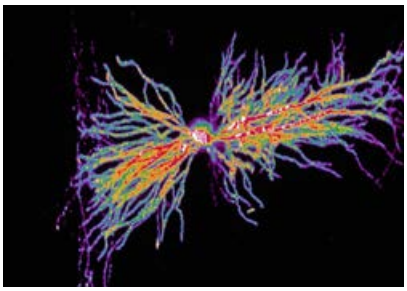
Volume 2: Research Profiles 2012/13

wellcome trust

Contents

Discoveries

Using neuroscience to further our understanding of obesity



Impact:

- A novel collaboration between neuroscientists and metabolic physicians is improving our understanding of how motivation and learning underpin responses to food.
- New techniques to explore the ways in which food-related stimuli can drive appetite have shown how hormonal and pharmacological manipulations could alter these stimuli.

Wellcome Trust funding

Senior Research Clinical Fellowship, 2011

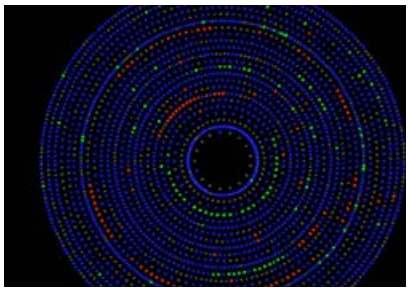
Biosciences Imaging Gp, Soton, Wellcome Images

Paul Fletcher is a Wellcome Trust Senior Research Fellow in Clinical Science at the University of Cambridge. He believes that the current obesity pandemic, driven by a combination of an unhealthy food environment and genetic vulnerability, could be better understood if we examine individuals' variability in basic reward-related behaviours – and beyond that, their underlying neural circuitry.

Working together with metabolic physicians, Fletcher is examining how the specific enhancement of motivation and learning found in compulsive overeating may be explained. His team has developed a series of tasks that explore the degree to which participants are willing to expend effort to obtain primary rewards such as food, as well as secondary (e.g. financial) rewards.

By analysing real-world eating behaviours, the researchers are identifying patterns of appetite, pleasure, decision-making and brain response within the same participants. This approach has already been used to test a possible new anti-obesity drug.

Understanding the processes behind the mutations that cause cancers



Impact:

- Researchers are uncovering the signatures of DNA mutations left behind in cancer cells to reveal the underlying processes that cause them and lead to the development of cancers.
- The research has received widespread media coverage, including from BBC News, Fox News and Sky News.

Wellcome Trust funding

Intermediate Clinical Fellowship, 2013

Cecile Duchesnes, Wellcome Images

When genetic mutations arise in cancer cells, the biological processes that cause them can leave behind an imprint on the cell's DNA. With a clearer picture of the traces of mutations, or 'signatures', it will be possible to understand how and why mutations arise, accumulate and lead to the development of different cancers and possible to find better ways to prevent or curb cancer development. Dr Serena Nik-Zainal, a Wellcome Trust Intermediate Clinical Fellow at the Wellcome Trust Sanger Institute, has identified several distinctive signatures of mutations in different breast cancers and is investigating their underlying cause. Some signatures may be caused by defects in the mechanisms that repair damaged DNA, so she is analysing the genomes of patients with naturally occurring defects in these mechanisms to see the mutation signatures they have accumulated since birth. The findings will contribute to a database of mutation signatures that clinicians and scientists can use for further research.

In the future, the routine sequencing of every cancer patient's DNA – and the identification of mutation signatures to better understand their cancer – could be used to inform treatment decisions for them and to help develop new treatments.

Bees remember plants with caffeinated nectar

Impact:

- Dr Geraldine Wright and her team have discovered that bees' memory is enhanced when caffeine found in citrus flower nectar affects the excitability of Kenyon cells, neurons that are important in learning and memory.
- This research has found that plants producing caffeine in their flower nectar have a competitive advantage in pollination – bees are three times as likely to keep going back.

Wellcome Trust funding
Project grant, 2010

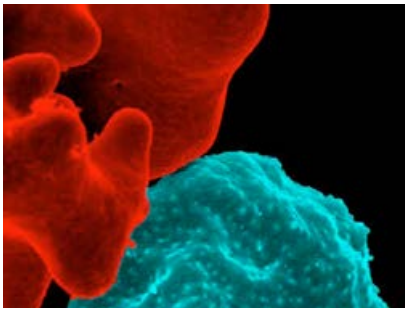
Annie Cavanagh, Wellcome Images

Dr Geraldine Wright at Newcastle University is studying how nutrition influences bees' memory and behaviour. Her research focuses on how the brain learns and remembers information about food, and she is beginning to determine whether bees can be addicted to substances such as caffeine and nicotine, both of which are found naturally in the nectar they consume in the wild.

Wright's team trained honeybees to extend their mouthparts to receive sucrose when exposed to a floral scent – something bees do naturally when foraging on flowers. They found that if the sugary food contained caffeine, the bees were three times as likely to remember a floral scent than bees rewarded with sucrose alone. They also found that the caffeine in the flower nectar of *Citrus* and *Coffea* plants is at a low level – if it were too high, the bees would find it bitter and be repulsed. The research implies that caffeine gives these plants a competitive advantage in pollination: the bees remember them and keep going back.

In humans, caffeine enhances cognitive performance and memory retention. Wright's team has found that caffeine also affects bees in a similar way – it affects the excitability of Kenyon cells, neurons that are important in learning and memory.

New drugs for malaria



Impact:

- A consortium led by Dr Thierry Diagana has identified two antimalarial drug candidates, which target *Plasmodium falciparum* and *Plasmodium vivax* parasites and are active against parasites resistant to existing drugs.
- One candidate is now being developed further by Novartis Pharmaceuticals, with the aim of developing a single-dose treatment for uncomplicated malaria.

Wellcome Trust funding
Strategic Award, 2012

NIAID, Flickr

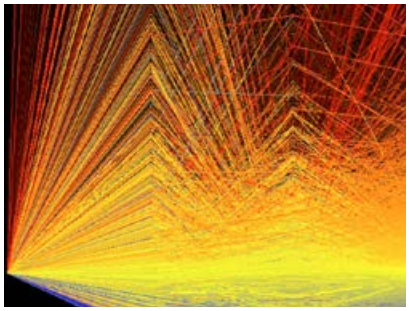
Almost half the world's population is currently exposed to malaria, which causes more than 660 000 deaths per year. Resistance to antimalarials is a serious problem, and many older drugs are now completely ineffective.

The Novartis Institute for Tropical Diseases – in partnership with the Genomic Institute of the Novartis Research Foundation, the Swiss Tropical and Public Health Institute, and the Biomedical Primate Research Centre – has identified two antimalarial drug candidates that target *Plasmodium falciparum* and *Plasmodium vivax* parasites and are active against parasites resistant to existing drugs.

The candidates are currently in phase II clinical trials and, as they have novel mechanisms of action, would be expected to help prevent the emerging threat of artemisinin drug resistance. The discovery programme and preclinical and early clinical development were supported by a Wellcome Trust Strategic Award, co-funded by the Medicines for Malaria Venture. One candidate is being further developed in phase IIa clinical trials with the aim of developing a single-dose treatment for uncomplicated malaria.

The team is also looking for a drug that can kill the liver stages of *P. vivax* – an unmet need. Researchers at the Biomedical Primate Research Centre have developed an *in vitro* liver-stage drug assay, which is being used to screen Novartis's library of compounds for potential drug candidates.

Uncovering the mechanisms that control genes



Impact:

- Dr Rob Klose and his team have uncovered a mechanism that links gene expression to changes in the three-dimensional shape of DNA.

Wellcome Trust funding

Senior Research Fellowship, 2012

Veronique Blanc and Qin Wang, Wellcome Images

Almost every cell in the body has the same genetic information, yet there are many differences in the structure and function of cells across the body. This is the result of a complex system of gene regulation, which determines how and when genes are read. Promoters are key regions of DNA that control access to a gene. In mammals, promoters often seem to be associated with parts of the genome called CpG islands.

Dr Rob Klose is studying gene regulation and CpG islands at the University of Oxford's Biochemistry department. He started his Wellcome Trust Senior Research Fellowship in 2013, moving onto the award straight from his Research Career Development Fellowship.

He undertook his Trust-funded PhD research at Edinburgh's Wellcome Trust Centre for Cell Biology, supervised by former Centre Director and long-standing Wellcome Trust programme grantholder Adrian Bird.

