapies. It has a research pharmacy that can safely prepare cancer drugs and handle innovative gene therapies and vaccines, and a neuropsychology suite that will enable high-quality studies of the brain. When the centre was officially opened, 25 research projects were already planned or underway, all seeking to bring the fruits of basic research to the hospital ward.

Breathing more easily

Respiratory illnesses such as influenza are a leading cause of death in low- and middle-income countries. Patients often need help breathing, but each year thousands die and many more suffer in rural community hospitals because of a lack of mechanical ventilators. The shortage in India alone is estimated to be over 1 million devices.

OneBreath, Inc., a Silicon Valley start-up company, has designed a new ventilator to solve this problem. It is precise, reliable and durable in harsh environments while also being affordable, portable and easy to repair. It is suitable for patients of all ages, from newborns to elderly people, and is easy to use by less skilled care-givers.

The Wellcome Trust has funded a collaboration between OneBreath and Vaatsalya, a company that operates in private hospitals across rural and suburban India, to undertake further testing and development of the ventilator. The aim is to ensure it is optimally designed for India's lower-income communities.

Battling dementia

Alzheimer's disease is the leading cause of dementia, affecting more than 400 000 people in the UK, a number that is expected to double by 2050. While there are a handful of drugs that can alleviate some of the symptoms, there is no effective treatment for this degenerative disease. People with Alzheimer's experience progressively worse confusion, aggression and memory loss, and live on average just seven years after they have been diagnosed.

Two hallmarks of Alzheimer's disease in the brain are 'plaques' and 'tangles', which are thought to be integral to the disease's development and progression. This means that finding ways to block the molecular pathways and proteins that contribute to the formation of plaques and tangles could lead to new drugs to treat or prevent the disease.

CoCo Therapeutics Ltd was formed in February 2013 to develop new drugs that target such a protein in the brain called retinoic acid receptor alpha (RARα). The company is building on research previously supported through the Wellcome Trust's Seeding Drug Discovery scheme. With this funding, Professor Jonathan Corcoran (now director of the Neuroscience Drug Discovery Unit, King's College London) identified a series of compounds that target RARα, and showed that these compounds can have an impact at several points of the Alzheimer's disease pathway. He also demonstrated that the compounds are safe and can reverse memory defects in disease models similar to the symptoms of Alzheimer's.

The company will now undertake preclinical evaluation of these compounds before testing them in patients. Should the next stages of development prove successful, drugs acting on RARα will be developed in an attempt to treat the causes of Alzheimer's, rather than just its symptoms.

The founding shareholders in CoCo Therapeutics are a venture capital firm called Advent Venture Partners, King's College and the Trust.

> "Our research has shown early promise in this area... This is an exciting step forward in the search for effective Alzheimer's disease treatments."
>
> **Professor Jonathan Corcoran, King's College London**

Over a million pages from the history of genetics have been digitised by the Codebreakers project.

Through the Wellcome Library website, researchers and curious minds across the world can now plot the story of DNA's discovery. Documents from the pioneering days of modern genetics have been collected together for the first time and made freely available in a £4 million digitisation project.

Codebreakers launched ahead of the 60th anniversary of Francis Crick and James Watson's seminal 1953 *Nature* paper that revealed the now-famous double helix structure of DNA. It holds the stories behind their discovery, told in more than a million pages of notes, letters, sketches, lectures, photographs and essays from the circle of brilliant minds that worked on solving the structure. Their work formed the cornerstone of much of today's biomedical research, from disease diagnosis to drug development.

Collected from the Wellcome Library's own holdings and five partner archives in the USA, London, Cambridge and Glasgow, the documents include notes by Crick, Watson, Maurice Wilkins, Rosalind Franklin and others. They are placed in the context of earlier research into the links between heredity and health, including the archives of the Eugenics Society, one of the most influential scientific organisations of the early 20th century.

The site permits access to the personal and professional thoughts, rivalries, blind alleys and breakthroughs of the scientists whose ideas transformed our understanding of life. Crick's preliminary sketches of the double helix and the pivotal X-ray diffraction 'photo 51' from Franklin's lab are obvious highlights, but there is huge value for historians and other researchers in being able to follow events through the scientists' own words. Content includes candid correspondence, keen professional insight and moving personal items, such as Peter Medawar's self-portraits, which he drew after suffering a stroke.

Codebreakers is the first phase of a major digitisation programme at the Wellcome Library that is bringing together books, archives, films, photographs and audio and placing them online. A further half-million pages have been added to Codebreakers since its launch in March 2013, and £5.8m has been set aside for the next phase of the Library's digitisation plans, which will focus on material relating to neurology and mental health.

wellcomelibrary.org/codebreakers

Maurice Wilkins shared a Nobel Prize for his work on the structure of DNA. *King's College London*

From left:

Understanding public attitudes to health and science is important for researchers and policy makers. *Helen Cathcart/Getty Images*

An exhibit from the *All About Me* gallery. *Eureka! museum*

Al-Zahrawi (Albucasis), an 11th-century Muslim physician, treating a patient. By Ernest Board. *Wellcome Library*

Wellcome Collection has embarked on a curious journey. *Wellcome Library*

Our survey said...

Conducted every three years, the Wellcome Trust Monitor is a survey designed to elicit reliable information about the UK's attitudes to health, biomedical research and science education. The results are made openly available as a resource for researchers and policy makers. The second wave of the survey was carried out for the Trust by Ipsos MORI and was published in May 2013.

A total of 1396 adults and 460 young people were asked about their attitudes, experience and knowledge relating to science and science education. For example, it was found that most people were comfortable with the terms 'DNA' and 'genetically modified', but half of the adults and young people had never heard of the phrase 'human genome'.

In general, the survey found that the public had a high level of interest in science: more than seven in ten adults and nearly six out of ten young people said they were interested in medical research. Despite this, understanding of how research is conducted was not strong, and levels of understanding were lower than in 2009. While two-thirds of adults and half of the young people recognised the concept of a controlled experiment in science, most could not articulate why this process is effective.

The Monitor also investigated topical issues, such as the widely reported rise in the use of certain drugs to improve concentration at work and in education. The survey found that only 2 per cent of adults and 1 per cent of young people said they had used cognitive enhancers, a result that challenges popular perceptions and emphasises the importance of collecting reliable data.

