In 2005, the Walport Report on Modernising Medical Careers sounded the alarm about the state of health of clinical academic training in the UK. 'Warning bells have been ringing for some time over the perilous state of academic medicine and dentistry,' the report said.

Research, it pointed out, is an essential part of a healthy NHS, but too many barriers face those seeking a clinical academic career: routes of entry and career paths were unclear; there was a shortage of properly structured and supported posts; and greater flexibility was required in the balance between clinical and academic training.

On the back of the report, and determined to rejuvenate academic training in the field, Cambridge set up the Clinical Academic Training Office (CATO) in 2009. Two years on, CATO's director Professor Edwin Chilvers is upbeat about its impact.

"Research training is a vital part of postgraduate training for people in all specialities, both hospital- and community-based," he explains. "We regard research training as an integral part of clinical training. It's not just about generating clinical academics – the professors and senior lecturers of the future – but also enriching the clinical practice of those who go on to become full-time NHS doctors."

Facilitating this training is where CATO comes in. By delivering high-level administrative and mentoring support for academic training programmes across the Clinical School, CATO shoulders the burden previously borne by individual departments and programme leads.

A key part of CATO's work is acting as the interface between the NHS (which in many cases is the employer), national and international, funding bodies such as the National Institutes of Health (NIH), Wellcome Trust and National Institute for Health Research (NIHR), the postgraduate deanery, (which is responsible for ensuring doctors are properly trained,) and the Clinical School, which is responsible for the academic component.

We hope, says Professor Chilvers, that "CATO brings the structure and support needed to enable clinicians to train as world class scientists with access to research and academic mentorship right the way through from undergratuate medical student level to postgraduate Foundation, Core and Specialist Training posts. Many of the programmes that offer this opportunity are now administered by CATO."

Responsible for more than half a dozen different programmes – funded by organisations from the NIHR and the Foundation Programme to the NIH, MRC and the Wellcome Trust – worth some £15 million a year, CATO has catalysed major changes in academic clinical training at Cambridge.

"A significant proportion of trainees working in the Cambridge University Health Partnership hospitals are academic trainees in one of these programmes," he says. "One example of this is the doubling in the number of Clinical Lectureships in the School over the past five years; these posts have been funded in part by the NIHR and CATO has played a key role in their establishment. So CATO provides the local hub for a very exciting uplift in clinical academic training occurring countrywide."

Another measure of its success is the fact that 70% of NIHR-funded Academic Clinical Fellows now go on to get nationally competitive Research Training Fellowship support, and a similar proportion of academic clinical lecturers go on to more senior fellowships. Crucially, those who are appointed from these schemes to NHS posts continue to have very research-active careers.

CATO has also been instrumental in delivering a raft of postgraduate qualifications for these trainees, including masters-level qualifications, and its ability to demonstrate the value of its work is helping secure further funding.

According to Professor Chilvers: "Having a strong administrative core in CATO acts as a sound springboard for Cambridge to compete nationally and internationally for further academic programmes. When these bids go in we need to show how they will be administered, and through CATO we can demonstrate we have all the necessary facilities, structures and know-how."

With many more programmes than most other medical schools in the UK, Cambridge ranks highly, thanks to CATO. "It's a model of how to do interface working in a modern academic health sciences centre," he concludes.

For more information on the Cambridge Academic Training Office, visit cato.medschl.cam.ac.uk

Rudolf Cardinal

I was a product of the Cambridge MBPhD Programme and began an NIHR-funded academic clinical fellowship in psychiatry in 2007; CATO was created two years later. Its energetic team have taken a lead in organising clinical academic training across specialities and grades, improving access to research training opportunities and making it significantly easier to organise academic training when multiple agencies (e.g. funding bodies, postgraduate deanery, university, NHS trusts) are involved. Following my ACF post I was awarded a Wellcome Trust postdoctoral fellowship for MBPhD graduates, to develop computational models of unsupervised attentional selection and competitive learning in the brain; I hope to pursue a career in clinical academic psychiatry.

Teaching old cells new tricks

Dr Ludovic Vallier

Much hyped by the media, stem cells have tremendous power to improve human health. As part of the Cambridge Stem Cell Initiative, Dr Ludovic Vallier's research in the Anne McLaren Laboratory for Regenerative Medicine shows how stem cells can further our understanding of disease and help deliver much-needed new treatments.

How do you study a human disease that has no equivalent in animals and where the human cells in question are so hard to grow outside the body they cannot be tested in the laboratory? The answer, until now, was with great difficulty. But by using a new stem cell technique, that is set to change.

Dr Ludovic Vallier, who holds an MRC Senior Fellowship in the Anne McLaren Laboratory for Regenerative Medicine, Department of Surgery at Cambridge in collaboration with Professor David Lomas (CIMR and Department of Medicine), works on a group of devastating genetic diseases affecting the liver.

"We target metabolic diseases of the liver, diseases such as alpha 1 antitrypsin deficiency. It's one of the most common single genetic disorders and the protein it affects – which is only produced by the liver – is really important because it controls activity of elastase in the lung. Without this control, people develop serious lung problems and the disease also affects the liver, so these patients develop liver failure," he explains.

The problem is that these diseases cannot be studied *in vitro* – in a dish – in the laboratory, he says: "You can't take cells from the liver of these very sick patients, and if you could they wouldn't grow, which means you don't have any way of screening drugs that could help treat these diseases."

Without effective drugs, the only current treatment is a liver transplant. "There is a huge shortage of organs and transplantation involves taking immunosuppressive drugs, which is heavy treatment especially in already fragile patients," Dr Vallier says. "And the disease is progressive so it's very complicated to manage."

Understandably, Dr Vallier is excited that a new method of producing stem cells developed in Japan has given him and other researchers a way of studying these diseases and screening potential drugs to treat them.

"The new technology consists of taking cells from skin and reprogramming them so that they become stem cells – cells that are capable of proliferating and differentiating into almost all tissue types," he says.

This reprogramming means a cell with a previously fixed identity can be taught a new one – in this case taking skin cells and reprogramming them to become liver cells. When the skin cells come from a patient with liver disease, these skin-turned-liver cells also have the disease, making them ideal for studying the disease and screening potential drugs to treat it.

According to Dr Vallier: "Because we can generate liver cells that mimic the disease of the original patient *in vitro*, that allows us to do basic studies that were impossible by biopsy or primary culture and also to do drug screening."

And because the skin cells can come from a whole range of people, it gives researchers access to a broad diversity of patients as well as overcoming some of the ethical concerns associated with embryonic stem cells.

"That's a very important step because it solves the problems associated with a limited stock of stem cells," he says, "and because it's a simple method, it is easily accessible to a wide number of laboratories."

Showing this can be done in a small number of liver patients in Cambridge is an important proof of concept, that supports the possibility that a similar approach might be applicable to a wide range of other serious diseases that still lack effective treatments, including neurodegenerative diseases such as Parkinson's and Alzheimer's Disease as well as heart diseases.

And Cambridge – which now has almost 30 groups doing stem cell research and strong links between academic researchers and clinicians – is perfectly positioned to make the most of this new technique.

"The Laboratory for Regenerative Medicine is starting to become an expert in this disease modelling and we are all part of a larger consortium, the Cambridge Stem Cell Initiative (SCI)" says Dr Vallier. "Together, we are putting together resources and scientific interest to really develop stem cells and their clinical application. The SCI is a unique consortium because it brings together a wealth of complementary expertise."

While this first revolution involves *in vitro* disease modelling and drug screening, Dr Vallier hopes this work will ultimately lead to personalised cell-based therapies where liver cells reprogrammed from a patient's own skin cells could be used in place of a liver transplant. "It will take time for us to assess this clinical use and show that it is safe as well as effective," he says, "but if you ask me again in five years I should be able to tell you whether we are going to do it."

For more information on the Cambridge Stem Cell Initiative, visit www.stemcells.cam.ac.uk

Mr Gavin Pettigrew, Professor Bradley and Professor Chris Watson leading research to increase access to transplantation

Expanding access to transplantation

Professor Andrew Bradley

In the UK, one in 20 people who need a kidney transplant will die waiting. With waiting lists expanding while the number of donors remains static, research in Cambridge is helping change policy and practice on kidney transplantation, giving more patients the chance of a new organ – and a new life.

"Transplants are a miracle of modern medicine," says Professor Andrew Bradley, Clinical Director of Transplant Surgery at the Cambridge Transplant Unit. More and more people need access to this miracle. Today, over 7,000 people in the UK are waiting for a new kidney – twice as many as ten years ago – yet only 800 kidneys become available each year, a number that is flat-lining.