Dr Klose was awarded the Lister Institute Research Prize in 2011 and was the first person in Oxford to win the prize, which built on his success in being named an EMBO Young Investigator in 2010. In 2012, in a paper published in *eLife*, Dr Klose's team showed that certain proteins that bind to CpG islands also affect chromatin – the complex packaging of proteins and DNA that orchestrates the overall three-dimensional shape of DNA.

A potential treatment for Alzheimer's disease

Impact:

- Professor Jonathan Corcoran has identified compounds, now undergoing preclinical development, that target the brain's retinoid signalling system.
- This method of action is one of the first to target the progression of Alzheimer's disease, not just its symptoms.

Wellcome Trust funding

Strategic Translation Award in seeding drug discovery, 2007, renewed 2010

Anthea Sieveking, Wellcome Images

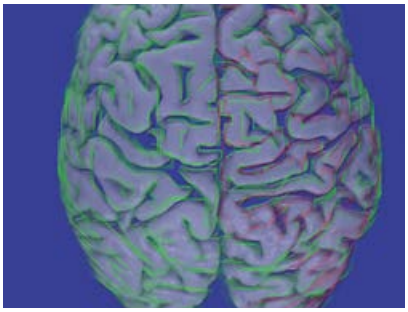
Alzheimer's disease, a leading cause of dementia, affects 417 000 people in the UK; its incidence is expected to double by 2050. The complex nature of the degenerative disease, and our limited understanding of its causes, have so far made it impossible to develop an effective treatment.

Retinoic acid receptors (RARs) form part of the brain's retinoid signalling system, which is responsible for maintenance in the adult brain. This system regulates a series of biological pathways that prevent the formation of amyloid plaques and neurofibrillary tangles in the brain, which are the hallmarks of Alzheimer's disease. RARα, in particular, represents a promising drug target.

Professor Jonathan Corcoran from Kings College London has identified a series of compounds that target RARα. He has successfully shown that these compounds work safely as selective RARα agonists to reverse the formation of amyloid plaques and improve memory function as the prelude to animal models of Alzheimer's disease.

A spin-out company, Coco Therapeutics Ltd, has been formed to pursue preclinical evaluation of the compounds before trials in humans. Should this research prove successful, RARα agonists may be the first treatment for Alzheimer's disease that affect not just the symptoms but the disease itself.

Understanding moral decisions



Impact:

- By combining behavioural economics and cognitive neuroscience, Molly Crockett has developed new tests to understand the brain mechanisms involved in moral decisions.
- This novel approach to cognitive neuroscience helps us understand when decision-making differs from the normal pattern.

Wellcome Trust funding

Sir Henry Wellcome Postdoctoral Fellowship, 2010

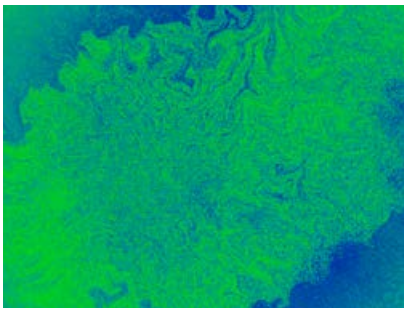
Heidi Cartwright, Wellcome Images

Neuroscientist Molly Crockett is studying altruism, morality and economic decision-making. During her Sir Henry Wellcome Postdoctoral Fellowship, she took the unusual step of studying in an Economics department. This has enabled her to apply the principles of behavioural economics – the study of the factors that influence people's economic decisions – to cognitive neuroscience, as they can be used to measure social behaviour in a quantitative way.

At the Wellcome Trust Centre for Neuroimaging, UCL, Crockett has developed new methods for measuring selfishness, altruism and empathy in the laboratory. These tests require people to make choices in response to certain scenarios; for example, an individual may have the option to forego a reward so that another person does not have to suffer a cost. Participants' brains are also scanned using functional MRI, which enables Crockett to infer the brain circuits involved in the different aspects of the decision-making process.

One important contribution to Crockett's work that comes from economics is normative modelling, which describes normal behaviour in certain conditions. Normative models can provide useful benchmarks for comparing individuals and can identify when an individual's decision-making differs from the normal pattern. Impairments in empathy, for example, are common to antisocial behaviour and a range of psychiatric disorders.

A novel approach to hospital-acquired infections



Impact:

- Researchers have demonstrated that a life-threatening hospital-acquired infection, *Clostridium difficile*, can be cured in mice.
- The study has provided a proof of concept to apply the same approach in humans.

Wellcome Trust funding

Programme grant, 2010

Derren Ready, Wellcome Images

One of the side-effects of antibiotic treatment is the destruction of the body's natural microbial community, which leaves the gut free to be colonised by aggressive, pathogenic bacteria such as *Clostridium difficile*. This bacterium has emerged over the past decade as the leading cause of antibiotic-associated diarrhoea in hospitals worldwide, and it causes a persistent infection that is difficult to treat effectively with further antibiotics.

Trevor Lawley and his team at the Wellcome Trust Sanger Institute used a mouse model of *C. difficile* infection to show that a mix of as few as six bacteria isolated from healthy mice can cure the infection, providing a proof of concept to apply this approach in humans. Their aim is to create a treatment where doctors transplant a handful of known bacteria that have been cultured in the lab. They are currently looking at bacteria from the guts of healthy people to identify which might be best for treatment.

Although human studies are underway in other centres, faecal transplantation remains on the fringes of modern medicine. This is partly because of the risk of introducing pathogens and partly because many people feel a natural aversion to the idea of transplanting faeces. However, using naturally occurring microbial communities to treat infection and reduce the use of antibiotics could have important implications – not only for *C. difficile* but also for other diseases associated with microbial imbalances, such as inflammatory bowel disease and obesity.

Progress for HIV prevention in sub-Saharan Africa

Impact:

- Researchers have shown for the first time the positive impact of antiretroviral therapy on the rate of new HIV infections in a community setting.
- Nurse-led, public-sector and community-based ART programmes can deliver substantial population-level reductions in the rate of new HIV infections.

Wellcome Trust funding

Major Overseas Programme, 2012

Wellcome Library, London

Research at the Africa Centre for Health and Population Studies in South Africa, which is funded by the Wellcome Trust, has shown that the HIV epidemic could be slowed by increasing the community coverage of antiretroviral therapy (ART). It is the first time that this positive impact has been demonstrated in a community setting.

The study, funded by NIH and the Wellcome Trust, was led by Professor Frank Tanser and published in *Science.* It repeatedly tested nearly 17 000 people for HIV between 2004 and 2011. All participants were uninfected at the start. The study used novel spatial statistical methods to compare new infection rates in communities in the Hlabisa subdistrict of KwaZulu-Natal, an area with high levels of HIV in adults and high poverty and unemployment. By linking their research with individual clinical records, Tanser's team was able to measure the proportion of all individuals with HIV receiving ART in a given community.

The researchers showed that an uninfected person in an area with the highest ART coverage (30 to 40 per cent of all HIV-positive individuals) was nearly 40 per cent less likely to become infected with HIV than a person in one of the areas with the lowest coverage (<10 per cent).

The findings are particularly welcome as they show that a feasible, health-system-based approach using ART in the real-world setting of rural South Africa can substantially reduce new cases of HIV in the population.

ADHD Voices

Impact:

- This project explored attitudes to treatment among children diagnosed with ADHD.
- Children with ADHD feel they benefit from medication because they regain control over their decision-making, and this finding is helping inform the debate surrounding holistic treatments for ADHD.

Wellcome Trust funding

Society and Ethics University Award (2006), associated Dissemination Award (2011)

Science Museum London, Wellcome Images

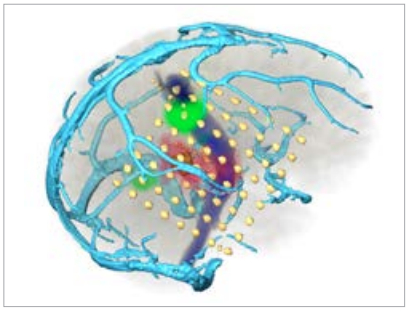
Attention deficit hyperactivity disorder (ADHD) is the most common behavioural disorder in the UK: it affects an estimated 2–5 per cent of school-aged children and young people. The ethical and social issues surrounding the disorder are complex and often controversial, particularly the question of whether to use stimulant drugs to treat children with diagnosed ADHD. Professor Ilina Singh, from King's College London, is principal investigator of the VOICES study (Voices On Identity, Childhood, Ethics and Stimulants: Children join the debate). The study looked at children's experiences with ADHD diagnosis and stimulant drug treatments, examining their attitudes to ADHD, behaviour, medication and identity. Researchers interviewed more than 150 children aged between 9 and 14 in the UK and the USA to understand their perspectives.

