This booklet highlights just some of the successes from the MRC's long-term commitment to funding Experimental Medicine research. All have relied on MRC funding, but often they would not have been possible without additional support from NHS trusts and charities.

As well as supporting Experimental Medicine through grants and fellowships – which are often multidisciplinary, combining human studies with in vivo or animal studies – the MRC also provides separate translational funding schemes specifically tailored to enable the experimental development of new treatments and diagnostics. Details of these funding opportunities are at: **www.mrc.ac.uk/Ourresearch/Boardpanelsgroups/TRG/TranslationResearch**.

This publication can be downloaded from the MRC website at **www.mrc.ac.uk/experimentalmedicine**.

MRC e-Val

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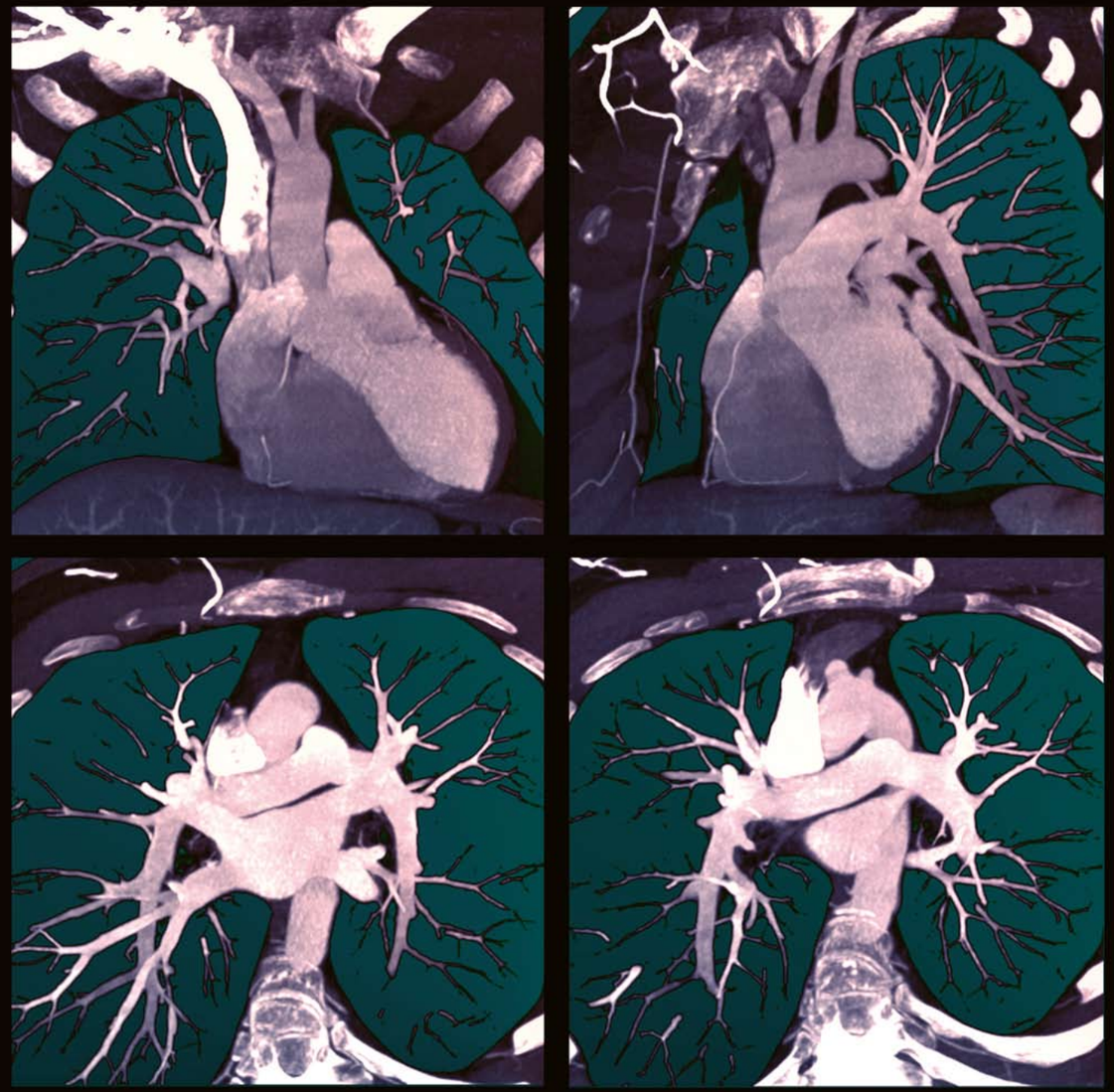
Experimental MEDICINE