"There is an increasing discrepancy between the huge number of patients waiting for a kidney transplant and the number of available organs," Professor Bradley says. "Waiting lists are going up but the number of organs is static."

Studies at Cambridge are improving access to kidney transplants – research that is changing national and international policy, as well as patients' lives.

Since the 1970s, most organs for transplant have come from so-called brain-death donors – people whose brains die before their hearts stop beating. But over the past decade the number of brain-death donors has declined because fewer people die due to traffic accidents and the way patients with head injuries are cared for has changed.

Another group of potential donors exists – people who have recently died from cardiac arrest – yet many surgeons believe kidneys from these cardiac-death donors are somehow inferior. A Cambridge-led study, however, has shown this is not the case.

Comparing hundreds of patients who received kidneys from either brain-death or cardiac-death donors, they found no difference in long-term kidney function or survival rates.

Unlike kidneys from brain-death donors, which are allocated nationally according to a points-based system, use of kidneys from cardiac-death donors still depends on local policy. In Cambridge, as result of the transplant team's research, over half of all transplanted kidneys now come from cardiac-death donors.

"Cardiac-death donors represent an extremely important and widely overlooked source of high-quality donor kidneys and have the potential to make a big difference to the number of kidney transplants done in the UK," Professor Bradley says.

"Using these kidneys has allowed us to double our transplant rates. If what we have achieved in our region was reproduced across the UK, we could increase the number of kidney transplants by between 50 and 100%."

The study could change the number of kidneys available and how they are shared throughout the UK. As a result of the findings, NHS Blood and Transplant (which manages and optimises the supply of blood, organs and tissues and raises the quality, effectiveness and efficiency of blood and transplant services) has set up a working group to decide whether these kidneys should be shared in the same – or similar – way to organs from brain-death donors.

And other studies done at Cambridge indicate the number of available organs could be expanded even further.

Transplant policies in the UK mean that many kidneys from potential donors who have died from primary brain tumours go unused because of cases where some recipients have developed cancer from the donated organ.

But research in Cambridge, which tracked thousands of patients using both the UK transplant registry and cancer registries in England, Wales and Northern Ireland, found that none of the 448 recipients who received organs from donors with brain cancer developed the disease.

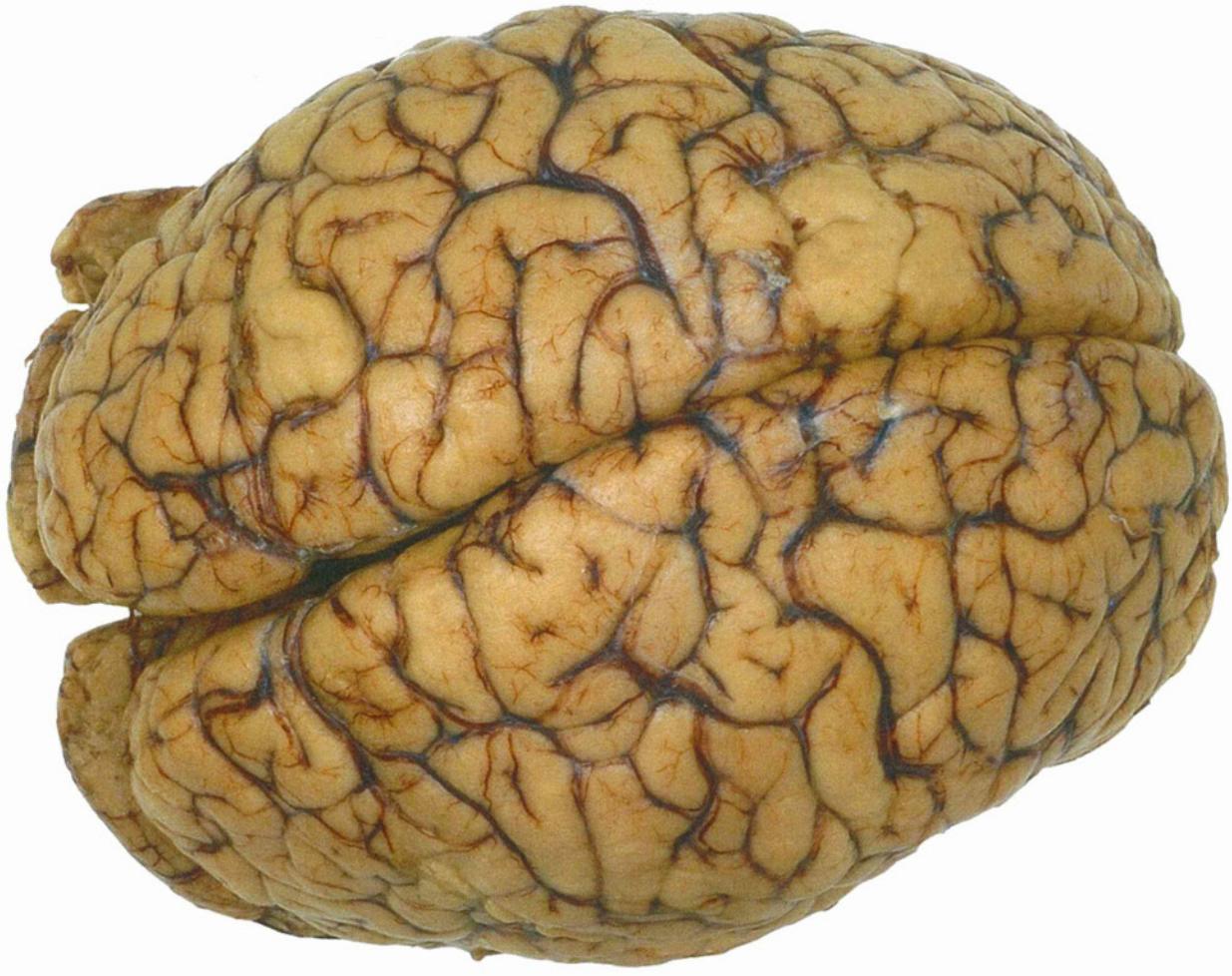
A kidney patient developing cancer from a donor is, Professor Bradley admits, catastrophic, but his research shows it's a rare occurrence that must be balanced against the risk of not getting a transplant. "We talk about patient and graft outcomes and survival, but if you don't get a transplant and get left on the waiting list, then for kidney transplants 5% of those on the waiting list die every year," he explains.

Similarly, work at Cambridge has shown that lengthening the time window within which kidneys can be removed after life support has been discontinued from one to four hours makes 30% more kidneys available without affecting the success of the transplant.

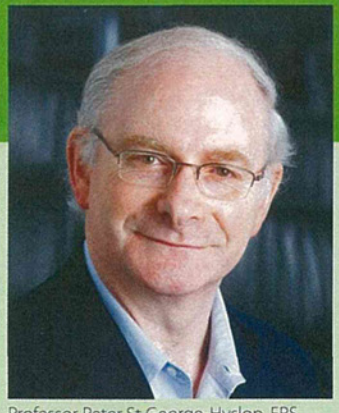
Through robust research, these studies are providing the evidence needed to change policies and practice, increasing access to transplantation and making a real difference to patients.

And making a difference is, Professor Bradley and his team point out, what their research at Cambridge is all about: "There are 23 kidney transplant centres in the UK. We're a close community. It's essentially a national service with common protocols, sharing schemes, and there are guidelines for many aspects of practice. What we hope is that our work informs those guidelines and gets taken up nationally and ideally internationally."

"It's very rewarding when you see things actually change," he concludes, "Moving from a situation of never sharing cardiac-death donor kidneys in the UK towards a sharing scheme where they can move around the country would be very satisfying."

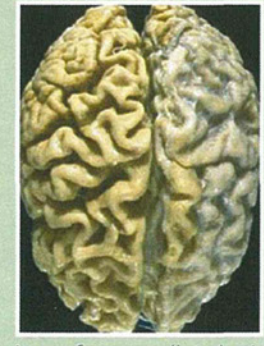


Physical sciences illuminate neurodegenerative diseases

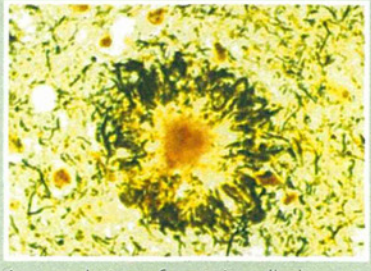


Professor Peter St George-Hyslop, FRS

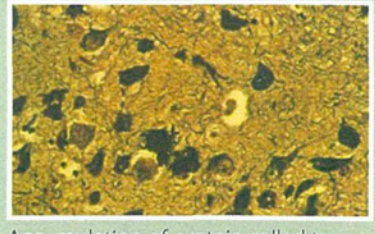
What do physicists, chemists, mathematicians and biologists have in common? One of the answers at Cambridge is a shared interest in unravelling the processes behind neurodegenerative diseases such as Alzheimer's, Parkinson's and Motor Neurone Disease.