In contrast to the common concern that medication with drugs such as Ritalin turns children into 'robots', Professor Singh's work indicated that children with ADHD tend to feel they benefit from medication because they regain control over their decision-making. The team also found that the impact of the ADHD label and its associated stigma was often greater than that of the drug treatment itself. In the UK, the diagnosis often led to bullying; in the USA, children tended to be more secretive about their diagnosis, leading to feelings of isolation.

A series of short animated films using excerpts from the interviews is hosted on the project's website, which also provides practical recommendations for families, doctors, teachers and children affected by the disorder.

Applications of research

Improving epilepsy operation outcomes



Impact:

- Professor John Duncan and team have developed software to build detailed 3D models of the brain, allowing neurosurgeons to carry out complex operations more safely.
- A prototype for the technology is helping surgeons plan and carry out surgery for epilepsy.

Wellcome Trust funding
Healthcare Innovation Challenge Fund, 2012

Image courtesy of John Duncan

More than 40 per cent of the 450 000 people with epilepsy in the UK continue to have seizures despite medication. These individuals can have operations to remove the source of the epilepsy in the brain, but surgery is complicated by the risks of damaging important anatomical and functional structures, which may have life-threatening consequences. Owing to the delicacy of these operations, accurate positioning and prior knowledge of brain structure and function are imperative.

Professor John Duncan and team from the Centre for Medical Image Computing and Neurosurgery at UCL are collaborating with Medtronic to develop new imaging techniques for neurosurgery. The system integrates information from an array of imaging technologies, including fMRI, EEG, MEG, CT and PET. It then provides a 3D visualisation of crucial brain function areas, connections and blood vessels, helping clinicians to effectively plan and carry out surgery.

Prototype software has been successfully tested in surgical planning for around 30 patients. A second prototype, EpiNav, is currently in the late stages of development and will feature an improved user interface and better integration with Medtronic's existing systems. This technology will improve the outcome of the hundreds of epilepsy surgery operations carried out each year and could potentially enable surgeons to operate in circumstances previously considered too risky.

Building an arsenic biosensor

Impact:

- Dr James Ajioka is developing an arsenic biosensor based on *Bacillus subtilis*, a harmless soil-dwelling bacteria.
- The biosensor will be incorporated into a cheap, portable device designed for testing drinking water in rural Nepal.

Wellcome Trust funding
Translation Award, 2012

N Durrell McKenna, Wellcome Images

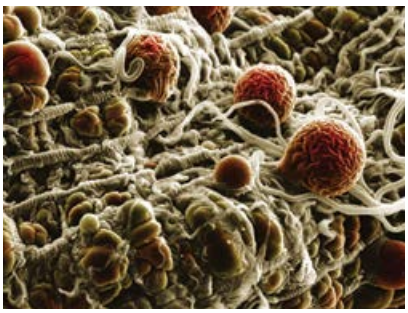
Arsenic contamination in drinking water affects around 100 million people in low- and middle-income countries. Arsenic testing requires samples to be transported to a laboratory; however, centralised testing is almost impossible to implement across the ten million tube wells in South Asia, especially in rural countries such as Nepal.

Dr James Ajioka from the University of Cambridge is building a cheap, portable testing kit based on engineered bacteria; the kit changes colour when it encounters arsenic. The concept was initially developed by students in the iGEM (International Genetically Engineered Machine) competition, and Dr Ajioka's team has successfully transferred their work to the bacterium *Bacillus subtilis*.

A strong relationship with stakeholders in Nepal, including local people, has ensured that local concerns and user requirements have influenced the design and marketing of the device at every step. This should promote good take-up by Nepalese villagers and, by empowering them to test their own water supplies, help to limit the burden of arsenic poisoning across the region.

The kits' benefits include a simple method, inbuilt safety features and a long shelf life.

An evidence base for malaria control



Impact:

- Abdisalan Noor's analysis of malaria risk and control has made major contributions to policy changes in some of Africa's most vulnerable countries.
- His research has underpinned the current Kenyan National Malaria Strategy, influenced regional policy and led the WHO to revise their guidelines.

Wellcome Trust funding

Intermediate Fellowship in Public Health and Tropical Medicine, 2011

Hilary Hurd, Wellcome Images

Abdisalan Noor uses spatial epidemiology to analyse the risk, control and treatment of malaria in Africa. Taking data on the prevalence of malaria infections in communities, malaria cases from health facilities and variations in climate, he develops high-resolution maps that show the geographic distribution of the disease and models that examine risk, people's access to control and treatment for the disease, and the impact of interventions.

Within the field of spatial epidemiology, Noor is considered the most prolific published leader in Africa. He has worked in collaboration with national programmes in Kenya, Somalia, Djibouti, Namibia, Nigeria, Tanzania and Sudan. His evidence has been used to develop national strategies, cost malaria action plans and improve intervention targeting. For the current Kenyan national malaria strategy, his evidence was used to inform the targeting of mosquito net distribution, indoor residual spraying, and case management and surveillance. His contribution led the World Health Organization to issue revised guidelines for universal free or highly subsidised coverage of mosquito nets.

Noor's work to improve the targeting of interventions is particularly important because malaria incidence is decreasing in many parts of Africa. He was awarded the African Union Scientific Award for Life and Earth Sciences for 2009, and in 2011 he was given a presidential appointment to serve as the Chairman of Kenya's National Council for Population and Development. Noor continues to help shape global malaria policy as the co-Chair of the Roll Back Malaria Monitoring and Evaluation Reference Group and a member of the WHO Global Malaria Strategy 2015–2025 steering committee.

He works at the KEMRI Wellcome Research Programme and is based in Nairobi.

Innovative retinal imaging device

Impact:

- Indian company Remidio have patented a novel illumination system for retina imaging that is cheaper and more compact than conventional technologies.
- Remidio's next generation of devices will be digital, telemedicine-ready and tailored to the needs of the Indian market.

Wellcome Trust funding
Award for R&D in Affordable Healthcare in India, 2012

Remidio

An estimated 50 million people with diabetes live in India. Many of them are likely to develop diabetic retinopathy, a secondary condition that can lead to blindness unless it is treated. It can be detected early when retinal imaging systems are used to photograph the back of a patient's eye; however, current imaging technologies are bulky and expensive, making them unsuitable for the rural areas of India, which generate 70 per cent of demand.

Remidio are developing new devices that use a novel, patented illumination system. The devices are compact, battery operated and a fraction of the cost of conventional systems.

Remidio have already delivered a hand-held ophthalmoscope and are testing hand-held smartphone-enabled and desktop digital versions of their retinal imaging systems.

Remidio will complete the development and evaluation of the clinical performance of the desktop and hand-held digital imaging systems, which can store images and transmit them via wireless network to a tertiary centre. If successful, the products would be suitable for use in rural communities and would help to diagnose diabetic retinopathy, glaucoma, age-related macular degeneration and ocular tumours.

Improving maternal and neonatal survival

Impact:

- Professor Anthony Costello has established a global network of community-based child mortality and morbidity surveillance in sub-Saharan Africa and south Asia.
- Trials show that the use of community-based peer learning for health can bring about significant reductions in maternal and neonatal mortality.

Wellcome Trust funding
Strategic Award, 2008

N Durrell McKenna, Wellcome Images

Maternal and neonatal mortality rates remain high in many low-income countries. One proposed solution focuses on community action, rather than centralised interventions, based on the concept that many small changes in behaviour can bring about significant improvements in survival rates in a cost-effective manner.

To test these ideas and inform policy makers, Professor Anthony Costello developed a global network of linked, community-based epidemiological surveillance sites in Bangladesh, India, Malawi and Nepal. Trials have tested two types of intervention – women's groups and volunteer peer counselling – to help deliver health messages and enable women to freely discuss hygiene, breastfeeding, preventive care and health-service accountability.

Epidemiological data from 150 000 births were recorded in seven trials. Overall, using the women's groups to raise awareness and implement health promotion strategies led to a 37 per cent reduction in maternal mortality and a 23 per cent reduction in neonatal mortality. In trials where at least 30 per cent of newly pregnant women joined the groups, the impact was even greater.