Another subject probed by the survey was the extent to which the public trust certain professions. Two-thirds of the adults trusted medical practitioners and university scientists to give them accurate information about medical research. This fell to just over one in ten for government departments and ministers. Journalists scored lowest on trustworthiness: only 8 per cent of adults trusted them to give accurate information about medical research, although this was an improvement on the 2009 figure of 4 per cent.

All the survey's datasets have been made publicly available free of charge through the UK Data Service to encourage and inform social science research, policy making and public engagement. Each successive wave of the survey will add to the longitudinal data so that public attitudes can be tracked as they evolve over time.

wellcome.ac.uk/monitor

> "Over 90 per cent of adults and young people think that medical research will lead to an improvement in the quality of life for people in the UK in the next 20 years."
>
> **Wellcome Trust Monitor report**

All about you

Eureka! is a fun, interactive children's museum and educational charity in Halifax, West Yorkshire. The museum, which emphasises the importance of play in learning, opened a new gallery this year, *All About Me*, with support from the Wellcome Trust.

All About Me welcomed its first visitors in March 2013. It harnesses the latest understanding in playful learning to captivate, stimulate and challenge children aged 0–11 on science, health and wellbeing. More than 100 multi-sensory, hands-on exhibits encourage them to explore how the body works, and imaginative spaces and activities invite them to enjoy and understand the uniqueness of their own bodies.

The new gallery was designed by experts working closely with children. It links to the National Curriculum while remaining an engaging and amazing experience for families, from role-playing in the *All About Me* health centre to exploring a giant sneezing nose.

Best accounts

In mid-13th-century Syria, a physician named Ibn Abi Usaybi`ah set himself the task of recording the entire history of medicine. In *The Best Accounts of the Classes of Physicians*, he traced 1700 years of medical practice, from its mythological beginnings in ancient Greece to the contemporary work of Islamic scholars, all interlaced with amusing poetry and anecdotes. Despite the significance of his text, no accepted translation has been produced in over 300 years of attempts.

This year, the Wellcome Trust awarded a Joint Senior Investigator Award to Professor Emilie Savage-Smith, University of Oxford, and Professor Simon Swain, University of Warwick, to assemble a team of scholars with all the specialist skills and knowledge required to tackle the task. They aim to make this book, the earliest comprehensive history of medicine, available for the first time in a reliable and readable form for academic and general readers alike.

Curious journey

Wellcome Collection is transforming, with the help of Stirling Prize-winning architects Wilkinson Eyre. New areas are being brought into use and the building's levels are being linked with a dramatic spiral staircase. As well as opening up more gallery space, the redevelopment will add a new restaurant and a studio for live events and activities.

The Wellcome Library will also change, with new facilities being created for researchers and the iconic Reading Room becoming a space where people can engage with the collections. Visitors will be encouraged not just to look at the objects on display here, but also to touch, handle and use them.

Due for completion in summer 2014, the work builds on six years of successful, popular exhibitions, and will equip Wellcome Collection to satisfy the growing public appetite for its characteristic blend of art and medicine.

Signature patterns of genetic mutation are revealing the specific biological processes that cause cancer.

Identifying every genetic mutation in thousands of individual tumours has enabled researchers to understand the causes of cancer better than ever before. An international collaboration led by Professor Sir Mike Stratton, Director of the Wellcome Trust Sanger Institute, studied genetic material in more than 7000 samples taken from people with the most common forms of cancer. In each case, the teams compared the DNA in samples from the cancerous tissue with the DNA in unaffected parts of the person's body. This revealed all the genetic mutations in the tumour.

The scientists found that the frequency of different mutations varied greatly in different types of cancer. They identified more than 20 'signatures' – specific patterns of mutations – and in many cases they also worked out the underlying biological process responsible.

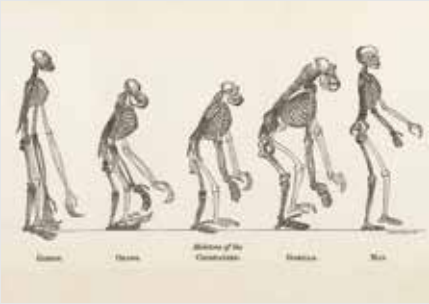
Some signatures were found in many types of cancer, whereas others were confined to just one. Some were associated with the age of the patient at diagnosis, exposure to known causes of genetic mutations, or defects in the mechanisms that maintain our DNA; but many were of unknown origin. Childhood cancers had the fewest mutations, while lung cancers related to chronic tobacco smoking and skin cancers caused by excessive exposure to ultraviolet light had the most.

Professor Stratton and colleagues published their findings in August 2013. Their list of mutation signatures will help to shed more light on the biological processes involved in human cancer. This, in turn, will lead to a better understanding of how cancers arise and how to combat them. The approach could also be brought to the front line of healthcare, improving clinical genetic testing so that it can help to identify people at a higher risk of a specific cancer and then taking steps to prevent it developing.

In a separate project, the Wellcome Trust awarded £2.7 million this year to help make such genetic testing a reality. Professor Nazneen Rahman at the Institute of Cancer Research, London, is leading a consortium to develop the required clinical infrastructure and education to increase access to genetic testing in the NHS. In collaboration with Illumina, a genetic sequencing company, she has developed a test that can analyse nearly 100 genes related to cancer risk within a few weeks for just a few hundred pounds.

Professor Rahman and her colleagues envisage a future where genetic testing for cancer is carried out by oncologists as a matter of course, giving patients better options for treatment.

A man with lung cancer, with X marking his radiotherapy site. *Christopher Anderson/Magnum Photos*



Unreal life

The Wellcome Trust supported Make Something Unreal Live 2013 – a science-themed game development competition for students across Europe – to encourage the next generation of developers and help bring science into the culture of the games industry. The winning team, called Dead Shark Triplepunch, were from Blekinge Institute of Technology in Sweden and triumphed with their entry, *Epigenesis*.

