Outputs, outcomes and impact of MRC research

2014/15 report

SECTION 2.5
Industry interactions and other collaborations
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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) or simply bringing together the critical mass required to tackle complex multidisciplinary problems. Collaboration as measured by co-authorship, particularly international co-authorship, has been shown to increase citation impact.

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.

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 in 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.

This publication comprises examples of where MRC-supported researchers have formed spin out companies and beneficial relationships with other organisations through collaborations and generating further funding. It is one in a series of chapters making up the 2014/15 Outputs, outcomes and impact of MRC research report. The information in this publication has largely been sourced from Researchfish. Quantitative information on numbers, locations and quantities of collaborations, further funding and spin out companies will be available in the Quantitative analysis chapter of this report once published.

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 — 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, 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 Foundation9.

“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™10.

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 201811. 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, Qubis13. 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, 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. This treatment has “the potential to be one of the biggest breakthroughs in asthma treatments in the past 20 years.” It also licensed the treatment to global biopharmaceutical company AstraZeneca 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.

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.

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

“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 (more than 1,000 people in Britain). 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,” said Richard.
In 2014 the results of Synairgen’s Phase II trial\(^\text{23}\), 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\(^\text{24}\) 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. 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. This mechanism is a new robust and effective way to produce the nerve cells lost in HD.

NeuroStemcellRepair 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 Therapeutics, 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. 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.

**Project reference number: G1002501**

### Antimicrobial resistance

**Further funding: Bacteria-eating viruses**

In 2014 **Professor Martha Clokie** was awarded £135,154 from AmpliPhi Biosciences Corporation 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.

**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, substituted or added. 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, 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

*Continued on page 10.*
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 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. 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. 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.

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. 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. 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.

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**Notes and references**

5. E James et al. “Structural and Mechanistic Basis for the Inhibition of Escherichia coli RNA Polymerase by T7 Gp2.” *Molecular Cell*, 2012. DOI: http://dx.doi.org/10.1016/j.molcel.2012.06.013
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. 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 the TcdC gene (involving modification, deletion and addition), the Minton laboratory showed that abnormal TcdC levels do not correlate with increased toxin production.

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. 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. 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. 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. 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), 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 responsible for plant biomass degradation into the chromosome of a butanol-producing *clostridia*. 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...
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.48

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.

This work was also funded through awards from the National Institutes of Health (NIH) 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.

SimOmics51, 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.”

– Dr Mark Coles
SimOmics co-founder

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 programme53. 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\textsuperscript{54}.

*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\textsuperscript{55}. 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\textsuperscript{56,57}.

In 2010 Professor Simmons published research demonstrating the specific role that NOD-2 plays in the innate immune system\textsuperscript{58}. 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 as 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\textsuperscript{59}. 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 as UCB\textsuperscript{60}, Abbvie\textsuperscript{61} and Ajinomoto\textsuperscript{62}, 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. 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, 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.

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. 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. 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. 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 in 2014. The company provides nanomedicine 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.

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. 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)\(^\text{74}\) to develop mechanism-based predictive test systems for human drug-induced liver injury (DILI)\(^\text{75}\). 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\(^\text{76}\), 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\(^\text{77}\), 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\(^\text{78}\) to produce Making Sense of Drug Safety Science\(^\text{79}\), 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. 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, The Telegraph, The Guardian and The Independent.

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.

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, 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.
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.

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. 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. 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.

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. The researchers demonstrated that drugs which target a survival factor called NF-κB 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-κB 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, 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. 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.

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 and Healio Cardiology.

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 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.

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\(^{100}\), 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\(^{101}\). 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\(^{102,103}\).

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\(^{104}\).

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
Collaborations: Treatment for mitochondrial neurogastrointestinal encephalomyopathy

Dr Bridget Bax at St George’s, University of London is collaborating with Swiss biopharmaceutical firm Orphan Technologies to develop and commercialise a treatment for mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), a rare and almost invariably fatal genetic disease.

MNGIE is caused by a defect in the gene coding for the enzyme thymidine phosphorylase, meaning that affected individuals produce little, or no, active enzyme. The enzyme is needed to break down the metabolites thymidine and deoxyuridine. Without it, these compounds accumulate in the body, causing damage to the mitochondria, the part of the cell that produces the energy it needs to function. Energy-dependent tissues, such as skeletal muscle and the nervous system, are therefore affected, causing symptoms including vomiting and weight-loss, neuropathy (nerve damage leading to loss of sensation and abnormal eye movements) and severe muscle weakness. Patients with this progressive disease live to an average age of 38. 200 cases have been identified globally, however, numbers are increasing and it is believed to be underdiagnosed.

Matched bone marrow transplants offer a potential cure, but these are limited by donor availability. They also carry significant risks of serious complications and the reported death rate is as high as 50 per cent.

