Reviewing translation at the MRC 2014

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This publication highlights some of the recent successes in translating the work of scientists in MRC units and institutes. It demonstrates the breadth of technologies at different stages of development. Each of these projects aims to bring new products to market, provide real improvements to human health or further scientific research.

The MRC has a rich history of impactful translational research, from antibody humanisation in the 1980s, to the development and commercialisation of innovative new platform technologies in more recent years (Heptares Therapeutics Limited and Bicycle Therapeutics Limited).

Bridging the gap between academic research and tangible societal benefit is often a complex challenge. MRC science needs to be effectively translated into powerful new therapies, diagnostics, devices, and research tools. Key to achieving this is to identify intellectual property (IP) generated that has potential commercial value, protect it through patents or other appropriate means, and ensure that it is effectively commercialised.

MRC scientists are supported by MRC Technology in these vital areas:

- Contracts and advice
- Development funding
- IP protection and management
- Drugs, devices, diagnostics
- Partnering with industry
- Consortia building

Contracts and advice

Contracts are vital in defining the relationship between collaborating organisations, protecting materials and intellectual property (IP) and ensuring effective commercialisation of IP. MRC Technology can assist and advise MRC scientists on contractual matters and agreements relating to technology development and commercialisation such as confidentiality agreements, material transfer agreements, collaboration agreements, licence agreements and spin-out related agreements.

Drugs, devices, diagnostics

MRC science leads to a broad range of novel medical and scientific solutions. These range from medical questionnaires to diagnostics, drugs and drug delivery technologies. MRC Technology aids this development through IP protection, helping to secure suitable funding and assisting in finding and securing vital collaborators and partner organisations.

In addition, MRC scientists can collaborate with MRC Technology's Centre for Therapeutics Discovery (CTD) and Centre for Diagnostic Development (CDD), providing access to antibody humanisation, small molecule drug and diagnostic development and validation.

Development funding

Promising research often requires further funding to progress towards commercial and/or therapeutic application. The Development Gap Fund (DGF) is a pre-seed translational fund available to MRC scientists to conduct translational research. Typical projects might include proof of concept studies, target validation components of drug discovery, assay development and device/diagnostic prototyping.

Funding is also available through the MRC's Developmental Pathway Funding Scheme (DPFS), from charities (including the Wellcome Trust and Cancer Research UK) and from other research councils

Partnering with industry

Intellectual property that has been appropriately protected can be licensed to an industry partner with the right expertise and resources to develop it further, advancing the science and benefiting patients by bringing products to the market.

IP protection and management

The MRC protects intellectual property (IP) created from the research efforts of its scientists using patents, copyrights, designs and trademarks. This IP can then be further developed, sometimes using development funding, and/or can be commercialised. Some technologies can be commercialised without IP protection, for example, cell lines and research reagents. MRC Technology can advise on all aspects of IP protection and is responsible for IP protection and management on behalf of the MRC.

Consortia building

Promising research can often require expertise in multiple disciplines to progress towards commercial applications. MRC Technology can assist with finding consultants/collaborators and build consortia through its network of contacts within industry and academia.

Cytosponge™ cell collection device and biomarker for *in vitro* diagnosis of upper gastrointestinal diseases

MRC Cancer Cell Unit

Prof Rebecca Fitzgerald

Conditions of the oesophagus, both benign and cancerous, cause significant morbidity and mortality worldwide. Cancer of the oesophagus is the eighth most common cancer and the fifth leading cause of cancer death globally. Diagnosis of both benign conditions and oesophageal cancer requires the use of hospital-based endoscopy and multiple biopsy sampling. This invasive procedure is both unpleasant to patients and costly to run.

Cytosponge and its associated diagnostic tests provide a cheaper, less invasive and early diagnosis of upper gastrointestinal disease. Cytosponge, an abrasive sponge enclosed in a capsule and attached to a piece of string, is capable of collecting cells from the surface of the oesophagus. The capsule is swallowed, dissolves in the stomach within five minutes and the sponge expands. It is withdrawn with the string and the sponge containing the cytological specimen is placed in preservative fluid and sent to a standard pathology lab.

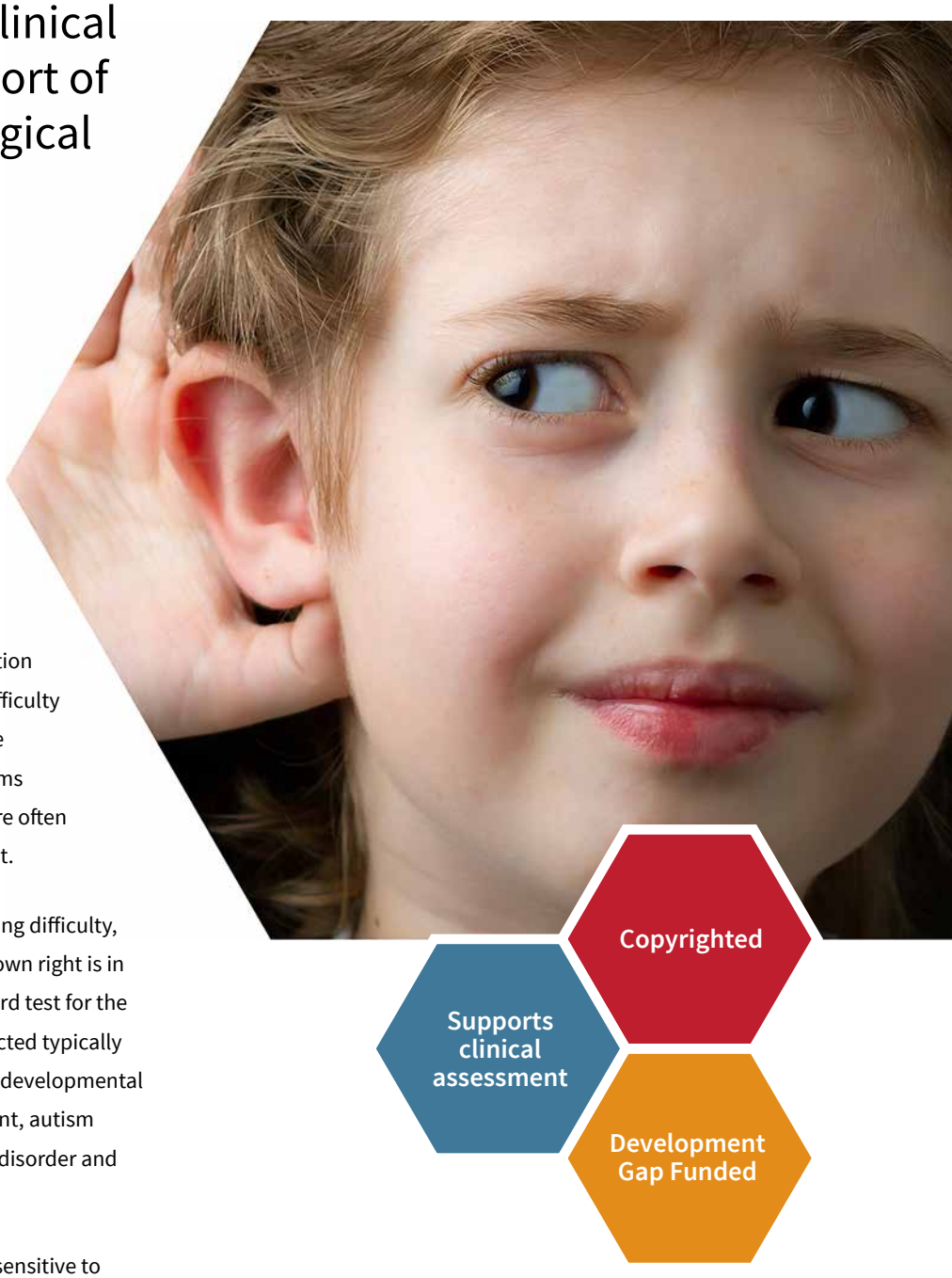
Cell specimens are processed and subjected to immunostaining for the presence of molecular biomarkers which Professor Fitzgerald identified, or for standard cytology (hematoxylin and eosin staining). Various oesophageal conditions can be detected, including dysplasia (from pre-cancerous Barrett's lesions to cancer), infections (e.g. *H. pylori*) and inflammation (e.g. oesophagitis).