Epigenesis is a futuristic multiplayer ball game played over rooftops. It incorporates the competition's genetics and genomics theme by allowing players to plant seeds that change the playing environment in the course of the game. Dr Josh Randall from the Wellcome Trust Sanger Institute worked with the team, explaining the concepts of epigenetics that inspired the game mechanics. The winning prize was a licence for software that will enable Dead Shark Triplepunch to publish *Epigenesis* commercially.

Parallel histories

Research has revealed that, throughout history, the spread of hepatitis B has coincided with human migration. Dr Dimitrios Paraskevis at the University of Athens carried out DNA testing to trace the evolution of hepatitis B virus and humans. They found a shared 40 000-year history dating back to when humans first left Africa.

The research, part-funded by the Wellcome Trust, also looked at non-human strains of hepatitis B found in gibbons, orang-utans and chimpanzees, and found evidence that the virus jumped to them from humans at least 6000 years ago.

Hepatitis B is a global public health problem, with approximately 600 000 deaths a year resulting from the virus despite the availability of a vaccine. Understanding the historical emergence, transmission and evolution of the disease may help to manage it more effectively today.

Zebrafish sequenced

In April 2013, the zebrafish (*Danio rerio*) was added to a select list of organisms that have had their genomes comprehensively sequenced. Its entire genetic material was analysed and the resulting high-quality sequence was then annotated with relevant biological information. This level of detail had previously been accomplished only with mice and humans.

Researchers at the Wellcome Trust Sanger Institute led the work, which revealed that 70 per cent of human genes that encode proteins are related to genes in the zebrafish, and that 84 per cent of genes known to be associated with human disease have a zebrafish counterpart.

The zebrafish has already proved vital for investigating diseases such as cancer, heart disease and muscular dystrophy. It can now help to uncover more of the biological processes responsible for common and rare diseases, opening up new avenues for developing drugs to treat them.

From left:

Screenshot from the development of *Epigenesis*. *Dead Shark Triplepunch*

Skeletons of primates, by B Waterhouse Hawkins, 1863. *Wellcome Library*

The zebrafish genome has been comprehensively sequenced. *Wellcome Images*

Light microscope image of sperm. *Joyce Harper, UCL/Wellcome Images*

> Our research demonstrates how genes could retain some memory of their past experiences... That could have profound consequences for future generations."
>
> **Dr Jamie Hackett, University of Cambridge**

Inheriting experience

It has long been known that the health effects of famine can persist for generations. The idea that offspring can inherit altered traits because of their parents' experiences conflicts with the conventional view of genetic inheritance, in which all of the information that gets passed to a child is determined by the DNA their parents were born with. But Wellcome Trust-funded research published this year showed how there can be exceptions to this rule.

The field of epigenetics developed as scientists began to understand how genes are regulated during our lives. Chemical tags attached to DNA, known as epigenetic marks, tell a cell to either use or ignore a particular gene. This allows genes to be switched on or off as required in response to particular conditions. However, epigenetic marks are erased during the production of sperm and egg cells, 'reprogramming' them so that genes can be passed on afresh in each new generation.

Dr Jamie Hackett at the University of Cambridge and colleagues were looking at how one type of epigenetic mark-up – methylation – is removed in mice. The process they studied turned out to be remarkably efficient and reset the genes as expected. The team identified a number of mechanisms that between them ensured cells were reprogrammed.

However, they also found that some methylation survived the reprogramming.

Epigenetic methylation accumulates over an individual's lifetime in response to factors such as nutrition or exposure to certain chemicals. It helps determine the body's response to the environment, switching genes on or off and so changing the way cells behave. Sometimes these changes lead to disease. If some methylation can escape reprogramming and be inherited, a child's genes and cells could be switched to the same settings as the parent's. The child might then be at a higher risk of certain diseases, even though they have not themselves experienced any environmental factors to warrant that epigenetic response.

Further research will provide a better understanding of the extent to which traits can be inherited epigenetically. If epigenetics plays a significant role in particular diseases, this work could provide information on how to identify and erase the critical marks and bring the risk of disease back down to normal.


DOCTOR

‘Wonder’ celebrated the art and science of the brain, combining a major neuroscience conference and engaging public events.

Over three days in April 2013, the Barbican Centre in London came alive with an interactive ‘street fair’ of experiments and demonstrations about the brain. It was held alongside a British Neuroscience Association conference. Almost 2000 delegates attended the conference and another 5000 people came to the street fair, playing videogames with their brainwaves, knitting neurons and going on a brain treasure hunt.

The event was the culmination of ‘Wonder: Art and science on the brain’, a month-long season of activities organised by the Barbican and the Wellcome Trust that attracted more than 15 000 people in total to its workshops, talks, films and performances. Highlights included the Salon Project, which re-created a *fin-de-siècle* Parisian salon to discuss the defining ideas of our time, and a lecture on consciousness from the University of Oxford’s Professor of Public Understanding of Science, Marcus du Sautoy.

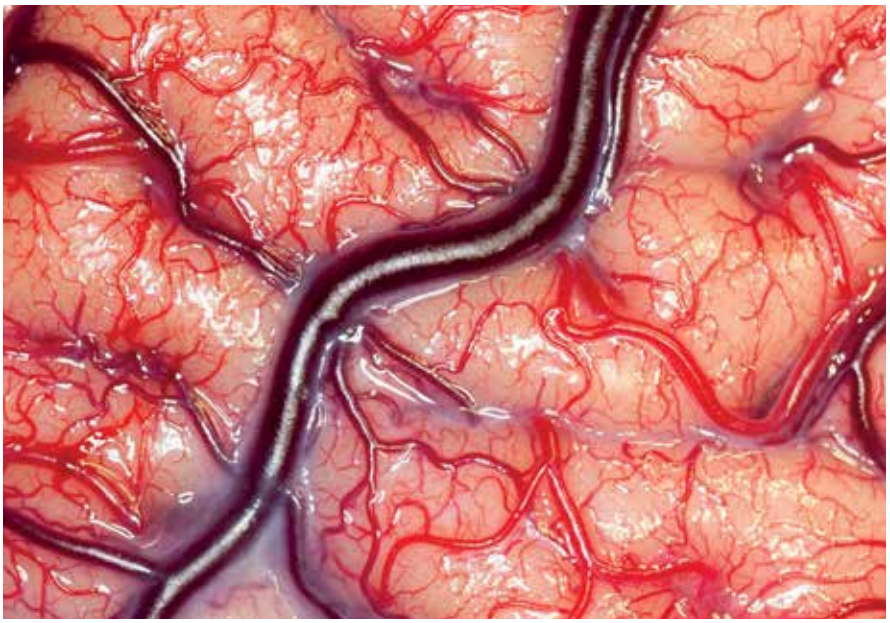
A programme of films included *Fiend Without a Face*, a B-movie classic from the 1950s. It tells the story of a scientist whose thoughts materialise as an army of invisible brain-shaped monsters that terrorise the American military. There were more serious contributions from neuroscientists and artists discussing topics such as the impact of London city life on the brain and the latest research into treating Parkinson’s disease by using stem cells.

