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MRC Medical Research Council

Outputs, outcomes and impact of MRC research

2014/15 report

ISBN 978-0-903730-22-8

When providing a citation for this document we recommend the following:

Medical Research Council (2016) *MRC Outputs, outcomes and impact of MRC research 2014/15 report.*
Publisher: Medical Research Council, London, UK.
ISBN: 978-0-903730-22-8

Any enquiries related to this publication should be sent to us at:

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This publication is available at https://www.mrc.ac.uk/successes/outputs-report/

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Mosquito on human skin at sunset. Image credit: Shutterstock | Ebola workers in Liberia. Image credit: Flickr/European Commission DG ECHO CC BY 3.0 | An image from the BoneFinder software. Image credit: Claudia Lindner, University of Manchester | Back of the eye showing intermediate age-related macular degeneration. Image credit: National Eye Institute, National Institutes of Health | Bacteriophage. Image credit: BlueSci. Cambridge University science magazine | Niall Kent. Image credit: Niall Kent, UCL

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Intellectual Property

Medical products

Software and technical products

Artistic and creative products

Spin outs

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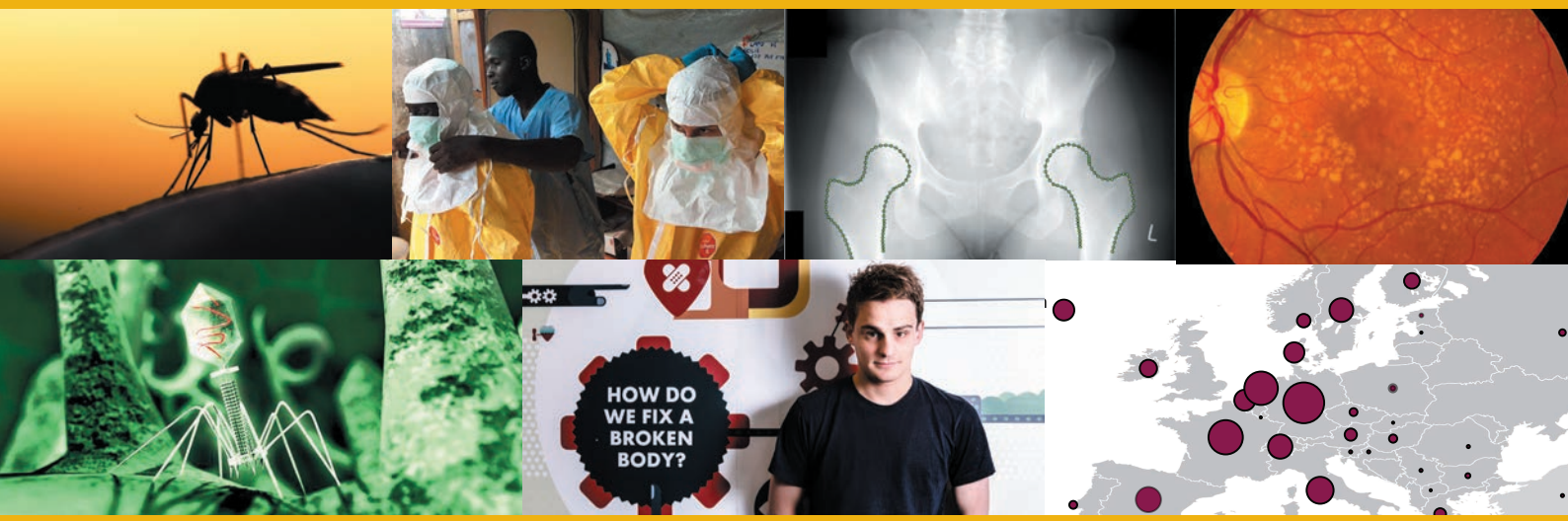

SECTION 1.0
Introduction

Section 1: Introduction

Overview

The MRC has been funding and conducting ground-breaking medical research for more than 100 years. From producing the first antibiotic and developing the first monoclonal antibodies to demonstrating the link between smoking and lung cancer, MRC-supported researchers have been at the forefront of medical advances that have had a profound impact on society[1].

In more recent years the MRC has done much to highlight the compelling evidence that investment in medical research leads not only to significant improvements in health but also economic prosperity[2]. The MRC's evaluation programme is set out in more detail in the MRC's strategic plan for 2014-19 *Research Changes Lives*[3].

For the MRC to better understand how research leads to impact, it must be able to capture and track the progress, productivity and quality of the research it funds. It does this predominantly through researchfish®[4], the online system used by researchers to feed back on the impact of their work (see the below section on researchfish® for more information on our data collection system and uses of the data). This approach is designed to encourage researchers to provide feedback on a wide range of different outputs, recognising that research delivers a diverse set of useful outcomes for society.

The *2014/15 Outputs, outcomes and impact* report showcases some of the latest developments and academic, societal and economic gains arising from MRC-funded research, as reported in researchfish®. Details of outputs from almost 6,000 MRC awards are drawn upon for this report. The majority of the MRC researchfish® dataset, along with information from the other research councils, is openly available for anyone to read and re-use via the Research Councils UK (RCUK) Gateway to Research[5]. The Gateway to Research aims to make available information about what the councils are funding and the outputs that have arisen from this work.

The results clearly demonstrate that MRC-supported research teams are making international impact; their work is delivering significant new health gains, and stimulating economic growth and changes to absorptive capacity across all sectors.

Journal articles remain the primary output reported by MRC-funded researchers, with publications resulting, either wholly or in part, from MRC funding in 85 per cent of awards. 29 per cent of MRC awards reported at least one publication within a year and 90 per cent reported at least one publication within five years. The impact of MRC research papers has consistently been shown to be twice that of the world average[6].

Almost half of our respondents (48 per cent) reported that their work had been supported by collaborations between 2006 and 2014. The nature of these collaborations varies greatly. They might take the form of industry interactions to begin research translation, such as **Professor Derek Mann's (University of Newcastle)** work with GlaxoSmithKline (GSK) to develop drugs that can stop or even reverse liver fibrosis[7]. Or they might be the coming together of many diverse organisations to drive innovation, such as the **Clinical Trials Transformation Initiative (CTTI)**[8]. This multi-stakeholder group, comprising more than 60 organisations, was established to increase the quality and efficiency of clinical trials.

Recipients of just less than half of our awards (47 per cent) reported that their research had attracted further funding, taking the total awarded to MRC-supported research groups to £4.2bn between 2006 and 2014, from more than 1,000 different funders. £286m (seven per cent) of this was from the private sector; including £135k from AmpliPhi Biosciences Corporation to **Professor Martha Clokie (University of Leicester)** to further develop bacteriophages — viruses that 'eat' bacteria — as a treatment for *Clostridium difficile*[9].

There were reports of more than 10,000 staff moving from MRC support between 2006 and 2014; the majority were researchers, post-doctoral researchers and research fellows, leaving to pursue roles in a natural career progression. More than half of MRC supported students (55 per cent) progressed to a postdoctoral research position and overall 60 per cent of staff remained in an academic organisation.

Researchers reported taking part in more than 35,000 engagement activities between 2006 and 2014. These included research that received substantial media coverage, such as that conducted by PhD student **Camilla Nykjaer** who demonstrated a link between light drinking by pregnant women and pre-term birth[10]. 2014 was the first year that the MRC invited PhD students to complete their own researchfish® return and 85 per cent of MRC students provided feedback.

Other activities reported in the engagement activities section included television appearances, festivals and open days, specifically to entertain, inform and educate the public about medical research. **Dr Sam Wass (Cognition and Brain Sciences Unit)** held an expert role on Channel 4's documentary *The secret life of four-year-olds*[11] and **Dr Alan Gow (Heriot-Watt University and University of Edinburgh)** took part in the *Edinburgh Fringe Festival* with a show called Brain training on trial, as part of the *Cabaret of dangerous ideas*[12].

MRC researchers reported that their work had had an influence on local, national or international policy in almost a quarter of awards, totalling more than 5,000 influences. These included citations in clinical guidelines, such as **Professor Rustam Al-Shahi Salman's (University of Edinburgh)** work on the American Heart Association guidelines for arteriovenous malformations of the brain[13].

Researchers also reported influences on policy-setting processes, such as **Professor Cornelis Kros** at the **University of Sussex** who was an expert witness at the 2014 Commission on Hearing Loss[14].

Recipients of almost a third of awards (28 per cent) reported that their work had resulted in the generation of research materials for others to use, from cell lines and transgenic animal models to databases and new techniques. These include a mathematical model to assess under which circumstances anti-virulent drugs would be useful in treating bacterial infections[15], a new method to analyse genome-wide DNA damage and repair[16] and a cell line to help investigate how an immune system process is regulated[17].

There are 1,213 reports of intellectual property in the researchfish® database, including a way to prevent *Campylobacter* bacteria from colonising poultry[18] and hydrogels — an economic method of storing and transporting stem cells[19].

Researchers reported that their work had led to the development of more than 1,200 medical products or interventions, 35 software or technical products and 112 artistic and creative products. The medical products ranged from genetic testing for rare diseases[20] to a successful trial of a hepatitis C vaccine[21]. Technical products included the first UK virtual clinical care pathway allowing patients to self-manage chlamydia infection[22], whilst creative products included a poem on the PROUD HIV trial[23].

The MRC has evidence of MRC-supported research leading to the creation or growth of more than 100 companies. Recent additions include ProAxsis Ltd, a company developing tests that will enable patients to monitor respiratory diseases at home[24] and PH Therapeutics, a company aiming to develop antibody therapies for pulmonary arterial hypertension, a collection of rare conditions characterised by high blood pressure in the arteries that supply blood to the lungs[25].

Recipients of 52 per cent of awards reported that their work had resulted in an award or personal recognition for either themselves or a member of their research group worthy of reporting. This might include an invitation to speak at a conference, being appointed to the editorial board of a journal or being awarded a research prize. Those awarded research prizes include **Professor Malcolm Jackson**, director of the **MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing (CIMA)** who was awarded the Lord Cohen Medal by the British Society for Research on Ageing, **Professor Hannah Gould** at **King's College London** who was awarded the 2014 Paul Ehrlich Award by the European Academy of Allergy and Clinical Immunology (EAACI) for 'Improving Experimental Research' and **Professor Anna Gloyn** at the **University of Oxford** who was awarded the 2014 Minkowski Prize by the European Association for the Study of Diabetes[26].

Further examples of these outputs can be found throughout the pages of the report, as well as the associated impact where reported. A full list of the case studies contained in the report is in the index.

Key

- Publications
- Collaborations and partnerships
- Further funding
- Next destination and skills
- Engagement activities
- Influence on policy, practice, patients and the public
- Research tools and methods
- Research databases and models
- Intellectual Property and licensing
- Medical products, interventions and clinical trials
- Artistic and creative products
- Software and technical products
- Spin outs
- Awards and recognition

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researchfish® is an online system, supported by Researchfish Ltd and used to collect information on the outputs, outcomes and impact of MRC-funded research. MRC-funded researchers are asked to record these data all year-round and, once a year, to formally submit this information to the MRC (usually between February and March).

Formerly MRC e-Val, the approach was licensed to Researchfish Ltd in 2012, which created a federated version of the system to allow it to be used by multiple funders to collect comparable research outputs. There are currently more than 100 research organisations and funders using researchfish®[27]. 2014 was the first year that all seven research councils used the system[28]. A harmonised approach to collecting output information suitable for all research disciplines will enable funders to obtain a common qualitative and quantitative view of the progress, productivity, quality and impact of the research they individually and collectively support. In 2015 the MRC also played an instrumental role in starting to align researchfish® with university and other researcher systems. In 2015, researchfish® was integrated with ORCID[29], a central registry of unique identifiers for individual researchers, meaning that information can be exchanged between the two systems and potentially between a wider range of research information systems.

The data collected — both qualitative and quantitative — is invaluable to the MRC and is used in a multitude of ways, from contributing to the evidence submitted to the Government to make the continued case for sustained investment in medical research, assessing progress against the MRC's Strategic Plan, *Research changes lives 2014-2019*[30], and importantly, making the data available to universities for re-use[31].

As noted above, the data collected through researchfish® are published on the RCUK Gateway to Research[32]. The MRC expects that the public availability of this data will help continue to encourage accurate and complete reporting within researchfish®. Further information on the research featured in this report can be found in the Gateway to Research by using the search function to enter the project reference number listed underneath each case study.

For more information on the history of researchfish® and its principles of use, please see:
http://www.mrc.ac.uk/funding/guidance-for-mrc-award-holders/researchfish/

2014 data collection

The November-December 2014 Data Gathering Period (DGP7) for researchfish® had a compliance rate of 94 per cent with 5,086 responses out of an expected 5,416.

Notes on the quantitative data

Percentages in this report are rounded up or down to the nearest whole number and so some may appear as zero if this represents less than half of one per cent and not all tables may sum to 100 per cent because of rounding.

Where instance of further funding are reported in currencies other than Pounds Sterling, the values are converted using an average exchange rate for each calendar year as reported on http://www.oanda.com/currency/historical-rates/.

One particular output, for example a publication or a collaboration, might have arisen from more than one award. In this report a particular output is always reported against each individual award where the unit of analysis is at the award level (for example the number of instances or distribution of activity). Duplicate outputs are removed, where possible, in analyses at the level of the type of output generated (for example publications per year, top five locations for collaborations). Duplicate outputs are removed using system-generated codes to indicate when a researcher has attributed an output to more than one award. This cannot identify duplicate outputs where researchers have entered similar information independently of one another. Supplemental information is used to identify duplicate outputs where available, for example PubMed Ids or Digital Object Identifiers (DOIs) can be used to generate unique sets of records for publications. In the case of further funding reports, the details of duration, amount of money and funding organisation are used.

In addition to de-duplication, outputs were also removed from analysis if the researcher indicated that they occurred before the start of the funding for their award. We have used the term valid and invalid in relation to these outputs. A valid output is one that was realised during or after the award to which it has been attributed. An invalid output is one realised before the start of the award to which it has been attributed. In most cases researchers are asked to indicate the year only for their outputs and not specify a month. This means that a one year difference in year could be almost two years in actuality (for example, January 2012 – December 2013). For removal from analysis a particular output would have to be in at least the year before the funding started.

Report by Ellen Charman with quantitative data and analysis provided by Craig Haskins, David Morgan and Jim Carter, **MRC Evaluation Team**.

End Notes

1. http://www.mrc.ac.uk/successes/
2. Health Economics Research Group, Office of Health Economics, RAND Europe. Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK. London: UK Evaluation Forum; 2008. http://www.mrc.ac.uk/publications/browse/medical-research-whats-it-worth/
3. http://www.mrc.ac.uk/research/strategy/
4. www.researchfish.com
5. http://gtr.rcuk.ac.uk/
6. For example see Figure 2, page 18 of MRC's 2014/15 Economic Impact report http://www.mrc.ac.uk/publications/browse/mrc-economic-impact-report-2014-15/
7. See page 152
8. See page 157
9. See page 141
10. See page 53
11. See page 49
12. See page 47
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16. See page 124
17. See page 113
18. See page 79
19. See page 83
20. See page 67
21. See page 75
22. See page 76
23. See page 77
24. See page 136
25. See page 155
26. See page 169
27. As at March 2016. An up-to-date list of organisations using researchfish® is at: https://www.researchfish.com/ourmembers
28. For details of RCUK policy on the collection of output information, background to the implementation of the researchfish® system and use of the data see http://www.rcuk.ac.uk/research/researchoutcomes/
29. http://orcid.org/
30. http://www.mrc.ac.uk/documents/pdf/research-changes-lives-2014-2019/
31. A list of the outputs that have drawn on researchfish® data can be found at http://www.rcuk.ac.uk/documents/documents/useresearchfishdatapublications2009-2015-pdf/
32. http://gtr.rcuk.ac.uk/

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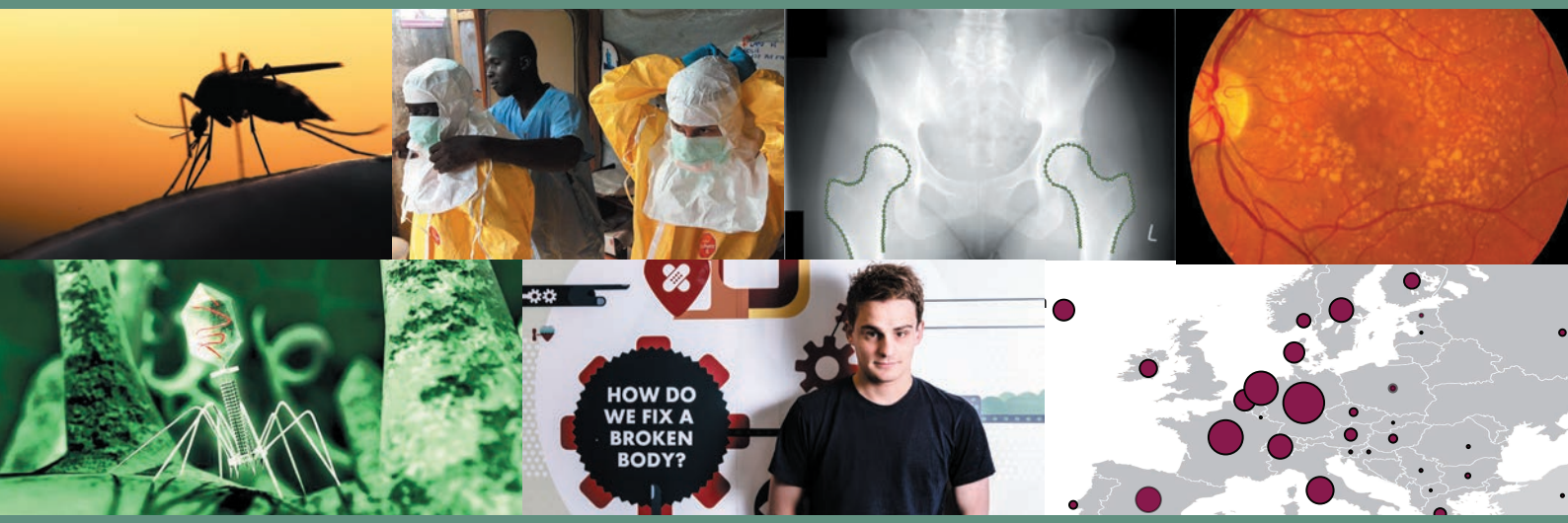

SECTION 2.0
Case studies

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MRC Medical Research Council

Outputs, outcomes and impact of MRC research

2014/15 report

SECTION 2.1
Published research

Published research

Peer-reviewed publications are an important primary output from research. Their main functions — communicating information, building a knowledge base and validating research quality — have remained largely unchanged since they first came into existence, around 350 years ago[33,34]. This is despite innovations in publishing and new models for accessing this information. Although we also capture information about 'secondary' publications and other forms of literature in researchfish®, such as systematic reviews, conference proceedings and books, this chapter mainly focuses on publications categorised by Thomson Reuters[35] as 'journal articles' and 'journal reviews'. This is not to imply that journal articles have greater merit in disseminating research findings than these alternative forms of literature. However significant attention has been paid to methods that seek to measure and benchmark the impact of journal articles using extensive citation datasets, a practice described as "bibliometrics"[36]. The importance of bibliometrics to scientists' career progression, and, in turn, their opportunity to influence scientific priorities[37], clearly highlights the need for funders, research organisations and peer reviewers to use metrics responsibly. This was a point emphasised in the HEFCE-commissioned *Metric Tide* report on the use of metrics in research assessment published in 2015[38].

Journal articles represent half of all output reports made via researchfish®. The MRC has had a policy requesting that researchers make research publications free to read at the point of access since 2006; the aim being that access to publicly-funded research should not be hindered by the reader needing subscriptions to publishers[39]. The MRC, along with other research funders, need comprehensive information about the publications arising from their funding and access to these publications to monitor the impact of these 'open access' policies.

Use of publications to measure interdisciplinarity

Recently there has been increased debate over support for interdisciplinary research in the UK[40]. One problem to advancing these discussions is that there is no credible, consistent or quantitative definition for 'disciplinarity'[41]. With such a rich publications dataset, the MRC is interested in exploring bibliometric and other analytical approaches to establish methods to track changes in disciplinarity. In 2014/15 the MRC commissioned a study with the Higher Education Funding Council for England (HEFCE) to apply subject categories to papers to analyse the disciplinarity of UK publication output. The study then compared this to the range of output from other countries[42]. Other work funded by the MRC is examining whether text mining of grant applications and papers can provide a consistent measure of disciplinarity[43]. This is part of a wider programme of work in collaboration with HEFCE and the research councils to examine the facilitators and barriers to encouraging interdisciplinary research.

Bibliometrics

THOMSON REUTERS

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After the Researchfish Ltd data-gathering period, bibliographic details of unique papers were provided to Thomson Reuters[44], who returned citation information for every publication that could be matched to the Thomson ISI Web of Science database[45]. The ISI database does not include all journals in which MRC researchers publish, which means that papers which are not indexed are left out from the following analysis. In addition, some papers, for

example, published in conference proceedings, do not have standard citations and they are also excluded. Citation data were however returned for around 97 per cent of the papers sent for analysis (70,616/72,983).

Citation impact of MRC papers

The citation of publications in other peer-reviewed research articles is often used as a proxy measure of academic and wider user impact. Citation counts can be normalised by scientific field and year of publication to provide a normalised citation impact (NCI). An NCI score of 1 means that the paper is behaving as would be expected for that subject area in that year, and this is referred to as the world average. An NCI of above 1 means that the paper is cited more often than would be expected and is above the world average. A further measure of publication impact is the number or percentage of articles that are either uncited or conversely, those deemed as highly cited (identified as those with an NCI score that is greater than or equal to 4)[46]. Having assessed several measures of citation impact and metrics, including the 'h index' and its variants, the MRC considers the NCI score to be the most consistent and robust bibliometric measure available, although the limitations of purely citation-based measures should be noted. For example the Thompson Reuters NCI is not designed to capture references to publications outside of scholarly literature. There is evidence that scholars are increasingly adopting the Internet to manage their everyday work[47] (online reference managers Zotero[48] and Mendeley[49] each claim to store over 40 million articles). This highlights the need for tools to capture the extent to which papers are downloaded from a wide range of repositories, alongside a growing interest in monitoring discussion of papers via social media and other networks. Although studies have shown that many researchers do not contribute to social media, there is evidence that promotion through social media can lead to higher downloads[50].

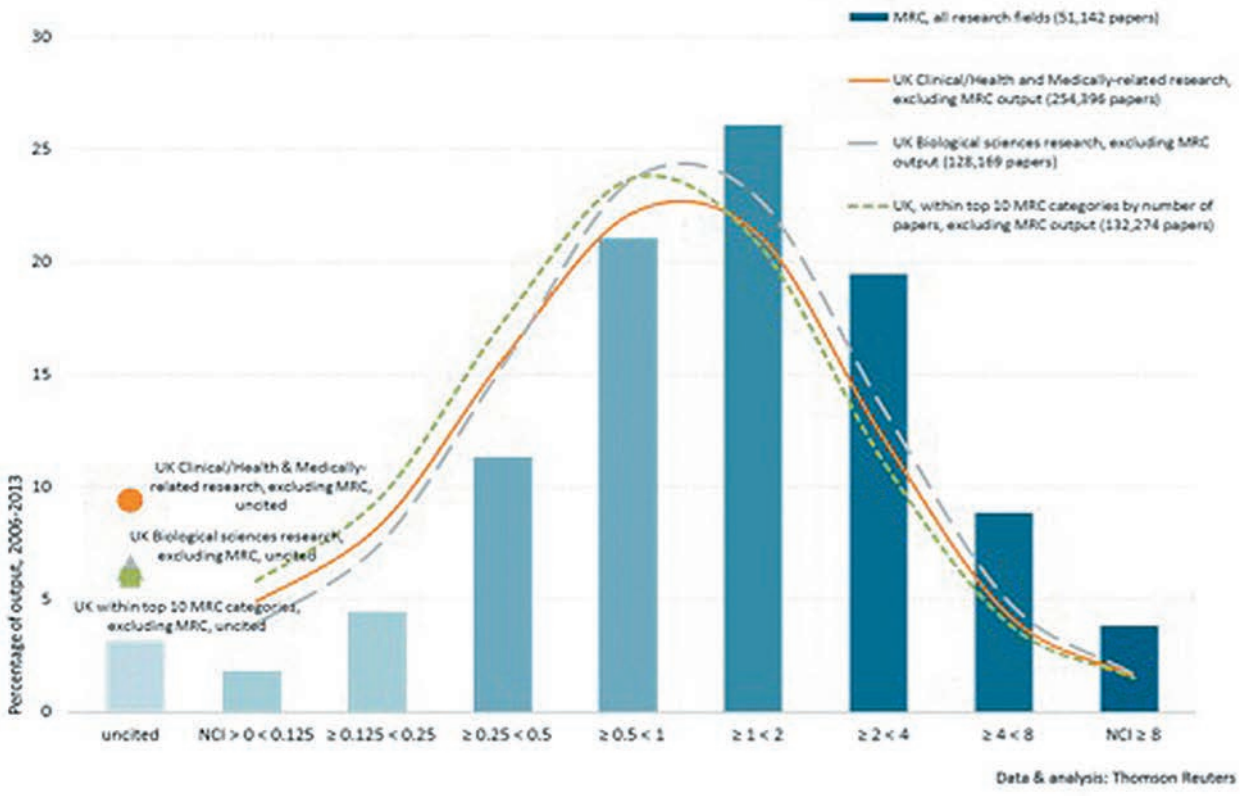
See the section below on Altmetrics for more information on measuring impact through the use of social media.

The average NCI across all MRC papers published between 2006 and 2013 is 2.08[51].

Figure 1 shows an Impact Profile ® of MRC publications between 2006 and 2013[52]. This enables an examination and analysis of the balance of MRC publications relative to world average, and in comparison to publications generated by other UK medically-related and biological sciences research. It shows the proportion of uncited papers and the proportion in each of the eight categories of relative citation rates, normalised to world average.

Table 1 shows the distribution of NCI for the top 20 subject areas (by number of publications)[53]

Figure 1: Impact Profile ® of MRC publications between 2006 and 2013



Of the six million papers published globally between 2006 and 2013, more than a fifth (21 per cent) have not been cited. Within the UK biomedical field this falls to between six and 10 per cent. In comparison, only three per cent of papers generated from MRC-funded research have not been cited.

MRC-funded research generates a greater percentage of highly-cited papers than other UK clinical and UK biological sciences research (12.7 per cent compared to 5.8 per cent and 6.5 per cent respectively). It also generates a greater percentage of 'very highly-cited' papers (identified as those with an NCI score that is greater than or equal to 8) than UK clinical and UK biological sciences research (3.8 per cent compared to 1.6 per cent and 1.7 per cent respectively).

Table 1: Distribution of NCI for the top 20 subject areas

Journal category	Average of category specific NCI
Neurosciences	2.24
Biochemistry and molecular biology	2.16
Cell biology	1.97
Genetics and heredity	3.88
Immunology	1.99
Clinical neurology	2.53
Public, environmental and occupational health	2.35
Psychiatry	2.54
Endocrinology and metabolism	1.81
Oncology	1.83
Infectious diseases	1.61
Virology	1.81
Medicine, research and experimental	2.38
Pharmacology and pharmacy	1.79
Nutrition and dietetics	1.86
Haematology	1.70
Microbiology	2.04
Developmental biology	1.56
Radiology, nuclear medicine and medical imaging	1.98
Biotechnology and applied microbiology	1.84

Number of papers	NCI 1 or more	NCI 1 or more %	NCI 4 or more	NCI 4 or more %	NCI 8 or more	NCI 8 or more %
12,351	7,253	59%	1,801	15%	522	4%
11,750	6,367	54%	1,426	12%	483	4%
7,681	4,131	54%	879	11%	243	3%
7,640	4,729	62%	1,873	25%	880	12%
6,769	3,615	53%	823	12%	241	4%
6,072	3,453	57%	954	16%	316	5%
5,566	2,818	51%	737	13%	228	4%
5,196	3,105	60%	844	16%	246	5%
5,038	2,593	51%	503	10%	133	3%
3,717	1,871	50%	328	9%	97	3%
3,173	1,506	47%	233	7%	87	3%
2,907	1,585	55%	273	9%	69	2%
2,658	1,414	53%	430	16%	157	6%
2,427	1,263	52%	246	10%	62	3%
2,377	1,199	50%	210	9%	50	2%
2,327	1,290	55%	214	9%	40	2%
2,182	1,345	62%	266	12%	49	2%
2,098	1,109	53%	135	6%	26	1%
2,066	1,183	57%	227	11%	57	3%
2,046	1,017	50%	220	11%	62	3%

Five of the top MRC publications by NCI between 2006 and 2013[54]

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis[55]

NCI: 104

This international study looked at the genetic relationship between five disorders in the Psychiatric Genomics Consortium[56]: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder and schizophrenia.

The disease-causing mechanisms of psychiatric disorders are largely unknown so diagnostic boundaries are difficult to define. However, genetic risk factors have been shown to play an important role[57] and genetic strategies are therefore widely used to assess potential overlaps.

The researchers examined single nucleotide polymorphisms (SNPs), the most common type of genetic variation among people, in people with these disorders. An SNP occurs when a single DNA building block — or nucleotide — is substituted with another, for example, cytosine (C) being replaced by thymine (T).

This study, the largest genome-wide analysis of psychiatric illness so far, is the first to provide evidence that specific SNPs are significantly associated with several childhood-onset and adult-onset psychiatric disorders. It showed that SNPs in four chromosomal regions were significantly associated with the development of the five disorders studied. The analysis provides the first genome-wide evidence that individual and combined genetic risk factors are shared between these five disorders, currently treated as distinct categories in clinical care. The finding that genetic variants have cross-disorder effects is a step towards helping clinicians understand why individual patients often present with the symptoms of more than one disorder. The study also indicates that genetic variation in a specific biological pathway may contribute to several disorders and so be a potential drug target.

This paper was reported by Professor Michael O'Donovan, deputy director of the **MRC Centre for Neuropsychiatric Genetics and Genomics, University of Cardiff** and chair of the schizophrenia work group. Core funding for the Psychiatric Genomics Consortium comes from the US National Institute of Mental Health (NIMH).

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial[58]

NCI: 88

This paper presents the results of a trial examining the link between use of the cholesterol-lowering drug simvastatin and a reduction in incidence of heart attacks, stroke and other vascular conditions. The study recruited 20,536 UK adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabetes who were randomly allocated to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo. The study concluded that taking 40 mg of simvastatin daily reduced the rates of heart attack and stroke by about one-quarter (after making allowance for non-compliance, the authors concluded that use would reduce these rates by about one-third).

This trial was conducted by researchers at the **MRC Clinical Trial Service Unit** and was funded predominantly by the MRC and British Heart Foundation. The study was the largest of its kind worldwide. In addition to examining the effects of simvastatin on particularly high-risk patient groups, it also provided evidence that the drug was effective for use in other groups, such as women and the over 70s, for whom there was uncertainty as to how worthwhile and safe the treatment was.

It is likely that the NCI of this paper has increased due to the media and public attention given to the use of statins in recent years following the publication of two BMJ articles referencing adverse effects of statins and the subsequent withdrawal of those statements[59].

An integrated map of genetic variation from 1,092 human genomes[60]

NCI: 67

This paper, from the 1,000 Genomes Project[61], describes the genomes of more than 1,000 people from 14 countries to show that individuals from different populations carry different rare and common genetic variants and that rarer variants show substantial geographic differences.

The 1,000 Genomes Project, which aims to build a resource to help understand the genetic contribution to disease, discovered more than 95 per cent of common genetic variants in its pilot phase[62]. However, rarer variants remain poorly characterised. It has been shown that rare variants are more likely than common ones to affect the structure or function of proteins and therefore to have biological or medical consequences[63]. Because rarer variants are more recent in origin, there are more likely to be geographical differences. Characterising these variants across various populations is therefore likely to identify many functionally-significant variants.

This study further shows that geographic differences are increased by purifying — or negative — selection, the process whereby harmful variants are removed from the population. It also shows that rare variants substantially

differ across biological pathways. This resource, which captures up to 98 per cent of accessible rare variants in these populations, will enable the further analysis of rare genetic variants.

This study was supported by numerous organisations around the world.

Clinical and biomarker changes in dominantly inherited Alzheimer's disease[64]

NCI: 59

This international study estimated the timing and sequence of changes in autosomal-dominant Alzheimer's disease in patients at risk for carrying a mutation for the disease. Autosomal-dominant diseases arise when just one copy of the affected gene is sufficient to cause the disease. Most cases of early-onset Alzheimer's disease, defined as patients diagnosed with the disease before the age of 65, are inherited through autosomal dominance.

The study used various methods including clinical assessment, brain imaging and biochemical analysis to calculate that changes in the brain begin at least 20 years before the estimated onset of symptoms. The researchers estimated that the genetic mutations increase circulating amounts of amyloid beta — misfolded proteins strongly implicated in Alzheimer's disease — which is followed by amyloid accumulation in the brain, accumulation of the tau protein, brain cell death and decreased glucose metabolism. It is after these biological changes have taken place that cognitive impairment can be detected, culminating in clinical impairment and eventually dementia. These findings suggest that a clinical dementia diagnosis is made late in the biological cascade of autosomal-dominant Alzheimer's disease.

These results support the hypothesis of a disease-progression biological cascade and suggest the possibility of a common pathophysiology — the functional changes associated with the disease — between autosomal-dominant Alzheimer's and the much more common 'sporadic' form.

The study recommends that treatment and prevention trials incorporate these changes to gauge the likelihood of future clinical success.

The paper was reported by **Professor Nick Fox** at **University College London**. It was predominantly funded by the US National Institute in Ageing.

Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease

NCI: 53

This study analyses data from genome-wide association studies (GWAS) looking at particular gene regions associated with both Crohn's disease and ulcerative colitis, the two most common forms of inflammatory bowel disease (IBD), which affects more than 2.5 million people of European ancestry[65].

The researchers have identified 71 new genetic associations, most of which are associated with both diseases. They also found that many of these genetic regions are also implicated in other immune disorders, including ankylosing spondylitis and psoriasis.

The researchers also found significant overlap between genetic susceptibility for IBD and mycobacterial infection. Further analysis showed shared biological pathways between the host's response to mycobacteria and those predisposing to IBD.

This study has increased the number of confirmed IBD susceptible genetic regions to 163, most of which are associated with both Crohn's disease and ulcerative colitis, and is substantially more than reported for any other complex disease.

In addition to MRC grants, the study was also funded by other organisations in the UK and overseas.

MRC papers published in 2014 already exhibiting high citation impact

A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria[66]

NCI: 112

This international study identified that a mutation in a region of the *K13* gene was associated with artemisinin resistance in the malaria-causing parasite *Plasmodium falciparum*.

Artemisinin-based combination therapies (ACT) are recommended by WHO as the first-line treatment for uncomplicated *P.falciparum* malaria. Expanding access to ACTs in malaria-endemic countries has been integral to the recent success in reducing the global malaria burden.

However artemisinin resistance, defined as an increased parasite clearance half-life or microscopically-detectable parasites on the third day of ACT treatment, is a growing problem. Resistance had been confirmed in five countries in the Greater Mekong Subregion in South East Asia in February 2015, being worst along the Cambodia-Thailand border.

The researchers, including those at the **University of Oxford**, used whole-genome sequencing of an artemisinin-resistant parasite line from Africa and clinical parasite isolates from Cambodia to identify the gene mutation and show its association with slow parasite clearance rates. This will be a useful molecular marker for large-scale surveillance efforts to contain artemisin-resistance in this South-East Asian region and prevent its global spread.

This study also benefited from funding by several other organisations and programmes, including the Global Fund Grant Malaria Program, the Bill and Melinda Gates Foundation and USAID, NIH and the Wellcome Trust.

Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis[67]

NCI: 85

A meta-analysis conducted by researchers at the **MRC Epidemiology Unit** has found there to be no association between saturated fat intake and heart disease, despite views to the contrary.

The researchers combined the results of 72 studies that had examined the link between fatty acids and heart disease (including heart attacks, coronary heart disease and angina). They found no significant evidence that saturated fats increase the risk of heart disease and additionally, no significant evidence that omega-6 and omega-3 polyunsaturated fats protect the heart. However some of the studies had included people with risk factors for heart disease or who currently had heart disease, so the results might not apply to the population as a whole. Despite this, the researchers highlight that further research is needed, particularly in people who are initially healthy.

The lack of association was seen in studies that looked at dietary intake, circulating levels in the blood and in randomised trials that had looked at supplementation effects.

The study was also funded by the British Heart Foundation, Cambridge National Institute for Health Research Biomedical Research Centre, and Gates Cambridge.

Schizophrenia Working Group of the Psychiatric Genomics Consortium Biological insights from 108 schizophrenia-associated genetic loci[68]

NCI: 75

A study led by **Professor Michael O'Donovan**, deputy director of the **MRC Centre for Neuropsychiatric Genetics and Genomics, University of Cardiff** has identified more than 100 genetic regions associated with schizophrenia, many of which were not previously linked to the condition.

In the largest known molecular genetic study of schizophrenia, the Schizophrenia Working Group of the Psychiatric Genomics Consortium used genome-wide association study (GWAS) arrays to identify 128 independent associations spanning 108 regions, 83 of which have not previously been reported. There were strong associations among genes expressed in the brain, demonstrating that the involvement of biological processes was highly likely. There were also associations among genes expressed in tissues with important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.

Individuals have a one per cent lifetime risk of developing schizophrenia. It is a debilitating condition associated with high death rates as well as personal and societal costs. There are drug treatments available for schizophrenia, however their effectiveness is poor for many patients. It is hoped that this will pave the way for well-informed experiments that will unlock the biology of this condition and ultimately, new treatments.

Core funding for the Psychiatric Genomics Consortium comes from the US National Institute of Mental Health (NIMH).

Open Access

Free and open access to publicly-funded research offers significant social, academic and economic benefits.

Open Access (OA) publishing, by improving access to information and knowledge, promotes[69]:

- the public benefit from publicly-funded research,
- enhanced transparency, openness, accountability and public engagement with research,
- closer links between research and innovation, with benefits for public policy and services, and for economic growth,
- improved efficiency in the research process itself, through increases in the amount of information that is readily accessible, reductions in the time spent in finding it, and greater use of the latest tools and services to organise, manipulate and analyse it,
- increased returns on the investments made in research, especially the investments from public funds, and
- the creation of a new model of scholarly communications.

The research councils have had individual OA policies for several years; the MRC's has been in place since October 2006. Research Councils UK (RCUK) developed a revised and common policy, which came into effect on 1 April 2013[70], in parallel with the findings of the 2012 Finch Report, which recommended a new approach to accelerate the transition to full OA.

RCUK commissioned an independent review in 2014 to assess the implementation of its revised OA policy[71]. The review panel made recommendations to help improve some of the processes involved in implementing and communicating the policy. It also underlined the lack of comprehensive data to assess how well the policy was being followed, and its broader impact on different disciplines.

Image credit: PLOS

The key aspect of the RCUK mandate for MRC-funded researchers is that whether a paper is published in an open access or subscription- based journal, all articles must be archived in Europe PubMed Central (Europe PMC) and made freely available as soon as possible, and in any event, within six months of the first on-line publication.

In order to measure how well this requirement is followed, the MRC analyses each year the publications which are recorded in researchfish®, and whether they are available in full text in Europe PMC. This provides a straight forward and reliable way to identify the proportion of papers openly available in line with the policy.

Graphs showing the proportion of unique MRC publications produced each year that are available in Europe PMC (as at March 2016) are in the quantitative analysis section 3.1.

Altmetrics

Altmetrics is a relatively new term, coined in 2010 by Jason Priem, a doctoral student in information science at the University of North Carolina. It can be defined as 'social media-based metrics[72] , which take into account digital use and sharing of data — such as through 'likes' on Facebook, being tweeted or cited on Wikipedia — when gauging impact[73].

To reflect the growing use of social media by academics — Procter R et al reported in 2010 that 13 per cent of UK academics frequently use Web 2.0[74] in novel forms of scholarly communications[75] — the research and academic community is making increasing use of altmetrics. Many journals now display some altmetrics on their sites automatically, either generated in-house or provided by an external service. There is some evidence that social media mentions of the scientific literature in biomedical research are more prevalent than other areas of research[76]. PLOS includes an online metrics tab for each article it publishes, showing views, downloads and social-media mentions. In addition, HEFCE allows scientists to use them when demonstrating social impact in reports for the Research Excellence Framework (REF).

Many consider that altmetrics should be applied with caution (Kwok R 2013). They do not always discriminate between positive and negative attention. Most altmetric analysis services rely on picking up URLs for the study, which are not always included in news items, so at best the metrics are partial. And, as with journal citations, social media 'citations' differ between years and disciplines (but currently there is no 'normalisation for this) — computational biology researchers, for example, tend to be more active on social media than others (Kwok R 2013).

Some studies have shown that there is a positive, albeit weak correlation with traditional methods such as citations[77,78]. It is proposed therefore that altmetrics and citations measure different types of impact and that altmetrics should be used to complement, rather than replace, traditional methods[79].

Altmetric[80], a London-based company set up to track and analyse the online activities around scholarly literature, published a list of the top 100 articles that had received the most online attention in 2014[81], using their data on social

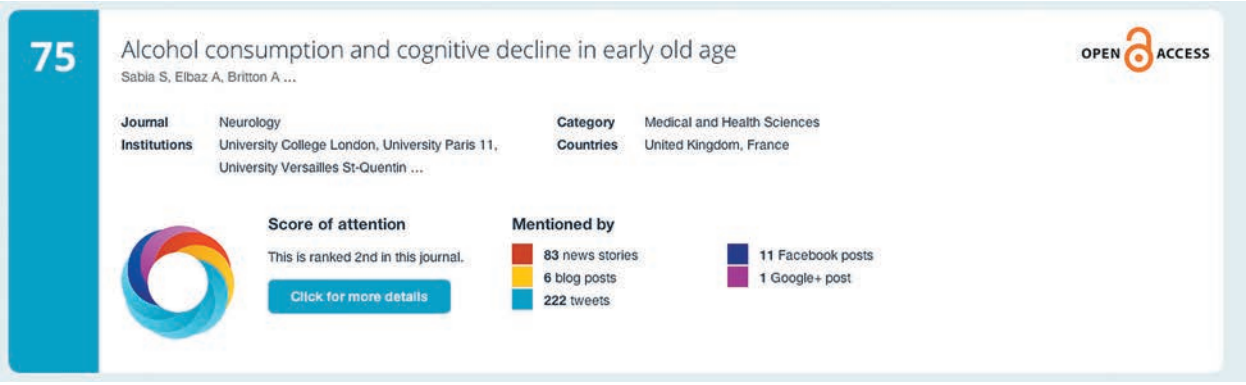
media. . There were a number of MRC-funded publications within the top 100. At number 41 was *Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections*[82], a report published in the New England Journal of Medicine (NEJM) which documented current trends in the Ebola epidemic and projected expected case numbers for the following weeks. Researchers from the **MRC Centre for Outbreak Analysis and Modelling** at **Imperial College London** were substantially involved in this work[83].

The article's 'Altmetric' score taken at the end of 2014. www.altmetric.com

At number 55 was *Alcohol and mortality in Russia: prospective observational study of 151 000 adults*[84], a study that showed that vodka was a major cause of the high risk of premature death in Russian adults. The study involved researchers from the **MRC Clinical Trial Service Unit and Epidemiological Studies Unit** (CTSU) at the **University of Oxford**.

The article's 'Altmetric' score taken at the end of 2014. www.altmetric.com

Alcohol consumption and cognitive decline in early old age[85] was at number 75. This research used data from the MRC Whitehall II study to show that excessive alcohol consumption in men (≥36 grams per day or three units per day) was associated with faster cognitive decline compared with light to moderate alcohol consumption.



The article's 'Altmetric' score taken at the end of 2014. www.altmetric.com

Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

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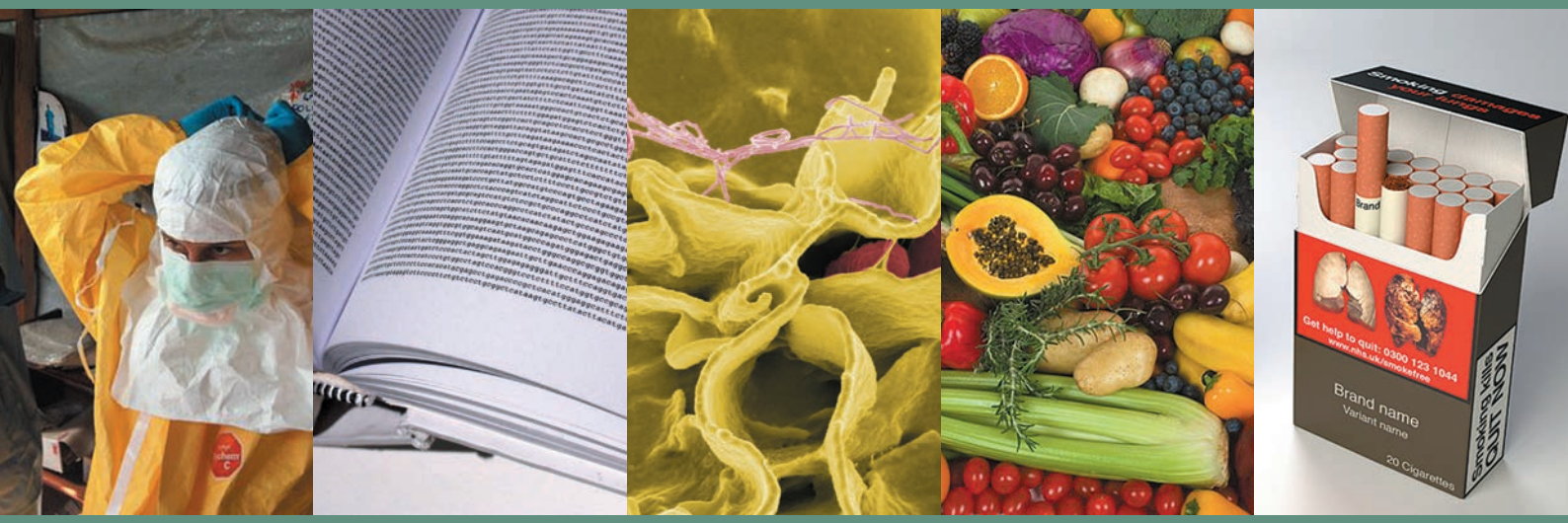
MRC Medical Research Council

Outputs, outcomes and impact of MRC research

2014/15 report



SECTION 2.2
Policy and engagement

Policy and engagement

Translating excellent research into improved policy has never been so important. This translation occurs via many different routes, but *engagement* — communicating and exchanging information and expertise — between researchers, the public and policymakers is crucial. Policymakers, including politicians, regulatory organisations and arms-length bodies, have a duty to use the best possible evidence to benefit society's health and wellbeing. Researchers are therefore encouraged to maximise opportunities for their findings to inform policy decisions.

This is not always a straightforward pathway however and academic research is not always ready for application or can easily be put into practice by policymakers.

This is why the MRC requires researchers to consider including ways to engage with the public, policymakers and other potential beneficiaries in their research design. Extending and improving this exchange is at the heart of our strategic plan[86]. The MRC recognises the importance of public engagement: helping the public to understand our scientific findings, reflecting their views in our decision-making and effectively communicating these policies.

The MRC has a long history of engaging and consulting with parliamentarians. The MRC regularly submits evidence[87] to inquiries and consultations by government departments and House of Commons and House of Lords Select Committees, drawing on the expertise of researchers and research boards as necessary. The MRC played an instrumental role in helping to ensure that the UK became the first country in the world to allow mitochondrial donation to prevent serious genetic diseases. The House of Lords voted in favour of the new regulations in February 2015, allowing the use of in vitro fertilisation (IVF) techniques to swap faulty mitochondrial DNA with donor egg mitochondrial DNA[88]. Our researchers are also often called upon as experts in particular areas of research to give advice or evidence.

MRC researchers contribute to the development and revision of clinical guidelines, including NICE and WHO guidelines. These are recommendations to clinicians on diagnosis, management and treatment in specific areas of healthcare based on systematic evidence. MRC researchers also influence policy through their membership of guideline committees, participating in national consultations, and training practitioners. The MRC has played a leading role in critical areas of research and subsequent policy and strategy development, from our public health work on obesity and smoking to the establishment of UK Biobank[89].

The MRC runs a varied public engagement programme[90] involving many researchers, from open days and participation in science festivals to our annual Max Perutz science writing competition[91]. But public engagement is not limited to these MRC-run events. The MRC encourages our scientists to engage, educate and inspire the public through various mediums, should that be taking part in exhibitions or workshops, giving lectures or being interviewed by the media. MRC researchers are often also involved in the many public engagement activities run through their own universities or research organisations.

All scientific achievements, from those arising from discovery science to those with research origins in the health sciences, require engagement with the public or policymakers to be successfully put into practice. This is the case whether they result from many years of focused research or are a moment of scientific serendipity.

This chapter comprises examples of where MRC-supported researchers have influenced policy and been involved in public engagement. The information in this chapter has largely been sourced from researchfish®[92].

The examples in this chapter are categorised by the following research areas:

- Global health
- Genomics
- Cardiovascular disease
- Kidney disease
- Infectious diseases
- Neurodegeneration and cognition
- Mental health
- Obesity, nutrition and physical activity
- Smoking
- Hearing

Each case study focuses on a predominant output type, but others might be referenced within it. The accompanying icons represent the relevant output types. A key to the list of output types is at the end of this chapter.

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — the *Gateway to Research*[93] — by entering the project reference number listed under each case study in the search field.

Global Health

Influence on policy: Reports on Ebola to the World Health Organization and other international stakeholders

Work at the **MRC Centre for Outbreak Analysis and Modelling** at **Imperial College London** has helped to inform and stimulate the international response to the on-going Ebola epidemic.

The Ebola outbreak was first reported to the World Health Organization (WHO) in March 2014 and can be traced back to a small village in south-eastern Guinea, where the initial infection occurred in December 2013[94]. However, it wasn't until the summer of 2014 that there was sufficient information available to appreciate the scale of the problem. The outbreak had quickly become the deadliest occurrence of the disease since its discovery in 1976. A team of more than a dozen researchers at Imperial College conducted vital work analysing the line lists — information on where the patients lived, who they were in contact with, their demographics and symptoms. They were able to track the spread of the epidemic through time to estimate the transmission rate and incubation period. By linking the Ebola cases together, the researchers were able to determine the risk factors for transmission and to identify the most effective interventions for agencies on the ground.

This work was used to provide reports on the current Ebola epidemic to the World Health Organization (WHO), the UK Government, the US Centers for Disease Control and Prevention (US CDC) and other international stakeholders.

Based on this analysis, the WHO declared the epidemic to be a "public health emergency of international concern in August 2014"[95]. As of 8 February 2015, the total number of reported cases was 22,894 and the number of deaths 9,177[96].

This work also fed into a report published in the New England Journal of Medicine (NEJM) in October 2014[97] which documented current trends in the epidemic and projected expected case numbers for the following weeks if control measures were not enhanced. The report found that cases of the disease were divided equally between the sexes. Until then, one view had been that women might be harder hit because they were more likely to care for the ill; another view had been that it would be men who might be more likely to bury the dead.

Ebola workers in Liberia.
Image credit: Flickr/European Commission DG ECHO CC BY 3.0

The report also made various recommendations, such as reducing the length of time from symptom onset to hospitalisation to curtail transmission in the community. The individual fatality rate was also lower for hospitalised patients.

As a result of their work, staff at the MRC centre were interviewed by several media outlets, including the *BBC*[98], *The Independent*[99], *Yahoo! News*[100] and *The Guardian*[101,102].

In addition to helping steer the emergency relief efforts in West Africa and controlling the epidemic, the evidence helped convey the seriousness of the situation, providing support for the public funding from Governments and charities. It is also important to note the contribution that such "real world" analysis of epidemics makes to UK resilience as the methods are also applied to monitoring and modelling disease outbreak scenarios in this country.

Project reference number: MR/K010174/1

Influence on policy: International rabies strategies

Part of **Professor Daniel Haydon's** research at the **University of Glasgow** involves analysing how large-scale infectious disease interventions work and how they can be improved. He has evaluated the success of mass dog vaccination programmes as a rabies prevention measure in Africa and Asia.

Rabies is a zoonotic viral disease – a disease that can be spread from animals to humans. It affects domestic and wild animals and is transmitted to people through contact with infectious material, usually saliva, via bites and scratches. It occurs in more than 150 countries and territories worldwide and causes more than 55,000 deaths each year, mainly in Africa and Asia[103]. The global cost of rabies is estimated to be more than US$6 billion including US$1.6 billion spent on post-exposure prophylaxis[104] — a course of vaccination given as treatment.

Domestic dogs are the primary source of the rabies virus transmitted to humans and growing evidence suggests that elimination of canine rabies is possible through sustained annual campaigns that achieve 70 per cent coverage.

Professor Haydon and colleagues were instrumental in developing a canine vaccination strategy between 2010 and 2013 to eliminate a rabies epidemic in Bali, Indonesia that had begun in 2008[105]. The team developed a computer model which they used to test different control strategies and to identify the key targets that would need to be met to eliminate rabies from the island. They estimated the transmission rate between dogs to be similar to cases in other countries, such as Tanzania, despite the dog population on Bali being at least 10 times higher. This finding supported evidence that aiming to control rabies spread by reducing dog population (such as through culling) would not be effective. The researchers showed that the control and elimination of rabies from the island was feasible using canine vaccination. In the first three years of the outbreak, 130 human deaths from rabies had been reported and more than 130,000 doses of post-exposure prophylaxis delivered to bite victims. The vaccination programme reduced the rate of human death by 90 per cent.

Additionally, **Professor Sarah Cleaveland**, also at the University of Glasgow, was a member of the committee that developed Kenya's national strategy for controlling and eliminating rabies[106]. The strategy, published in October 2014, is the first of its kind in Africa and aims to eliminate rabies in Kenya by 2030.

Professor Sarah Cleaveland was also a member of the World Health Organization (WHO) Expert Consultation on Rabies, which published its second report in 2013[107].

Project reference number: G0901135

Influence on policy: Setting WHO post-2015 global tuberculosis targets

Tuberculosis (TB) is an infection caused by the bacterium *Mycobacterium tuberculosis*. It is spread through inhaling tiny droplets from the coughs or sneezes of an infected person.

Approximately one third of the world's population has latent TB, which means they are infected with *M. tuberculosis* but are not yet ill with the disease and cannot therefore transmit it. Around 10 per cent of people with latent tuberculosis will then go on to develop the full disease. However, this rate is higher in people with compromised immune systems, such as those with HIV, malnutrition or diabetes.

In 2013 nine million people became ill with TB and 1.5 million died from the disease. Evidence suggests that without proper treatment, up to two thirds of people with the disease could die from it. TB occurs in every part of the world; however, more than 95 per cent of cases and deaths from the disease are in developing countries[108].

Dr Richard White at the **London School of Hygiene and Tropical Medicine** was part of the WHO expert group that provided the modelling evidence used to set the targets for the *WHO tuberculosis prevention, care and control after 2015* strategy[109]. This follows on from previous strategies[110] and aims for a 75 per cent reduction in TB deaths[111] and a 50 per cent reduction in the incidence rate by 2025, increasing to 95 and 90 per cent respectively by 2035.

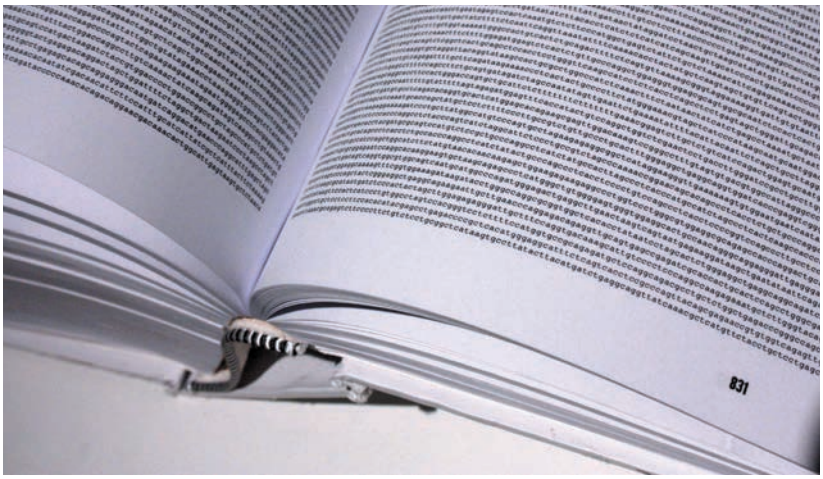
Ever since the MRC was set up to specifically tackle TB in 1913, it has played an important role in TB research. Recently, the MRC has funded global TB trials, shed light on the evolution of the disease[112], furthered knowledge of its cellular processes to identify new drug targets[113], and been instrumental in determining the best combination of treatments[114,115].