Showcasing successes of MRC research



Foreword

Experimental Medicine describes research that aims to identify the intricate mechanisms that cause disease or demonstrate proof of concept of the validity and importance of new discoveries or treatments in development.

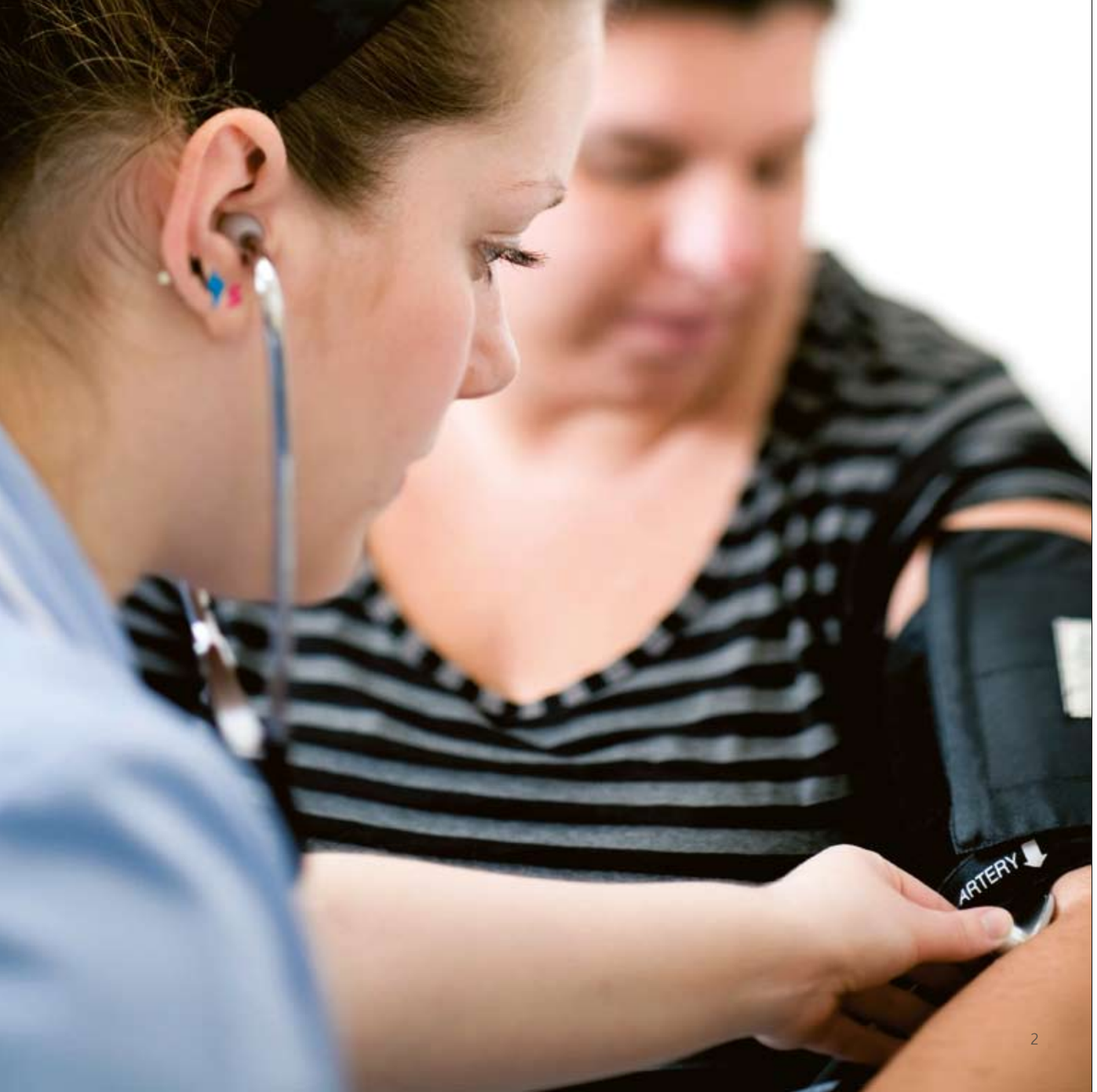
In recent years, the MRC has introduced a series of targeted strategic initiatives to encourage and enable such studies, but this has just been the start of our long-term commitment to Experimental Medicine.