Professor Roger Kneebone, one of the Wellcome Trust’s Engagement Fellows, ran an inflatable operating theatre. It takes just three minutes to put up and can be used to instruct surgeons and nurses about complicated operations at far less cost than the real thing. Though built as a tool for surgical education, it was equally capable of entertaining people at the street fair with interactive surgical demonstrations.

In a fascinating talk, comedian Ruby Wax took her audience on a journey from the heights of fame to the depths of mental illness and back. Over time she has learned to cope with her depression, which has spurred her to study for degrees in neuroscience. Wax’s experience, perception and understanding of her condition offered a unique insight into the way our minds work.

The idea for the ‘Wonder’ season began when the British Neuroscience Association asked the Trust to help organise some public engagement during its conference. The result was a big programme of intriguing and fun experiences that brought scientists, artists and the public together to explore the wonders of our brains.

‘Wonder’ included a huge range of public events and activities celebrating the brain. *Wellcome Images, Susana Sanroman, Tommy Ga-Ken Wan, Barbican*



Cutting-edge imaging

Of the 450 000 people with epilepsy in the UK, around 40 per cent have seizures that do not respond to anti-epileptic drugs. For these people, an operation to remove epileptic foci – the parts of the brain where their seizures start – is the only option that offers a possible cure. However, if the epileptic foci are too close to vital parts of the brain, surgery may not be possible.

Although such operations are often successful at stopping seizures, they carry a risk of damaging important structures within the brain. Damage to language centres, blood vessels or key areas of connectivity can have serious and lasting effects. Accurate positioning and prior knowledge of the individual's brain structure is essential. At University College London, Professor John Duncan is collaborating with colleagues in neurosurgery and the UCL Centre for Medical Image Computing, and with Medtronic – the world's largest medical technology company – to develop new imaging techniques that will help make epilepsy surgery even safer, and thereby available to more people.

Professor Duncan's new system integrates information from an array of medical imaging techniques, including functional magnetic resonance imaging, tractography, electroencephalography, magnetoencephalography, computed X-ray tomography and positron emission tomography. It combines the information from these sources in a single three-dimensional visualisation that shows the critical brain areas, connections and blood vessels. Surgeons can then use the visualisation to plan their line of attack on the epileptic foci and avoid potential obstacles and hazards.

Prototype software has been successfully tested in planning surgery for around 30 patients this year. In many cases, the surgical teams decided to altered their initial approach thanks to input from the imaging system.

A second prototype is in the late stages of development before testing. It has an improved user interface and better integration with Medtronic's existing technology, allowing it to work in concert with the system that is already used to position instruments during neurosurgery.

This work is being funded through the Health Innovation Challenge Fund, jointly supported by the Wellcome Trust and the Department of Health. The resulting technology will improve outcomes for the hundreds of people who undergo surgery for epilepsy each year in the UK, and it might allow surgeons to operate in cases previously considered too risky. The software will also be suitable for other types of brain surgery, such as the removal of brain tumours, potentially creating better surgical options for patients in the UK and around the world.

"I would hope that over the next 10–20 years, our treatment will get more sophisticated, will be more precise, and that, little by little, more and more people will have their epilepsy entirely controlled."

Professor John Duncan, University College London

From left:

A live human brain, exposed for an epilepsy test. *Robert Ludlow, UCL Institute of Neurology/Wellcome Images*

Children's views give valuable insights into ADHD. *MamiGibbs/Getty Images*

'Anger' cartoon. *Lester Magoogan/Wellcome Images*

The structure of the ear, after James Stewart, 1800. *Wellcome Library*

ADHD voices

The ethical and social issues surrounding attention deficit hyperactivity disorder (ADHD) are complex and often controversial, particularly the question of whether to use drugs to treat children diagnosed with the condition. Professor Ilina Singh, from King's College London, was funded by the Wellcome Trust to examine children's attitudes to ADHD, behaviour, medication and identity. Researchers interviewed more than 150 children aged 9 to 14 in the UK and the USA to understand their perspectives and experiences.

In contrast to the common concern that drugs like Ritalin turn children into 'robots', Professor Singh found that children with ADHD tended to feel they benefited from medication by regaining control over their decision making. A series of short animated films using excerpts from the interviews is on the project's website, which also provides practical advice to support families, doctors, teachers and, most importantly, children affected by ADHD.

adhdvoices.com

Emotional processing

Our susceptibility to anxiety and depression depends in part on how positively or negatively we think. The Wellcome Trust co-funded a study led by Professor Ian Goodyer at the University of Cambridge to examine factors influencing different mindsets among 15-to-18-year-olds, a group at relatively high risk of mental illness.

The childhood experiences of 238 adolescents were assessed. Their DNA was also tested to see which version they had of a particular gene that helps regulate serotonin, a brain chemical associated with mood. Then they were asked to evaluate words as positive, negative or neutral, to test how they processed emotional information.

The research found that teenagers with a particular version of the gene who had also been exposed to family arguments or violence growing up were more likely to have symptoms of anxiety or depression. They also had difficulty evaluating the words correctly, suggesting that a simple test of emotional processing might be able to pick up indicators of mental health problems.

Hear and there

The brain normally works out where sounds are coming from by comparing information from both ears. Differences in volume and in the time it takes a sound to reach each ear help us to localise the source. Children with glue ear, a common middle-ear infection, are less able to use these clues to identify the direction of noises, and the impairment sometimes persists in later life.

