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 pages 9-10). 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 20), 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 27).

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 5), a nasal spray to help improve eye contact in patients with autism (see pages 7-8) and the first successful vaccine trial for hepatitis C (see pages 13-14). 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 17), and the development of hydrogels, a unique solution for stem cell storage and transport (see pages 22-25).

This publication 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. It is one of 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 and type of products and intellectual property will be 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 — 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, and five new rare diseases are described in medical literature each week. 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. 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. 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. 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. 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. These tests around 40-60 UK and international patients each year.

Professor Johnson has also contributed to an EU FP7 collaborative project, SysCilia, 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 cilia (ciliogenesis).

*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. 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.

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, The Independent and the Daily Mail. 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.

Project reference number: MC_EX_G0802457

“This research was only possible because of the great collaboration between medical and engineering sciences.”

– Dr Christoffer Nellaker
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\(^1\). Autism is a lifelong developmental condition that affects how a person communicates and relates to other people\(^2\). 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\(^3\). 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\(^4\). Professor Baron-Cohen has previously demonstrated that eye contact is reduced in many people with autism, beginning in early infancy and lasting into adulthood\(^5\). He and his team subsequently developed and evaluated The Transporters\(^6\), 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\(^7\).

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 and why some people have more or less empathy than others. His research showing that increased exposure to testosterone in the womb is associated with autistic traits in children is often discussed in news articles and programmes on autism and the differences between male and female brains. These include those by the BBC and The Economist. 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. 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.

Professor Baron-Cohen has also developed a test that assesses a person’s level of empathy. In *Reading the mind in the eyes* participants are shown 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.

*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.

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 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.

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. It is estimated that around 700,000 people die from antibiotic-resistant infections each year worldwide, 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. 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 professionals are also encouraged to use the Imperial College App (IAPP) tool to support and encourage prudent use and prescribe antimicrobials.
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. 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 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 obese43, 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 problems44.

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 Wyeth45 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 obesity46. 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. Depending on their type of insulin therapy, patients are advised to monitor their glucose levels at least two to six times a day. 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. 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.

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

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 award, have developed a small, wearable patch around 1cm² 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\textsuperscript{53}. 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\textsuperscript{54} and Stanford University in the USA, have published the first results of an early clinical trial of a hepatitis C vaccine\textsuperscript{55}. 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\textsuperscript{56}. 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\textsuperscript{57}. 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\textsuperscript{58}.

The vaccine generated very high numbers of both CD4\textsuperscript{+} and CD8\textsuperscript{+} 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, a UK Clinical Research Collaboration (UKCRC) 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. 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.
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.

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. 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\(^6^5\). 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\(^6^6\).

More than 1,000 people die from asthma in the UK each year\(^6^7\). 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\(^6^8\). 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*

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**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\(^6^9\). 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. 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.

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.

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.

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. Professor Ala‘Aldeen 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).

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 ReNeuron⁷⁶, 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 recognition⁷⁷. 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 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 involved⁷⁸, ⁷⁹.

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 type⁸⁰. 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 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, 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. 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. The annual UK expenditure on atopic eczema in the mid-nineties was estimated to be £465 million.

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.

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 26.
Hydrogels: a unique solution for stem cell storage and transport

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 was pivotal to the initial development of the technology and BBSRC support, including a Pathfinder grant, funding from the Bioprocessing Research Industry Club (BRIC), 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 cryopreservation5. 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 eye6,7. 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
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.

“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 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.”

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

1. Project reference number: G0900877 http://gtr.rcuk.ac.uk/project/A53DD38E-6782-461F-98E5-B0D9EFEDA382
2. BRIC: http://www.bbsrc.ac.uk/business/collaborative-research/industryclubs/bric/bric-index.aspx
3. Dr Che Connon: http://www.reading.ac.uk/pharmacy/about/staff/c-jconnon.aspx
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-1B, MIF*, and *TNF-α*, which code for proteins involved in the inflammatory response, predict a lack of response to antidepressants⁸⁷.

Depression was first linked to inflammation in the early 1980s when high levels of inflammatory markers were shown in patients with depression⁸⁸. Since then, studies have shown that one third of those with major depression have raised inflammatory markers⁸⁹. 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*⁹⁰ and the *Daily Mail*⁹¹. He is frequently asked by media sources to comment on research or events relevant to his field, including by the *Huffington Post*⁹², *The Telegraph*⁹³,⁹⁴ and *The Guardian*⁹⁵.

*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. 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.

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.

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. 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 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. It also promotes uncontrollable blood vessel growth (angiogenesis), needed by tumours to provide sufficient oxygen and nutrients to support their growth. In patients with advanced ovarian cancer, high IL6 blood levels correlate to poor prognosis.