Project reference number: MR/J005088/1

Genomics

Engagement activities: Functional genome

Professor Chris Ponting is a professor of genomics — the study of genome structures, function, evolution and mapping — at the **University of Oxford**. He has contributed to many landmark genome sequencing projects, including sequencing the human, mouse, rat and chicken genomes. The primary focus of his research is using genome-scale data sets to identify or prioritise genes that are mutated in human disease.



The printed human genome fills a book.
Image credit: Stephen C Dickson CC BY-SA 4.0

In 2014 Professor Ponting and colleagues published research suggesting that only 8.2 per cent of the human genome was functional[116]. To reach this figure, the researchers identified how much of our genome had avoided being changed over 100 million years of mammalian evolution. They took this to indicate that this DNA has important functions that need to be retained. This finding will speed up the ability to track down genetic mutations in disease as researchers can prioritise genetic differences that occur in the conserved portion of the genome. This research received media coverage, including articles published in *The Telegraph*[117] and the *Daily Mail*[118].

Project reference number: MC_U137761446

Cardiovascular disease

Influence on policy: NICE guidelines on Hypertension: Clinical management of primary hypertension in adults

Hypertension — or high blood pressure — affects around 30 per cent of people in England. If left untreated, it increases a person's risk of a heart attack or stroke. Hypertension was the leading risk factor for the overall global burden of disease in 2010[119].

MRC-funded researcher **Professor Bryan Williams** at **University College London** is recognised as one of the world's leading authorities in the field of hypertension research. Taking an experimental medicine approach, he focuses on developing clinically applicable models for the human non-invasive assessment of aortic pressure — the blood pressure at the root of the aorta, the main blood vessel that takes blood away from the heart. Professor Williams led the team that conducted the Conduit Artery Functional Endpoint (CAFE) study, which suggested that central aortic blood pressure may be more predictive of cardiovascular events such as a stroke or heart attack, than the traditional peripheral blood pressure measurements, taken at the top of the arm[120].

Professor Williams chaired the NICE *Clinical management of primary hypertension in adults* guidelines group, published in 2011[121]. These guidelines reflected a shift in focus from the importance of diastolic (minimum) pressure towards the greater importance of systolic (maximum) pressure in people aged 60 years and older. The content of these guidelines was supported by evidence provided by Professor Williams' research, specifically an MRC-funded study that showed that different types of hypertension at different stages of life had different cardiovascular effects, the results of which were published in 2014[122]. This study demonstrated that diastolic blood pressure was a less powerful predictor of most cardiovascular diseases than systolic pressure.

The findings may also support the early use of treatment in younger people with mild blood pressure elevations. Professor Williams is currently leading the TREAT CASP study[123], part-funded by the MRC. This study aims to determine whether it is preferable to use central aortic pressure to measure high blood pressure in young men to better identify who would be most likely to benefit from treatment and so reduce the number of people who suffer from heart attacks or strokes. This will use a pioneering device developed by Professor Williams whilst at the University of Leicester that could revolutionise the way blood pressure is measured and monitored for the first time in more than a century. The device, which is similar to a wristwatch, uses a sensor on the wrist to record the pulse wave. Using computerised mathematical modelling, scientists are able to accurately read the aortic pressure from this information. The device, which was developed in conjunction with Healthstats, a biotechnology company in Singapore, won the 2011 Times Higher Education award for 'Outstanding contribution to innovation and technology'.

Project reference number: UD99999967

Influence on policy: American Heart Association guidelines for arteriovenous malformations of the brain

Professor Rustam Al-Shahi Salman is an academic clinician at the **University of Edinburgh** who studies cerebral haemorrhages, or bleeds on the brain. Cerebral haemorrhages occur when a blood vessel bursts in the brain. They cause around 15 per cent of all strokes, and affect about 10,000 adults in the UK — and about 1.5 million adults worldwide — each year.

> ***"There are few AVM guidelines other than those produced by the AHA, so the AHA's guidelines tend to affect practice worldwide. This edition of the guidelines will be influenced by our population-based study and the ARUBA randomised trial that my group oversaw in the UK."***
>
> ***– Professor Al-Shahi Salman***

Professor Al-Shahi Salman has recently shown that treating patients with arteriovenous malformations in the brain increases their risk of stroke when compared to not treating them. An arteriovenous malformation (AVM) is a tangle of blood vessels with the arteries directly connected to the veins. This means that blood from the arteries drains directly into the veins without stopping to supply the normal tissues in that part of the body with oxygen and nutrition.

AVMs can occur in any part of the body but most commonly in the brain or spine. They contain weakened blood vessels which may burst from the high pressure of blood flow from the arteries, causing bleeding, which in the brain can lead to brain damage and death. Brain AVMs affect approximately one in 2,000 people and around one per cent of affected adults suffer a stroke as a result of their AVM each year.

However, Professor Al-Shahi Salman has found that over a 12-year period, patients who chose not to have their AVM treated by trying to remove or block the tangle of blood vessels were less likely to have a stroke or die from related causes[124].

In 2014, Professor Al-Shahi Salman was appointed to the American Heart Association guidelines committee for arteriovenous malformations of the brain. The guidelines, due to be published in 2016, will include the results of his study.

Professor Al-Shahi Salman says, "There are few AVM guidelines other than those produced by the AHA, so the AHA's guidelines tend to affect practice worldwide. This edition of the guidelines will be influenced by our population-based study and the ARUBA randomised trial that my group oversaw in the UK."

Project reference number: G108/613

Kidney disease

Influence on policy: NICE guidelines on Eculizumab for treating atypical haemolytic uraemic syndrome (aHUS)

Research led by **Professor Tim Goodship** at the **University of Newcastle** has had a significant impact on the prognosis of patients with atypical haemolytic uraemic syndrome (aHUS). His research has benefited from a combination of MRC, Northern Counties Kidney Research Fund and other medical research charity funding.

> ***"Eculizumab offers people with aHUS the possibility of avoiding end-stage renal failure, dialysis and kidney transplantation, as well as other organ damage."***
>
> ***– Sir Andrew Dillon***

aHUS is a rare, life-threatening progressive disease that primarily affects kidney function. It affects around 200 people in the UK, with 20-30 more people diagnosed each year. The disease causes blood vessel inflammation and blood clot formation, which damages vital organs, particularly kidneys, and eventually leads to organ failure. Eight per cent of patients die on initial manifestation of the condition and 50 per cent of surviving patients will need long-term dialysis within two years. The outcome of kidney transplantation for patients is poor due to the high risk of disease recurrence and subsequent kidney loss. The five-year transplant survival for patients is 51 per cent.

Professor Goodship and colleagues identified mutations in the genes coding for complement system proteins in 1998 and showed that genetic abnormalities caused 70 per cent of cases. The complement system is part of the body's innate immune system. Its role is to induce inflammation to help the body remove pathogens and fight infection. However the genetic abnormalities in aHUS cause the complement system to be uncontrollably and excessively activated.

Building on this research, Professor Goodship, in collaboration with Professor Giuseppe Remuzzi from the Mario Negri Institute in Italy, showed that the underlying mutation strongly predicted the kidney transplant outcome. Indeed, the five-year survival rate for transplant patients known to have a genetic abnormality is just 30 per cent.

As a result of this research, an NHS diagnostics service has been established, which now tests for five of the genes implicated in the condition. This screening can identify those patients who do not have the gene mutations and are therefore more likely to benefit from a kidney transplant.

Professor Goodship also conducted trials into the use of monoclonal antibody and complement-inhibitor, eculizumab, to treat the genetic cases of the disease. On demonstrating its effectiveness, both the US Food and Drug Administration and the European Medicines Agency approved its use in 2011.

NICE National Institute for Health and Care Excellence

NICE logo.
Reproduced with permission from NICE.

Based on this research and despite the high cost of treatment[125], the NHS approved the use of eculizumab to treat aHUS and NICE published its guidelines for use in January 2015[126].

NICE chief executive Sir Andrew Dillon said: "Eculizumab offers people with aHUS the possibility of avoiding end-stage renal failure, dialysis and kidney transplantation, as well as other organ damage."[127]

Project reference number: G0701325

Infectious diseases

Engagement activities: Antimicrobial resistance media coverage

Professor Laura Piddock is a professor of microbiology at the **University of Birmingham**. She is a leader in the field of antimicrobial resistance (AMR) research and also a prominent spokesperson on the growing concern of AMR. She is director of Antibiotic Action[128], an independent UK-led global initiative that aims to inform and educate about the need to discover, research and develop new treatments for bacterial infections.

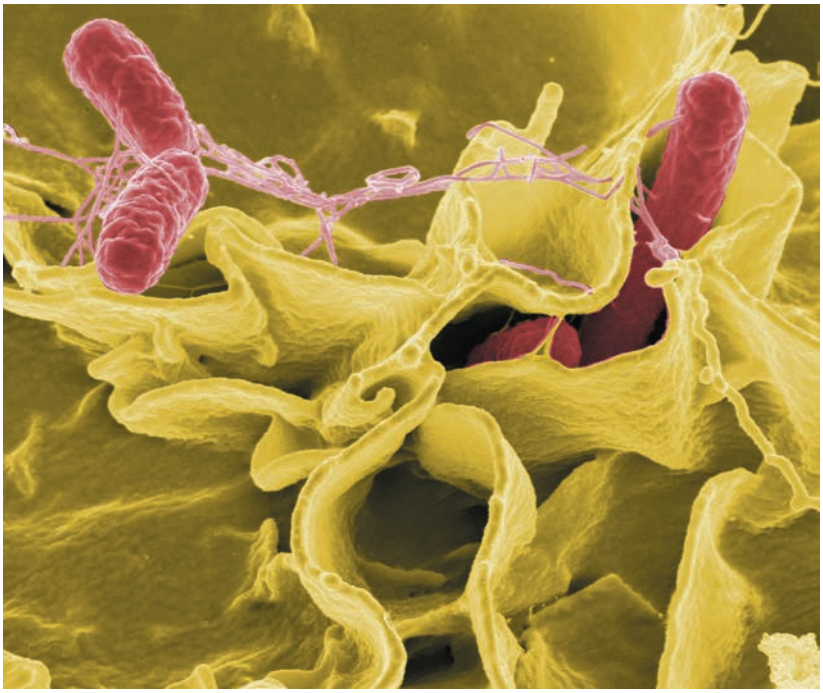
> ***"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them..."***
>
> ***Sir Alexander Fleming***

Since 1928, when Sir Alexander Fleming accidentally discovered penicillin growing on a petri-dish of bacteria, antibiotics have saved the lives of countless numbers of people and animals. Their discovery is seen as one of the most important scientific achievements of the 20th century. But overuse and misuse of antibiotics has contributed to the emergence of resistance. Sir Alexander Fleming himself, on collecting a Nobel Prize for his discovery, predicted the dawn of this battle, saying, "It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them..."

There are high proportions of antibiotic resistance in bacteria causing common infections, such as urinary tract infections, pneumonia and bloodstream infections in all regions of the world. Highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant Gram-negative bacteria cause a high percentage of hospital-acquired infections. There were about 450,000 new cases of multidrug-resistant tuberculosis (MDR-TB) in 2012 and extensively drug-resistant tuberculosis (XDR-TB) has been identified in 92 countries.

Professor Piddock's research focuses on how bacteria develop resistance to antibiotics, particularly in the systems that allow antibiotics to be transported in and out of bacteria. Professor Piddock recently discovered a mutation in the gene coding for *Salmonella* Typhimurium's efflux pump — the mechanism that enables the bacteria to expel toxins — which makes it more efficient at pumping some antibiotics out of the cell[129]. In the international study, the researchers sequenced the genome of a *Salmonella* Typhimurium strain contracted by a patient who had failed to respond to the antibiotic ciprofloxacin. They discovered the mutation in the efflux pump gene *acrB* and that it changed the binding of drugs to the pocket of the pump. Computational studies showed that this was partly due to an altered structure. Importantly, the researchers discovered that this mutation caused an increased susceptibility to other drugs due to reduced pumping. The finding that this single mutation can cause resistance to some drugs but susceptibility to others informs those developing new antibiotics.

This research received media interest in early 2015, including articles published in *The Telegraph*[130] and *Yahoo! News*[131].



Colour-enhanced scanning electron micrograph showing Salmonella Typhimurium (red) invading cultured human cells.
Image credit: Rocky Mountain Laboratories, NIAID, NIH.

Professor Piddock has been interviewed by numerous media outlets on the growing problem of antibiotic resistance, including the *BBC*[132], *The Guardian*[133] and the *Daily Express*[134].

In 2014 the research councils launched a cross-council initiative on AMR research, which is being led by the MRC. This will see all seven councils working together to tackle AMR. A joined-up, multi-disciplinary approach is essential and so the initiative will coordinate the work of medical researchers, biologists, engineers, vets, economists, social scientists, mathematicians and designers. It is only through tackling the problem at every level and in every environment that we will be able to take the next steps towards a solution. Some of the groundwork for this initiative is showcased in a timeline of research and series of case studies[135].

Project reference number: G0501415

Influence on policy: Participation in Acting on Campylobacter Together (ACT) campaign

Professor Sarah O'Brien researches zoonoses — diseases that can be transmitted from animals to humans — at the **University of Liverpool**. She was part of the Food Standard Agency (FSA)'s Acting Together on Campylobacter (ACT) accelerated solutions event in June 2014 that brought together representatives from government, retailers, caterers, poultry producers and processors, and consumer organisations to agree actions that could be taken to reduce campylobacter. This event directly influenced the development of the FSA's campylobacter risk management programme to decrease campylobacter levels in UK-produced chickens.

Campylobacter is the most common cause of food poisoning in the UK, considered to be responsible for around 280,000 cases each year, more than salmonella, *E. coli* and listeria combined[136].

Contaminated poultry causes around four in five cases of campylobacter poisoning in the UK. The latest report from the FSA revealed that 73 per cent of shop-bought chickens are contaminated with the bacterium, with 19 per cent testing positive at the highest level[137].

Image credit: Food Standards Agency

The infection causes symptoms such as severe diarrhoea, abdominal pain, fever, and sometimes vomiting. Symptoms usually persist for between two and 10 days, but in severe cases can continue for up to three weeks. Infection can sometimes lead to other complications such as the development of irritable bowel syndrome (IBS) and rarely, Guillain-Barré syndrome – a serious and sometimes permanent condition of the nervous system.

The FSA estimates that the infection causes more than 100 deaths each year in the UK and that the annual cost to the economy is £900 million.

Project reference number: MC_U122785837

Neurodegeneration and cognition

Engagement activities: Edinburgh Fringe Festival

Dr Alan Gow is an assistant Professor of Psychology at **Heriot-Watt University** and part of the **University of Edinburgh's Centre for Cognitive Ageing and Cognitive Epidemiology**.

His research focuses on the lifestyle factors that have an impact on health and wellbeing in old age, particularly cognitive ageing, such as physical activity and social and intellectual activities.

Dr Gow took part in the 2014 Edinburgh Fringe Festival with a show called *Brain training on trial*[138], as part of the *Cabaret of dangerous ideas*[139]. He reviews the top 'brain-training' smartphone apps in light of their unverified claims of being supported by research. He also covered this topic in a blog post for *Research the headlines*[140].

He had previously published research showing that people over 70 who took regular exercise showed less brain shrinkage over a three-year period than those who did little exercise[141]. The study of 700 people did not however find there to be any benefit to brain health from participation in social or mentally-stimulating activities. Research has shown that greater brain shrinkage is linked to problems with memory and thinking. The researchers also showed that those who were more physically active had fewer 'damaged' areas in the brain's white matter — the brain tissue consisting of nerve fibres that transmits signals from one part to another. This research received media attention in 2012, resulting in articles by the *BBC*[142] and the *Daily Mail*[143].

Project reference number: MR/K026992/1

Engagement activities: Muscular Dystrophy Campaign (MDC) Duchenne and Becker impact day

Professor Steve Winder's research at the **University of Sheffield** focuses on the role of the cell adhesion and signalling protein dystroglycan in diseases such as muscular dystrophy and cancer.

Professor Winder gave a talk on the use of anti-cancer drugs to treat Duchenne Muscular Dystrophy (DMD) at the Muscular Dystrophy Campaign (MDC)'s Duchenne and Becker impact day in June 2014.

The muscular dystrophies (MD) are a group of inherited genetic conditions that gradually cause the muscles to weaken, leading to an increasing level of disability. Duchenne muscular dystrophy (DMD) is one of the most common and severest forms, affecting around one in 3,500 boys in the UK. It usually affects boys in early childhood and individuals with the condition will usually only live into their 20s or 30s. There is currently no cure, though various treatment avenues are being explored by MRC researchers.

DMD is caused by a mutation in the *DMD* gene, the largest gene on the X chromosome. The *DMD* gene encodes the protein dystrophin, an important part of muscle tissue that provides structural stability. Mutations in the DMD gene result in complete loss of the protein, rendering it non-functional. The loss of the dystrophin protein ultimately leads to the degeneration of muscle fibres, progressive weakness and premature death.

Dystroglycan is a transmembrane protein that binds to a protein called laminin on the outside of the cell and dystrophin on the inside of the cell, forming the dystrophin glycoprotein complex (DGC). The loss of dystrophin leads to the loss of this complex. Professor Winder has shown that this is because the absence of dystrophin causes increased tyrosine phosphorylation of dystroglycan (adding a phosphate group to the tyrosine amino acid of dystroglycan)[144]. It is believed that this then signals the degradation of the DGC by proteasome enzymes, leading to the symptoms experienced in DMD. There are anticancer drugs that inhibit this process, which has been shown to be implicated in some forms of cancer. Drugs that work in a similar way may hold the potential to also treat DMD. Professor Winder received interest from the charity Action Duchenne to fund future research as a result of the talk he gave. Professor Winder also gave a presentation on the same topic to Action Duchenne's International DMD Conference in London in November 2014.

Professor Winder has patented the use of tyrosine phosphorylation inhibitors as a treatment for DMD[145].

Further information on the MRC's research into DMD is available in the *Outputs, outcomes and impact of MRC research 2013-14 (Development of products, research materials and intellectual property pages 7-8)* report[146] and in the MRC's film *Celebrating 100 years of life-changing discoveries: Dale to Davies*[147].

Project reference number: G0701129

Engagement activities: *The secret life of four-year olds*

Dr Sam Wass, developmental psychologist at the **MRC Cognition and Brain Sciences Unit** was featured on Channel Four's *The secret life of four-year olds*[148], a documentary observing a group of four-year olds as they meet for the first time in a specially-adapted nursery. Dr Wass' expertise in the development of attention during childhood was put to good use as he explored how the children made friendships, stood up for themselves and found their place in a new social group. The programme was first broadcast in February 2015.

In 2015 Dr Wass published research suggesting that frequent eye movement in babies could show differences in visual processing and be a subtle early indicator of autism spectrum disorders[149].

Project reference number: MC_UP_A060_1104

Mental Health

Influence on policy: Co-author of 2014 Chief Medical Officer (CMO) annual report on public mental health

Dr Hind Khalifeh's research at **University College London** looked at violence against adults with severe mental illness[150]. Dr Khalifeh showed that women with severe mental illness were up to five times more likely than the general population to be victims of sexual assault and two to three times more likely to suffer domestic violence[151]. The MRC and Big Lottery-funded study found that 40 per cent of women surveyed with severe mental illness had suffered rape or attempted rape in adulthood, of whom 53 per cent had attempted suicide as a result. In comparison, in the general population, seven per cent of women had been victims of rape or attempted rape, of whom three per cent had attempted suicide. The study also showed that 12 per cent of men with severe mental illness had been seriously sexually assaulted, compared with 0.5 per cent of the general population. The results of this study received various media coverage, including an article in the *Daily Mail*[152].

Annual report of the Chief Medical Officer 2013.
Reproduced with the permission of the Department of Health.

Dr Khalifeh co-authored the chapter on *Violence and mental health* in the Chief Medical Officer (CMO) 2013 annual report, which was on mental health[153]. This chapter included a proposal that healthcare staff need additional training, including awareness that people with mental health problems have a two to tenfold risk of being a victim of violence compared with the general population. This proposal is reflected in the CMO's main recommendations; that there should be a period of specific mental health training in GP training and that a core part of this should include specific training for awareness about the consequences of violence on mental health across the life course.

Project reference number: G0802434

Engagement activities: Role of the habenula in negativity

Dr Jonathan Roiser's research at **University College London (UCL)** focuses on the neurobiological mechanisms underlying psychiatric symptoms. In 2014 he published research showing that a small area of the brain — the habenula — plays a key role in how humans predict, learn from and respond to negative experiences[154]. Animal studies had shown that the habenula fires up when subjects experience or expect to experience adverse events. However, due to the habenula's small size (less than 3mm in diameter), this response had been difficult to see on scans. The researchers developed a high-resolution functional Magnetic Resonance Imaging (fMRI) technique which was used in conjunction with computational modelling to examine the response of the habenula during a set of reinforcement learning tests.

The 23 participants were shown several abstract images. The images followed by either punishment (electric shocks), a reward (of money), a loss (of money) or no response. For certain images, a punishment or reward followed each time but for others this varied - leaving people uncertain whether they were going to feel pain or not. The researchers found that the habenula was activated when people saw images associated with shocks. The habenula activity was stronger and faster the more certain the individual was that a particular image would result in a punishment.

The researchers propose that these responses in the habenula guide behaviour towards reward and away from punishment or negative events. This suggests a potential role for the habenula in disorders such as depression. Professor Roiser had previously reported abnormalities in habenula structure and function in patients with depression[155]. This research received national and international media coverage, including articles by the *BBC*[156], *ITV*[157], the *Daily Mail*[158] and the *New York Times*[159].

Project reference number: G0901275

Obesity, nutrition and physical activity

Influence on policy: NICE guidelines on Managing overweight and obesity in adults – lifestyle weight management services

Professor Paul Aveyard's systematic reviews on weight management programmes[160] were used as evidence in the NICE guidelines on *Managing overweight and obesity in adults – lifestyle weight management services*[161].

Professor Susan Jebb's earlier research at the **Human Nutrition Research (HNR)** group showed that participating in commercial weight management programmes, such as Weightwatchers and Slimming World, can lead to a greater weight loss than from following the advice of a doctor[162]. Following this, Professor Aveyard at the **University of Oxford** has begun a clinical trial to determine the effectiveness of two weight-loss interventions involving GPs raising the issue of weight with patients presenting to their GP for reasons other than weight management[163]. In the control group, the GP will simply encourage weight loss by emphasising the benefits to health. In

the intervention group, GPs will advocate referral to a weight management service and make that referral immediately. The main outcome will be weight loss after one year, however, patients' and GPs' reactions will also be assessed.

This is an important step in translating Professor Jebb's discovery into practice.

Project reference number: MR/J000515/1

Influence on policy: Citations in public health guidelines on physical activity

Physical inactivity is considered to be the fourth leading cause of global mortality[164], being linked to cancers, heart disease and diabetes. The World Health Organization estimates that around 3.2 million people die each year as a result of physical inactivity[165]. Public Health England (PHE) cautioned in 2014 that half of women and one third of men were damaging their health through lack of physical activity[166]. Physical inactivity is also a huge financial burden, costing the NHS an estimated £900 million each year[167].

Everybody active, every day – an evidence-based approach to physical activity.
Image credit: Public Health England
© Crown copyright 2015

The aim of the MRC's **Epidemiology Unit (EU)** at the **University of Cambridge** is to study "the genetic, developmental and environmental determinants of obesity, type 2 diabetes and related metabolic disorders and [how this] contributes to the prevention of these disorders". Since its establishment in 2003, research at the unit has provided key evidence demonstrating the links between both diet and physical inactivity and health. In 2009, researchers at the EU demonstrated an association between time spent physically inactive or sedentary and increased levels of insulin in the blood, a predictor of type 2 diabetes and cardiovascular disease[168]. The following year, research undertaken at the unit shows that for each hour per day participants spent in front of the television, their risk of death from heart disease multiplied by a factor of seven per cent[169]. In 2014 the unit showed, using computer modelling, that the health benefits of the London Cycle Hire scheme outweighed the negative impacts from injuries and exposure to air pollution. This has helped to make the public health case for cycle hire schemes[170].

Research at the unit has contributed to the development of many public health guidelines. Research demonstrating the link between sedentary behaviour in both adults[171] and children[172] was used as evidence in the revision of the UK Chief Medical Officers' recommendations on physical activity[173], which places an increased emphasis on the avoidance of prolonged periods of sedentary time[174].

In October 2014 Public Health England (PHE) published *Everybody active, every day*, a national evidence-based strategy to support all sectors in embedding physical activity into daily life and making it an easy, cost-effective and 'normal' choice in every community in England[175]. Several of the recommendations in this strategy are supported by, and cite, research undertaken at the Epidemiology Unit. This research includes studies showing that cycling to work increases

in towns with town-wide cycling initiatives[176], providing new, high-quality, traffic-free cycling and walking routes encourages people to get about more by foot and by bike[177], and that campaigns to improve children's health should be directed at whole families[178].

Much of this research has been led by the UK Clinical Research Collaboration (UKCRC) Centre for Diet and Activity Research (CEDAR)[179], hosted by the EU.

Project reference number: MC_UP_1001/2

Engagement activities: Expert commentary on healthy diet

Dr Nita Forouhi at the **MRC Epidemiology Unit** has provided expert commentary on many diet-related studies during the past year, has been quoted in numerous media articles and has given advice to various television programmes, including BBC's *The One Show* and *Trust me, I'm a doctor*[180].

Fruit and vegetables.
Image credit: Flickr/Christer Barregren

Dr Forouhi wrote a comment piece for *The Telegraph*[181] on a study conducted at University College London showing the association between fruit and vegetable consumption and risk of death by cancer and heart disease. The study showed that eating seven or more portions of fruit and vegetables reduces the specific risks of death by cancer and heart disease by 25 per cent and 31 per cent respectively. Dr Forouhi commented that the study showed that eating more fruit and vegetables was beneficial and therefore supported the 'five-a-day' message, reassuring the public that this health recommendation is right. She advised however that it did not warrant increasing the advice to 'seven-a-day' or more. She highlighted that less than a third of the UK adult population and ten per cent of young people aged 11-18 eat five or more portions and so efforts would better be spent in getting the population to meet the current guidelines.

Research led by Dr Forouhi on the relationship between saturated fat and type 2 diabetes also received considerable media attention in 2014. The international EPIC-InterAct study found that saturated fatty acids can be associated with both an increased and decreased risk of developing the disease, depending on the type of fatty acids present in the blood.

The researchers analysed the blood of 12,403 people who developed type 2 diabetes and 16,154 individuals who did not, from 340,234 adults across eight European countries. Using a sophisticated method of high-speed blood analysis,

developed especially for the project by researchers at **MRC Human Nutrition Research**, they determined the proportion of each of the nine fatty acids in blood samples from the study participants and related this with later incidence of type 2 diabetes.

They found that saturated fatty acids with an even number of carbon atoms in their chain, such as those found in red meat and fried food, were associated with a higher risk of type 2 diabetes, while the odd-chain saturated fatty acids, found in dairy products such as yoghurt, were associated with a lower risk.

This research received media attention from *The Guardian*[182], *The Telegraph*[183], the *Huffington Post*[184] and the *Daily Mail*[185].

Project reference number: MC_UP_A100_1003

Engagement activities: Alcohol consumption in pregnancy

Research by an MRC-funded PhD student at the **University of Leeds** on the link between light drinking by pregnant women and pre-term birth led to national media coverage and the Royal College of Obstetricians and Gynaecologists (RCOG) changing its guidance on alcohol consumption.

Evidence about the damaging effects of heavy drinking in pregnancy is well-established. However, the link between light alcohol consumption and adverse outcomes, such as pre-term labour and low-birth weight, is less clear. The current guidance issued by the Department of Health is that pregnant women and women trying to conceive should avoid alcohol altogether and never drink more than 1–2 units once or twice a week.

Camilla Nykjaer used data from the Caffeine and Reproductive Health (CARE) Study[186], a prospective cohort of 1,303 pregnant women aged 18-45 years. The study used questionnaires to assess alcohol consumption before pregnancy and for the three trimesters separately. She found that the association with adverse birth outcomes such as low birth weight and pre-term birth were strongest in pregnant women consuming more than two units of alcohol a week and in trimesters one and two. However, the study also showed that even women adhering to the Department of Health guidance in the first trimester still doubled their risk of giving birth to a premature or underweight baby[187].

Camilla gave interviews with various media outlets, resulting in national coverage including articles by the *BBC*[188], and *The Times*[189].

Following this media interest, Camilla was approached by the Royal College of Obstetricians and Gynaecologists (RCOG) to review their guidance on alcohol consumption in pregnancy. The resulting guidance, recommending that women trying to conceive and pregnant women in the first trimester do not consume any alcohol at all, was published in February 2015[190].

Project reference number: Not currently available.

Smoking

Influence on policy: Smoking reduction

The MRC funds the **UK Centre for Tobacco and Alcohol Studies** (UKCTAS) through the UK Clinical Research Collaboration[191]. The UKCTAS is a leading international centre of tobacco and alcohol research and policy excellence with an extensive research programme. Work conducted by researchers at the centre has been used in various reports to steer national policy on smoking reduction.

Smoking is the biggest cause of avoidable death and health inequalities in the UK. It causes more than 100,000 deaths each year in the UK[192] and costs the economy £14bn[193]. Since the ground-breaking discovery in 1957 by MRC researchers Sir Richard Doll and Sir Austin Bradford Hill that smoking was a cause of lung cancer, the MRC has been at the forefront of research into the dangers of smoking[194]. This led to national public health campaigns and a 50 per cent reduction in the number of people who smoke. There are however still around 10 million people in the UK who continue to smoke —just over one in five of the adult population[195] and so continued research, that can be translated into changes to policy and influential public health campaigns, are key.

How a standardised packet of cigarettes might look if standardised packaging of tobacco products were introduced.
Image credit: Department of Health

Sir Cyril Chantler published his independent report *Standard packaging of tobacco* in April 2014[196]. This report concluded that standardised packaging of tobacco products, in conjunction with the current tobacco control regime, is very likely to lead to a modest but important reduction in the uptake and prevalence of smoking and therefore a positive impact on public health. Sir Cyril substantially uses research by the UKCTAS as evidence for his report, particularly the 2012 'Stirling report'[197], led by the University of Stirling, which he considers "the most extensive and authoritative piece of work on the issue of standardised packaging". The report found strong evidence that plain packaging would reduce the attractiveness and appeal of tobacco products, it would increase the noticeability and effectiveness of health warnings, and it would reduce the use of design techniques that may mislead consumers about the harmfulness of tobacco products. On the day the report was published, the Government announced that it was minded to introduce regulations to provide for standardised packaging.

Professor Ann McNeill, deputy director of the UKCTAS, was an author of the 2014 *Standard packaging for tobacco products* report[198], a summary of recent evidence on the effectiveness of standardised packaging as a tobacco control strategy. The report includes new data from the Australia and United Kingdom International Tobacco Control Policy Evaluation Projects (the ITC Project), for which Professor McNeill was a principle investigator. The report notes that

after implementation of standard packaging in Australia in 2013, the noticeability of health warnings doubled, from 34 to 66 per cent. Support for standard packaging among smokers and non-smokers also increased from 28 per cent to 51 per cent. The report concludes that it is clear that standardised packaging is effective and important for public health. It recommends that standardised packaging for tobacco products be introduced in the UK without delay.

Work conducted by researchers at the UKCTAS has formed a substantial part of the evidence used by the Government in their draft regulations for standard packaging. In March 2015, MPs voted in favour of standard cigarette packaging by 367 to 113. The legislation is set to be voted through by the House of Lords in Spring 2015.

Researchers at the centre have also contributed to the debate on the use of electronic cigarettes. **Professor John Britton**, director of the UKCTAS, and colleague **Dr Ilze Bogdanovica**, authored *Electronic cigarettes*, a report commissioned by Public Health England[199]. They concluded that as evidence suggests that current smokers are willing to use electronic cigarettes as an alternative to tobacco, they offer vast potential health benefits. They however state that maximising those benefits, whilst minimising harms and risks to society such as 'normalising' smoking and promoting nicotine addiction, needs appropriate regulation, monitoring and risk management.

Professor Britton has also been consulted by various media sources because of his expertise. He featured in a 2014 *BBC* documentary on why thousands of young people still take up smoking despite the health risks and regulation[200]. He has also been interviewed by media outlets including *The Guardian*[201], *The Telegraph*[202] and *Sky News*[203].

Professor Britton received a CBE for his work in respiratory medicine and his research into tobacco control in the 2013 Queen's New Year Honours.

Project reference number: MR/K023195/1

Hearing

Influence on policy: Expert witness to Commission on Hearing Loss

Professor Cornelis Kros at the **University of Sussex** was an expert witness for the 2014 Commission on Hearing Loss, established by the International Longevity Centre UK (ILC-UK), a leading think-tank on longevity, ageing and population change. The final report, published in July 2014, highlights the growing numbers experiencing hearing loss, the associated mental and physical health problems and the subsequent loss to the economy[204].

There are an estimated 10 million people in the UK with hearing loss. This number is set to increase significantly due to the rising number and proportion of older people. By 2031, it is expected that there will be 4.1 million people in the UK with hearing loss — nearly 20 per cent of the total population. Hearing loss can lead to individuals experiencing communication difficulties, becoming socially isolated and developing mental and physical health problems. Recent research has also linked hearing loss and dementia[205]. This report estimates the cost to the economy of hearing loss-linked unemployment to be almost £25bn per year. The report reasons that many of the impacts of hearing loss both

for the individual and society could be negated by better support for those with hearing loss, including improved provision, take-up and use of hearing aids.

Professor Kros gave expert testimony to the commission, providing evidence for the need for early detection and giving examples of technology that can be used flexibly, such as in the home. He highlighted the flaws of relying on an audiogram to fully assess the intricacies of hearing loss, which was specifically quoted in the report. His evidence fed directly into the report's recommendations.

This report may have influenced the Parliamentary early day motion on hearing loss that was tabled in February 2015 and supported by 41 MPs. The motion calls on the Government to request that the NHS asks NICE to prioritise developing a hearing loss clinical guideline to establish and maintain quality standards for patients suffering hearing loss.

The MRC is also working with other research councils and organisations to improve technology for hearing aids. The cross-council Lifelong Health and Wellbeing programme held a workshop in 2014 to bring together the NHS, Action on Hearing Loss, academic experts and hearing aid manufacturers to identify the research challenges and possible solutions to problems experienced by hearing-aid wearers. Following the workshop, £5.6m has been made available by the research councils to support the development of networks and research projects to build new multidisciplinary and cross-sector collaborations. These will further explore areas for potential multidisciplinary research to improve hearing aids[206].

Project reference number: MR/K005561/1

Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

End Notes

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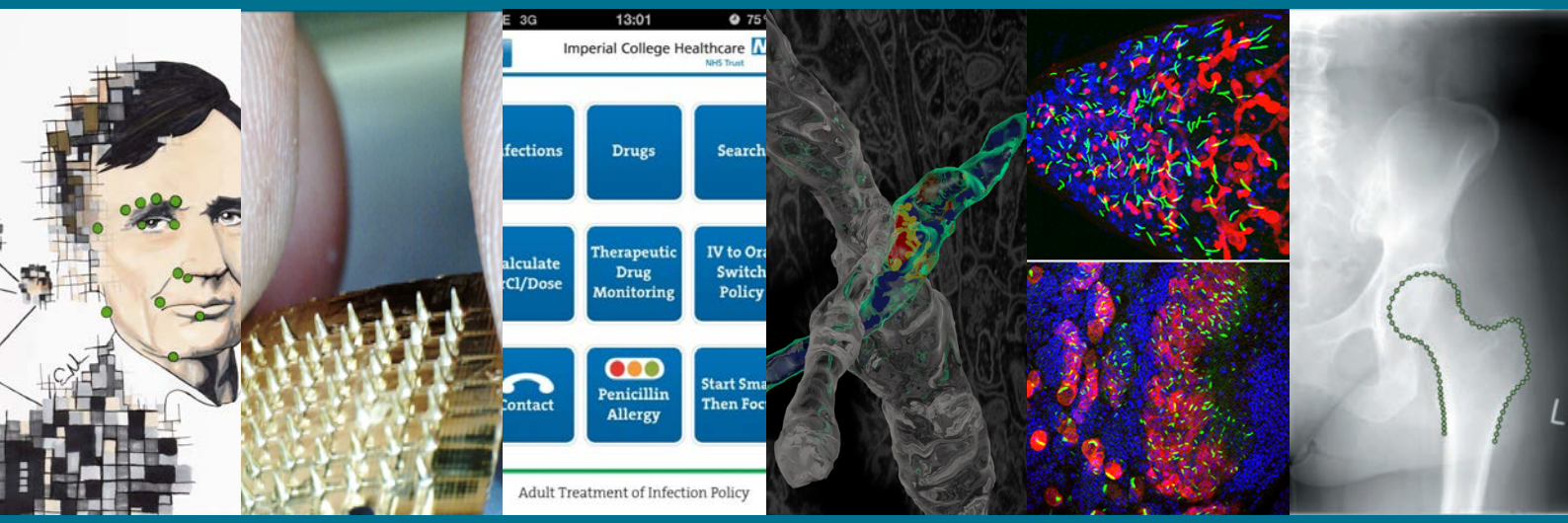
Outputs, outcomes and impact of MRC research

2014/15 report



SECTION 2.3
Development of products and intellectual property

Development of products and intellectual property

New products, from vaccines and other therapies to technological advances for disease monitoring and diagnostics, are important and direct impacts from the MRC's research.

There is a long history of MRC discovery science leading to new products and interventions that have widespread impact, from the early development of the first antibiotic, penicillin, through to stem cells and monoclonal antibodies. The MRC provides sustained support for significant and pioneering research and has done much in partnership with others to ensure important UK discoveries can be rapidly translated into practice. Included in this chapter are tools to help healthcare professionals more prudently use antibiotics in the face of the serious and growing problem of antimicrobial resistance (see page 71). Also included is work that has regenerated the first fully-functioning organ grown in a living mammal from cells made in the lab (see page 82), and the development of a humanised monoclonal antibody as a potential treatment for age-related macular degeneration, the leading cause of blindness in the over 60s in the Western world (see page 89).

MRC research groups are helping to develop many other new treatments and medical interventions, including genetic testing for a rare group of diseases called ciliopathies (see page 67), a nasal spray to help improve eye contact in patients with autism (see page 69) and the first successful vaccine trial for hepatitis C (see page 75). Discoveries are reported at every development stage, from taking early steps to identify a novel aspect of biology to marketing a new product that will hopefully be widely adopted. We highlight some examples of products that have progressed from an early to later development stage across the years that the MRC has been compiling feedback from researchers on their output.

The MRC has collected information on both *artistic* and *technical* products this year for the first time, acknowledging the often interdisciplinary impact of medical research.

Where these products cover 'new' functional or technical aspects, researchers take steps to ensure their discoveries are recognised as intellectual property. New intellectual property recorded by MRC researchers include a method to prevent colonisation in poultry by campylobacter, the most common cause of food poisoning, which may indicate a step toward developing new products in future (see page 79), and the development of hydrogels, a unique solution for stem cell storage and transport (see page 83).

This chapter includes many other examples of where MRC researchers are developing medical, technical and artistic products and interventions and where these have been granted patents or been copyrighted. The information in this chapter has largely been sourced from researchfish®[207]. Quantitative information on numbers and type of products and intellectual property is available in the *Quantitative analysis* chapter of this report.

The examples in this chapter are characterised by the following research areas:

- Rare diseases
- Mental health
- Neurodegeneration and cognition
- Antimicrobial resistance
- Obesity
- Metabolic diseases
- Infectious diseases
- Cardiovascular diseases
- Regenerative medicine
- Synthetic biology
- Stratified medicine
- Immunotherapy
- Gene sequencing and genetic engineering
- Global health
- Musculoskeletal disorders
- Cell biology
- Progressed medical products

Each case study focuses on a predominant output type, but others might be referenced within it. The accompanying icons represent the relevant output types. A key to the list of output types is at the end of this chapter.

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — the *Gateway to Research*[208] — by entering the full project reference number listed under each case study in the search field.

Rare diseases

A rare disease is defined by the European Union as one that affects less than five in 10,000 people. There are between 5,000 and 8,000 distinct rare diseases[209], and five new rare diseases are described in medical literature each week[210]. Each disease affects less than 0.1 per cent of the population. However, taken collectively, one in seven people — 17 per cent — will be affected by a rare disease at some point in their lives. This equates to three million people in the UK, 30 million in Europe and 350 million people worldwide. Indeed, if those three million people in the UK had the same disease, it would be a large public health problem.

It is estimated that the MRC spends around 10 per cent of its translational budget on research into rare diseases[211]. MRC researchers have played a significant role in identifying the genetic basis for many rare inherited diseases. Studying rare diseases often sheds new light on biological processes which have wider relevance to understanding health and disease.

Medical products: Genetic testing for ciliopathies

Genetic testing for a group of rare diseases was made available in 2013 thanks to researchers at the **University of Leeds** identifying some of the responsible genes.

In 2006 **Professor Colin Johnson** identified, for the first time, a genetic cause of Meckel-Gruber syndrome, a rare, lethal, neurodevelopmental disorder[212]. The gene involved, MKS3/TMEM67, encodes a new transmembrane protein called meckelin.

Further work conducted by Professor Johnson showed that Meckel-Gruber syndrome was the most severe in a group of developmental conditions called 'ciliopathies'. Ciliopathies are disorders caused by mutations in the genes encoding proteins making up the cilia, resulting in their abnormal structure or function[213]. Cilia are finger-like projections extending from cells that are either 'motile' (or moving) or 'primary'. The motile cilia function, for example, to keep the airways free of dirt and mucus whereas the primary cilia act as a cellular 'antenna' to detect and respond to chemical or mechanical cues.

Working with colleagues from Paris, Rome and San Diego, Professor Johnson identified additional genes responsible for causing Meckel-Gruber and another ciliopathy, Joubert syndrome, in 2010[214]. The team showed that mutations in the TMEM216 gene, encoding transmembrane protein 216, caused Meckel-Gruber and Joubert syndromes. They also showed that the faulty TMEM216 gene stopped cells from making a protein needed for signalling. This poor communication can prevent the neural tube from developing correctly in growing embryos, leading to brain defects. Affected embryos can also develop abnormalities in the eyes, extra fingers or toes and multiple cysts in their kidneys. These defects are often only picked up on a 12-week ultrasound scan. Meckel-Gruber syndrome is predominantly incompatible with life, and children born with Joubert syndrome often have motor disability and mental developmental delays.

This research has enabled genetic testing to be made available by the Yorkshire Regional Genetics Service[215]. These test around 40-60 UK and international patients each year.

Professor Johnson has also contributed to an EU FP7 collaborative project, *SysCilia*[216], for whole systems approaches to examine cilia function and its disruption in human genetic disease at the molecular level. A major part of the *SysCilia* project has been genetically screening for genes that can contribute to maintaining and building cillia (ciliogenesis)[217].

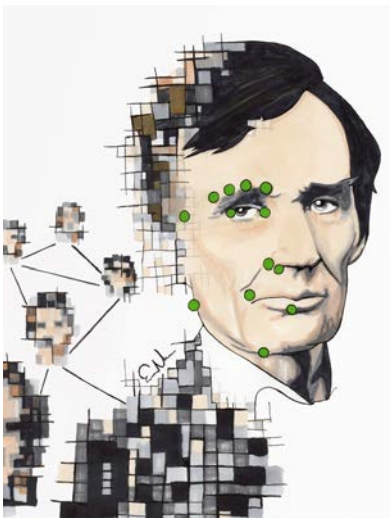
Project reference number: MR/K011154/1

Medical products: Facial recognition technology to diagnose rare genetic diseases

Dr Christoffer Nellaker at the **MRC Functional Genomics Unit, University of Oxford** has developed facial recognition technology that could help diagnose rare genetic diseases.

Around 30-40 per cent of genetic disorders, including Down's syndrome and Marfan syndrome, involve changes to the face or skull[218]. This is because many genes are involved when the face and head develop and so if there is a DNA change in one of these genes it is very likely that it will cause a change to the head or facial structure.

The new software is based on research involving thousands of pictures of previously diagnosed patients. It is able to 'learn' the facial features characterising each disorder and recognise which to look for and which to ignore when suggesting a diagnosis. It will also be able to group together patients with unknown disorders who have similar skull structures and facial features. This will potentially enable doctors to identify new disorders and the DNA variations that cause them.



An artistic representation of the facial recognition software. *Image credit: Emma Nellaker.*

The software is based on an algorithm that uses basic equipment and so could fairly easily be adapted for use in countries where genetic disease diagnosis is not readily accessible. It could help narrow down the tests needed to diagnose an individual, critical in healthcare systems where money is a factor in determining how many tests are carried out.

Dr Nellaker developed the software in collaboration with Professor Andrew Zisserman at the university's department of engineering science who was funded by the Engineering and Physical Sciences Research Council (EPSRC).

This research received media coverage in *New Scientist*[219], *The Independent*[220] and the *Daily Mail*[221].

The researchers are now taking this forward with an MRC Methodology Research Fellowship and a MRC Methodology Research Grant. Collaborations are being formed with clinicians around the world with the aim to bring this to patients as soon as possible.

> ***"This research was only possible because of the great collaboration between medical and engineering sciences."***
> ***– Dr Christoffer Nellaker***

Project reference number: MC_EX_G0802457

Mental health

Medical products: Understanding autism

Professor Simon Baron-Cohen, director of the **Autism Research Centre** (ARC), **University of Cambridge**, and colleague **Dr Bonnie Auyeung** have shown that using an oxytocin nasal spray increases the frequency and duration of eye contact in patients with autism[222].

Autism is a lifelong developmental condition that affects how a person communicates and relates to other people[223]. It also affects how they see the world around them. As a spectrum condition, people with autism will share certain difficulties, but there are differences in the way it affects them. Some people may be able to live independent lives, but others will have accompanying learning difficulties and need lifelong specialist help. There are currently few behavioural or drug treatments available to improve the key social difficulties associated with autism.

Direct eye contact is considered to be one of the most important platforms for social interaction and communication in humans[224,225]. Sensitivity to information from the eyes and appropriate use of eye contact in social contexts may also help to develop more complex skills needed for social understanding and behaviour[226,227]. Professor Baron-Cohen has previously demonstrated that eye contact is reduced in many people with autism, beginning in early infancy and lasting into adulthood[228]. He and his team subsequently developed and evaluated *The Transporters*[229], a BAFTA-nominated children's animation series to help young children with autism look more at faces and improve their emotion recognition and understanding. The evaluation results showed that children with autism had significantly improved emotion recognition and understanding after regularly watching the series for four weeks[230].

Oxytocin is a hormone made by the brain and various studies have shown it plays an important role in social understanding and behaviour. It is released during childbirth and breastfeeding and is thought to help form attachment between mother and child.

Several genetic studies of autism, including one conducted at the ARC, which is part-funded by the MRC, have found differences in the genes related to oxytocin and some have also shown reduced blood plasma oxytocin levels.

Trials investigating oxytocin delivered intravenously in people with autism have shown it leads to improved emotion recognition. The advantage of the nasal spray method of delivery is that the oxytocin acts directly on the brain. Whilst intravenous oxytocin affects blood levels, it is not known if these correlate with levels in the brain. The nasal spray would also be easier to administer.

This study evaluated natural social behaviour during a semi-structured interview via video link in 37 males diagnosed with either autism or Asperger syndrome and 37 typically-developing males aged between 18 and 56. They were randomly assigned to be given either an oxytocin spray or placebo. Participants were asked questions about their wellbeing, journey to the research centre and their views on participating in research.

The researchers found that oxytocin significantly increased participant gaze to the eye region of the interviewer's face in both the autism and typically-developing groups. This effect was significant in both the frequency and duration of the eye contact.

Following on from this research, MRC PhD student **Richard Bethleham** is currently conducting a trial with oxytocin using functional magnetic resonance imaging (fMRI) to measure brain changes during empathy and reward tasks.

Professor Baron-Cohen has authored many books on autism and empathy, exploring differences in the male and female brains[231] and why some people have more or less empathy than others[232]. His research showing that increased exposure to testosterone in the womb is associated with autistic traits in children[233,234] is often discussed in news articles and programmes on autism and the differences between male and female brains. These include those by the *BBC*[235,236] and *The Economist*[237]. Professor Baron-Cohen and Dr Auyeung recently advanced this research by demonstrating in 2014 that prenatal testosterone and other sex hormone levels are raised in individuals later developing autism[238]. This study was conducted in collaboration with the State Serum Institute in Copenhagen and the Danish National Biobank which stores amniotic fluid by mothers who underwent amniocentesis, a prenatal test.

He is frequently called upon by media sources to advise or comment on research in this field. In 2015 it was announced that he would be an advisor to a BBC2 documentary in which people with neurological disabilities, including autism, Tourette's and Down's Syndrome, attempt to find jobs[239].

Professor Baron-Cohen has also developed a test that assesses a person's level of empathy. In *Reading the mind in the eyes*[240] participants are shown 36 pairs of eyes and have to select one of four words that best describes what each person is thinking or feeling, for example, jealous, thoughtful, anxious or arrogant. This test is an important research tool and has been widely used in independent studies.

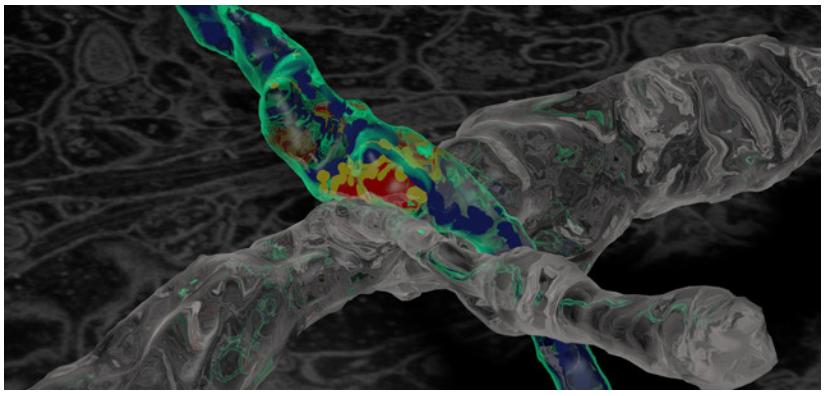
"This is one of the earliest non-genetic biomarkers that has been identified in children who go on to develop autism."
– Professor Simon Baron-Cohen

Project reference number: G0600977

Neurodegeneration and cognition

Artistic and creative products: Image of regrown central nervous system nerve

Dr Vincenzo De Paola and his team at **Imperial College London** demonstrated in 2013 that contrary to previous opinion, certain injured nerves in the central nervous system (CNS) can spontaneously extend to follow a new pathway through the brain[241].



An extending nerve (blue) meeting an existing nerve (grey). *Image credit: Drs Vincenzo De Paola, Graham Knott, Alison Canty and Lieven Huang.*

Dr De Paola used ultra-precise laser microsurgery to cut a nerve in the

CNS of adult mice and then, with two different microscopy techniques[242] and time-lapse imaging, showed its regrowth through the brain. His 3D reconstruction of an extending nerve making new connections was selected by the **MRC Clinical Sciences Centre's** *Biomedical Picture of the Day* in July 2013[243].

Project reference number: MC_U120088464

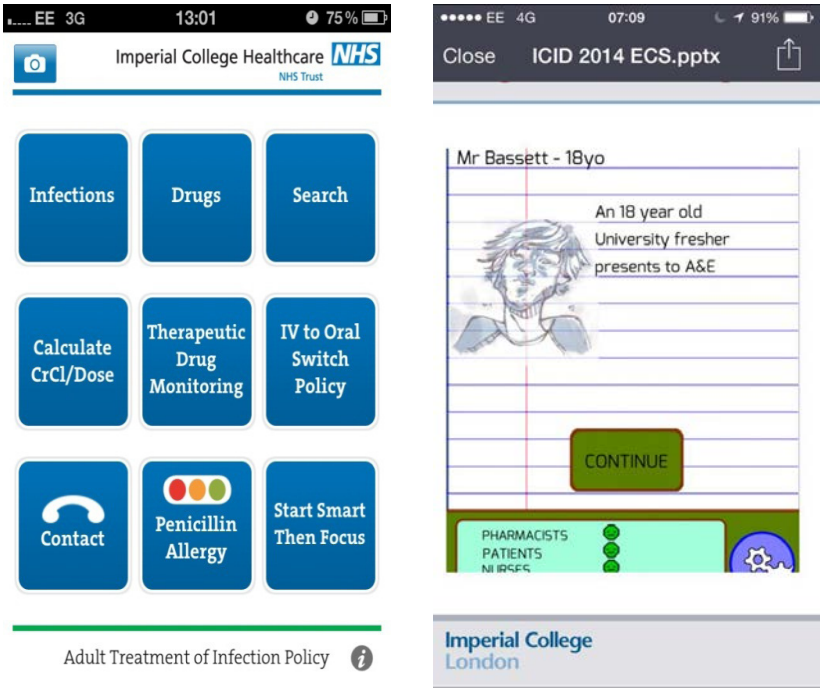
Antimicrobial resistance

Medical products: Tools to support and encourage the prudent use of antimicrobials by healthcare professionals

Professor Alison Holmes at **Imperial College London** is developing various tools to support and encourage healthcare professionals to more prudently use and prescribe antimicrobials.

Antimicrobial resistance, the ability of microorganisms such as bacteria, viruses and fungi to evolve and become resistant to antimicrobial treatments, is a serious global health issue. The overuse and misuse of antibiotics in both agriculture and human medicine has contributed to their growing ineffectiveness. Certain strains of tuberculosis, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*, for example, do not respond well to current antibiotics. Public Health England (PHE) reported in 2014 that around one in five infections involving E.coli bacteria in 2013 were resistant to a commonly-used antibiotic (ciprofloxacin), an 18 per cent increase from 2010[244]. It is estimated that around 700,000 people die from antibiotic-resistant infections each year worldwide[245], a figure that is projected to rise to 10 million by 2050.

In 2015 NICE reported that nine out of 10 GPs say they feel pressured to prescribe antibiotics and 97 per cent of patients who ask for them are prescribed them. This contributes to the 10 million prescriptions each year deemed to be unnecessary. As a result, NICE published new stricter guidelines on antimicrobial stewardship in August 2015[246]. These recommend that healthcare professionals do not issue immediate prescriptions for patients likely to have self-limiting conditions, those that will usually get better without treatment. Rather, patients should be asked to return if their symptoms persist or can be issued with date-delayed prescriptions. Healthcare



From left to right, the IAPP app and a screenshot from On call: antibiotics. *Image credit: Imperial College London.*

professionals should also spend more time discussing with their patients why they cannot always receive antibiotics and the issue of antimicrobial resistance. These guidelines will be followed up with corresponding guidance for the general public.

In 2011 Professor Holmes developed the Imperial Antibiotic Prescribing Policy (IAPP) smartphone app in conjunction with the Imperial College Healthcare NHS Trust's antibiotic review group[247]. The app helps healthcare professionals choose the most appropriate course of treatment to ensure antimicrobials are prescribed appropriately. It was used more than 4,800 times in the first month and during the first three years, it has been consulted more than 105,000 times. The app has an average of 316 active users each month. 85 per cent of those who responded to a post-implementation survey considered that the IAPP added to their knowledge base regarding antimicrobial prescribing and 96 per cent found that it influenced their prescribing practice.

Following the success of the IAPP project, Professor Holmes and her team have established a collaboration with the engineering faculty at Imperial College. In a pilot project, the researchers have developed an enhanced mobile application to support antibiotic-prescribing decisions. The ENIAPP[248] employs an algorithm that uses patient case memory of antibiotic recommendations. It currently has a case memory of around 2,000 patients and has been used in 200 clinical interactions. The project has recently been awarded funding for further development and implementation.