Professor Andrew King, a Wellcome Trust Principal Research Fellow at the University of Oxford, studies how the brain compensates for such hearing loss. He carried out a study with ferrets, using removable earplugs to induce temporary hearing loss in one ear. He found that the ferrets were still able to localise sounds by relying more on the way the shape of their unblocked ear filtered the noise. The finding could lead to new therapies for glue ear and could also inform the way hearing aids are designed.

Wellcome Trust scientists were at the forefront of research efforts this year after a new infectious disease emerged.

Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified after the death of a Saudi Arabian man in June 2012. The cases recorded since then have claimed the lives of dozens of people in Saudi Arabia and a small number in other parts of the world, including the UK.

MERS-CoV belongs to the same family of viruses as severe acute respiratory syndrome (SARS) coronavirus, of which there were fatal epidemics in southern China in 2002 and 2003. However, little was known about the origin and characteristics of the new virus. By studying an outbreak of MERS-CoV in a hospital in the eastern Saudi province of Al-Hasa in spring 2013, an international team of scientists provided some urgently needed insight.

Researchers at the Wellcome Trust Sanger Institute developed a 'deep sequencing' technique to rapidly analyse MERS-CoV genomes from the outbreak. Their approach used the minuscule levels of viral genetic material present in samples taken from patients. When used in combination with bespoke computer programs, the process reduced the time needed for genome analysis from weeks to days.

The researchers then characterised how the disease had spread using a combination of advanced genetics and clinical monitoring tools. They confirmed that the virus was being transmitted from person to person and that the genetic changes accumulated by the virus were consistent with it replicating within one patient before transferring to the next.

Further analysis revealed that all the coronaviruses in this particular outbreak came from a common ancestor that appeared between February and April 2013. Later research by the team found three distinct varieties of MERS-CoV among 21 patients. Their genetic analysis suggests that the virus evolved and diversified in animals and then infected humans, probably on more than one occasion.

The outbreak was contained effectively in the hospital, demonstrating that clinical measures can control MERS-CoV. However, research has already provided vital new information about the virus that will help clinicians minimise its spread, and further research will add to our understanding of it, including determining how long it is contagious for. This will help healthcare services and clinicians develop and implement the best strategies to prevent new infections.

The new coronavirus was first identified in Saudi Arabia. *Reuters*

Trading sickness

Professor Mark Harrison's new book, *Contagion: How commerce has spread disease*, is a historical study of the links between contagious illness and commerce. Director of the Wellcome Unit for the History of Medicine at the University of Oxford, Professor Harrison argues that, throughout history, trade has been the most important factor in the spread of infectious diseases. His book, published in late 2012, also examines the emergence of public health around the globe, and the surprisingly common abuse of measures intended to improve sanitation for economic, political and military gain.

The book came out of a Trust-funded project making the first large, systematic attempt to understand the historical relationships between globalisation, health and medicine. By bringing a historical perspective to bear on contemporary issues, and working with policy makers and academics from other disciplines, Professor Harrison aims to inform future policies and practices that influence the spread of infectious diseases.

Foot and mouth

Researchers from the Pirbright Institute and the Universities of Oxford and Reading have found a way to make a more effective vaccine against foot and mouth disease. Outbreaks of the virus in livestock can disrupt agriculture on a national scale, but existing vaccines to control it all have limitations. The new vaccine is more stable, easier to transport and suitable for manufacture without requiring high-security facilities.

The scientists programmed cells to produce copies of the foot and mouth virus's outer shell without including its infectious genetic core. When injected into cows, this activated the animals' immune responses, protecting them against several common strains of the virus for nine months, without at any stage involving live viruses. Work at the Diamond Light Source synchrotron, which is co-funded by the Wellcome Trust, helped show the effects of modifying the structure of the viral shell, enabling a more stable vaccine to be developed.

Similar techniques could be applied to related human viruses, such as polio.

Stopping the spread of HIV

Research from the Africa Centre for Health and Population Studies, supported by the Wellcome Trust, has confirmed that antiretroviral drugs not only improve the life expectancy of people with HIV but also reduce transmission rates.

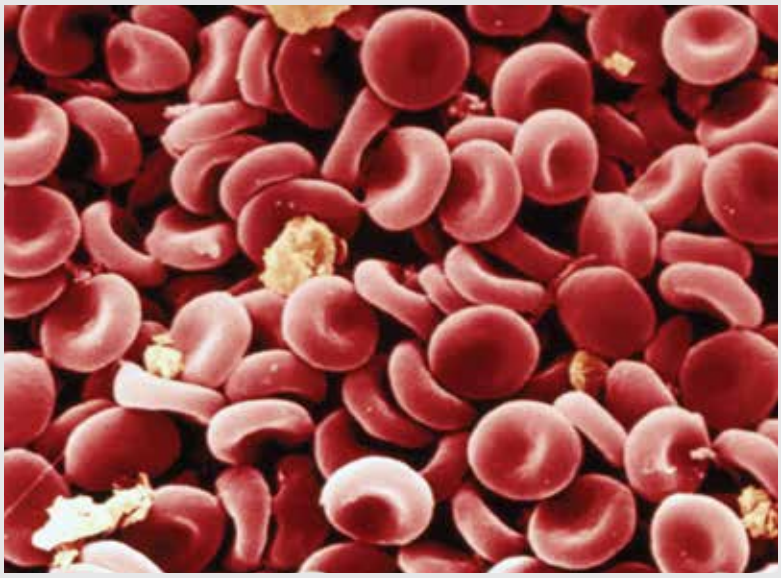
A 2011 study had found that taking the drugs as prescribed brought levels of HIV so low that there was almost no chance of infecting a sexual partner. However, it was unclear whether this would be true in the 'real world', where people are less likely to adhere to treatment regimes and there are more diverse sexual behaviours.

The new research, published in *Science* in February 2013, was carried out in a large population in KwaZulu-Natal, South Africa. In communities where at least a third of people infected with HIV were taking antiretroviral drugs, the rate of new infections was significantly lower than in communities where fewer people were being treated. This shows that treatment helps stop the spread of HIV and AIDS, benefiting the wider community as well as individuals.