Cytosponge is suitable for large-scale screening campaigns and does not require local anaesthetic and highly trained medical practitioners. Cytosponge and associated analysis could cost the NHS £50 per examination, compared to £200 per endoscopy.

Clinical studies to test the prototype and the biomarkers were funded through the MRC's Development Gap Fund (managed by MRC Technology) and Cancer Research UK grants. The sensitivity and specificity of the Cytosponge biomarker test was 90% and 93.5% respectively, comparing favourably with current screening tests for breast, prostate and colorectal cancer.

MRC Technology filed patent applications to protect the device and various biomarkers for prognostic and diagnostic purposes and licensed the technology to Covidien for further development. Cytosponge is now CE-marked and received Food and Drug Administration (FDA) approval in November 2014. Product launch is expected in 2016.

ECLIPs: Streamlines clinical assessment and support of children with neurological hearing disorders



MRC Institute of Hearing Research

Dr Johanna Barry
Prof Dave Moore

Auditory Processing Disorder (APD) is a condition whereby children have normal hearing but difficulty listening in noisy environments, such as in the classroom. Because they share many symptoms common to children with hearing loss, they are often referred to audiologists for further assessment.

Although APD seems to be some form of hearing difficulty, its status as a valid diagnostic category in its own right is in doubt. This is because there is no gold standard test for the disorder and children suspected of being affected typically also share symptoms common to other neurodevelopmental disorders such as specific language impairment, autism spectrum disorder, dyslexia, attention deficit disorder and hyperactivity disorder.

Based on the hypothesis that parents will be sensitive to symptoms that can distinguish children with APD from children with other diagnoses, researchers at the MRC Institute of Hearing Research developed a report-based measure (questionnaire) of listening difficulties. Although the questionnaire cannot be used to diagnose one disorder over another, it has been shown to support clinical assessment and management. Ultimately, researchers hope that the questionnaire will be used in schools to identify children at risk and improve the efficiency of decisions about the most appropriate referral route.

The work was funded through the MRC Development Gap Fund, which is a fund managed by MRC Technology and used to enhance translational research within MRC units.

MRC Technology produced copies of the questionnaire and an instruction manual to enable distribution to clinical audiologists and researchers. The long term aim is to license the questionnaire to a publisher of education/health questionnaires to ensure widespread distribution.

Dr Barry said that “parents have commented on how user friendly and easy to understand the questionnaire is, while clinicians have found the results informative. Importantly, we have found the questionnaire to be sensitive to children at risk in the classroom who haven’t been identified through more traditional routes”.

Advancing therapies for rare genetic disorders

MRC Laboratory of Molecular Biology

Dr Mike Gait

Cell-nuclear RNA-targeting antisense oligonucleotides that promote exon skipping are a promising gene therapy for the treatment of a wide range of progressive debilitating neuromuscular disorders that can affect children, including Duchenne muscular dystrophy (DMD), spinal muscular atrophy and myotonic dystrophy.