She is also developing POCAST, a Point-Of-Care Antimicrobial Stewardship Tool to be used on mobile devices and computers by GPs in primary care. POCAST uses the evidence-based Public Health England (PHE) primary care guidelines on infections and presents it in a user-friendly way, enabling the GP to obtain information about treating a particular infection at the click of a button. The tool links to various resources, such as websites, to help diagnose and manage infections. In future it will also include local antimicrobial guidelines. Once the tool has been refined, it is planned for it to be launched nationally. The tool has been developed in close collaboration with PHE and the department of primary care at Imperial College NHS Trust.

Professor Holmes is also developing *On call: antibiotics*, an electronic prescribing game to support and encourage prudent antimicrobial use in acute care. The game allows doctors, nurses and pharmacists to manage virtual patients attending a simulated hospital. Racing against the clock and the increasing workload, players receive information about the symptoms experienced by patients and have to diagnose and manage the cases. To be successful, players have to appropriately use antibiotics and antibiotic-prescribing behaviours.

The game provides immediate feedback on the players' performance, highlighting the impact of decisions on other professionals and the wider hospital environment. Future versions will allow players to include their feedback on their professional portfolios. Since it was launched in 2012, it has been downloaded almost 5,000 times from more than 30 countries. The research team is currently applying for funding to tailor a version for members of the public.

Project reference number: G0800777

Obesity

Obesity is one of the greatest threats to health today. Research has shown that being overweight or obese severely increases the risk of developing potentially life-threatening conditions such as type 2 diabetes, heart and liver disease and some cancer types, including breast and bowel.

The number of people classified as overweight or obese has sharply risen in recent years and this has had a huge effect on the health of society and the economy. Figures released by Public Health England in March 2015 showed that in 2013, 62 per cent of adults were overweight or obese[249], with a body mass index (BMI) of more than 25 and 30, respectively. The number of adults classed as obese has increased by 60 per cent in the last two decades (from 15 per cent in 1993 to 25 per cent in 2013). Health problems associated with being overweight or obese cost the NHS around £5 billion each year, compared to £3 billion each for smoking and alcohol-associated health problems[250].

Medical products: Synthetic gut hormones to reduce appetite

Professor Sir Stephen Bloom at **Imperial College** is developing analogues — drugs with the same chemical structure — of gut hormones he has shown reduce appetite and increase energy expenditure, offering a potential new treatment for obesity.

Professor Bloom is a pioneer of obesity research, having discovered several gut hormones and established their effect on appetite regulation. He identified that the naturally-occurring hormone oxyntomodulin (OXM) both reduces appetite and increases energy expenditure. This discovery led to the creation of spin out company Thiakis, which was sold to Wyeth[251] in 2008 for a reported £100 million. Thiakis/Pfizer has since developed analogues of OXM — drugs with the same chemical structure. The MRC is currently funding the development of Professor Bloom's 'medical bypass', a combination of drugs based on glucagon and other gut hormones, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), that increase during a surgical bypass causing weight loss.

Professor Bloom is also working on another appetite-reducing tool, an 'intelligent microchip', with fellow Imperial College academic Professor Chris Toumazou. This chip is designed to work through its attachment to the vagus nerve, which plays a role in controlling appetite. The chip detects the chemical signals emitted by the nerve that indicate hunger and then sends modulated messages to the brain, reducing the urge to eat.

Professor Bloom's decade-spanning research on obesity was originally borne out of his clinical work with diabetic patients, 90 per cent of whom were type 2 diabetics due to excess weight or obesity[252]. And so it was a stroke of serendipity that led to Professor Bloom discovering that the hormones he was researching in connection to diabetes actually controlled appetite.

> ***"If UK limited is to prosper, we have to develop science-based industries. Pharmaceuticals is a good exemplar but success absolutely depends on a thriving bioscience base in academia."***
>
> ***– Professor Sir Stephen Bloom***

Professor Bloom's research has been extensively supported by the MRC. He said, "If UK limited is to prosper, we have to develop science-based industries. Pharmaceuticals is a good exemplar but success absolutely depends on a thriving bioscience base in academia."

Project reference numbers (amongst others): MR/J010731/1, MR/L013088/1, G1000474, MR/K02115X/1

Metabolic diseases

Medical products: New patch device for continuous glucose monitoring

Dr Nick Oliver and colleagues at **Imperial College London** have developed a 'patch' device containing microscopic needles for continuous glucose monitoring (CGM) in type 1 diabetes.

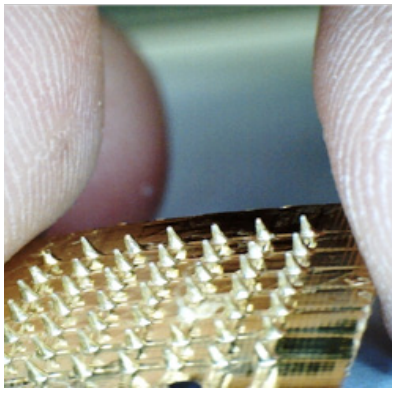
People with type 1 diabetes need to regularly monitor their own glucose levels so they can take appropriate action should they become too low (hypoglycaemia) or high (hyperglycaemia). Over the last two decades, it has been established that good glucose control is associated with significantly reduced serious long-term complications of the disease[253]. Depending on their type of insulin therapy, patients are advised to monitor their glucose levels at least two to six times a day[254]. However, these readings fail to provide information on the context, for example, whether the level is increasing or decreasing. In many cases, they also fail to provide sufficient warning of pending hypoglycaemia or hyperglycaemia, thus limiting the patient's ability to take action.

CGM machine use is slowly increasing, however, in the UK, funding for them is awarded on a case-by-case basis[255]. Existing monitors also require skin puncture to access interstitial fluid, the solution that surrounds tissue cells, and to sense its glucose content. Their use is associated with discomfort and, due to there being a lag time between changes in blood glucose and interstitial fluid glucose, their accuracy is questionable in hypoglycaemia[256].

Developing a painless continuous glucose monitor is regarded as the top research priority by patients with diabetes[257].

There has been extensive research into microneedle technology for drug delivery and its advantages include painless insertion and low infection risk.

Based on this technology, the Imperial researchers, funded by an MRC Confidence in Concept[258] award, have developed a small, wearable patch around 1cm^2 containing microscopic needles. These needles only penetrate the outermost skin layer and so access the interstitial fluid without stimulating skin nerve fibres or reaching blood vessels within the skin layers. The patch has a large surface area and so has the potential to improve sensitivity and accuracy. Early tests have demonstrated its ability to respond accurately to variable glucose concentrations and to penetrate the outermost skin layer without breaking the skin. The device is also fairly cost-effective in comparison to existing monitors and so will potentially increase CGM use.



A close up of the patch. *Image credit: Dr Nick Oliver, Imperial College London.*

The device is currently undergoing clinical trials in healthy volunteers and in people with type 1 diabetes[259]. Initial data suggest the device is well-tolerated and efficacy studies in people with type 1 diabetes are starting later in 2015.

Project reference number: MC_PC_12015

Infectious diseases

Medical products: Successful trial of hepatitis C vaccine

Professor Eleanor Barnes and colleagues at the **University of Oxford**, in collaboration with the Italian biotechnology company Okairos[260] and Stanford University in the USA, have published the first results of an early clinical trial of a hepatitis C vaccine[261]. The vaccine was found to be safe and well-tolerated in the 15 healthy volunteers who took part in the Phase I trial.

The hepatitis C virus (HCV) is an adenovirus that infects 170 million people around the world and is a major cause of liver disease, including liver cancer[262]. Unlike Hepatitis A and B, there is currently no vaccine for HCV. Treatment can often have severe side effects such as anaemia, reduced immune system functioning, depression and flu-like symptoms; it is also expensive and only partially effective. Between 15 and 50 per cent of people clear the infection spontaneously and are free of the virus; however, the majority become chronically infected, with the virus remaining in the body for many years. It is estimated that around 215,000 people in the UK have chronic HCV. Between 10 and 40 per cent of people with untreated chronic HCV will go on to develop liver cirrhosis. Around one in five people with cirrhosis will then develop liver failure, and one in 20 will develop liver cancer.

Studies have shown that HCV may be particularly susceptible to a T-cell vaccination strategy[263]. Host genetic and antiviral immune responses have shown that T-cells — white blood cells — play a critical role in viral control during infection. HCV frequently changes the makeup of its external coat and so the researchers' focus was on designing a vaccine to generate a T cell response to the more constant internal parts of the virus.

To overcome the issue of existing anti-adenoviral immunity in humans (such as to common ailments caused by adenoviruses like colds) that might limit vaccine efficiency, the MRC-funded researchers had previously developed chimpanzee and human adenoviruses unable to replicate to be used as vaccine vectors, or carriers[264].

The vaccine generated very high numbers of both CD4+ and CD8+ T cells, which previous studies have shown to be important in viral control, targeting multiple HCV targets.

A trial to test the efficacy of the vaccine is now underway among intravenous drug users in two sites in the USA. It is the first hepatitis C vaccine to reach this stage of clinical trials.

The trial was also funded by the European Union, with support from the Oxford Martin School at the University of Oxford and the National Institute for Health Research Oxford Biomedical Research Centre.

The latest results demonstrate the necessity of sustained investment in research over time. They furthermore highlight the importance of working with industry and international partners and the willingness of MRC-funded researchers to engage in such collaborations.

Professor Barnes is now developing second generation vaccines as part of her MRC Senior Fellowship, with the aim of generating those that can target multiple HCV strains with different genetic makeups.

Project reference number: MR/K010239/1

Software and technical products: The first UK online virtual clinical care pathway allowing patients to self-manage chlamydia infection diagnosed in the community

Dr Tariq Sadiq at **St George's, University of London** has helped develop a web-based tool that allows patients to receive a chlamydia diagnosis via their smartphone and use it to get an online clinical assessment, advice and treatment without having to go to a GP or clinic.

This has been developed in partnership with Professor Claudia Estcourt at Barts Health NHS Trust and other members of the eSTI2 collaboration[265]; a UK Clinical Research Collaboration (UKCRC)[266] initiative that aims to improve the diagnosis and management of sexually-transmitted infections (STIs).

STIs are a serious health problem in the UK, particularly in young heterosexual people and men who have sex with men (MSM). There were around 440,000 infections diagnosed in 2014, almost half of which (47 per cent) were chlamydia[267]. Chlamydia is a bacterial infection that is often symptomless and so people are unaware that they have it. If left untreated, the infection can spread to other parts of the body and lead to long-term health problems, such as pelvic inflammatory disease (PID), epididymo-orchitis (testicle inflammation) and infertility.

The chlamydia online care pathway. *Image credit: The eSTI2 collaboration.*

One way to improve diagnosis and treatment rates would be to develop more rapid and accessible testing and care.

The chlamydia online care pathway is electronically linked to pharmacies and so once a diagnosis has been received, the patient does not need to return to the clinic to receive a prescription. It also enables patients to link in with healthcare workers at any point in the pathway.

The researchers have conducted pilot trials in collaboration with the National Chlamydia Screening Programme, Barts and the London Healthcare Trust and St George's Healthcare NHS Trust. The results show that patients can safely be managed using an online pathway with very high numbers being treated in short time periods.

Project reference number: G0901608

Artistic and creative products: Poem on the PROUD HIV trial

Dr Sheena McCormack at the **MRC Clinical Trials Unit** (CTU) performed a poem based on the principles of pre-exposure prophylaxis (PrEP) as a public health strategy in preparation for the PROUD HIV trial at the end of the inaugural lecture for her Imperial College Professorship in 2013[268].

The PROUD (Pre-exposure Option for reducing HIV in the UK: Immediate or Deferred) trial reported in 2015 that PrEP is highly protective against HIV for gay and other men who have sex with men (MSM) in England[269,270]. The study, run in partnership with Public Health England (PHE) and 12 NHS Trusts, looked at whether offering daily HIV PrEP to MSM was a reliable way to prevent them from becoming infected if exposed to the virus. The results showed that PrEP was highly protective for this group, reducing the infection risk by 86 per cent.

The researchers highlighted that the MSM who took part in the trial who did not get PrEP in the first year were at very high risk of HIV and that PrEP is therefore highly effective in a real-world setting. The sexual health research clinics that took part in the PROUD study integrated PrEP into their existing HIV risk reduction package.

Project reference number: MC_U122861322

Intellectual property: Using anti-microRNAs to prevent severe asthma attacks caused by viral infections

Dr Tilman Sanchez-Elsner at the **University of Southampton** has patented the use of anti-microRNAs to prevent severe asthma attacks caused by viral infections — or exacerbations.

There are around 235 million people with asthma worldwide[271]. The disease is characterised by airflow obstruction that, over time, tends to become irreversible. This irreversibility, caused by airway remodelling and tissue death, is associated with both treatment resistance and exacerbations. It was MRC-funded researcher **Professor Stephen Holgate**, also at Southampton, who discovered that cold and other viral infections worsened asthma attacks. Further work showed that in patients with asthma, the cells lining the lungs — the epithelium — are unable to destroy the virus as they would normally because they cannot make sufficient levels of the anti-viral protein, interferon beta[272].

More than 1,000 people die from asthma in the UK each year[273]. Asthma exacerbations are also estimated to cost £1.2 billion in lost productivity, £850 million in NHS health care provision and £161 million in social security costs in the UK each year.

MicroRNAs are short non-coding RNA sequences that regulate gene expression. It is thought that they play a role in cell growth, mobility and death. Dr Sanchez-Elsner has demonstrated that in asthma, the microRNAs are dysregulated, disrupting the immune system functions of the lung[274]. He showed that in macrophages — a type of immune cell — microRNA dysregulation decreases the secretion of interferon beta which in turn increases levels of pro-inflammatory protein TNF-alpha. This reduces the ability of macrophages to bind with, and therefore clear, pathogens from the airways.

Dr Sanchez-Elsner has therefore patented the use of anti-microRNAs as a way to reduce viral exacerbations. He is currently in discussions with pharmaceutical companies to take this forward to pre-clinical trials.

Project reference number: MR/K001035/1

Medical products: Repurposing heat shock protein inhibitors to treat human respiratory syncytial virus

Professor Julian Hiscox at the **University of Liverpool** is developing heat shock protein (HSP) inhibitors as a treatment for human respiratory syncytial virus (HRSV). HRSV usually causes minor respiratory tract infections in adults and children; however it can be severe in infants at risk of acute lower respiratory tract infections[275]. It is the most common cause of bronchitis in children under the age of two years.

Professor Hiscox's research focuses on how respiratory and emerging viruses interact with the host cell. He has identified cellular proteins that can act either in a pro-viral or anti-viral way.

Through his work, Professor Hiscox has identified that HSP inhibitors can have substantial anti-viral effects. He has demonstrated their effectiveness in cell-based models. HSPs are involved in the folding, assembly and activity of other proteins, including proteins that promote the growth and survival of tumour cells. Their activity is increased when cells are exposed to taxing environmental conditions, such as infection, inflammation and toxins.

HSP inhibitors are being investigated as part of anti-cancer treatments. As such, there is a lot of data that demonstrates their safety and effectiveness in human and animal models. These compounds can be 'repurposed' for other uses, such as anti-viral compounds. This is significantly advantageous over traditional drug development as the drug has already passed numerous toxicity and safety tests. It therefore considerably reduces the risk that the drug will fail due to safety concerns, saving both time and money. The approach is also unlikely to lead to drug-resistant viruses.

Professor Hiscox is currently seeking industrial collaboration to further develop HSP inhibitors for this purpose.

Professor Hiscox's other focus is the Ebola virus. In collaboration with Public Health England (PHE) using the same technologies developed to look at HRSV, he examined which proteins inside a host cell are used by the virus to help it reproduce[276]. He identified that one viral protein, VP24, disrupts signalling in infected human cells and so impairs the fight against the virus. The researchers then examined whether there were any drugs already in existence that could block VP24's function. One such drug was Ouabain, used to treat heart disease. They showed that administering this drug reduced viral replication in cells.

Project reference number: MR/K000276/1

Intellectual property: Preventing campylobacter bacteria from colonising poultry

Professor Dlawer Ala'Aldeen at the **University of Nottingham** patented a way to prevent or reduce campylobacter jejuni (C.jejuni) bacteria colonisation in poultry in 2013[277].

Campylobacter is the most common cause of food poisoning in the UK, considered to be responsible for around 280,000 cases each year, more than salmonella, *E. coli* and listeria combined[278].

Contaminated poultry causes around four in five cases of campylobacter poisoning in the UK. The latest report from the Food Standards Agency (FSA) revealed that 73 per cent of shop-bought chickens are contaminated with the bacterium, with 19 per cent testing positive at the highest level[279].

The infection causes symptoms such as severe diarrhoea, abdominal pain, fever, and sometimes vomiting. Symptoms usually persist for between two and 10 days, but in severe cases can continue for up to three weeks. Infection can sometimes lead to other complications such as the development of irritable bowel syndrome (IBS) and rarely, Guillain-Barré syndrome – a serious and sometimes permanent condition of the nervous system.

The FSA estimates that the infection causes more than 100 deaths each year in the UK and that the annual cost to the economy is £900 million.

However, its prevention and treatment has been hindered by a poor understanding of the molecular interaction between the host and bacteria.

In 2014 Professor Ala'Aldeen and his team reported that they had identified two bacterial surface molecules, flagellin protein FlaA and the major outer membrane protein (MOMP), that bind to human and poultry epithelial cells[280]. Professor Ala'Aladeen has also shown that the adherence of C.jejuni to epithelial cells can be partially inhibited by human histo-blood group antigens (BgAgs). BgAgs are sugars that occur naturally on human red blood cells. They are also expressed on the surface of epithelial cells, such as the cells lining the gastrointestinal tract and can be secreted in bodily fluids such as saliva and breast milk. The patent therefore covers natural or synthetic BgAg compounds that bind to FlaA or MOMP to block the bacterium's interaction with poultry cells, reducing poultry colonisation and therefore transmission to humans.

Project reference number: G0901696

Cardiovascular disease

Medical products: Developing a new anti-clotting drug

Dr Helen Philippou is developing a new anticoagulant (anti-clotting) drug at the **University of Leeds** to prevent blood clots from developing in veins and arteries.

A blood clot forms when a blood vessel is injured. Small cells in the blood called platelets and circulating proteins accumulate to plug the site of damage and prevent blood from leaking out of the vessel. However, this is serious and potentially fatal if it occurs in a deep vein (such as in deep vein thrombosis – DVT), the blood vessels carrying blood from the heart to the lungs (pulmonary embolism) or the arteries; which is a common cause of heart attacks or strokes (blood clots in the brain)[281].

Blood clots cause around 225,000 deaths each year in the UK and most commonly affect people who are unwell or cannot move around much. The standard therapy to both prevent and treat blood clots are anticoagulants, such as warfarin. Patients with an abnormal heart rhythm (atrial fibrillation) are five times more likely to have a stroke. Warfarin can reduce this risk of stroke by 64 per cent. However, warfarin is a difficult drug to administer because it needs to be monitored with a blood sample each month to ensure the correct level is in the body. Warfarin also has the risk of causing major bleeding for around 3 in 100 patients taking it, of which, 1 in 8 will die. New drugs, such as dabigatran, rivaroxaban and apixaban, have been approved for long-term use to treat patients with atrial fibrillation. However, although their use has the advantage of not needing to be monitored, they are still all at risk of causing bleeding. This is because these drugs work by dissolving the proteins in the clot.

Dr Philippou has however identified small molecules that prevent the proteins from accumulating in the first place. She is developing a drug based on these that would therefore reduce the risk of bleeding. This would also mean that patients at higher risk of developing blood clots can be treated with higher drug doses without worrying about bleeding. She has since received £725k in funding from the British Heart Foundation (BHF) for further development and

is awaiting a funding decision on work to optimise the molecules to make them more 'drug-like'. It is anticipated that partnering with large pharma will take place in the near future to take the drug into clinical trials.

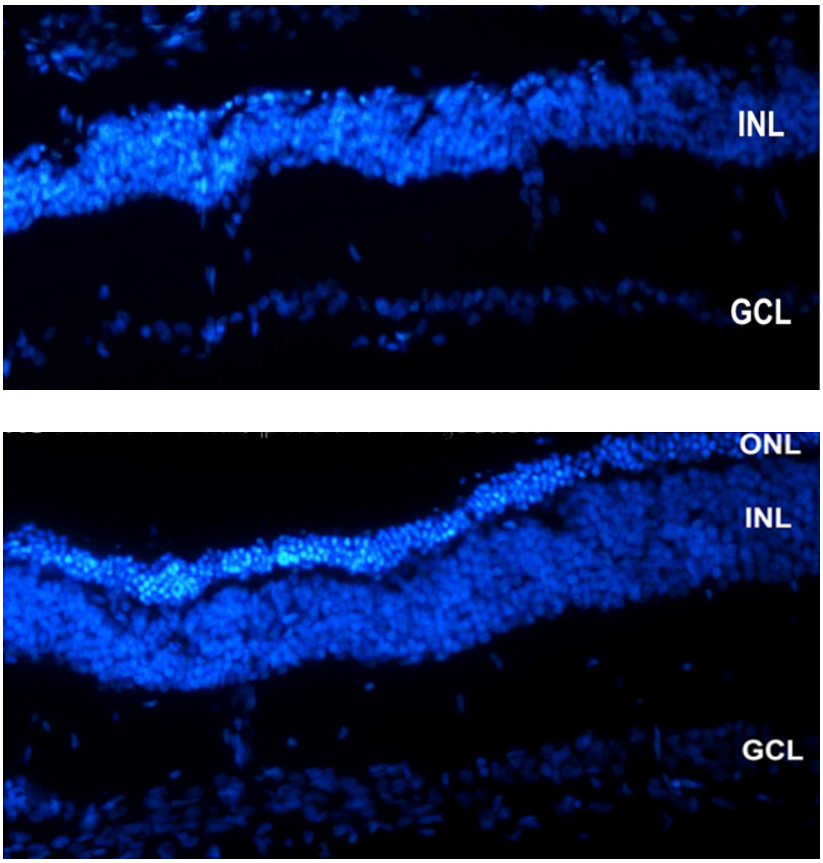
Project reference number: G1001502

Regenerative medicine

Medical products: Developing a treatment for inherited blindness

Dr Anthony Vugler at **University College London** (UCL) is working with ReNeuron[282], a UK-based stem cell company, to develop a treatment for retinitis pigmentosa (RP), the leading cause of inherited vision loss.

RP refers to several genetic eye disorders that affect the retina, the part of the eye that receives and converts light energy into signals that are sent to the brain for visual recognition[283]. The condition is caused by gene mutations leading to the degeneration of the retinal photoreceptor cells, first in the periphery and at later stages of the disease, more centrally. This causes a gradual progressive reduction in vision from peripheral (side) to central vision and then eventual, complete blindness.



The first image shows a rat's retinal degeneration with a missing outer nuclear layer (ONL). The ONL contains photoreceptor cells. The second image shows ONL preservation after hRPC transplantation. *Image credit: Dr Anthony Vugler, UCL.*

The condition affects around 1 in 3,000 to 4,000 people. Its onset ranges from infancy to mid-thirties and the rate of deterioration varies; these are affected by the different gene mutations involved[284,285].

Funded by the MRC/Innovate UK Biomedical Catalyst, Dr Vugler has conducted several pre-clinical studies to assess the effectiveness and safety of using human retinal progenitor cells (hRPCs), generated by ReNeuron, to treat RP. Progenitor cells are similar to stem cells in that they are undifferentiated, however unlike, stem cells, they have a limited capacity for self-renewal, and are often destined to become a particular cell type[286]. Dr Vugler has shown that when transplanted into the retina of rats with retinal degeneration, the hRPCs preserve existing photoreceptors and significantly slow vision loss. He has also shown that the hRPCs can safely integrate into the normal retina without damaging the host

retinal structure and visual function. This means it may be possible to integrate these cells at comparatively early disease stages. These experiments also suggest that in addition to slowing vision loss in RP, hRPCs could also be used for the long-term, sustained delivery of therapeutics to treat other retinal diseases.

ReNeuron has received regulatory approval from the US Food and Drug Administration (FDA) for a Phase I/II trial of this hRPCs therapy at Massachusetts Eye and Ear[287] in the US. The trial, which the company hopes to start by early 2016, will evaluate the safety, tolerability and effectiveness of the treatment in up to 15 patients with advanced RP.

Project reference number: MC_PC_13038

Medical products: Growing a fully-functioning thymus

Professor Clare Blackburn and colleagues at the **MRC Centre for Regenerative Medicine**, **University of Edinburgh**, have, for the first time, grown a complex, fully-functioning organ in a living animal from cells made in the lab. The researchers who, earlier in 2014, reported that they had rejuvenated a thymus in elderly mice[288], have now grown the same organ by reprogramming cells called fibroblasts.

The thymus is one of the first organs to degenerate in normal healthy individuals. As we age, it becomes smaller and less effective, making us more susceptible to infection and less able to benefit from vaccination. By the age of 70, the thymus is around a tenth of the size of an adolescent's.

A protein called Forkhead box N1 (FOXN1) is critical for thymic epithelial cells (TECs) to develop. TECs are a key cell-type of the thymus, and required for T-cell — immune cell — development.

The researchers increased levels of FOXN1 in mouse embryonic fibroblasts. This was sufficient to convert the fibroblasts into functional TECs. They then combined the induced TECs (iTECs) with other thymus cells and grafted the resulting cell mixture onto the kidneys of adult mice. After four weeks, the cells had produced well-formed organs with the same structure as a healthy thymus.

The researchers hope that with further refinement their lab-produced TECs could form the basis of a readily available thymus transplant treatment for people with a weakened immune system. This includes patients who have received a bone-marrow transplant (for example, to treat leukaemia). It could also offer hope to the one in 4,000 babies born each year in the UK with a malfunctioning or completely absent thymus (due to conditions such as DiGeorge syndrome). These cases may sometimes be treated with infusions of extra immune cells, or transplantation of a thymus organ soon after birth, but both are limited by a lack of donors and tissue-rejection problems.

The study was also funded by Leukaemia & Lymphoma Research, the Darwin Trust of Edinburgh, and the European Union Seventh Framework Programme.

Project reference numbers: G0300058, MR/K017047/1

Intellectual property: Hydrogels – a unique solution for stem cell storage and transport

Dr Che Connon at the **University of Reading** has developed a new method for transporting living cells such as stem cells. The technology, where cells are encased within a 'hydrogel', allows clinicians and the stem cell industry to store cells at room temperature for up to two weeks.

Further information on this research, jointly funded by the MRC and BBSRC, is in the case study on the following page.

Project reference number: G0900877

Synthetic biology

Intellectual property: Developing a moisturiser using unnatural amino acids

University of Reading PhD student **Natasha Arezki** has patented a combination of unnatural amino acids she has produced and found to have skin moisturising action.

Dry skin is a common condition experienced by most people at some point in their life. It often worsens during cold and dry winter months and becomes more prevalent with age[289]. Many people also experience more extreme dry and inflammatory skin conditions; there are around 5.7m people in the UK with eczema and 1.8 million people with psoriasis[290]. The annual UK expenditure on atopic eczema in the mid-nineties was estimated to be £465 million[291].

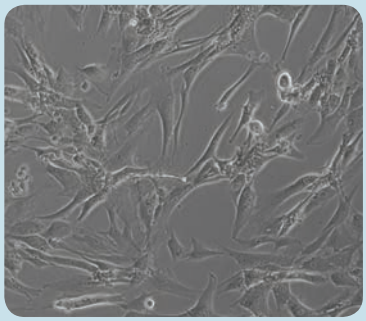
These skin conditions are partly caused by reduced natural moisturising factor (NMF) levels. NMF is composed of free amino acids that make up the protein filaggrin in the stratum corneum — or outer skin layer. Filaggrin's function is to aggregate and align keratin filaments which help to maintain the skin's structure. It is broken down almost as soon as the keratin fibres have been formed.

The NMF components attract and bind water from the atmosphere and deeper skin layers. NMF dissolves in the water it has absorbed and the hydrated NMF forms bonds with the keratin fibres. This reduces the forces between the fibres and increases the elasticity of the stratum corneum. This elasticity makes the skin appear healthy and supple and helps prevent cracking or flaking due to mechanical stress. It was MRC-funded researcher **Professor Irwin McLean** at the **University of Dundee** who first reported that loss of function genetic mutations in the filaggrin gene were associated with atopic eczema[292].

Natasha Arezki has identified and produced unnatural amino acids with the ability to attract and bind to water molecules. They therefore have the ability to improve the skin's moisture retention. She has also discovered that these amino acids increase the absorption of certain lipophilic — fat soluble — and, to a lesser extent, some hydrophilic — water soluble — drugs.

Continued on page 88.

Hydrogels: a unique solution for stem cell storage and transport



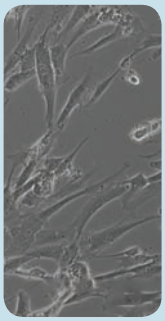


Image: Adipose derived stem cells following release from storage in hydrogels after two weeks.
Credit: Dr Che Connon/University of Reading.

BBSRC and MRC funding for research at the University of Reading had led to the development of a new method for transporting living cells such as stem cells. The technology, where cells are encased within a 'hydrogel', allows clinicians and the stem cell industry to store cells at room temperature for up to two weeks.

Hydrogels provide the cell therapy industry with an alternative to freezing cells for transport, which can be complex and expensive, greatly increasing the number of places that could make use of such therapies.

MRC funding[1] was pivotal to the initial development of the technology and BBSRC support, including a Pathfinder grant[2], funding from the Bioprocessing Research Industry Club (BRIC)[3], and a Sparking Impact award played an important role in financing its further development.

The research is led by Che Connon, Professor of Tissue Engineering at Newcastle University and formerly Team Leader for Tissue Engineering and Cell Therapy Laboratory at the University of Reading, where much of the hydrogel work took place, and builds on his background in tissue engineering of the cornea.

So far Connon has established Non-Disclosure Agreements with 25 companies interested in using the technology, allowing them access to Connon's research to assess the potential commercial applications. The researchers are also discussing with clinicians how hydrogels could benefit stem cell therapies currently undergoing or soon to enter clinical trials. Finally, the researchers have an evaluation licence in place with a veterinary medicine company to explore the use of hydrogels for transporting livestock semen for artificial insemination.

Stem cells by post

Cell therapies, where patients are treated with cells taken from themselves or from a donor, have been used since the 1960s when the first bone marrow transplants

IMPACT SUMMARY

BBSRC and MRC-funded research by Dr Che Connon at the University of Reading has led to the development of hydrogels for storing and transporting living cells such as stem cells.

The stem cell industry has expressed an interest in the technology. As a result, the researchers have:

- Signed 25 Non-Disclosure Agreements with interested companies, and 12 material transfer agreements.
- Established an evaluation licence with a veterinary medicine company to use the hydrogels for transporting livestock semen for artificial insemination.
- Discussed the hydrogels with clinicians, with a view to incorporating their use into stem cell therapies currently under development.

were conducted. The number of cell therapies is likely to increase in future, as researchers explore the potential of stem cells to treat a wide range of illnesses. One market research report suggested that the global stem cell market is likely to grow from $3.8Bn in 2011 to around $6.6Bn by 2016, and is increasing annually by 11.7%[4].

The rapidly expanding stem cell industry faces a number of challenges, however, including how best to store and transport fragile living cells without damaging their ability to treat disease. At the moment, stem cell manufacturers and clinicians must freeze cells in a process known as 'cryopreservation'. Frozen cells are expensive to transport, as they must be kept cold, and complicated to use, requiring facilities to thaw and culture the cells at their destination.

The hydrogels used by Connon allow cells to survive outside the laboratory without the complex and bulky infrastructure required for cryopreservation[5]. The hydrogels used are produced from a natural compound called alginate, extracted from seaweed, which is already widely used in food production and in medicine. "Out of the lab, you don't need to change the media or do anything to it. You can leave [the cells in the hydrogel] in a container of any sort, at room temperature, for two weeks. They'll sit there quite happily, and you get 80% viability," says Connon.

> "It's not very technologically challenging – it's quite simple, actually."

As a result, the technology would allow stem cells to be shipped from their point of manufacture to the places where they are needed. In many of these places, such as clinics in rural Africa, it is difficult, if not impossible, to maintain the 'cold-chain' of refrigeration to keep cells frozen. In addition, these clinics may not have the cell culture facilities and technicians required to make use of frozen cells. Cells encapsulated in hydrogels do not need to be kept cold during transport and can be used straight away.

"You can send them out to all parts of the world, which is personally quite exciting," says Connon. "With this technology you could start to see cell-based therapy being used in remote clinics in India, Africa, basically anywhere that can receive post."

From cornea to clinic

Connon made his hydrogel discovery while carrying out research supported by an MRC-funded grant to investigate whether it was possible to take corneal epithelial cells from a donor, encase them in a hydrogel and apply that directly to the surface of a patient's eye[6,7]. There is a pressing need for new treatments for diseases of the cornea, as the increasing prevalence of laser-eye treatment to correct eyesight is reducing the supply of donated corneas available for transplants. Corneal stem cells could offer an alternative, and were one of the earliest areas of stem cell research alongside bone and blood.

During the MRC-funded research "I noticed the cells within the

BRIC

BRIC was established in 2005 by BBSRC, EPSRC and industry to support and develop the UK bioprocessing research community, and enable knowledge transfer between the science and engineering base and industry. BRIC includes 15 industry members, as of June 2012. The first phase of BRIC awarded £13.7M of funding to 25 research projects. The second phase, which began in 2010 and will run for five years, will award a total of £10M.

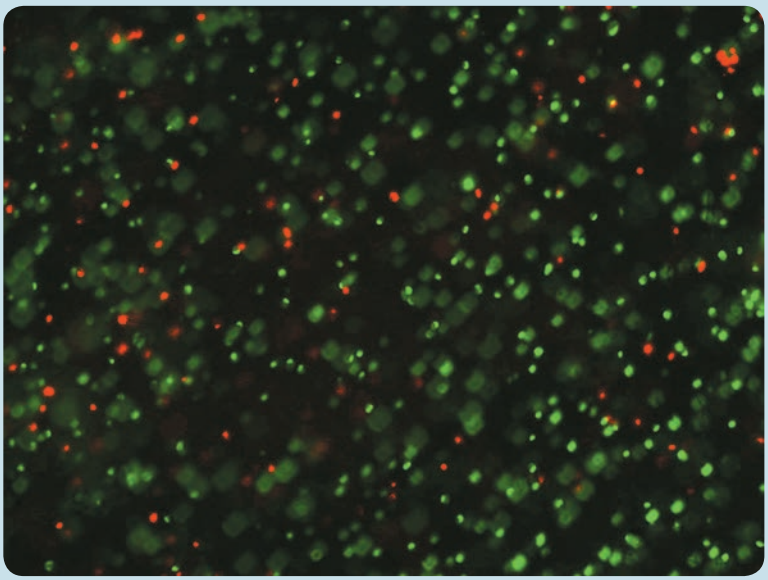


Image: Live stem cells (green) and dead stem cells (red) stain following release from hydrogels after two weeks in storage.
Credit: Dr Che Connon/University of Reading.

hydrogel were not respiring greatly." Connon explains. "Would that allow them to remain viable in less hospitable environments and, specifically, outside the cell culture medium?"

Further investigation showed that, because the hydrogel suppressed respiration in the cells, they could survive in the hydrogel outside normal laboratory conditions for up to two weeks.

BRIC by BRIC

Following the MRC grant, Connon sought funding from BBSRC to further develop the hydrogel technology. This led to a BBSRC Pathfinder grant in 2009 to conduct a market analysis of the current state of cell transportation and cell storage. The analysis found that there was no current alternative to cryopreservation and indicated that the hydrogels could be commercially valuable.

Connon then received £30K from the University of Reading to improve his proof of concept, which enabled a postdoctoral researcher to expand on the initial discovery. In particular, the researchers were able to look at how different cell types responded to encapsulation in the hydrogels, and how the cells fared over time. This led to Connon's first grant from the Bioprocessing Research Industry Club (BRIC), in 2011, co-funded by BBSRC and EPSRC.

From BRIC, Connon received a one-year enabling award, which helped him put limits on the technology – to find out how long cells could be stored for, what density of cells could be stored in the hydrogel, and how these varied for different cell types. With that knowledge, Connon won a full BRIC grant, which began in October 2013.

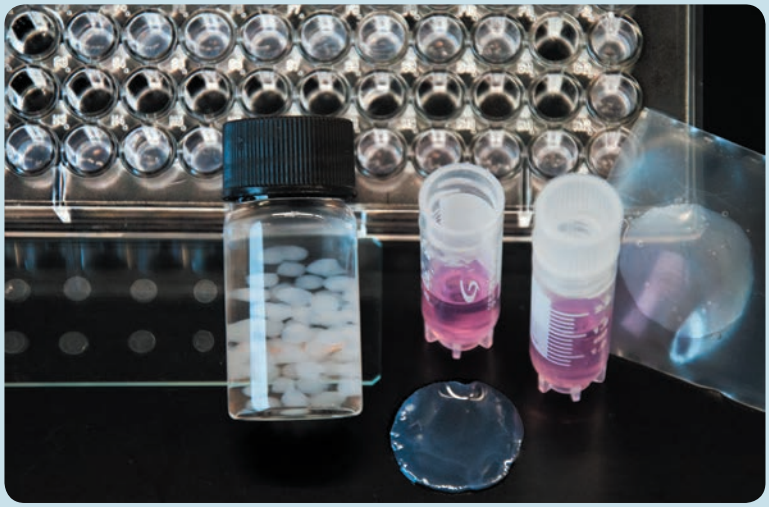


Image: A variety of applications for the hydrogels, including gel discs, beads and socalled 'ready plates' - 96 well plates in which cells are stored and used when required for experimental purposes.
Credit: Dr Che Connon/University of Reading.

"More importantly, BRIC gave me access to key industrial contacts, primarily in bioprocessing, but a lot of the people there are also interested in cell culture and products revolving around cell culture more generally," says Connon.

Talking to industry representatives has enabled Connon to ensure his research takes account of their needs, for instance by allowing him to see whether processes could be scaled-up to industrial quantities.

In parallel, Connon also used a database managed by the Cell Therapies Catapult[8] to identify clinicians planning or running stem cell clinical trials. The researchers contacted these clinicians to explain the hydrogel technology and to discuss how the clinicians could incorporate it into their methods once their therapies were well-advanced.

Sparking Impact

A BBSRC Sparking Impact Award in 2013 provided a small amount of funding for a post-doctoral researcher in Connon's lab to demonstrate their hydrogel technology to industry. This resulted in 25 Non-Disclosure Agreements with interested companies, and around 12 material transfer agreements. It was also a valuable training exercise for the post-doctoral researcher involved, as she developed experience in talking to industry representatives.

The Sparking Impact award also led to an evaluation licence with a veterinary medicine company interested in using hydrogels to encapsulate sperm cells from livestock. These are used to artificially inseminate farm animals such as cattle, avoiding the cost of transporting animals for breeding, as well as allowing farmers to use the sperm from high quality males for their herds.

At the moment they rely on cryopreservation, but it is not always possible to maintain a reliable cold chain on the farm. According to Connon, "anything that can simplify the delivery will be of benefit to [farmers] and, hopefully, have a greater success rate."

What next?

The hydrogel technology is still being developed, and Connon's research (supported by the BRIC grant awarded in 2013) is now focussing on two areas. The first encompasses the biological questions around the effects of the hydrogel on the encapsulated cells; in particular, what mechanism suppresses the cells' respiration? Connon's group are also focussing on a single type of stem cell - adipose-derived mesenchymal stem cells – to establish clear limits to the technology.

In parallel, Connon is working with Dr Andrzej Pacek at the School of Chemical Engineering in Birmingham to scale-up the technology using a stirred bioreactor system to create beads of gel containing the therapeutic cells. "It's early days," says Connon, "but we should end up with a way of processing billions of cells in beads that could then be shipped at ambient temperature."

Connon is also developing other techniques using hydrogels to improve corneal stem cell transplantation. In 2013 the MRC awarded him £0.5m to develop a method to control the stiffness of corneal tissue in order to improve corneal stem cell attachment. Connon had previously used collagen gels of differing stiffness to prove that these stem cells are exquisitely sensitive to the biomechanics properties of these substrates. He showed that corneal stem cells differentiate when grown on stiff collagen gels and that reducing this stiffness reduces their differentiation.

Notes and references

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2. BRIC: http://www.bbsrc.ac.uk/business/collaborative-research/industryclubs/bric/bric-index.aspx
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8. Cell Therapies Catapult: https://ct.catapult.org.uk/ The Catapults receive core funding from Innovate UK, the Technology Strategy Board.

Continued from page 83.

UK-based pharmaceutical company MedPharm is now taking this patent forward and has extended it to the US and several other countries. There are several companies interested in licensing the product for drug absorption and for its moisturising properties.

Project reference number: Not currently available.

Stratified medicine

Medical products: Developing test to predict responses to antidepressants

Professor Carmine Pariante at **King's College London** has demonstrated that levels of genes encoding inflammatory cytokines — small proteins involved in cell signalling — are able to predict patients' responses to antidepressants. It is planned for this knowledge to help develop a test that would enable the right treatment choice.

Professor Pariante showed in 2012 that higher levels of the genes *IL-1ß*, *MIF*, and *TNF-α*, which code for proteins involved in the inflammatory response, predict a lack of response to antidepressants[293].

Depression was first linked to inflammation in the early 1980s when high levels of inflammatory markers were shown in patients with depression[294]. Since then, studies have shown that one third of those with major depression have raised inflammatory markers[295]. Research has also shown that inflammatory diseases are associated with greater rates of major depressive disorder (MDD) and that patients treated with pro-inflammatory cytokines are at greater risk of developing major depressive illness.

Professor Pariante's research often receives media attention. In 2015 he published research showing that people born to mothers who are depressed during pregnancy are up to three times more likely to have depression in later life. This research was published in articles in *Health Canal*[296] and the *Daily Mail*[297]. He is frequently asked by media sources to comment on research or events relevant to his field, including by the *Huffington Post*[298], *The Telegraph*[299,300] and *The Guardian*[301].

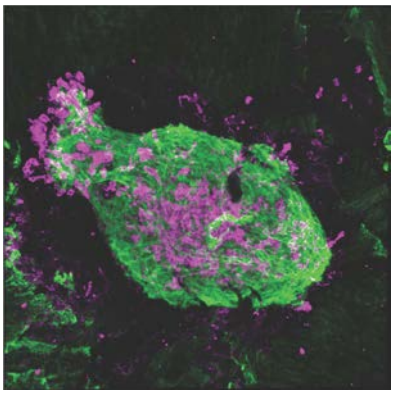
Project reference number: MR/J002739/1

Immunotherapy

Medical products: Humanised monoclonal antibody as potential treatment for age-related macular degeneration

Professors Stephen Moss and **John Greenwood** at **University College London** have developed a humanised monoclonal antibody as a potential treatment for age-related macular degeneration (AMD).

AMD is an eye condition that affects the macula — a tiny part of the retina at the back of the eye[302]. Neovascular AMD (the 'wet' form) develops when the network of tiny blood vessels in the macula undergo structural changes and, as a result, grow uncontrollably in a manner severe enough to cause vision loss. AMD causes problems with central vision; it may make the central vision distorted or blurry, and eventually may cause a blank patch in the centre of vision. It is the leading cause of blindness in people over the age of 60 in the Western world. About 25 per cent of over 60s in the UK have AMD-caused visual loss, a figure that is expected to triple within the next 10-20 years. Although some advances have been made to treat AMD, the most effective therapies generally benefit fewer than half the patients affected and often only delay vision loss.



Vascular lesion in a mouse retina. The green staining shows the mass of tiny blood vessels and the purple cells are macrophages (immune cells) that are recruited to the lesion and secrete molecules to stimulate blood vessel growth. *Image credit: Dr Sabu Abraham.*

Antibodies are proteins that recognise and fight foreign invaders, such as bacteria or viruses. Monoclonal antibodies are tailored in the lab to recognise specific desirable targets, such as a marker on a cancer cell or a pregnancy hormone. It was MRC Laboratory of Molecular Biology (LMB) researchers Georges Köhler and César Milstein who originally discovered a method to isolate and reproduce monoclonal antibodies in 1975, for which they won the 1984 Physiology or Medicine Nobel Prize. Originally developed as a tool for studying the immune system, monoclonal antibodies now treat millions of patients, with global revenues worth nearly $75 billion in 2013[303].

Professors Moss and Greenwood have discovered a new protein, LRG1, of previously unknown function, that they have shown to be produced in high levels by the abnormal blood vessels affected in retinal vascular disease[304]. They have demonstrated that it is this protein that causes the blood vessels' uncontrollable growth (angiogenesis). The researchers have developed an antibody that blocks LRG1's function, which they have shown to be effective in combination with another monoclonal antibody that blocks blood vessel formation by targeting a different pathway. This therefore maximises the effectiveness of this treatment. The researchers have recently been awarded funding through the Biomedical Catalyst scheme to perform first-in-human studies in patients with neovascular AMD and hope to soon begin Phase I clinical trials.

As the antibody blocks blood vessel growth, it might also be useful in treating certain cancers, which rely on angiogenesis to provide the oxygen and nutrients needed for tumour growth.

Project reference number: G0902206

Medical products: Developing an antibody to treat ovarian cancer

Professor Frances Balkwill at **Queen Mary University of London** is developing an anti-interleukin 6 antibody to treat relapsed ovarian cancer. In 2011 she published Phase II clinical trial results[305] showing that the protein interleukin 6 (IL6) has tumour-promoting actions and that the antibody, siltuximab, can inhibit these actions.

Ovarian cancer causes few symptoms until it has spread widely in the abdomen. When a woman is diagnosed with ovarian cancer she is treated with surgery and chemotherapy. However after a period of one to four years, the cancer usually returns and is very difficult to treat. More than 7,000 women are diagnosed with ovarian cancer in the UK each year. It is the fifth most common cancer in women after breast, bowel, lung and uterine cancers.

Interleukin 6 is a protein secreted by immune cells to stimulate an inflammatory immune response during infection and after trauma, such as burns or tissue damage. In cancer however, this usually helpful molecule is produced at the wrong place and time. Studies have shown that IL6 helps tumour cells to survive and also increases their resistance to chemotherapy[306]. It also promotes uncontrollable blood vessel growth (angiogenesis), needed by tumours to provide sufficient oxygen and nutrients to support their growth[307]. In patients with advanced ovarian cancer, high IL6 blood levels correlate to poor prognosis[308].

Professor Balkwill conducted a Phase II clinical trial of siltuximab in eighteen women with recurrent ovarian cancer. In eight patients, the disease stabilised and in four patients, this lasted at least six months[309]. However, sustained responses were not achieved.

Professor Balkwill received a £1.5m programme from Cancer Research UK in 2013 to take this work forward[310]. She had previously shown that inflammatory cytokines such as IL6 interact with other inflammatory molecules in ovarian cancer cells. In 2015 she showed that inhibiting IL6 production increased EGFR signalling and ERK activation that compensated for, and reduced the efficiency of, anti-IL6 antibodies. Professor Balkwill further showed that using anti-IL6 antibodies in combination with a drug called gefitinib that inhibits EGFR signalling enhanced their anti-cancer activity[311].

Professor Balkwill is also actively involved in science communication for non-specialist audiences, especially young people. She is director of the Centre of the Cell[312], a biomedical science centre for children, educational website and outreach project in East London. Since its opening in September 2009, the Centre has engaged with more than 100,000 participants.

Professor Balkwill has authored 13 children's books on science, aiming to educate children about cells and molecular biology[313]. These books have been translated into at least 12 foreign languages with more than half a million copies sold worldwide. She won the 1991 Copus Science Book Prize for her first two, *Cells are us* and *Cell wars*.

Project reference number: G0501974

Gene sequencing and genetic engineering

Intellectual property: Optimised genome modification tools for *Drosophila*

Drs Fillip Port and **Simon Bullock** at the **MRC Laboratory of Molecular Biology** (LMB) have licensed optimised genome modification tools for the model organism *Drosophila* to three commercial companies that produce transgenic *Drosophila* flies for the research community.

Researchers at the University of California reported in 2012 that an immune-like system in bacteria that could cut open and make a change to an invading virus' DNA could be modified to recognise, and subsequently change, any DNA sequence[314]. The CRISPR system uses an enzyme called Cas9 to cut specific DNA sequences when guided to a particular site in the genome by short RNA molecules.

Since 2012, CRISPR has been used as a simple and versatile gene modification tool in many model organisms and in cultured mammalian cells. Many MRC-funded researchers are using CRISPR to identify and characterise genes implicated in particular diseases. Researchers at the Francis Crick Institute[315] applied to the Human Fertilisation and Embryology Authority in 2015 for a research license to use CRISPR on IVF embryos to investigate why some women have repeated miscarriages.

Drs Port and Bullock have generated transgenic flies expressing Cas9 and plasmids for producing the guiding RNA molecules. These tools have been distributed widely to the academic research community, being used by more than 300 laboratories[316]. The tools have been licensed to the three commercial companies under royalty-bearing agreements.

Project reference number: MC_U105178790

Software and technical products: First software for analysing Oxford Nanopore Technologies sequencing data

Dr Nick Loman at the **University of Birmingham** has developed Poretools[317], the first published software that can analyse DNA sequencing data produced by Oxford Nanopore Technologies (ONT)[318].

ONT, a company formed by MRC-funded **University of Oxford** researcher **Professor Hagan Bayley** in 2005, developed a 'new-generation' of DNA sequencing technology using engineered protein membrane nanopores. The technology is able to detect single molecules and it is unnecessary to amplify the DNA which means that long fragments can be sequenced without losing quality.

In May 2014, ONT released MinION™, a portable device the size of a USB memory stick and costing under $1,000, for electronic single-molecule sensing. Sequencing with MinION produces raw signals that reflect the ionic current at each

pore by a DNA molecule. The resulting files for each read sequence are stored in a format called 'FAST5'. However, until now, there has been no software available with the ability to analyse this data format.

Poretools, an open source tool, is able to convert data in the FAST5 format to either FASTA or FASTQ, both text-based formats representing nucleotide sequences, to enable the user to compare the data with sequence alignment and/or assembly software.

In 2014 Professor Loman and colleagues used this software to analyse a Salmonella outbreak at a hospital in Birmingham. Within two hours of receiving samples from the hospital, the researchers had sequenced the bacterium, confirmed that it was Salmonella, determined its strain and showed that all cases were part of the same cluster[319].

Professor Loman's team also used the software to sequence Ebola genomes in April 2015. As at September 2015, the team had sequenced 130 genomes and played an important role in tracking disease transmission. The team have also confirmed that the MinIONs are now 90 percent accurate—a significant improvement over their performance at launch[320].

Project reference number: MR/J014370/1

Artistic and creative products: Film to illustrate how genomics is being used to understand the Malaria parasite

Drs Oliver Billker and **Julian Rayner** at **The Wellcome Trust Sanger Institute** worked with artist Deborah Robinson in 2013 to create *Parasite*, a film exploring how genomics is being used to understand the *Falciparum* parasite that causes malaria and how this may be used to establish new ways to prevent or treat the disease[321]. Deborah used sections of archival films from the Wellcome Collection and Imperial War Museum library which depict the 'mass eradication' campaign attempts to control the disease in the 20th Century. She used software to corrode the footage to emphasise the cyclical and recurrent nature of the disease.

Parasite was selected for the 2013 Shanghai International Science and Art exhibition where it won an award for excellence in science and art.

Project reference numbers: G0501670, MR/J002283/1

Global Health

Software and technical products: Linking census data to health records in South Africa

Professor Margaret Thorogood at the **University of Warwick**, with colleagues at the University of the Witwatersrand (Wits), South Africa, is developing a database to link census data with information on patients visiting medical clinics in north eastern South Africa[322].

The database is part of a randomised trial aiming to provide information to help South Africa's health policy makers improve the country's care of chronic long-term conditions, such as hypertension (high blood pressure). Hypertension is currently poorly managed in the country. The South African Department of Health is rolling out the use of community health workers who visit households, deliver medication, and encourage patients to take their medication. However, there is still uncertainty about how best to use these community health workers, and whether this initiative will prove cost-effective.

The researchers are testing a lower-resource model using clinic-based lay (community) health workers to support the nurses who run the clinics. The lay health workers have been managing an appointment's system, reminding patients of their appointments, helping nurses with the pre-packing of medications and giving support and advice to the long-term patients. These clinics are based in the Agincourt Health and Demographic Surveillance System (HDSS) site where an annual census is also conducted.

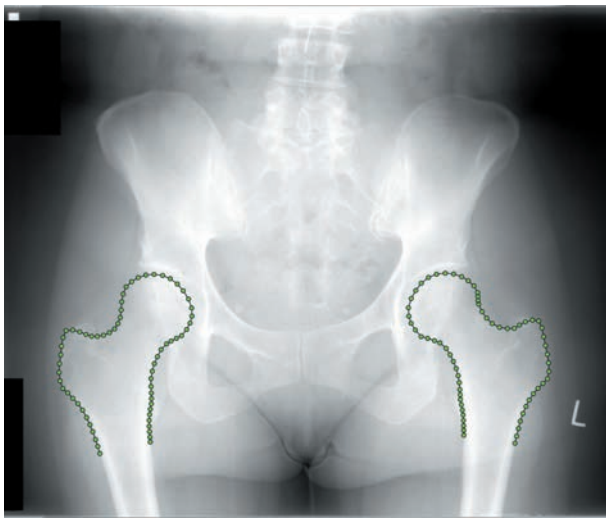
The new database links information on the patients' clinic visits to their demographic surveillance record, which includes up to 20 years of individual and household-level data. The database is being continued following the end of the original trial, supported by further research funding. Moreover, the complex system for creating and managing such a database is now being exported to other HDSS sites. The database, which will be similar to the UK's general practice databases, will have huge potential for both health service management and research.

Project reference number: MR/J016020/1

Musculoskeletal disorders

Software and technical products: BoneFinder – software to determine bone shape in x-rays

University of Manchester PhD student[323] **Claudia Lindner** and colleagues began developing BoneFinder, software to help analyse bone shape in x-rays, in 2011. It automatically outlines bones on radiograph images, saving thousands of hours of manual work[324,325,326]. The software is designed to automatically pick out bone shapes in images, rather than relying on researchers and doctors to do this manually.



An image from the BoneFinder software.
Image credit: Claudia Lindner

Identifying bone outlines plays an important role in disease diagnosis, preoperative planning, and treatment analysis. It is particularly important in arthritis, which affects more than 30 per cent of over 65s and costs the UK economy around £30 billion each year.

The software can already identify hips and now, with £300k in funding from the Engineering and Physical Sciences Research Council (EPSRC), the researchers will adapt it to map out knees and hands and to learn to identify other bones and structures in the body.

The funding will also allow further development to ensure the system is accurate enough to be used in hospitals for faster diagnosis of problems in patients. In April 2015 BoneFinder was awarded the first prize in an ISBI (International Symposium on Biomedical Imaging) Grand Challenge on dental x-ray image analysis[327]. The goal was to automatically detect anatomical structures in radiographic images of the skull for the analysis of dental abnormalities. BoneFinder achieved similar accuracy to that of two experienced doctors.

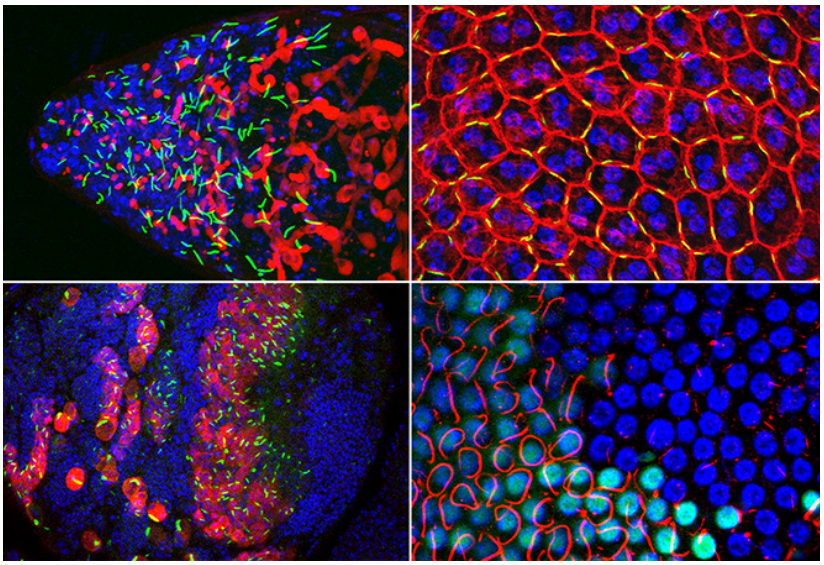
The software has been licensed to more than 20 research groups worldwide, including the University of Oxford and the University of California in San Francisco where it is used to study the relationship between hip bone shape and osteoarthritis.