When scaled up, these methods are an effective, inexpensive way of boosting the survival of children and their mothers. In Orissa, India, the state government has scaled up 35 000 groups based on this model. Costello hopes to use policy-relevant studies of this kind to influence national governments, health ministries, and partner organisations such as WHO, UNFPA and Save the Children.

Spider silk properties inspire meniscal implants

Impact:

- With the use of new techniques based on how spiders spin silk, meniscal implants with remarkable strength and resilience have been manufactured.
- The implant has been successfully tested in sheep and will now be trialled in humans.

Wellcome Trust funding
Translation Award, 2009

William Warby, Flickr

Spider silk is six times stronger than high-tensile steel, twice as elastic as nylon and readily accepted by the human body, making it an attractive prospect for regenerative medicine. Orthox, which was founded by Dr Nick Skaer, is a spin-out company based near Oxford that develops medical devices formed from silk protein and focuses on their potential use as implants to treat knee injuries.

Meniscal injury is an unsolved clinical problem caused by damage to the cartilage pads that function as shock absorbers in the knee. Damage is commonly associated with ageing, obesity and sport injuries and can cause chronic pain and mobility problems.

Skaer and colleagues have developed a material made from silk, dubbed FibroFix™, that has very similar properties to meniscal cartilage.

A proprietary technique is used to extract silkworm silk proteins and cast them into the shape of the meniscus, using processes developed from an understanding of how spiders spin silk proteins. This can then be surgically implanted into injured patients. Once in place, it is hoped the implants will perform the same function as the cartilage they replace and provide a scaffold for regrowing tissue.

After successful trials in sheep, a second Translation Award was granted in 2013 to proceed to first-in-man studies and extend the technology to articular cartilage repair. If human trials show that the implants are well tolerated, they could eventually be used in some of the 1.3 million meniscal arthroscopies performed in high-income countries each year.

MRI brought to neonatal care

Impact:

- GE Healthcare is developing an MRI scanner for use in neonatal intensive care units.
- The new scanner will be smaller and quieter than conventional machines, which should minimise sick infants' disturbance and stress when being scanned.

Wellcome Trust funding
Strategic Translation Award, 2009

Wellcome Library, London

Magnetic resonance imaging (MRI) is a ubiquitous tool in medicine, but the technology has not had a significant impact on neonatal care. This is because existing devices are large, noisy, and incompatible with the life support and monitoring equipment required to support neonates. Furthermore, conventional MRI machines are usually installed far away from neonatal intensive care units, requiring children to be transported across hospitals or even cities.

A neonatal MRI scanner designed for use in neonatal intensive care units is being developed by GE Healthcare, with funding from the Wellcome Trust. The machine has been engineered specifically to meet the needs of fragile newborns. The workflow has been designed so that infants are disturbed as little as possible when they are transferred from the incubator to the scanner.

Trials of a prototype are set to begin in hospitals in Boston and Sheffield in early 2014. If the equipment is shown to be safe, it could be used as an additional tool alongside ultrasound scanning to improve diagnosis. The machines could prove invaluable in helping to mitigate common neurodevelopmental disorders such as cerebral palsy, epilepsy and learning difficulties.

Avatar therapy for auditory hallucinations

Impact:

- Dr Julian Leff is developing a novel therapy that uses computer-generated faces to assist in the treatment of people with schizophrenia who hear voices.
- The therapy showed excellent results in a pilot study and is now being independently trialled with a larger group of patients.

Wellcome Trust funding
Translation Award, 2012

Adrian Cousins, Wellcome Images

Hearing voices can be an intrusive or even terrifying symptom of schizophrenia. Around a quarter of people with schizophrenia continue to experience auditory hallucinations despite available drug treatments, and alternative talking therapies have shown limited efficacy.

Avatar therapy, developed by Dr Julian Leff from the Institute of Psychiatry, is a radical approach in which patients are encouraged to visualise and interact with the entity they believe is talking to them. Software allows the patients to generate a 3D animated face – an avatar – that is tweaked to match the appearance and sound of the imagined character. The computer system enables a therapist in a different room to maintain a dialogue with the patient and to give a persona and a voice to the avatar. Patients are encouraged to confront the entity and to assert control.

A pilot study involved 16 patients taking six half-hour sessions, and they all showed a reduction in the severity of their auditory hallucinations. Three of the patients, who had been hearing voices for 13 years, stopped hearing voices completely within three weeks of initiating avatar treatment. A Wellcome Trust Translation Award is funding a larger independent trial with 90 patients in London; if the pilot study results are replicated, avatar therapy could offer a cost-effective new treatment for thousands of individuals in the UK and abroad.

Engagement

Understanding transient neonatal diabetes

Impact:

- For the first time, a meeting was held to bring together all known UK families of patients with transient neonatal diabetes.
- Subsequently, 69 per cent of UK patients have joined the International Transient Neonatal Diabetes Register, which aims to gather ongoing clinical information on patients.

Wellcome Trust funding
People Award, 2010

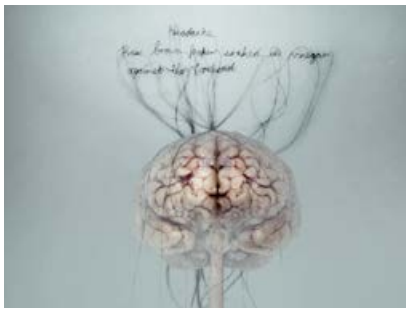
Anthea Sieveking, Wellcome Images

Between 1 in 215 000 and 1 in 400 000 babies born in the UK are diagnosed with diabetes soon after birth. In about half of these cases, they are diagnosed with transient neonatal diabetes, which is associated with low birth weight and high blood sugar levels. By the time they are 18 months old, most children are no longer classed as diabetic, but the diabetes can relapse at times of physiological stress or as the person gets older. Almost 70 per cent of transient neonatal diabetes is caused by epigenetic modifications on chromosome 6.

Professor Karen Temple and her team at Southampton University held a one-day meeting for all known people with transient neonatal diabetes in the UK and their families, plus researchers, healthcare professionals and some international patients. The meeting, which was the first event of its kind, enabled patients and their families to gain a clearer understanding of the field of epigenetics, in which chemical modifications can influence the function of particular genes.

As well as introducing patients to each other, the meeting allowed researchers to establish the International Transient Neonatal Diabetes Register, funded by Diabetes UK, which aims to gather ongoing clinical information to determine why diabetes recurs in a subset of patients as they age. This study could have implications for more common causes of diabetes. More than 60 per cent of British patients have joined, and newsletters and a website (**www.southampton.ac.uk/geneticimprinting**) have been developed.

Brains: The mind as matter



Impact:

- Wellcome Collection's temporary exhibition on brains attracted over 100 000 visitors.
- The show received critical acclaim and has been restaged in Manchester's Museum of Science and Industry.

Wellcome Trust funding
Wellcome Collection funding

Helen Pynor. Courtesy the artist and GV Art

In spring 2012, Wellcome Collection staged a temporary exhibition dedicated to the human brain – *Brains: The mind as matter*. The exhibition explored what humans have done to brains in the name of medical intervention, scientific enquiry, cultural meaning and technological change.

More than 150 objects were displayed, including brain tissue, artworks, manuscripts, videos and photographs. Works by contemporary artists including Helen Pynor, Annie Cattrell and Susan Aldworth were featured alongside historical exhibits, such as a skull from 2200–2000 BCE illustrating trepanning and 19th-century phrenological equipment. The exhibition was accompanied by a programme of events, which provided the opportunity to collaborate with the research community, and a fully illustrated book written by Marius Kwint and Richard Wingate.

During its 79-day run, there were more than 100 000 visits to the exhibition, including a higher than usual proportion of first-time Wellcome Collection visitors. The show was featured in the *Lancet* and *New Scientist* and was covered in several BBC broadcasts and newspapers. As a result of its popularity in London, the exhibition was restaged at the Museum of Science and Industry, Manchester, in the summer of 2013.

Art in Global Health

Impact:

- The experimental Art in Global Health project has linked together new global audiences for science and art.
- The scheme received national press coverage in its six countries, and each project resulted in at least one 'show' (most of which were held in nationally significant venues).

Wellcome Trust funding
Internal funding Award International Engagement Award 2012

Miriam Syowia Kyambi and James Muriuki

The Art in Global Health initiative attempted to celebrate the differences and similarities in scientific research in different cultures and contexts. Bringing together new audiences, the scheme placed a local artist-in-residence in six of the Trust's largest scientific centres around the globe – the Major Overseas Programmes in Kenya, Malawi, South Africa, Thailand and Vietnam, and the Sanger Institute in Hinxton, UK. Over six months, the artists investigated the research being undertaken, engaged with scientists and communities, and presented their creative works.