“

We only have a limited window of opportunity to stop this infection from spreading to the community and spreading to more organisms.”

Dr Tom Frieden, Director of the US Centers for Disease Control and Prevention



Antibiotic persistence

A next-generation antibiotic, developed with support from the Wellcome Trust, is set to enter a phase III clinical trial by the end of 2013 to see how well it treats a group of bacterial infections that are resistant to nearly all currently available antibiotics. The news is welcome, given rising concerns throughout the world about drug-resistant bacteria, particularly infections acquired by patients in hospitals.

Five years ago, the Trust’s Seeding Drug Discovery initiative awarded £4.1 million to Achaogen, a biopharmaceutical company, to support work on new treatments for life-threatening infections caused by bacteria that are resistant to multiple drugs. With this and other funding, preclinical results and a phase I trial quickly followed, and a successful phase II trial was reported in 2012.

Achaogen’s lead drug, plazomicin, targets a group of bacteria called carbapenem-resistant Enterobacteriaceae (CRE). Infection with these bacteria most commonly occurs in people receiving hospital treatment for other conditions. They can kill up to half of all people who become infected with them in their blood, and have been categorised by the US Centers for Disease Control as an “urgent” public health threat, requiring immediate and aggressive action.

In September 2013, Achaogen announced agreement with the US Food and Drug Administration on the design and planned analyses of the phase III trial of plazomicin. The drug has already shown activity against CRE in the laboratory, but the new trial, in patients with bloodstream infections and pneumonia caused by CRE, will show whether plazomicin is better than the few existing antibiotics that remain for treating such infections. If successful, the trial should provide Achaogen with the necessary evidence to apply for approval of plazomicin.

Plazomicin is a new type of aminoglycoside antibiotic, a class that includes widely used drugs such as gentamicin and amikacin. However, plazomicin has been engineered to overcome the mechanisms that have made many bacteria resistant to other aminoglycosides. This work is currently being supported by the Biomedical Advanced Research and Development Authority in the USA, and as well as CRE, the drug is being developed to treat *Yersinia pestis*, which causes pneumonic and bubonic plague, and tularaemia, a bacterial disease spread to humans by ticks and other insects.

Achaogen is also researching different ways to target these bacteria. After support from the Trust at a critical stage of drug development, these efforts are helping to expand the pipeline of future treatments available to counter potentially devastating bacterial diseases.

From left:

A rat stows aboard a trading ship. By Albert Lloyd Tarter, 1940s. *Wellcome Library*

Incinerating livestock in the 2001 UK foot and mouth outbreak. *Odd Andersen/AFP/Getty Images*

Buying condoms. *Karen Kasmauski/Getty Images*

Red blood cells. *EM Unit, UCL Medical School, Royal Free Campus/Wellcome Images*

Artworks, artefacts and performances can help people explore attitudes and perspectives on death.

From November 2012 to February 2013, Wellcome Collection's exhibition *Death: A self-portrait* explored the complex and contradictory subject of death. Taboos about mortality are embedded in culture, although the subject has long been a source of fascination to artists.

Death investigated the value of art in developing ideas about the body and the end of life. Visitors were met with a showcase of works from the unique collection of Richard Harris, a former antique print dealer from Chicago. Over several decades, Harris has amassed a wealth of artworks and artefacts devoted to the iconography of death. Some 300 items from his collection were brought to the UK for the exhibition, including paintings, historical objects, anatomical illustrations and ephemera from across the world.

One of five themes in the exhibition was the contemplation of death throughout the ages, illustrated through memento mori including works by Andy Warhol, Adriaen van Utrecht and Robert Mapplethorpe, together with exquisite Japanese netsuke miniatures and porcelain, bronze and ivory skulls. Another theme was violent death, chronicling artists' reactions to war and murder. A number of rare prints by Rembrandt, Dürer and Goya were on display, evoking chaos and brutality but also aesthetic beauty. The most disturbing exhibits invited viewers to question the boundary between curiosity and morbidity, and to challenge their own attitudes to mortality.

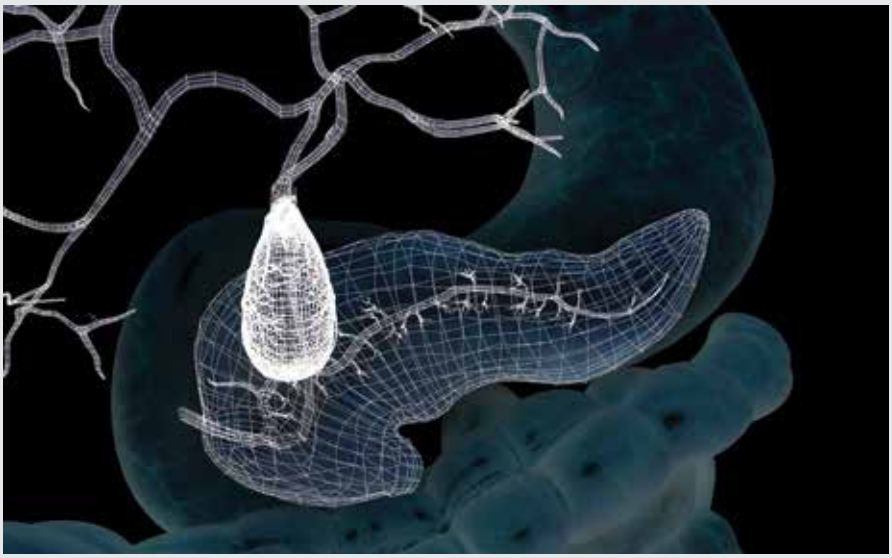
Described in one review as "engrossing, thought-provoking and sometimes even funny", the exhibition attracted 136 000 visitors.

Ethical and emotional issues surrounding the end of life provided the backdrop for *Killing Roger* at the 2013 Edinburgh Festival Fringe this summer. The Wellcome Trust supported this production, by theatre company Sparkle and Dark, in which conscientious, opinionated teenager Billy volunteers to visit an old man in his home: the cantankerous, chain-smoking Roger.