Loss of nerve cells in brain



Accumulation of protein called Amyloid beta-peptide (Abeta) in brain as Amyloid or Senile plaques



Accumulation of protein called tau in neurons as Neurofibrillary tangles

As more people live to a ripe old age, an increasing number of us will develop neurodegenerative diseases such as Alzheimer's. Despite the escalating economic costs and human misery associated with these diseases, we still know relatively little about how they develop or how best to tackle them.

Alzheimer's is the most common neurodegenerative disease. "It's an enormous problem and we're not doing very well at the moment in slowing the disease or treating its symptoms effectively," says Professor Peter St George-Hyslop.

Neurodegenerative diseases such as Alzheimer's are difficult to study for several reasons. "One is that it's not easy to get pieces of living brain," he explains. "It's also a disease where patients become unable to speak for themselves, so unlike people with AIDS or breast cancer they aren't demonstrating outside the houses of Parliament demanding funding."

Although charities and campaigners are doing sterling work raising the profile of Alzheimer's, until recently attitudes to neurodegenerative disease had much in common with the way we viewed cancer 50 years ago.

"We are, for Alzheimer's, like where we were for cancer in the 1950s, when people didn't like to talk about it, were frightened or ashamed of it. And therapeutically we are in the same place; although we are beginning to learn about these diseases we don't yet have much in the way of effective therapies," Professor St George-Hyslop says.

One crucial discovery is that proteins misfolding in the brain form clumps or aggregates and these play a major role in causing neurodegenerative diseases. When these proteins misfold they take on certain characteristics that become noxious to cells, but what we need to know now is why these proteins misfold, which aggregates do the damage, and how that damage occurs.

Which is where physics, chemistry and mathematics enter the biological picture.

Professor St George-Hyslop leads a group of experts from disparate disciplines, each bringing different tools and different ways of working to the study of neurodegenerative diseases.

What began in late 2008 as a series of meetings has now developed into a 12-strong group funded by a £5.3 million Strategic Award from the Wellcome Trust and Medical Research Council. "It's a very interesting group of people who came together because they wanted to come together. They each knew they had something to contribute but also that they needed something else – some skills, some knowledge, some point of view – from another member of the group," he says.

"The biologists among us knew there were techniques that the physicists and chemists had that could help us. They in turn knew we had some biological knowledge that would help them apply, in a sensible way, their very good and insightful physical and chemical tools."

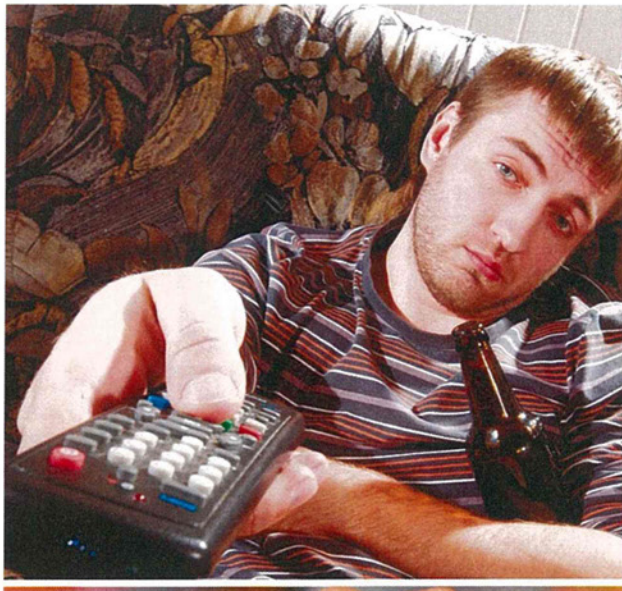
Among the group is Professor David Klenerman from the Department of Chemistry. One of the inventors of rapid, high-throughput DNA sequencing, he is now applying this knowledge to protein misfolding. From the same department comes Professor Michele Vendruscolo, a theoretical physicist working on the mechanics and thermodynamics of protein misfolding. Professor Chris Dobson, who is also from the Department of Chemistry works on protein misfolding in neurodegenerative diseases, while from the Department of Chemical Engineering and Biotechnology Dr Clemens Kaminski brings modern laser spectroscopy tools that allow you to watch these proteins misfold inside living cells in real time.

The group has applied these physical tools to study nematode worms in which a mutation produces the same protein misfolding that causes disease in humans. "That ability to see these things as they happen in a living model give us a much greater understanding compared with previous techniques, which essentially involved grinding up biological samples and examining them after these processes had occurred," Professor St George-Hyslop explains.

"What's important is the marriage of the physical tool with the biological question," he says. And he hopes that by revealing where these misfolded proteins act, these new tools could help researchers develop ways of blocking the damage they cause in both Alzheimer's and other neurodegenerative diseases.

"The primary goal is to understand what the beginning and the middle parts of the process are. We know what the end is – the cell dies and you get a disease – but if you know why the cells get sick and what the mechanisms are then you have a better chance of preventing or halting it," says Professor St George-Hyslop. "Our goal is to provide that fundamental knowledge of cause and mechanism. Hopefully from that will come some idea of which parts of those pathways you can monitor as a diagnostic and which parts you can block or change as a treatment."

More recently, the group has been enlarged by a £4.5 million grant from the National Institute of Health Research to support an extension of the Cambridge Biomedical Research Centre via the creation of a Biomedical Research Unit in Dementia for translational research. This has allowed the inclusion of researchers in immunology and in brain imaging from the department of Medicine and the Wolfson Brain Imaging Centre.



New unit boosts research on changing behaviour to improve public health

Professor Theresa Marteau

Bringing together experts from a broad range of disciplines, Cambridge's new Behaviour and Health Research Unit (BHRU) will provide policy makers with new evidence on ways of changing behaviour to improve health across the population.

It seems at once the simplest and most complex of health problems: by eating healthily, not smoking, being more active and cutting down on alcohol, we can live longer, healthier lives. Why, then, do so many of us ignore this advice?

April 2011 saw the launch of Cambridge's new Behaviour and Health Research Unit (BHRU). Funded by the Department of Health's Policy Research Programme, the Unit's remit is to develop and evaluate ways of changing behaviour at a population level to improve health and reduce health inequalities. Something that, so far, many countries have tried to do, with limited success.

The Unit brings together a team of experts from the University of Cambridge, two MRC units in Cambridge (Epidemiology and Human Nutrition Research), RAND Europe and the University of East Anglia. As well as researchers from the Clinical School, the Unit includes David Spiegelhalter, Winton Professor of Public Understanding of Risk at the Centre for Mathematical Sciences. The range of disciplines covered includes behavioural science, neuroscience, anthropology, economics and epidemiology.

This mix is what marks out the new Unit, says its Director and Honorary Professor of Behaviour and Health, Theresa Marteau. "It's a range of disciplines, some of which have been addressing similar problems but from different perspectives, for example bringing in neuroscience as well as epidemiology and behavioural science to understand the behaviour that contributes to population health and ill-health."

Insights from behavioural and neurosciences into the basis of everyday behaviour will be particularly important. "We will focus on two key systems. The first is the reflective, goal-directed system driven by our values and intentions. We want to lose weight, we intend to eat less. The second system is the more automatic system that is driven by immediate feelings and habits. These two systems operate sometimes synergistically as well as antagonistically in shaping our behaviour," she says.

So, despite intending to eat less, we find we have bought the chocolate bar at the checkout. "As neuroscience increasingly reveals how our behaviour is governed by unconscious processes, we understand better how advertisers and retailers shape our behaviour, unfortunately often to the detriment of our health. The trick is to see how we can capitalise on this understanding to develop more effective interventions that cue healthier behaviours."

Focusing on four key behaviours – diet, physical activity, smoking and alcohol consumption – the Unit's research programme has two overlapping strands, primary research and synthesis of existing evidence.

According to Professor Marteau: "It's good science to start with what we know, based on rigorous evidence synthesis, and design new studies that contribute to the existing evidence."