The artists responded to the opportunity with a range of approaches and topics. In Vietnam, Lena Bui used a zoonosis theme and presented an exhibition of drawings, sculpture, photographs and video. In Malawi, Elson Kambula's sculpture, photographs and film explored the gaps between traditional and modern medicine that influence research; they were presented to more than 5000 people at an arts festival and an exhibition. B-Floor Theatre in Thailand presented *Survival Games*, a physical theatre production on the battle between humans and infectious diseases, and more than 1200 people attended their performances in Bangkok. The projects in Kenya and South Africa used photography to explore the relationship between research centres and the communities that they work with, and more than 1000 people attended the exhibition at the National Museum of Nairobi. In Hinxton, Katie Paterson – inspired by genomic archaeology – made a fossil necklace of 170 specially carved beads, charting the development of life on earth.

The exhibition *Foreign Bodies, Common Ground* drew on elements from the project and was shown at Wellcome Collection in late 2013.

Human+ at Science Gallery Dublin

Impact:

- The *Human+* exhibition successfully reached its target audience of young adults: 60 per cent of visitors were under the age of 34.
- The exhibition attracted significant positive media attention, including articles in the *Guardian*, *New Scientist* and *Wired* (UK edition).

Wellcome Trust funding
Society Award, 2010

Embryo III, *Steve Barrett*

Human+, a flagship exhibition that ran at the Science Gallery Dublin in spring 2011, explored human enhancement and advances in science and technology. By promoting collaborations between artists and scientists, the exhibition drew together a range of installations, from a euthanasia roller coaster to a petunia–human hybrid expressing a human blood protein in its veins.

The gallery is located on the campus of Trinity College, Dublin, and one of its main aims is to attract young adults. During its four-month run, more than 42 000 people visited *Human+*, 40 per cent of whom were students and 95 per cent of whom said they would recommend the exhibition to a friend. Trained undergraduate students also acted as gallery 'mediators' and ran discussion sessions at local schools.

As part of its Lab in the Gallery programme for the public, *Free Will* featured scientists taking DNA samples from visitors to investigate the presence of a receptor that is thought to indicate a preference for risk taking. The Gallery also hosted panel evenings and discussion events, and it produced a publication to accompany the exhibition.

The exhibition attracted positive media attention both in Ireland and internationally, including articles in the *Guardian* and *New Scientist*, as well as radio coverage. An international tour of the exhibition is currently under consideration.

Research leaders

Professor Scott Waddell

Impact:

- Professor Scott Waddell has uncovered some of the neural pathways crucial for memory formation, consolidation and expression in the fruit fly *Drosophila*.
- He discovered that transposons, mobile DNA elements, generate genetic 'mosaicism' in a subset of neurones in the fly brain that are important for memory formation.

Professor Scott Waddell is a Wellcome Trust Senior Research Fellow at the Centre for Neural Circuits and Behaviour (CNCB) in Oxford, which he helped establish with the Director, Professor Gero Miesenböck. He began his research into the mechanisms governing learning and memory in fruit-fly brains when a Wellcome Trust International Prize Travelling Fellowship enabled him to move to Massachusetts Institute of Technology (MIT) as a postdoctoral fellow.

One of Waddell's successes at MIT was identifying two neurones in the *Drosophila* brain that are fundamental to memory: disrupting them prevented a fly remembering information it had learned previously. Waddell's group also located small groups of neurones controlling motivated behaviour. Switching these cells on or off determined whether hungry flies will pursue a smell they have previously associated with food. These discoveries emphasised the importance of precisely studying small neural networks, or even individual neurones, to understand brain function.

The CNCB, which was jointly founded by the Wellcome Trust and the Gatsby Charitable Foundation, opened in 2012. Leading a research group at the new centre, Waddell has added physiological recordings to his studies of the fly brain. This has already been incorporated into new discoveries, including the finding that flies use dopamine during reward learning in a similar way to other animals.

In 2013, Waddell and colleagues reported the importance of transposons in generating genetic diversity in fly brains. Transposons, which can alter gene expression and cause mutations by changing their position within the genome, were found to be mobile in neurones important for memory and notably inserted into memory-relevant genes. This raises the possibility that transposons may alter the expression of these genes, leading to behavioural differences between individual flies. It is also possible that the accumulation of disruptive transposon insertions over time may cause degeneration of brain function.

As one of the most widely used animal models, *Drosophila* has repeatedly shown its usefulness in gaining biological insights that can help to improve our understanding of humans. Waddell intends to continue his work with the fly to explore the neural mechanisms behind the formation, consolidation and retrieval of memories.

Funding

1997
Wellcome Trust International Prize Travelling Fellowship
1999
Merck/MIT Fellowship
2003
Edward Mallinckrodt Jr. Foundation Fellowship
2003
The National Institute of Medical Herbalists Project Grant
2008
The National Institute of Medical Herbalists Project Grant
2011
Wellcome Trust Senior Research Fellowship
2011
The National Institute of Medical Herbalists Project Grant
2013
Wellcome Trust Enhancement Funding

Achievements

1991
Awarded biochemistry degree, University of Dundee
1996
Awarded PhD, University of London
1996
Postdoctoral fellowship, MIT
2000
Waddell S et al. (2000) The amnesiac gene product is expressed in two neurons in the Drosophila brain that are critical for memory. Cell 103:805–13.
2001
Assistant Professor, UMass Medical School
2004
Keene AC et al. (2004) Diverse odor-conditioned memories require uniquely timed dorsal paired medial neuron output. Neuron 44: 521–533.
2007
Krashes MJ et al. (2007) Sequential use of mushroom body neuron subsets during Drosophila odor memory processing. Neuron 53:103–15.
2007
Associate Professor, UMass Medical School
2009
Krashes MJ et al. (2009) A neural circuit mechanism integrating motivational state with memory expression in Drosophila. Cell 139:416–27.
2011
Burke CJ, Waddell S. (2011) Remembering nutrient quality of sugar in Drosophila. Curr Biol 21:746–50.
2011
Professor, Centre for Neural Circuits and Behaviour (CNCB)
2012
Burke CJ et al. (2012) Layered reward signalling through octopamine and dopamine in Drosophila. Nature 492:433–7.
2013
Perrat PN et al. (2013) Transposition-driven genomic heterogeneity in the Drosophila brain. Science 540:91–5.

Professor Annette Dolphin

Impact:

- Professor Annette Dolphin has defined many of the mechanisms in neurones that regulate voltage-dependent calcium channels and neurotransmitter release.
- She has also elucidated the mechanism of chronic pain drugs such as gabapentin.

Professor Annette Dolphin has dedicated her career to the study of cellular processes in the human nervous system. Working in her graduate field, animal models of Parkinson's disease, convinced Dolphin that a detailed, rigorous approach was required to understand the basic science behind neurological diseases. She added electrophysiology skills to her background skills in biochemistry, equipping her to investigate neurological mechanisms at their most fundamental level.

At St George's Hospital Medical School, and then the Royal Free Hospital School of Medicine (which was later to become part of UCL), she made several seminal contributions to understanding the regulation of voltage-dependent calcium channels and neurotransmitter release. Both processes are important for the function of the synapses that control communication with neighbouring cells. Disruption of synaptic behaviour in the nervous system has been linked with many disorders, including chronic pain.

Voltage-dependent calcium channels are particularly difficult to characterise because each channel is made up of three subunits, and there are different forms of each subunit. This gives rise to a variety of calcium channels with unique properties. A total of 14 Wellcome Trust grants since 1987 have supported Dolphin's work to define some of these subunits and their interactions.

One notable achievement has been to show the mechanism of action of gabapentin, a drug widely used for various chronic neuropathic pain conditions. Dolphin showed that by binding to one subunit of a calcium channel (α2δ), the drug interferes with its function, thereby inhibiting its trafficking to the cell surface. This serves to reduce aberrant pain signals being sent to the brain from the peripheral nerves.

Alongside her research, Dolphin has been a prominent campaigner for women in science: she is the founding Chair of UCL's gender equality group and sits on the Biochemical Society's policy committee. She has been particularly vocal on the subject of gender disparity in academic prizewinners.