A variety of scientists have embraced the challenge of working in this field and this booklet highlights examples of some of the exciting work already being carried out.

These case studies have been identified using the MRC's evaluation system, MRC e-Val. They show how support for Experimental Medicine research has led directly to some of the 64 new products and interventions, reported across the whole MRC portfolio, that are currently in early stages of clinical assessment.

Experimental Medicine is a crucial step in the translation of research into patient benefits. The MRC continues to offer a number of schemes to support the application of Experimental Medicine. I hope reading these examples of scientists turning their laboratory findings into something that really makes a difference to patients will inspire more researchers to engage in these schemes, apply for funding and realise the full potential of their research.

Sir Leszek Borysiewicz
MRC Chief Executive



The MRC's mission is to improve human health through research and while significant knowledge comes from molecular, cellular and animal studies, often it is only through in-depth human studies that we can effectively untangle complex diseases.

One such study from Dr Farooqi and Professor O'Rahilly at the University of Cambridge has given important insights into the relationship between high blood pressure and obesity:

A NEW GENETIC LINK BETWEEN HIGH BLOOD PRESSURE AND OBESITY

Dr Sadaf Farooqi and Professor Stephen O'Rahilly – an Experimental Medicine grant

With funding from a specific MRC Experimental Medicine call, Dr Sadaf Farooqi and Professor Stephen O'Rahilly at the University of Cambridge have increased our understanding of **the mechanisms of disease in obesity** and related metabolic disorders, leading to new knowledge on how best to target therapies. Among other things, they have studied the effects of a gene called melanocortin 4 receptor (MC4R), which works in the brain to control bodyweight.

Obesity is often associated with high blood pressure and in many people losing weight reduces blood pressure. Dr Farooqi and Professor O'Rahilly carried out an **in-depth study** of a specific group of patients whose obesity was due to defects in MC4R. The research showed that despite severe obesity, patients with MC4R deficiency were less likely to have high blood pressure. By comparing MC4R-deficient patients with people of the same weight but with a normal MC4R gene, they found that patients who had lost the MC4R signal in the brain had a lower response to stress. They went on to show that the link between MC4R, weight and blood pressure can work both ways. Working with researchers at Lilly Inc in the USA, the research team found that in overweight volunteers, a new drug that increases the action of MC4R caused an increase in blood pressure. Together, these results show that MC4R is a key link between the body's systems for **controlling weight and blood pressure**.

By focusing on patients with severe forms of disease from an early age, Dr Farooqi and Professor O'Rahilly, with continuing support from the MRC and the Wellcome Trust, are identifying other genetic defects that will **help the investigation of diet and drug treatments**. These types of in-depth human studies not only help the families of those patients involved, but also provide insights into more common forms of obesity and associated complications.

Experimental Medicine is the investigation of normal and disease processes in healthy people and patients, and how they can be changed by different approaches such as drug treatments or vaccines. It can be a challenging approach but has huge potential to deliver clinical benefits.

The MRC has supported these types of investigation through Experimental Medicine Awards: for example, Professor Adrian Hill, from the University of Oxford, has demonstrated how a new way of delivering a malaria vaccine could greatly improve its effectiveness; and Professor Steve Bloom and Dr Waljit Dhillo from Imperial College London have discovered a new drug to treat a cause of infertility in some women.