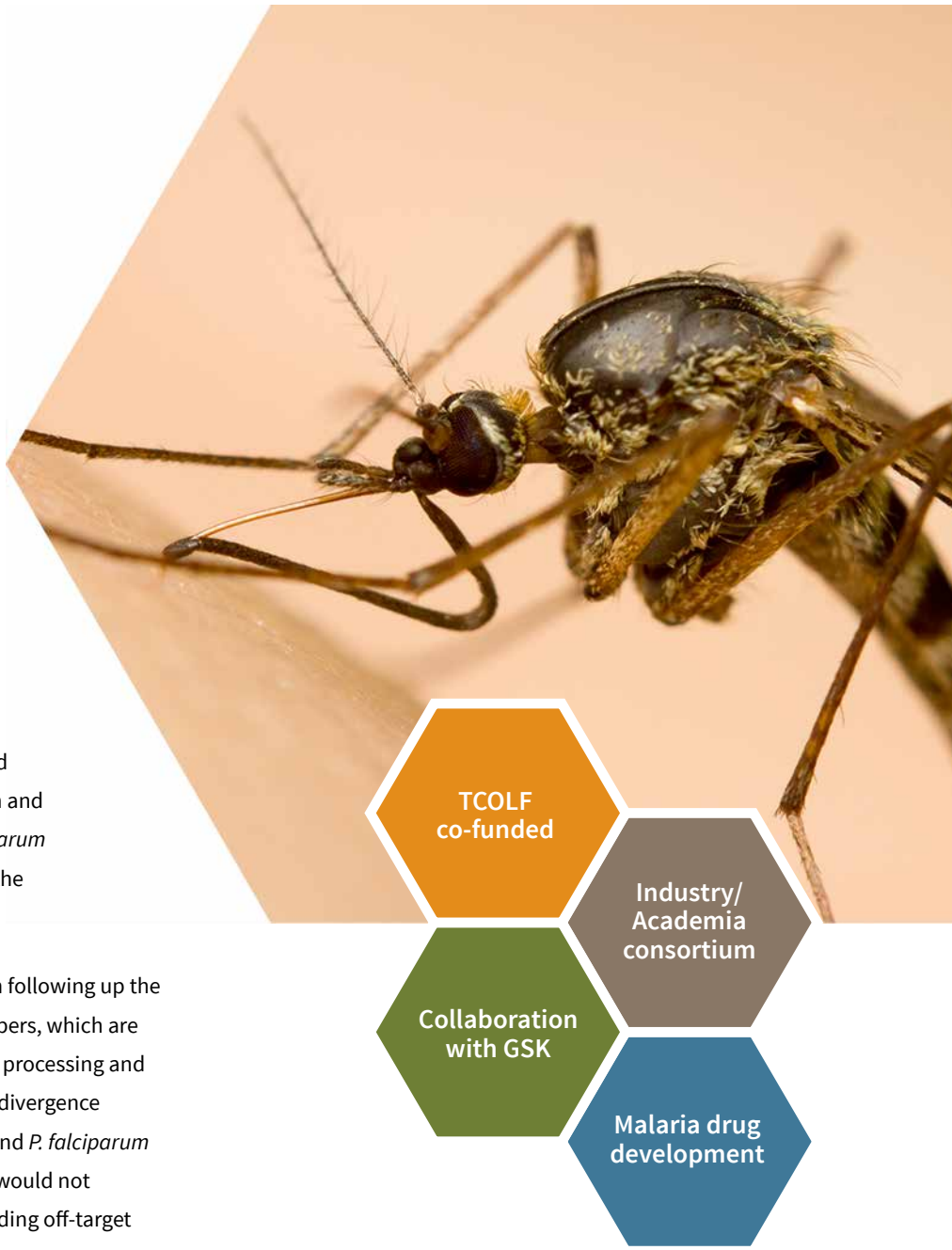
A number of companies have developed such RNA-targeting therapeutics, but have failed to demonstrate sufficient efficacy in clinical studies. It is thought that a key reason for these failures is the relatively low levels of the therapeutic oligonucleotide reaching the pre-mRNA target in the cell nucleus.

Dr Mike Gait and his team developed a novel drug delivery technology: cell-penetrating peptides called Pip, based originally on a known protein transduction peptide called Penetratin. In collaboration with Professor Matthew Wood's laboratory at the University of Oxford, they demonstrated the potential for Pip peptides to deliver exon-skipping oligonucleotides to muscle cells and dramatically increased expression of the protein dystrophin in mouse models of DMD.

A Health Innovation Challenge Fund collaboration between the MDEX-Consortium (a team developing treatments for DMD including Mike Gait and his research/clinical collaborators at University College London, University of Oxford, Royal Veterinary College and Royal Holloway University of London) and the rare diseases company, Shire, has led to this technology being moved towards the clinic, with scale up of drug manufacture and preclinical testing underway.

The MRC patents protecting the technology are also being licensed to other industry partners with compatible drug cargoes in need of a delivery system, with the aim to maximise patient benefit.