A Wellcome Trust Senior Investigator Award granted in 2012 will support her use of techniques such as patch-clamp electrophysiology and optical imaging to further elaborate on the functional behavior of the α2δ subunit. Dolphin anticipates that new insights will provide a template for novel mechanisms of drug action.

Funding

1987
Wellcome Trust Project Grant
1990
Wellcome Trust Project Grant
1991
Wellcome Trust Programme Grant
1992
Wellcome Trust Programme Grant
1992
Wellcome Trust Project Grant
1993
Wellcome Trust Equipment Grant
1994
Wellcome Trust Research Leave Award
1997
Wellcome Trust Equipment Grant
1998
Wellcome Trust Project Grant
2000
Wellcome Trust Project Grant
2001
Wellcome Trust Programme Grant
2002
Medical Research Council Programme Grant
2002
Wellcome Trust Project Grant
2006
Biotechnology and Biological Sciences Research Council Project Grant
2006
Wellcome Trust Programme Grant
2009
Medical Research Council Strategic Grant
2010
Medical Research Council 4 year Project Grant
2012
Medical Research Council 3 year Project Grant
2012
Wellcome Trust Senior Investigator Award

Achievements

1973
Awarded Biochemistry degree, Oxford
1973
Diploma Distinction Molecular Basis of Drug Action, Oxford University
1977
Awarded PhD, Institute of Psychiatry
1977
Postdoctoral Fellowship, College de France, Paris
1979
Yale University School of Medicine Fellowship
1980
Scientific Staff Position, National Institute for Medical Research
1981
Dolphin AC, Greengard P. (1981) Serotonin stimulates phosphorylation of protein I in the facial motor nucleus of rat brain. Nature 289:76–9.
1983
Lecturer St Georges Hospital Medical School
1985
Dolphin AC, Prestwich SA. (1985) Pertussis toxin reverses adenosine inhibition of neuronal glutamate release. Nature 316:148–50.
1986
Sandoz Prize of British Pharmacological Society
1991
Pfizer Prize in Biology
1994
GL Brown Prize of the Physiological Society
1999
Elected Fellow of Academy of Medical Sciences
2004
Viard P et al. (2004) PI3K promotes voltage-dependent calcium channel trafficking to the plasma membrane. Nat Neurosci 7:939–46.

Research leaders: Histories

2005
Cantí C et al. (2005) The metal-ion-dependent adhesion site in the Von Willebrand factor-A domain of α2δ subunits is key to trafficking voltage-gated Ca2+ channels. Proc Natl Acad Sci 102:11230–5.
2006
Dolphin AC. (2006) Gender: missing the prizes that can inspire a career. Nature 442:868.
2008
Hendrich J et al. (2008) Pharmacological disruption of calcium channel trafficking by the α2δ ligand gabapentin. Proc Natl Acad Sci 105:3628–33.
2009
Bauer CS et al. (2009) The increased trafficking of the calcium channel subunit α2δ -1 to presynaptic terminals in neuropathic pain is inhibited by the α2δ ligand pregabalin. J Neurosci 29:4076–88.
2010
Davies A et al (2010). The α2δ subunits of voltage-gated calcium channels form GPI-anchored proteins, a post-translational modification essential for function. Proc Natl Acad Sci 107:1654–9.
2012
Hoppa MB et al. (2012) α2δ couples calcium channels to neurotransmitter release sites to control release probability. Nature 486:122–125.

Professor Grahame Hardie

Impact:

- Professor Grahame Hardie defined the AMPK system and discovered its crucial role in managing energy in cells.
- He also elucidated the mechanism behind antidiabetic and anticancer drugs, such as metformin and salicylates.

In the cell, a dynamic system of metabolic pathways is required to maintain a balance between the supply, consumption and storage of energy. Exploring the mechanisms underpinning this energy management can bring valuable insights into common non-communicable diseases, including type 2 diabetes.

In 1988, early in his career, Professor Grahame Hardie realised that a single protein – AMP kinase (AMPK) – was central to the regulation of the energy-carrying molecule adenosine triphosphate (ATP) in rat liver cells. A pathway involving AMPK becomes active during times of metabolic stress, stopping energy-intensive processes and promoting the breakdown of fats and carbohydrates to generate ATP. During subsequent research, supported by several Wellcome Trust grants, it became clear that AMPK acts as an energy sensor and regulates a raft of cell processes in all animals, including humans.

These discoveries triggered a great deal of interest, driven in part by the development in Hardie's lab of a set of antibodies based on characterisation of crucial phosphorylation sites, which could be used as biomarkers to monitor AMPK function. Further research showed that AMPK has key roles in regulating glucose uptake, the oxidation of fatty acids and mitochondrial function. AMPK activation also explains many metabolic changes in muscle tissue that are induced during exercise.

By demonstrating that the AMPK system mediates the effect of hormones such as leptin and ghrelin, further research showed that the system affected crucial physiological functions such as appetite and insulin sensitivity. Hardie's lab also helped to elucidate the mechanism of action of the frontline antidiabetic drug metformin, which is currently prescribed to 100 million people worldwide. Their studies also helped to explain the protective effects that exercise has against the development of obesity and type 2 diabetes.

In 2003 Hardie found a link between AMPK and the tumour suppressor LKB1; since then, he has been exploring the connections between AMPK pathway dysfunction and the development of cancer. With the support of a 2011 Wellcome Trust Senior Investigator Award, Hardie hopes to improve our understanding of how anticancer drugs work through the investigation of novel activation pathways for AMPK.

Funding

1977
Medical Research Council Grant
1980
Medical Research Council Grant
1980
Medical Research Council Grant
1980
Medical Research Council Grant
1984
Medical Research Council Grant
1985
Medical Research Council Grant
1986
Science and Engineering Research Council Grant
1986
Wellcome Trust Project Grant
1987
British Heart Foundation Grant
1988
Wellcome Trust Project Grant
1989
British Heart Foundation Grant
1989
Science and Engineering Research Council Grant
1991
Agricultural and Food Research Council Grant
1992
Wellcome Trust Programme Grant
1994
Wellcome Trust Project Grant
1995
Biotechnology and Biological Sciences Research Council Grant
1996
Medical Research Council Grant
1996
Wellcome Trust Project Grant
2000
Medical Research Council Grant
2001
European Commission RTD Grant
2002
Wellcome Trust Programme Grant
2005
European Commission Integrated Project EXGENESIS
2007
Wellcome Trust Programme Grant
2011
Wellcome Trust Senior Investigator Award
2013
Cancer Research UK Grant

Achievements

1971
Awarded degree in Biochemistry from Cambridge University
1974
Awarded PhD in Biological Sciences from Heriot-Watt University
1987
Carling D et al (1987). A common bicyclic protein kinase cascade inactivates the regulatory enzymes of fatty acid and cholesterol biosynthesis. Febs Lett3:217–22.
1988
Munday MR et al. (1988) Identification by amino acid sequencing of three major regulatory phosphorylation sites on rat acetyl-CoA carboxylase. Eur J Biochem 175:331–8.
1991
Published student textbook, *Biochemical Messengers*
1994
Appointed Professor of Cellular Signalling, Dundee
1994
Corton JM et al (1994). Role of the AMP-activated protein kinase in the cellular stress response. Curr Biol 4:315–24.

Research leaders: Histories

1996
Hawley SA et al.(1996) Characterization of the AMP-activated protein kinase kinase from rat liver, and identification of threonine-172 as the major site at which it phosphorylates and activates AMP-activated protein kinase. J Biol Chem 271:27879–87.
1998
Elected Fellow of the Royal Society of Edinburgh
2002
Elected Fellow of the Academy of Medical Sciences
2003
Hawley SA et al. (2003) Complexes between the LKB1 tumor suppressor, STRADα/β and MO25α/β are upstream kinases in the AMP-activated protein kinase cascade. J Biol 2:28.
2004
Scott JW et al. (2004) CBS domains form energy-sensing modules whose binding of adenosine ligands is disrupted by disease mutations. J Clin Invest 113:274–84.
2005
Hawley SA et al. (2005) Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase. Cell Metab 2:9-19.
2007
Elected Fellow of the Royal Society
2008
Rolf Luft Award (International Prize for Endocrinology and Metabolism)
2008
Honorary Degree, Medical University of Bialystok, Poland
2010
Received the Novartis Medal and Prize of the Biochemical Society
2012
Hawley SA et al. (2012) The ancient drug salicylate directly activates AMP-activated protein kinase. Science 336:918–922.