A NEW DRUG TREATMENT FOR INFERTILITY

Professor Stephen Bloom and Dr Waljit Dhillo – an Experimental Medicine grant

Amenorrhea is the term used to describe a condition where women have no periods and are, therefore, infertile; they also have an increased risk of osteoporosis and fractures, which has been associated with increased illness and earlier death. In many women the cause is a problem in the hypothalamus and this is termed hypothalamic amenorrhea. With an MRC Experimental Medicine grant, Dr Waljit Dhillo and Professor Stephen Bloom at Imperial College London carried out the **first clinical study** to examine the effectiveness of a hormone called kisspeptin as a treatment for women with hypothalamic amenorrhea.

Kisspeptin is made naturally within the body and plays a critical role in the regulation of the release of sex hormones. It is a key component in controlling the menstrual cycle in healthy women: those lacking kisspeptin function do not go through puberty and remain sexually immature. Professor Bloom's group showed that treating women with hypothalamic amenorrhea with injections of kisspeptin, administered twice-weekly for two months, successfully stimulated the release of luteinising hormone and follicle stimulating hormone, both of which are **essential for fertility**, and did not cause any side effects.

These findings must now be confirmed in large-scale randomised trials before any new treatment can be brought into clinical practice. However, this MRC-funded research is an **incredibly important step towards finding a treatment** for certain types of infertility, benefiting in particular the thousands of women affected by hypothalamic amenorrhea in the UK.

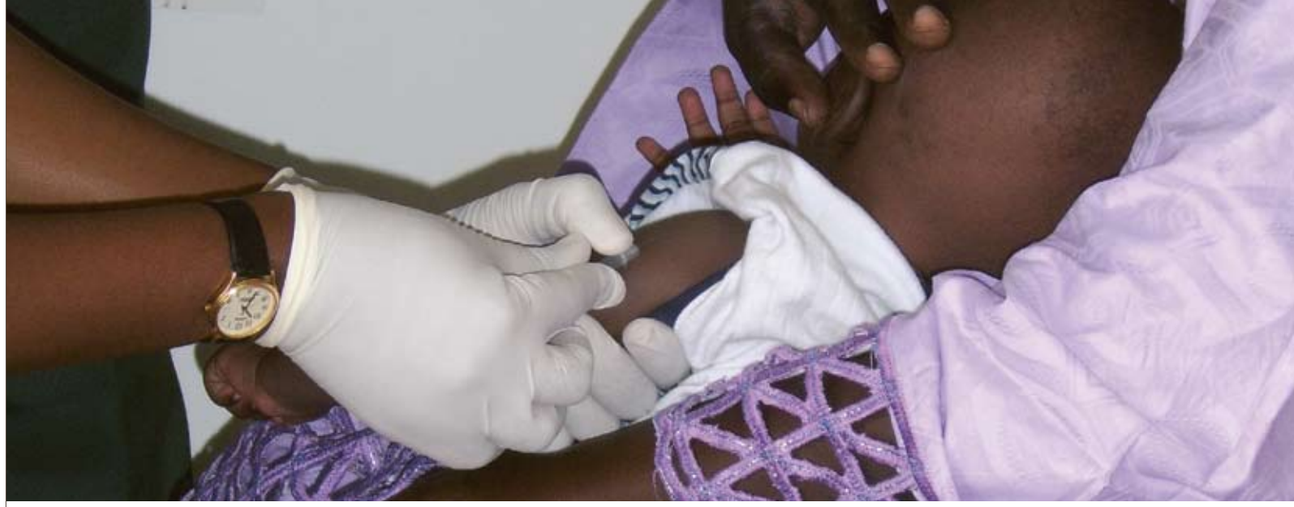


image credit: Martin Ota, MRC Fajara

A NEW WAY OF DELIVERING A MALARIA VACCINE

Professor Adrian Hill – an Experimental Medicine Grant

Malaria is a mosquito-borne infectious disease. Each year it affects up to 500 million people, killing between one and three million, the majority of whom are young children in sub-Saharan Africa. Professor Adrian Hill is director of the Jenner Institute at the University of Oxford: one of the aims of his group is to develop a new vaccine against malaria. With **strategic funding** from the MRC, Professor Hill investigated the safety and efficacy of one potential new vaccine using an immunology based approach.

