

THE MRC 'PIPELINE'

Research and development by the MRC that could lead to significant new clinical applications within the next five years



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Introduction

The MRC works with public and private sector researchers, regulators, and a broad range of stakeholder communities to ensure research of the highest quality is translated into tangible benefits for society as a whole.

The time from bench to bedside in medical research and development can be very long. For the development of a therapeutic product such as a drug from an invention or scientific observation, the timeline can range from seven to more than 20 years. Other products such as devices, medical devices and diagnostics have shorter times to market but still generally involve some degree of regulatory approval process. In all cases, there is a large attrition rate, particularly through the very early stages of development.

It is not usually feasible for the MRC to fund a project all the way from basic research to clinical application: for example, the development of a new drug to licensing can cost as much as \$1 billion over 10 years. However, we can achieve our mission of improving the health and wealth of the UK by supporting our world-class researchers at an early stage in the process, helping them to identify opportunities for turning scientific knowledge into new treatments or diagnostics, and encouraging interaction between our researchers and the pharmaceutical and biotech industries. We can also help the development and testing of new treatments by supporting the process through identifying markers and models of disease, the most appropriate experimental designs, and most suitable measures of effectiveness.

Through the MRC's new evaluation survey, **MRC e-Val**, which asks all currently and recently (within three years) funded principal investigators to report on the many and varied outcomes and impact of their research, we know that:

- **24 new products and interventions** based on MRC research were launched onto the market between 2006 and 2009.
- MRC research has been cited in over **70 international clinical guidelines** since 2006, including 15 guidelines issued by the National Institute for Health and Clinical Excellence (NICE) in the UK.

Realising the potential of MRC research

The MRC's translational research strategy, developed in partnership with the National Institute for Health Research (NIHR) and other partners in the Office for Strategic Coordination of Health Research (OSCHR), and other organisations, is designed to increase the scale and speed of progress from scientific discovery to clinical benefit. As well as providing input to the strategy, our partners are vital in enabling the MRC to implement it.

As clearly stated in *Research Changes Lives*, the MRC strategic plan 2009-2014, we want to make certain that research of the highest quality is translated into benefit for society. Our range of translational funding schemes ensures that promising projects are pulled through proof-of-concept and preclinical phases, to experimental medicine and beyond.

In 2008, the MRC introduced a 'managed programme' of funding for translational research, available to researchers at universities as well as within our units. The managed programme consists of two schemes. First, the **Developmental Pathway Funding Scheme** (DPFS), which supports preclinical development of novel therapies, interventions and diagnostics, and any necessary research tools for development of therapeutics. Second, the **Developmental Clinical Studies** (DCS) scheme, which covers exploratory clinical research as far as phase I and II trials, the natural next stage in development.

The managed programme supports goal-orientated, structured development, giving priority to research that will lead directly to new treatments, and providing specialist advice and access to high-cost facilities. This scheme complements the general support already available through grants and fellowships for exploratory experimental medicine research into understanding human disease and the effects of treatments.

There is a deliberate overlap between DPFS and DCS to seamlessly support the development of new therapeutics and diagnostics from the fundamental discovery stage through preclinical development to first-in-man clinical trials. In both schemes, projects are based on scientific milestones, with decisions on progression taken on the likelihood of success at each milestone with the possibility of termination if the research results or project progress are unlikely to achieve the planned objectives.

Between them, DPFS and DCS have already supported **over 90 projects**, including more than 60 different potential therapeutic interventions – a total commitment of **over £40 million**. As potential new treatments and diagnostic techniques develop within these schemes, they look to take later-stage support from the MRC-funded **Efficacy and Mechanism Evaluation** (EME) scheme. This initiative, managed by the NIHR for the MRC, supports the evaluation of innovative treatments in large-scale, multi-centre clinical trials.

Experimental medicine

Experimental medicine is a core element of the MRC's overarching translational research strategy. The MRC is the lead public sector organisation for Experimental Medicine on behalf of OSCHR, and also coordinates the UK Clinical Research Collaboration (UKCRC) Experimental Medicine Funders Group, which draws together the interests and strengths of key partners to ensure that the UK maintains an attractive international profile in the area.

Translational projects from earlier Experimental Medicine calls for proposals are now coming to fruition: the MRC is working with the grantholders to provide advice and connections, ensuring that the successful projects can progress through to patient benefit either in partnership with the commercial sector or with further public funding. This research activity has involved **nearly 2,500 patients and volunteers** who took part in early-stage clinical trials to test new therapeutic agents, vaccines and psychological interventions.