Identifying kinases for *Plasmodium falciparum* survival



MRC Toxicology Unit

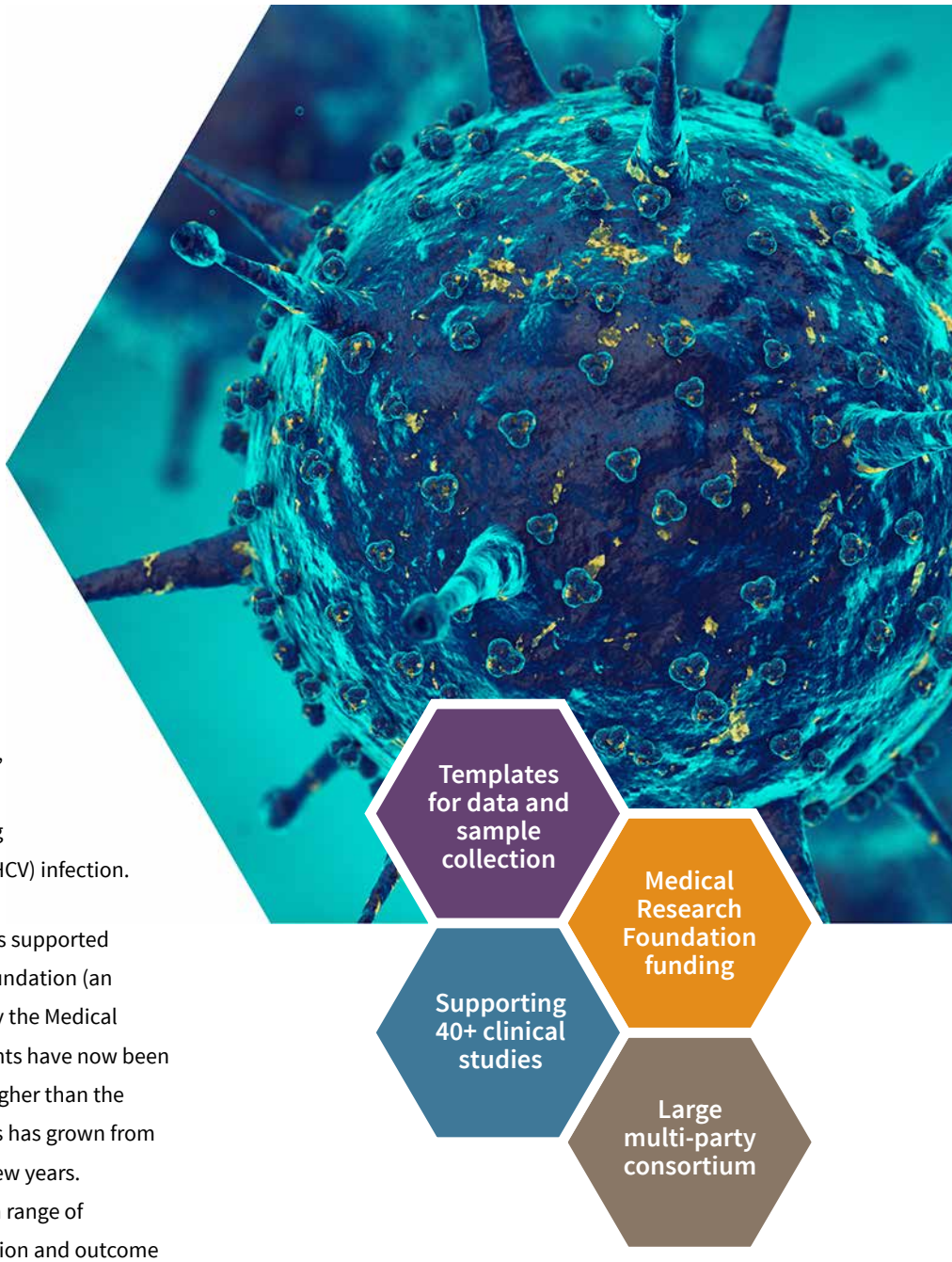
Prof Andrew Tobin

Plasmodium falciparum is one of the Plasmodium species that causes malaria. In 2013 there were an estimated 198 million cases of malaria, with 584 000* deaths (*World Health Organisation). Professor Andrew Tobin and collaborators identified 36 *Plasmodium falciparum* kinases essential for parasite survival during the intracellular erythocytic phase.

Professor Tobin and his team are interested in following up the organism's CDK-like kinase (CLK) family members, which are proposed to play non-redundant roles in RNA processing and alternative splicing. As there is a high level of divergence between CLK family members of the human and *P. falciparum* kinomes, it is hoped that chemical inhibitors would not cross-react with human kinases, thereby avoiding off-target adverse and/or toxic outcomes.

Professor Tobin obtained a Development Gap Fund award via MRC Technology to work with GSK scientists in Tres Cantos (Spain), and screen compound libraries from GlaxoSmithKline, MRC Technology, and Medicines for Malaria Venture for chemical inhibitors of this family of kinases. The work is co-funded by the Tres Cantos Open Lab Foundation (TCOLF), giving access to an open innovation environment for diseases of the developing world. TCOLF is providing both funding and in-kind contributions, as well as hosting the screening. This provides access to industrial-scale screening facilities as well as drug discovery expertise in order to expedite the development of potential new drugs in this area of great medical need.

Leading hepatitis C virus research



MRC-University of Glasgow Centre for Virus Research

Dr John McLauchlan

It is estimated that around 215,000 people in the UK have chronic hepatitis C.

HCV Research UK, a consortium of academics, clinicians and healthcare professionals, was established in 2011 with the aim of promoting collaborative research into hepatitis C virus (HCV) infection.

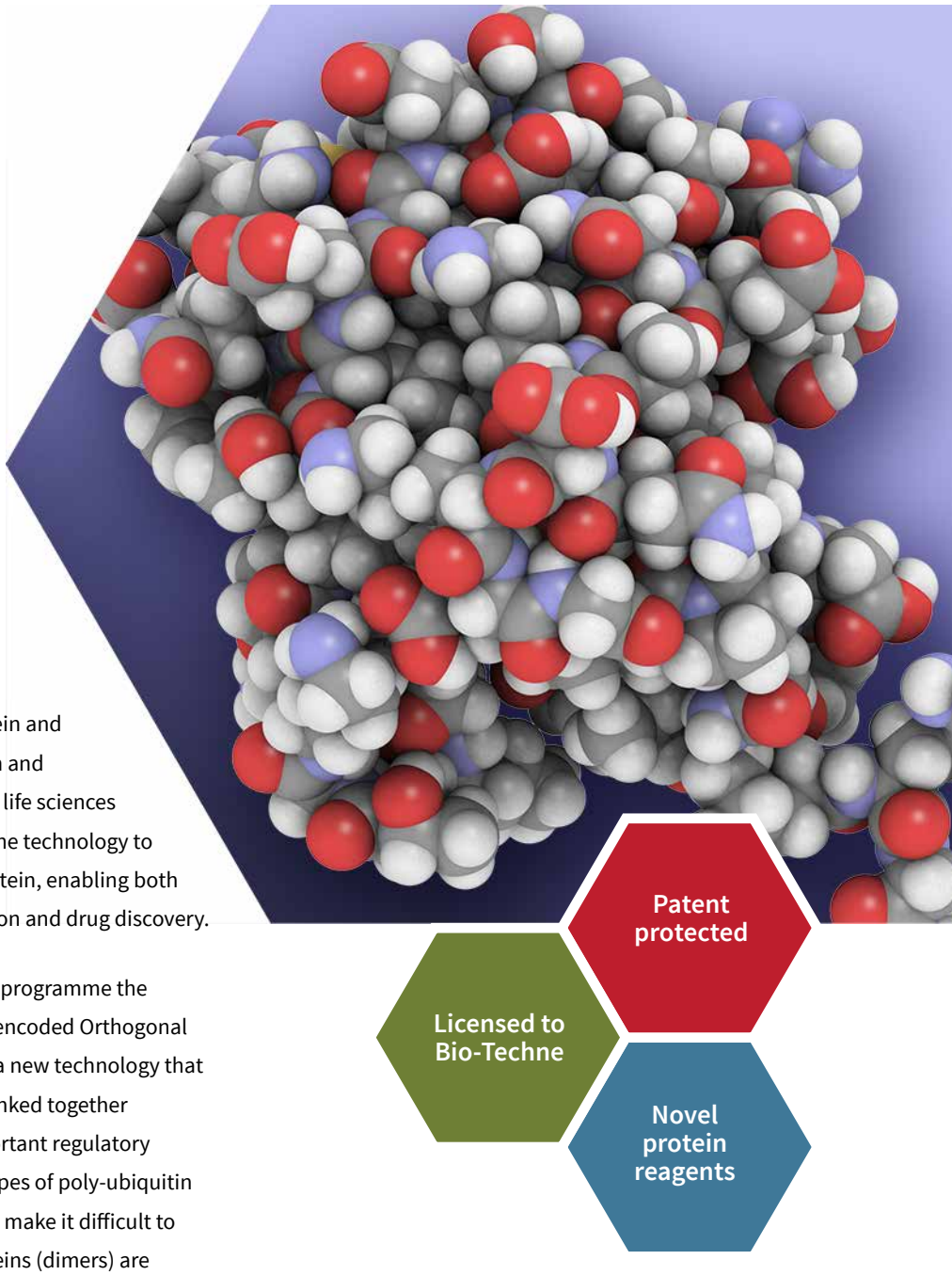
The initiative, led by Dr John McLauchlan, was supported by a £2M grant from the Medical Research Foundation (an independent registered charity established by the Medical Research Council). 10,200 HCV-infected patients have now been recruited into a national cohort, which was higher than the initial target. The network of recruitment sites has grown from 18 clinical centres to almost 60 over the last few years. For each patient, a clinical database records a range of demographic data including disease progression and outcome from treatment. In addition, HCV Research UK has established a biobank of samples from patients recruited into the study for research studies.