One of the Unit's new primary research studies involves studying on-line food purchasing using a virtual, online supermarket. Using this, researchers will be able to vary the way purchasing decisions are presented to thousands of 'shoppers', as well as altering how foods are presented.

"The virtual online supermarket provides the opportunity to run a large number of experiments in which we can change different features in a systematic way to identify the most promising interventions to take forward in real-life experiments," she explains.

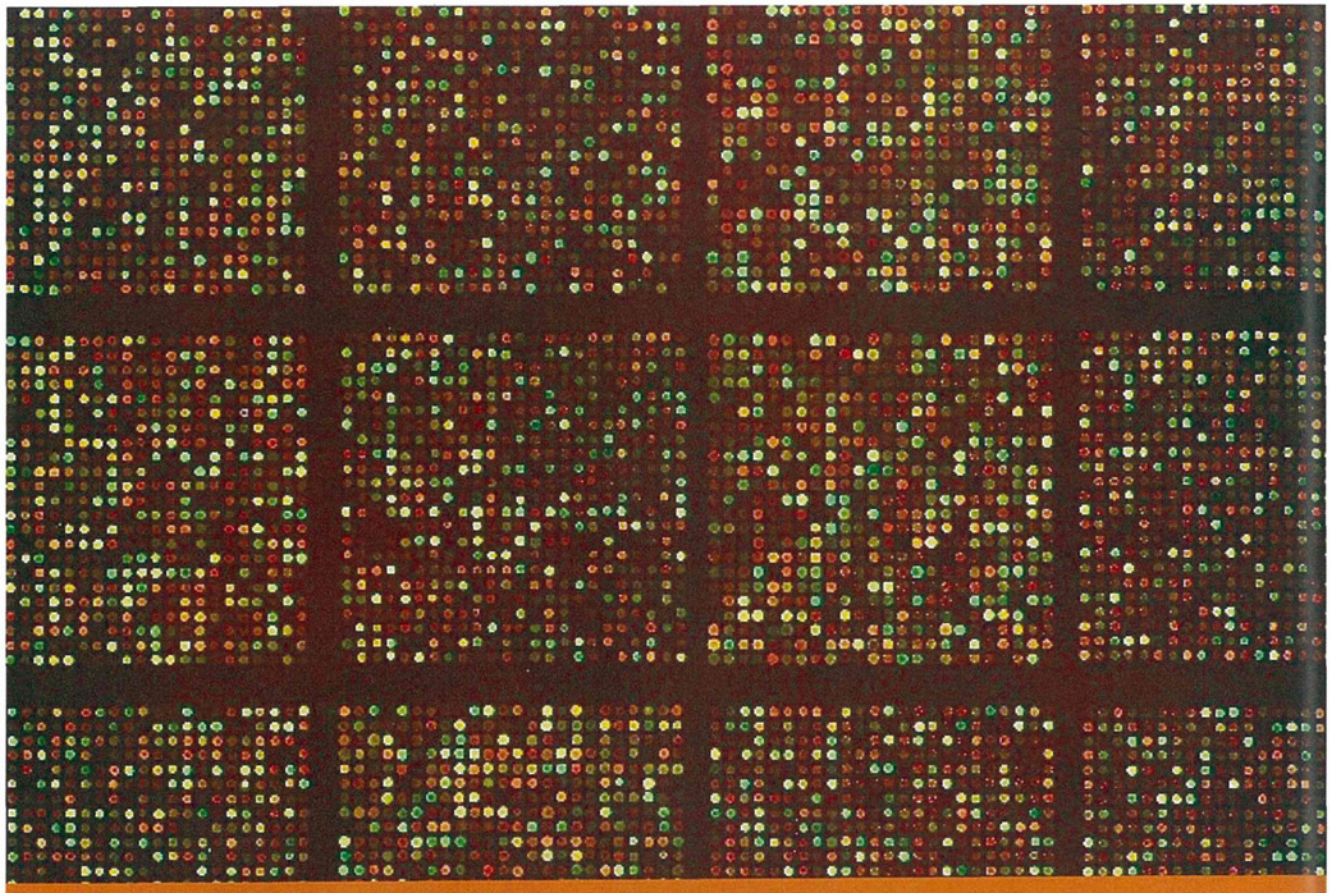
How, for example, do our brains deal with a chocolate bar that looks very inviting but carries a nutritional label warning us about its calorie count? And does a web site adorned with fruit and vegetables prime people to buy more of this type of food?

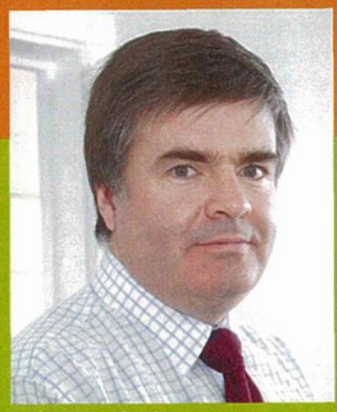
The virtual online supermarket goes to the heart of what researchers in the field call 'choice architecture' and how consumers might be 'nudged' into making healthier choices.

To be useful to policy makers, interventions need to be acceptable as well as effective, so another strand of research at BHRU is examining the public and political acceptability of interventions, something particularly relevant to alcohol.

According to Professor Marteau: "The majority of smokers want to quit and the majority of those who are overweight want not to be so. By contrast, most people in the UK don't want to reduce how much alcohol they consume. In part reflecting this, only half the population favours any kind of pricing policy to reduce alcohol consumption. This raises questions about the basis upon which such judgments are based. What happens if the evidence about the effectiveness of alcohol policies is presented not in terms of health but, for example, in terms of road accidents or violence? Does this alter how acceptable people find policies that at first glance they reject? How sensitive are people's judgments to the weight of evidence including its uncertainty? Exploring these questions using experiments grounded in qualitative work could shed light on the complex relationship between science and policy in health and other areas of public policy.

For more information on the Behaviour and Health Research Unit, visit www.bhru.iph.cam.ac.uk

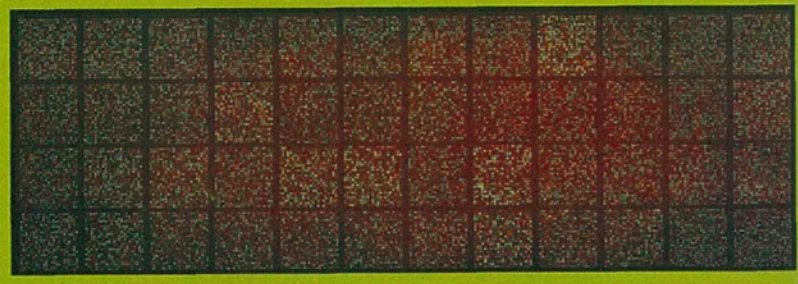




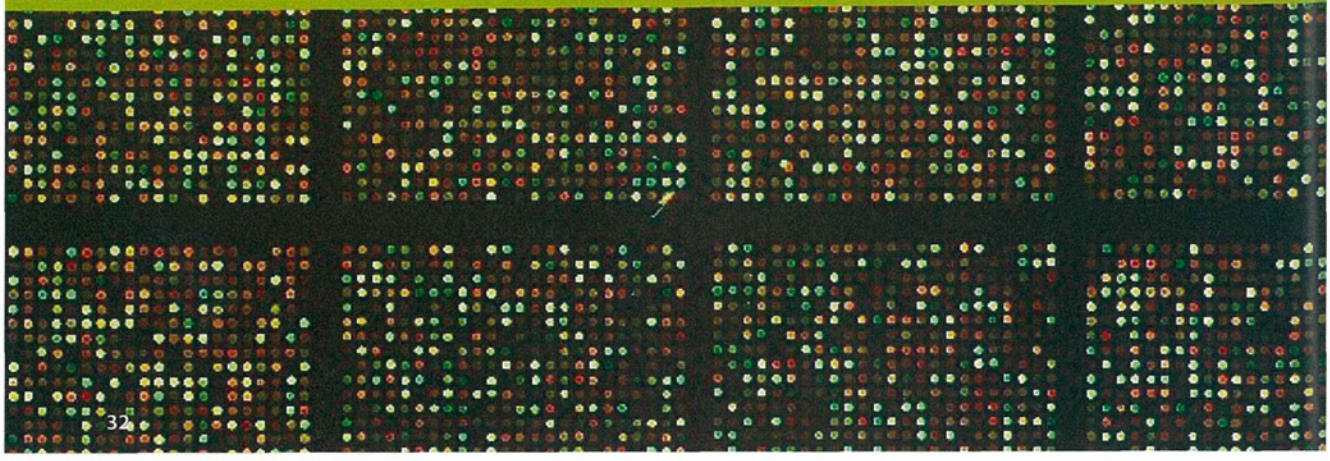
Professor Ken Smith

Improving outcomes for autoimmune diseases

They are chronic, debilitating but highly variable conditions. Now, researchers are discovering that different autoimmune diseases seem to be underpinned by common genetic signatures, and that these signatures could change the way doctors treat patients with these common and often life-threatening diseases.