Investing in translational infrastructure

The MRC's translational initiatives also include investments in improving the infrastructure and skills needed for translation. With extra funding as part of the MRC's translational strategy, MRC Technology (MRCT) built on the success of its Drug Discovery Group in working with intramural scientists to create the **MRCT Centre for Therapeutics Discovery** (CTD), which is accessible by the broader academic community. It provides specialist translational infrastructure and expertise to support small molecule and antibody based therapy development for university projects funded by the DPFS grant scheme and other sources. The CTD increased its capacity for taking on projects by about 65 per cent this year, coupled with a major 'Call for Targets' campaign and a significant number of visits to high profile institutes and universities to encourage academics to collaborate with the CTD.

MRCT has contributed to the development of **over 10 per cent** of the worldwide pipeline of therapeutic antibodies.

Achievements

Here is a selection of recent MRC science and inventions that are already benefiting patients or may lead to improved patient care within the next five years. There are many others that will hopefully deliver over a longer period.

In the clinic:

AAA screening

In 1997, the MRC began funding a study – the UK Multicentre Aneurysm Screening Study (MASS) – into the effectiveness of screening men over 65 for **abdominal aortic aneurysms** (AAAs). This research has provided most of the evidence for screening programmes now in place in England (available in seven areas from 2009; nationwide by 2013), Scotland (starting in 2011) and the US (available through Medicare from 2007). Equally important is the data from following the original study participants. The most recent MRC-funded research from the MASS trial shows that screening men aged 65 to 74 once is cost-effective and halves the number of deaths from AAAs over 10 years.

<http://www.mrc.ac.uk/Newspublications/News/MRC006173>

Evidence-based practice

A 2009 study funded partly by the Medical Research Council found that **compression stockings** had no effect in preventing deep-vein thrombosis (DVT) – a life-threatening form of blood clot that can travel up into the heart or lungs – in stroke patients. Cutting the use of surgical stockings for stroke patients saves the NHS £7 million and 320,000 hours of nurses' time a year.

<http://www.mrc.ac.uk/Newspublications/News/MRC006071>

Targeted formulations

Lack of appropriate antiretroviral formulations for HIV-infected children has been one of the major constraints to scaling up of treatment in HIV-infected children in resource limited countries. **Triomune Baby/Junior** is a fixed dose combination of three drugs in a new formulation specifically developed for children. A European and Developing Countries Clinical Trials Partnership (EDCTP) grant to the MRC and partners in Zambia, Italy and the Netherlands funded a study that contributed to the approval of Triomune Baby/Junior for use in HIV-infected children in August 2007. Approval allowed these drugs to be used in programmes and projects supported by US organisations. Triomune Baby/Junior drugs are now widely used in Zambia, Uganda and Zimbabwe, and many sub-Saharan African countries may soon also benefit from using these products.

<http://www.mrc.ac.uk/Newspublications/News/MRC004073>

Understanding epilepsy

A non-invasive scanning technique called EEG-fMRI is being developed to improve **surgical treatment for epilepsy**. With MRC funding, Professor Louis Lemieux at the Institute of Neurology has shown that combining information derived from quantitative electroencephalograph (EEG) measurements with the analysis of functional magnetic resonance imaging (fMRI) results in a better understanding of 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 in patients with drug-resistant epilepsy. EEG-fMRI can also provide predictive information regarding the likely outcome of surgery. Identifying patients unlikely to benefit from surgery avoids unnecessary operations. Professor Lemieux has several international collaborations ensuring wide implementation of this new technique and enabling increased benefit to patients worldwide.

<http://www.ion.ucl.ac.uk/departments/epilepsy>

Therapeutic antibodies

The therapeutic antibody market is currently worth around \$40bn and growing. MRC antibody-related inventions over the last 25 years have spawned a large number of marketed therapeutic antibody products.

There are three key technologies which have led to therapeutic interventions: 'antibody humanisation' or CDR grafting (invented by Sir Greg Winter, MRC LMB); 'phage display' (also invented by Sir Greg Winter, MRC LMB) and the 'humanised transgenic mouse' (invented by Bruggeman and Neuberger, MRC LMB) all of which were invented in the late 1980s or early 1990s. This is testament to the long development path of therapeutics.

Currently marketed products derived from these technologies include **Avastin** (cancer; now the world's highest grossing drug), **Herceptin** (breast cancer), **Tysabri** (multiple sclerosis), **Actemra** (rheumatoid arthritis), **Humira** (rheumatoid arthritis and psoriasis) and **Vectibix** (colorectal cancer). The first four are derived by CDR grafting, Humira from phage display and Vectibix from transgenic mice.