The consortium now supports more than 40 separate studies and underpins the MRC-funded STOP-HCV initiative, which aims to optimise therapies for patients infected with HCV.

MRC Technology worked with Dr McLauchlan and the founding organisations to establish the initial structure, processes and contractual agreements for HCV Research UK. Dr McLauchlan said the input from MRC Technology at the early stages was vital for establishing a formally agreed framework to create a network of sites, which has helped to streamline the addition of other sites to HCV Research UK, providing the necessary cohesion to build an impressive cohort of HCV-infected patients.

MRC Technology also provided advice and a template for the conditions under which data and samples are provided to researchers, which now forms the basis for the interactions with academic groups and the pharmaceutical industry.

Protein synthesis technology to enable biological regulation and drug discovery



MRC Laboratory of Molecular Biology

Prof Jason Chin
Dr Satpal Virdee

A method for linking proteins together with specific chemical bonds, developed in the Laboratory of Molecular Biology (LMB)'s Protein and Nucleic Acid Chemistry division by Jason Chin and Satpal Virdee, has been licenced to the global life sciences company Bio-Techne. The company will use the technology to join ubiquitin or other proteins to a target protein, enabling both fundamental research into biological regulation and drug discovery.

The group has been pioneering methods to reprogramme the genetic code of living organisms. Genetically encoded Orthogonal Protection and Activated Ligation (GOPAL) is a new technology that allows cells to produce proteins that can be linked together in a precise way. Ubiquitin is a small but important regulatory protein that can form polymers of different types of poly-ubiquitin chains. The different ways of linking ubiquitin make it difficult to produce samples in which two ubiquitin proteins (dimers) are linked at a desired position on the protein. However, the GOPAL technology makes it possible to produce high quality dimers of ubiquitin that are linked at specific positions on ubiquitin through specific chemical bonds.

Bio-Techne produces tools and resources for research and clinical diagnosis to help scientists understand biological processes and diseases. The licence will enable Bio-Techne to use the GOPAL technology, initially for developing specific dimers of ubiquitin, then for investigating other potential protein modifications. The technology will help produce new protein reagents that can be used in research and drug discovery.

The patent protecting the GOPAL technology was licenced to Bio-Techne by MRC Technology on behalf of the MRC.

Touchscreen application for screening stroke patients in community care

MRC Cognition and Brain Sciences Unit

Dr Tom Manly

Cognitive assessment after stroke is mandated by the Department of Health but is currently not fulfilled by NHS Services due to lack of resource. At present, cognitive assessment needs to be carried out by specialist neuropsychologists, however there are few of these specialists in NHS Trusts and they are expensive. Driven by this significant unmet need, Dr Tom Manly saw an opportunity to adapt the cognitive tests used in research to a touchscreen (tablet based) application for quick assessment of cognitive function and mood in stroke patients.

With support from MRC Technology, a collaborative project team was assembled, including Professor Glyn Humphries (University of Oxford), Dr Andrew Bateman (Cambridgeshire Community Services NHS Trust) and software developer Ounce Technology. An application to the MRC Development Gap Fund (DGF) was successful and funded software development to create a tool for use in validation studies.

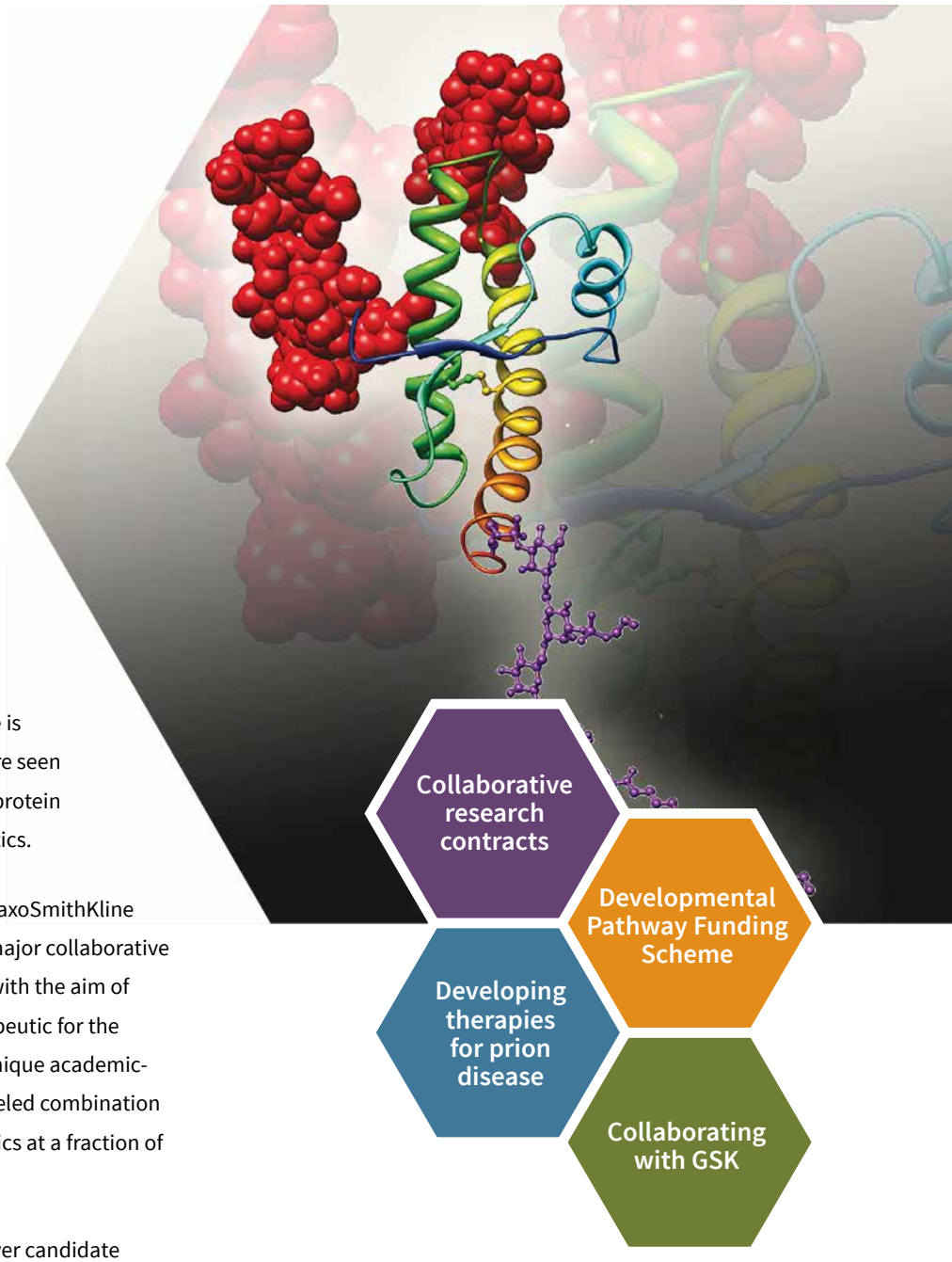
This software is called The Cambridge and Oxford Automated Screening Test (COAST). The COAST application is aimed at occupational therapists and other health care workers in NHS community services as they make rounds visiting discharged stroke patients.