Project reference number: Not currently available.

Cell biology

Artistic and creative products: Images of Cytoophidia

Professor Ji-Long Liu studies cell organelles — the 'small organs' found within the cells of every living thing — at the **MRC Functional Genomics Unit** (FGU) at the **University of Oxford**. These organelles, including the cell nucleus and mitochondria, ensure that our cells function as they should. If they do not work properly, this causes disease or even death.



Cytoophidia light up as green filaments in the Drosophila testis (upper-left), brain (lower-left), and accessory gland (upper-right) with a fluorescent fusion to CTP synthase (Chen, K., et al. [2011]. J. Genet. Genomics 38, 391–402). Exceptionally long, red filaments appear in follicle cells with green nuclei in the Drosophila ovary (lower-right) when a specific CTP synthase isoform is expressed inside of them.
Image credit: Azzam, G., and Liu, J.L. [2013]. PLoS Genet. 9, e1003256.

In 2010 Professor Liu reported that an enzyme called CTP synthase was compartmentalised in cytoophidia in fruit flies[328]. He has subsequently demonstrated that CTP synthase can join together to form long chains — or filaments in human cells[329]. He therefore showed that cytoophidium represent a new type of compartment in cells, which have remained unchanged throughout evolution. Recent studies from Professor Liu's group and others suggest that cytoophidia formation can promote enzymatic activity[330,331].

Professor Liu produced several images of the structures that were featured on the covers of various journals, including *BioEssays* (March 2011[332]), the *Journal of Genetics and Genomics* (September 2011[333] and May 2015[334]) and the *Journal of Cell Science* (October 2015[335]).

His images were also selected for *Cell's* Picture Show in 2013[336].

Project reference number: MC_U137788471

Progressed medical products

We have now collected data in researchfish® for seven years and so have the ability to track a medical product's progress from one data collection period to another. Studies have shown that it can take from a few years to decades for discoveries to be translated into practice, given the huge variety of products and interventions that arise from medical research[337]. The following examples are medical products that have shown significant progress in a few recent years.

Developing a malaria vaccine

Professor Simon Draper at the **University of Oxford** reported in 2011 that he had developed a vaccine against blood-stage *Plasmodium falciparum*, the deadliest malaria species[338].

Malaria is a life-threatening parasitic disease transmitted to people through the bites of infected mosquitos[339]. It is prevalent in many tropical parts of the world, predominantly in Africa, Asia and South America. It caused around 500,000 deaths in 2013, mostly in African children.

It is unlikely that vaccines based on the whole parasite organism will be scalable or easy to administer and therefore research has been concentrated on vaccines encoding malaria proteins — *subunit vaccines*. Phase III clinical trials of a subunit vaccine[340] have just been completed in Africa however it was only shown to be 35 per cent effective against severe disease in young children[341].

Little progress has otherwise been made in malaria vaccine development in the past 10 years. One reason is likely to be because efforts have focused on malaria proteins that are highly recognised by the immune system. They have therefore evolved to cope with immune pressure. Additionally, large amounts of antibody are required to neutralise the parasite, difficult to achieve with human vaccination.

Professor Draper and colleagues have subsequently identified a protein called PfRH5 that binds a protein called basigin on the red blood cell's surface – an interaction that is essential for the blood-stage parasite's ability to invade the cells. They have shown that this interaction can be blocked by low levels of antibody and also that it has limited variation across different parasite strains. This means that the vaccine-induced antibodies have neutralised all strains of the *P.falciparum* malaria parasite to date.

The researchers were awarded an MRC Industry Collaboration Agreement in 2012 to further develop vaccines targeting PfRH5 and collaborated with ExpreS2ion[342], a contract research organisation based in Denmark to develop a production process suitable for clinical grade protein vaccine manufacture.

Professor Draper reported that the vaccine will enter a Phase Ia clinical trial in early 2016[343].

In 2014 the researchers, working with **Professor Matt Higgins**, also at the **University of Oxford**, made available the crystal structures of PfRH5 to help guide the design of other vaccines against the blood-stage parasite[344].

Project reference numbers: MR/K025554/1, G1100086, G1000527

Antifungal therapy for HIV-associated cryptococcal meningitis in Africa

Professor Thomas Harrison at **St George's, University of London** is working to optimise the antifungal treatment regimens for HIV-associated cryptococcal meningitis in Africa.

Cryptococcal meningitis, a fungal infection of the tissues covering the brain and spinal cord, is one of the most common causes of death in patients with AIDS. It is associated with up to 500,000 deaths each year in Africa alone. Many patients die from the infection because the current recommended treatment — amphotericin B for two weeks — is difficult to give in hospitals in developing countries; it is relatively expensive, needs to be given intravenously and has serious side effects that often start in the second week. The alternative oral tablet treatment that is available — fluconazole — is cheap and commonly used but is much less effective.

Improvements in treatment have been slow because current drugs take a long time to clear the infection and traditional trials need many patients so they are therefore slow and expensive to conduct. Professor Harrison has however developed a new way to test the activity of new drug combinations and dosages in small numbers of patients by measuring the rate of decrease in the amount of fungus in the patients' cerebral spinal fluid (CSF)[345].

Professor Harrison and colleagues have developed new treatment regimens and conducted several clinical trials into their effectiveness. The regimens are more effective than Fluconazole alone and are also more sustainable in resource-poor settings than two weeks of amphotericin B. The studies have greatly influenced the IDSA (Infectious Diseases Society of America) and WHO cryptococcosis guidelines published in 2010[346] and 2011[347], both of which Professor Harrison co-authored.

The researchers showed in a Phase II early clinical evaluation that a short course of amphotericin B (five-seven days) was much better tolerated than the standard two-week course and was not associated with any decline in the infection clearance rate[348,349]. This negates several issues associated with the two week course. They also showed that high-dose fluconazole together with another drug called flucytosine was considerably more effective than fluconazole alone[350].

Professor Harrison is now testing both regimens in a Phase III clinical trial. They are being evaluated against the aspirational standard of two-weeks amphotericin B treatment. The trial is being conducted in collaboration with the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), the Liverpool School of Tropical Medicine (LSTM), the Malawi-Liverpool Wellcome Trust Unit in Blantyre, the University of North Carolina Project in Lilongwe, the University Teaching Hospital in Lusaka, Zambia and centres in Cameroon and Tanzania.

Project reference numbers: G0501476, G1100814

Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

End Notes

207. researchfish® is the online system used by the MRC and many other funders in the UK and worldwide to collect information on research outputs, outcomes and impact. For more information, please see http://www.mrc.ac.uk/funding/guidance-for-mrc-award-holders/researchfish/
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2014/15 report

SECTION 2.4
Research materials

Research materials

The materials generated in the course of research are many and diverse. They may include new biological models (which may be whole living organisms or cell cultures engineered for a particular purpose), databases containing information about experimental observations or instructions for new techniques. These materials are tangible evidence of the research process and, although usually generated exclusively for the original research programme, they may be used more widely in other research projects. Using these materials may open up entirely new lines of enquiry and/or accelerate research in closely-related fields or even entirely different disciplines. These spill-over benefits are important outputs of MRC-supported research. Feedback captured via researchfish® aims to identify where studies have generated research materials and, importantly, where these have been used by others. It is at the stage *when the materials are actively being used by others* that the MRC is interested in receiving details of the research material.

Funding organisations are interested in ways to encourage research materials to be shared to increase the impact of their support, reduce wasteful duplication and improve reproducibility of research. A good example is the effort made to improve the accessibility of data that underpins research studies. The rise of the internet has made it relatively straightforward to share data freely. The potential societal benefits from opening up research data are expected to be significant, from inspiring new research which stimulates economic growth and new investment to increasing resource efficiency and building public trust. The research councils, among other research and higher education organisations in the UK, are part of the UK Open Research Data Forum[351]. The research councils also published their first draft Concordat on Open Research Data in September 2015. This concordat intends to establish open research data as the desired position for publicly-funded research over the long-term[352]. All published research council-supported work is expected to include a statement outlining how underlying datasets can be accessed by others.

One initiative that helps researchers discover potentially useful datasets and, importantly, acknowledge the originators in a standard way (by providing DOIs — digital object identifiers — for datasets) is Datacite[353]. Formed in London and now based in the Germany National Library of Science and Technology, it includes 6.5 million datasets and other objects.

The importance of making research datasets publicly available, even ahead of peer-reviewed publication, is also becoming increasingly acknowledged. This is particularly the case in areas where speed is of the essence, for example in infection outbreaks, such as the recent Ebola epidemic. Real-time reporting and analysis by MRC-supported researchers helped enable a rapid response[354]. Similarly, research on hospital outbreaks of Salmonella and MRSA[355] have benefited from genetic information being immediately and openly available.

The MRC and MRC-supported researchers recognise the importance of sharing datasets and other research materials with fellow scientists in the UK and around the world in advancing medical research. This might be on a more informal basis, as part of research collaboration[356], or through MRC facilities and national or international science infrastructure[357].

MRC-funded facilities includes, amongst others:

- MRC Harwell – an international centre for mouse genetics[358] (see case study *Research databases and models: International Mouse Phenotyping Consortium*),
- UK Brain Bank Network – brain banks[359] to store post-mortem brain and central nervous system (CNS) tissue donated by the public for diagnosis and research into disorders (see case study Research tools and methods: Brain and spinal cord tissue), and

- Population Cohort Directory – population cohorts[360], tracking subsets of the population to better understand the role of biological, environmental and lifestyle factors shaping human health (see case studies *Research databases and models: Database of HIV patients and Research databases and models: The Twins Early Development Study (TEDS) dataset*).

Often the distinction between creating a new research material and developing a new product is a difficult one to make. Demand for materials, models or methods may mean that it is more efficient for these to be manufactured and distributed by a commercial partner. Or, at an earlier stage, the potential of a particular material to be developed into a marketable product may be identified. Alternatively, the development of a new product may be curtailed but, nevertheless, intermediate assays or reagents could be usefully provided to others as a research material. So some research materials may be equally relevant to the development of new products section and outputs in this section may result in reports in the research materials section.

This chapter includes detailed examples of the many types of research materials created during the process of MRC-supported research. The information in this chapter has largely been sourced from researchfish®[361]. Quantitative information on numbers and types of research materials is available in the *Quantitative analysis* chapter of this report.

The examples in this chapter are characterised by the following research areas:

- Stratified medicine
- Regenerative medicine
- Antimicrobial resistance
- Infections and immunity
- Metabolic disease
- Neurodegeneration and cognition
- Mental health
- Global health
- Gene sequencing and genetic engineering
- Economic evaluation of healthcare
- Drug development

Each case study focuses on a predominant output type, but others might be referenced within it. The accompanying icons represent the relevant output types. A key to the list of output types is at the end of this chapter.

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — the *Gateway to Research*[362] — by entering the full project reference number listed under each case study in the search field.

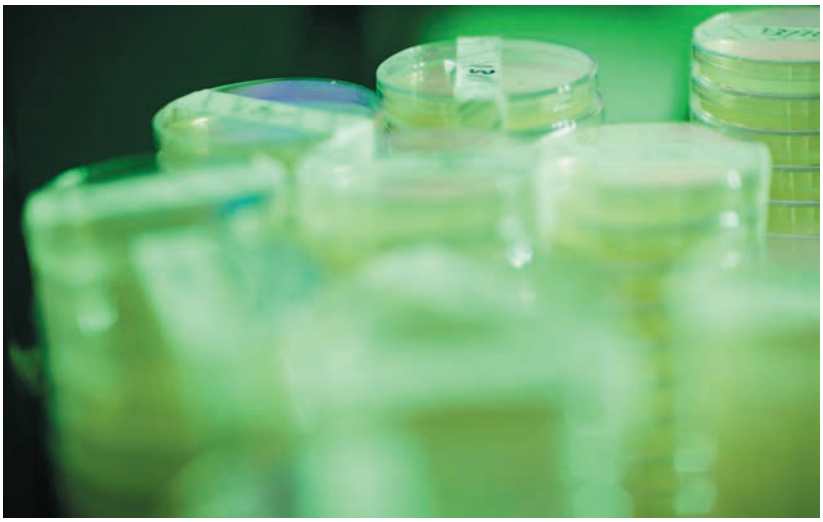
Stratified medicine

Research tools and methods: Screening device to predict how patients will respond to leukaemia chemotherapy

Dr Elizabeth Anderson, **Professor Vyvyan Salisbury** and colleagues at the **University of the West of England** are developing a rapid and inexpensive screening device based on bacterial biosensors to predict how patients will respond to leukaemia chemotherapy.

The test will initially be used for Acute Myeloid Leukaemia (AML), an uncommon but potentially fatal cancer in which white blood cells multiply rapidly and unchecked in the bone marrow and blood. Around 2,600 patients are diagnosed with AML each year in the UK[363]. On average, 20 per cent of people with the disease will survive for five years or more after diagnosis, however, the chances of survival are greater the younger the patient[364].

AML patients are usually treated with the anti-cancer agent cytarabine (Ara-C) in different doses. Ara-C might be combined with other agents, such as Fludarabine, to increase its effectiveness. However due to differences in the genetic makeup of the abnormal blood cells, up to 40 per cent of patients do not respond to this first course of chemotherapy treatment. The lack of response is only apparent after weeks of treatment, by which time, the patient may already have experienced severe side-effects.



The bacterial biosensor. *Image credit: E.Anderson/V.Salisbury, UWE.*

AML progresses rapidly and aggressively and so it is important to treat it as soon as possible; weeks' delay can have severe consequences. Dr Anderson and Professor Salisbury are therefore developing a quick and simple device that will test blood or bone marrow samples for a response to the combined therapy before it is started. It will use a bioluminescent bacterial biosensor that has been genetically modified to give out increased amounts of light in response to the active form of the drug within leukaemia cells. It accurately measures drug uptake and conversion to the active drug form. The results will ensure that the patient receives the right combination of chemotherapy drugs in the correct dose to meet their needs and prevent delays in effective treatment. The test will be particularly useful for patients whose leukaemic cells are sensitive to low chemotherapy doses. This will allow them to be treated with minimum drug doses with fewer side effects. The test will also benefit elderly patients, for whom AML incidence is increasing and survival rates decreasing. It will help determine whether the benefits of undertaking aggressive chemotherapy outweigh the risks in patients who might have other health conditions.

The researchers have previously developed a similar test to measure the response of AML patient blood or bone marrow samples within eight hours to Ara-C as a lone treatment[365]. Using the test on 71 patient samples, it showed good agreement with a standard laboratory cytotoxicity test and when compared to 53 known patient outcomes, had a test efficiency of 83 per cent.

Preliminary studies indicate that the new test, developed in collaboration with Randox Laboratories[366], predicts the effectiveness of the combined Ara-C/fludarabine therapy.

The researchers plan to extend the test to include other relevant drug combinations for AML treatment.

Project reference number: MR/J005207/1

Regenerative medicine

Research tools and methods: Genetically-modified cell line to repair damaged nerve

PhD student **Danielle Stevenson** and colleagues at **King's College London** and **University College London** genetically modified mouse embryonic stem cells in 2014 to restore function to muscles made unusable by damaged nerves[367].

Nerves damaged by disease or injury do not always regenerate. This can lead to permanent loss of voluntary motor function and muscle paralysis. Therapies involving transplanted stem cells have previously shown some promise. However the new neurons derived from the transplanted cells cannot communicate with the central control systems that would normally regulate movement[368,369].

The researchers therefore genetically modified mouse embryonic stem cells to express both a neurotrophic factor — a protein that promotes the survival, development and function of neurons — and a light-sensitive ion channel to enable the optical stimulation of muscle function.

The researchers then grafted these stem cells into branches of the sciatic nerve that had been denervated — had their nerve supply cut off. The engrafted neurons not only reinstated the nerve supply to the lower back leg muscles, but also enabled their function to be restored in a controllable manner using optogenetic — light — stimulation.

Until now, most research using optogenetics has focused on brain studies. This study suggests that the technique could be used to encourage the regeneration of lost nerve cells. There is the potential for this therapy to be adapted for use in humans however further research is needed to determine, for example, whether it could be used on a patient without anaesthesia. It would also need to be ascertained how to control the flow of electricity from the cells to the muscle — in the study, repeated activations led to deformed muscle structure.

Project reference number: Not currently available.

Antimicrobial resistance

Research databases and models: Mathematical model of anti-virulence drugs to treat bacterial infections

Dr Sara Jabbari and colleagues at the **University of Birmingham** developed a mathematical model in 2014 to assess under which circumstances anti-virulent drugs would be successful at treating bacterial infections.

It has recently been suggested that a new focus in the battle against antimicrobial resistance[370] should be developing anti-virulence drugs as a second line of defence[371]. This treatment weakens bacteria by reducing their virulence – their ability to invade the host's tissues and cause disease. Anti-virulence drugs would be able to target various mechanisms, such as bacterial adhesion to host cells, toxin delivery or virulence gene regulation, which are all needed for successful infection[372].

This should then allow infections to be cleared through the body's natural defence mechanisms. This is particularly important in preventing resistance from developing as there should be little selective pressure exerted on the organism and therefore a predominantly resistant population would be less likely to emerge. However, many believe that these would not be sufficiently powerful to clear existing infections, restricting their potential application to preventative measures, for example, for use during surgery.

The researchers have developed a mathematical model that provides a theoretical framework to show the circumstances under which anti-virulence drugs may or may not be successful. Using this model they have shown that by combining the advantages of antibiotics with those of anti-virulence drugs, it is possible to identify treatment strategies that would efficiently clear bacterial infections, while preventing the resistant sub-populations from emerging. Their findings therefore strongly support continued research into anti-virulence drugs and demonstrate their use beyond infection prevention.

Dr Jabbari made this model available, pre-publication, on an electronic pre-print repository[373]. This generated interest from other international research groups, with whom she was able to liaise to carry out further tests on the mathematical model prior to publication. The research is now available as an Open Access article[374]. Her group is currently building on this to make the model specific to particular types of anti-virulence drugs using data from her experimental collaborators in the Krachler (University of Birmingham) and Wolf and Huebinger (UT Southwestern Medical Centre at Dallas) groups.

Project reference number: G1002093

Research tools and methods: Device to monitor antibiotic effectiveness

Dr Till Bachmann at the **University of Edinburgh** led a project which worked on a device that aims to monitor, at an early stage, the effectiveness of an antibiotic therapy. The final test will detect bacterial RNA, extracted from bacteria in a whole blood sample using a microfluidic device that can process this solution for analysis. This will test the effectiveness of an antibiotic therapy. The study showed that the microfluidic separation of bacteria from human blood did not widely change the bacteria and expression of the bacterial RNA on a whole genome scale and can thus be used for further development.

Project reference number: MC_PC_12014

Infections and immunity

Research tools and methods: Mice with deleted immune cells

Dr Andrew McKenzie and his team at the **MRC Laboratory of Molecular Biology (LMB)** have produced mice in which the group 2 innate lymphoid cells (ILC2s) can be temporarily deleted. This has enabled the researchers, together with colleagues at the University of Oxford, Trinity College Dublin and the University of Glasgow, to discover a role for ILC2 in activating the adaptive immune system.

ILC2s are part of the innate immune system. The innate immune system is activated on initial contact with a new pathogen and responds in a generic way. Unlike the adaptive immune system it does not confer long-lasting immunological memory to the host. However it does give the adaptive immune system time to launch an effective response, which can take around a week from first exposure[375].

ILC2s offer protective immunity to helminth (parasitic worm) infection. They are also negatively implicated in allergy and asthma. These cells rapidly multiply in response to helminth infection, before the adaptive immune cell response is mobilised.

The group produced a mouse strain in which ILC2s can be depleted temporarily through administering a diphtheria toxin. They showed that ILC2 deletion weakened the adaptive immune response by way of fewer T cells (immune cells) being produced during infection. The researchers also showed that a signalling molecule produced by the T cells increases ILC2 multiplication. This feedback system contributes to the immune systems' mutual maintenance and expansion.

Project reference number: MC_U105178805

Research tools and methods: Cell line to help investigate the regulation of an immune system process

Dr Pierre Guermonprez and colleagues at **King's College London** have developed immortalised mouse cell lines in which the genes thought to play a role in an immune process called cross-presentation have been silenced. Immortalised cells have the artificial ability to divide indefinitely. Together with the knock-out genes, these provide an important tool for studying the functions of these cells.

Cross-presentation is a mechanism whereby the dendritic cells — a specific type of immune cell — ingest and process dead cells carrying external antigens. Antigens are proteins that are recognised by, and activate, other immune cells called T cells.

The researchers have previously identified a structure called a lipid body within the dendritic cells that stores fat and regulates antigen cross-presentation[376]. They have produced cell lines with knock-out genes responsible for autophagy — whereby cells ingest part of themselves to produce energy quickly in cases of stress. Autophagy also takes place in lipid bodies and so the researchers believe that the process might regulate the digestion of dead cells and production of the cell-surface antigen.

They used CRISPR[377], the innovative new gene modification tool, to modify the relevant genes regulating lipid metabolism to silence them.

Mouse models are currently used in genetic studies of dendritic cells as there are currently no other immortalised dendritic cellular models. This technology will therefore provide an efficient and economical model to study key mechanisms in dendritic cells and importantly, reduce the numbers of mouse models required.

Project reference number: MR/K01241X/1

Research databases and models: UK Primary Sjögren's Syndrome Registry (UKPSSR)

Professor Wan-Fai Ng at the **University of Newcastle**, together with colleagues at the Freeman Hospital and University Hospital of Birmingham, established the UK Primary Sjogren's Syndrome Registry (UKPSSR)[378], a national research biobank of people with Primary Sjögren's Syndrome (PSS), in 2011.

PSS is a chronic autoimmune condition affecting up to three per cent of adult in the UK. It most commonly affects people aged 40-60 years, 90 per cent of whom are women[379]. Although the most common symptoms are dry eyes and mouth, joint pain and extreme fatigue, it can affect any part of the body. People with the condition are also 15-20 times more likely to develop non-Hodgkin lymphoma – cancer of the lymphatic system. Many patients also have a poor quality of life and a significant number are unable to work because of their disease. Unfortunately, little is currently known about what causes it and there are no effective treatments.

The researchers identified the need for the database following several developments in PSS research. The UK Sjögren's Interest Group, a national network of healthcare professionals across the UK, developed standardised methods to assess patients with PSS. This has enabled researchers to test and compare specific treatments. Several promising new therapies have been developed in recent years and there have also been advances in research technologies.

The database now includes more than 750 clinically well-characterised patients with associated biobanked samples across 35 centres. It provides a unique and valuable resource for clinical and academic studies as well as identifying patients for clinical trials.

By 2015, the resource had led to the publication of more than 15 peer-reviewed publications. These included research showing that variants of genes involved in both the innate — the initial — and adaptive immune systems greatly increased the risk of developing the condition[380]. Research undertaken using the biobank also showed an association between genes involved in a specific inflammatory pathway — NF-κB — and the condition[381]. The database also enabled researchers to show that patients with PSS are twice as likely as individuals of the same sex and age to experience two key risk factors for heart disease – high blood pressure and hypertriglyceridemia, high blood levels of the fatty molecule triglyceride[382].

The researchers have also identified a microRNA — a short non-coding RNA sequence that regulates gene expression — biomarker for PSS patients with lymphoma to substantially improve the detection of this cancer.

Research using the biobank has also attracted further funding, including £950k from Arthritis UK to conduct a clinical trial into the use of the monoclonal antibody rituximab in PSS, a further MRC grant (£450k) to understand the pathogenesis of fatigue and additional grants from the Sir Jules Thorn Charitable Trust, British Sjögren's Syndrome Association and the National Institute for Health Research (NIHR).

Project reference number: G0800629

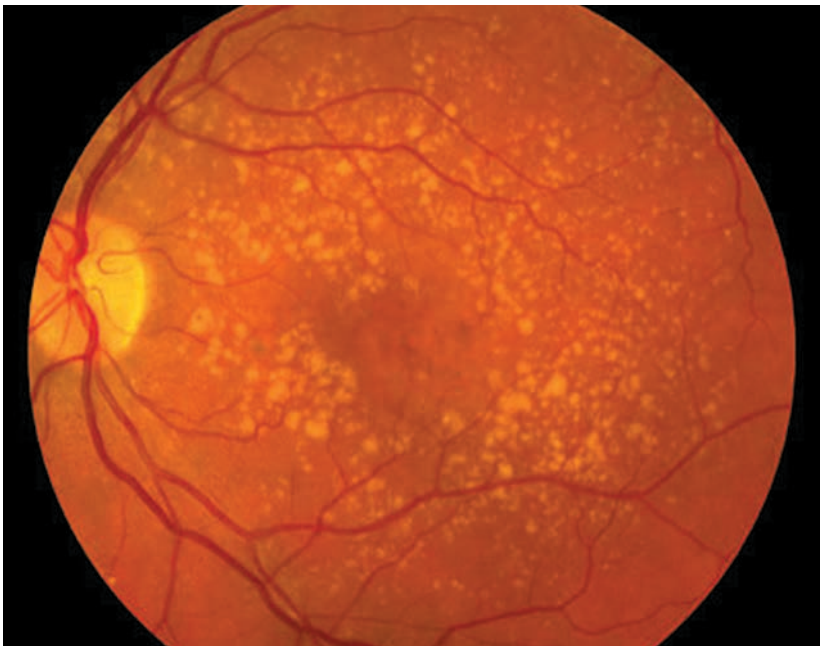
Research tools and methods: Eye tissue repository

In January 2015, **Dr Simon Clark** and colleagues at the **University of Manchester** launched an eye tissue repository as part of the Manchester Eye Bank. The researchers established a work-flow as part of the corneal transplantation service. After the cornea is removed for transplantation, eye tissue that also has consent to be used for research is dissected and its constituent parts stored for future studies. The tissues are categorised according to types of retinal dystrophy — progressive visual function disorders — that may be present, and in particular, whether they have developed age-related macular degeneration (AMD), and the genes sequenced.

It is primarily a resource for the researchers' own work, but they hope in the future to make it a national repository for eye research in the UK.

Dr Clark's research is investigating how two different versions of the same gene may radically alter a person's risk of developing AMD. AMD is an eye condition that affects the macula — a tiny part of the retina at the back of the eyes[383]. AMD causes problems with central vision; it may make the central vision distorted or blurry, and eventually may cause a

blank patch in the centre of vision. It is the leading cause of blindness in people over the age of 60 in the Western world. About 25 per cent of over 60s in the UK have AMD-caused visual loss, a figure that is expected to triple within the next 10-20 years.



Back of the eye showing intermediate age-related macular degeneration.
Image credit: National Eye Institute, National Institutes of Health

Recent research has shown an immune system gene, coding for complement factor H (FH), to be a strong risk factor for AMD. FH is responsible for ensuring that the complement system — the part of the innate immune system that induces inflammation to help the body remove pathogens and fight infection — does not accidentally attack our own tissues and cells. It does this by adhering to these tissues and cells, preventing activation of the complement system. However around 35 per cent of people of European descent have a different version of this gene (402H as opposed to 402Y) which binds less well to a specific region of the macula called the Bruch's membrane. This leaves the macular open to tissue damage and ultimately cell death, resulting in the vision loss.

Dr Clark has however recently made a discovery with important implications for the way researchers approach developing treatments for AMD. He found that there is actually very little FH in the macular; instead it mainly contains a smaller, related protein called factor H-like protein 1 (FHL-1)[384]. FHL-1 comes from the same gene as FH and its structure is identical to the first third of FH, which is where the protein ends. However, the 402H variant occurs early in the FH gene and therefore FHL-1 also has this same difference. Dr Clark also suggests that a group of closely-related genes (called FHR) encode proteins that help regulate the immune system.

To further this research, working with Dr Richard Unwin, also at the University of Manchester, Dr Clark developed a targeted proteomics (protein-analysis) method for identifying FH, FHL-1 and the FHR genes in a biological sample. No previously-developed method has been able to differentiate between all seven factor H type proteins. Dr Clark has used this to demonstrate the presence of FHL-1 and FHR1-3 on Bruch's membrane for the first time. Dr Clark also produced a specific anti-FHL-1 antibody enabling the detection of the protein. This has demonstrated that it is FHL-1 that is responsible for immune system regulation in the macula and not FH as previously assumed. This will change the way that researchers attempt to develop AMD treatments.

Project reference number: MR/K024418/1

Research databases and models: Database of HIV patients

During her MRC-funded PhD[385], **Dr Alicia Thornton** at **University College London (UCL)** used an important MRC-funded national health data resource to shed light on the prognosis of patients co-infected with HIV and hepatitis B and/or C – and how to improve their treatment.

Dr Thornton used the UK Collaborative HIV Cohort (UKCHIC) from 2011-2014 to identify a subset of individuals who are also infected with hepatitis B and/or C, additionally collecting details of their liver disease stage and treatment. This dataset showed that around seven per cent of HIV-positive individuals in the UK are also infected with hepatitis B while around 10 per cent are also infected with hepatitis C[386].

She then used this data to investigate health outcomes for co-infected patients, showing there to be an increased risk of death among co-infected individuals compared to those who have HIV alone. This increase in mortality may be partly reduced when an individual is successfully treated for their hepatitis and when their HIV infection is controlled. The data is being used on an on-going basis to answer further questions posed by clinical collaborators and will be vital in monitoring use and effectiveness of new hepatitis C treatment regimens. In addition, the data has been used in a mathematical model of hepatitis C infection among men who have sex with men (MSM).

The MRC-funded UKCHIC study was set up in 2001 to bring together data relating to the clinical care and treatment of HIV so that researchers could investigate the clinical outcomes, response to treatment and spread of the disease in the UK[387]. The database contains routinely-collected information on HIV-positive individuals aged over 16 years who have attended a collaborating centre[388] for care from 1996. It currently contains more than 45,000 records of patients, providing an important data source to monitor the uptake and response to therapy among individuals with HIV in the UK.

Research using this data has highlighted the importance and success of early diagnosis and treatment with anti-retroviral therapy (ART). The UKCHIC study had previously shown that the life-expectancy of HIV-positive individuals treated with ART improved by nearly 16 years between 1996 and 2008 in the UK but that some groups had a reduced life-expectancy due to late diagnosis and subsequent delayed start to treatment[389]. Research published in 2015 showed that successfully-treated HIV-positive individuals have a normal life expectancy[390]. It also showed that patients with a low white blood cell count before or after starting ART were at an increased risk of death, but if patients' white blood cells responded well to treatment, they would still significantly improve their life expectancy.

In addition to co-infection with hepatitis B and C, another of the database's research themes is HIV and pregnancy. There are an increasing number of HIV-infected women in the UK and pregnancies in HIV-infected women. This is predominantly due to increased survival rates in women receiving treatment and earlier HIV diagnosis resulting from the introduction of antenatal HIV screening in the UK. In 2015 UKCHIC researchers demonstrated that pregnancy is associated with increased liver enzyme levels in women on antiretroviral therapy (ART), reinforcing the need to regularly monitor liver biomarkers during pregnancy[391].

Project reference number: Not currently available.

Metabolic disease

Research tools and methods: Mouse model with gene mutation affecting metabolism

Professor Houman Ashrafian at the **University of Oxford** has generated a mouse model with a gain-of-function mutation in a gene that has been found to play a role in metabolic function. This model can be used to investigate potential treatments for obesity and diabetes – both by the Oxford team and researchers elsewhere.

As with much of the rest of the world, the rates of obesity and type 2 diabetes are rapidly increasing in the UK. Obesity is one of the greatest threats to health today. Figures released by Public Health England in January 2014 showed that 64 per cent of adults are now overweight or obese[392], with a body mass index (BMI) of more than 25 and 30, respectively. The number of adults classed as obese has increased by 60 per cent in the last two decades (from 15 per cent in 1993 to 25 per cent in 2014). The number of people diagnosed in the UK with diabetes has increased from 1.4 million in 1996 to 3.9 million today, an estimated 90 per cent of whom have type 2[393]. Obesity and diabetes often cause complications such as heart disease, high blood pressure, stroke, cancer, visual impairment and joint disease.

Health problems associated with being overweight or obese cost the NHS around £5 billion every year, compared to £3 billion each for smoking and alcohol-associated health problems[394].

In addition to the impact on the NHS, they are associated with disability, loss of earnings and reduction in life expectancy (by an estimated nine years).

Overweight man holding a measuring tape. *Image credit: Shutterstock*

Both obesity and type 2 diabetes are chronic metabolic diseases reflecting a complex interaction between an individual's genetics, behaviour and environment (for example, food intake and physical activity).

Typical weight-loss strategies include diet and exercise, but for many people these can be difficult to implement and adhere to. Weight-loss surgery may be an option for some, however it is expensive and only offered to a small proportion of those affected – around 6,000 procedures are performed each year in the UK[395]. While some drug treatments are available, their long-term effectiveness and safety are unclear. Accordingly, there is a major unmet need for new drug therapies to be identified.

It has recently been determined that major classes of diabetes drugs, such as metformin, indirectly act on the protein AMP-activated protein kinase (AMPK) leading to various metabolic effects[396]. This is believed to play a role in some of the drugs' benefits. There has therefore been much interest in the possibility that direct activators of AMPK may provide an effective treatment for obesity and diabetes.

As a result, it is important to better understand how AMPK regulates the body's energy balance, particularly relating to appetite regulation by the brain. Professor Ashrafian and colleagues have developed a 'gain-of-function' mouse model by using gene-targeting to induce an activating genetic alteration in gamma2, a subunit of the AMPK gene. The researchers have shown that whole-body AMPK activation via this subunit exerts complex effects in multiple key metabolic organs such as the brain and pancreas. The researchers are using this model in a long-term benefit analysis of whole body AMPK activation, essential to the design of effective drug treatments for metabolic disease based on the AMPK system.

Project reference number: MR/K019023/1

Neurodegeneration and cognition

Research tools and methods: MRI protocol to investigate brain health

Professor Klaus Ebmeier at the **University of Oxford** put together a magnetic resonance imaging (MRI) protocol for the Whitehall II study in 2012 allowing him to collect information about brain shrinkage, white matter integrity, blood flow and brain networks. He has related this information to detailed health outcomes and neuropsychological tests[397].

Combining long-term information from 800 people collected through the Whitehall II study with the MRI data will enable him and colleagues to examine the connection between risk and protective factors and brain changes. The Whitehall II study is the second part of the Whitehall cohorts, established at University College London (UCL) in 1985 to examine the links between social circumstances and health. By September 2011 the study of more than 10,000 civil servants had accumulated 25 years of social, behavioural and biological data, making it a unique study of ageing. Of the original group, more than 6,000 continued on to Phase II, which has concentrated on life course factors affecting health and personal functioning in later life.

During the 20th Century, the average life expectancy for people in the developed world increased dramatically, from around 50 to more than 75 years of age. This was due to various factors, including improvements in public health, nutrition and medicine. An MRC-funded study published in 2015 predicted the average life expectancy for male babies born in 2030 to be 85.7 years and for females 87.6 years[398]. In comparison, the average life-expectancy for male babies born in 2012 is 79.5 years and females 83.3 years.

However, the risk of developing certain diseases rises exponentially as a person ages, putting increased pressure on medical and social care costs and resources. For example, dementia affects one in 20 people over 65 and one in six people over 80. The proportion of people with dementia doubles for every five-year age group[399]. And according to some estimates, the number of people with neurodegenerative diseases will quadruple in the next 20 years[400].

A better understanding of the mechanisms of neurodegenerative diseases and the factors associated with protection against age-related dysfunction is essential in developing the means for prevention and treatment.

***Whitehall**. Image credit: George Evans, CC BY-SA 2.0 http://creativecommons.org/licenses/by-sa/2.0, via Wikimedia Commons*

The MRI examination consists of various advanced MRI techniques that can assess the volume of grey and white matter from different brain structures. Reduced grey matter — structural tissue that processes information — and white matter — containing nerve fibres that transmit signals from one area of the brain to another — have been associated with future disease and age-related cognitive dysfunction. It also includes Diffusion Tensor MRI, which measures the degree to which the random motion of water molecules is restricted in the brain's white matter in the direction of the nerve fibres. This reflects the quality of white matter fibre connections. It further includes a technique called BOLD fMRI that acquires brain activity images over 10 minutes. This enables the reconstruction of functional brain networks that are active in unison, even 'at rest'. Finally, various MRI sequences (such as FLAIR and T2*) are able to detect abnormal tissue in the brain and 'microbleeds'.

The Whitehall imaging protocol and data have been used to refine studies developed within the Oxford Functional MRI of the Brain (FMRIB) Analysis Group, for example, UK Biobank[401] and the Connectome project, a five-year effort to characterise brain connectivity and function and their variability in healthy adults[402].

Project reference number: MR/J004022/1

Research tools and methods: Brain and spinal cord tissue

Dr Olaf Ansorge at the **University of Oxford** helped set up the UK MRC Control Brain Bank in 2011, as part of the Thomas Willis Brain Collection[403].

Largely because of increasing life expectancies, the number of people with brain diseases such as dementia and Parkinson's disease, which are largely untreatable, is steadily increasing. There have been substantial advances in genetics and disease modelling in the laboratory. However it is increasingly recognised that further breakthroughs require direct study of the human brain. In particular, it is important to understand how the expression of new risk genes for disease is regulated in parts of the normal brain compared to the diseased brain. However, brain donations from healthy individuals have been in short supply compared to donations from those with specific neurodegenerative diseases. While patients with these diseases are encouraged to donate their brain tissue after death, this is not the case for healthy individuals. Although, when approached sensitively, next-of-kin are often willing to help with tissue donation following a relative's death.

The UK MRC Control Brain Bank therefore integrates patient services for bereavement and transplant coordination to increase donations of healthy brains and those from individuals with rare neuropsychiatric diseases. This approach has resulted in around 20 extra brain donations each year. Brain and spinal cord tissue held in the brain bank is made available to national and international researchers via the MRC's UK Brain Banking network under strict guidelines for use and disposal. The tissue is being used in various projects by academic and industry partners. Controls alone have contributed to more than 45 research projects to date and the Oxford Brain Bank has been cited as a tissue provider in 71 peer-reviewed scientific articles since 2012[404].

Dr Ansorge also introduced to the MRC Brain Bank network, in 2013, a method to systematically and rapidly freeze anatomically-preserved brain tissue slices using a liquid nitrogen vapour vessel. This modifies a protocol originally developed at the New York brain bank. Analysis showed that the microscopic anatomy and genetic material were better preserved using this technique and no ice crystals were formed. This method greatly improves analysis of individual cell types in the brain, helping to obtain a better understanding of why certain cells may be vulnerable or resistant to disease. This method has been adopted by several other brain bank centres, including the Edinburgh Brain Bank and four centres of Autism Brain Net in the USA, who are developing a partnership with the Oxford bank.

Research tools and methods: *Drosophila* model of neurodegeneration

Dr Adrian Isaacs at **UCL Institute of Neurology** and colleagues at the **MRC Prion Unit** have produced a *Drosophila* model of neurodegeneration caused by a mutation in the *C9orf72* gene.

The *C9orf72* gene encodes C9ORF72, a protein that was recently found to regulate essential processes involved in the transport and breakdown of cellular components in nerve cells[405]. In 2011 a mutation in the *C9orf72* gene was found to be the major cause of frontotemporal dementia (FTD), the second most common form of early-onset dementia after Alzheimer's disease, and amyotrophic lateral sclerosis (ALS), a degradation of motor nerves that eventually causes respiratory failure and death an average three years after onset[406,407]. This gene mutation inserts a repeating six-letter string of nucleotides GGGGCC into the DNA sequence. In most people without this mutation there are up to 30 repeats of this nucleotide sequence but in people with the mutation the sequence is repeated many more times. Further investigation into the mutation had been hampered by the large size of the expansion, making it impossible to make the thousands of DNA copies needed to study the gene. Dr Isaacs' colleague at the Prion Unit, Dr Simon Mead, developed a reliable Southern blot method of approximating the *C9orf72* expansion size to help investigate, for example, the number of repeats needed to cause disease and the feasibility and accuracy of diagnostic testing[408].

Dr Isaacs and his team, in collaboration with Professor Linda Partridge at UCL Institute of Healthy Ageing and Max Planck Institute for the Biology of Ageing, have now developed a *Drosophila* model with the gene mutation to understand how it causes disease. The researchers used the model to show in 2014 that toxic dipeptide repeat (DPR) proteins generated by the expanded *C9orf72* gene sequence were the major cause of the disease[409]. However, they also demonstrated that aggregates of RNA, caused by the repeated sequence, are most abundant in the frontal cortex of the brain[410], which has the greatest amount of nerve cell loss. This therefore raises the possibility that different disease presentations could be caused by the different contributions of RNA or DPR protein toxicity.

The researchers have supplied research groups from around the world with the *Drosophila* models; for example, to Professor Jeff Rothstein at John Hopkins University in Baltimore[411], Professor Fen-Biao Gao at the University of Massachusetts Medical School[412] and Professor Nancy Bonini at the University of Pennsylvania.

Project reference number: MR/J004022/1

Mental health

Research databases and models: The Twins Early Development Study (TEDS) dataset

Professor Robert Plomin and colleagues at **King's College London** set up the MRC-funded Twins Early Development Study (TEDS) in 1994. TEDS, the largest and one of the foremost studies of its kind in the world, has gathered information from more than 15,000 pairs of twins to provide insight into how both nature — the genetic material we inherit from our parents — and nurture — our environment — contribute to individual differences in areas such as cognition, learning abilities and behaviour. More than 5,000 pairs of twins have provided DNA samples which are used together with the rest of the data to gain a greater understanding of how genes influence our abilities and behaviours. The aim is for this research to help us better understand the complexities of child and adolescent development.

The researchers have developed a user-friendly database of this information which is being used by more than 100 collaborators, including researchers across the UK, United States, Australia, Singapore, France, Germany, Austria, Sweden, Finland, the Netherlands and Hungary.

TEDS twins on A-level results day.
Image credit: Twins Early Development Study, King's College London

Researchers, using this data, showed in 2015 that autism spectrum disorder and milder autistic traits are both caused largely by genetic factors[413]. The study included twins who had not yet been diagnosed but had high levels of autism traits, and low-risk twins as well as those with diagnosed autism spectrum disorder. This contrasts with most previous evidence, which has focused on those with a confirmed diagnosis. The study found that associations between identical twins) were higher than in non-identical twins, resulting in heritability estimates of 56-95 per cent. The study found very little evidence for shared environmental effects.

In 2014, researchers used this data to show that although intelligence makes a major contribution to the heritability of educational achievement, other broad areas of behaviour, such as personality and mental health, also account for genetic influence on GCSE scores[414]. Together with intelligence, these areas account for 75 per cent of the heritability of GCSE scores. These results highlight the importance of genetics in educational achievement; they also support the trend in education towards personalised learning.

Researchers also used this data in 2014 to show how pictures of children drawn by four-year-olds predicted their level of intelligence at the age of 14. By analysing the similarity of pictures drawn by identical and non-identical twins, they

were able to deduce that differences in children's drawing was influenced by genes[415]. They also found that drawing at age four and intelligence at age 14 had a strong genetic link.

Professor Plomin was ranked among the 100 most eminent psychologists in the history of science in a paper published in *The Review of General Psychology* in 2002[416].

Project reference number: G19/2

Global health

Research tools and methods: Detecting asymptomatic malaria infections

Researchers at the **MRC Unit, The Gambia** have developed a sensitive method to detect asymptomatic malaria infections, which will help to increase the success of malaria elimination efforts.

Malaria is a life-threatening disease caused by the parasite *Plasmodium* and transmitted to people through the bites of infected mosquitos[417]. It is widespread in many tropical parts of the world, predominantly in Africa, Asia and South America. It caused around 500,000 deaths in 2013, mostly in African children.

Control programmes aimed at decreasing local transmission require *Plasmodium* parasites to be effectively detected in both symptomatic patients and asymptomatic carriers[418]. Asymptomatic carriers generally have much lower parasite levels compared to symptomatic patients, below which, the standard diagnostic tests such as microscopy become less reliable[419]. It is important to identify as many malaria-infected carriers as possible so that they can be treated and transmission interrupted. The ideal diagnostic test to support malaria elimination programmes should therefore have high sensitivity to detect most, if not all, infected individuals.

Molecular methods such as polymerase chain reaction[420] (PCR) — molecular 'photocopying' — reliably detect low-grade and asymptomatic infections. However, it is difficult to use PCR in field settings because of the equipment and infrastructure that are needed[421].

During her PhD, **Dr Cheryl Eniyou Oriero**, under the supervision of **Dr Davis Nwakanma** and **Professor Umberto D'Alessandro**, developed a loop-mediated isothermal amplification (LAMP) technique that targets the genome of an organelle in *Plasmodium falciparum* called the apicoplast[422]. LAMP is a technique that amplifies the DNA and is carried at a constant temperature. It therefore reduces the amount of equipment needed compared to traditional methods.

The group has shown that the LAMP test can produce reliable results the same day as screening[423]. It is able to detect a higher proportion of low-density malaria infections than other methods and may be used for systematic screening and treatment in the field. The apicoplast genome it targets is unique to the parasite which ensures high specificity.

Project reference number: MC_UP_A900_1117

Research tools and methods: Rabbit model of cryptococcal meningitis

Professor William Hope and colleagues at the **University of Liverpool** have produced a rabbit model of cryptococcal meningitis which he used to help demonstrate in 2014 that a reduced duration of treatment for the disease was just as effective as the current recommended dose[424].

Cryptococcal meningitis is a serious fungal infection of the covering the brain and spinal cord with a death rate of 60-70 per cent and which can also cause brain damage, hearing loss and seizures[425]. It affects around one million people in the world each year and recent estimates suggest that it kills more people in sub-Saharan Africa each year than tuberculosis. It most commonly occurs in individuals with an impaired immune system, predominantly as a result of AIDS.

Unfortunately there are relatively few active anti-fungal drugs and each has significant limitations. The best clinical outcomes result from early rapid killing of the fungus in the brain. This is usually achieved in the UK with a two-week course of intravenous antifungal therapy amphotericin B deoxycholate (dAmB). However it is not possible to administer intravenous drugs for any length of time in the developing world. As a result, the best therapy is not given and clinical outcomes are not satisfactory.

Professor Hope developed a rabbit model of the disease, which he has used alongside mouse models and bridged to humans by using mathematical modelling techniques, to show that the effect of three days of therapy was the same as that of daily therapy for 14 days.

Using the rabbit model, Professor Hope was able to show that the cerebrospinal (CSF) fluid, a fluid found in the brain and spine, and part of the brain called the cerebral parenchyma, respond differently to dAmB. A shorter course of dAmB results in prompt fungicidal activity in the CSF but not in the parenchyma. Results of clinical trials however show that it is the rate of decline of the fungus in the CSF that is associated with overall survival[426].

While it is possible that a portion of morbidity and mortality is related to sub optimally-treated parenchymal disease, results of clinical trials suggest that the rate of decline of yeast in the CSF is an important prognostic marker and is associated with overall survival.

The researchers are now aiming to begin a clinical trial of a short course of amphotericin B in sub-Saharan Africa[427].

Project reference number: G1001760

Gene sequencing and genetic engineering

Research tools and methods: Tools to detect genome-wide DNA damage and repair

Professor Simon Reed and colleagues at the **University of Cardiff** have developed a new method to analyse genome-wide DNA damage and repair.

DNA damage, such as physical or chemical damage from the environment, including ultraviolet (UV) radiation from sunlight, occurs on a regular basis. Each of our cells experiences around 10,000 DNA-damaging events each day[428]. If unrepaired, the majority of this damage would lead to rapid erosion of the genetic information as replication of damaged DNA during normal cell division can permanently alter — or mutate — the genetic code. DNA damage is widely associated with the development of many diseases, including cancers, neurodegeneration and heart disease[429].

We however possess various DNA-repair pathways which, together, are fundamental to DNA stability. People who inherit defects in the genes controlling the DNA-repair pathways are more likely to develop certain cancers and other diseases.

The aim of Professor Reed's research is to better understand how one of these repair pathways, nucleotide excision repair (NER), operates. To do this, he has developed a new method to rapidly screen entire genomes for DNA damage and to measure their repair[430]. There are currently technologies available to examine DNA damage and repair; however these can only examine DNA damage and repair in selected genes[431]. Professor Reed's technique uses microarrays to monitor UV-induced DNA damage and its repair. It is able to examine repair events throughout genomes at a high resolution to identify variations in repair rate and whether changes in chromatin structure (consisting of DNA, proteins and RNA) aid the repair.

The technique, patented in 2008[432], may also be used to monitor the targets of anti-cancer chemotherapies that act through damaging DNA, or to test potential therapies for their genotoxicity.

The researchers published two papers in 2015; the first describes the latest version of the 3D-DIP-ChIP method for detecting genetic lesions in human cells, including those induced by chemotherapeutic drugs cisplatin and oxaliplatin[433]. The second reports the bioinformatics software they developed for analysing the genomic datasets generated[434].

As a result of this research, Professor Reed has embarked on a collaboration with Agilent Technologies[435], a US-based research and development company. He has been awarded a £250k Knowledge Transfer Partnership award from Innovate UK to develop this method for genotoxicity testing, two BBSRC CASE studentships with GlaxoSmithKline (GSK) and, more recently, with AstraZeneca. He has also been awarded £1.5 million in a Cancer Genetics BRU award from the National Institute for Social Care and Health Research (NISCHR)[436]. This has recently been expanded with the award of £4.5 million from the Welsh Government to form the Wales Cancer Research Centre, which was officially launched in October 2015[437].

Project reference number: MR/K000926/1

Research databases and models: International Mouse Phenotyping Consortium (IMPC)

Researchers at the **Mammalian Genetics Unit** at **MRC Harwell** helped establish the International Mouse Phenotyping Consortium (IMPC)[438,439] in 2011. The IMPC is a worldwide network of research institutions with the ability to generate targeted knock-out mutations for the 20,000 known and predicted mouse genes to determine their function. This builds upon the International Knock-out Mouse Consortium (IKMC), set up after the mouse genome was sequenced in 2002[440]. The mouse is a particularly important research model for various reasons. Its genetics are fundamentally very similar to that of humans (>95 per cent at the gene level), it has similar physiology and anatomy, it is relatively low-cost compared to other mammals and benefits from nearly 100 years of genetic study.

Its mice are preserved in repositories and made available to the scientific community representing a valuable resource for basic scientific research as well as generating new models for human diseases.

Dr Ann-Marie Mallon and colleagues have developed computational tools and analytical techniques to characterise the phenotypes, or biological traits, of mice that have had single genes disabled. MRC Harwell is the IMPC data coordination centre and so she uses these techniques to integrate, analyse and compare the large datasets deposited. All data is collected, annotated, validated and quality-controlled before it undergoes rigorous statistical analysis[441,442]. This needs substantial standardisation and the researchers have refined a set of standard operating procedures (SOPs)[443] that are used for all IMPC phenotyping tests at all centres.

IMPC data has been substantially used in research. It has recently been used by Japanese researchers to suggest that a deficiency in a membrane protein associated with the tight junction – a barrier between epithelial cells - causes the degenerative loss of hair cells in the cochlea - the part of the ear responsible for hearing – leading to a type of human deafness[444]. It was also used by researchers in the US to show that TREM2 deficiency eliminates certain macrophages – a type of white blood cell – in the brain which reduces inflammation and the accumulation of amyloid and tau accumulations, strongly believed to play a role in Alzheimer's disease[445]. A global research team, partially-funded by the MRC, discovered in 2012 that a rare variant of the TREM2 gene greatly increased the risk of developing Alzheimer's disease, but until now the reason was unknown[446]. Further examples of where IMPC data has been used in important scientific discoveries are on the IMPC website[447].

Project reference number: MC_U142684171

Economic evaluation of healthcare

Research tools and methods: Simulation model for prostate cancer

Whilst at **Brunel University, Professor Joanne Lord**[448] led a project in 2012 on the use of simulation modelling in NICE Clinical Guidelines. As part of this project, Sarah Willis[449], Dr Paul Tappenden[450] and Dr Alex Miners[451] developed a model that reflects the treatment pathway for patients with prostate cancer, as recommended by NICE. The model simulates the tests and treatments patients would receive to estimate the associated costs and health outcomes in terms of quality-adjusted life years (QALYs).

Clinical guidelines are drawn up by a Guideline Development Group (GDG) after considering the benefits, harms and costs of various diagnostic and treatment options. As they are usually very broad and cover large complex care pathways for different groups of patients, the approach to assessing clinical and economic evidence is selective. Evidence about cost-effectiveness is usually drawn from literature or original evaluations conducted by guideline economists and specific topics for economic analysis are prioritised. However there are potential risks with this process, for example, cost-effectiveness estimates might not be available for some topics and economic analysis methods might be inconsistent at different points in the pathway.

A full pathway model is an alternative approach to economic evaluation. Although it requires an initially large time and resource investment, once developed, it should enable many cost-effectiveness questions to be answered and be sufficiently flexible to address unanticipated questions that might arise during or after guideline development.

Professor Lord and colleagues have therefore established the Modelling Algorithm Pathways in Guidelines (MAPGuide) project to test the feasibility and usefulness of full pathway modelling in NICE clinical guidelines.

The researchers developed an economic model for the prostate cancer treatment pathway as part of this project. Using this model, they showed that brachytherapy — a form of radiotherapy whereby the radioactive sources are placed in or near the tumour itself — was more cost-effective and resulted in a higher QALY gain than other types of therapy.

Based on this cost-effectiveness evidence and associated clinical evidence, NICE included a new recommendation in its 2014 updated clinical guidelines to consider using brachytherapy combined with external beam radiotherapy for men with intermediate and high-risk localised prostate cancer[452].

Project reference number: G0901504

Drug development

Research tools and methods: Platform to predict effective drug combinations

Professor Manfred Auer at the **University of Edinburgh** developed in 2014 a platform which uses publicly-available structure and function information on small molecules together with disease pathway maps to predict effective drug combinations.

His team is currently testing the resulting drug, development and experimental compound combinations in various cancer cell lines. They have already identified Intellectual Property-free combinations producing strong synergistic effects. He is currently pursuing commercialisation opportunities.