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. However, sustained responses were not achieved.

Professor Balkwill received a £1.5m programme from Cancer Research UK in 2013 to take this work forward. 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.

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, 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. 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. 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 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. 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, the first published software that can analyse DNA sequencing data produced by Oxford Nanopore Technologies (ONT).

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 cluster113.

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 launch114.

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 disease115. 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. 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 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. The software is designed to automatically pick out bone shapes in images, rather than relying on researchers and doctors to do this manually.

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. 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.

In 2010 Professor Liu reported that an enzyme called CTP synthase was compartmentalised in cytoophidia in fruit flies. He has subsequently demonstrated that CTP synthase can join together to form long chains — or filaments in human cells. He therefore showed that cytoophidia 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.

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

His images were also selected for *Cell*’s Picture Show in 2013.

*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. 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.

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, 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 have just been completed in Africa however it was only shown to be 35 per cent effective against severe disease in young children.

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 Pfalciparum 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, 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.

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.

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).139

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 2010140 and 2011141, 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 rate142,143. 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 alone144.

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
SECTION 2.3: Development of products and intellectual property

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. 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/
2. http://gtr.rcuk.ac.uk/
6. Research conducted at the University of Birmingham.
34 https://www.questionwritertracker.com/quiz/61/Z4MK3TKB.html
36 Two-photon microscopy and retrospective focused ion beam-electron microscopy, http://bpod.mrc.ac.uk/archive/2013/7/28
39 Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. NICE guidelines NG15 http://www.nice.org.uk/guidance/ng15
40 https://www1.imperial.ac.uk/departmentofmedicine/divisions/infectiousdiseases/cipm/other_cipm_related_projects/smartphone_app_for_antibiotic_prescribing/
41 Enhanced antibiotic-prescribing through a CBR-based Imperial Antibiotic Prescribing Policy smartphone application.
44 Wyeth was acquired by Pfizer in 2009.
50 http://www.mrc.ac.uk/funding/browse/confidence-in-concept-scheme/
51 Clinical Assessment of a Novel Microprobe Array Continuous Glucose Monitor for Type 1 Diabetes. ClinicalTrials.gov Identifier: NCT01908530. https://clinicaltrials.gov/ct2/show/NCT01908530?term=microneedle&amp;r ank=1
52 Now part of GSK.


http://www.esti2.org.uk/

http://www.ukcrc.org/


https://www.youtube.com/watch?v=hXxr01cgb_M

The initial results were released at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, Washington in February 2013. https://www.mrc.ac.uk/news/news/proud-study-shows-pre-exposure-prophylaxis-is-highly-protective-against-hiv-infection/


http://www.who.int/mediacentre/factsheets/fs307/en/

For more information on Professor Holgate’s work on asthma and his spin out company Synairgen, please see the Synairgen case study on pages 4-5 of Section 2.5: Industry interactions and other collaborations.

Asthma UK http://www.asthma.org.uk/


Campylobacter. Food Standards Agency http://www.food.gov.uk/science/microbiology/campylobactervidenceprogramme


http://www.reneuron.com/


Royal National Institute of Blind People http://www.rnib.org.uk/eye-health/eye-conditions/retinitis-pigmentosa


http://www.masseyeandear.org/


http://www.nhs.uk/Conditions/Psoriasis/Pages/Introduction.aspx


http://www.nhs.uk/Conditions/Psoriasis/Pages/Introduction.aspx


97. For more information about the MRC’s input to the development of monoclonal antibodies and what diseases they treat, please see the MRC Insight blog post From tool to therapy: a timeline of monoclonal antibody technology. http://www.insight.mrc.ac.uk/2015/08/17/from-tool-to-therapy-a-timeline-of-monoclonal-antibody-technology/#more-4944


106. https://www.centreofthecell.org/

107. http://www.amazon.co.uk/Frances-R.-Balkwill/e/B001HNZ2H0/ref=dp_bryline_cont_book_1


109. The Francis Crick Institute is a consortium of six of the UK’s most successful scientific and academic organisations - the Medical Research Council (MRC), Cancer Research UK (CRUK), the Wellcome Trust, UCL (University College London), Imperial College London and King’s College London. http://www.crick.ac.uk/


115. http://www.sanger.ac.uk/about/engagement/art.html

116. The research was approved by the Wits Human Research Ethics Committee, the University of Warwick Biomedical and Scientific Research Ethics Subcommittee and Mpumalanga Provincial Government Research and Ethics Committee.

117. Now a research associate.

118. http://personalpages.manchester.ac.uk/staff/claudia.lindner/default_files/curr_project_bonefinder.htm


134. RTS,S/AS01, developed by GSK.


137. https://clinicaltrials.gov/ct2/show/NCT02181088