Cognitive assessment can help target appropriate rehabilitation for patients based on their particular impairments. There is no stroke-specific screening tool to assess cognitive deficit currently available. Although paper-and-pencil tests exist for use in research settings, they are time-consuming to carry out and require trained staff to conduct and score the results, so are not appropriate for clinical use.

However, the translation of these tests into a touchscreen format enables automation of the test and scoring and also for a suite of tests to be carried out rapidly (10-20 min), which makes it attractive for routine use in clinical settings.

Subsequent to the DGF project, Dr Manly and Professor Humphries successfully applied for a Wellcome Trust Health Innovation Challenge Fund award to enable further development of COAST. This ongoing project aims to collect normative data from healthy volunteers (against which patient scores are interpreted) to establish the clinical validity of the tests in stroke patients, run a field evaluation trial in an NHS community stroke services setting, and continue the software development work to integrate with NHS systems and prepare the application for commercialisation. It is envisaged that a successful outcome will lead to licensing to an existing provider of neuropsychological tests and the adoption of COAST into community care practice.

Small molecule therapies for prion disease



MRC Prion Unit

Prof John Collinge
Dr Mark Farrow

Human prion diseases (including CJD) are rapidly progressive, invariably fatal, neurodegenerative conditions for which there is currently no treatment. Although rare, they are seen as prototypic neurodegenerative diseases of protein misfolding and also as tractable for therapeutics.

The MRC Prion Unit has been working with GlaxoSmithKline Pharmaceuticals (GSK) R&D since 2005 on a major collaborative project funded by the Department of Health with the aim of developing an effective small molecule therapeutic for the treatment of prion disease in humans. This unique academic-industrial collaboration provided an unparalleled combination of expertise to tackle prion disease therapeutics at a fraction of normal commercial costs.

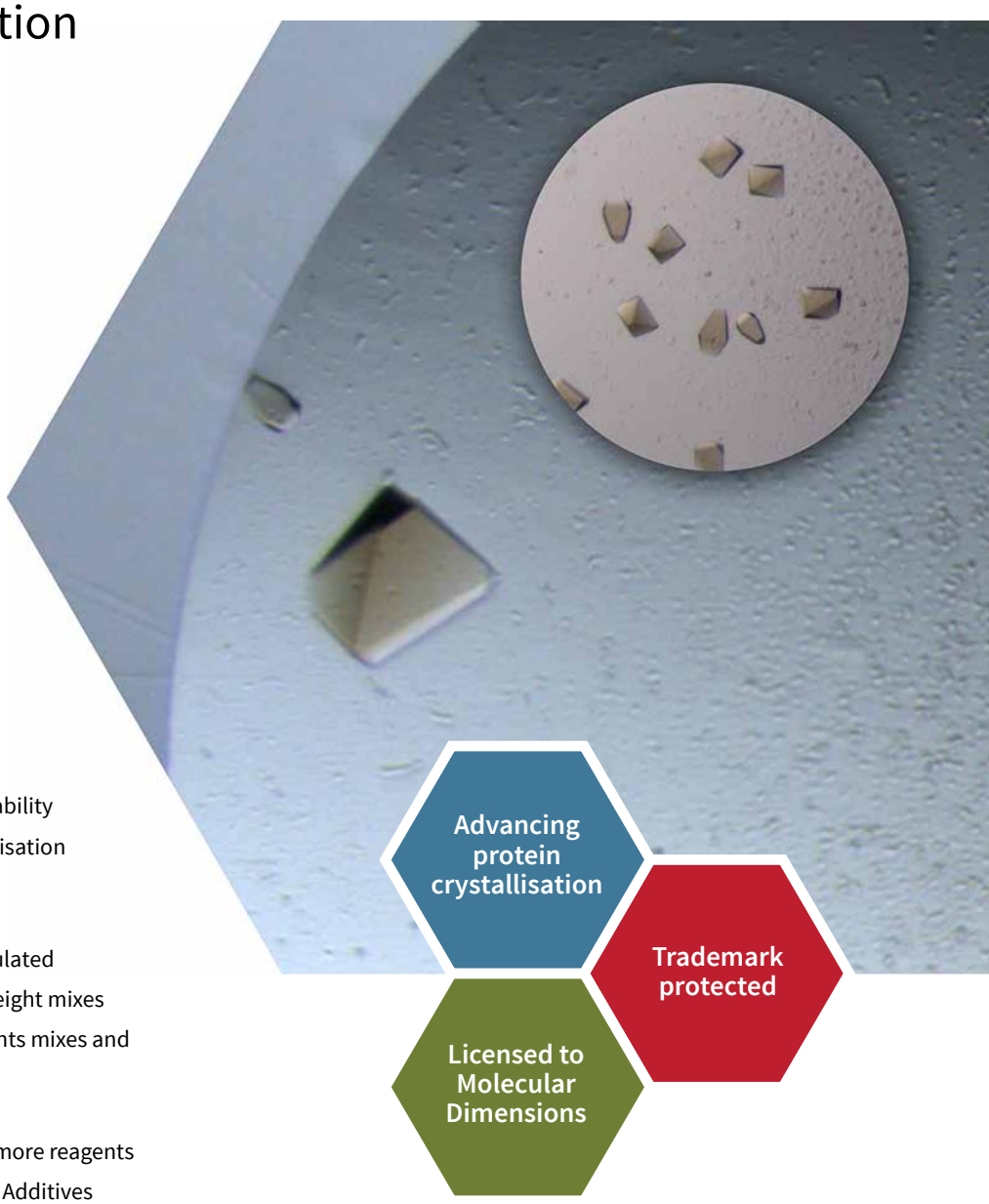
In order to progress this collaboration to deliver candidate therapeutics into preclinical development, Dr Mark Farrow and Prof John Collinge have successfully applied to the Biomedical Catalyst: Developmental Pathway Funding Scheme (DPFS) with GSK as the industrial partner. This ongoing project aims to generate lead candidate compounds for use in subsequent clinical trials.