Dr Bax and colleagues are world leaders in developing erythrocytes (red blood cells) as vehicles for carrying therapeutic proteins in the blood. They are working with Orphan Technologies to investigate the effectiveness of using a patient’s own red blood cells to carry the missing thymidine phosphorylase in circulation. Pre-clinical safety tests in dogs and mice did not reveal any potential serious toxicities that would prevent using the treatment — erythrocyte thymidine phosphorylase (EE-TP) — in a phase II clinical trial in patients with MNGIE. EE-TP has so far been compassionately used in three patients with MNGIE which has reduced plasma thymidine and deoxyuridine concentrations and provided significant clinical improvement.

The collaboration aims to confirm the safety and clinical effectiveness of EE-TP in a European-wide clinical study in 10 patients with MNGIE. This work is supported by a £3.2m MRC Industry Collaboration Agreement (MICA), awarded through the Biomedical Catalyst in 2013.

Dr Bax said, “MNGIE is a relentlessly progressive degenerative disease and for a majority of patients there are no treatment options other than supportive care. Our team is committed to addressing the unmet needs of these patients. The MICA award will enable us to accelerate the regulatory development of EE-TP, with the ultimate hope that EE-TP will benefit patients with MNGIE and that patients globally have equal access.”

Dr Bax has received further funding as a result of this work, including grants from charities such as the Purine Metabolic Patients’ Association (PUMPA) and the United Mitochondrial Disease Foundation.

Project reference numbers: MR/K025406/1, G0902179

“The MICA award will enable us to accelerate the regulatory development of EE-TP, with the ultimate hope that EE-TP will benefit patients with MNGIE and that patients globally have equal access.” — Dr Bridget Bax
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), 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.

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 mosquitoes. 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.

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 and Sanofi, 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)\textsuperscript{117}, 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\textsuperscript{118}, improving the reporting of adverse events to investigators\textsuperscript{119} and trial safety assessment\textsuperscript{120}. 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\textsuperscript{121}. 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\textsuperscript{122}. 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\textsuperscript{123}. The UK’s Life Science Strategy\textsuperscript{124} 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\textsuperscript{125}.

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

1. Meta-analysis is a statistical technique for combining the findings from independent studies. Meta-analysis is most often used to assess the clinical effectiveness of healthcare interventions.


3. International comparative performance of the UK research base (Elsevier 2013)


5. www.mrc.ac.uk/documents/xls-csv/spin-out-company-list/

6. 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/]

7. http://gtr.rcuk.ac.uk/


13. [http://netscientific.net/]

14. [http://www.qubis.co.uk/]

15. [www.mrc.ac.uk/documents/xls-csv/spin-out-company-list/]

16. [http://www.neurostemcell.org/]

17. [http://www.talisman-therapeutics.com/index.html]

18. [http://www.amphibio.com/]

19. [http://www.mrc.ac.uk/funding/guidance-for-mrc-award-holders/researchfish/]

20. [http://www.ipgroupplc.com/]


23. Results initially released in 2012.

24. [http://www.ipgroupplc.com/]


27. [http://www.neurostemcellrepair.org/]


29. [http://www.amphibio.com/]


31. [http://www.mrc.ac.uk/funding/guidance-for-mrc-award-holders/researchfish/]


44. http://www.ruf.rice.edu/~rau/phys600/whitesides.htm


46. http://www.c1net.co.uk

47. http://www.sbrc-nottingham.ac.uk


50. Including: A multi-faceted approach to identifying epigenomic dyfusion in Alzheimer’s disorder and associated neuropsychiatric co-morbidities: discovering epigenetic biomarkers in brain tissue and peripheral blood (£966k) and Epigenetics of Alzheimer’s Disease (£92.7k)


54. www.nc3rs.org.uk


SECTION 2.5: Industry interactions and other collaborations

60. http://www.ucbpharma.co.uk/home
61. www.abbvie.co.uk
64. http://www.biomotiv.com/
70. http://www.britishsocietynanomedicine.org/what-is-nanomedicine.html
71. Hartkoorn RC et al. HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by SLCO1B1 polymorphisms. *Pharmacogenetics and Genomics*. February 2010 - Volume 20 - Issue 2 - pp 112-120 doi: 10.1097/FPC.0b013e328335b02d
76. http://www.senseaboutscience.org/
79. NICE ‘sets price too high for NHS medicines’. BBC. February 2015. [http://m.bbc.co.uk/news/health-31507861](http://m.bbc.co.uk/news/health-31507861)
84. To be broadcast in November 2015.
85. To be broadcast in November 2015.
86. [http://www.umotif.com/](http://www.umotif.com/)


98. http://www.cochrane.org/


100. http://phtherapeutics.com/


108. http://www.mrc.ac.uk/innovation/mrc-industry-collaboration-agreement-mica/


110. Including grant of £99k in 2014 to develop knock-out cell culture models to investigate the underlying molecular mechanisms contributing to the neuronal aspects of MNGIE.

111. http://www.mmv.org/

112. http://www.imperial.ac.uk/people/l.okell