Research environment

Wellcome Unit for the History of Medicine, Oxford

Impact:

- The Unit has become the world's leading centre for the study of medicine in the former colonies and in the history of war and medicine.
- Many students supervised at the unit have gone on to gain Research Fellowships or permanent teaching positions.

Wellcome Trust funding

Medical History and Humanities Strategic Award, 2004; History of Medicine Enhancement Award, 2009

Wellcome Library, London

The Wellcome Unit for the History of Medicine at Oxford, which was founded in 1972, has an established reputation as a world leader in the history of malaria. Under the guidance of Professor Mark Harrison and with funding from a Strategic Award, the Unit has become the world's leading centre for colonial and postcolonial medicine. It also has significant research strengths in the history of veterinary medicine and animal diseases, psychiatry and empire, war and medicine, and the history of leprosy. The Unit has produced many well-received monographs, edited collections, and research papers and articles in these areas.

As part of the Strategic Award, two new postgraduate degrees were established – a one-year MSc and a two-year MPhil programme. A large number of students trained and supervised at the Unit have secured academic posts as research fellows and lecturers in the history of medicine, both within the Unit and further afield. The Unit now attracts many visiting fellows and research associates from across the world.

In addition to capacity building, the forays into new areas have strengthened interdepartmental and inter-institutional collaboration. The Unit is now home to the Global Project on the History of Leprosy (funded by the Nippon Foundation), which is building an openly accessible database of leprosy archives from around the world as a tool for researchers interested in the modern history of leprosy (**www.leprosyhistory.org/**).

Wellcome Trust Monitor (Wave 2)

Impact:

- The Wellcome Monitor provides the most accurate picture to date of the UK's views on health, biomedical research and science education.
- The Monitor's methodology has been adopted by the UK Department for Business, Innovation and Skills for its next Public Attitudes to Science survey.

Wellcome Trust funding

Internal funding

The Wellcome Trust Monitor is conducted every three years to survey public opinion on issues surrounding health, biomedical research and science education. The second wave of the survey was carried out by Ipsos MORI in 2012. A report, summary infographics and data were disseminated to media outlets, policy makers and science communicators in May 2013.

In the Monitor, a random sample of 1396 adults and 460 young people across Britain answered questions on their attitudes, experience and knowledge relating to science and science education. The Monitor found that more than seven in ten adults, and nearly six out of ten of young people, expressed a high level of interest in medical research. However, knowledge of how research is conducted is weak, and levels of understanding and interest have fallen since 2009. Although 67 per cent of adults and 50 per cent of young people recognised the concept of a controlled experiment in science, most could not articulate why the process is effective.

The Monitor also asked about topical issues, such as use of 'cognitive enhancers' and attitudes towards them. The survey found much lower levels of use than had been previously reported, illustrating the importance of using a robust survey methodoogy – an approach that has now been adopted by the Department for Business, Innovation and Skills for their next Public Attitudes to Science survey. The Monitor's data are freely available via the UK Data Service to encourage high-quality secondary research on public attitudes to biomedical science.

Effective health surveillance systems in Malawi

Impact:

- SPINE, a new electronic healthcare surveillance system, is helping policy, planning and research in southern Malawi.
- Healthcare professionals can carry out more effective patient management, and patients benefit from simple print-outs of diagnoses, tests and prescriptions.

Wellcome Trust funding
Major overseas programme, 2008

N Durrell McKenna, Wellcome Images

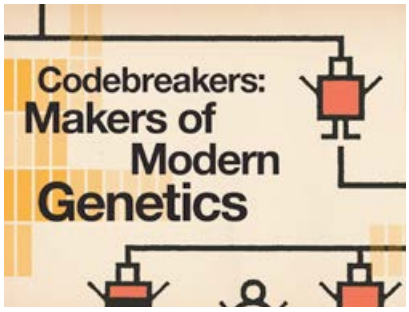
In low-income countries such as Malawi, a major obstacle to effective healthcare is the limited availability of accurate data on the disease burden of the population. Hospital admissions are often recorded using paper-based methods, which are cumbersome and unreliable.

A new electronic system has been introduced at the Queen Elizabeth Central Hospital in Blantyre, Southern Malawi, by Professor Rob Heyderman of the Malawi–Liverpool–Wellcome Trust Clinical Research Programme and colleagues from the University of Malawi College of Medicine and the Ministry of Health. SPINE (the Surveillance Programme of Inpatients and Epidemiology) aims to improve patients' care, as well as disease surveillance.

When a patient is seen, a member of the clinical team records their HIV status, antiretroviral use, diagnosis, treatment and outcome on the system; this enables clinicians to quickly access the records of readmitted patients. SPINE has been operational since 2009. It features a touchscreen interface, which is accessible even for staff with minimal computer literacy, and it has password protection. Patients also benefit from easy-to-read print-outs of diagnoses, tests and prescriptions.

The wealth of clinical data provided also helps research and will be strengthened further by the forthcoming integration of laboratory records. SPINE uses low-power technology and is stable in environments where power failures are common.

Codebreakers: The makers of modern genetics



Impact:

- More than 1.5 million pages relating to modern genetics have been digitised and made freely available on the Wellcome Library website.
- This project has digitised collections still under copyright and helped inform the Trust's approach to reform of copyright legislation in the UK and across the EU.

Wellcome Trust funding
Internal funding

Codebreakers: The makers of modern genetics is a free online collection of more than 1.5 million digitised pages of books and personal archives. Included are the papers of Crick, Watson, Wilkins and Franklin, the people who discovered the structure of DNA in 1953. The collection includes first-hand notes, letters, lectures, photographs and drawings (including Crick's iconic sketches of the double helix), in addition to scientific literature. Codebreakers contains the archives of 20 scientists and organisations, helping to place modern genetics in a broader scientific, historic and cultural context.

The project was made possible by a collaboration between the Wellcome Library and five partners: Cold Spring Harbor Laboratory Library, King's College London, UCL, Glasgow University and the Churchill Archives Centre have all digitised some of their collections to place alongside the Library's. The Wellcome Library website will provide free online access to these materials, and having this content (which was previously dispersed across two continents) in one online location will make it easier for researchers to explore the connections between the collections.

Codebreakers has also challenged the assumption that copyright holders would be resistant to allowing works still under licence, such as textbooks, being made freely available. The project has helped inform the Trust's approach to reform of copyright legislation in the UK and across the EU.

The Kenyan Consortium for National Health Research

Impact:

- The CNHR programme is enabling Kenya to build in-country capacity and expertise to fund health research.
- The Consortium has funded a significant programme of national health research and is working to facilitate greater links between research, policy and practice.

Wellcome Trust funding

Health Research Capacity Strengthening (HRCS) fund, 2009

Wellcome Library, London

The Kenyan Consortium for National Health Research (CNHR) is a not-for-profit organisation established to implement a programme of national health research funding supported by the Wellcome Trust and the UK Department for International Development (DFID). For the first time, Kenya has a significant within-country fund for health researchers that is awarded through a transparent, competitive and peer-reviewed national process.

CNHR was established in 2009 under the Health Research Capacity Strengthening Initiative – a £10m, six-year programme that was jointly funded by DFID and the Wellcome Trust. Led by Professor Gilbert Kokwaro as Director, it supports a programme of health research capacity-strengthening activities, which are locally developed and managed by CNHR staff to generate health research knowledge and to improve its use in evidence-based decision-making, policy formulation and implementation in Kenya.

As part of this programme, CNHR has selected and supported four Centres of Research Excellence to enable collaborative research in areas of strategic relevance to Kenya (including vector biology, pharmacology and health systems research). A postdoctoral research fellowship and re-entry grant scheme are linked to these centres.

Six senior research leadership grants have been awarded, with associated PhD studentships, to create research teams. A popular and highly competitive internship programme now has a cohort of 40 graduate interns, 26 of whom have already received further funding for postgraduate training.

The Consortium's annual national dialogue workshop aims to improve communication between researchers and government policy makers and to broaden the research base used to inform policy and practice. With support from PricewaterhouseCoopers Kenya and staff at the Wellcome Trust and DFID, the Consortium has established effective financial reporting, grants management and governance.

Within Kenya, the CNHR programme is visible and valued by the national government, with strong links to the new National Commission for Science, Technology and Innovation, as well as to research institutes and universities in the country. The CNHR programme has led to improved communication between Kenyan research organisations and facilitated research collaboration. In recognition of its contribution to the country's development, the Consortium was granted income-tax-free status in Kenya in 2012.