During the DPFS application process MRC Technology provided guidance on how intellectual property (IP) would be managed and protected, results exploited and revenue shared between partners.

MRC Technology helped complete the IP and commercialisation sections of the DPFS: Case For Support form and negotiated a full collaboration agreement with GSK on behalf of the Prion Unit after the award was made that allowed the project to start on schedule.

An MRC Technology representative also attends regular project meetings and deals with any contractual issues that arise on behalf of MRC.

Morpheus® crystallisation screens for protein crystal production



MRC Laboratory of Molecular Biology

Dr Fabrice Gorrec

Determining protein structures by X-ray crystallography has multiple challenges, especially the low yield of quality diffraction crystals. This low yield is due to the lack of stability of the protein samples, but Morpheus crystallisation screens help to overcome this problem.

Each Morpheus crystallisation screen is formulated *de novo* following a 3D grid approach, where eight mixes of additives are combined with four precipitants mixes and three buffer-systems (8x4x3 = 96 conditions).

Each Morpheus condition therefore includes more reagents than in traditional screens (9-12 instead of 3). Additives integrated into the Morpheus conditions are selected based on their high occurrence in the Protein Data Bank (the universal archive for protein crystals data). This to ensure that the additives that are integrated into the screen are the ones most likely to have an impact on protein stability and crystallisation.

The Morpheus II screen follows the original Morpheus screen that is used with great success in many laboratories and was licensed to Molecular Dimensions Ltd in 2008.

The Morpheus II screen integrates reagents that are not seen in other screens such as metal cations which can both induce new contacts between proteins and help to solve the phase problem (a common issue while processing the crystal diffraction data). As a consequence, the screen should have an impact not only on crystallisation but also on the overall structure determination process.

MRC Technology filed a trademark application for Morpheus which has now proceeded to registration in Europe and the United States. MRC Technology, on behalf of the MRC, also completed an exclusive license deal with Molecular Dimensions Ltd for the Morpheus additive screen and Morpheus II screen in 2014.