One of the ways in which the body naturally tries to fight malaria is through white blood cells called CD8 T cells, which are capable of clearing the liver of infected cells. To provide complete protection against malaria, an effective vaccine must be able to stimulate a substantial increase in the numbers of these CD8 T cells. Up until now, this has been difficult to achieve. However, by using a '**prime-boost' malaria vaccine** (when an initial inoculation of a vaccine is followed by another vaccination with a different vaccine type), Professor Hill has successfully induced high levels of CD8 T cells in human volunteers. He has also shown that this increase in protective cells links well with vaccine efficacy. Prime-boost vaccines often use an adenovirus as a vehicle to initiate or prime the immune response. Professor Hill's malaria vaccine was developed using a new simian adenovirus, combating the problem that sometimes occurs when people's natural immunity to human adenovirus prevents a vaccine from being successful.

Not only would a highly effective vaccine against malaria **substantially reduce the global disease burden**, but the approach taken in this MRC-funded research could also influence vaccination strategies to tackle many other diseases.

Measuring how diseases vary between patients and over time is sometimes only possible after years of development of research tools, working with very carefully categorised subgroups of patients.

Professor Stephen Holgate has received long-term MRC investment in his research at the University of Southampton, which has involved detailed genetic investigations of a cohort of patients with asthma. Just two of his many successes are described here, relating to the discovery of a susceptibility gene for asthma and a potential new treatment in the form of inhaled interferon beta. Professor Louis Lemieux at the Institute of Neurology has developed a new imaging technique to identify which patients with drug resistant epilepsy will benefit most from surgery, improving safety and efficacy of treatment and increasing overall patient benefit.

NEW TECHNOLOGY TO AID THE TREATMENT OF EPILEPSY

Professor Louis Lemieux, research grant

Epilepsy is the most common serious neurological condition. Sufferers experience recurrent seizures and there is no cure at present. Medication is available to treat epilepsy, but some people find that their symptoms cannot be adequately controlled through drug treatments and so surgery may be considered to eliminate their seizures. Professor Louis Lemieux's group at the Institute of Neurology's Department of Clinical and Experimental Epilepsy has been working on the development of a **new**, **non-invasive scanning technique** called EEG-fMRI to improve surgical treatment.

MRC funding has allowed Professor Lemieux to show for the first time that for patients with drug-resistant epilepsy, combining information derived from quantitative electroencephalograph (EEG) measurements with the analysis of functional magnetic resonance imaging (fMRI) can result in a **better understanding of the brain's activity**. By developing methods and algorithms to localise epileptic activity and investigating how seizures are distributed, Professor Lemieux's team has shown that EEG-fMRI is a unique way of providing information on the origin of seizures and other epileptic EEG patterns, which is important to help patients who require surgery. The team has received further funding from the charity Action Medical Research, and a hospital-based prospective study is underway using this technique in patients with drug-resistant epilepsy.

Similarly, the team has shown that EEG-fMRI can also provide **predictive information** regarding the likely outcome of surgery. This useful prognostic marker can help the team identify patients who would be unlikely to benefit from surgery, so avoiding unnecessary operations. Professor Lemieux has several overseas collaborations ensuring the wider implementation of this new technique and enabling **increased benefit to patients worldwide**.

A NEW THERAPEUTIC TARGET AND A NEW TREATMENT FOR ASTHMA

Professor Stephen Holgate – an MRC Professorship and research grants

Asthma is an inflammatory condition of the airways which affects an **increasing number of people** – currently about 300 million people worldwide. Professor Stephen Holgate is MRC Clinical Professor of Immunopharmacology at the University of Southampton where he leads an interdisciplinary research team working on the underlying mechanisms of asthma.