The autoimmune transcriptome – fluorescent spots whose intensity reflects the level of all genes expressed in CD8+ T lymphocytes from a patient with active systemic vasculitis.



We all rely on our immune system for protection against infection and disease. But for a significant proportion of us, that immune system mistakenly attacks our body's own, healthy cells.

Known collectively as autoimmune diseases, the term encompasses some 80 different conditions from type-1 diabetes and rheumatoid arthritis to lupus and vasculitis, and around one in ten of us will suffer from an autoimmune disease at some stage during our life.

Although therapies exist, treating patients with certain autoimmune diseases is not straightforward. Within the same condition the disease can be much more aggressive in some patients, which, combined with the fact that current treatments often have significant side effects, presents clinicians with a dilemma.

According to Professor Ken Smith of the Cambridge Institute for Medical Research and Department of Medicine: "When people present with these conditions, treatment is pretty standardised, so everybody with the same diagnosis gets much the same approach to treatment. That's because at the moment we can't tell which patient will have the more aggressive disease."

Being able to accurately predict this however, would make a major difference to patients. "In Crohn's Disease, for example, there is a very effective treatment called anti-TNF therapy, but the trouble is it has side-effects," Professor Smith explains. "Currently, we minimise that toxicity by taking a conservative approach to treatment, only giving anti-TNF therapy to those whose disease flares up repeatedly."

"That means that if you don't have aggressive disease, you don't get unnecessary treatment, which is good. The problem is that if you have aggressive disease your therapy is delayed and it's very clear that this delay reduces the effectiveness of treatment."

Working with patients at Cambridge University Hospitals and using the latest microarray technology at the Cambridge Institute for Medical Research, Professor Smith and his team have discovered a way of identifying which patients are destined to have an aggressive form of these diseases.

By taking blood samples from patients with lupus or vasculitis, measuring gene expression – the process by which information encoded in our genes is converted into proteins and other large molecules that perform specific functions in our bodies – and then tracking the course of these patients' disease, the team found a key difference between those whose lupus or vasculitis proved aggressive and those with less aggressive disease.

"We found in one specific white cell, the so-called killer T cell, people had one of two different gene expression patterns. The difference was very distinct. And after three years it became very clear that the people in the smaller group – around one third of the patients – had a 90% chance of relapsing disease while the other two-thirds had only a 10% chance," he says.

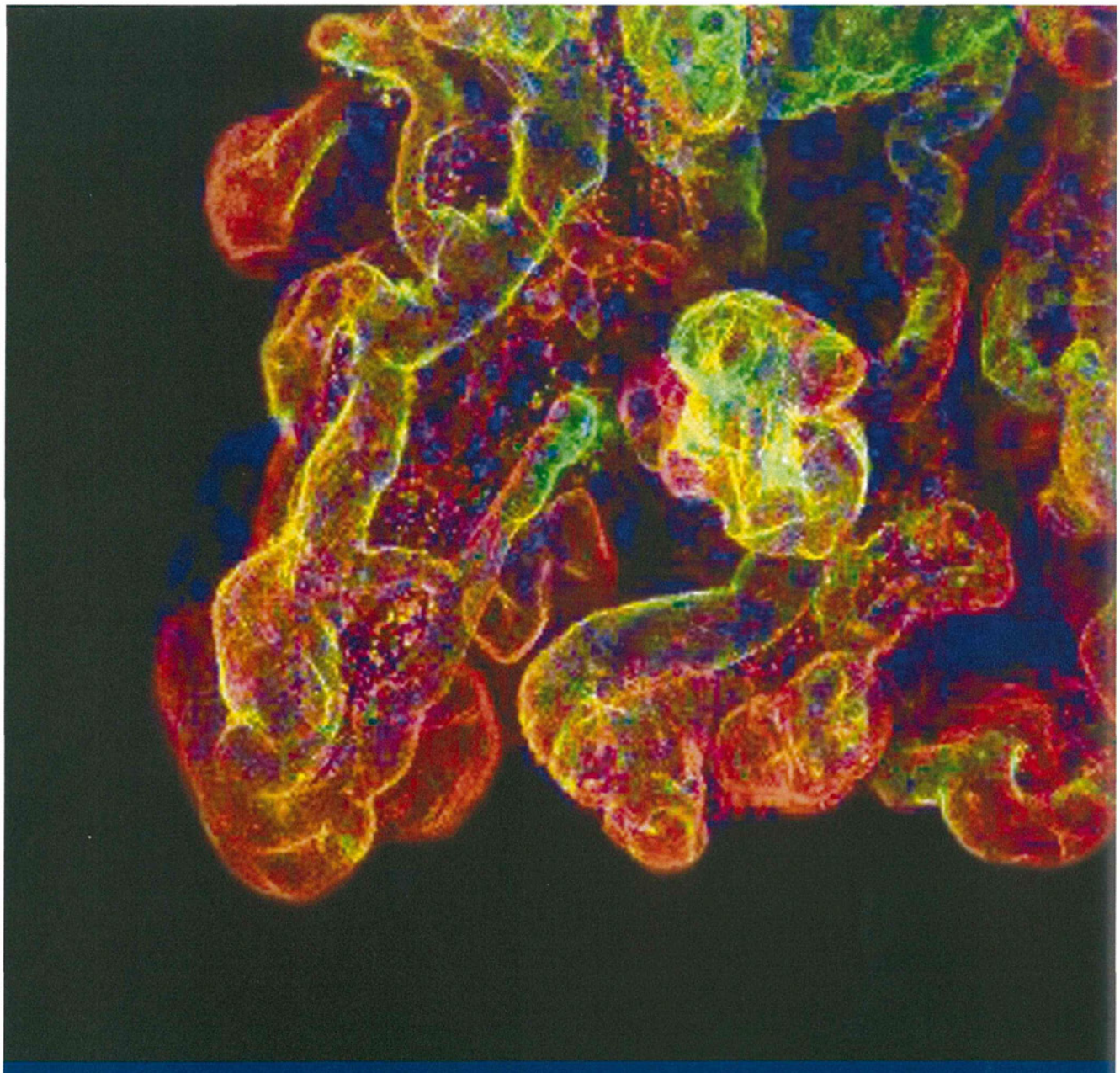
Repeating the blood tests with Crohn's Disease and ulcerative colitis they found the same split emerged. "If anything, it was even more striking," says Professor Smith. "Gene expression patterns in these white cells divides patients into two groups when they present, and these predict long-term outcome over three years so we can tell which will have more aggressive disease even though at the outset they look indistinguishable from each other clinically."

Of the four diseases so far studied – lupus, vasculitis, Crohn's Disease and ulcerative colitis – the same pattern holds. "Even though they are different diseases there is a common pattern that is determining outcome which is very interesting scientifically," he reflects.

With the test now patented, the team is setting up further research in Crohn's patients that will use the test to guide therapy. "We would hope that by treating some patients earlier, treatment would be more effective and that long-term disease-related damage in these patients – which often requires surgery – would be reduced."

The research shows what can be achieved by combining well-defined patient populations with advanced genomic technology, and by forging strong links between lab and clinic. "That's been critical, and it's why Cambridge is a good place to do this work: it's our laboratory excellence integrated with the clinic that enables this to happen," says Professor Smith.

The implications for patients with these and other diseases could be far-reaching, he believes: "We can begin to define prognostic biomarkers – in other words tests that should allow us to predict long-term disease behaviour – and that is the first step on the road to 'personalised medicine'. If that's successful, we'll roll out the test in Crohn's and do similar studies in other diseases," he says. "The fact that this works in four conditions suggests it might work in many others."



Professor Gordon Smith

Delivering better ways of preventing stillbirth

Despite recent dramatic reductions in cot death rates in the UK, and the development of sophisticated screening for Down's syndrome, preventing stillbirth is proving tougher to tackle. Now, a major study under way at Cambridge could change all that.

In the UK, one in every 200 women reaching their 24th week of pregnancy will have a stillborn baby. That means stillbirth is ten times more common than cot death and three times more common than Down's syndrome.