Played by a life-sized puppet, Roger is close to death and begins to ask Billy some awkward questions: "Could you kill someone? What if they asked you to?" The play evolves as a conversation between the two characters, covering philosophy and ethics – often antagonistic but tempered with humour.

Sparkle and Dark have continued the project, which proved popular with critics and audiences, with new dates announced in the autumn and a series of symposia to accompany the performances.

'Life and Death' postcard, c.1900–10.
The Richard Harris Collection/Wellcome Images



From left:

Digital illustration showing the pancreas (centre). *MedicalRF.com/Getty Images*

Heart muscle made from induced pluripotent stem cells. *Jose Silva/Wellcome Images*

Scientists are working to discover the cellular bases of ageing-related diseases. *Catherine MacBride/Getty Images*

A six-week-old embryo. *Neil Harding/Getty Images*

Artificial pancreas

The pancreas is where our bodies produce hormones such as insulin that regulate levels of sugar (glucose) in our blood. If control of blood sugar is compromised it causes diabetes, which if untreated can have severe consequences. In type 1 diabetes, which accounts for about 10 per cent of diabetes cases in the UK, the specialised cells in the pancreas that make insulin have been destroyed, leaving blood sugar levels unchecked.

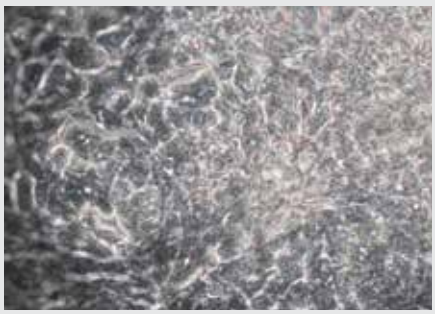
Most patients with type 1 diabetes attend specialist clinics and have to receive either daily insulin injections or the continuous infusion of insulin through a pump to compensate for the missing hormone. But these treatments can inadvertently produce prolonged episodes of high or low blood sugar. This is because fluctuations in blood sugar during ordinary activities such as eating and exercising are not necessarily timed to coincide with injections of insulin. Such episodes can have long-term effects including blindness, kidney failure and heart disease.

With funding from the Wellcome Trust, a team led by Professor Christofer Toumazou at the Institute of Biomedical Engineering, Imperial College London, has developed a device that continuously manages a person's response to meals as well as to other factors such as exercise and illness. It mimics the behaviour of a healthy pancreas by automatically delivering insulin and other hormones to control blood sugar levels in response to changes detected by a glucose sensor. Linking sensors with a hormone delivery system has been tried before; however, the new system is different because it is based on the responses of pancreatic cells to glucose, providing physiological control, and it is the first to be fully implemented on a miniature microchip.

So far, 20 people with type 1 diabetes have tested the artificial pancreas, with positive results, and the team was successful in securing further funding from the Trust this year to undertake clinical evaluation and get regulatory approval for the device. They also hope to integrate a monitor that measures heart rate and physical activity, allowing even more refined control during exercise or stress.

Hundreds of thousands of people in the UK alone have diabetes. Providing a way to control blood sugar levels that fits in with their lives would have a major impact on quality of life for a large and growing section of the population.

> "This is a fantastic time for the merge between engineering and medicine… The next big application area of the microchip, of the digital revolution, will be biology. It will be the human body."
>
> **Professor Christofer Toumazou, Imperial College London**



Stem cell science

In December 2012, researchers led by Dr Amer Rana from the University of Cambridge described an efficient and convenient way to make induced pluripotent stem cells from a blood sample.

Pluripotent stem cells can change into any other type of cell in the body, offering huge potential for medicine, but are difficult to obtain from adults. However, it is possible to induce normal adult cells to become pluripotent stem cells, by 'turning back the clock' to give them the right properties. The work, co-funded by the Wellcome Trust, suggests that induced pluripotent stem cells could be made routinely from patients' own blood cells and then used to treat conditions such as heart disease.

A month earlier, the Trust and the Medical Research Council announced a £12.75 million initiative to create a bank of induced pluripotent stem cells derived from 500 healthy volunteers and 500 people with genetic diseases. The resulting collection will be a comprehensive resource for investigating how genetic variation affects cell behaviour and disease.

Protein preservation

Researchers at the University of Dundee have uncovered a fundamental process in cells that may be relevant to ageing-related diseases such as cancer and dementia. Many of the thousands of proteins that make up animal cells require modification after they are produced, and a gene called OGT is the master regulator of one way of doing this. But abnormal levels of the OGT enzyme are found in some forms of cancer, diabetes and dementia, suggesting it is disrupted in these diseases.

Led by Professor Daan van Aalten, a Wellcome Trust Senior Research Fellow, the Dundee team used crystallography and chemical probes to reveal how OGT works. Their findings open the door to the design of chemical compounds that can alter the level of the OGT enzyme, which will help determine its role in these common diseases and may lead to new treatments.

Future families

Professor Susan Golombok spoke about the 'modern family' at the Cheltenham Literary Festival in October 2012. A Wellcome Trust Senior Investigator at the University of Cambridge, Professor Golombok researches new family forms with an emphasis on the relationships between parents and children, and on children's social and emotional development. She has studied families with same-sex parents, single-parent families and families with children conceived by assisted reproductive technologies such as IVF.

Her talk addressed the possible impact of mitochondrial transfer. This technique, developed to prevent the inheritance of mitochondrial diseases, is based on IVF but with a donor providing a tiny proportion of DNA alongside the mother's and father's. Some people have expressed concerns about 'three-parent babies' – a misleading description – but Professor Golombok's research has consistently shown that children conceived using assisted reproductive technologies are no more likely to experience psychological problems than children conceived naturally. She said family structure is much less important than the quality of the relationships.

Sustaining Health will support research that draws out the connections between the changing environment and our future health.

With the world's population predicted to reach 9 billion by 2050, people's health and wellbeing will become increasingly threatened by lack of access to clean water, nutritious food and sanitation, and by environmental factors such as poor air quality and climate change. These interlinked global challenges are already growing as more of us live in towns and cities and our changing lifestyle choices contribute to the rise of obesity and chronic diseases.