Working with a large patient cohort funded in part by an MRC research grant, Professor Holgate discovered ADAM33, a susceptibility gene for severe asthma. By studying the airways of volunteers with chronic corticosteroid refractory asthma, his team has since shown that ADAM33 is involved in changing the airway wall in chronic asthma, with gene variants allowing more or less angiogenesis - formation of new blood vessels - as the disease worsens. This mechanism is potentially a **new therapeutic target** and Professor Holgate's continuing research is likely to lead to important advances in asthma treatment.

MRC funding has also enabled the team to carry out research which integrates evidence gained from cell lines, animal models and patients and healthy volunteers. They have shown that interferon beta deficiency caused worse symptoms in virally-induced asthma and in chronic obstructive pulmonary disease (COPD). As a result, inhaled interferon beta is being developed as a **new treatment** through a **spinout company**, Synairgen, led by Professor Holgate and his colleagues Professors Donna Davies and Ratko Djukanovic. The technology that underpins the company's work stems from at least 20 years of research, much of which has been supported by **substantial long-term investments** from the MRC.

As well as grant funding, sometimes over many years, it is vital that clinical research infrastructure is supported by UK Health Departments and local NHS institutions.

The following examples show where NHS trusts have provided substantial support. For Professor David Edwards at Imperial College London, Hammersmith Hospital has provided crucial resources to support his research into developing a new treatment for brain injury at the time of birth. The treatment is now being put into practice across the whole of the NHS. Professor Ian McKeith's research that resulted in a new diagnostic tool for Lewy body dementia was developed using the Newcastle Brain Tissue Resource, which is run in partnership by the MRC, local NHS trusts and Newcastle University.

A NEW DIAGNOSTIC TOOL FOR DEMENTIA

Professor Ian McKeith – research grant

The Newcastle Brain Tissue Resource (NBTR) is a tissue bank that stores brains donated to medical research. Established more than 25 years ago, it is now run as a **partnership** between the MRC, local NHS trusts and Newcastle University. Studies at NBTR were the first to show the importance of Alzheimer's disease and Lewy body dementia as major causes of cognitive impairment in older people.

Using the important infrastructural resource of the NBTR, Professor Ian McKeith, Professor of Old Age Psychiatry at the Institute for Ageing and Health in Newcastle, and his team have been working on developing a new diagnostic tool using an Experimental Medicine approach. They first demonstrated reduced activity of the dopamine transporter in post mortem brains of people with Lewy body dementia and then, in a highly productive collaboration with GE Healthcare involving patient volunteers, they developed 'dopamine transporter SPECT brain imaging', a **new diagnostic test for Lewy body dementia**. Being able to distinguish Lewy body dementia from other types of dementia is highly significant clinically because of important differences in patient management and outcome. The test now has EU marketing authorisation and is likely to bring great benefit to patients, improving the accuracy of diagnosis and enabling the investigation of possible new treatments.