Project reference number: MC_G0802522

Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

End Notes

351. http://www.researchinfonet.org/research-data/open-research-data-forum/
352. http://www.rcuk.ac.uk/research/opendata/
353. https://www.datacite.org/
354. See the case study *First software for analysing Oxford Nanopore Technologies sequencing data* on pages 29-30 of the *Development of products and intellectual property* chapter of the *Outputs, outcomes and impact of MRC research 2014/15 report* or at https://www.mrc.ac.uk/news/browse/software-and-technical-products-first-software-for-analysing-oxford-nanopore-technologies-sequencing-data/
355. See the case study on MRC researchers using whole genome sequencing to target antimicrobial resistance: https://www.mrc.ac.uk/documents/pdf/whole-genome-sequencing/
356. For more information and case studies on collaborations formed by MRC researchers, please see the *Industry interactions and other collaborations* chapter of the *Outputs, outcomes and impact of MRC research 2014/15 report*. http://www.mrc.ac.uk/successes/outputs-report/industry-interactions-and-other-collaborations/
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361. researchfish® is the online system used by the MRC and many other funders in the UK and worldwide to collect information on research outputs, outcomes and impact. For more information, please see http://www.mrc.ac.uk/funding/guidance-for-mrc-award-holders/researchfish/
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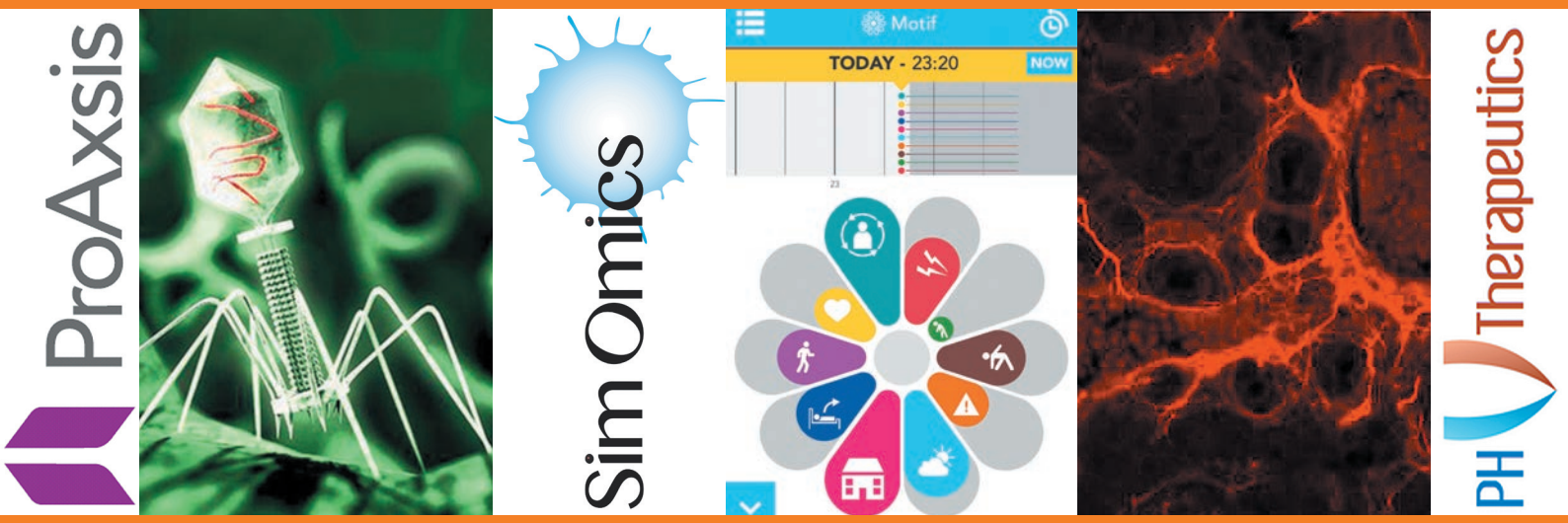
MRC Medical Research Council

Outputs, outcomes and impact of MRC research

2014/15 report



SECTION 2.5
Industry interactions and other collaborations

Industry interactions and other collaborations

In this section we summarise feedback collected in researchfish® about researcher interactions with industry and reports of wider collaboration. We also include information about the way that researchers develop their research programmes by obtaining further funding and commercialising their ideas via spin out companies.

Research collaboration

Research collaborations might take the form of joint funding, exchanging expertise, staff and facilities, accessing datasets (for example when conducting meta-analyses[454]) or simply bringing together the critical mass required to tackle complex multidisciplinary problems[455]. Collaboration as measured by co-authorship, particularly international co-authorship, has been shown to increase citation impact[456].

Feedback from researchers via researchfish® shows that collaborations are frequently global, cross-sector and interdisciplinary, and are essential to maximise translational impact from research. Interactions with industry are a particular interest, recognising the important role that commercial partners have in developing new products and processes based on the knowledge from publicly-funded discovery science.

The MRC would like to understand better how successful interactions are started, and how these collaborations flourish. researchfish® data is providing evidence of the extent of collaboration across the MRC portfolio which is complementary to details obtained from applications for funding (which include the proposed collaborator at the time of application) and bibliographic details (which identify the co-authors of papers arising at various stages throughout the project or programme).

During a period of constrained public finances it is even more important for researchers to pool resources and expertise to enable access to wide-ranging facilities and equipment[457].

Further funding

In addition to establishing and maintaining collaborations, researchers obtain funding to continue or expand on their work. This *further funding* may be competitively won, at least in part, because of MRC support. Success in obtaining further funding may indicate that the research group has established a high quality track record and is therefore able to present attractive proposals for future research.

Spin out companies

University and other research organisations may also advance the work of MRC research groups by creating and developing spin out companies. Forming spin out companies is one route to commercialising discoveries, through developing new product and processes, but also has positive economic impact through employment and direct investment into the UK.

Further information on all of the MRC's spin out companies, including formation date and number of employees, is available on the MRC's website[458].

This chapter comprises examples of where MRC-supported researchers have formed spin out companies and beneficial relationships with other organisations through collaborations and generating further funding. The information in this chapter has largely been sourced from researchfish®[459]. Quantitative information on numbers, locations and quantities of collaborations, further funding and spin out companies is available in the *Quantitative analysis* section of this report.

The examples in this chapter are categorised by the following research areas:

- Chronic respiratory disorders
- Regenerative medicine
- Antimicrobial resistance
- Neurodegeneration and cognition
- Inflammation and immunity
- Stratified medicine
- Liver disease
- Cardiovascular disease
- Rare diseases
- Global health
- Research ethics and integrity

Each case study focuses on a predominant output type, but others might be referenced within it. The accompanying icons represent the relevant output types. A key to the list of output types is at the end of this chapter.

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — the *Gateway to Research*[460] — by entering the full project reference number listed under each case study in the search field.

Chronic respiratory disorders

Spin out: ProAxsis Ltd

Research conducted by **Dr Lorraine Martin** and **Professor Brian Walker** in the **School of Pharmacy, Queen's University, Belfast (QUB)** helped in 2013 to establish ProAxsis Ltd[461], a company developing tests that will enable patients to monitor their diseases at home.

Supported by an MRC Confidence in Concept award, ProAxsis is developing unique molecules called ProteaseTags™ which can selectively detect and bind to proteases, including those which are disease biomarkers — substances that indicate a disease state or severity. Proteases are enzymes that break down proteins, and if unregulated, their activity can trigger or exacerbate diseases including cancer, Alzheimer's disease and chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis.

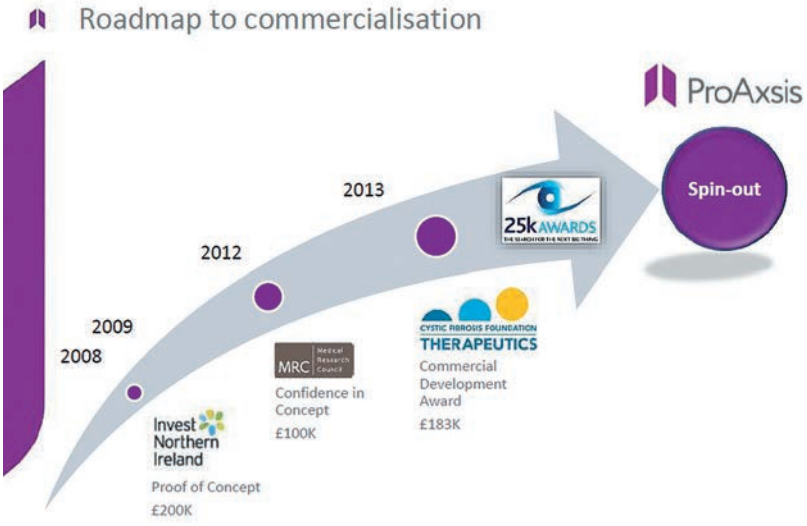
ProAxsis has incorporated its patented ProteaseTags™ technology into easy-to-use home tests that will enable patients with chronic diseases to monitor their conditions within the home. The company has initially focused on producing a point-of-care test for COPD and cystic fibrosis. Point-of-care tests are those done in the vicinity of the patient, without the need to send the sample to a laboratory for analysis. The result, NEATstik™, will enable patients to measure neutrophil elastase activity, known to correlate with COPD and cystic fibrosis severity and which is an early marker of disease worsening. The aim is to prompt early treatment at home, reducing the need for hospital admission and more invasive, expensive treatment.

ProAxsis received £183,000 in additional funding from US-based charity the Cystic Fibrosis Foundation[462].

> ***"Things started to move very quickly when we got an MRC Confidence in Concept award as this then helped us to secure financial support from the Cystic Fibrosis Foundation (CFF) in the US. That's been a fantastic endorsement for us."***
>
> ***– Dr Martin , CEO and ProAxsis co-founder***

"Things started to move very quickly when we got a Medical Research Council Confidence in Concept award as this then helped us to secure financial support from the Cystic Fibrosis Foundation (CFF) in the US. That's been a fantastic endorsement for us", says Dr Martin (CEO and ProAxsis co-founder).

In September 2014 the company won a €50k Instrument award from the first round of EU Horizon 2020 funding for small businesses, the first company in Northern Ireland to do so. This will fund a Phase 1 feasibility study of NEATstik™[463].



Pathway leading to company formation. *Image credit: Dr Lorraine Martin*

Point-of-care devices, which also include home glucose, cholesterol and pregnancy tests, are a rapidly growing market and expected to be worth around $27.5 billion by 2018[464]. Dr Martin believes the potential market for ProAxsis' tests could be up to $6bn.

Dr Martin has been supported throughout by the Commercial Development team at QUB, which has included being awarded a Research Enterprise Fellowship. The company is supported by medical technology investment company NetScientific and QUB's own technology transfer office, Qubis[466]. The company plans to create up to eight new jobs over the next few years.

Project reference number: MC_PC_12021

Spin out: Synairgen plc

2014 was an exciting year for Synairgen plc[467], the **University of Southampton** spin out set up by MRC-funded researchers. Its Phase II clinical data, showing that 'difficult-to-treat' asthmatics — those who respond poorly to steroid treatment — benefited from treatment with its novel drug SNG001 (inhaled interferon beta), were published[468]. This treatment has "the potential to be one of the biggest breakthroughs in asthma treatments in the past 20 years"[469]. It also licensed the treatment to global biopharmaceutical company AstraZeneca[470] in a multi-million pound deal that will see the further development of the drug. AstraZeneca aims to bring SNG001 to market at the earliest opportunity.

> ***"This is a perfect example of how the follow-on relationships between taxpayer-funded research, universities, investment groups, SMEs and large pharma can work for the benefit of the taxpayer."***
>
> ***– Richard Marsden, CEO of Synairgen***

Synairgen was founded in 2003 by world-renowned asthma specialists **Professors Donna Davies**, **Ratko Djukanovic** and **Stephen Holgate** at the University of Southampton. Professor Holgate received an MRC Clinical Professorship in 1987 to investigate the causes of asthma, which led to his discovery that cold and other viral infections worsened asthma attacks — or exacerbations. Further work showed that in patients with asthma, the cells lining the lungs — the epithelium — are unable to destroy the virus as they would normally because they cannot make sufficient levels of the anti-viral protein, interferon beta. Tests in virus-infected cells showed that this ability could be restored by adding interferon beta back into the cells.

"The MRC's investment in me as far back as 1987 started a long-term investment in asthma-related research in Southampton. This investment has now delivered a potential drug for asthma and COPD airway attacks that targets the cause of why such patients are so susceptible to virus infection. Without this initial confidence shown in me by the MRC, none of this would have occurred," said Professor Holgate[471].

The researchers, via Synairgen, patented this discovery in 2004 with the help of investment company IP Group[472].

"Synairgen was vital in protecting this discovery — without the company; we may not have patented it, meaning that it wouldn't have progressed," adds Richard Marsden, CEO of Synairgen.

In 2012 the researchers published the first clinical trial results of inhaled interferon beta in asthma patients. They gave interferon beta to patients at the first sign of a cold, which appeared to protect them from viral exacerbations, particularly those with severe asthma.

"This is an area of vast unmet need. Globally, around 250,000 people die each year as a result of asthma[473] (more than 1,000 people in Britain[474]). And the 10-20 per cent of the population with 'difficult-to-treat' asthma accounts for around 80 per cent of UK asthma-related health expenditure[475]," said Richard.

In 2014 the results of Synairgen's Phase II trial[476], which showed that after administration with inhaled interferon beta, patients with more 'difficult-to-treat' asthma experienced a 50 per cent reduction in moderate or severe exacerbations, were published.

The same year, the company signed an exclusive licence agreement with AstraZeneca for the use of inhaled interferon beta for the treatment of respiratory tract viral infections (developed as drug SNG001). This saw a $7.25 million upfront payment and potential development and commercial milestones of up to $225 million as well as royalties on future sales. This deal again highlighted the importance of university spin-out companies.

"It is unlikely that big pharma would do a deal of this magnitude directly with a university. It required a company such as Synairgen to apply specialist expertise in putting together an overall package to license the drug to one of the major franchise holders in the global respiratory sector," said Richard.

AstraZeneca will begin further Phase II work in 2015 with the aim of bringing the drug to market at the earliest opportunity. The drug also has the potential to work in a similar way in patients with chronic obstructive pulmonary disease (COPD).

"This is a perfect example of how the follow-on relationships between taxpayer-funded research, universities, investment groups, SMEs and large pharma can work for the benefit of the taxpayer," said Richard.

So what's next for Synairgen?

The company is assessing new respiratory-based opportunities which could be clinic-ready by 2016. It has developed advanced cell models and has built up a biobank containing clinical samples of blood, sputum, lung cells and tissue samples in a selection of well-characterised asthma and COPD patient volunteers as well as of healthy control subjects. It will use these to further analyse the complex interactions between disease and triggers of disease within lung tissue to validate and progress new drugs ready for exploring further collaborations with large pharmaceutical companies.

Project reference number: G0900453

Regenerative medicine

Collaborations: NeuroStemCell

Professors Austin Smith and **Roger Barker** at the **University of Cambridge** and **Stephen Dunnett** at **Cardiff University** were part of the NeuroStemCell[477] collaboration, a world-leading consortium aiming to take stem cell-based therapies for Parkinson's Disease (PD) and Huntington's Disease (HD) into the clinic. The collaboration, funded by the European Community's Seventh Framework Programme between 2008 and 2013, brought together 13 academic partners and three SMEs from six European countries with the diverse expertise needed to reach this goal.

PD and HD are both progressive diseases characterised by the death of specific nerve cells in the brain and subsequent loss of cognitive and motor functions. PD affects around one in 500 people in the UK and HD about 12 in 100,000. There is currently no cure for either disease. PD and HD are however ideal candidates for restorative stem cell-based therapies. Stem cells — cells that can differentiate into specialised cells — offer a promising way to replace the lost mesencephalic dopamine (mesDA) nerve cells in PD and GABAergic medium-sized spiny nerve cells in HD. To further develop this approach, alternative sources of therapeutically-effective cells derived from stem cells are needed.

In 2014 the consortium published research demonstrating the production of dopamine nerve cells from embryonic stem cells[478]. The researchers transplanted the nerve cells produced in the laboratory into mouse and rat models of Parkinson's disease. The team successfully restored the brain functions enabling the animal to recover.

In 2015 Professor Dunnett and colleagues generated GABAergic nerve cells from human Pluripotent Stem Cells (hPSCs) using activin A, a protein important in cell signalling[479]. This mechanism is a new robust and effective way to produce the nerve cells lost in HD.

NeuroStemcellRepair[480] is the follow-on four-year programme aiming to take forward this work and the final steps towards the clinic.

Project reference numbers: MC_PC_12009, G0500794

Spin out: Talisman Therapeutics

Dr Rick Livesey's research on human stem cell models for Alzheimer's disease at the **University of Cambridge** underpins Talisman Therapuetics[481], a stem cell drug discovery company set up in 2013.

Alzheimer's disease is the most common form of dementia, affecting around 500,000 people in the UK[482]. It is a progressive disease, meaning that the symptoms, from memory problems and confusion to behavioural changes and speech and language difficulties worsen over time. There are currently no treatments or cure, however different routes are currently being explored by MRC-supported researchers. Alzheimer's disease is estimated to arise ten years before the brain cell damage is so extensive as to cause symptoms. Research suggests that to have the greatest impact on disease progression, patients should be treated in this 'pre-clinical' stage. Biological markers in the blood and cerebrospinal fluid are therefore being explored as potential early disease indicators.

Talisman Therapeutics has developed human stem cells to produce disease-relevant brain nerve cells replicating different stages of the Alzheimer's disease process. This means that early-stage stem cell models can be used to identify compounds that have a greater relevance to the disease process.

Animals do not develop Alzheimer's disease and so developing an alternative model to study the disease is critical. And one advantage to using human stem cells is that the amyloid plaques formation and subsequent nerve cell death that occurs during Alzheimer's disease takes place over several months rather than decades in patients.

The company has collaborations with several pharmaceutical companies and has eight employees.

Dementia, including Alzheimer's disease, is one of today's greatest public health challenges. There are an estimated 44 million people with dementia worldwide. This is set to almost double by 2030 and more than triple by 2050. The global cost of dementia was estimated in 2010 to be $604 billion, more than one per cent of the world's gross domestic product[483].

Project reference number: G1002501

Antimicrobial resistance

Further funding: Bacteria-eating viruses

In 2014 **Professor Martha Clokie** was awarded £135,154 from AmpliPhi Biosciences Corporation[484] to further develop bacteriophages — viruses that 'eat' bacteria — as a treatment for *Clostridium difficile*. AmpliPhi Biosciences Corporation is a US-based biotechnology company seeking to advance the fight against antimicrobial resistance through developing bacteriophage treatments.

Further information on this research and other work on bacteriophages is in the case study on the following page.

This case study is one of a series featuring research into antimicrobial resistance, funded by the MRC, BBSRC and EPSRC[485].

Project reference number: G0700855

Further funding: Developing treatments for and harnessing the potential of *Clostridia*

Professor Nigel Minton is a world leader in developing and using gene technologies to better understand the disease-causing and non-disease-causing clostridia bacteria. He has developed gene inactivation methods enabling genes to be removed[486,487], substituted or added[488]. Such technologies are important because it is only when a gene is no longer functional that it is possible to understand what it does. Indeed, it was the inability to make mutants in clostridia that held back for many years progress in understanding the organism's biology. Since the emergence of the tools developed in the Minton laboratory at the **University of Nottingham**, and in particular the ClosTron[489], hundreds of clostridium mutants have been made worldwide.

Many mutants made in the Minton laboratory have been in *Clostridium difficile*. This bacterium is a major cause of antibiotic-associated diarrhoea, and in severe cases can be life-threatening. There were 14,867 reported cases from April 2012 to March 2013. The research in Professor Minton's group is focused on those *C. difficile* factors that determine its ability to cause disease and, in particular, toxins and endospores. They have helped clarify the roles of toxin A and toxin B as *C. difficile's* two main virulence factors — molecules produced by pathogens that contribute to their disease-causing functions. Using ClosTron, they showed that *C. difficile* producing either one or both toxins displayed cell toxicity in vitro, in a culture outside of a living organism, that translated directly into virulence in vivo, inside a living organism. By producing the first ever double-mutant strain of *C.difficile*, in which both toxin genes were inactivated, Professor Minton's team were able to completely remove virulence[490,491]. Using the subsequently improved gene-deletion tools, they went on to explore why certain strains predominate in outbreaks and cause more severe disease, so-called 'hypervirulent'. It was widely believed that a protein called TcdC inhibited toxin levels and therefore hypervirulence resulted from higher toxin production due to low TcdC levels. However, through precise alterations to

Continued on page 144.

Bacteria-eating viruses

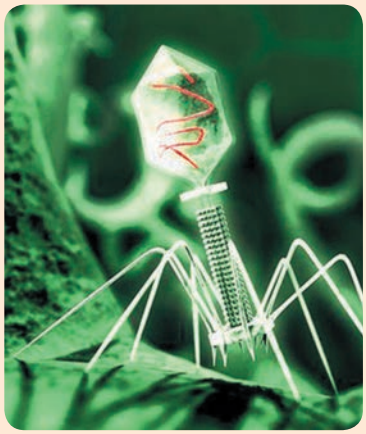


Image: Bacteriophage.
Credit: BlueSci. Cambridge University science magazine.

With the ever-growing threat of antimicrobial resistance, there is a critical need for alternatives to antibiotics. MRC-funded researchers at the University of Leicester are pursuing one such route. A team led by Dr Martha Clokie has isolated bacteriophages — viruses that 'eat' bacteria — targeting the hospital superbug Clostridium difficile or C. difficile.

Bacteriophages were discovered and used as a therapy for bacterial infections almost 100 years ago, long before the development of antibiotics. Dr Frederick Twort, a British bacteriologist and later recipient of MRC funding, is credited with their initial discovery in 1915. French-Canadian scientist Felix d'Herelle later developed them to treat infections following his independent discovery of them in 1917.

To date however, they are not in widespread use. Although phages did reach commercial production in the 1940s, and have been used to treat several bacterial infections, treatment does not produce consistent results. In the pre-antibiotic area, many aspects of phage biology were not well understood. Doses of phages often did not contain enough viable viruses to be effective, and viruses were used that did not kill the intended bacteria[1]. There were also problems with the production of a stable contaminant-free phage stock. Perhaps the greatest barrier to phage acceptance in the west was the inadequate scientific methods used by researchers, such as the exclusion of placebos in trials[2]. With the advent of the antibiotic dawn, phage research and production were all but shelved, with the exception of Eastern Europe and the former Soviet Union where they continue to be used therapeutically.

Renewed interest

Now the threat of widespread antimicrobial resistance has sparked a renewed interest in phages. Dr Clokie has been studying phages for 14 years. She says, "As their natural enemy, phages specifically target and kill bacteria. They encode a diverse set of gene products that can potentially be exploited as novel antimicrobials. They have the advantage over antibiotics of being much more specific and, as they can self-replicate at the site of an infection, they are able to clear infections that antibiotics can't reach." Over the past few years, Dr Clokie has isolated and characterised 40 different phages that infect *C. difficile* — the largest known set of these phages. Of these, she has developed a specific mixture that has proved to be effective against 90 per cent of the most clinically relevant *C. difficile* strains seen in the UK. The US pharmaceutical company AmpliPhi are funding the further development of these phages, with the aim of testing them in Phase I and Phase II trials. This will involve optimising phage preparations for maximum effectiveness against *C. difficile* infections and establishing production, storage and delivery systems for the phage mixture. Dr Clokie will evaluate the effectiveness of the therapy and dosing regimes in collaboration with Dr Gill Douce at the University of Glasgow.

Dr Clokie says, "The number of bacteriophages that exist on Earth, combined with their vast genetic diversity and exquisitely specific interactions with bacterial hosts means that they have the potential to offer a real solution for the treatment of a range of human pathogens. A lot of fundamental science needs to be carried out in order to ensure that we understand how to best exploit them."

Phage products

A potential problem with systemic phage use is the possibility that they may be seen as foreign by the body's immune system and be destroyed. Delivery of phages also needs to be investigated. To prevent them being damaged by the acidity of the digestive system when ingested, phages would need to be encapsulated or stabilised. A way around these problems might be to use the products of phages rather than the whole organism[3].

In 2010, a team of researchers at the MRC Centre for Molecular Bacteriology and Infection (CMBI), also funded by BBSRC, determined the structure of Gp2 — a protein produced by the phage T7 that disables *E. coli* cells[4]. In 2012, they demonstrated how Gp2 blocks the action of the bacteria's RNA polymerase — an enzyme that enables the instructions in the bacteria's genes to be read and turned into proteins[5]. The researchers now plan to identify small molecules that mimic the structure and function of Gp2 and use these as the basis for new drugs to combat bacterial infections.

Different bacterial infections will require different treatment solutions, but it is hopeful that both whole phage particles and their products can be developed as important alternative treatments for human infection.

Notes and references

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Continued from page 141.

the TcdC gene (involving modification, deletion and addition), the Minton laboratory showed that abnormal TcdC levels do not correlate with increased toxin production[490].

Professor Minton's other main focus is the endospore. An endospore is a dormant, non-reproductive, 'seed-like' structure and one of the most highly resistant life-forms on earth. It allows the bacterium to survive exposure to extremes of temperature, dehydration, radiation, disinfectants and oxygen. Whilst *C.difficile's* toxins are recognised to cause its pathogenicity, it is the bacterium's capacity to produce spores that lies at the heart of the disease it causes. This is because spores play a pivotal role in the spread of infection. The processes of spore formation (sporulation) and germination (return of the dormant spore to toxin-producing cells), therefore, represent key intervention points. The Minton group was the first laboratory to make mutants in both the sporulation and germination pathway[492]. Subsequently they showed that the germination of different *C. difficile* samples varied in response to bile salts and that although the bile salt chenodeoxycholate inhibits spore germination of some, it does not inhibit the germination of all strains[493]. This work forms the basis of a collaboration with researchers at the University of Nevada, Las Vegas and The Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences in Detroit. In 2014 the researchers received $3.2m from the National Institutes of Health to develop synthetic bile salts and evaluate their effectiveness in treating *C.difficile* by preventing spore germination.

Pathogenic species like *C. difficile* give the bacteria a bad name. Most clostridium species are benign, and have many medical and industrial applications. C. sporogenes spores, for example, may be used as a delivery system for treating cancer[494]. This is because injected spores localise to, and selectively germinate in, the oxygen-deficient centres of solid tumours, a property that can be used to deliver anti-tumour drugs. The Minton laboratory subsequently used its gene tools to create a novel C. sporogenes strain that produced a tumour-specific drug which reduced, and in some cases cured, an in vivo tumour model[495]. Clinical trials are planned in early 2016.

The diversity of clostridial species' natural catalysts has tremendous potential for industry processes. Funded by the Biotechnology and Biological Sciences Research Council (BBSRC)[496], Professor Minton seeks to adapt certain species to produce chemicals and biofuels from renewable feedstock. Butanol, for example, is a natural product of many clostridial species and represents a superior biofuel to ethanol. Professor Minton has shown that his gene tools may be used to introduce a molecular nanomachine[497] responsible for plant biomass degradation into the chromosome of a butanol-producing *clostridia*[498]. In recent years the focus has shifted to the C1 gas feedstocks, carbon monoxide and carbon dioxide. These gases may be injected into the liquid medium of fermentation vessels where they are consumed by the bacteria and converted into useful chemicals and fuels. Fortunately, C1 gases are an abundant resource, and may be derived from non-food sources such as waste gases from industry as well as 'synthesis gas' produced from the gasification (heating) of sustainable resources, such as biomass and domestic/ agricultural wastes, and from microbial activity in anaerobic digesters and managed landfill sites. By using non-food, waste gas as a feedstock for chemical and fuel production, competition with food and land resources is avoided while at the same time providing benefits to the environment and society through reduced green house gas emissions. Professor Minton leads a BBSRC Network in Industrial Biotechnology and Bioenergy (NIBB), C1net: Gas Fermentation[499] and is the director of a newly awarded £14.3m BBSRC/EPSRC Synthetic Biology Research Centre (SBRC) focused on making platform chemicals from C1 gases[500].

Project reference number: G0601176

Neurodegeneration and cognition

Further funding: Epigenetics in Alzheimer's disease

Professor Jonathan Mill at the **MRC Social, Genetic and Developmental Psychiatry Centre, King's College London** and the **University of Exeter** published research in 2014 demonstrating that epigenetic changes in the brain play a role in Alzheimer's disease[501].

Epigenetic changes — changes to the expression or activity of genes, rather than the underlying DNA sequence — are believed to be one mechanism by which the environment can interact with the genome. Epigenetic changes are potentially reversible and so therefore may provide targets for drug development.

Post-mortem examinations of patients with the disease have revealed that particular parts of the brain, such as the entorhinal cortex, are more susceptible to Alzheimer-induced changes, whereas others, including the cerebellum, remain unaffected.

The international study showed that people with more Alzheimer's disease-related changes in the brain had greater epigenetic changes to the DNA within the ANK1 gene, encoding a protein believed to play a role in cell motility, activation and proliferation. This was particularly the case in the entorhinal cortex, and also detected in other cortical regions affected by the disease. Conversely, no significant changes to the ANK1 DNA in less affected brain areas were observed. The research used brain tissue from three different brain banks, including the MRC London Brain Bank for Neurodegenerative Disease at King's[502].

This work was also funded through awards from the National Institutes of Health (NIH)[503] and Alzheimer's Research UK.

Project reference number: G9817803

Inflammation and immunity

Spin out: SimOmics

Electronics and immunology research might not be a traditional pairing. However, computing advances and new modelling techniques are increasingly offering cost and time-effective ways to explore the mechanics of biological systems.

> ***"Working across disciplines allows us to address key problems in immune function and infectious disease that we simply could not work on by ourselves."***
>
> ***– Dr Mark Coles***
> ***SimOmics co-founder***

SimOmics[504], formed in June 2014, results from more than seven years' work at the **University of York** by **Professor Jon Timmis**, Professor of Intelligent and Adaptive Systems in the university's electronics department and MRC-funded Senior Lecturer in Immunology, **Dr Mark Coles**. The company has developed tools to support computer models that predict the effects of potential drugs and the immune system's response. By increasing the use of computer simulations, SimOmics aims to reduce the need for animal and patient trials and enable manufacturers to focus on the products most likely to succeed.

"Working across disciplines allows us to address key problems in immune function and infectious disease that we simply could not work on by ourselves. This has led to us forming both the York Computational Immunology Laboratory (which includes investigators from the Centre for Immunology and Infection, Electronics, Computer Science and Mathematics departments) and the spin out company SimOmics," said Dr Coles.

The researchers had previously developed a computer model of pre-natal lymphoid tissue formation[505]. This tissue, which includes white blood cells, helps the body mount an immune response and the model was designed to help understand the results of laboratory experimentation. They tracked cell behaviour and calculated cell responses. The model simulates the three cell populations known to be involved in lymphoid tissue development and their behaviour, dependent on the current state of the cell and the cell's location. Using this model, the researchers were able to identify key pathways in lymphoid tissue formation and suggest how such pathways could be investigated in the laboratory.

SimOmics recently released its Evidence Bioscience platform, which enables users to link primary data sources to simulations. The company is currently applying for grants to further develop this core product.

In 2014 the company was part of a multi-sector team securing almost £1m from the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs)-sponsored CRACK-IT programme[506]. This will fund the Phase 2 development of a computer-based "virtual laboratory" to aid the search for new treatments for

leishmaniasis, a worldwide parasitic disease. The computer model will help to predict the effectiveness of different drugs, vaccines and other treatments. Using this technology is expected to significantly reduce the number of rodents needed for pre-clinical drug and vaccine development — a typical rodent study for new antibiotics or vaccines might involve up to 100 animals per candidate drug[507].

Project reference number: G0601156

Further funding: Understanding the immune response in Crohn's disease

Professor Alison Simmons is a clinical scientist and NIHR research professor at the **University of Oxford** where she focuses on the innate immune response in inflammatory bowel diseases (IBD) such as Crohn's disease.

Crohn's disease affects at least 115,000 people in the UK[508]. It is believed to result from a breakdown in immune tolerance to intestinal microbes in people with a given genetic background. It causes inflammatory lesions to develop in the mucus membrane layer of the stomach, resulting in symptoms such as bloody diarrhoea, abdominal pain and weight loss. Steroids and anti-inflammatory drugs are an effective treatment in some patients, however others do not respond and require surgery to remove areas of inflammation.

Variations in the gene encoding NOD2 — a protein found in immune cells that acts as a receptor for microbial pathogens — were first identified and implicated in Crohn's disease in 2001[509,510].

In 2010 Professor Simmons published research demonstrating the specific role that NOD-2 plays in the innate immune system[511]. NOD2 is expressed in a limited number of tissues, including the intestine. The research showed that on recognising a microbe, NOD2 activates autophagy — a process of engulfing and degrading the invader — in immune cells. Its normal role is to defend against the intracellular bacteria causing diseases such tuberculosis, leprosy and salmonella. Crohn's cells expressing NOD2 variants show defects in this process, leading to abnormal persistence of microbes and triggering inflammation.

Professor Simmons has since mapped the NOD2 signalling cascade in more detail. This research has shown that not only does the signalling cascade control bacterial destruction, it controls other innate immune functions that are also defective in Crohn's patients[512]. By defining this signalling cascade in molecular detail, Professor Simmons aims to identify targets for drug design for patients with defects in this cascade. It is hoped that this information will be able to help stratify the disease; identifying groups of patients with particular molecular defects that would be amenable for specific therapeutic approaches.

Professor Simmons has recently received various funding awards to progress this work, from the Sir Jules Thorn Charitable Trust, NIHR and various pharmaceutical companies, such UCB[513], Abbvie[514] and Ajinomoto[515], a Japanese food and chemical corporation, for research into NOD2 interactions in Crohn's.

Professor Simmons was also named the first Oxford-Harrington Scholar in November 2014. The Oxford-Harrington Scholarship programme is at the heart of a new collaboration between the University of Oxford and the Harrington

Discovery Institute at University Hospitals, Cleveland, in the US[516]. The scholarship program will provide support to clinical scientists for preclinical drug research and early-stage clinical trials. As part of the scholarship, Professor Simmons will receive up to $100,000 over two years from the institute, another $100,000 in matching funds from outside sources, and the chance to work with BioMotiv[517], a private company aligned with the institute.

Project reference number: MC_UU_12010/7

Collaborations: Uncovering how fever stimulates HIV replication

Professor Ariberto Fassati at **University College London** worked with Professor Olivier Schwartz at the Pasteur Institute in Paris in 2012 to show that fever may stimulate HIV replication[518].

The Human Immunodeficiency Virus (HIV) infects and kills CD4 T-cells in the immune system. This eventually leads to immune system failure, and the body becomes vulnerable to opportunistic infections and cancer, at which stage it is usually considered to have progressed to acquired immunodeficiency syndrome (AIDS). It takes, on average, 10-15 years for an untreated person to advance to AIDS.

Fever consists of hyperthermia — an increase in body temperature to 38-40° C — and an associated inflammatory response. Fever is generally beneficial, enhancing people's immune response. However, in people with HIV, fever, which occurs at various stages of the disease, is associated with an increased viral load — the amount of HIV in the body. Professor Fassati and collaborators showed that elevating temperature to 39.5°C stimulates HIV replication in CD4 T-cells, increasing it by up to seven fold. Their results also indicated that hyperthermia may help HIV to reactivate from latency — a period of dormancy. This may explain why antiretroviral-treated patients with controlled disease can experience transient bursts of HIV replication, termed viral blips. It also may explain why concurrent infections, such as malaria, causing episodic fever lasting two-three days, are also associated with an increase in viral load.

In 2013 there were around 107,800 people living with HIV in the UK[519]. People with HIV can expect a near-normal life expectancy if diagnosed promptly, thanks to advances in antiretroviral treatment. However, in many parts of the world, such as sub-Saharan Africa, antiretroviral drug availability is extremely limited. The MRC has a long history of supporting HIV research, going back as far as 1983 when it set up a working party on AIDS. Treatment research is primarily aimed at better understanding how to manage antiretroviral therapy and discovering the optimum combinations of drugs for patients at different stages of disease[520]. In 2015 a major international trial co-led by the MRC Clinical Trials Unit found that starting antiretroviral treatment early, rather than waiting until the disease has damaged a person's immune system, reduced the risk of developing serious illnesses[521]. Despite antiretroviral therapy being very effective in treating HIV, it does have serious side effects. Until now, it was not clear whether it was better for a person to wait until their immune system had been weakened by the disease before starting treatment for life or starting while they were still healthy. Results from the Strategic Timing of Antiretroviral Treatment (START) trial are likely to change guidelines worldwide, including those issued by the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE).

Project reference numbers: G9721629, MC_U122886352

Stratified medicine

Spin out: Tandem Nano Ltd

Research conducted by **Professor Andrew Owen** and **Professor Steve Rannard** at the **University of Liverpool** helped to establish Tandem Nano Ltd[522] in 2014. The company provides nanomedicine[523] technologies to improve the action, delivery, use and behaviour of poorly soluble compounds.

Drug treatment frequently fails for reasons including toxicity and, often in the case of antimicrobial therapies, because the virus or bacteria mutates, making it resistant to the drug.

People often respond differently to the same drug treatment. This might be because some do not adhere to the dosing instructions. But in many cases it is due to their individual genetics combined with poor oral absorption of the drugs.

Professor Owen's previous work has shown that HIV drugs are actively pumped across gut and liver cells by transporters — membrane proteins that transport solutes, such as ions and drugs. Professor Owen has also shown that individuals with certain variants in the genes encoding these proteins influence the blood concentrations of HIV drugs in patients. Too much of the drug can lead to toxicity, whereas too little can result in drug resistance. He specifically demonstrated that one particular variant was associated with a higher drug (lopinavir) concentration[524,525].

Professor Owen's team have also published extensively on the association between the genetic variants in enzymes and other transporters and drugs used to treat infectious diseases. The ultimate aim is to use this information to develop tests that will enable doctors to give the right drug in the right concentration to the right patient.

This work has also provided many laboratory tools that the Liverpool team have been using to accelerate the translation of nanomedicines as a further way to improve drug delivery. This approach uses nanoparticles to increase the amount of drug that reaches the blood or to deliver drugs directly to specific cells, thus bypassing the effects of membrane transporters. That is Tandem Nano's aim and so far 24 patents have resulted from its technology, with 46 patent applications currently pending. The team has also received Medicines and Healthcare Regulatory Agency (MHRA) and ethical approval for two human clinical trials of oral HIV nanomedicines, planned for 2015.

Project reference number: G0800247

Collaborations: Drug safety

The **MRC Centre for Drug Safety Science (CDSS)** at the **University of Liverpool** was set up in 2008 to investigate the mechanisms of adverse drug reactions (ADRs), or side effects. Centre researchers have shown that ADRs cause around 6.5 per cent of all adult admissions to hospitals and occur in 15 per cent of in-patients, costing the NHS an estimated £637 million each year[526]. ADRs can result in a drug being withdrawn or its use restricted. This may then impede the prescription

of otherwise effective drugs for the majority of patients who benefit from the drug without developing ADRs. Drug safety also impacts on the profitability of the pharmaceutical industry and thus the UK's economy.

The centre has developed collaborations with various pharmaceutical companies to investigate how drugs cause tissue injury, aiming to improve drug safety screening and ultimately produce safer drugs for patients.

Industry interactions are overseen by an Association of the British Pharmaceutical Industry (ABPI)-sponsored Industry Programme Manager whose remit is to develop pre-competitive interactions with pharmaceutical companies. Many of these interactions have been cultivated from a workshop programme that brings together academics, industry scientists and regulators to address specific issues in drug safety science.

Professor Kevin Park leads a major European programme funded by the Innovative Medicines Initiative (IMI)[527] to develop mechanism-based predictive test systems for human drug-induced liver injury (DILI)[528]. This partnership involves 12 pharmaceutical companies, five SMEs and eight other academic institutions. The CDSS is evaluating existing and emerging *in-vitro* model systems, such as primary cells and stem cell-derived cells in various structures including 2D and 3D tissue models, to develop best practice procedures for pre-clinical safety testing. Two of the companies have already changed their internal screening activities because of data generated from the MIP-DILI project. The CDSS is also involved in the IMI-funded SAFE-T consortium[529], consisting of 11 pharmaceutical companies, playing a leading role in evaluating novel clinical biomarkers as a way to predict, detect and monitor drug-induced liver injury.

In the IMI-funded WEB-RADR project[530], CDSS scientists are working with seven pharmaceutical companies to detect new drug side effects by mining publicly available web and social media content. The project is developing a mobile application where patients and clinicians will be able to directly report potential medicine side effects. This aims to determine whether ADRs reported and identified via social media lead to a faster response to harmful side effects.

Training is an important activity for the CDSS. **Professor Sir Munir Pirmohamed** leads the North West England MRC Fellowship Scheme in clinical pharmacology, a joint scheme with the University of Manchester that is expanding expertise in UK clinical pharmacology. With support from two pharmaceutical and two contract research organisation (CRO) partners, clinical fellows may work with industry as part of their training activities. Separately, in the IMI-funded SafeSciMet training programme, CDSS staff run week-long training courses for industry scientists as part of their continuous professional development.

In 2013 **Dr Neil French** and **Dr Dominic Williams** from the CDDS collaborated with Sense about Science[531] to produce *Making Sense of Drug Safety Science*[532], a guide explaining why it's impossible to create a drug without side effects, and how understanding more about side effects can help tailor drugs to patients.

Sense about Science is a UK charity working with more than 6,000 researchers to help people make sense of scientific evidence in public debate.

Project reference number: MR/L006758/1

Further funding: Economic evaluation of healthcare technologies

The Team for Economic Evaluation and Health Technology Assessment (TEEHTA) specialises in the economic impact of healthcare technologies at the **University of York**. In February 2015, the team published MRC-funded research demonstrating that the £30,000 per quality-adjusted life year (QALY) threshold currently used by NICE to decide whether to recommend funding for a new drug is too high[533]. This threshold is used to gauge whether the health benefits of a new drug are greater than the health lost because the additional resources required are not available to offer effective treatments to other NHS patients. The researchers estimated that £13,000 of NHS resources adds one QALY to the lives of NHS patients and so more harm is being done to other NHS patients when NICE approves more costly drugs. This research showed that the NHS is currently paying too much for new drugs because the amount the NHS can afford to pay for the benefits that new drugs offer is lower than previously thought. The research received considerable media coverage, including articles in the *BBC*[534], *The Telegraph*[535], *The Guardian*[536] and *The Independent*[537].

Dr Cynthia Iglesias, part of the TEEHTA, received £102,000 in 2014 from Innovate UK to investigate the economics of stratified medicine in rheumatoid arthritis. Dr Iglesias showed that there was some evidence to show that stratified approaches to treating a patient with rheumatoid arthritis may be cost-effective. However, there were gaps in the economic evidence base needed to support introducing stratified medicine in rheumatoid arthritis into healthcare systems. There was also uncertainty about how stratified approaches will impact future patient preferences, outcomes and costs when used in routine practice[538].

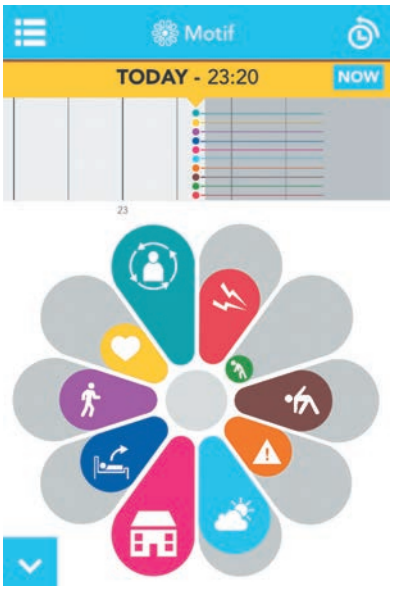
Project reference number: G0501892

Collaborations: Smartphone app to monitor musculoskeletal disease

With support from an MRC Confidence in Concept award, **Dr William Dixon** at the **University of Manchester** is working with UMotif[539], a digital health company, to develop a smartphone app to help patients with musculoskeletal disease such as rheumatoid arthritis.

Disease severity is usually assessed in the clinic through history-taking and examination however no measurement takes place between visits and so constant disease progression is not monitored.

Worsening disease is associated with reduced activity. Dr Dixon is therefore using smartphone technology such as GPS and accelerometers — measuring position and motion — to test the hypothesis that disease severity can be assessed by collecting information from a patient's smartphone with little burden on the patient.



A screenshot of the app.

Developing an algorithm for disease severity using this data will enable optimum management in the clinic and early and long-term intervention assessments in research. However, such development requires patients to regularly report their disease symptoms over a long period of time. The study is combined with a project that seeks to identify the association between weather and joint pain, and to which patients easily relate. In this project, patients report their daily symptoms using the app and the GPS signal pulls their local weather data. Meanwhile, the GPS and accelerometer data are collected to help develop the disease severity algorithm.

This work is currently being piloted and will be featured in a future episode of BBC's *Trust me, I'm a doctor*[540].

Project reference number: G0902272

Liver disease

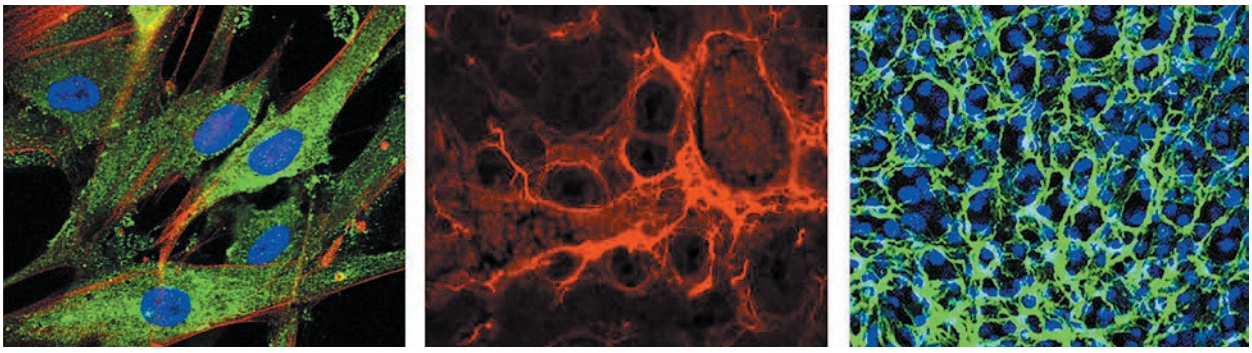
Collaborations: Developing drugs to treat liver fibrosis

Professor Derek Mann at the **University of Newcastle** is working with GlaxoSmithKline (GSK) to develop drugs that can stop or even reverse liver fibrosis.

Tissue fibrosis is caused by scars that develop in response to cellular damage by viruses, bacteria, toxins or dietary factors including alcohol. The scars form to contain the areas of damage while tissue healing takes place. However, if tissues are subjected to repeated damage over extended periods of time, scars are more difficult to break down and they can spread to other parts of the organ, rendering it non-functional. As the organ responsible for detoxification, the liver regularly encounters a high quantity of pathogens and so is particularly susceptible to damage.

Chronic liver disease is currently the only common cause of death that is on the rise in the UK[541]. The number of deaths from the disease have increased 400 per cent since 1970 and, in people younger than 65 years, have risen by almost five times[542]. This is due to growing rates of hepatitis C infection, alcoholic liver disease and non-alcoholic fatty liver disease, associated with obesity, high blood pressure and diabetes.

Professor Mann and his team had previously identified that a specialised cell in the diseased liver called the liver myofibroblast promoted scar formation, maintenance and spread[543].



L–R: Stained myofibroblast cells; Stained fibrotic liver; Stained liver slice.
Image credit: Fibrosis Group, University of Newcastle

Liver myofibroblasts are produced predominantly by changes to the properties and behaviour of hepatic stellate cells, the liver cells that normally function to store vitamin A. Upon injury or infection, these cells transform into myofibroblasts, producing vast quantities of scar tissue. Professor Mann was part of an international study that confirmed that manipulating these myofibroblasts can stop and even reverse fibrosis[544]. The researchers demonstrated that drugs which target a survival factor called NF-kB promote the removal of myofibroblasts from the liver without affecting other liver cells required for healthy function. They showed that a molecule called IKK-beta plays an important role in controlling NF-kB and so IKK-beta inhibitors are one possibility for treatment.

The work with GSK aims to identify existing drugs or new compounds that target myofibroblasts to treat fibrosis. This research is also investigating epigenetic markers — changes that affect the expression or activity of genes without changing the underlying DNA sequence — to identify patients most at risk from developing fibrosis and who would best benefit from new therapies. The work has already contributed to an ongoing clinical study and a pipeline of new molecular targets, some of which are in drug development at GSK.

The collaborative contract with GSK has been extended until the end of 2016 and increases the amount of GSK funding to £1.4m.

Project reference number: MR/K001949/1

Collaborations: Mechanisms in fatty liver disease

Dr Richard Parker at the **University of Birmingham** formed a partnership with ChemoCentryx[545], a US-based biopharmaceutical company, in 2013 to research the role of chemokine receptor CCR2 in fatty liver disease and its potential for treatment.

Most chronic liver disease results from an inflammatory response to liver injury, causing scarring and eventually leading to liver failure. The inflammation is caused by white blood cells entering the liver tissue from the bloodstream. This response is controlled by chemokines, signalling proteins present in the liver and their corresponding receptors on white blood cells.

ChemoCentryx's lead drug candidate, CCX140, is an inhibitor of chemokine receptor CCR2 which binds to the chemokine CCL2. CCL2/CCR2 signalling has been suggested to play a significant role in various kidney diseases including those caused by diabetes. ChemoCentryx has successfully completed a Phase II trial using CCX140 to block CCL2/CCR2 action in patients with diabetic nephropathy.

Dr Parker has shown that levels of its associated chemokine, CCL2, are increased in patients with non-alcoholic fatty liver disease[546]. These results demonstrate a role for CCR2 and Dr Parker is currently investigating with ChemoCentryx whether inhibiting CCR2 has the potential to treat the disease.

Project reference number: G1100448

Cardiovascular disease

Collaborations: Thrombolytic treatment soon after stroke reduces risk of disability

The **MRC Clinical Trial Services Unit (CTSU)** published results of a large meta-analysis in 2014 showing that more stroke patients could benefit from thrombolytic treatment — drugs to break up or dissolve blood clots — but that it needs to be administered promptly after the first signs of illness[547].

Emergency treatment with thrombolytic drug alteplase significantly improves the chances of a good outcome when administered within four and a half hours of symptom onset but, although still worthwhile, its benefit reduces the later it is given.

Dr Jonathan Emberson and colleagues conducted a meta-analysis of individual patient data from nine major trials, involving more than 6,700 patients, using alteplase to treat acute ischaemic stroke.

Global collaborators provided participant data and other supporting information from their own trials and through regular meetings, provided input to the questions to be addressed, prepared analysis plans and discussed results.

Data showed that alteplase treatment significantly increased the odds of a good stroke outcome — defined as no significant disability three to six months after stroke — with faster treatment offering the best chance of recovery.

The odds of a good stroke outcome were 75 per cent greater for patients given alteplase within three hours of initial stroke symptoms, compared with those who did not receive the drug. For those given the drug between three and four and a half hours post-stroke, there was a 26 per cent increased chance of a good outcome, while for those with a delay of more than four and a half hours in receiving treatment, there was a 15 per cent increase in the chance of a good recovery.

The study received coverage in medical-specialist media, including articles in *Medscape*[548] and *Healio Cardiology*[549].

The MRC has played an important role in developing the use of meta-analysis — combining the results of independent studies — in medical research. **Professor Archie Cochrane** at the **MRC Epidemiology Research Unit** in Cardiff conducted a pioneering meta-analysis which demonstrated the beneficial effects of aspirin in heart disease . Professor Cochrane's call for medicine to be evidence-based inspired the formation of The Cochrane Collaboration[551] in 1993. The Cochrane Collaboration is a not-for-profit organisation which gathers the best available scientific evidence about interventions and shares the findings with practitioners, governments and the public. For further information on Professor Cochrane's work, please see the MRC *Insight* blog post: Behind the picture: *Archie Cochrane and the Welsh coal miners*[552].

Project reference number: MC_U137686849

Rare diseases

Spin out: PH Therapeutics

Dr Allan Lawrie's MRC-funded research in pulmonary arterial hypertension (PAH) at the **University of Sheffield** provides the foundation for PH Therapeutics[553], a company aiming to develop antibody therapies for this disease.

PAH comprises several rapidly progressive conditions characterised by high blood pressure in the arteries that supply blood to the lungs. This raised blood pressure is caused by a combination of sustained blood vessel narrowing and inward growth of blood vessel wall cells. PAH leads to breathing difficulties and heart failure and thus has a massive effect on quality of life and life expectancy. The median life expectancy for patients is five-six years following diagnosis. There are currently around 6,000-7,000 patients with the disease in the UK, although it is expected that more remain undiagnosed[554]. Current drug treatments, such as anti-clotting drugs and calcium channel blockers, only target the blood vessel narrowing and do not act against the cell growth. These drug treatments cost between £5,000 and £300,000 per patient each year.

Dr Lawrie has identified two proteins, osteoprotegerin (OPG) and TNF-related apoptosis-inducing ligand (TRAIL), found at increased levels within both affected patients' blood vessels and in animal models of the disease[555,556].

He has also demonstrated that OPG and TRAIL cause the main cells from blood vessel walls to grow, suggesting that they may have an active role in disease.

Dr Lawrie showed that targeting OPG or TRAIL with antibodies — 'Y'-shaped proteins produced by white blood cells that identify and neutralise pathogens or proteins — in rodent disease models can not only stop the disease from progressing, but can cure it[557].

These studies are the first to demonstrate how important OPG and TRAIL are in PAH and to highlight their potential as new targets against which to develop drugs.

Further work has demonstrated that OPG increases TRAIL levels within the blood vessel wall cells and that TRAIL is critical to disease progression.

Supported by an MRC Industry Collaboration Agreement (MICA), PH Therapeutics aims to develop and screen anti-OPG antibodies for their ability to block the growth of these cells, first in cell culture, and then in animal models. This work will identify a lead antibody for clinical trials.

Project reference number: MR/L023040/1

Global Health

Collaborations: Medicines for Malaria Venture

Dr Lucy Okell, Professor Azra Ghani and colleagues at **Imperial College London** have collaborated with the Medicines for Malaria Venture (MMV)[558], a global private-public consortium aiming to discover and develop affordable antimalarial treatments, since 2012.

Dr Okell and the Imperial College group are developing mathematical models and analysing disease data to better understand malaria burden, the impact of public health interventions and to inform malaria control policy[559].

MMV awarded £317,000 to Dr Okell and Professor Ghani to apply this work to assess the impact and cost-effectiveness of both existing antimalarial drugs and other drugs in development.

Malaria is a life-threatening parasitic disease transmitted to people through the bites of infected mosquitos[560]. It is prevalent in many tropical parts of the world, mostly in Africa, Asia and South America. It caused around 500,000 deaths in 2013, mostly in African children.

The first part of the project has been to assess the benefits of two major drug regimens —artemether–lumefantrine (AL) and dihydroartemisinin–piperaquine (DHA–PQP) — for treating uncomplicated cases caused by the *Plasmodium falciparum* malaria parasite in Africa. *Falciparum* is the deadliest species and one of the most common. Treatment has been traditionally based on cure rates for individuals and cost. However, now that many countries are aiming to substantially reduce malaria burden, the drug's ability to reduce transmission is also increasingly relevant.

Clinical trial data had shown that DHA–PQP provides longer protection against reinfection, while AL is better at reducing patient infectiousness. Dr Okell combined data on the transmission-reducing effects and cost of these two drugs with location-specific information on transmission intensity, population density, treatment access and costs in a mathematical model simulating drug pharmacokinetics, malaria transmission and treatment[561].

Dr Okell found that DHA-PQP had a slightly higher estimated impact than AL in 64 per cent of the population at risk in Africa. As DHA-PQP has higher cost estimates, there is a slightly greater cost per case prevented, except in areas with high seasonally varying transmission where the impact is particularly large. Dr Okell's research therefore suggests that tailoring the treatment policy to location would be cost-effective in reducing malaria burden.

Further ongoing work includes evaluating the benefits of artesunate-amodiaquine, another commonly used antimalarial drug in Africa, and developing models to simulate what happens if patients do not take the full course of antimalarial drugs.

In addition to the support provided by MMV, Dr Okell has also received input from the pharmaceutical companies Sigma-Tau Pharmaceuticals Inc[562] and Sanofi[563], in the form of access to clinical trial data.

Project reference number: G1002387

Research ethics and integrity

Collaborations: The Clinical Trials Transformation Initiative (CTTI)

Professor Martin Landray at the **Clinical Trials Service Unit (CTSU)** at the **University of Oxford** is part of the Clinical Trials Transformation Initiative (CTTI)[564], a multi-stakeholder group established to increase the quality and efficiency of clinical trials.

The initiative, set up by the Food and Drug Administration (FDA) in 2008, comprises more than 60 organisations worldwide. The initiative has made various recommendations, on matters such as the effective clinical trial monitoring[565], improving the reporting of adverse events to investigators[566] and trial safety assessment[567]. Several papers authored by Professor Landray have fed into these recommendations.

Clinical trials are the gold standard for determining the safety and efficacy of new treatment and prevention options. Patients benefit from trials because there may be therapeutic benefit from receiving the experimental treatment, as do health services that run them because take up of new treatments may be quicker and treatments may be more tailored to the national population[568]. Companies and the public sector also benefit from trials that deliver clear answers in a complex development process that can cost more than $1bn per medicine[569]. There are also economic benefits in attracting industry trial activity to countries; it is estimated that one per cent of the biopharma-sponsored clinical trial market share represents up to $280m in patient recruitment-related revenues[570]. The UK's Life Science Strategy[571] places emphasis on making the UK an attractive place for clinical research and the number of UK clinical trials, UK patient recruitment, and the UK's share of global industry sponsored trials have all increased in recent years[572].

Project reference number: MC_U137686860

Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

End Notes

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2014/15 report

SECTION 2.6
Awards and recognition

Awards and recognition

The MRC celebrates the awards and wider recognition won by our researchers. Awards, prizes and other means of recognition in part acknowledge the quality of research undertaken by MRC scientists. Certain 'markers of esteem', such as being appointed to the editorial board of a journal or attracting visiting staff, can also be seen to have a wider impact on the research and teaching community. Measures of esteem are used internationally by some funders alongside citation analysis, peer review and research income as indicators of research quality[573].