To promote new research in this area, the Wellcome Trust launched a funding scheme called Sustaining Health in July 2013. A £5 million fund will support pilot projects that seek to define and investigate these issues and the impact of our behaviour as individuals and societies.

It is not just the human population that we need to consider. To maintain a stable environment, we may well need to conserve the world's flora and fauna as well. This raises more social and political questions that reach across national borders. The goal of the scheme, therefore, is to build a robust evidence base to inform policy and develop fresh approaches to preventing and mitigating the health risks of a rapidly changing world.

Researchers funded through Sustaining Health will lead the way in responding to present and future environmental and social challenges. These awards will kick-start research projects in the areas of behaviour change, global nutrition, health impacts of climate change and ecological public health. It is hoped that the projects will build capacity for interdisciplinary research and go on to attract more substantial funding from the Trust's other biomedical and translational funding programmes.

Understanding relationships between the environment, human behaviour and health will help us make informed choices about the future, but the research that underpins that understanding and the actions that follow will require the engagement of many different communities working together. So applications were particularly encouraged from cross-sector collaborations between academic organisations, industry, non-governmental organisations and government agencies.

The initial call prompted more than 400 'concept notes' from around the world. Fifty-two of those were invited to submit a preliminary application and the first funding decisions will be made in spring 2014.

Economic development and population growth, in Kuala Lumpur as elsewhere, raise environmental and public health concerns. *Malcolm Chivers*

Cohort champion

Brazilian epidemiologist Professor César Victora has become the first Wellcome Trust Senior Investigator to tackle the challenge of connecting environment, nutrition and health. His award, made in July 2013, recognises his success in managing cohort studies of children in Pelotas, Brazil. These studies recruited large numbers of children at birth and monitored breastfeeding, nutrition and growth throughout infancy.

Professor Victora has won acclaim for research examining the effects of social inequality on health, and he was influential in establishing the Consortium of Health Orientated Research in Transitioning Societies (COHORTS), a collaboration between five large cohort studies in low- or middle-income countries. The current COHORTS analyses are based on nearly 11 000 people who have been followed up since childhood.

With his Investigator Award, Professor Victora will continue to monitor and predict trends in child health and nutrition, as well as communicating his findings so they can be used to address current health problems and anticipate future developments.

London's Pulse

The digitisation of one of the most heavily consulted archives in the Wellcome Library was completed in early 2013. Written accounts, graphs, tables and charts compiled by the Medical Officers of Health for London from the mid-19th century onwards are now available in the free online resource London's Pulse.

Between 1848 and 1972, Medical Officers of Health oversaw numerous services contributing to the wellbeing of London's population. Their reports, which covered statistics on births and deaths as well as subjects such as pollution, sanitation, housing and food safety, offer an invaluable source of primary information about public health in 19th- and 20th-century Britain.

London's Pulse, which includes search and download options, launched in October 2013. Easy access to the records will help the work of public health researchers, epidemiologists and practitioners, as well as medical and social historians.

wellcomelibrary.org/moh

Who's the Pest?

Insects have a huge influence on the environment, affecting agriculture, nutrition and human health. This complex relationship was the focus of a season of events at Wellcome Collection in spring 2013. 'Who's the Pest?', run jointly with travelling bug festival Pestival, featured a series of debates, interactive exhibits and cooking demonstrations, examining insects as friends, enemies and meals. The free sessions encouraged discussion between designers, chefs, entomologists, environmentalists and the public.

Among the highlights was a specially commissioned game that placed players alternately in the position of ants or humans in the battle for a vegetable patch. The potential of insects as a source of food for humans was a strong theme in many events, including tastings hosted by renowned research institute Nordic Food Lab and insect-eating researcher Professor Marcel Dicke.

From left:

A mother and daughter in Sao Paolo. *Eduardo Anizelli/LatinContent/Getty Images*

A leaflet offering advice from the Medical Officer of Health, c.1929–39. *Wellcome Library*

'Who's the Pest?' explored many aspects of insects, including their deliciousness.

Nutritional standards are a crucial health issue the world over. *Lonely Planet/Getty Images*

Access to nutrition

In the world today, 1.4 billion people are obese and 870 million are undernourished. Many countries face the dual burden of malnutrition among poorer people and rising obesity among the emerging middle classes, and there is growing recognition that international businesses can play a significant role in tackling both challenges. Food and drink manufacturers are increasingly being called on to improve access to more nutritious products and to positively exercise their influence on consumer choice and behaviour.

In March 2013, the Access to Nutrition Index (ATNI) published, for the first time, an impartial measure by which companies can be assessed on such activities. ATNI is funded by the Global Alliance for Improved Nutrition, the Bill & Melinda Gates Foundation and the Wellcome Trust. It assesses the commitments, performance and disclosure practices of the world's 25 largest food and beverage manufacturers as measured against accepted best practice.

Companies were evaluated on corporate governance, product formulation, marketing practices and engagement activities, all in the context of promoting healthy behaviour and access to nutrition. Governments, international organisations, academics and investors were involved throughout the process. ATNI, therefore, is a benchmark allowing companies to compare their approach to nutrition against their peers'.

Danone, Unilever and Nestlé were top performers in the 2013 ATNI report, receiving the best scores on both the obesity and undernutrition rankings. However, all the companies had significant room for improvement, with the highest score just 6.3 out of a possible 10 points. The report also highlighted that Danone and Nestlé have been reported to be in breach of the International Code of Marketing of Breast-milk Substitutes. The authors recommended that these companies, along with other manufacturers of breast-milk substitutes, take immediate action to ensure full compliance.

The index will be recalculated and published every three years, alongside Spotlight Indexes assessing the largest companies operating in individual countries such as India, Mexico and South Africa. Improved monitoring of food and drink manufacturers should be good not only for public health, but also for the food and drink companies and the long-term sustainability of their industry.

accesstonutrition.org

"Hopefully, indexes such as the ATNI can be used to increase the buy-in of stakeholders and to monitor corporate behaviour by reinforcing companies with the best business practices and identifying those that fail to improve."

***Lancet* editorial**

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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** We regret to report that Michael Neuberger died on 26 October 2013 and Anthony Pawson died on 7 August 2013.*

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