Yet compared with cot death, rates of stillbirth have fallen little over the past decade. And whereas women now have access to sophisticated screening for Down's syndrome, the way we screen for stillbirth still relies on little more than a tape measure.

According to Professor Gordon Smith of the Department of Obstetrics and Gynaecology: "When we think of serious complications of pregnancy one of the most common is stillbirth. But if you look at how we screen for stillbirth, for the general low-risk population – which is the population that has most stillbirths because there are more of them – the only currently recommended way of screening is measuring the size of the uterus with a tape measure."

For parents, a stillborn baby is tragedy. Many of these tragedies could be prevented given better ways of predicting which women are at most risk. Which is why in 2008 Professor Smith set up the Pregnancy Outcome Prediction Study (POPS).

One the largest and most robust studies of its kind, the four-year, National Institute for Health Research-funded study involves more than 4,000 volunteers – women in their first pregnancies who agree to take part in the research when they book their first scan at the Rosie Maternity Hospital in Cambridge.

As well as their routine ultrasound scans at 12 and 20 weeks, the women have blood tests, and additional research scans at 28 and 36 weeks, and when they give birth a sample of the placenta is kept and stored. Combining all this information will, Professor Smith believes, provide a clearer picture of how best to identify women at increased risk of stillbirth.

"The aim of POPS is to try and identify whether there's a combination of ultrasound and biochemical markers that better predict high-risk pregnancy, and which when applied in a screening programme would reduce the number of stillbirths," he says.

"The basic premise is that by studying the placenta and comparing it with controls, we can identify the things which are different in the placenta of a complicated pregnancy. And the rationale for studying the placenta is that there's a great deal of evidence to indicate that many stillbirths are related to an abnormal placenta."

Knowing which women are at higher risk of stillbirth would allow clinicians to decide how best to intervene to reduce that risk. "Initially, we would see this information being used to predict complications at term, 37 weeks and beyond, which is when one third of stillbirths occur," Professor Smith explains.

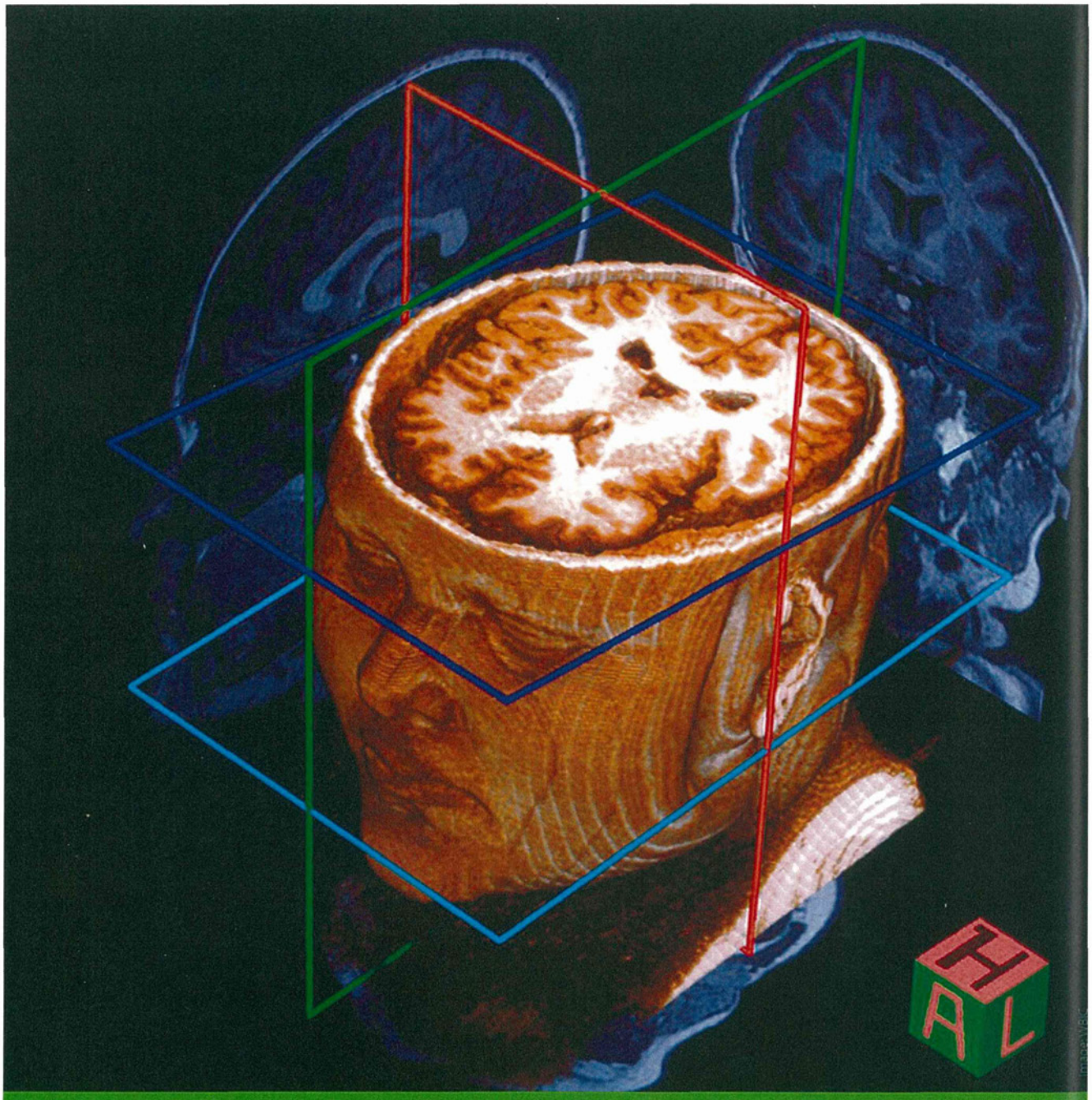
"One of the key things for me is the prospect of intervention, and the most obvious intervention is to deliver the baby early. Stillbirth often results from a diseased placenta so it's hard to treat, but once a woman reaches the 37th or 38th week of pregnancy you have the option of inducing labour," he says.

"Or it might be that we simply monitor the baby continuously during labour, or advise against certain women giving birth at home or in a midwife-led unit."

Cambridge is ideally placed to conduct a study like POPS. As well as having hundreds of willing volunteers, "Cambridge is probably the strongest centre in the world for people with an interest in the biology of the placenta," says Professor Smith. "We also have the Centre for Trophoblast Research, which brings together clinical and non-clinical researchers working on the placenta, and we have close links with the School of Biological Sciences, the Gurdon Institute and the Babraham Institute."

Coupled with great researchers, Cambridge excels in clinical research design, without which developing screening to reduce stillbirth would be impossible, he says: "Good scientists need well-defined material to study, and what we have in POPS is real excellence in clinical research design coupled with excellent basic science."

If the results from POPS do identify ultrasound and biochemical markers that predict risk of stillbirth, the next stage would be a trial to test the effectiveness of the screening and intervention. "The ultimate aim would be for our work to become part of a NICE guideline, changing the ante-natal care women receive," he says. "It's early days but our initial analysis looks very promising."



Joining forces to tackle obesity

Professor Sadaf Farooqi

It's a complex and growing problem, and one that costs the NHS over £1 billion a year. Now, Cambridge scientists are joining forces with pharmaceutical firm GSK in the search for urgently needed new drugs to treat obesity.

People tend to view obesity as a simple matter of what you eat and how much exercise you do but, like many health problems, the truth is rather more complicated.

"Our thinking has shifted," says obesity expert Professor Sadaf Farooqi of the Institute of Metabolic Science. "People have realised the simple response of 'go on a diet and do some exercise' is a bit prehistoric. We're not saying these things aren't important, but they don't help people who are already severely obese and it is those patients for whom we need to find treatments because of the problems they face."

And those problems are serious. As well as being more likely to suffer from depression, people with a body mass index of more than 30 are at significantly greater risk of developing type 2 diabetes, heart disease, stroke and certain types of cancer.

Researchers at Cambridge have made important discoveries about obesity in recent years. By studying people with rarer, genetic forms of obesity Professor Farooqi has found that there are strong genetic and biological determinants of weight, which are disrupted to cause obesity. "This shows us there are circuits for regulating our appetite and our weight, and understanding these are crucial if we are to find new treatments," she explains.

To do this metabolic scientists like Professor Farooqi are working with neuroscientists like Professor Paul Fletcher from the Department of Psychiatry. Until recently, he says, studies examining how people control their food intake have often stopped below or in the 'foothills' of the brain. The developing programme of research however, draws together neuroscientists working within the Behavioural and Clinical Neuroscience Institute and the Institute of Metabolic Science.