The MRC seeks details of the prizes, awards and other types of recognition received by MRC researchers to better understand the ways in which researchers are recognised for their contributions to academia and the wider society.

A selection of the ways in which our scientists have reported being recognised can be found throughout this chapter of the report, characterised by the following:

- Appointed to the editorial board of a journal or book series
- Membership of learned societies
- Attracted visiting staff or internships to laboratory
- Research prizes
- 2014 Orders of Chivalry

Appointed to the editorial board of a journal or book series

An engaged and expert editorial board is essential to the success of peer-reviewed journals[574]. Rost and Frey suggest that membership of the academic editorial board of a professional journal can be used as an indicator of research quality because it demonstrates a scholar's reputation among peers. It recognises their contributions to the research community in terms of reading and reviewing the work of others[575].

Researchers primarily reported appointments to the editorial boards of journals, including renowned publications such as *Science*, *Cell* and *Nature*, and a small number gave details of editing or producing content for a book. Such recognition yielded significant impact for researchers. This included:

- An increased international profile of the researcher, their research group and their research field.
- A subsequent increase in opportunities for international collaborations and networking.
- Enhanced coordination between disparate areas of research, leading to improved and interdisciplinary working.
- Being able to influence the strategic direction and scientific priorities of the journal and subsequently, the area's scientific community.
- Having early access to cutting-edge research and direct interaction with prominent researchers in the field.
- Improving the quality of the journal's articles and influencing its success.

Dr Elisabeth Ehler at **King's College London** was asked by Springer Publishing in 2013 to edit a book on cardiac cytoarchitecture. The book, *Cardiac cytoarchitecture: how to maintain a working heart*[576], was published in 2015 and

offers the first overview of the cell biology of heart disease of its kind. It is intended to be of interest to cell biologists and cardiologists alike. As at January 2016, the e-book had five Mendeley readers and almost 4,000 chapter downloads[577].

Professor Hanns Lochmüller at the **University of Newcastle** was appointed as joint editor-in-chief of the new *Journal of Neuromuscular Disorders*[578] in 2014 in recognition of his contribution to the field. The journal is 'dedicated to providing an open forum for original research in basic science, translational and clinical research that will improve our fundamental understanding and lead to effective treatments of neuromuscular diseases'.

Professor Lochmüller is coordinating RD-Connect[579], a six-year global project that is linking genomics data with biobanks and clinical bioinformatics tools to produce a central research resource for rare diseases. Funded by the EU's Seventh Framework Programme, this project is helping to negate certain difficulties of rare diseases research – the lack of data harmonisation across disease type, genomic data, biomaterial availability and research data sets.

Professor Rustam Al-Shahi Salman at the **University of Edinburgh** was appointed as a senior editor on the editorial board of new journal *Evidence-based pre-clinical medicine*[580] in 2014. The journal 'publishes open access, high quality systematic reviews, meta-analyses and protocols summarizing data from animal studies on a subject relevant to human health'. The datasets it uses are all held in a public repository and the journal provides tools to access this data.

Dr Stephanie Cragg at the **University of Oxford** was appointed as an Associate Editor at the new Nature Publishing Group journal *Parkinson's Disease* in 2014 as a result of her expertise in the area. The open access journal is dedicated to highlighting the most important scientific advances in Parkinson's disease research.

Membership of learned societies

MRC researchers reported being made a Fellow of several learned societies, including Fellows of the Academy of Medical Sciences, the Royal Society, the Royal Society of Edinburgh and the Society of Biology. Being awarded a Fellowship of these societies is a testament to the researchers' exceptional contributions to, and eminence in, the research field.

Each year, the Royal Society elects up to 52 new fellows, from a group of more than 700 nominations made by the existing Fellowship, through a peer-review process that culminates in a vote by current fellows.

The Academy of Medical Sciences elected 44 new Fellows in 2013, bringing their total to 1,094; the Royal Society of Edinburgh elected 47 new Fellows in 2013, which brought their total to more than 1,500.

Researchers reported that this recognition increased the profile of the individual and group leading to increased opportunities for networking and collaboration, enabled the researcher to influence national policy and enhanced awareness of the scientist's particular field.

Attracted visiting staff or internships to laboratory

Many MRC researchers attracted visiting staff or internships from around the world to their laboratories – an indication of the wide reach of their reputation within their field. These included hosting researchers aiming to learn or refine techniques or scientific methods, those holding scholarships or fellowships and visiting collaborators.

Dr Gerrit Koop at Utrecht University in The Netherlands was awarded funding to work as a visiting researcher **Dr Mark Holmes'** laboratory at the **University of Cambridge** in 2014. This collaboration led to the discovery of a novel staphylococcal toxin.

Professor Ji-Long Liu at the **MRC Functional Genomics Unit (FGU)** at the **University of Oxford** attracted a visit from Chinese researcher Dr X Yu. Dr Yu received a scholarship from from the Chinese Academy of Sciences to study the biology of the cytoophidium, a new organelle discovered in Professor Liu's laboratory. This visit led to greater international awareness of Professor Liu's cytoophidia research.

Professor Neil Ferguson at the **MRC Centre for Outbreak Analysis and Modelling** reported that he had hosted Professor Marc Lipsitch from the Harvard School of Public Health for one year from 2014. This led to increased collaboration between the two institutions. Professors Ferguson and Lipsitch were co-authors on a paper discussing biases when estimating case fatality rates in outbreaks and ways of reducing them, published in 2015[581].

Dr Flaviano Giorgini at the **University of Leicester** hosted an honorary visiting fellow in 2014. This enabled work exploring the influence of aggregation-prone proteins on the toxicity of the mutant huntingtin protein in the context of Huntington's disease to be undertaken. This work has led to further studies by a PhD student in the lab and the start of a collaboration with Professor Mick Tuite at the University of Kent.

Research prizes

Award holders highlighted a large number prizes awarded either to the principal investigators personally or to a member of their team. Researchers reported prizes being awarded for many reasons, including contribution to their field, lifetime achievement, outstanding public engagement, academic papers and posters and presentations (often made by students or early-career scientists).

The primary reported impact of such recognition was the increased profile of the scientist and of their work. Others received invitations to present at prestigious conferences and many reported increased career progression opportunities. Several received monetary awards which they used to further their research.

Professor Helen Griffiths, chair of the British Society for Research on Ageing, presents Professor Malcolm Jackson with his award.

Professor Malcolm Jackson, director of the **MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing (CIMA)** at the **University of Liverpool** was awarded the Lord Cohen Medal by the British Society for Research on Ageing[582] in 2014. The medal is the highest award for services to gerontology in the UK and honours individuals who "have made a considerable contribution to ageing research, either through original discoveries or in the promotion of the subject of gerontology in its broadest aspect".

Professor Jackson specialises in the sources and functions of reactive oxygen and nitrogen in skeletal muscle with regards to ageing and the causes of age-related skeletal muscle mass and function loss.

In 2014 he also chaired a joint NASA/ESA and Japanese Space Agencies panel evaluating projects submitted for research programmes on the International Space Station. The role that gravity plays in biological processes at the molecular, cellular, organ and whole organism level was one area applications had been sought in and many of the proposed projects were in the musculoskeletal field.

Professor Hannah Gould at **King's College London** was awarded the 2014 Paul Ehrlich Award by the European Academy of Allergy and Clinical Immunology (EAACI)[583] for 'Improving Experimental Research'. The EAACI medal awards are the academy's highest distinction and honour distinguished scientists who have contributed significantly to Allergology and Clinical Immunology. Her research is focused on the basis of allergic disease and the biology of Immunoglobulin E (IgE), the antibody produced by the immune system in response to an allergen.

Professor Anna Gloyn at the **University of Oxford** was awarded the 2014 Minkowski Prize by the European Association for the Study of Diabetes (EASD)[584] for her research contribution to the advancement of knowledge concerning diabetes. As the recipient of this award, Dr Gloyn delivered the 49th Minkowski lecture at the 50th EASD Annual Meeting in Vienna in September 2014. The title of her lecture was *Unravelling causal mechanisms in diabetes pathogenesis.*

Professor Richard Hayes, alongside **Professor Rosanna Peeling**, at the **London School of Hygiene and Tropical Medicine** was awarded the 2014 George MacDonald Medal[585] in recognition of outstanding research leading to the improvement of health in tropical countries. Professor Hayes, a professor of epidemiology and international health, has been a leading figure in tropical epidemiology for more than 30 years, and has conducted ground-breaking research on a wide range of public health problems of developing countries, including sickle cell disease, malaria, HIV and TB.

Image credit: UCL Creative Media Services

Professor Robin Ali at the **University College London Institute of Opthalmology** was awarded the *Journal of Human Gene Therapy's* Pioneer Award[586] in 2014. This recognised his proof-of-concept studies that have demonstrated the feasibility of using gene therapy and cell transplantation to treat the dysfunction and degeneration of retinal cells, as well as his work on the first clinical trial for inherited retinal degeneration.

A team of researchers at the **MRC Clinical Trials Unit** won the 2014 British Medical Journal (BMJ) UK Research Paper of the Year[587] for a paper published in The Lancet on the Anti-retroviral research for Watoto (ARROW) trial[588]. The trial, involving more than 1,000 children from Uganda and Zimbabwe, looked at how best to treat children with HIV. It showed that modern HIV treatment regimens of three or four antiretroviral drugs can be delivered safely without routine laboratory testing to check for side effects. This could help to treat more children with HIV in Africa, where access to laboratories is limited. The judges commented that, "It was a fantastic achievement to do this trial, and its results really matter. It will make a difference and change practice. The team's collaboration was very strong. It was good to see, too, that the trial's drugs and diagnostic tools were donated."

Dr Victoria Cowling in the **MRC Protein Phosphorylation and Ubiquitylation Unit** at the **University of Dundee** was awarded the British Society for Cell Biology's first Women in Cell Biology Early Career Award Medal in 2015[589]. The prize was established to celebrate the 50th anniversary of the society and honours an outstanding female cell biologist who has started her own research group in the UK within the previous seven years. Dr Cowling's group discovered that the messenger RNA (mRNA) cap is dynamically regulated in the cell and integrates diverse signalling pathways to drive changes in protein synthesis. The group is currently exploring the mRNA cap as a therapeutic target with which to inhibit cancer call and parasite growth.

Dr Niall Kent[590] at **University College London** won the Royal Academy of Engineering's JC Gammon Award in 2014 for his innovative dental bone graft material, Aerograft. Aerograft is a synthetic material that is more effective than existing bone replacements and can be tailored to specific procedures. Bone replacements are used by dentists when a patient is missing bone or when more bone is required, for example, during implants. It is thought that aerograft could be used in almost 600,000 dental operations worldwide each year. Very little progress has been made in this field in the past 50 years and so this presents a significant improvement to existing bone substitutes.

This award will grant Dr Kent access to support from some of the UK's most successful entrepreneurs and business leaders through membership of the Academy's *Enterprise Hub*[591]. The award also includes a prize of £15,000 for the growth of his start-up company.

Professor Oliver Howes at **Imperial College London** was awarded the British Association for Psychopharmacology (BAP)[592]'s Senior Clinical Award in 2014 to honour excellence in the field. His recent work has focussed on the effects of antipsychotic drugs on the endocrine system and the causes of cognitive impairment in schizophrenia.

Dr Suzi Gage at the **University of Bristol** and **Professor Carmine Pariante** at **King's College London** were both awarded the BAP's Public Communication Prize in 2013. This award rewards excellence in both clinical and non-clinical science communication to the public in the area of psychopharmacology. Dr Gage was recognised for her *Guardian* blog, *Sifting the evidence*[593], her Research Fest 2012 talk on tobacco and cannabis[594] and her contributions to the 2013 *ScienceGrrl* blog[595]. Professor Pariante was honoured for his article in the *Huffington Post* on the London riots[596], the public information he produced for the BAP on how antidepressants work[597] and his 2012 talk at T*he Times* Cheltenham Science Festival on the depressed brain[598].

Thomson Reuters produces an annual list of *Highly Cited Researchers* recognising leading researchers in the sciences and social sciences from around the world[599]. About three thousand researchers earn this distinction each year by writing the greatest number of reports officially designated by Essential Science Indicators as Highly Cited Papers – ranking among the top one per cent most cited for their subject field and year of publication.

Several MRC researchers featured on the 2014 list in diverse research fields. These include:

Professor Philippe Froguel at **Imperial College London** in the field of molecular biology and genetics.

Professor George Davey-Smith at the **University of Bristol** in the fields of both clinical medicine and social sciences.

Dr Simon Frost at the **University of Cambridge** in the field of computer science.

Queen's 2014 Honours

Professor Michael Owen at **Cardiff University** was **Knighted** for **services to neuroscience and mental health**. Professor Owen's research into the genetic risk factors for complex psychological and neurodegenerative disorders such as Alzheimer's and schizophrenia has been funded by the MRC for more than 20 years. He has played a fundamental role in leading international collaborations, substantially increasing the number of genes identified to play a part in the development of Alzheimer's.

Professor David Spiegelhalter, Winton Professor of the Public Understanding of Risk at the University of Cambridge, and former Programme Leader at the **MRC Biostatistics Unit** was **Knighted** for **services to statistics**. For nearly 20 years, Professor Spiegelhalter has led the development of WINBUGS[600], software for the Bayesian analysis[601] of complex statistical methods. This has enabled Bayesian statistical methods to be used widely in medicine and other fields. He has worked on many clinical trials and drug safety and advised the Healthcare Commission on using statistical methods to guide hospital inspections. He also advised the Blackett Review of High Impact Low Probability Events on the information leaflet for women invited for breast cancer screening and on statistical education in schools.

Image credit: David Bishop, UCL Health Creatives.

Professor Catherine Law at **University College London** was appointed as a **Commander of the British Empire** for **services to public health**. Professor Law's research focuses on child public health, particularly relating to cardiovascular risk factors, physical growth and inequalities in child health. Her current research concentrates on obesity in children and how foetal and early childhood growth contributes to lifetime health, how public policy might influence current trends in childhood obesity, and how national and local interventions to prevent childhood obesity can be developed and evaluated.

Professor David Mabey at the **London School of Hygiene and Tropical Medicine (LSHTM)** was appointed as a **Commander of the British Empire** for **services to health development in Africa and Asia**. Professor Mabey has conducted research on trachoma — a bacterial eye infection caused by *Chlamydia trachomatis* — and genital *C.trachomatis* since the early 1980s. Most of his field work has been done in The Gambia and Tanzania, and he also runs a laboratory at the LSHTM where has worked on how *C.trachomatis* causes disease and how the immune system responds. He worked on the Mwanza intervention[602] trial which showed that it was possible to reduce HIV transmission by better managing other STIs at the primary health care level.

Professor Carole Goble at the **University of Manchester** was awarded a **Commander of the British Empire** for **services to science**. Professor Goble's research focuses on knowledge and information management, the interoperability of applications and new ways of publication and curation. She is a leader of the UK's e-Science programme, working for more than 10 years on information solutions for scientists, particularly clinicians and life scientists.

Professor David Williams at **Loughborough University** was awarded an **Order of the British Empire** for **services to science and engineering**. Professor Williams established one of Europe's first biomaterials laboratories in 1968 and his research has focused on developing, evaluating and using biomaterials in medical devices and regenerative medicine. As director of the UK Centre for Tissue Engineering, he has concentrated on the increasingly important issues of material biocompatibility and also on the infrastructure issues associated with the transition from medical device technology to regenerative medicine.

Professor Sarah Cleaveland at the **University of Glasgow** was awarded an **Order of the British Empire** for **services to veterinary epidemiology**. Professor Cleaveland and colleagues were instrumental in developing a canine vaccination strategy between 2010 and 2013 to eliminate a rabies epidemic in Bali, Indonesia that had begun in 2008[603]. The vaccination programme reduced the rate of human death by 90 per cent[604].

Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

End Notes

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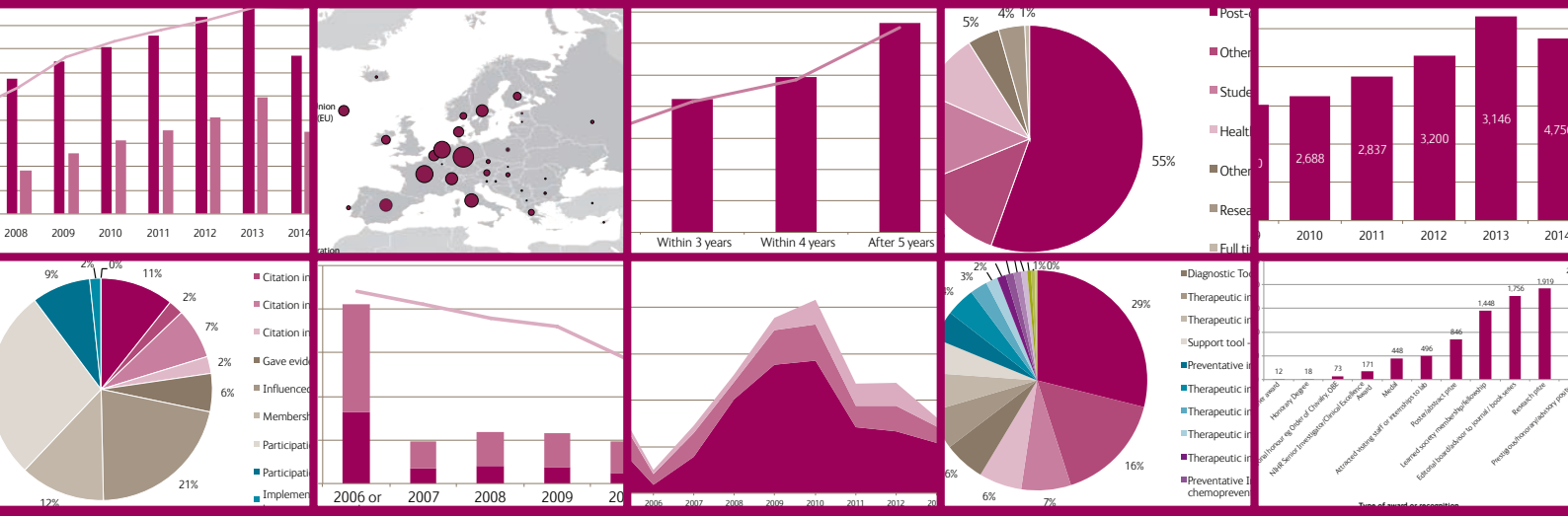
researchfish®
capture • evidence • share • inform

MRC Medical Research Council

Outputs, outcomes and impact of MRC research

2014/15 report



SECTION 3
Quantitative analysis

3.1 Publications

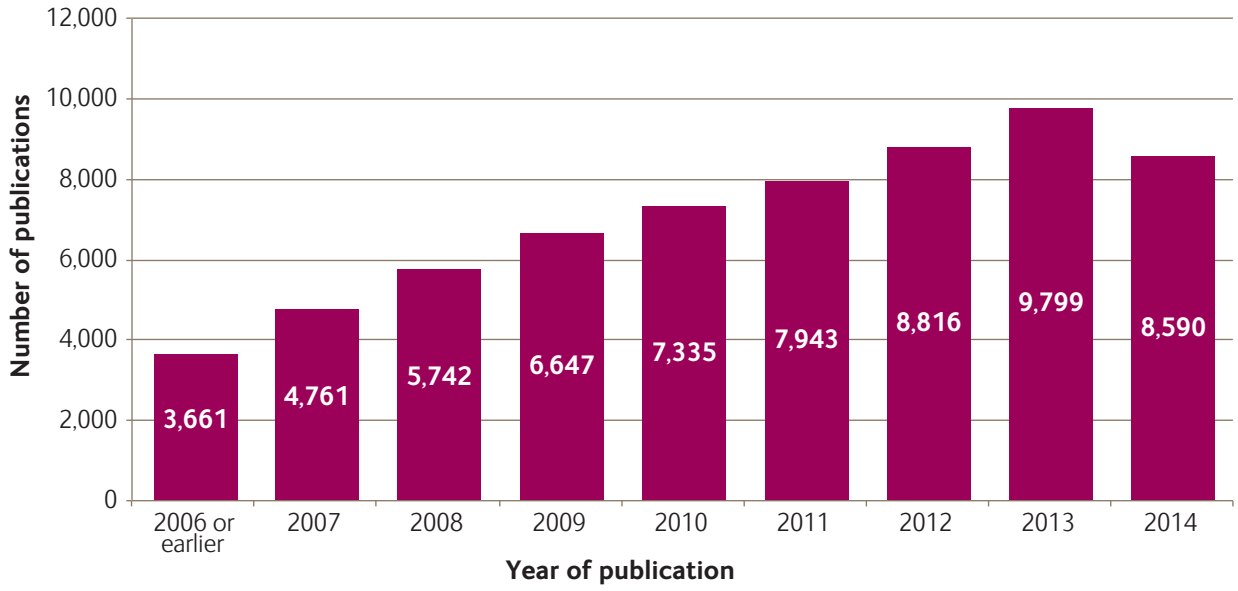
Summary

- MRC researchers reported publications[605] resulting, either wholly or in part, from MRC funding in 85 per cent of awards[606].
- There were 94,732 reports of publications, of which 63,294 are unique publications. Table 1 and figure 1 show the number of unique publications for each year since 2006.
- The average number of publications per award reporting at least one publication was 19 (18.63).
- More than a fifth of all awards (23 per cent) reported the generation of more than 16 publications.

Table 1: Number of unique publications for each year since 2006

Year	2006 or earlier	2007	2008	2009	2010	2011	2012	2013	2014	Total
No. of publications	3,661	4,761	5,742	6,647	7,335	7,943	8,816	9,799	8,590	63,294

Figure 1: Number of unique publications for each year since 2006



Publications by year

- 89 per cent of awards starting in 2006 or earlier have yielded at least one publication. Publications take time to produce and recent awards will naturally be less likely to have resulted in a publication. However, two thirds (67 per cent) of awards starting in 2013 and more than one third (37 per cent) of awards starting in 2014 report the production of at least one publication so far. Table 2 and figure 2 show the distribution of publications by award start year.
- Recipients of 29 per cent of awards reported their first publication within one year of the award starting. This had increased to 90 per cent after five years. The time between the start of the award and report of first publication is shown in table 3 and figure 3.

Table 2: Distribution of publications by award start year

Start year	Number of awards	Number with at least one publication	Number with no publications	Percentage with at least one publication
2006 or earlier	2,059	1,835	224	89%
2007	484	443	41	92%
2008	586	541	45	92%
2009	572	528	44	92%
2010	477	437	40	92%
2011	418	375	43	90%
2012	517	418	99	81%
2013	657	439	218	67%
2014	195	73	122	37%
TOTAL	**5,965**	**5,089**	**876**	**85%**

Figure 2: Distribution of publications by award start year

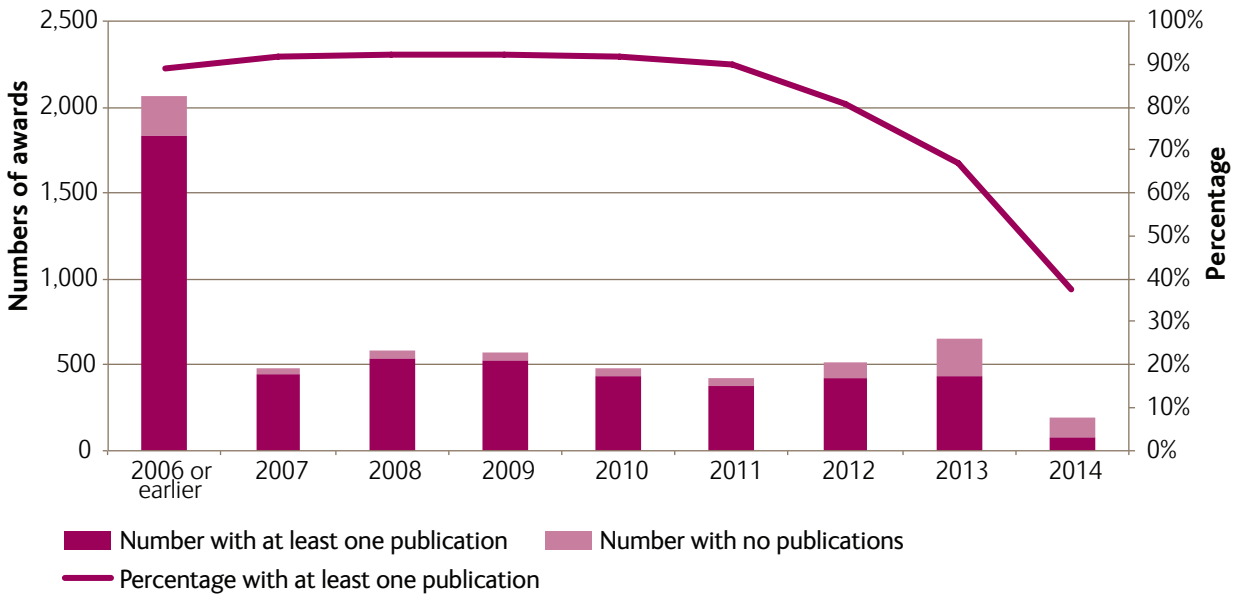
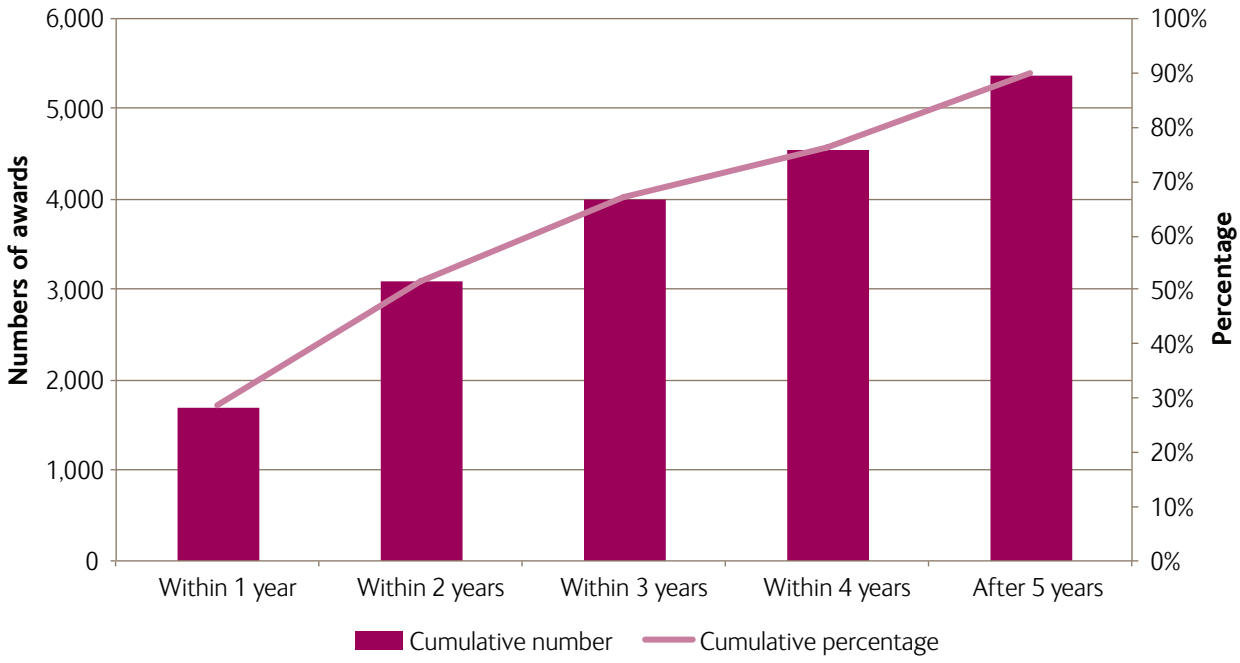


Table 3: Time to report first publication by number of awards

First publication	Number with at least one publication	Cumulative number	Cumulative percentage
Within 1 year	1,690	1,704	29%
Within 2 years	1,316	3,086	52%
Within 3 years	830	4,008	67%
Within 4 years	467	4,552	76%
After 5 years	786	5,362	90%

Figure 3: Time to report first publication by number of awards



Publications by co-author

Co-authorship of publications provides an insight into the patterns of research collaboration; it can indicate the variety and even duration of collaborations. Bibliographic information was purchased from Thomson Reuters on MRC research papers, including the names and addresses of all co-authors on a paper. The address data includes country information and this is used for basic geographic analysis.

Open Access

Figures 4-6 show the proportion of unique MRC publications produced each year that are currently available in Europe PMC (as at March 2016). The data is divided into intramural and extramural figures, as well as showing both combined. The proportion of papers reported via researchfish®, published in 2014, that are openly accessible in Europe PMC is 42 per cent. This can be divided into intramural papers (45 per cent openly accessible in Europe PMC) and extramural papers (41 per cent openly accessible in Europe PMC). It should be noted that this will include publications that are not subject to the Open Access policy (for example, books).

Due to time lags in publishing, ID assignment and Europe PMC processing, one would expect lower absolute numbers of publications and proportional compliance in the most recent year, and that these would increase with the next data gathering period.

We will work with Europe PMC to obtain further information about whether these papers were openly accessible within six months of publication, and to filter our results with respect to publication types that have to comply with the open access policy.

Figure 4: *Europe PMC availability by publication year*

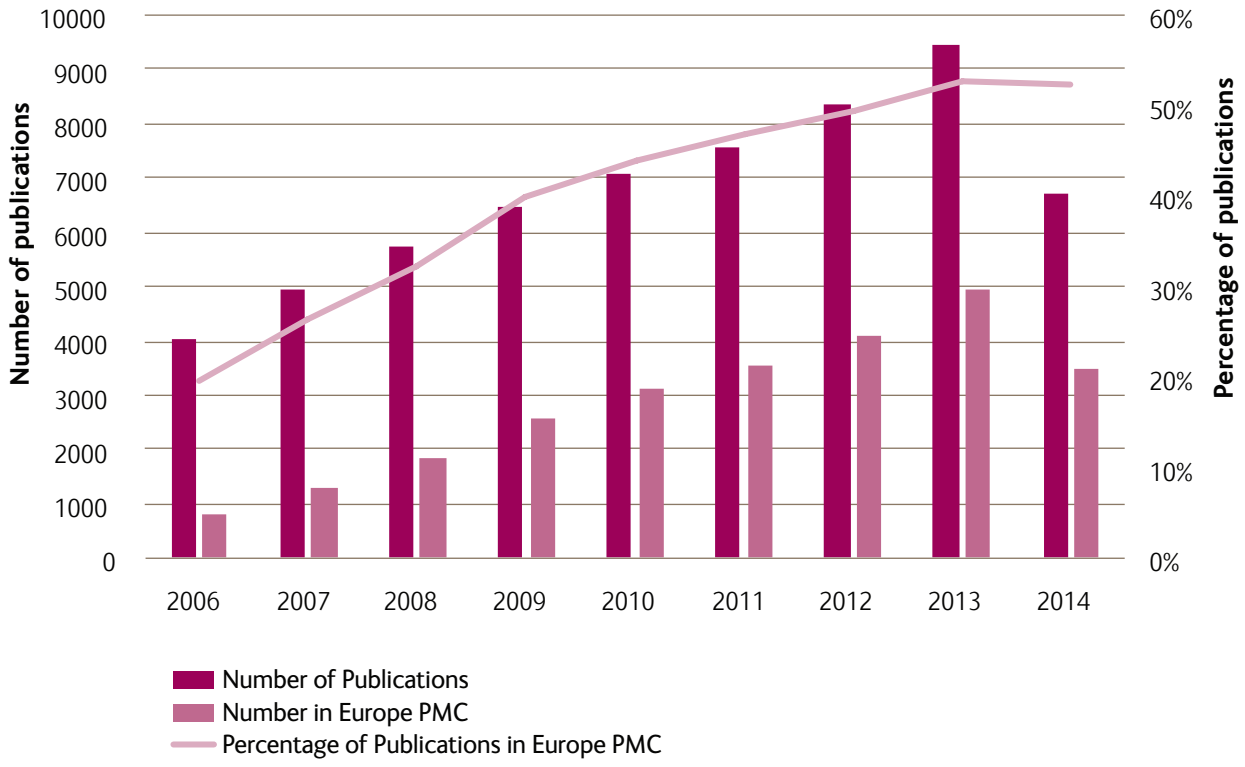


Figure 5: Europe PMC availability of intramural papers by publication year

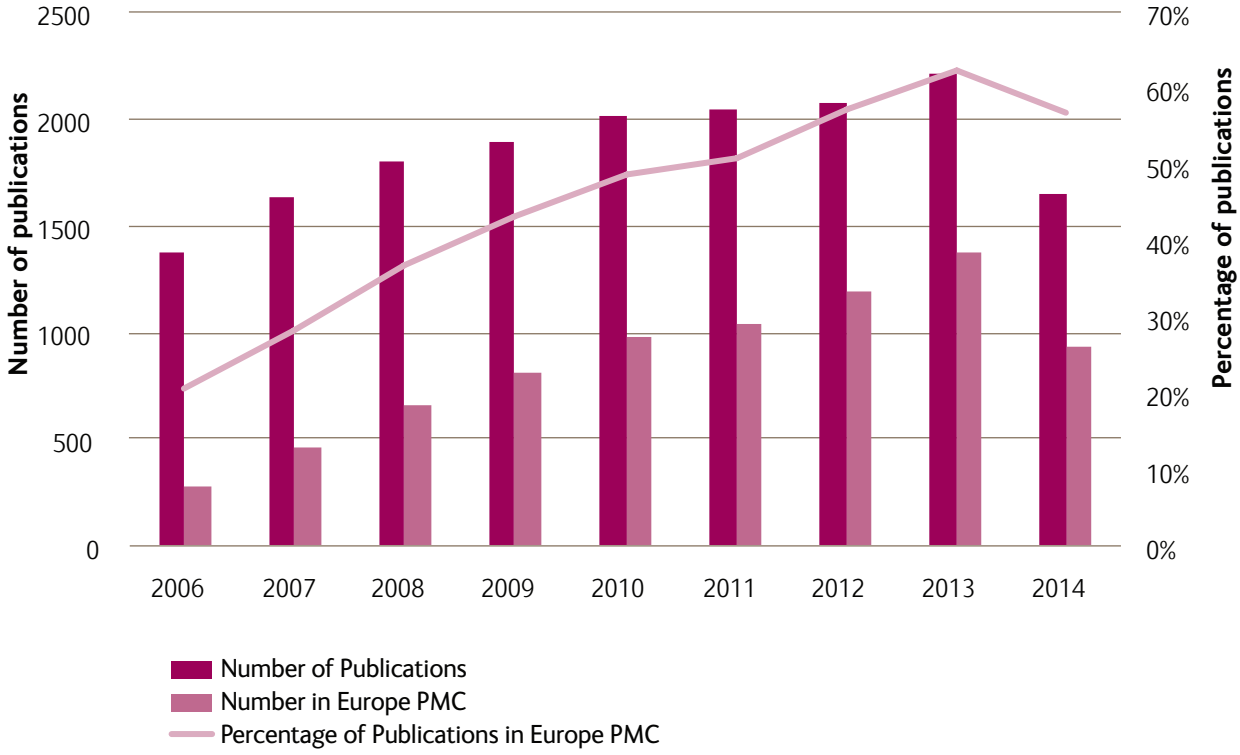
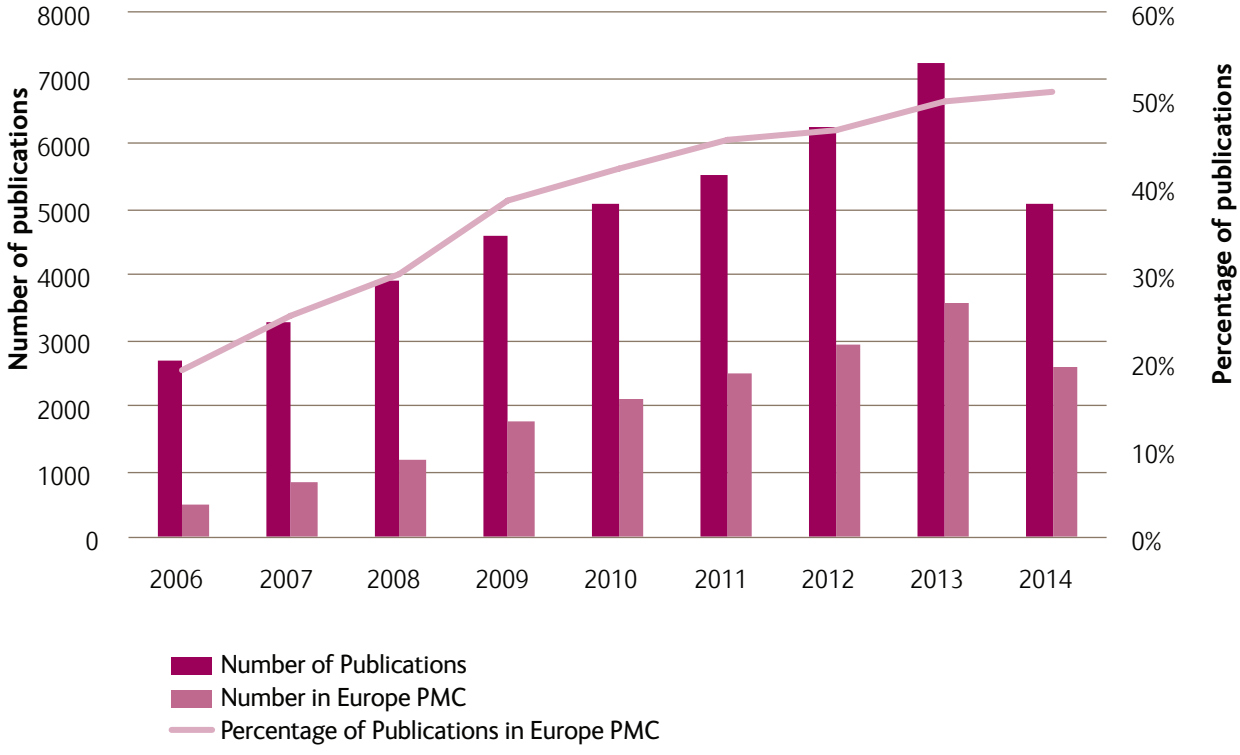


Figure 6: Europe PMC availability of extramural papers by publication year



3.2: Collaborations

Summary

- Recipients of 48 per cent (2,870) of awards reported that they had established a collaboration which they could evidence, for example with co-publications, co-funding or exchange of materials and expertise.
- The average number of collaborators[607] linked to awards reporting at least one collaboration was 5.86, a small change from last year's figure of 5.42.
- Six per cent (331) of awards were highly collaborative, with these recipients reporting at least 10 different collaborators.

Collaborators by year

- It takes time for researchers to set up collaborations and so there will naturally be fewer collaborations resulting from more recent awards. Recipients of 53 per cent of awards starting in 2006 or earlier had collaborations linked to them compared to 15 per cent of awards starting in 2014. The number of collaborators per award by starting year of the award is shown in table 1 and figure 1.
- 18 per cent of awards reported at least one collaboration within one year of the award starting, compared to 45 per cent after five years. The time between the award start date and collaboration starting is shown in table 2 and figure 2.

Table 1: Number of collaborators by award start date

Start year	Number of awards	Number with at least one collaboration	Number with no collaborations	Percentage with at least one collaboration
2006 or earlier	2,059	1,087	972	53%
2007	484	224	260	46%
2008	586	317	269	54%
2009	572	306	266	53%
2010	477	234	243	49%
2011	418	167	251	40%
2012	517	176	341	34%
2013	657	163	494	25%
2014	195	30	165	15%
TOTAL	**5,965**	**2,704**	**3,261**	**45%**

Figure 1: Number of collaborators by award start date

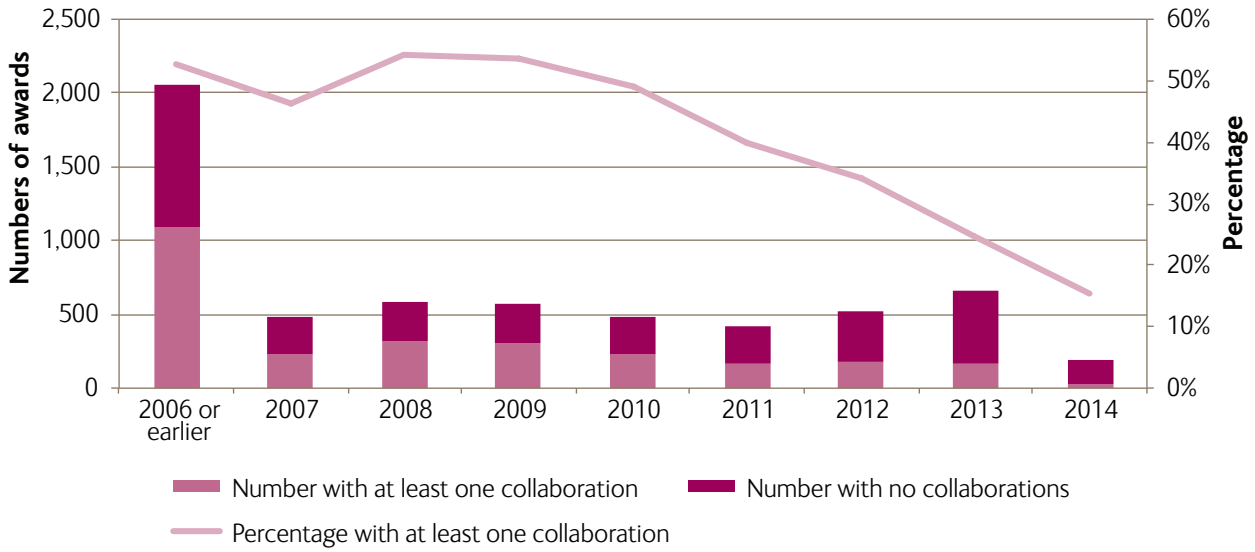
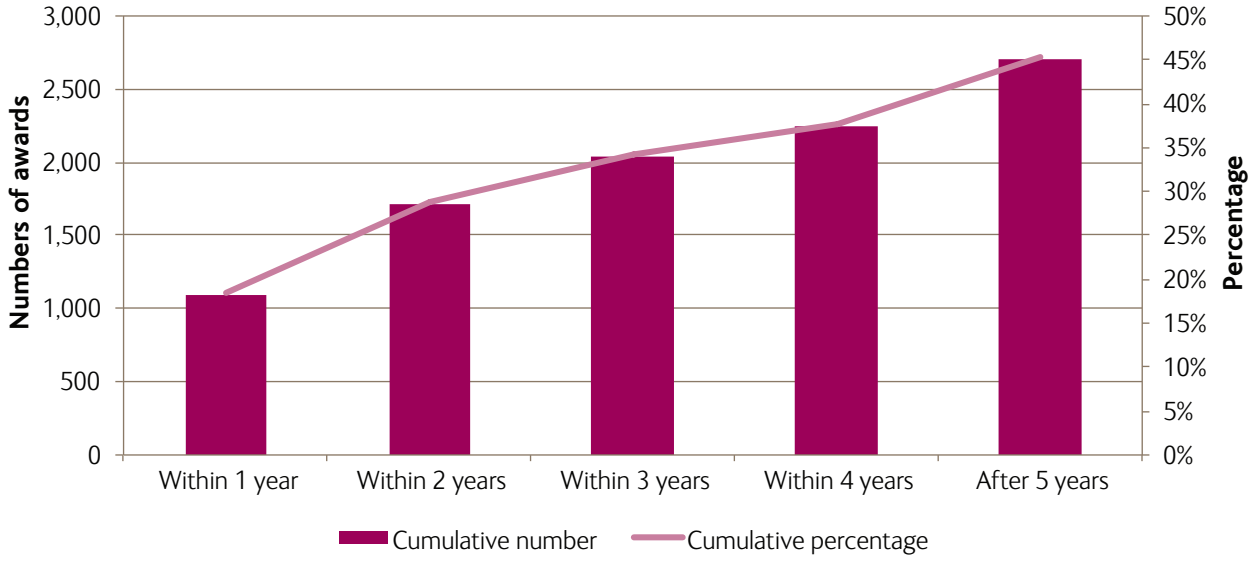


Table 2: Time between award start date and collaboration

First collaboration	Number reporting	Cumulative number	Cumulative percentage
Within 1 year	1,098	1,098	18%
Within 2 years	623	1,721	29%
Within 3 years	322	2,043	34%
Within 4 years	206	2,249	38%
After 5 years	455	2,704	45%

Figure 2: Time between award start date and start of collaboration



Collaborators by location

- The majority of collaborators were from the United Kingdom (56 per cent), followed by the rest of Europe (18 per cent) and North America (14 per cent)[608].
- Table 3 shows the numbers of collaborators by location. Figures 3 and 4 illustrate the distribution of international (excluding Europe) and European (excluding UK) collaborators respectively[609].
- Figure 5 shows the top 25 location countries (excluding the UK) for number of unique collaborators. The United States remains the largest single source for collaboration with MRC research outside the UK, accounting for almost one third (31 per cent) of unique collaborations reported.

Table 3: Number of collaborators by location

Location of collaboration	Number of collaborations	Percentage of total
United Kingdom	8,583	56%
Europe	2,825	18%
North America	2,110	14%
South America	202	1%
Asia	496	3%
Africa	266	2%
Oceania	354	2%
Global	264	2%
Unknown	332	2%
Total	**15,432**	**100%**

Figure 3: Distribution of international (excluding Europe) collaborators[610]

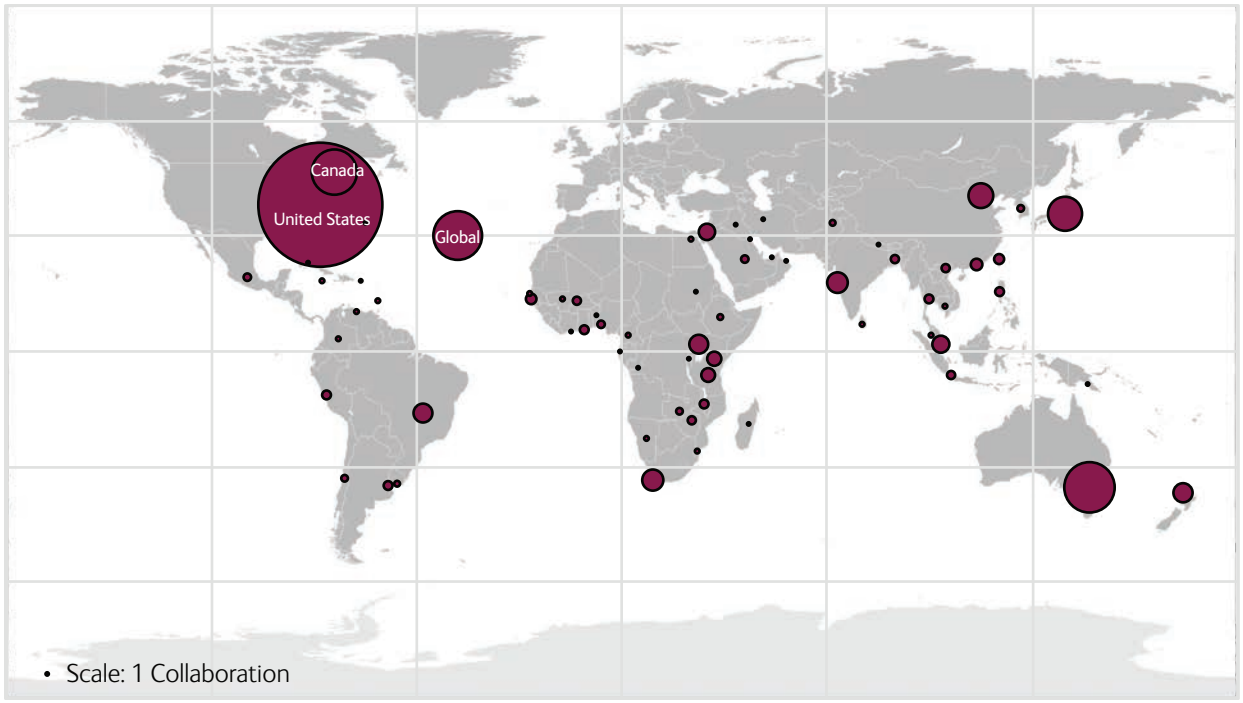


Figure 4: Distribution of European (excluding UK) collaborators[611]

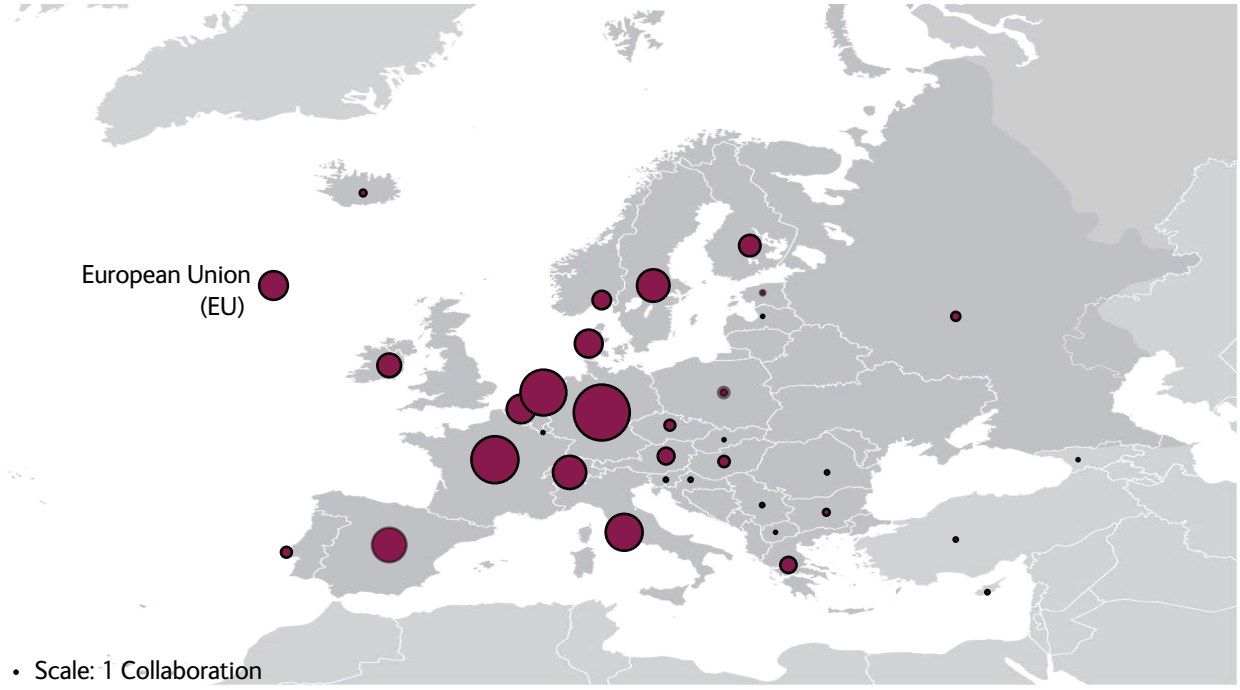
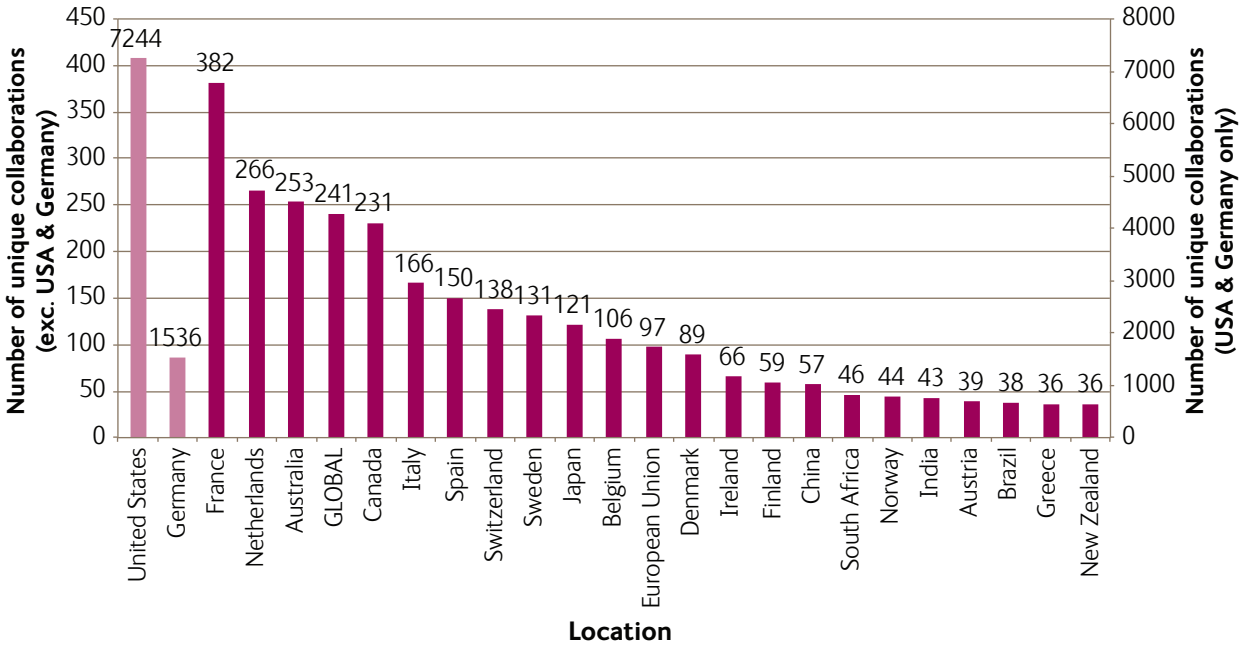


Figure 5: *Top 25 countries (excluding the UK) for number of unique collaborators*



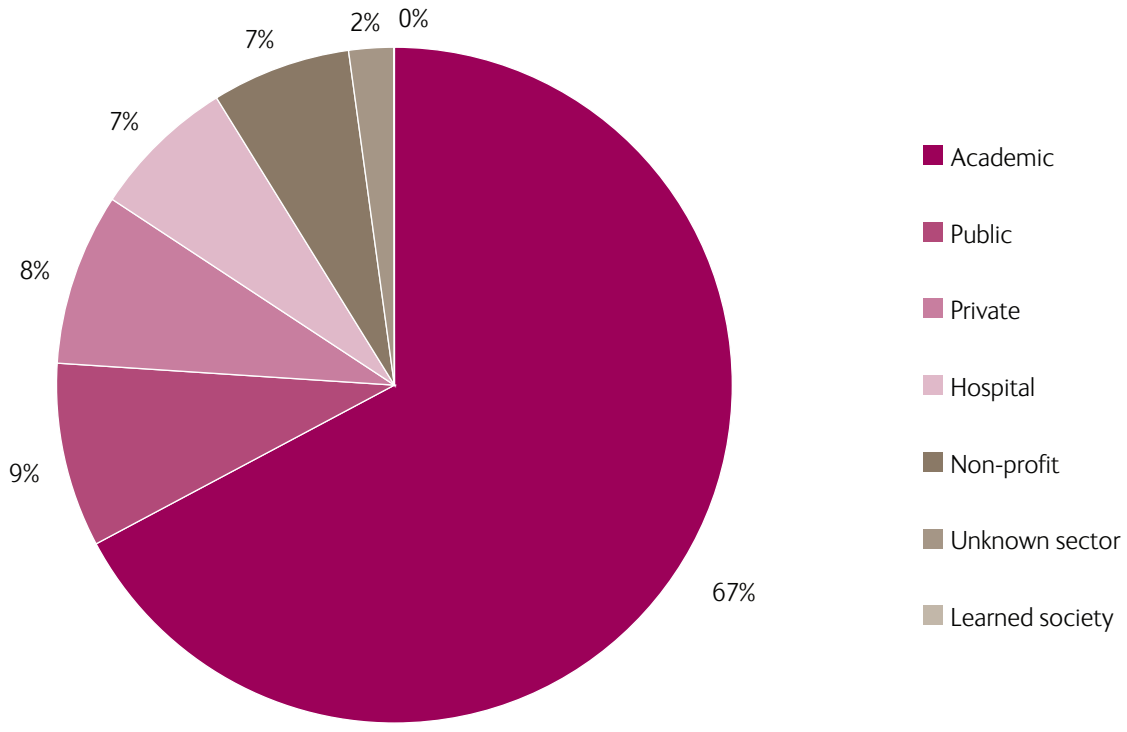
Collaborators by sector

- researchfish® data allows us to see the extent to which MRC researchers are engaging with collaborators from different sectors, including from the private sector.
- The majority of collaborators were from academia (67 per cent), followed by the public sector (8.8 per cent), the private sector (8.3 per cent) and hospitals (6.9 per cent). These proportions show a slight increase in collaborations in academia and the private sector (+9% and +1% respectively) and a slight decrease in collaborations in the public sector and 'unknown' (-6% and -4% respectively) compared to 2013/14 (see table 4 and figure 6).