In addition, there are a large number of additional interventions at various stages of clinical development. About a dozen molecules in phase III clinical development are likely to become generally available to UK patients within the next five years (subject to both regulatory approval and scrutiny by NICE). They include:

Alzheimer's disease

Bapineuzumab: anti-beta amyloid peptide antibody (Elan/Wyeth)

Solanezumab: anti-soluble amyloid beta antibody (Eli Lilly)

Recent onset type I diabetes

Teplizumab: anti-CD3 antibody (Eli Lilly)

Crohn's disease

Vedolizumab: anti- $\alpha 4\beta 7$ integrin antibody (Millennium/Takeda)

Osteoarthritis

Tanezumab: anti-NGF (Pfizer)

Lupus

Belimumab: anti-BAFF antibody (Human Genome Sciences / GlaxoSmithKline)

Approved by regulators:

Cool treatment

The first effective treatment for brain damage caused by oxygen starvation at birth (asphyxia) has been developed by scientists at the MRC Clinical Sciences Centre at Hammersmith Hospital, working with colleagues around the world. Birth asphyxia can lead to severe and permanent brain damage or death. In the UK around 1,400 infants a year are affected, two in every thousand full-term births.

'Hypothermic neural rescue therapy' – cooling the baby's body temperature by a few degrees – reduced the risk of death and disability in babies suffering birth asphyxia and led to fewer cases of cerebral palsy in survivors. In May 2010, hypothermic neural rescue therapy was deemed "safe and effective" for NHS use by the National Institute for Health and Clinical Excellence (NICE).

<http://www.mrc.ac.uk/Newspublications/News/MRC006361>

Meningitis vaccine

MenAfriVac, a 40-cent vaccine developed through the Meningitis Vaccine Program (MVP) to protect against life-threatening meningococcal meningitis, received prequalification from the World Health Organization in June 2010. This follows a phase II trial, part-funded by the MRC, which showed that the vaccine was not only safe, but generated up to 20 times more antibodies than the current vaccine. The results suggested the vaccine would be effective for a number of years and more effectively protect communities from the periodic group A meningitis infections that sweep through sub-Saharan Africa every eight to 10 years.

<http://www.mrc.ac.uk/Newspublications/News/MRC003805>

In development:

Curing blindness

MRC grants funded the work of Professor Pete Coffey, whose aim is to develop a **stem cell-based therapy** to replace cells lost in age-related macular degeneration (AMD), which affects around a quarter of people over 60, causing severe visual impairment and even blindness. The initial research relied on work at the University of Sheffield deriving human embryonic stem cell lines, also funded by the MRC. In 2009, Professor Coffey entered a collaboration with Pfizer to bring together the pioneering research funded by the MRC and Pfizer's expertise in design and delivery of therapeutics. Assuming the team gets regulatory approval, the first phase of clinical trials in humans could start as early as 2011, with a view to developing a surgical cell therapy for AMD by 2012.

<http://www.mrc.ac.uk/Newspublications/News/MRC005888>

Preventing bowel cancer

MRC research has shown that a quick one-off screening test, the **'Flexi-Scope' test**, could cut the risk of developing bowel cancer by a third and save thousands of lives. Around one in 20 people in the UK will develop bowel cancer during their lifetime. It is the UK's second biggest cancer killer, causing over 16,000 deaths each year. A 16-year MRC-funded study showed that a single flexible sigmoidoscopy examination in men and women aged between 55 and 64 reduced the incidence of bowel cancer by a third. Over the course of the study, bowel cancer mortality was reduced by 43 per cent in the group that had the Flexi-Scope test. Research commissioned by the Department of Health, published in the journal *Gut* in 2006, suggested that a screening programme based on this test would save the NHS £28 for every person screened.

<http://www.mrc.ac.uk/Newspublications/News/MRC006794>

Diagnosing cancers

Professor Nick Coleman and colleagues at the MRC Cancer Cell Unit in Cambridge have shown that minichromosome maintenance (MCM) proteins can substantially improve the early diagnosis of several common cancers by acting as markers for malignancy and pre-malignancy. MCM testing is being developed for the early detection of **cervical, lung and colorectal cancers**.

<http://www.mrc.ac.uk/Newspublications/News/MRC004911>

Sponge test

Dr Rebecca Fitzgerald, also at the MRC Cancer Cell Unit, is working on an inexpensive and simple device that can detect a precursor of oesophageal cancer called **Barrett's Oesophagus (BE)**. The majority of cases of BE are undiagnosed and therefore even efficacious chemoprevention measures and endoscopic treatments are unlikely to reduce the population mortality from **oesophageal cancer**. Population screening for BE has therefore been advocated. Dr Fitzgerald's approach involves the patient swallowing a capsule sponge cell sampling device that collects cells to be examined for changes characteristic of BE, and also stained to detect MCMs, which would indicate early cancer. Development Gap Funding from MRCT has resulted in the manufacture of a regulatory approved sampling sponge which is currently being successfully employed in a primary care study. A large, well-known diagnostics company is interested in the kit and is providing reagents free of charge for the study.