Silicate stabilisation technology

MRC Human Nutrition Research

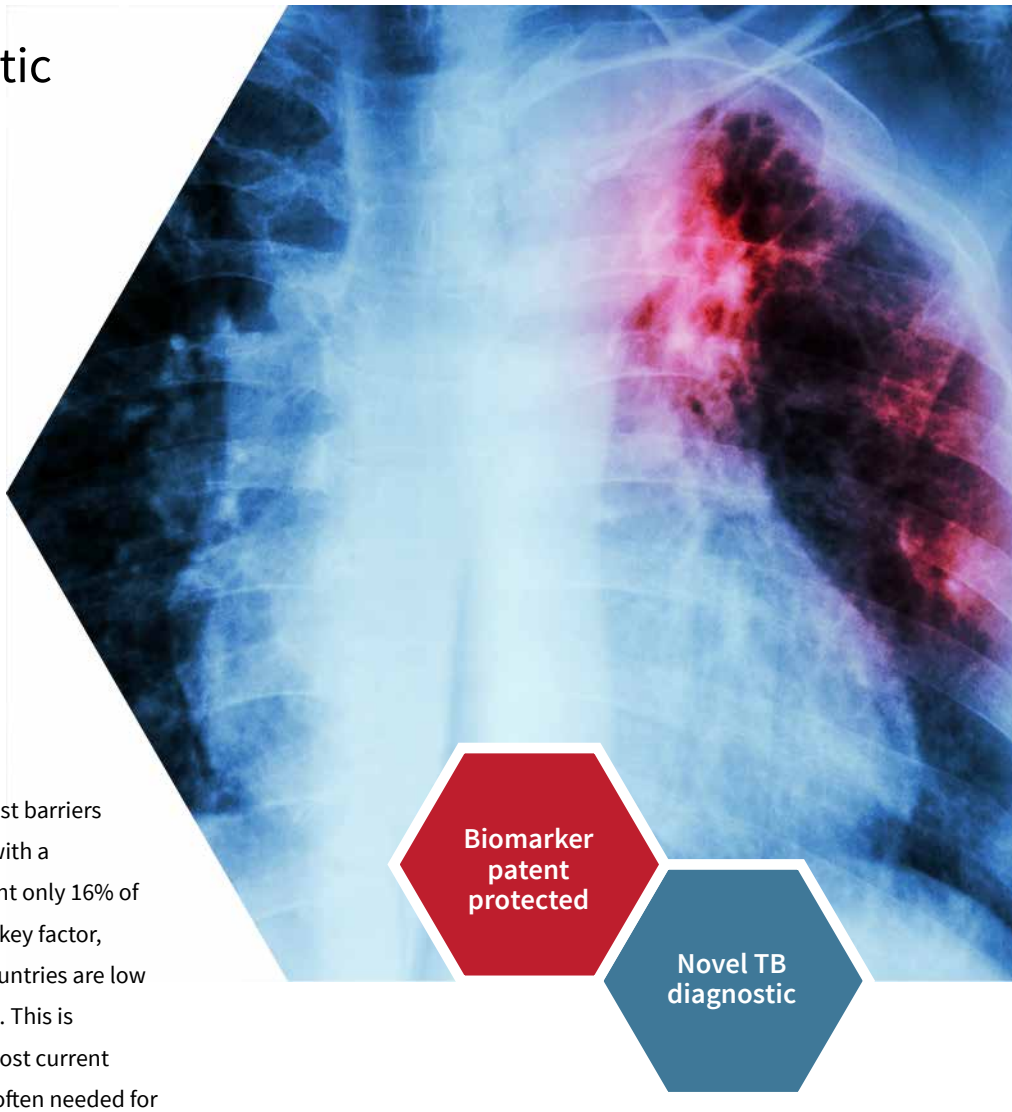
Dr Jonathan Powell

Dr Jonathan Powell has been researching the physiological role of silicon for many years and has recently developed a novel technology that enables stabilisation of silicate compositions for long periods. Silicates normally polymerise and then precipitate unless at very dilute concentrations and this problem has prevented the development of formulations that would have therapeutic use, especially at the nano scale. MRC's technology enables the silicates to be maintained in a pharmacologically useful form. MRC Technology filed a patent to protect this technology in 2013.

HS Pharma is a US biotechnology company focused on the development of silicate-based therapeutics targeting infectious disease and oncology. They have developed a strong relationship with Dr Powell's group over several years, including funding a PhD studentship aiming to investigate the mechanism of action of their lead therapeutics, HS-7 and HS-X.

Although effective in preclinical models, HS Pharma's technology would substantially benefit from MRC's stabilisation technology to progress into clinical development. In November 2014, MRC and HS Pharma signed an exclusive licence agreement under which HS Pharma acquired global rights to develop and commercialise the patented silicate stabilisation technology. The company continues to work closely with Dr Powell and aims to reach the market initially with anti-bacterial wound healing creams, while continuing preclinical development of oncology applications with a view to entering clinical trials within the next few years.

An inexpensive point-of-care diagnostic for tuberculosis



MRC Unit The Gambia

Dr Jayne Sutherland

Tuberculosis (TB) is the cause of roughly 1.5 million deaths each year, and represents a major global health crisis. Despite a growing burden, the diagnosis of TB is one of the largest barriers to effective disease control. Currently, those with a laboratory confirmed diagnosis of TB represent only 16% of the TB patient population. Lack of access is a key factor, particularly as many of the highest burden countries are low income communities with poor infrastructure. This is exacerbated by the relatively slow speed of most current diagnostics, meaning that multiple visits are often needed for patients to receive a diagnosis. As a consequence, there has been a recent focus on the need to improve TB diagnosis, with experts estimating that just increasing test speed alone could save roughly 100,000 lives annually and increasing accessibility around a further 50,000 lives.

To this end, Dr Jayne Sutherland has worked to characterise key markers present in the sputum of TB patients that can be used to distinguish between patients with TB and those with other respiratory diseases. Dr Sutherland's work has produced a set of biomarkers that can accurately distinguish these patient groups and should allow development of low cost, robust and rapid diagnostic platforms suitable for very basic care settings.

MRC Technology has worked with Dr Sutherland to protect this work through a patent and to facilitate ongoing efforts to develop the diagnostic technology. The aim of this project will be to translate these key markers into a rapid and effective point-of-care diagnostic test, having a significant impact on global health.

Protecting and translating research with MRC Technology

MRC Technology was set up as an independent company and charity by the Medical Research Council in 2000 to look after the MRC's intellectual property (IP) and technology transfer needs. It now also offers these services to other academic organisations and medical research charities.

MRC Technology assists MRC scientists to protect their work, achieve its potential and maximise impact. IP can be protected in order to facilitate investment in further development through patents, copyright, designs or trademarks. Protected or unprotected IP can then be licensed to an industry partner with the aim to develop it into a product for patient benefit or further scientific research.

Drug targets and diagnostics can be advanced through MRC Technology's Centre for Therapeutics Discovery (CTD), which has world-class skills in antibody humanisation and small molecule discovery and development, while the Centre for Diagnostic Development (CDD) offers collaborative diagnostic assay development and validation.

Every MRC scientist is partnered with an MRC Technology Business Manager, who will keep in regular contact to maintain awareness of research progress and they will advise if the research has commercial potential. Business Managers can also assist when scientists discuss their research with other organisations and are readily available to aid researchers n their interactions with industry.

To find out more, please contact your Business Manager

020 7391 2700

info@tech.mrc.ac.uk

mrctechnology.org/our-people

Populating the MRC Reagents Catalogue

Do you have any useful research reagents at the back of your freezer? If so, they could be commercialised to benefit the wider scientific community.

The MRC Reagents Catalogue contains monoclonal antibodies, polyclonal antibodies, mice, vectors and cell lines generated by MRC researchers. It enables researchers to make useful research tools available to the wider scientific community without directly having to deal with enquiries.

Reagents are commercialised via partnerships with several major reagents companies including Millipore, eBioscience and Cedarlane Labs. For antibodies, an arrangement with ECACC (European Collection of Cell Cultures) ensures that antibody hybridomas only need be provided once, saving scientists from the burden of continued provision. The MRC Reagents Catalogue generates around £300,000 per year which funds further MRC research. In addition, income generated is potentially eligible for the MRC Awards to Inventors scheme (applies to reagents created from 1 April 2012 onwards).

Scientists can submit a reagent for potential commercialisation by completing this form:

mrctechnology.org/reagents

Unit visits PRIZE DRAW

MRC Technology will be available in person to discuss the translation of your reagents at the CSC in June and at the LMB in July (dates to be confirmed).

All eligible completed reagent forms received by 30 September 2015 will be entered into a prize draw operated by MRC Technology to win £500 for the relevant laboratory.

If you have any questions about:

Development funding

IP protection and commercialisation

Distributing reagents

Potential therapeutics

Diagnostics

Drug targets

Consortia building

Contracts and advice

PROTECTING YOUR WORK

MAXIMISING ITS IMPACT

ACHIEVING ITS POTENTIAL

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