Table 4: Collaborators by sector

Sector	Number of instances	Percentage of collaborations
Academic	10,373	67.2%
Public	1,361	8.8%
Private	1,270	8.2%
Hospital	1,066	6.9%
Non-profit	1,027	6.7%
Unknown sector	332	2.2%
Learned society	3	0.0%
Multiple	0	0.0%
Total	**15,432**	**100.0%**

Figure 6: Number of collaborators by research sector



3.3 Further funding

Summary

- Researchers reported instances of further funding in 47 per cent of awards.
- 12,140 instances of further funding were reported.
- The average number of instances of further funding for those who had reported further funding was four (4.33).
- Recipients of 202 awards (three per cent) reported more than 10 instances of further funding.

Further funding by year

- As with other output types, it takes time to apply for, obtain and initiate new grants and so recent awards will be naturally less likely to result in instances of further funding. Recipients of 65 per cent of grants starting in 2006 or earlier had reported further funding, compared to 25 per cent of grants starting in 2014. The number of awards reporting at least one instance of further funding by the year the award started is shown in table 1 and figure 1.
- Thirteen per cent of awards reported instances of further funding within one year, compared to 56 per cent after five years. Table 2 and figure 2 show the time between the start of the award and when the further funding started by award.

Table 1: *Number of awards reporting further funding by award start date*

Start year	Number of awards	Number with at least one instance of further funding	Number without any further funding	Percentage with at least one instance of further funding
2006 or earlier	2,059	1,337	722	65%
2007	484	332	152	69%
2008	586	387	199	66%
2009	572	380	192	66%
2010	477	283	194	59%
2011	418	214	204	51%
2012	517	224	293	43%
2013	657	217	440	33%
2014	195	49	146	25%
TOTAL	**5,965**	**3,423**	**2,542**	**57%**

Figure 1: Number of awards reporting further funding by award start date

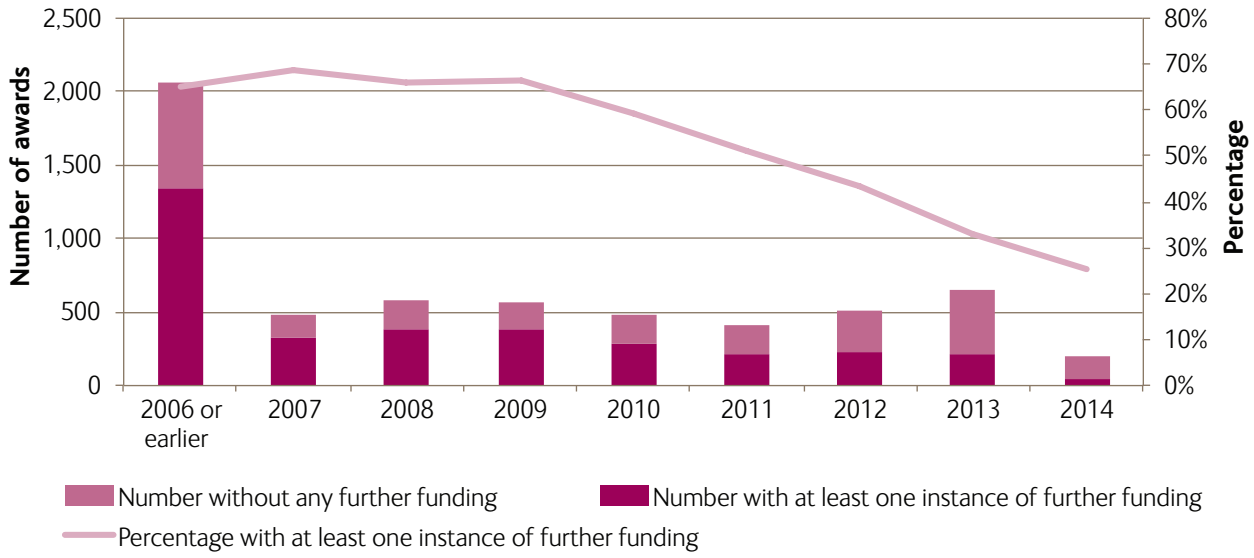
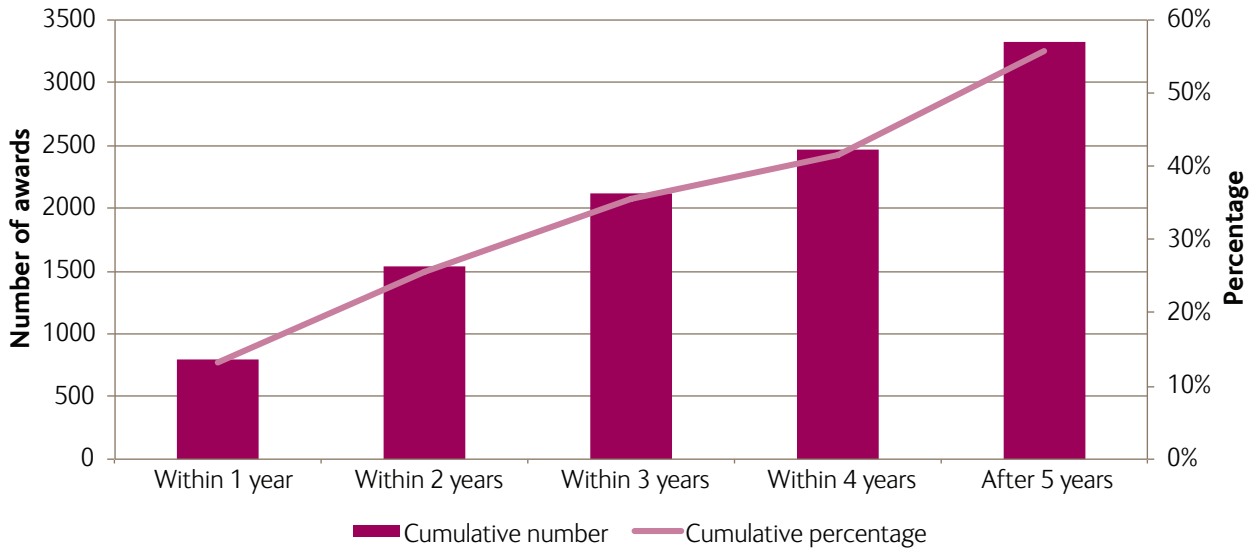


Table 2: Time between start of the award and further funding

First instance of further funding	Number reporting at least one instance of further funding	Cumulative number	Cumulative percentage
Within 1 year	788	788	13%
Within 2 years	745	1,533	26%
Within 3 years	586	2,119	36%
Within 4 years	354	2,473	41%
After 5 years	856	3,329	56%

Figure 2: Time between start of the award and further funding

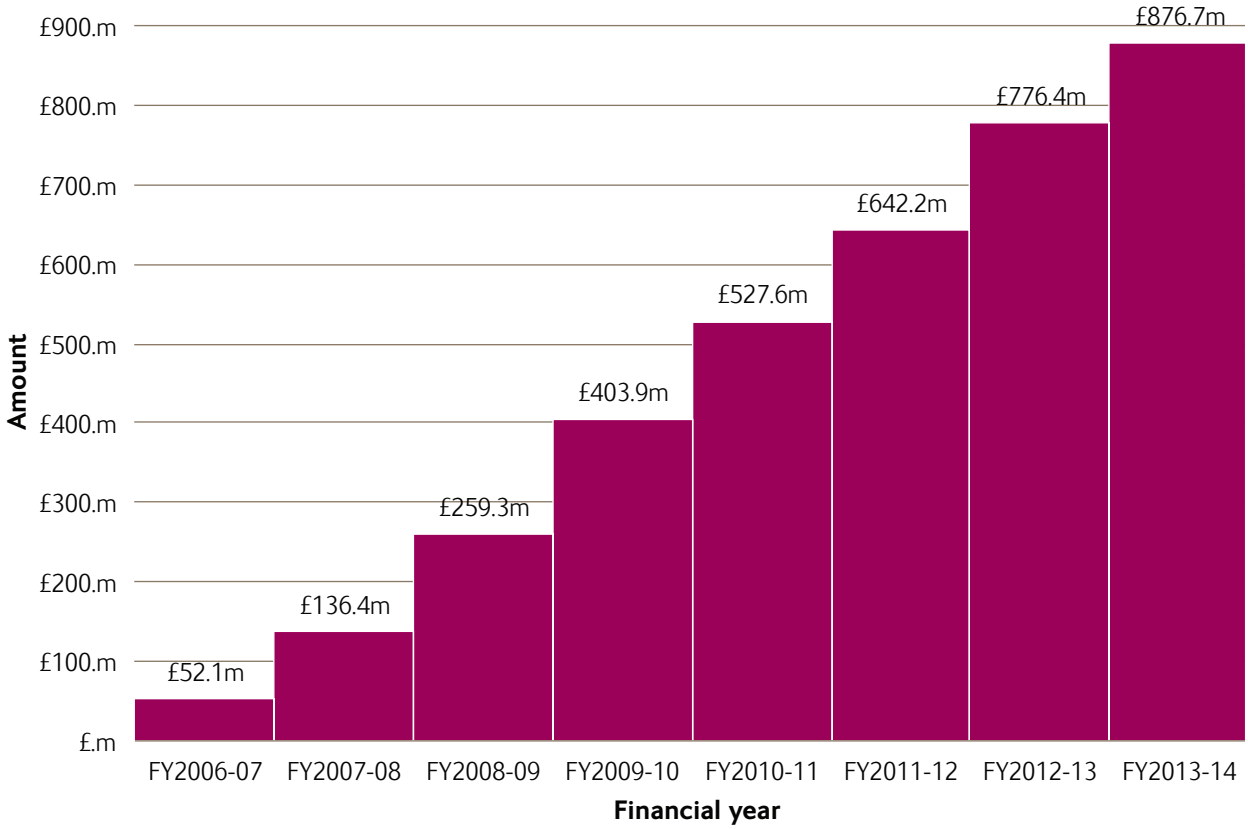


Further funding by value

- Researchers reported a total value of £4.2bn in further funding[612] since 2006, with the average total value being £1.5m amongst those reporting further funding. 12 per cent of awards received more than £1m in further funding.
- A total value of £877m was reported to have been leveraged in 2013/2014, which is an increase on last year's total of £698m. The value of further funding by year is shown in figure 3.

In 2015 data from the MRC researchfish® dataset was used to investigate the relationship between public funding for research and private investment in science[613]. This analysis provided evidence for estimates that £1 of public funding for research leverages between £1.1 and £1.6 in private sector funding. In this study, and according to Organisation for Economic Co-operation and Development (OECD) definitions, charity funding for research was considered as part of the 'private' sector.

Figure 3: Value of further funding by year



Further funding by location and sector

- The sources of further funding have been coded for country and sector to gain a greater understanding of the importance of other countries, governments, companies and non-profit organisations that support the same research teams as the MRC.
- The majority of further funding reported in researchfish® was leveraged from the United Kingdom between 2006 and 2014 - 71 per cent of further funding (£2.9bn). 13 per cent of further funding (£529m) was obtained from the rest of Europe, as shown in table 3 and figure 4.
- A further 13 per cent of further funding (£534m) was obtained from North America, with the remaining three per cent (£140m) obtained from other continents or global institutions. Table 4 and figure 5 shows the amount of further funding by global location (excluding Europe).

  The largest value of further funding between 2006 and 2014 came from non-profit organisations (£1.9bn – 46 per cent of the total further funding reported), which highlights the importance of medical research charities to the funding of medical research in the UK. The next largest source of funds was the public (mainly government) sector (£1.4bn – 34 per cent of the total further funding reported). Table 5 and figure 6 show the value of further funding by sector.
- Seven per cent of further funding (£286m) was leveraged from the private sector between 2006 and 2014. In 2013/14, this figure was £197m (six per cent). However it should be highlighted that the detail of collaborations shows that private sector contributions are mostly 'in kind'. These are difficult to monetise, but likely to represent a substantial investment in research.
- The Wellcome Trust provided the largest value of further funding, contributing £712m between 2006 and 2014. This was followed by the National Institute for Health Research (£492m). The top 10 funders by value are shown in table 6.
- The largest overseas funder was the European Commission, contributing £337m between 2006 and 2014, followed by the National Institutes of Health (£159m).
- The largest single private sector funder is Merck & Co., Inc., providing around £136m in this period.

Figure 4: *Amount of further funding by location (European, excluding UK)*

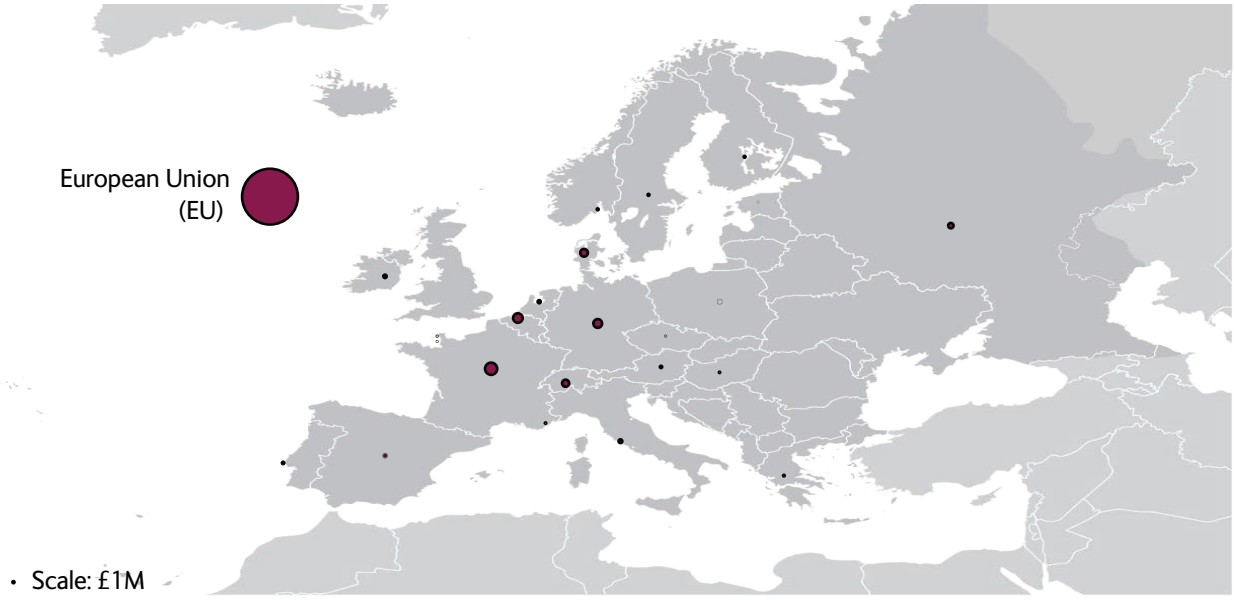


Table 3: Amount of further funding by location (European, excluding UK)

Country	Amount	Percentage
European Union (EU)	£670m	86%
France	£32m	4%
Belgium	£19m	2%
Germany	£16m	2%
Denmark	£13m	2%
Switzerland	£11m	1%
Russian Federation	£6m	1%
Italy	£3m	0%
Ireland	£2m	0%
Netherlands	£2m	0%
Spain	£2m	0%
Portugal	£1m	0%
Austria	£1m	0%
Sweden	<£1m	0%
Finland	<£1m	0%
Norway	<£1m	0%
TOTAL	**£782m**	**100%**

Table 4: Amount of further funding by location (International, excluding Europe)

Country	Amount	Percentage
United States of America	£507m	74%
Global Institutions	£100m	14%
Canada	£28m	4%
Australia	£22m	3%
Hong Kong	£11m	2%
Japan	£7m	1%
Tunisia	£4m	1%
India	£3m	0%
Pakistan	£2m	0%
Saudi Arabia	£1m	0%
China	£1m	0%
South Korea	<£1m	0%
Colombia	<£1m	0%
New Zealand	<£1m	0%
Israel	<£1m	0%
Qatar	<£1m	0%
TOTAL	**£690m**	**100%**

Figure 5: Amount of further funding by location (international, excluding Europe)

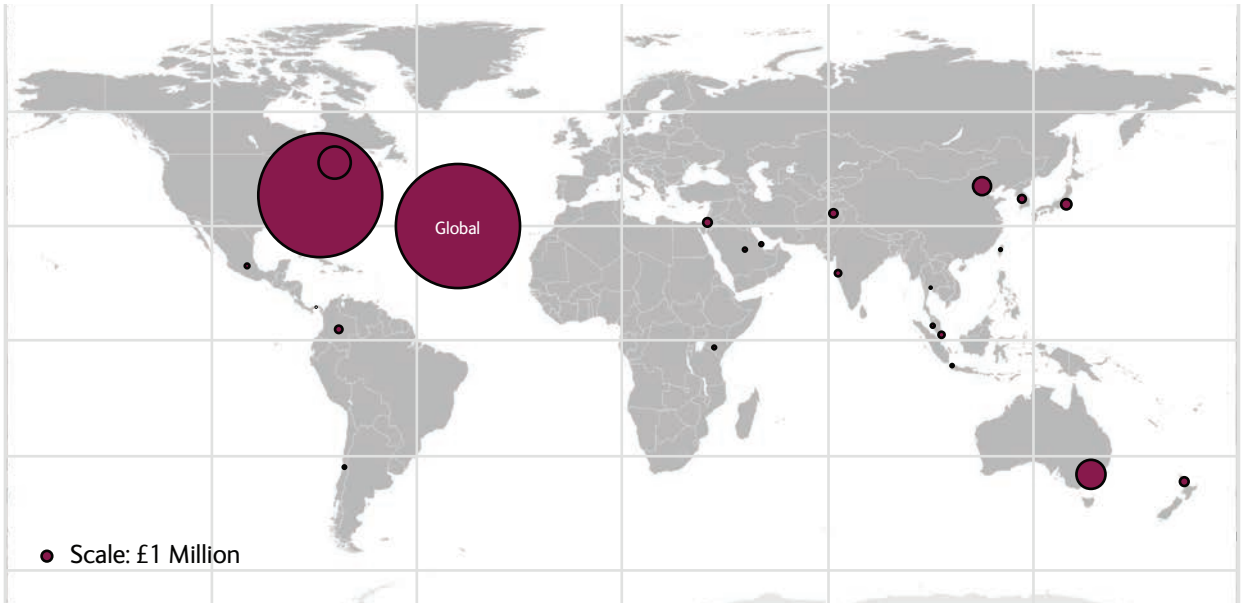


Table 5: Value of further funding by sector

Sector	Amount	Percentage
Non-profit	£1,881m	46%
Public	£1,376m	34%
Academic	£493m	12%
Private	£286m	7%
Hospital	£53m	1%
Learned society	<£1m	<1%
Multiple sectors	£0m	0%
Unknown	£0m	0%
TOTAL	**£4,090m**	**100%**

Figure 6: Percentage of further funding by sector

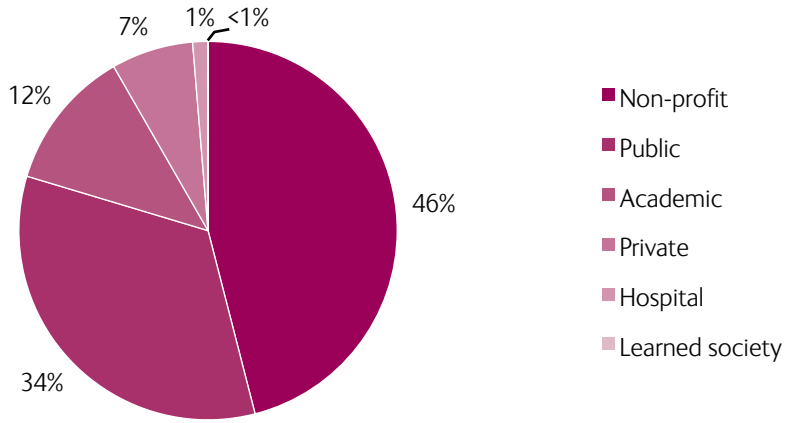


Table 6: Top 10 funders by value

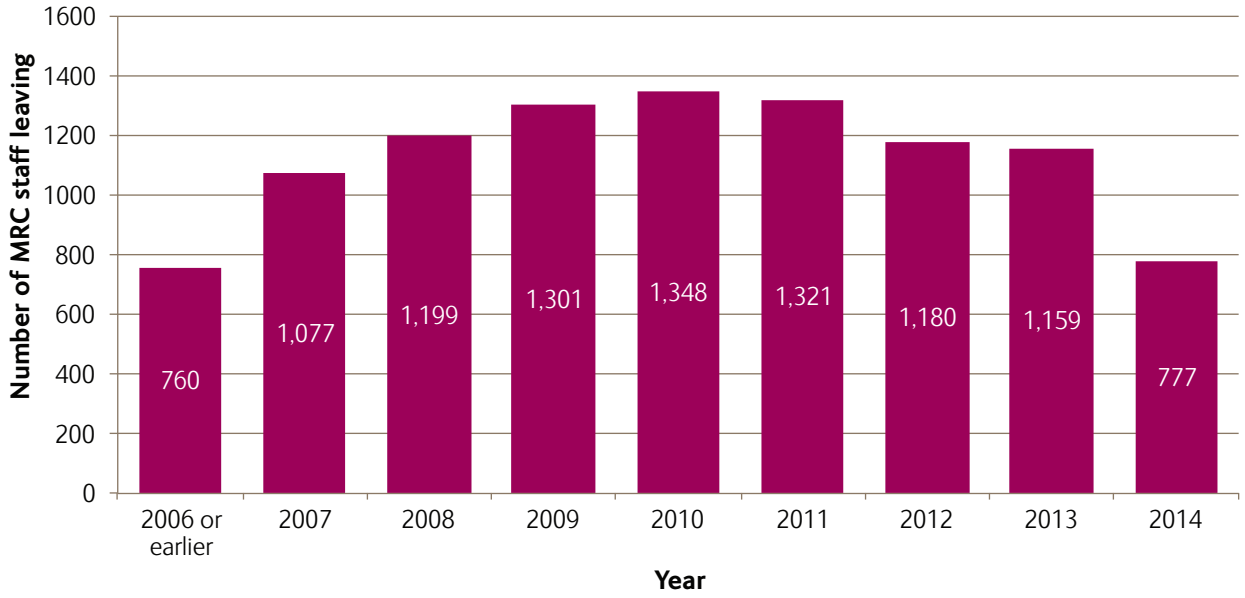
Top funders	Pro-rated spending
The Wellcome Trust	£712m
National Institute for Health Research (NIHR)	£493m
European Commission (EC)	£337m
Biotechnology and Biological Sciences Research Council (BBSRC)	£184m
Cancer Research UK (CRUK)	£170m
National Institutes of Health (NIH)	£159m
Engineering and Physical Sciences Research Council (EPSRC)	£146m
Merck & Co, Inc (MSD)	£136m
British Heart Foundation (BHF)	£111m
Bill and Melinda Gates Foundation	£109m

3.4 Next destination

Summary

- Principal investigators reported details of staff who had left MRC support in 51 per cent of MRC awards, with 10,209 reports between 2006 and 2014[614].
- On average, there were three instances (3.36) reported per award (for those awards where it was reported staff had left).
- Figure 1 shows the number of staff leaving MRC support by year, as reported in researchfish®. The data includes people leaving MRC awards that have terminated, people leaving for opportunities elsewhere or retiring, and people leaving fixed-term positions such as studentships.

Figure 1: Number of staff leaving MRC support by year



Positions held at the MRC and future positions

- 35 per cent of staff leaving the MRC were in a post-doctoral position, 23 per cent held a researcher position, 17 per cent were research fellows and 17 per cent were research students. The distribution of all roles held is shown in figure 2.
- The majority of next destinations for research students leaving the MRC were described as 'post-doctoral researcher' (56 per cent), followed by 'student' (13 per cent). A breakdown of next destinations of research students is shown in figure 3.
- The majority of post-doctoral researchers left MRC support to take up a further post-doctoral position (56 per cent), followed by research fellow/project leader (18 per cent). A breakdown of next destinations of post-doctoral researchers is shown in figure 4.
- Overall, 61 per cent of staff remained in the academic (university-based) sector. 10 per cent of leavers moved into the private sector. figure 5 shows a breakdown of next destinations by sector. These results are very similar to those published last year.

Figure 2: Distribution of roles held by staff leaving the MRC

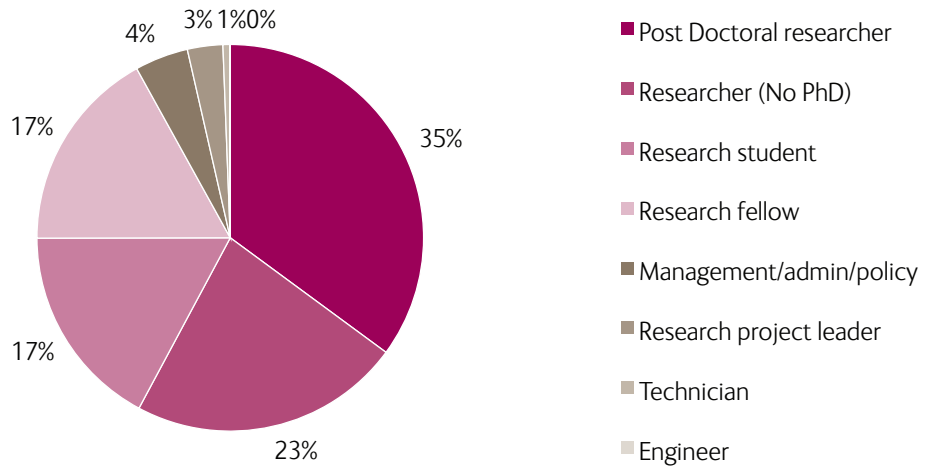


Figure 3: Distribution of next destinations of research students

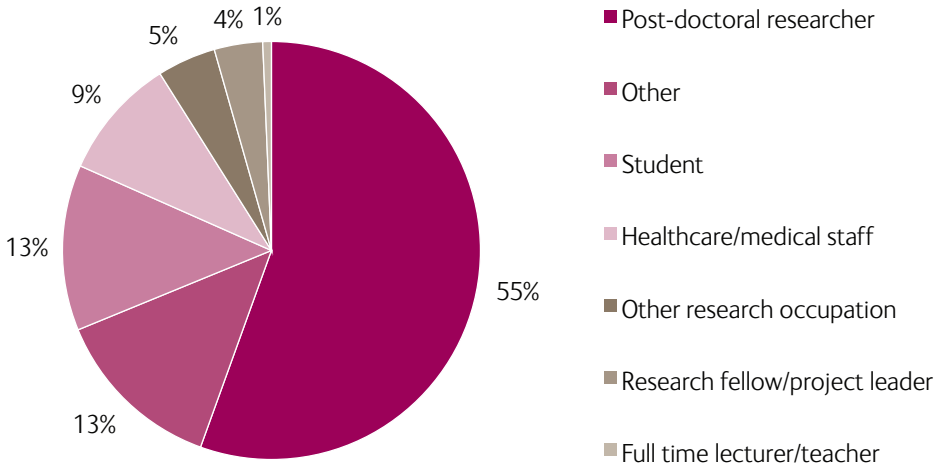


Figure 4: Distribution of next destinations of post-doctoral researchers

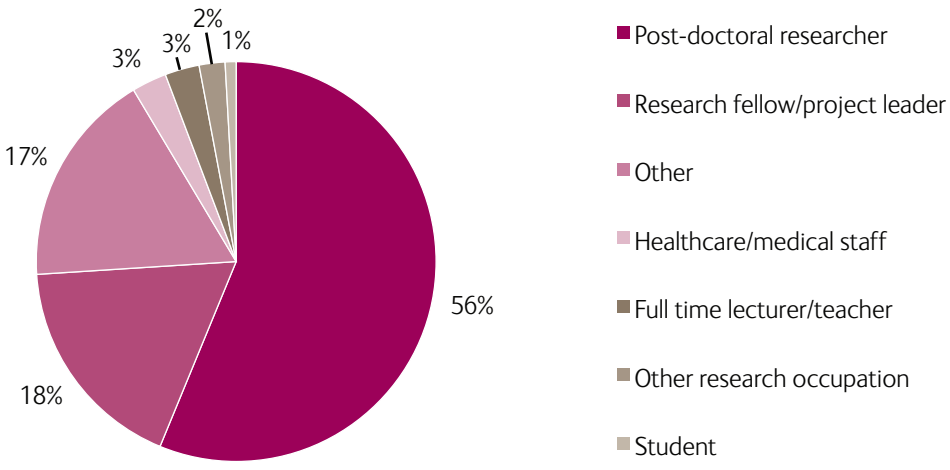
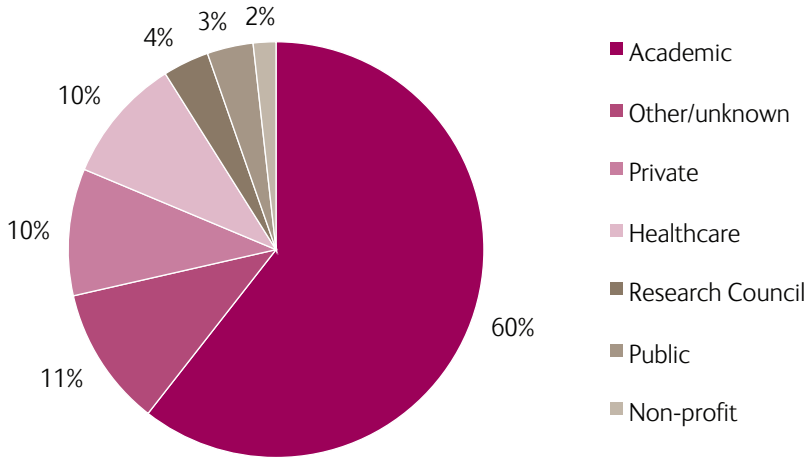


Figure 5: Distribution of next destinations by sector



3.5 Engagement activities

Summary

- Researchers reported participating in engagement activities outside of academia in 59 per cent of awards, an increase on last year's figure of 56 per cent.
- The total number of engagement activities reported between 2006 and 2014 was 35,765[615].
- The average number of engagement activities per award (for awards reporting engagement activities) was 10 (10.05), an increase on last year's average of seven.
- 15 per cent of all awards reported more than 10 engagement activities, again an increase on last year's figure of 11 per cent.
- Some of the increase in reporting in this section may be due to adding the option to report scientific conferences.

Engagement activities by year

- There were 4,756 instances of engagement activities starting in 2014. A breakdown of engagement activities per year is shown in figure 1.
- The longer that an award has been running, the greater number of opportunities to participate in engagement activities there are. Recipients of 63 per cent of awards starting in 2006 or earlier reported at least one engagement activity, compared to 35 per cent of awards starting in 2014. The number of awards reporting at least one engagement activity by start year is shown in table 1 and figure 2.
- Twenty two per cent of awards reported at least one engagement activity within one year of the award starting compared to 60 per cent after five years. The time between the award starting and the engagement activity taking place is shown in table 2 and figure 3.

Figure 1: Breakdown of engagement activities per year

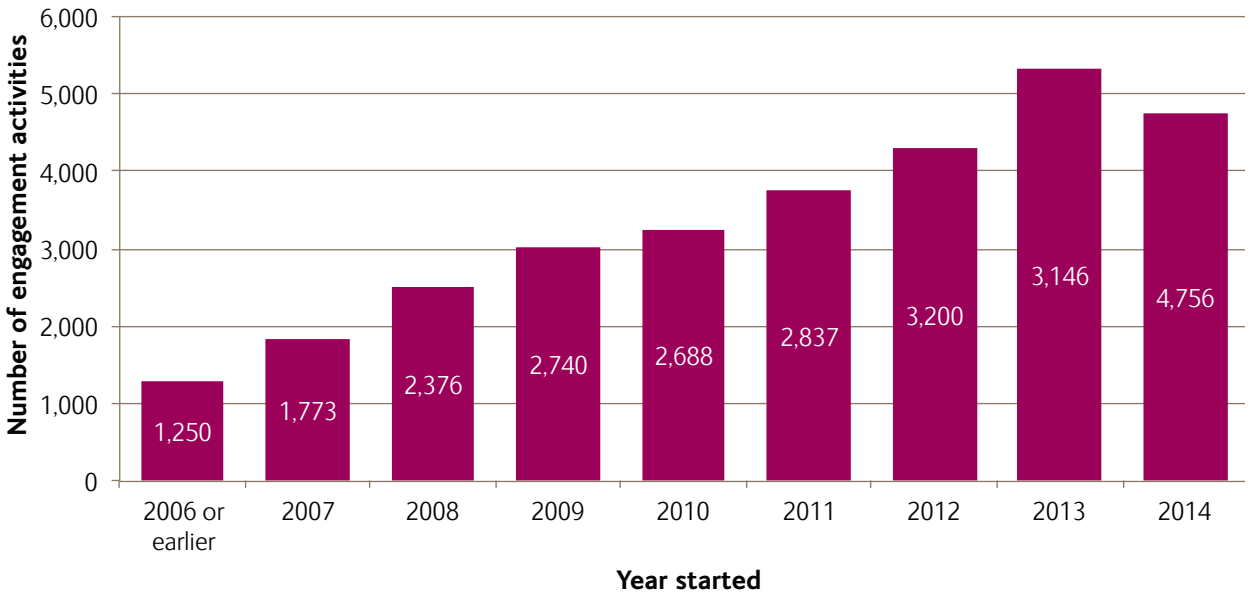


Table 1: Number of awards reporting at least one engagement activity by start year

Year	Number of instances	Number with at least one engagement activity	Number with no engagement activities	Percentage with at least one engagement activity
2006 or earlier	2,059	1,291	768	63%
2007	484	321	163	66%
2008	586	390	196	67%
2009	572	366	206	64%
2010	477	300	177	63%
2011	418	239	179	57%
2012	517	283	234	55%
2013	657	302	355	46%
2014	195	68	127	35%
TOTAL	**5,965**	**3,560**	**2,405**	**60%**

Figure 2: Number of awards reporting at least one engagement activity by start year

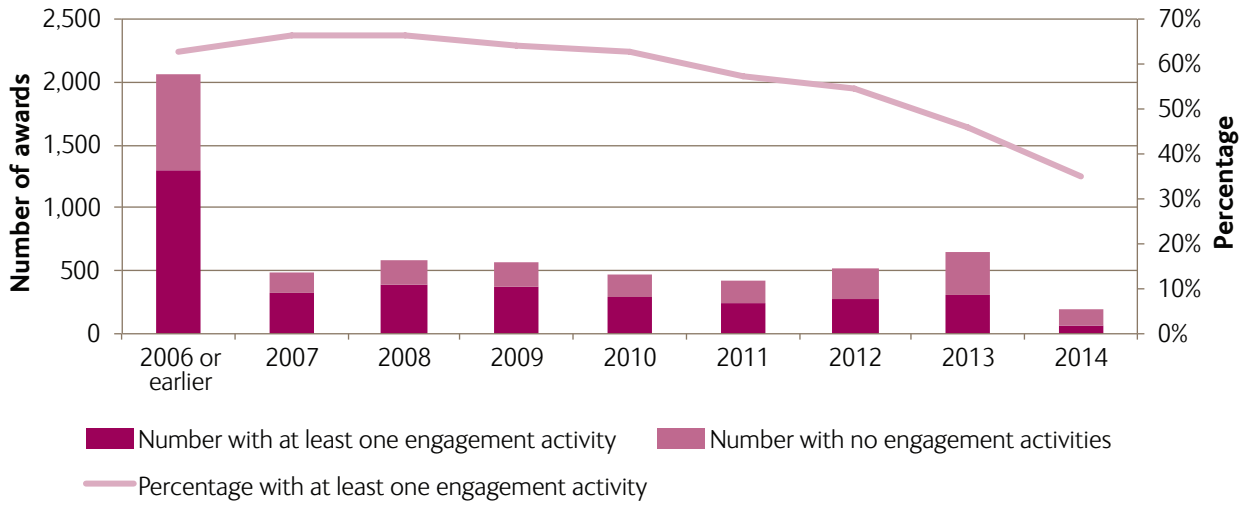
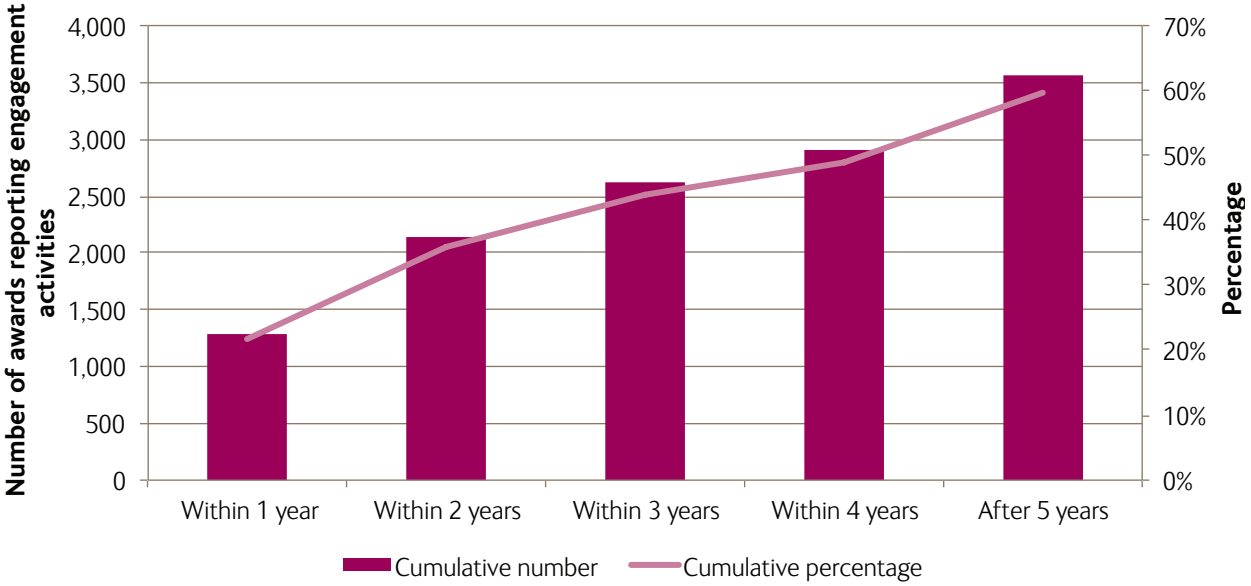


Table 2: Time between the award starting and engagement activity taking place

First public engagement activity	Number with at least one engagement activity	Cumulative number	Cumulative percentage
Within 1 year	1,294	1,294	22%
Within 2 years	841	2,135	36%
Within 3 years	496	2,631	44%
Within 4 years	285	2,916	49%
After 5 years	644	3,560	60%

Figure 3: Time between the award starting and engagement activity taking place



Engagement activity by type and audience

- Engaging with audiences outside of academia[616] is an important part of the research process. It helps to enhance understanding of complex topics, communicate the importance of research carried out and inspire future careers in science.
- The most popular method of engagement was a talk or presentation (37 per cent), followed by participation in an activity, workshop or similar (16 per cent). A full breakdown of engagement activities by type is shown in table 3 and figure 4.
- Around a third of engagement activities were aimed at the public/other audiences (30 per cent), while 13 per cent were aimed at health professionals and 19 per cent at other academic audiences. A more detailed breakdown of engagement activities by audience type is shown in table 4 and figure 5.

Table 3: Engagement activities by type

Engagement activity	Number of instances	Percentage
A talk or presentation	11,009	37%
Participation in an activity, workshop or similar	4,864	16%
A magazine, newsletter or online publication	3,559	12%
Scientific meeting (conference/symposium etc)	3,388	11%
A formal working group, expert panel or similar	2,716	9%
A press release, press conference or response to a media enquiry.	2,347	8%
Participation in an open day or visit at my research institution	2,192	7%
Total	**30,075**	**100%**

Figure 4: Engagement activities by type

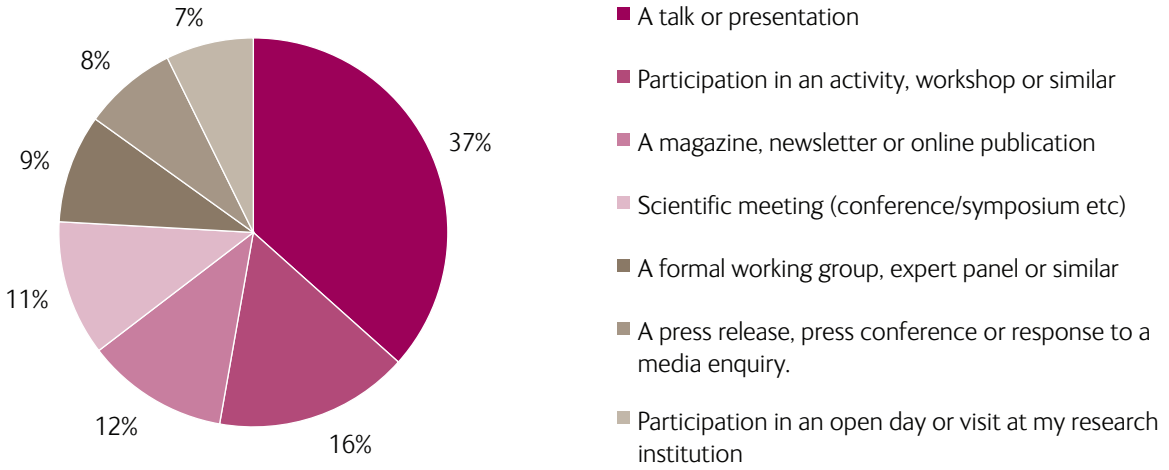
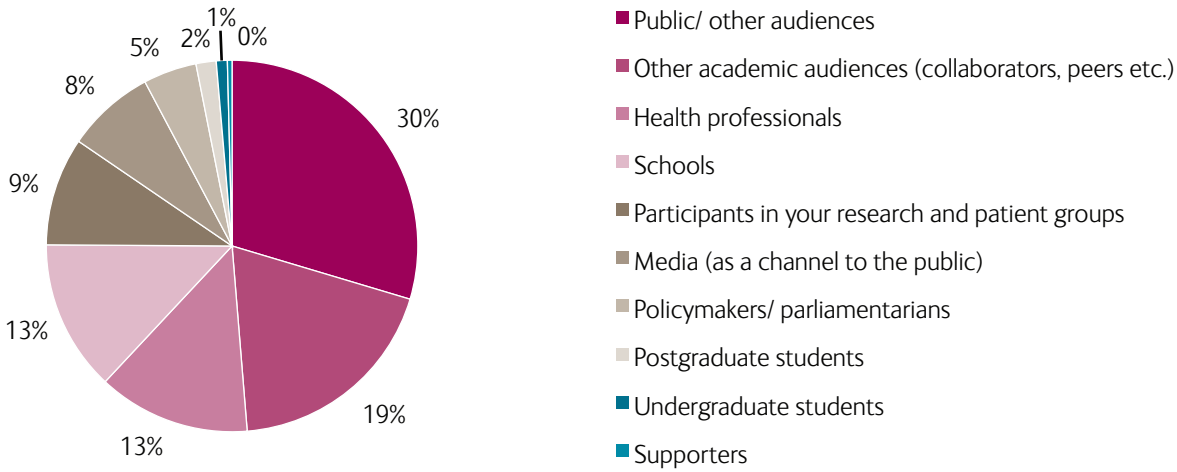


Table 4: Engagement activities by audience type

Audience type	Number of instances	Percentage
Public/ other audiences	8,385	30%
Other academic audiences (collaborators, peers etc.)	5,400	19%
Health professionals	3,755	13%
Schools	3,718	13%
Participants in your research and patient groups	2,669	9%
Media (as a channel to the public)	2,181	8%
Policymakers/ parliamentarians	1,315	5%
Postgraduate students	497	2%
Undergraduate students	272	1%
Supporters	114	0%
TOTAL	**28,306**	**100%**

Figure 5: Engagement activities by audience type



3.6 Influence on policy

Summary

- MRC researchers reported 5,017 examples of influences on policy between 2006 and 2014.
- Influences on policy were reported in more than a fifth (23 per cent) of all awards. In these awards, the average number of influences on policy was three (3.64).

Influences on policy by year

- A total of 416 policy influences started in 2014. A breakdown of policy influences by year is shown in figure 1.
- As with other output types, there is naturally a time lag between the award being made and the influence on policy being realised. More than a quarter (26 per cent) of awards made in 2006 or earlier reported at least one policy influence, compared to just eight per cent in 2014. Table 1 and figure 2 show the number of policy influences by award start year.
- 23 per cent of awards reported at least one policy influence within five years after the award starting, compared to five per cent within one year. Table 2 and figure 3 show the time taken to report the first policy influence.

Figure 1: Policy influence by year realised

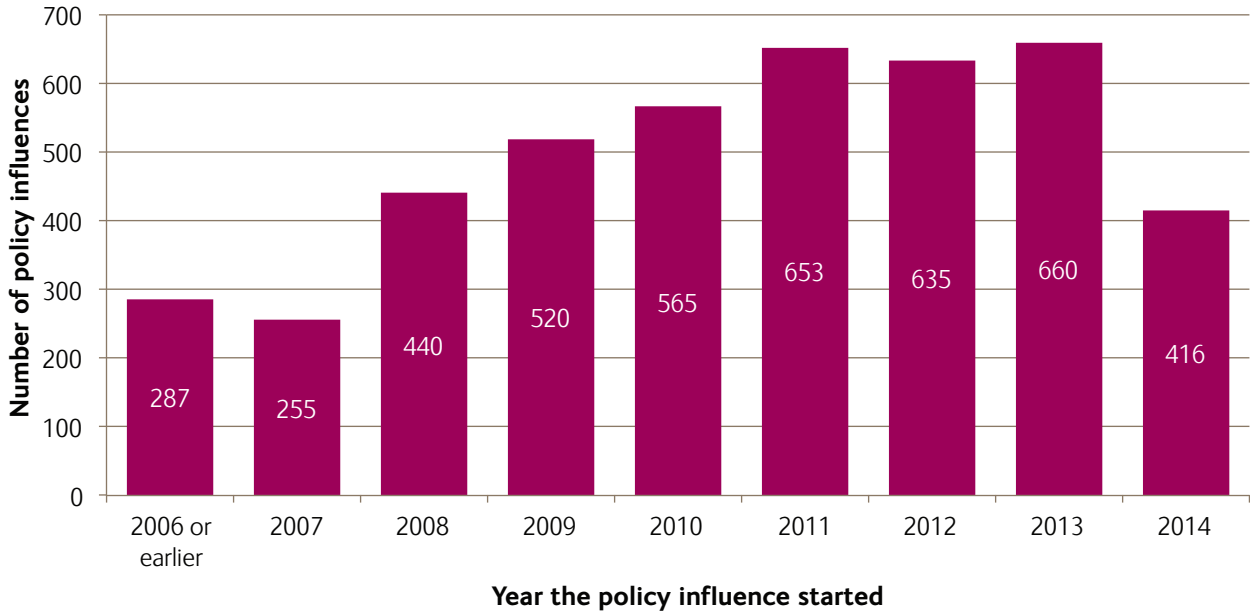


Table 1: Policy influence by award start year

Year	Number of awards	Number with at least one policy influence	Number with no policy influences	Percentage with at least one policy influence
2006 or earlier	2,059	544	1,515	26%
2007	484	120	364	25%
2008	586	153	433	26%
2009	572	153	419	27%
2010	477	126	351	26%
2011	418	85	333	20%
2012	517	89	428	17%
2013	657	92	565	14%
2014	195	16	179	8%
TOTAL	**5,965**	**1,378**	**4,587**	**23%**

Figure 2: Policy influence by award start year

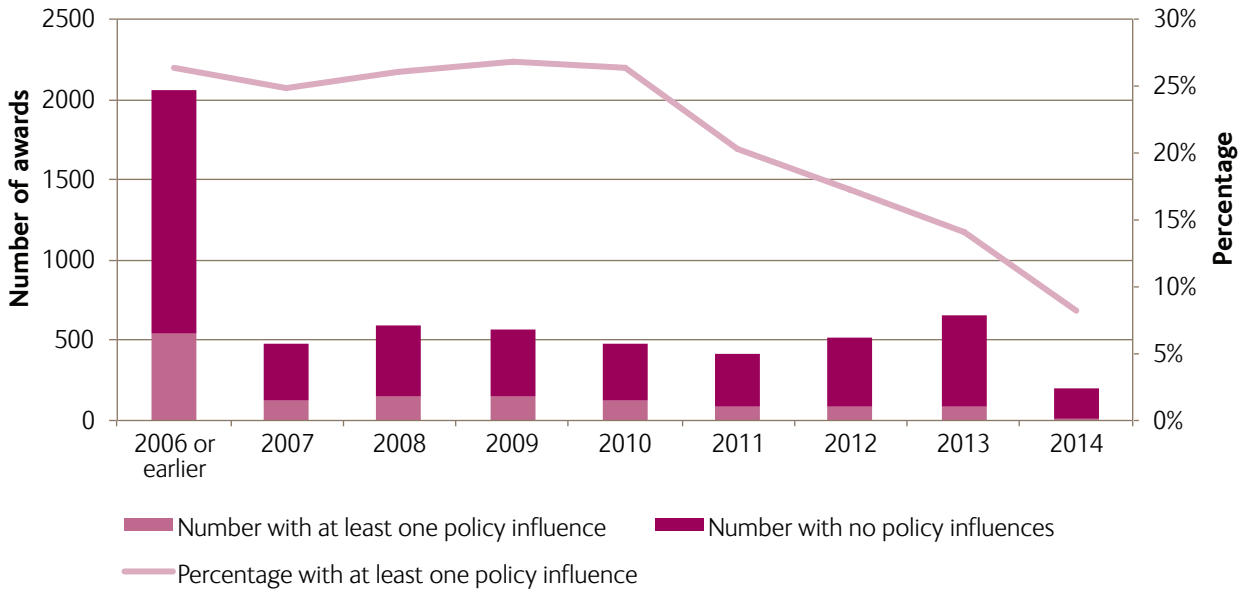
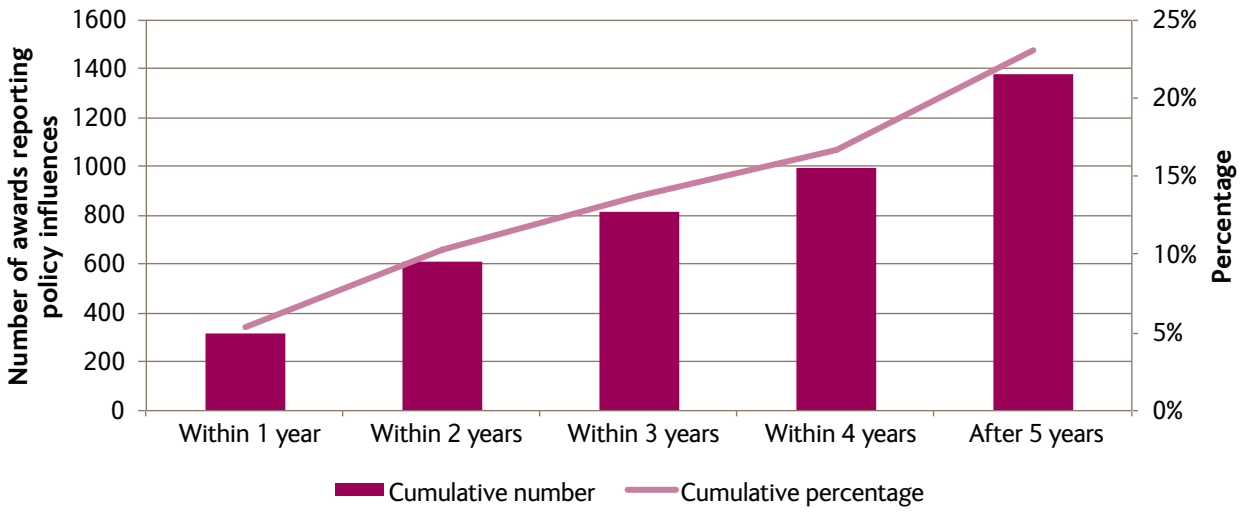


Table 2: Time taken to report first policy influence

First instance of policy influence	Number	Cumulative number	Cumulative percentage
Within 1 year	319	319	5%
Within 2 years	295	614	10%
Within 3 years	203	817	14%
Within 4 years	181	998	17%
After 5 years	380	1,378	23%

Figure 3: Time taken to report first policy influence



Policy influence by type and location

- Once unique policy outputs have been identified, the type of policy influence can be divided into citations in key policy documents (1,003/4,419 - 23 per cent of all policy influences) and influences on policy setting processes (3,416/4,419 – 77 per cent.
- A breakdown of policy influence by type is shown in table 3 and figure 4.
- Just over half of all policy influences (56 per cent – the sum of UK and UK local/regional only) occurred in the UK. A further 25 per cent of policy outputs had a multiple country/international influence, and the remaining 19 per cent occurred in continental regions outside of the UK. A breakdown of policy influences by location is shown in table 4 and figure 5.