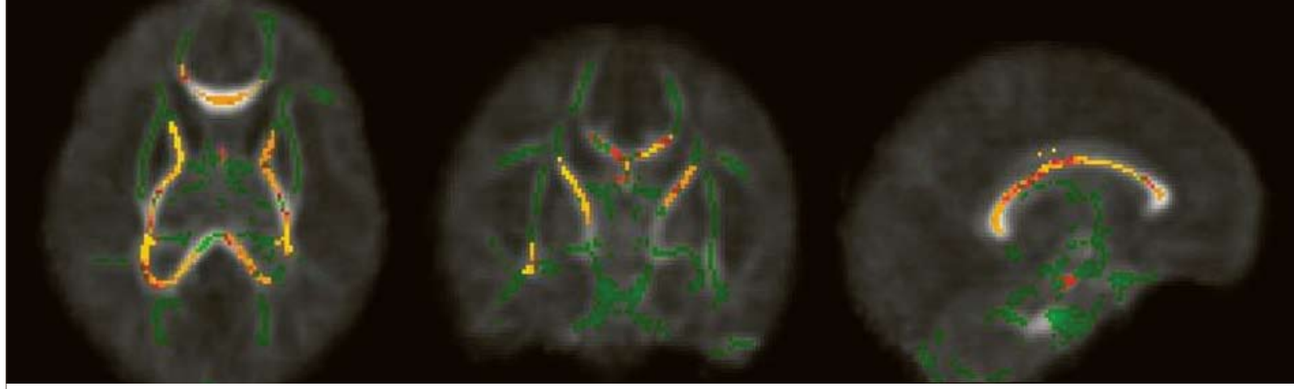


image credit: David Edwards, MRC Clinical Sciences Centre

A NEW THERAPY TO PREVENT BRAIN INJURY AT BIRTH

Professor David Edwards – institute funding and Experimental Medicine grants

Professor David Edwards and his group at the MRC Clinical Sciences Centre at Hammersmith aim to improve care for newborn infants, in particular to reduce the incidence and severity of brain injury from oxygen starvation at the time of birth.

If babies don't get enough oxygen (asphyxia) they suffer severe and permanent brain damage. Up until now there have been no specific treatments available, but through a collaborative, long-term translational research programme which included substantial MRC investment, Professor Edwards and colleagues in Auckland, London and Bristol have developed the **first effective treatment** for this serious problem. They showed that 'hypothermic neural rescue therapy' - cooling the baby's body temperature to 34˚C – reduces the risks of death and disability in babies suffering birth asphyxia, and leads to fewer cases of cerebral palsy in survivors. A special 3.0 Tesla magnetic resonance (MR) scanner for neonatal research (part-funded by the MRC) was vital for these studies. Based in the neonatal intensive care unit at Hammersmith Hospital and using methods developed over several years, it enabled Professor Edwards to provide direct evidence that cooling reduced brain damage.

The team's research has not only led to a simple and cost-effective clinical therapy, but it has also provided **proof of principle** that neural rescue is possible. They are now using their novel MR imaging biomarkers in early phase studies of other neuroprotectant treatments such as xenon gas or melatonin. The MRC has supported this research through Experimental Medicine grants.

The work of Professor Edwards and his colleagues has **changed clinical practice**, having been the subject of discussions and publications by the National Institutes of Health in America, and the topic of a review by the National Institute for Health and Clinical Excellence (NICE) in the UK. NICE has already given preliminary guidance that the treatment should become part of normal NHS practice.

It is clear that we can translate science into new treatments and diagnostics better, cheaper and more safely through more sophisticated studies in small groups of patients at an early stage.

Professor MacLullich at the University of Edinburgh has used early-stage investigations to develop a new method for diagnosing delirium, a major cause of morbidity and mortality in older people. He has already secured further MRC support to take this research further.

A NEW DIAGNOSTIC TOOL FOR DELIRIUM

Professor Alasdair MacLullich – a Clinician Scientist Fellowship

Delirium is an acute, severe and distressing state of confusion that affects at least one in 10 hospital patients. Its causes and mechanisms are poorly understood and there are **no effective treatments**. One hypothesis being tested by Professor Alasdair MacLullich, an MRC Clinician Scientist at the University of Edinburgh, is that delirium might result from abnormally high and sustained cortisol levels produced by acute illness, injury or surgery.

Professor MacLullich has developed a new method for collecting biomarkers of delirium from patients' cerebrospinal fluid (CSF). Using this technique he found that **CSF cortisol levels were higher in patients with delirium**. A Clinical Research Fellowship grant resulting from this work will help to develop these findings. Should a causal role for cortisol be established, it would open up antiglucocorticoid therapies as an important potential treatment for delirium.

The lack of accurate detection and monitoring of delirium is also impeding progress in understanding this common and serious condition. As a further result of his MRC-funded research, Professor MacLullich worked with volunteer patients to develop a **new computerised testing device** for the objective detection of attentional deficits in delirium. He has received further MRC funding to commercialise the device.

Delirium can result in long-term disability and prolonged hospital stay. There is also an association with increased mortality rates in patients with delirium, while in hospital and also in the months following discharge. By developing techniques to **improve diagnosis and treatment**, Professor MacLullich's research will result in substantial patient benefit by helping to reduce these complications.