The Gurdon Institute

Impact:

- The co-localisation of outstanding researchers in the fields of developmental and cancer biology has resulted in several major breakthroughs.
- The Gurdon Institute has supported the careers of dozens of world-class researchers and boasts four 'home-grown' Fellows of the Royal Society.

The Wellcome Trust–Cancer Research UK Institute was founded in 1989 as a high-profile example of strategic partnership between the two organisations. The Institute was inaugurated in the heart of Cambridge University and aims to stimulate complementary research in the fields of developmental biology and cancer biology. The Wellcome Trust continues to supply the core funding and provides numerous grants to individual scientists.

In 2004 the Institute was renamed the Gurdon Institute in honour of one of its founding members, Sir John Gurdon. In 2012 Gurdon was awarded a Nobel Prize for his work with cloning in the 1960s.

Although the Institute is made up of independent research groups, one of its founding tenets is promoting formal and informal interaction within the building.

One of the many collaborations there saw Azim Surani and Steve Jackson working together on genome-wide reprogramming in the mouse germ line, using their complementary expertise in epigenetics and DNA maintenance pathways. They showed that DNA demethylation in the mouse primordial germ cells is mechanistically linked to single-stranded DNA breaks and the activation of the 'base excision' repair pathway.

An abundance of other ground-breaking research has emerged from the Gurdon Institute. For example, Rick Livesey's group has developed a way of turning human stem cells into cortical neurons. The cultured neurons form functional networks of excitatory synapses in the lab and can be used to model human cortical diseases.

Under the leadership of the current director, Professor Daniel St Johnston, the Gurdon Institute celebrated its 21st anniversary last year and has seen the number of Royal Society Fellows in the building rise to six. Four of these researchers developed their entire careers in the building.

Funding

The Wellcome Trust and Cancer Research UK continue to offer the Institute backing in the form of core funding, Fellowships, individual awards and equipment grants.
Other sources of funding, both direct and indirect, include the European Commission, BBSRC, MRC, the Royal Society, NIH, the European Molecular Biology Organization, HFSP, the Isaac Newton Trust, the Association for International Cancer Research, the Alzheimer's Research Trust, the Federation of European Biochemical Societies, the Japan Society for the Promotion of Science, the Ramon Areces Foundation, the March of Dimes, the Sankyo Foundation of Life Science, the Wenner-Gren Foundation, the Erasmus Programme, the Amgen Scholars Programme, the Croucher Foundation, the Woolf Fisher Trust, the Darwin Trust, the Thai Government, the Liechtenstein Government, the Turkish Government, the Cambridge Cancer Centre, Gates Cambridge Scholarships, Riken, SystemsX.ch, GSK and KAUST.
(From the Gurdon Institute's annual report, 2013.)

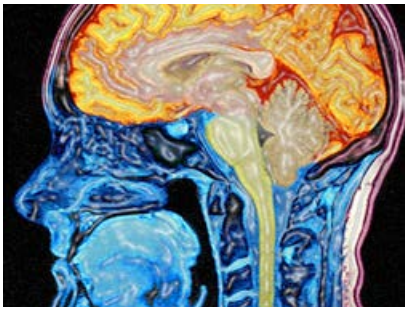
Achievements

1989
Wellcome Trust–Cancer Research UK Institute of Cancer and Developmental Biology is founded
1991
Wellcome Trust–Cancer Research UK Institute of Cancer and Developmental Biology is opened
1994
White RJ et al. (1994) Differential regulation of RNA polymerases I, II, and III by the TBP-binding repressor Dr1. Science 266:448–50.
1994
Colledge WH et al. (1994) Disruption of c-mos causes parthenogenetic development of unfertilized mouse eggs. Nature 370:65–8.
1996
Bannister AJ, Kouzarides T. (1996) The CBP co-activator is a histone acetyltransferase. Nature 384:641–3.
2000
Fraser AG et al. (2000) Functional genomic analysis of C. elegans chromosome I by systematic RNA interference. Nature 408:325–30.
2004
Institute renamed the Gurdon Institute
2002
Saitou M et al. (2002) A molecular programme for the specification of germ cell fate in mice. Nature 418:293–300.
2003
Construction of The Henry Wellcome Building of Cancer and Developmental Biology completed.
2005
Falck J et al. (2005) Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. Nature 434:605–11.
2007
Sartori AA et al. (2007) Human CtIP promotes DNA end resection. Nature 450: 509–514.
2008
Hajkova P et al. (2008) Chromatin dynamics during epigenetic reprogramming in the mouse germ line. Nature 452:877–81.
2009
Gurdon won the 2009 Albert Lasker Basic Medical Research Award, along with Shinya Yamanaka
2010
Hajkova P et al. (2010) Genome-wide reprogramming in the mouse germ line entails the base excision repair pathway. Science 329:78–82.
2011
Dawson MA et al. (2011) Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature 478:529–33.
2012
Shi Y et al. (2012) A human stem cell model of early Alzheimer's disease pathology in Down syndrome. Science Translational Medicine 4:124ra29.
2012
Bagijn MP et al. (2012) Function, targets, and evolution of Caenorhabditis elegans piRNAs. Science 337:574–8.
2012
Shi Y et al. (2012) Directed differentiation of human pluripotent stem cells to cerebral cortex neurons and neural networks. Nature Protocols 7:1836–46.
2012
John Gurdon wins Nobel Prize for Physiology or Medicine.
2013
Hackett JA et al. (2013) Germline DNA demethylation dynamics and imprint erasure through 5-hydroxymethylcytosine. Science 339:448–52.

Wellcome Library, London

Influence

Health-related findings in research



Impact:

- The Wellcome Trust has explored the complex issues surrounding the disclosure of health-related findings.
- The Wellcome Trust, MRC and Health Research Authority have developed a framework to be published in early 2014 to help researchers consider whether – and how – to provide feedback.

Wellcome Trust funding
Internal funding

Mark Lythgoe and Chloe Hutton, Wellcome Images

In any study involving human participants, researchers could make a finding that is relevant to an individual's health. For example, a brain imaging study could reveal a potential tumour or a genetic study could indicate that a participant has a high risk of developing a particular disease. Internationally, there is a growing trend to inform individuals of these health-related findings (HRFs); however, despite the complexity of the issues and the rapidly changing environment, there has been little guidance for researchers considering whether and how HRFs should be reported to study participants.

Over the past four years, the Wellcome Trust has undertaken several activities connected to HRFs. These included a review of the international literature, which focused on legal and ethical issues, and an analysis of the cost implications of feedback. Research on public attitudes to HRFs found that in general, there is a strong preference for participants to be informed, particularly where their conditions are serious and treatable.

Building on this work, the Wellcome Trust and Medical Research Council consulted with the research community, patients and the public to develop a framework on HRFs, which will be published in early 2014. The Health Research Authority plans to adopt the framework, which will support researchers and Research Ethics Committees as they consider the complex issues surrounding HRFs.

Access to Nutrition Index

Impact:

- The new Access to Nutrition Index assessed the nutrition-related performances of the 25 largest global food and beverage manufacturers.
- The Index is proving an important tool to encourage debate and catalyse action to tackle the global problems of obesity and undernutrition.

Wellcome Trust funding
Internal funding

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The food industry has a vital part to play in addressing the serious global problems of obesity and undernutrition. Recognising this, and seeing the need for an impartial way to assess companies' commitment to solving these problems, the Wellcome Trust partnered with the Bill and Melinda Gates Foundation in 2008 to fund the development of the Access to Nutrition Index (ATNI).

The first Index was published in March 2013 and assessed the nutrition-related commitments, performance and disclosure practices of the 25 largest global food and beverage manufacturers. Companies were evaluated on corporate strategy and governance related to nutrition, formulation and delivery of appropriate and affordable products, and positive influence on consumer choice. The companies that performed best were Danone, Unilever and Nestlé, but the Index found that even these could do much more to increase people's access to nutritious products. The marketing of breastmilk substitutes was an area of particular concern.

The Index received substantial media attention, and companies have already engaged in discussions with ATNI about how to improve their performance. A supporting Investor Statement has 39 signatories, who collectively manage more than $2.6 trillion in assets.

A follow-on Index will be published in 2015, and three Spotlight Indexes assessing food manufacturers in India, Mexico and South Africa will be launched shortly.

Wellcome Trust

We are a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health. We support the brightest minds in biomedical research and the medical humanities. Our breadth of support includes public engagement, education and the application of research to improve health. We are independent of both political and commercial interests.

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