"There's an increasing acceptance that if we are going to understand how the incredible pandemic of obesity has come about, we have to think about the higher-order functions of the brain," he says. "You can think of the brain as one big organ that's very finely tuned to avoid punishments and look for rewards in the environment, and food is one of our favourite rewards. So as well as the metabolic level, we need to understand how this translates into day-to-day human behaviours."

Professor Ed Bullmore

Professor Paul Fletcher, Bernard Wolfe Professor of Health Neuroscience

Inspiration and funding for this work comes from the Bernard Wolfe Heath Neuroscience Fund. In 2009, Professor Fletcher and Professor Farooqi also joined forces with the pharmaceutical company GSK in a new academic/industry incubator. By allowing the academics access to GSK's Clinical Unit in Cambridge, the incubator provides the support and resources that have enabled them to conduct an ambitious study evaluating a new obesity drug being developed by GSK.

According to Professor Fletcher: "The incubator draws together scientists to work on a project that has a real translational clinical meaning, and offers them resources and opportunities to collaborate and do ambitious studies on new compounds."

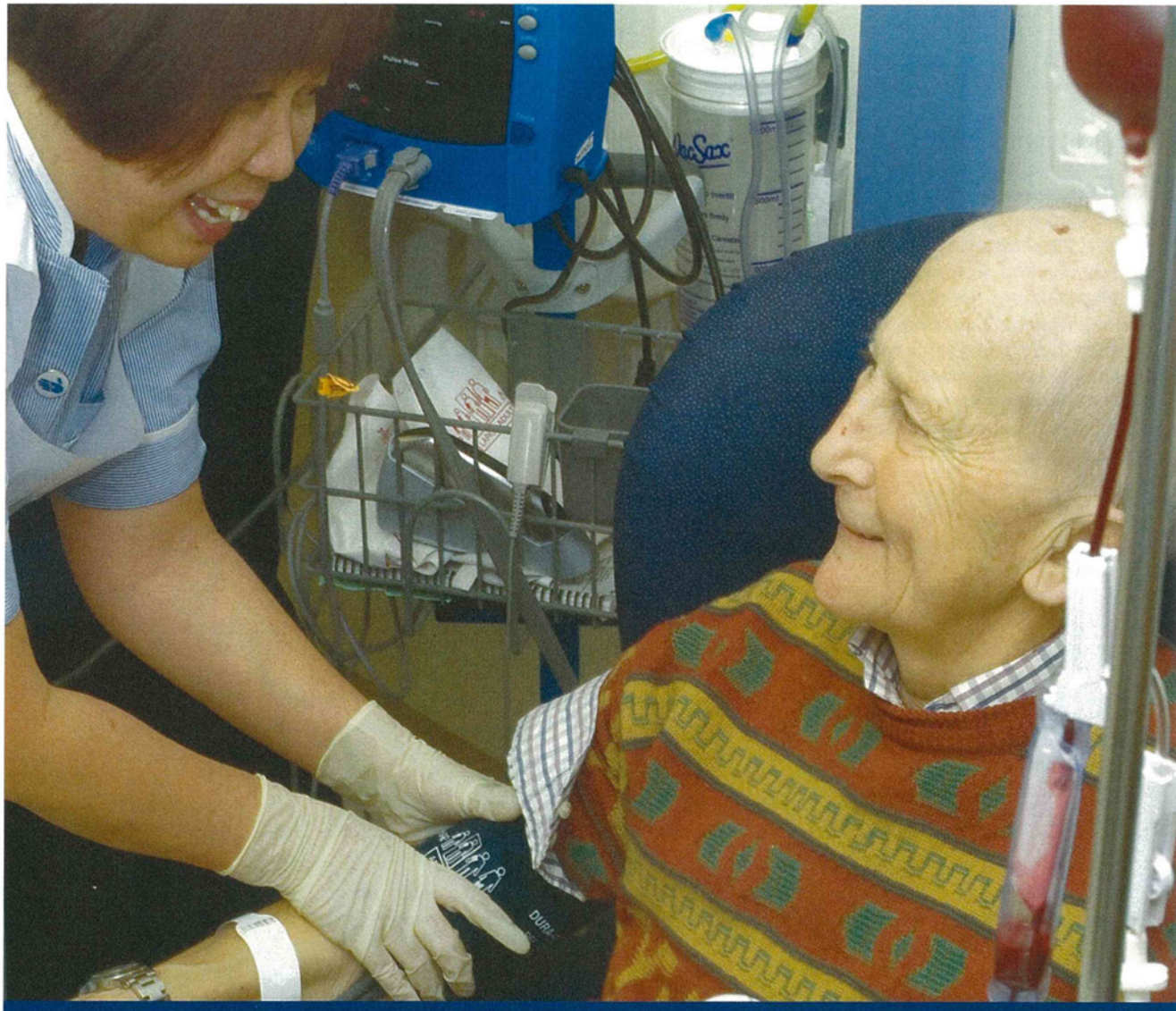
Working with a group of 60 volunteers recruited by GSK, the study's focus is a drug that targets so-called mu opioid receptors in the brain. "We think these receptors affect craving or desire to eat food, particularly high-fat foods, so if you can suppress these cravings with this drug you might have an effective treatment for obesity," Professor Farooqi explains.

Among the questions the study is seeking to answer are: does the drug affect metabolism; what impact does it have on food choices and weight loss, and how does it affect the way people's brains respond when they are exposed to food or food-related stimuli?

Answering the latter involves investigating brain responses using brain scanning or functional Magnetic Resonance Imaging. "With the brain scanner we show people pictures of delicious and less appetising foods, ask them to make food choices, and observe the activity of different regions of the brain both on and off the drug," says Professor Fletcher.

Both Fletcher and Farooqi are convinced that working together is the only way to tackle as complex problem as obesity. "The challenge is to harness findings from genetic, metabolic and neuroscience observations in order to help develop new treatments," he says, "and then make sure that as academics we continue to collaborate well with industry to work out how best to investigate where those should be used. But it really is about joining forces and bringing combined expertise to a complex problem."

"The incubator development of this new drug to control over-eating behaviour has been a great example of the University of Cambridge working innovatively and effectively with GSK to deliver a project in which the two organisations have worked closely together to achieve an outcome that might have been beyond the reach of either of them alone, said Ed Bullmore, who has played a leading role working half-time for GSK as Head of the Clinical Unit Cambridge and half-time for the University as a Professor of Psychiatry.



From blue sky to bedside in cancer research

Doing clinical research is a huge challenge. Understanding complex diseases and developing new ways of treating them requires an enormous amount of brain power. But the strict regulations governing research mean running the trials is equally taxing. Which is where the Cambridge Cancer Trials Unit makes all the difference.

Professor Duncan Jodrell

Professor Tim Eisen

Professor Dave Tuveson

Set up a decade ago by Dr Pippa Corrie, the Cambridge Cancer Trials Centre (CCTC) now has 92 staff and with 109 studies open to recruitment and 96 in follow-up. Such a large number of trials are needed because cancer is not one disease but an umbrella term for over 200 different diseases, each of which requires different treatment. The CCTC also hosts the West Anglia Cancer Research Network (WACRN), which is crucial to make cancer trials available to people across our region. This has worked very well and WACRN has consistently been one of the best performing networks in the country over many years.

But what does the CCTC do, and what makes it so successful? "It's very much a collaboration between Cambridge University Hospitals NHS Foundation Trust, Cancer Research UK and the University," says Professor Tim Eisen, who took over as director of the CCTC in 2006. "With an NHS department offering treatment to patients throughout our region and a highly successful oncology science base in Cambridge, we're linking the very pragmatic with the very blue sky, which will allow us to ask highly scientific questions on a population basis."

Under Professor Eisen's leadership, the CCTC has changed its focus over the past four years, particularly in terms of the kinds of studies it majors on.

"Whilst continuing to offer entry to high quality trials as widely as possible, we are gradually focusing our own academic effort on translational work in clinical research. These are sophisticated studies which link the the laboratory to the patient. It's often called 'bench to bedside' but the reverse is also true. The work is focused in certain tumour types – breast, prostate, oesophageal, pancreatic, ovary, and lung cancer," he says. "And we've put a lot of academic firepower behind early-phase trials and translational work, led by Professor Duncan Jodrell."

Compared with late-phase studies, which test a new treatment on large numbers of patients to discover whether or not it's better than the current standard, early-phase trials are investigations into new treatments for which no large-scale data exist.