As the pace of progress in basic science speeds up, more sophisticated clinical studies are needed to put new discoveries in context.

The MRC takes the lead on Experimental Medicine for the Office for Strategic Coordination of Health Research (OSCHR) and, working with the funding partners, is committed to building on the UK's strengths in experimental research and developing them further. Professor David Neal's research at the University of Cambridge shows the potential of the MRC and the National Institute for Health Research (NIHR) working together for patient benefit.

A NEW DIAGNOSTIC TEST FOR PROSTATE CANCER

Professor David Neal – a Research Grant

Professor David Neal leads on an MRC-funded project called ProMPT (Prostate cancer – Mechanisms of Progression and Treatment) which is a **collaborative translational research group** across six UK universities studying advanced and progressing prostate cancer. Specifically, the group studies the molecular pathology of prostate cancer in man.

One aspect of this significant MRC grant relates to the discovery of a new diagnostic marker from the team's investigation of an RNA helicase protein called p68. They are developing monoclonal antibodies which can detect changes in activated p68 in clinical samples taken from prostate cancer patients with advanced disease. The group is also looking at ways of blocking the action of this protein, which could potentially lead to new drugs. This work has led to collaboration with three **pharmaceutical companies** who are interested in taking the approach further.

Research from ProMPT and a related **NIHR-funded project** called the ProtecT study (Prostate testing for cancer and Treatment) has played a key role in the creation of a **spin-out company** called Pro-cure Therapeutics. Negotiations for alliances with major pharma companies in the stem cell field are at an advanced stage and two research collaborations with international pharma have already been completed.

Professor Neal and the team of collaborators are continually producing a wealth of information on prostate cancer linked to their MRC and NIHR funded studies. They are rapidly translating the data they are accumulating from their tissue collections into patient benefit, including carrying out the largest clinical trial of surgery in prostate cancer worldwide.

Partnership between the MRC and the NIHR demonstrates how support for early phase studies can deliver translational 'pull-through' into late phase trials.

Launched in 2008, the Efficacy and Mechanism Evaluation (EME) programme is funded by the MRC and managed by the NIHR on our behalf. It provides an important bridge in the pathway between early phase Experimental Medicine research and late phase effectiveness and cost effectiveness (NIHR HTA type) trials.

A NEW TREATMENT FOR COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

Professor Ian Nicol Ferrier – a Strategic Grant

Depression is one of the most common mental health problems, with at least one in six adults suffering from the condition at some time in their life. For several years Professor Ferrier and colleagues at the Institute of Neuroscience in Newcastle University have explored the emerging relationship between the function of the hypothalamic-pituitary-adrenal (HPA) axis and, in particular, levels of the stress hormone cortisol in different patient groups with depression.

Supported by an MRC strategic grant they demonstrated that mifepristone, a corticosteroid receptor antagonist and an effective antiglucocorticoid, improved neurocognitive impairment and depressive symptoms in patients with bipolar disease. These small-scale clinical studies have provided **proof of principle** that focusing on this pathway might provide a therapeutic route in depression, and have helped to identify elements of the underlying pathophysiological mechanisms involved. This early phase experimental medicine work has also provided robust validated clinical and psychological data for use in future late phase trials.

Consequently, Professor Ferrier and colleagues have secured funding from the **EME programme** for a late phase IIb/III definitive efficacy trial. The ADD (Anti-glucocorticoid augmentation of anti-Depressants in Depression) study will investigate metyrapone, a drug that decreases cortisol levels, in 180 patients who have not recovered from depression using standard antidepressants. This trial incorporates a number of other assessments to further examine the underlying mechanisms and effects of metyrapone.

Professor Ferrier and co-investigators also have **strategic funding** from the MRC to establish an intensively phenotyped cohort of 180 bipolar II patients from the primary and secondary care services in one geographical area. This cohort will form the core for further treatment trials and observational studies.

For information on the EME scheme see: **http://www.eme.ac.uk**.