<http://www.hutchison->

[mrc.cam.ac.uk/Research/Rebecca_Fitzgerald/clinical_studies.html#BEST](http://www.hutchison-mrc.cam.ac.uk/Research/Rebecca_Fitzgerald/clinical_studies.html#BEST)

Seeing in 3D

In 2004 at the MRC Human Genetics Unit in Edinburgh, Dr James Sharpe invented a technique called **Optical Projection Tomography (OPT)** microscopy, which allows the 3D imaging of biological specimens in the range of 3 to 100mm across. OPT is now an established technique in developmental biology and has generated powerful 3D images of developing mouse and chick embryos. In addition, it has been applied to tissue biopsy samples from humans with a view to studying tissue structure and gene expression in disease. OPT has the potential to replace certain areas of histology in a clinical setting: having taken, fixed and stained tissue biopsies as usual, they can then be imaged without sectioning in a few minutes delivering 3D virtual tissue models that can be sectioned in any plane on a computer and analysed quickly by a pathologist at their desk. Research instruments are already on the market, and there may be clinical diagnostic devices available within five years. A proof-of-concept study looking at colon polyps and bowel cancer has begun in collaboration between MRCT, the University of Dundee and NHS Tayside. We hope that a successful study will lead to rapid uptake of the technology by a diagnostics company.

http://genex.hgu.mrc.ac.uk/OPT_Microscopy/optwebsite/frontpage/index.htm

Spinout success

Asthma affects about 300 million people worldwide. Professor Stephen Holgate, MRC Clinical Professor of Immunopharmacology at the University of Southampton, leads an interdisciplinary research team working on the underlying mechanisms of asthma. Part of his research integrates evidence gained from cell lines, animal models and patients and healthy volunteers, and has 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. 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 investment from the MRC.

<http://www.synairgen.com/>

Early potential:

Ovarian cancer screening

Preliminary results from the **UK Collaborative Trial of Ovarian Cancer Screening** (UKCTOCS) show that in the first screen of 100,000 women, ovarian cancer or borderline tumours were detected in 87 women and missed in 13 women who went on to develop the disease within a year. Almost half (48 per cent) of 58 cancers detected were found at an early stage. UKCTOCS is the largest trial of its kind ever run to investigate ovarian cancer screening and is using two methods: either a blood test or an ultrasound scan. The trial will conclude in 2014 and if the findings are positive it could pave the way for a national ovarian cancer screening programme. UKCTOCS is funded by the MRC, Cancer Research UK and the NIHR, and is supported by The Eve Appeal.

<http://www.mrc.ac.uk/Newspublications/News/MRC005697>

Slowing liver damage

A significant proportion of patients with hepatitis C develop a type of liver damage called fibrosis. MRC-funded researchers at Imperial College London are conducting a two-year trial to find out whether **warfarin** can slow the development of fibrosis in hepatitis C patients who have had a liver transplant. The study will show if warfarin has any beneficial effect and provide information regarding factors associated with liver fibrosis post-transplantation. If beneficial, the treatment could quickly enter clinical use as warfarin is already approved by regulatory authorities, and further studies could be done to see whether warfarin helps hepatitis C patients who have not had to have a liver transplant.

<http://www.mrc.ac.uk/Newspublications/News/MRC004716>

Research tools:

In vitro compartmentalisation technology

In the late 1990s, Andrew Griffiths at the MRC Laboratory of Molecular Biology (LMB) invented a method for producing stable, aqueous-in-oil emulsions that allowed the effective generation of billions and billions (10^{12}) of miniature reaction vessels in a test tube. The technique can be used for ultra high throughput screening or the generation of multiple reaction products including novel proteins, enzymes and nucleic acids. The technology was licensed to two companies that have already developed commercial products on the market and we expect to see further developments in the next five years, which will create valuable healthcare benefits in diagnostics and drug discovery.

GPCR stabilisation for drug discovery

G-Protein Coupled Receptors (GPCRs) play a crucial role in many diseases and are the site of action of 25 to 30 per cent of current drugs: they represent a major area of interest for pharma companies. However, these membrane proteins are inherently unstable when removed from their membrane environment, restricting drug discovery technologies for this target class to cell-based methods. Richard Henderson and colleagues at MRC LMB have invented a GPCR stabilisation technology known as StaR[®] (Stabilised Receptor). This technology platform was the basis of the MRC start-up company Heptares Therapeutics plc, www.heptares.com, where they apply powerful but hitherto unavailable discovery techniques to GPCRs. These techniques, combined with medicinal chemistry and antibody technologies, create a fully integrated drug discovery platform. Although at a relatively early stage, we could see novel drugs developed using this technology in the early stages of clinical research within five years.



MRCT works with scientists from MRC-funded units and collaborating organisations to discover and protect healthcare innovations.

We combine technology transfer, small molecule drug discovery and therapeutic antibody functions in order to convert knowledge into commercial success.



MRC e-Val is an online survey to gather outputs, outcomes and impacts arising from MRC-funded research.

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