"It might be the first time you've used a particular drug in humans, or you may want to get an early indication of how effective it might be," Professor Eisen explains.

As far as researchers are concerned, however, it's the day-to-day business of running trials that makes CCTC so valuable. Setting up a clinical trial involves a series of legal, ethical, financial, administrative and data management hurdles that researchers need help clearing. "The CCTC is a central facility that enables researchers to do their best work," he says.

A case in point is Professor David Tuveson, who works on pancreatic cancer. The number six cause of death due to cancer in the UK, where it kills 7,500 people a year, pancreas cancer is common but little discussed.

"It's thought to be a rare cancer but that's not so," says Professor Tuveson of Cancer Research UK's Cambridge Research Institute. "It's just a cancer people don't talk about very often because patients don't live very long after they are diagnosed. Pancreatic cancer is a quiet killer that doesn't have the public recognition of the more common cancers."

Until recently, researchers were puzzled by what made the disease so resistant to chemotherapy. Now, Professor Tuveson and his laboratory may have part of the answer.

"Pancreas cancer is a lethal disease. We understand the basic genetic problems underlying pancreatic cancer, but we don't understand why these genetics changes lead to such an intractable illness. What my laboratory concentrates on is providing an answer to this mystery," he explains.

By developing a mouse model of the disease, they have begun to solve the mystery. According to Professor Tuveson: "Pancreas tumours are a big scar sprinkled with little nests of cancer cells. In this respect they are very different from other types of carcinoma. And because of this structure, they're just aren't enough blood vessels to get drugs into the tumour."

Using this discovery, they are working on ways to disrupt the scar tissue so that they can deliver drugs into the tumour. "We have devised a method that increases the number of blood vessels in the tumour, and at the same time decreases the amount of scar tissue, by using a hedgehog pathway inhibitor (HPI). It's a developmental pathway that is very important for scar tissue formation, so the HPI shrinks the scar tissue and allows blood vessels to increase in number. Then," he says, "you can deliver various drugs more effectively."

A clinical trial is now under way to find out how giving patients the HPI affects the structure of their tumour. If the hypothesis is correct – and the HPI boosts the blood supply to the tumour – the team will go on to test it in combination with chemotherapy. To support this work, Professor Jodrell's team has recently developed a method to measure chemotherapy concentrations in pancreatic tumours.

The CCTC, with the support of Professor Eisen and Professor Jodrell, has made all the difference. According to Professor Tuveson: "It's helped coordinate all the legal, ethical, medical and financial aspects of doing an investigational trial. So without the CCTC, there would be no trial."

For more information on the Cambridge Cancer Trials Centre, visit www.oncology.cam.ac.uk/research/themes/cctc.html

High-risk hearts: a South Asian epidemic

Why is heart disease increasing at a greater rate in South Asia than in any other region globally? Large-scale population studies in Pakistan and Bangladesh aim to discover the basis of a little-studied public health problem of epidemic proportions.

From left: Dr Emanuele Di Angelantonio, Dr Danish Saleheen, Dr Rajiv Chowdhury and Professor John Danesh

Photo: Mark Mniszko

"The study of vascular disease among people living in South Asia has been comparatively neglected," said Professor John Danesh, Head of the Department of Public Health and Primary Care. "South Asians number 1.5 billion people worldwide, yet until recently there have been few powerful studies tailored to evaluate the distinctive genetic, biochemical and lifestyle risk factors affecting this group."

Now, two population studies jointly led by Professor Danesh and other researchers at the Department of Public Health and Primary Care hope to find some answers. With 35,000 participants, the Pakistan Risk of Myocardial Infarction Study (PROMIS) is the most powerful study so far to search for biological and other risk factors for Cardiovascular Disease (CVD) among Pakistanis. And, despite commencing only in January 2011, the Bangladesh Risk of Acute Vascular Events (BRAVE) study already exceeds any previous Bangladeshi study in scale.

PROMIS

"Pakistan is a country of 187 million people, yet fewer than 1,000 patients have been assessed in previous epidemiological studies of heart disease," said Dr Danish Saleheen, who jointly leads PROMIS. "When I was a medical student in Pakistan, infrastructure was lacking to conduct large-scale genetic investigations in that region. Moreover, there were not any instruments or studies that could specifically investigate lifestyle and dietary exposures which are very specific to South Asia in relation to conditions like heart attacks and stroke."

He began a project with colleagues in Pakistan to investigate what it might be about South Asians that makes them more vulnerable to the development of heart diseases. Were local dietary practices, such as the use of ghee as cooking fat, to blame? Or the many non-cigarette-based ways of consuming tobacco, including chewing, sniffing and ingesting? Or cultural habits such as marriage between first cousins? Or environmental influences such as contaminants in food and water?

After Dr Saleheen moved to Cambridge in 2006 as a Cambridge Commonwealth Trust scholar, the study design was optimised, long-term funding was secured, and full-scale recruitment commenced under the joint leadership of Professor Danesh. It now recruits patients with heart disease, stroke or diabetes at a rate of 10,000 per year from 13 institutes across Pakistan through the Centre for Non-Communicable Diseases in Karachi, whose current Director is Dr Saleheen.

The study is poised to yield a harvest of novel findings. For example, it has recently contributed to the discovery of nine genes for coronary artery disease and six separate genes for type 2 diabetes, with the findings published in *Nature Genetics*. Other detailed analyses are in progress with the support of more than £10 million in research funding from the US National Institutes of Health, Wellcome Trust and British Heart Foundation.

Perhaps where PROMIS will have its greatest potential impact will be the evaluation of local risk factors that can be modified. "We are beginning to identify distinctive factors which increase the risk of, or protect against, heart diseases," said Dr Saleheen. "For instance, consumption of ghee and indigenous types of tobacco, including 'naswar', increases the risk of heart attack. Through PROMIS, we are now able to pinpoint the contribution of these factors in a more precise manner than ever before."

BRAVE

Of all South Asian countries, Bangladesh probably has the highest rates of CVD and yet is the least studied. Dr Rajiv Chowdhury, who is himself from Bangladesh, explained the severity of the situation: "In the late 1990s it was estimated that there would be a 100% increase in CVD across South Asia by 2020. But, when you look at Bangladesh, there has already been a 3,500% increase. In the global combat against CVD, Bangladesh is a country 'missing in action'."

Gates Scholar Dr Chowdhury jointly leads the BRAVE study, which began seven months ago in pilot form in readiness for a subsequent large-scale study. "One important objective is to build an epidemiological resource – the first in Bangladesh – to be shared between the Bangladeshi and UK collaborators with equal intellectual partnership," said Dr Chowdhury, who jointly leads the study with Dr Emanuele Di Angelantonio and Professor Danesh. "The biorepository will be used to test current and future hypotheses relating to potential risk factors to help shape local and global cardiopreventive policies."

Dr Chowdhury is certain that, as in Pakistan, crucial risk factors will be discovered: "Bangladesh has the highest rate of urbanisation and population density in South Asia, and is facing the worst threats of climate change globally. Factors associated with such extraordinary circumstances may have influenced the population's massive shift in epidemiology towards increased CVD. Equally, it could be linked to suboptimal nutrition, widespread environmental contaminants such as arsenic in ground water and plants, or specific vulnerabilities in the genetic or metabolic make-up that have yet to be discovered."

Awards

2010

Fellow of the Academy of Medical Sciences

Professor Gordon Smith
Professor Maria Spillantini

Wellcome Trust Principal Research Fellowship

Professor David Owen
Professor David Ron (2009)

Wellcome Trust Senior Research Fellowship in Clinical Science

Dr James Rowe
Dr David Savage

Pilkington Teaching Prize 2010

Dr John Firth
Dr Mark Lillicrap

Inbev-Baillet Latour Healh Prize 2010

Professor Stephen O'Rahilly

Dale Medal of the Society of Endocrinology

Professor Stephen O'Rahilly

Donald Ware Waddell Award Arizona Cancer Centre, USA

Professor Sir Bruce Ponder

2010 Zulch Prize by Max Planck Society on behalf of the Gertrud-Reemtsma Foundation

Professor Alastair Compston

2010 McCulloch and Till Award from International Society for Haematology

Professor Berthold Göttgens

International Still birth Alliance Distinguished Researcher award

Professor Gordon Smith

Carl Camras Translational Research Award

Professor Keith Martin

British Society for Matrix Biology Fell Muir Award 2010

Professor Gill Murphy

Minkowski Prize (European Association for the Study of Diabetes 2010)

Dr Fiona Gribble