Table 3: Policy influence by type

Influence Type	Number	Percentage
Key policy documents		
Citation in clinical guidelines	472	11%
Citation in clinical reviews	96	2%
Citation in other policy documents	326	7%
Citation in systematic reviews	109	2%
Policy-setting processes		
Gave evidence to a government review	246	6%
Influenced training of practitioners or researchers	946	21%
Membership of a guideline committee	547	12%
Participation in an advisory committee	1,226	28%
Participation in a national consultation	378	9%
Implementation circular/rapid advice/letter	72	2%
Other	1	0%
TOTAL	**4,419**	**100%**

Figure 4: Policy influence by type

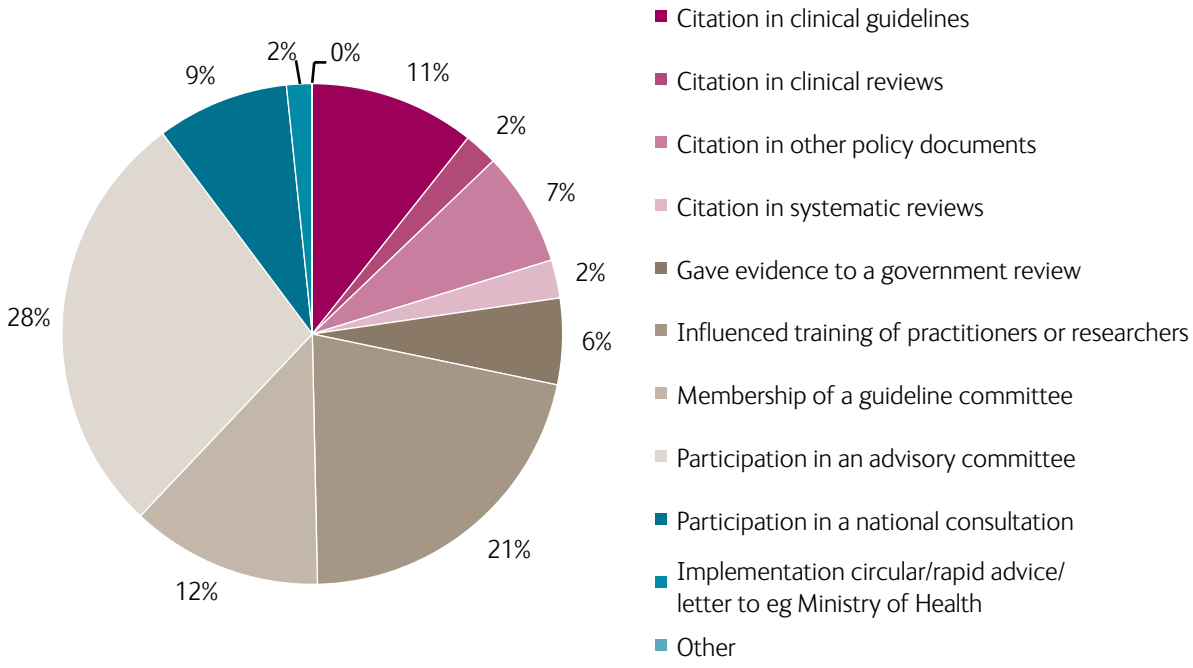
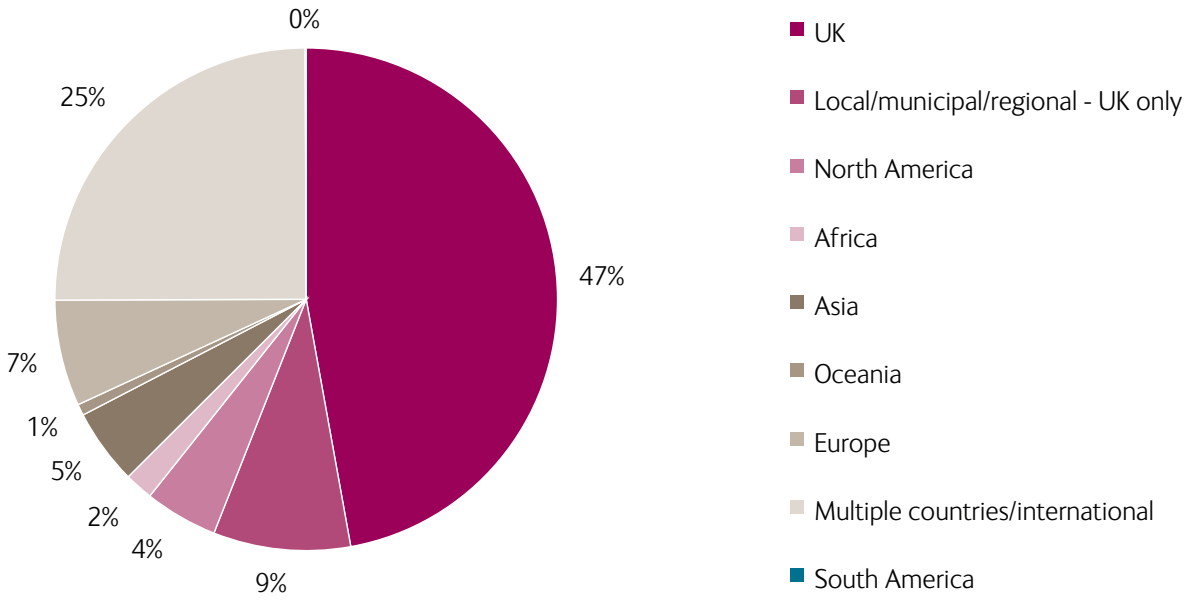


Table 4: Policy influence by location

Location of policy influence	Number	Percentage
UK	2,084	47%
Local/municipal/regional - UK only	390	9%
North America	208	5%
Africa	81	2%
Asia	215	5%
Oceania	32	1%
Europe	302	7%
Multiple countries/international	1,104	25%
South America	3	0%
TOTAL	**4,419**	**100%**

Figure 5: Policy influence by location



3.7 Research materials – tools and methods, databases and models

Summary

- researchfish® subdivides research materials into two categories; 'research tools and methods' and 'research databases and models'.
- Recipients of 1,682 (28 per cent of total) awards reported that their work had produced research tools or methods for others to use. Research databases or models were reported in 150 (three per cent of total) awards.
- The average number of research tools and methods for awards reporting at least one instance was two (2.3). Of the 209 reports of research databases and models, the average number reported per award was one (1.39).

Research tools and methods by year

- Between 2006 and 2014, 3,839 reports of research tools or methods have been made. The year when the research tools and methods were first made available is shown in figure 1.
- The longer that an award has been running, the greater number of opportunities there are to create and share research materials. 40 per cent of awards starting in 2006 or earlier resulted in the production of a research tool or method, compared to five per cent of awards starting in 2014. Table 1 and figure 2 show the number of materials reported by award start year.
- 28 per cent of awards reported at least one research tool or method within five years[617], compared to just five per cent within one year. Table 2 and figure 3 show the time taken to report the first research tool or method.

Figure 1: Distribution of when the research tool or method was first made available

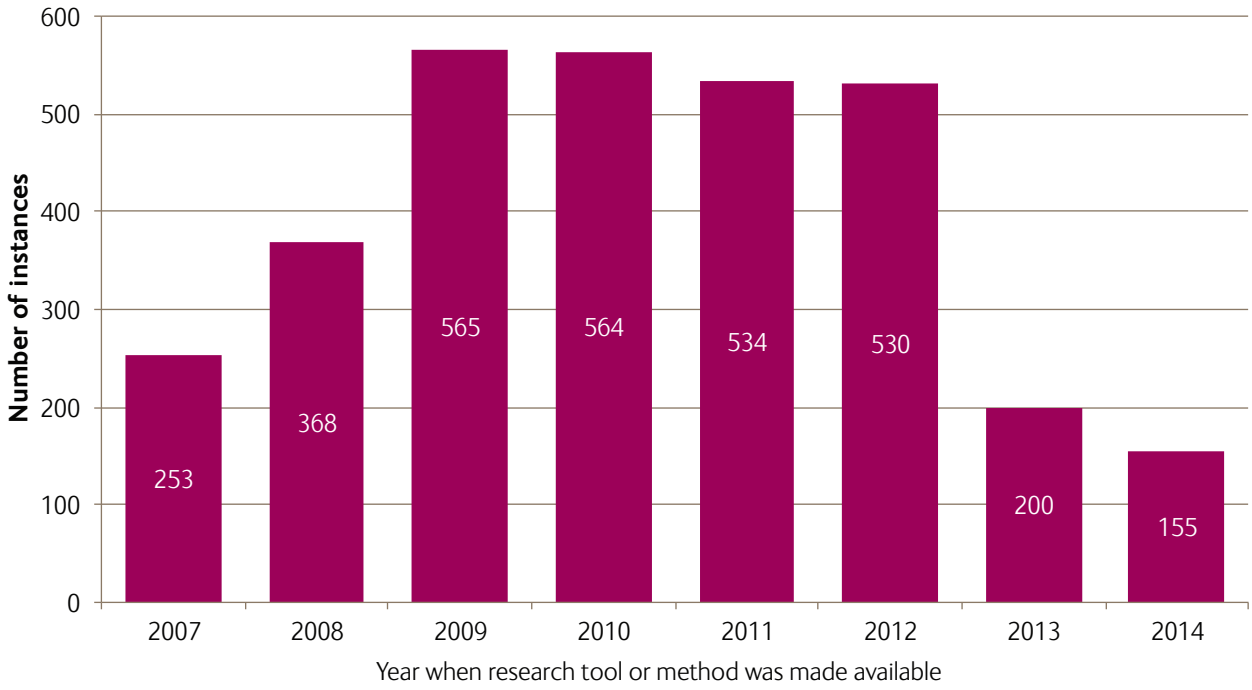


Table 1: Research materials by award start year

Year research tool or method first available	Number of awards	Number with at least one research tool or method	Number with no research tool or method	Percentage with at least one research tool or method
2006 or earlier	2,059	818	1,241	40%
2007	484	179	305	37%
2008	586	200	386	34%
2009	572	185	387	32%
2010	477	124	353	26%
2011	418	66	352	16%
2012	517	59	458	11%
2013	657	45	612	7%
2014	195	9	186	5%
TOTAL	**5,965**	**1,685**	**4,280**	**28%**

Figure 2: Research tools and methods (RTOM) by award start year

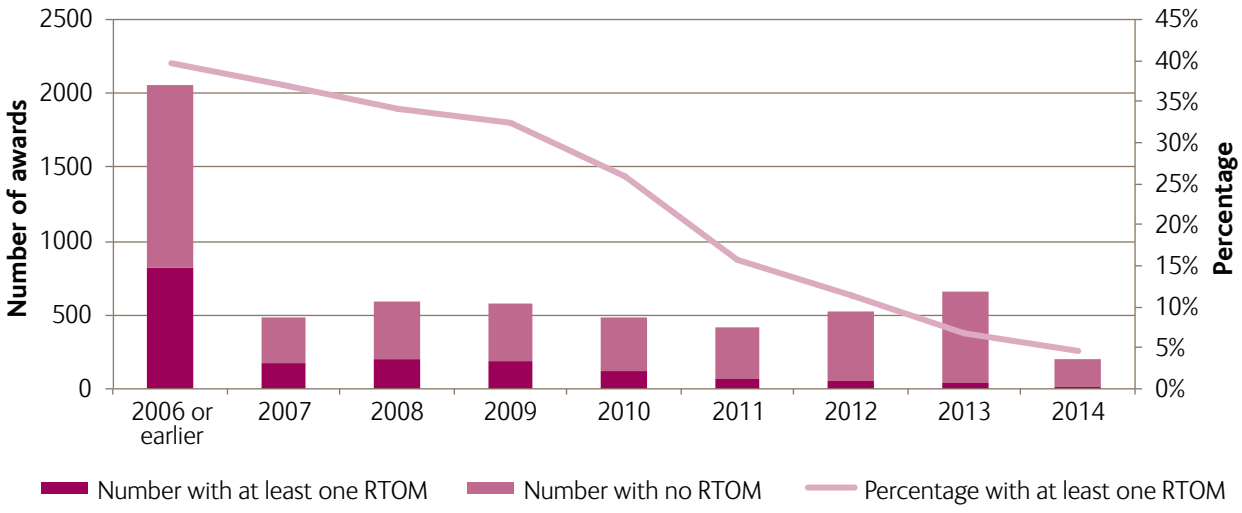
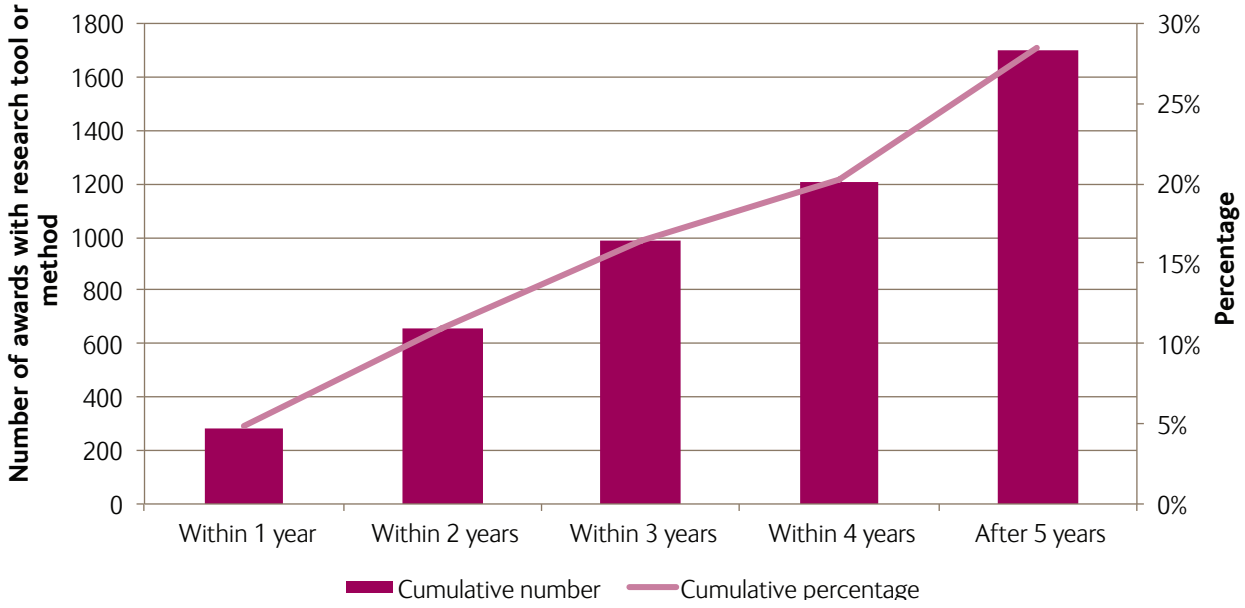


Table 2: Time taken to report the first research tool or method

Research tool or method first available	Number reporting at least one research tool or method	Cumulative number	Cumulative percentage
Within 1 year	287	286	5%
Within 2 years	370	657	11%
Within 3 years	320	983	16%
Within 4 years	220	1,205	20%
After 5 years	488	1,698	28%

Figure 3: Time taken to report the first research material



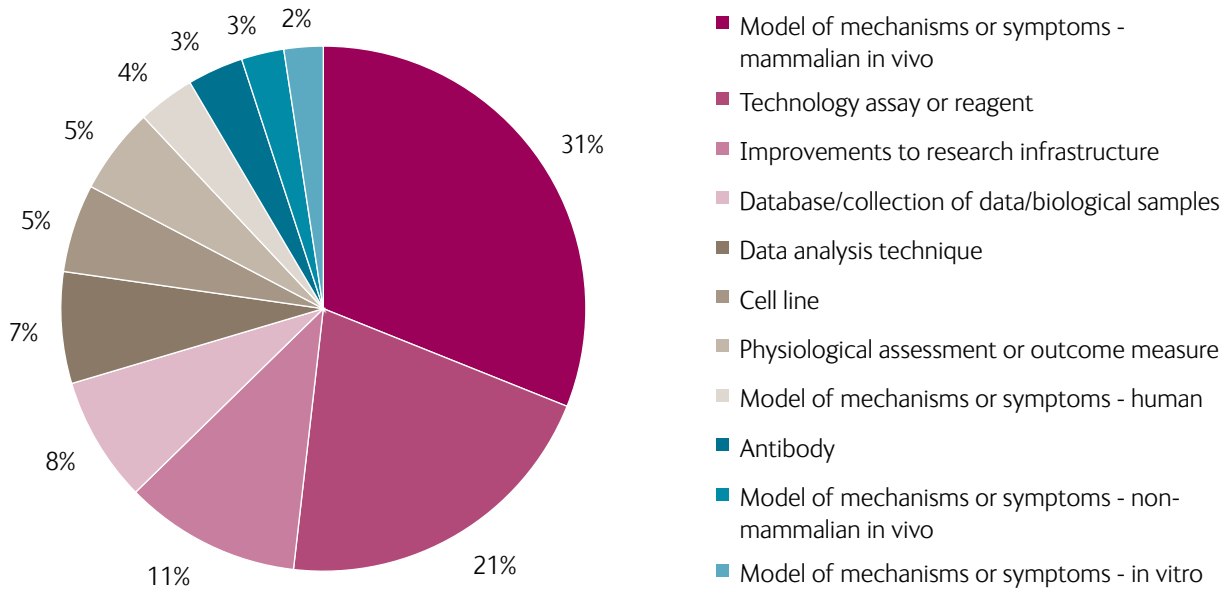
Research tool or method by type

» Models of mechanisms or symptoms – non-mammalian in vivo were the most common type of research tool or method reported (28 per cent), followed by database/collection of data/biological samples (19 per cent). Table 3 and figure 4 show a breakdown of the type of research tool or method reported.

Table 3: Research tool or method by type

Type of research tool or method	Number	Percentage
Model of mechanisms or symptoms - mammalian in vivo	1,018	31%
Technology assay or reagent	680	21%
Improvements to research infrastructure	356	11%
Database/collection of data/biological samples	253	8%
Data analysis technique	225	7%
Cell line	178	5%
Physiological assessment or outcome measure	174	5%
Model of mechanisms or symptoms - human	115	4%
Antibody	113	3%
Model of mechanisms or symptoms - non-mammalian in vivo	86	3%
Model of mechanisms or symptoms - in vitro	79	2%
TOTAL	**3,277**	**100%**

Figure 4: Research tool or method by type



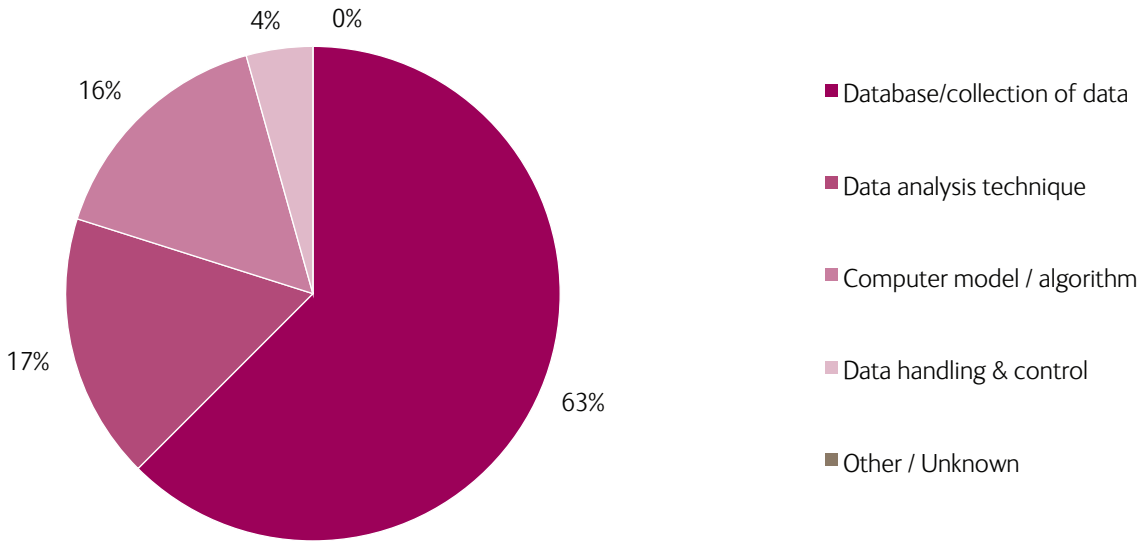
Research database or model by type

» Database/collection of data were the most common type of research database or model reported (63 per cent), followed by data analysis technique (17 per cent). Table 4 and figure 5 show a breakdown of the type of research database or model reported.

Table 4: Research tool or method by type

Type of research database or model	Number of instances	Percentage
Database/collection of data	115	63%
Data analysis technique	32	17%
Computer model/algorithm	29	16%
Data handling and control	8	4%
Other /unknown	0	0%
TOTAL	**184**	**100%**

Figure 5: Research database or model by type



3.8 Intellectual property

Summary

» The MRC dataset contains details of 1,213 discoveries in the intellectual property section. These include 83 reports of copyrighted works, 309 reports of discoveries for which formal protection was not possible or required, and 661 reports relating to published and granted patents.

Intellectual property by year

» Creating intellectual property can take a long time and therefore the longer that an award has been running for, the greater number of opportunities there are to create a patentable idea. 12 per cent of awards starting in 2006 or earlier reported at least one item of intellectual property, compared to two per cent of awards starting in 2013 and none from awards starting in 2014. Table 1 and figure 1 show the distribution of awards by start date and whether they have reported at least one item of intellectual property.

» Eight per cent of awards reported at least one instance of intellectual property after five years[618], compared to one per cent within one year. Table 2 and figure 2 show the time taken to report the first instance of intellectual property. In future analyses we will look to see if this elapsed time is different across the different 'types' of intellectual property.

» Supplemental analyses will be added in future to examine the way in which publicly-funded research is cited in these patents and the organisations that are noted as applicants on the patents.

Table 1: *Intellectual Property (IP) by award start date*

Year	Number of awards	Number with at least one IP	Number with no IP	Percentage with at least one IP
2006 or earlier	2,059	243	1,816	12%
2007	484	43	441	9%
2008	586	55	531	9%
2009	572	54	518	9%
2010	477	37	440	8%
2011	418	22	396	5%
2012	517	27	490	5%
2013	657	12	645	2%
2014	195	0	195	0%
TOTAL	**5,965**	**493**	**5,472**	**8%**

Figure 1: Intellectual Property by award start date

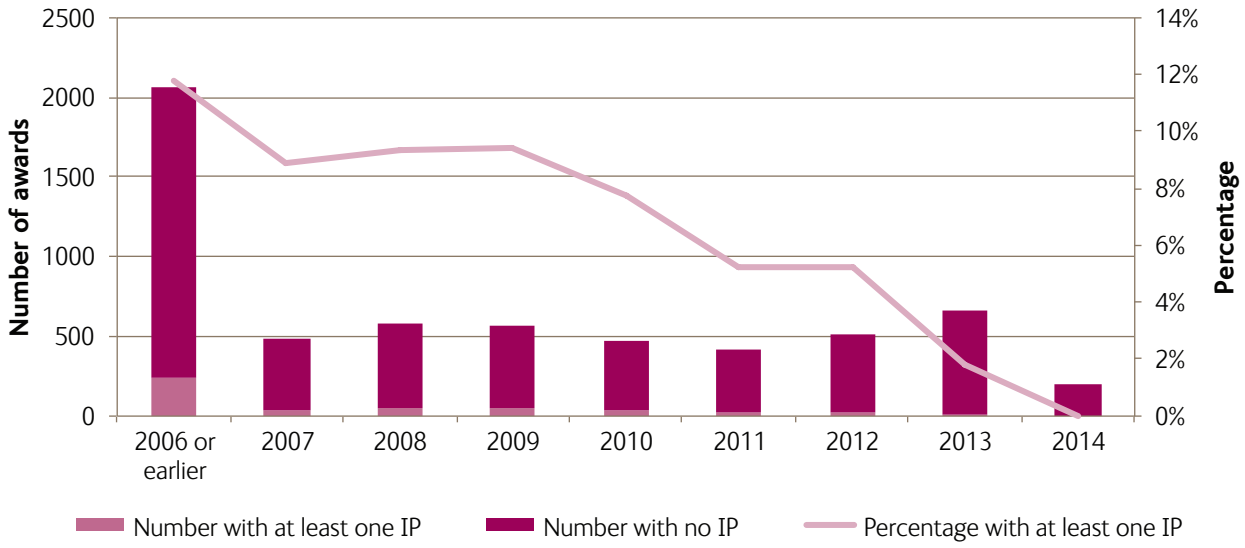
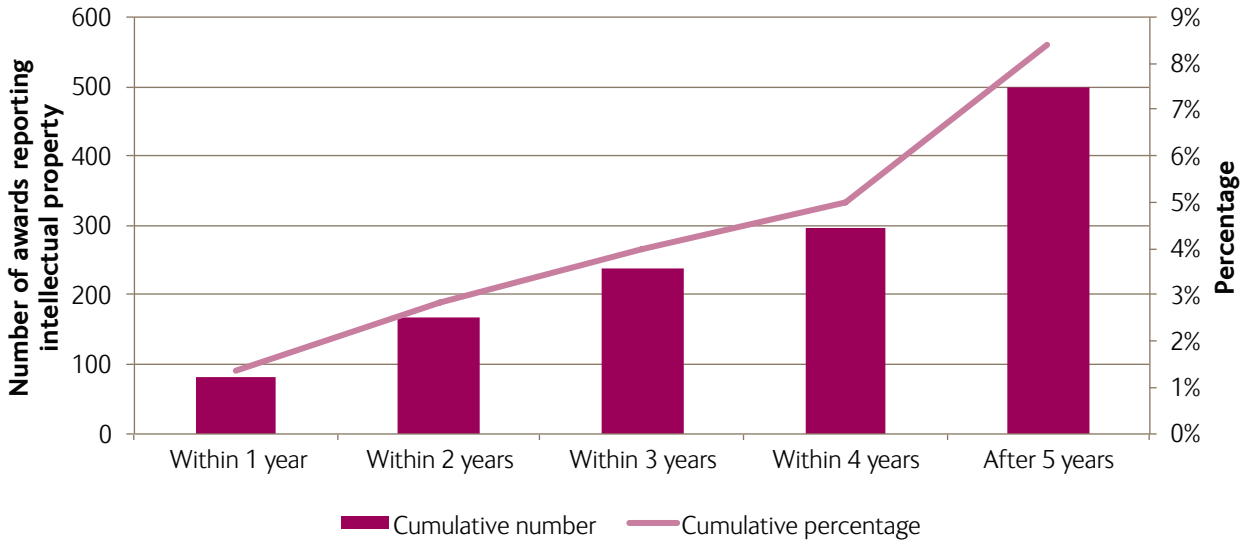


Table 2: Time taken to report the first instance of intellectual property

First instance of intellectual property	Number of instances	Cumulative number	Cumulative percentage
Within 1 year	80	81	1%
Within 2 years	88	168	3%
Within 3 years	68	237	4%
Within 4 years	57	297	5%
After 5 years	200	500	8%

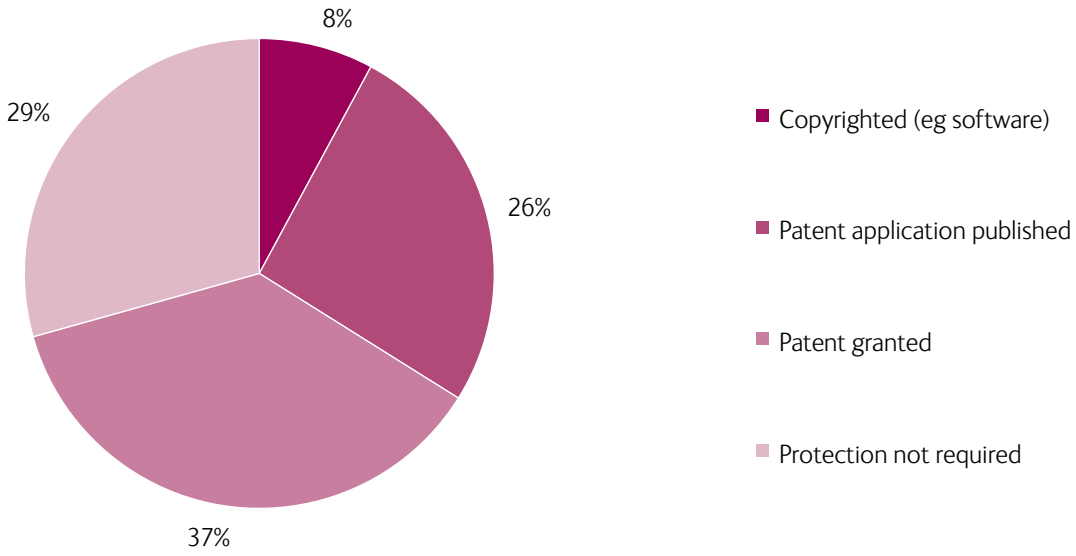
Figure 2: Time taken to report the first instance of intellectual property



Intellectual property protection by type

» 37 per cent of reports in this section concerned a granted patent. Figure 3 gives a breakdown of the type of intellectual property reported.

Figure 3: Type of intellectual property protection reported



Licensing of intellectual property

» 23 per cent of discoveries overall (246/1,081) were reported as 'licensed' by 2014. This is similar to the proportions reported in the last two years, and in our previous report from 2010, we suggested that this seemed reasonable in light of similar data from other organisations[619].

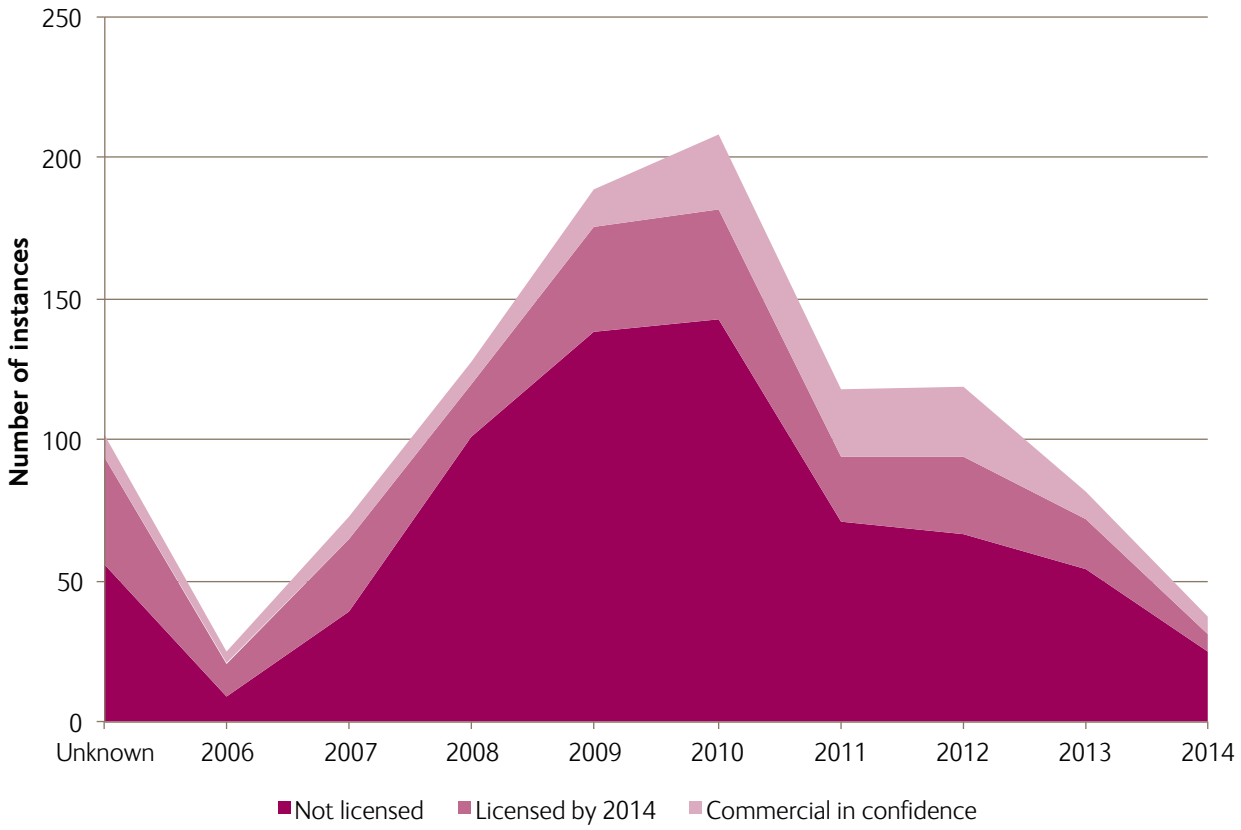
» 12 per cent of intellectual property was reported as 'commercial in confidence' so no details could be provided (132/1,081); it would be reasonable to assume that some of these cases will translate into new licenses in due course.

» The license status of intellectual property in 2014 by the year protection was granted is shown in table 3 and figure 4.

Table 3: License status of intellectual property in 2014 by year of protection

Year	Patent status			
	Not licensed	Licensed by 2014	Commercial in confidence	TOTAL
Unknown	56	38	8	**102**
2006	9	12	4	**25**
2007	39	26	8	**73**
2008	101	19	8	**128**
2009	138	38	13	**189**
2010	143	39	26	**208**
2011	71	23	24	**118**
2012	67	27	25	**119**
2013	54	18	10	**82**
2014	25	6	6	**37**
TOTAL	**703**	**246**	**132**	**1,081**

Figure 4: License status of intellectual property in 2014 by year of protection



3.9 Products and interventions

Summary

- Researchers reported that their work had led to the development of 1,254 medical products or interventions. This type of output was linked to 12 per cent of awards (740/5,984). The average number of medical products and interventions reported per award (of those awards reporting products or interventions) was two (1.69).
- From 2014, researchfish® also provides researchers with the opportunity to report separately on software and technical products and artistic and creative products. In total, MRC-funded researchers reported 35 software and technical products (from 16 awards) and 112 artistic and creative products (from 68 awards).
- As can be seen in the chapter on case studies drawn from this section, this is particularly important information with regards to research outcomes. We know from telephone surveys of MRC principal investigators that there is significant under-reporting of the developments arising from MRC research in this section, and so will be working to improve reporting in this area. A targeted effort to capture the details of trials linked to MRC research, which should be reported in this section, brought excellent results with more than 200 trials now linked to MRC research.

Medical products and interventions by type

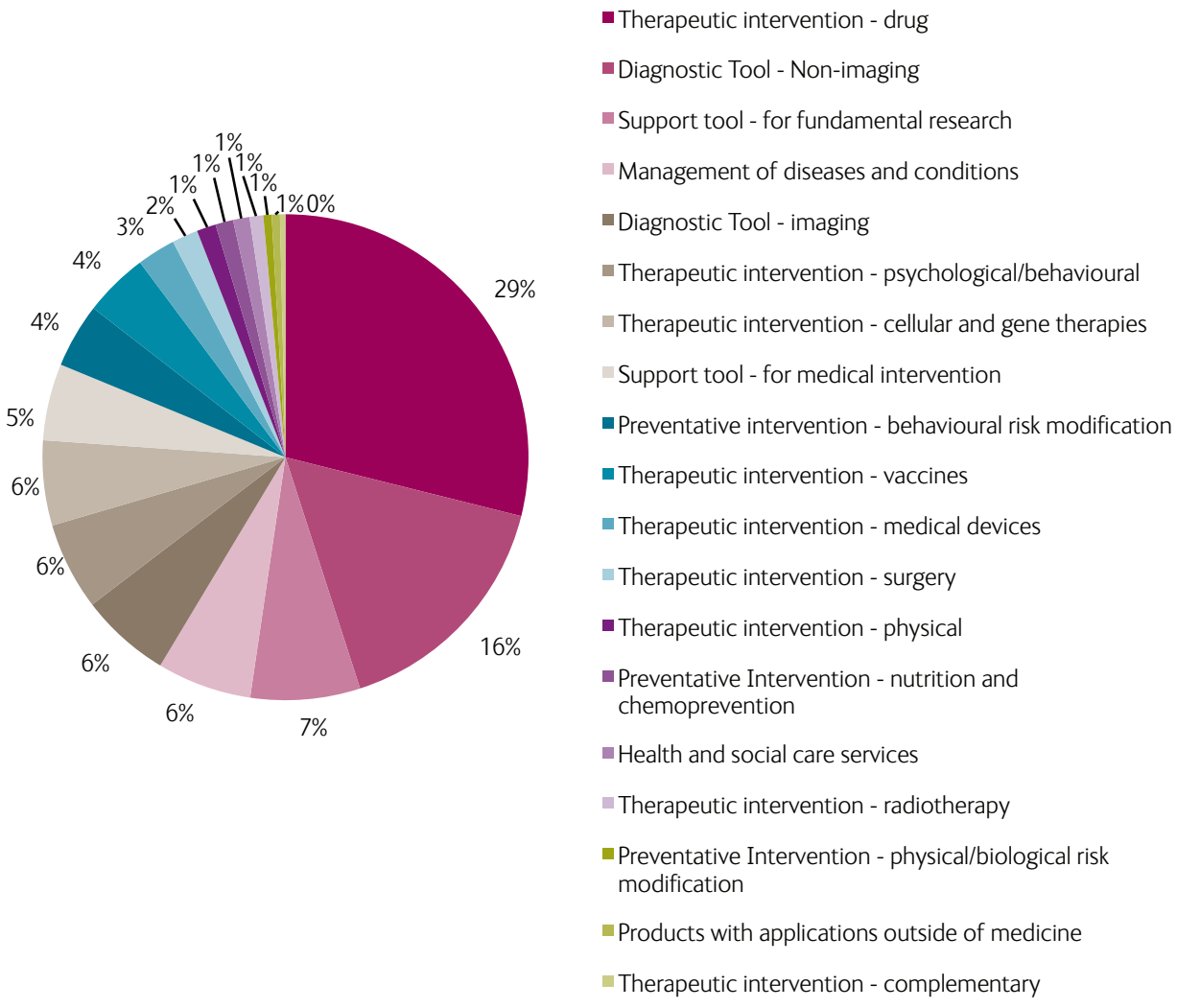
- The most common type of medical product or intervention in development was 'Therapeutic Intervention – Drug', reported by 319 awards (29 per cent of all products and interventions reported). This was closely followed by the Diagnostic Tool – non-imaging, reported by 177 awards (16 per cent of all products and interventions). The breakdown of products and interventions by type is shown in table 1 and figure 1.

Table 1: Breakdown of medical products and interventions by type

Product type	Number of instances	Percentage
Therapeutic intervention - drug	317	29%
Diagnostic Tool - Non-imaging	177	16%
Support tool - for fundamental research	80	7%
Management of diseases and conditions	69	6%
Diagnostic Tool - imaging	66	6%
Therapeutic intervention - psychological/behavioural	64	6%
Therapeutic intervention - cellular and gene therapies	62	6%
Support tool - for medical intervention	56	5%
Preventative intervention - behavioural risk modification	47	4%
Therapeutic intervention - vaccines	47	4%
Therapeutic intervention - medical devices	28	3%
Therapeutic intervention - surgery	19	2%
Therapeutic intervention - physical	14	1%

Product type	Number of instances	Percentage
Preventative Intervention - nutrition and chemoprevention	13	1%
Health and social care services	12	1%
Therapeutic intervention - radiotherapy	10	1%
Preventative Intervention - physical/biological risk modification	6	1%
Products with applications outside of medicine	6	1%
Therapeutic intervention - complementary	4	0%
TOTAL	**1,097**	**100%**

Figure 1: *Breakdown of medical products and interventions by type*



Medical products and interventions by development stage

- A total of 144 awards reported medical products and interventions as being launched onto the market since 2006, with a further 23 awards reporting products and interventions currently undergoing the process of market authorisation.
- There were 359 reports of medical products and interventions in early- or late-stage clinical evaluation demonstrating the strengthening pipeline of developments supported via the MRC's investment in experimental medicine.
- There were 567 reports of medical products in initial or refinement stages, demonstrating the strength of the MRC's investment in discovery and translational science. The inclusion of DPFS projects in 2011 has significantly added to the number of projects in early developmental stages.
- Table 2 and figure 2 show the distribution of medical products and interventions by development stage. Figure 3 shows the distribution of medical products and interventions by type and development stage.

Table 2: *Medical products and interventions by development stage*

Product development stage	Number of instances	Percentage
Initial development	343	31%
Refinement, non-clinical	126	12%
Refinement, clinical	98	9%
Early clinical assessment	231	21%
Late clinical evaluation	128	12%
Market authorisation	23	2%
Small-scale adoption	80	7%
Wide-scale adoption	64	6%
Total	**1,093**	**100%**

Figure 2: *Medical products and interventions by development stage*

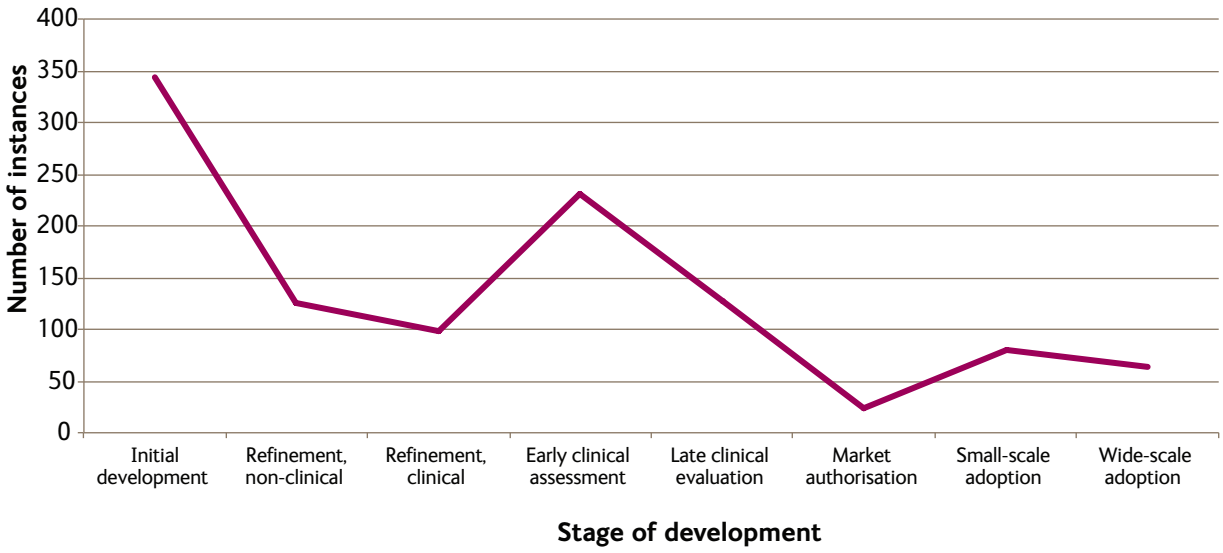
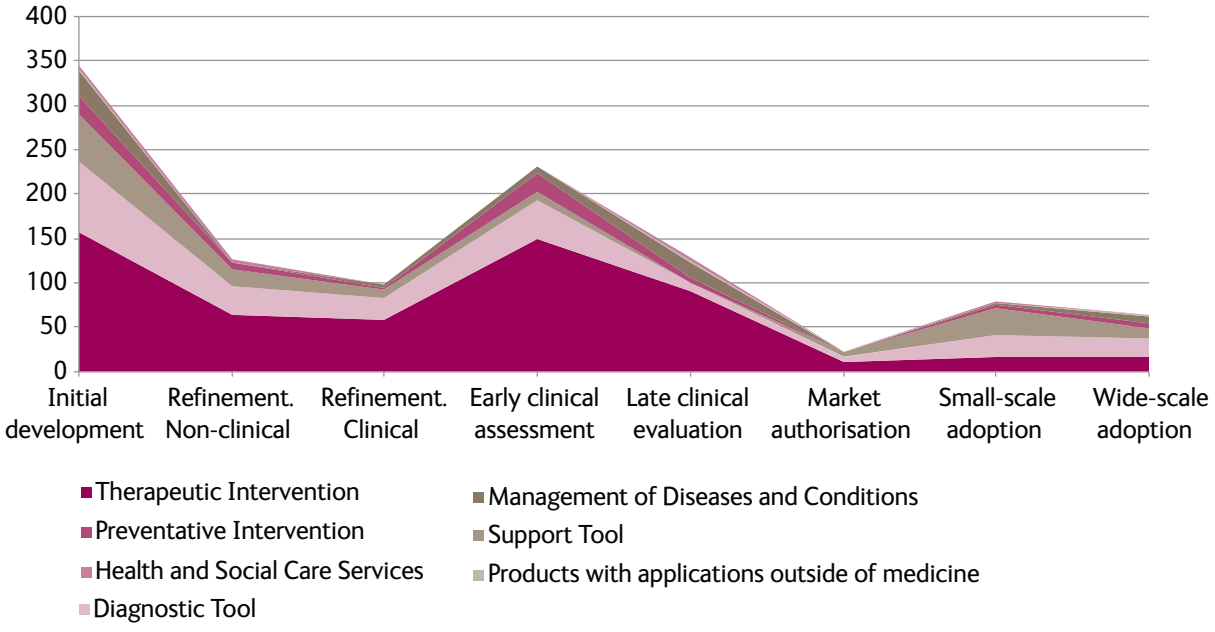


Table 3: Distribution of medical products and interventions by development stage and type

Product Development Stage	Therapeutic Intervention	Diagnostic Tool	Support Tool	Preventative Intervention	Management of Diseases and Conditions	Products with applications outside of medicine	Health and Social Care Services	Total	%
Initial development	158	79	54	20	28	3	3	**345**	**31%**
Refinement. Non-clinical	64	33	19	7	0	0	3	**126**	**11%**
Refinement. Clinical	59	25	8	2	4	0	0	**98**	**9%**
Early clinical assessment	150	43	9	22	8	0	0	**232**	**21%**
Late clinical evaluation	90	10	1	5	17	1	4	**128**	**12%**
Market authorisation	11	6	5	0	1	0	0	**23**	**2%**
Small-scale adoption	16	26	29	5	2	0	2	**80**	**7%**
Wide-scale adoption	17	21	11	5	8	2	0	**64**	**6%**
Total	**568**	**243**	**136**	**66**	**69**	**6**	**12**	**1100**	
%	**52%**	**22%**	**12%**	**6%**	**6%**	**1%**	**1%**		

Figure 3: Distribution of medical products and interventions by development stage and type



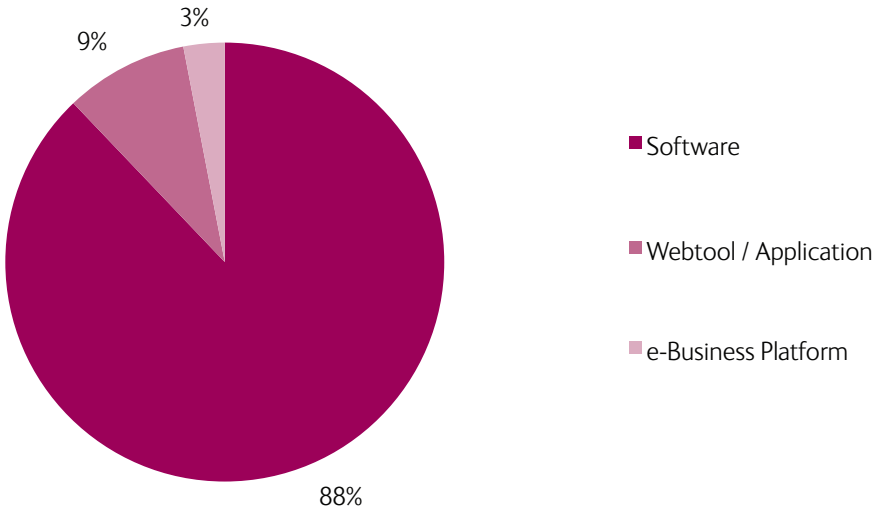
Software and technical products by type

» The most common type of software or technical product reported was 'Software' (88 per cent of total). The breakdown of software/technical material by type is shown in table 3 and figure 4.

Table 3: Breakdown of software and technical product by type

Type of software and technical product	Number of instances	Percentage
Software	29	88%
Webtool/application	3	9%
e-Business platform	1	3%
TOTAL	**33**	**100%**

Figure 4: Breakdown of software and technical product by type



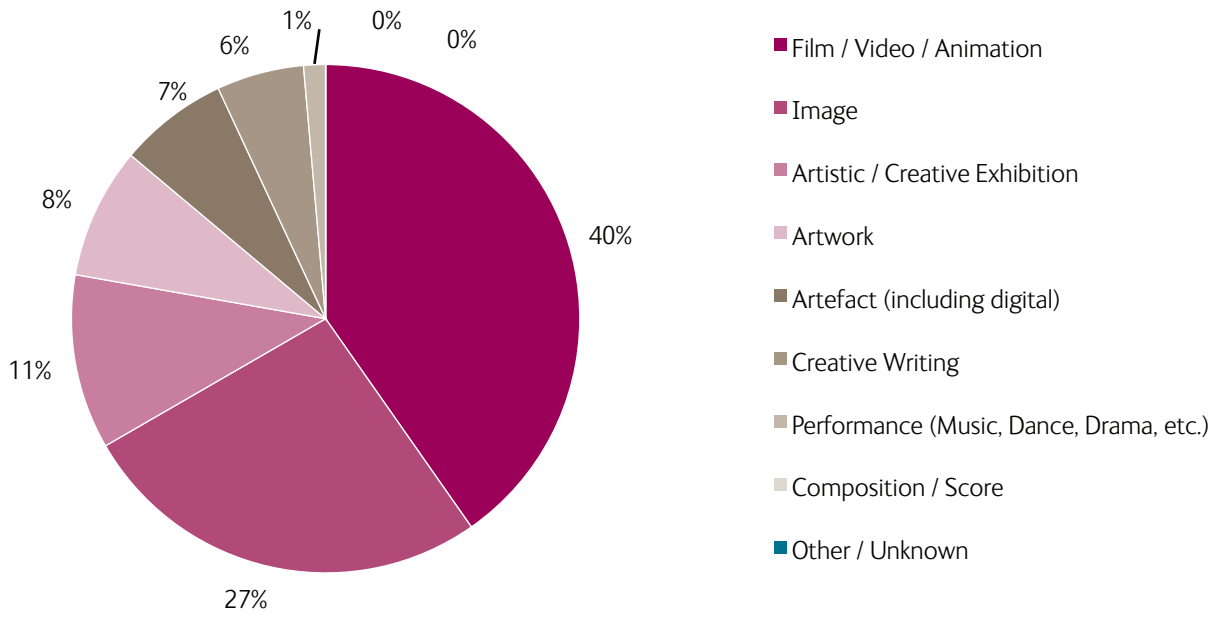
Artistic and creative products by type

» The most common type of artistic or creative product was 'Film/Video/Animation', (40 per cent of total reported). The breakdown of artistic and creative products by type is shown in table 4 and figure 5.

Table 4: Breakdown of artistic and creative product by type

Type of artistic and creative product	Number of instances	Percentage
Film/video /animation	29	40%
Image	19	26%
Artistic/creative exhibition	8	11%
Artwork	6	8%
Artefact (including digital)	5	7%
Creative writing	4	6%
Performance (music, dance, drama, etc.)	1	1%
Composition/score	0	0%
Other/unknown	0	0%
TOTAL	**72**	**100%**

Figure 5: Breakdown of artistic or creative product by type



3.10 Awards and recognition

Summary

- Recipients of 52 per cent of awards reported that their work had resulted in formal recognition or award for them personally or members of their team.
- The average number of reports per award (of those reporting recognition) was seven (6.70).
- In total, researchers made 20,790 reports in this section; a large increase on last year's figure of 16,317.

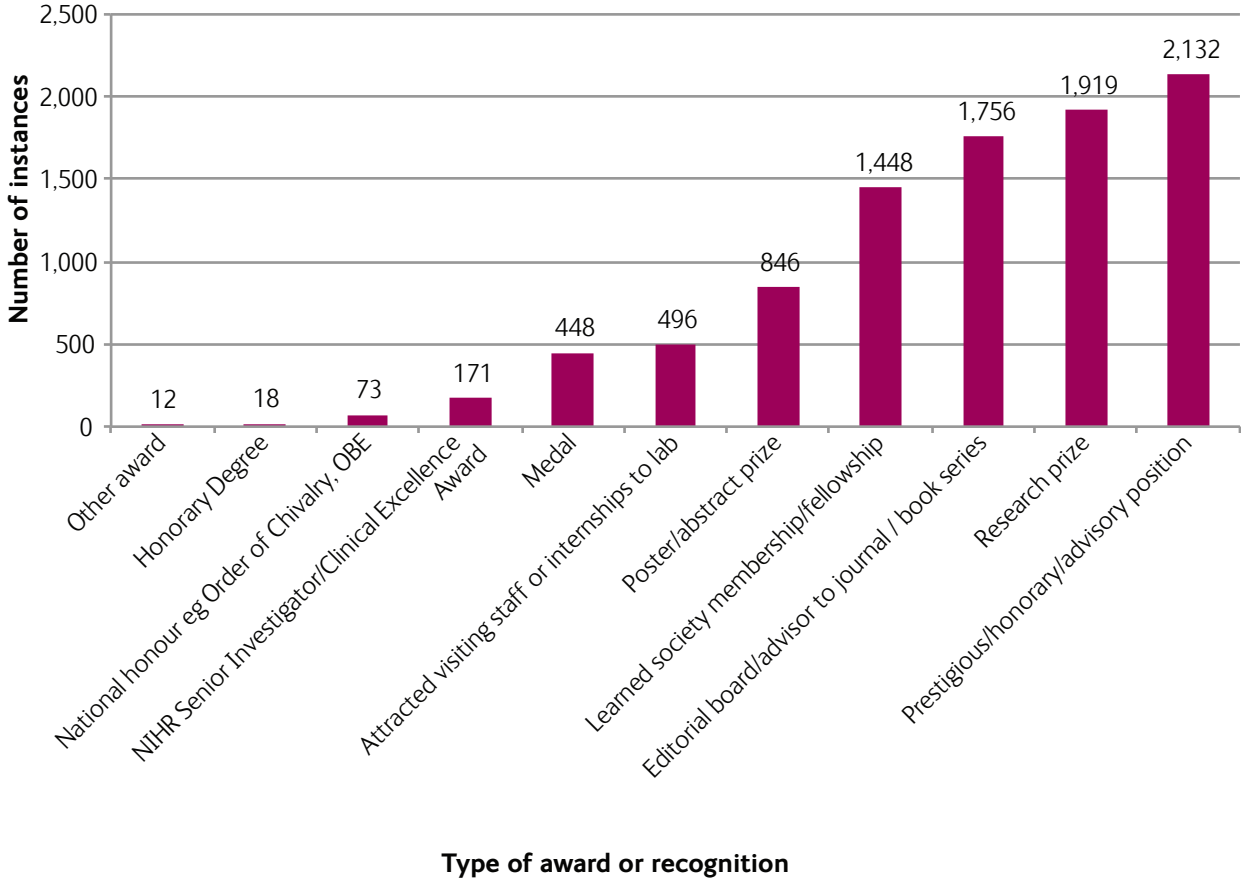
Awards and recognition by type

- The most common form of award or recognition was being personally invited as a speaker at a conference (46 per cent), followed by being appointed to a prestigious/honorary/advisory position to an external body (12 per cent) and appointed to the editorial board of, or as an advisor to, a journal or book series (11 per cent).
- Table 1 and figure 1 show the distribution of types of award and recognition.

Table 1: Awards and recognition by type

Type of awards and recognition	Number of instances	Percentage of total
Personally invited as speaker at a conference	7,856	46%
Prestigious/honorary/advisory position to an external body	2,132	12%
Research prize	1,919	11%
Appointed to the editorial board of, or advisor to, a journal or book series	1,756	10%
Awarded honorary membership, or a fellowship, of a learned society	1,448	8%
Poster/abstract prize	846	5%
Attracted visiting staff or internships to laboratory	496	3%
Medal	448	3%
NIHR Senior Investigator/Clinical Excellence Award	171	1%
National honour eg Order of Chivalry, OBE	73	0%
Honorary Degree	18	0%
Other award	12	0%
Total	**17,175**	**100%**

Figure 1: Distribution of type of award and recognition



Key to output types


Publications


Collaborations and partnerships

Further funding


Next destination and skills


Engagement activities


Influence on policy, practice, patients and the public


Research tools and methods

Research databases and models

Intellectual Property and licensing


Medical products, interventions and clinical trials


Artistic and creative products


Software and technical products


Spin outs


Awards and recognition

End Notes

604. All primary, peer-reviewed publications that were published in refereed journals from 01.01.06 onwards, in which the PI or members of their research group were named as authors.
605. Where more than one award claims to have contributed to a publication, each is credited equally. This means that several thousand publications are counted multiple times.
606. Researchers reporting a collaboration via researchfish® can list any number of partner organisations as party to that collaboration. For the purposes of this summary analysis all partners across all collaborations are referred to as 'collaborators' linked to an award. So if two collaborations, each involving two partner organisations, are attributed to an MRC award, it is noted that four 'collaborators' are linked to this award.
607. In this analysis, the occurrence of non-unique collaborators from different locations is counted, so for example, if three MRC researchers indicated that they collaborated with the same partner in North America, this would be counted three times. Collaborators with more than one location, for example, the United Nations, or multi-national companies, are categorised as 'global'.
608. Each map has a number of circles and each circle's size represents the number of non-unique collaborators reported with each particular country. Global collaborations are also listed and the scale is noted.
609. Circles are centred around the countries' capital cities.
610. Circles are centred around the countries' capital cities.
611. This is the estimated expenditure of further funding during the time frame of researchfish®, rather than a reported commitment of further funding. Estimates of expenditure are based on the assumption that the spending is distributed evenly over the period reported. For example, if a researcher reported £100k of funding from 1 December 2012 until 1 December 2014, it is estimated that 50 per cent of this award or £50k will have been spent in the period covered by the 2013 data-gathering period.
612. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/438763/bis-15-340-relationship-between-public-and-private-investment-in-R-D.pdf
613. Reported in researchfish®.
614. Researchers are advised to report any recurring activities only once.
615. researchfish® is a federated system with all subscribing funders able to contribute to development of the question set. The range of options in this section changed in 2012 to include activities where the audience was primarily academic although MRC researchers were advised to continue to prioritise the reporting of activities that included engagement outside of academia. In table 3 it can be seen that despite this, more than 3,000 reports of scientific meetings were added by MRC researchers to this section.
616. The time between the start of the award and the influence being reported.
617. The time between the start of the award and the intellectual property being reported.
618. A study of more than 1,200 patents published by the University of California and the University of Columbia in all disciplines between 1980 and 1994 found that 41 per cent of these were licensed by 1992. A similar study of 686 patents published by the Memorial Sloan-Kettering Cancer Centre and Dana Faber Cancer Institute between 1983 and 2003, also found that 41 per cent of these were licensed by 2007. Other studies have indicated a lower proportion of patents licensed (for example, 25 per cent of NASA patents published between 1994 and 2002 were licensed by 2007).

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ISBN: 978-0-903730-22-8