Showcasing translation of Medical Research Council science

2015

MRC Medical Research Council

This publication highlights some of the recent successes in translating the work of scientists in Medical Research Council units and institutes. There is also a look back at earlier research which continues to make an impact today. 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.

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.

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.

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, on a revenue sharing basis, with MRC Technology's Centre for Therapeutics Discovery (CTD) and Centre for Diagnostics Development (CDD), providing access to antibody humanisation, small molecule drug and diagnostic development and validation.

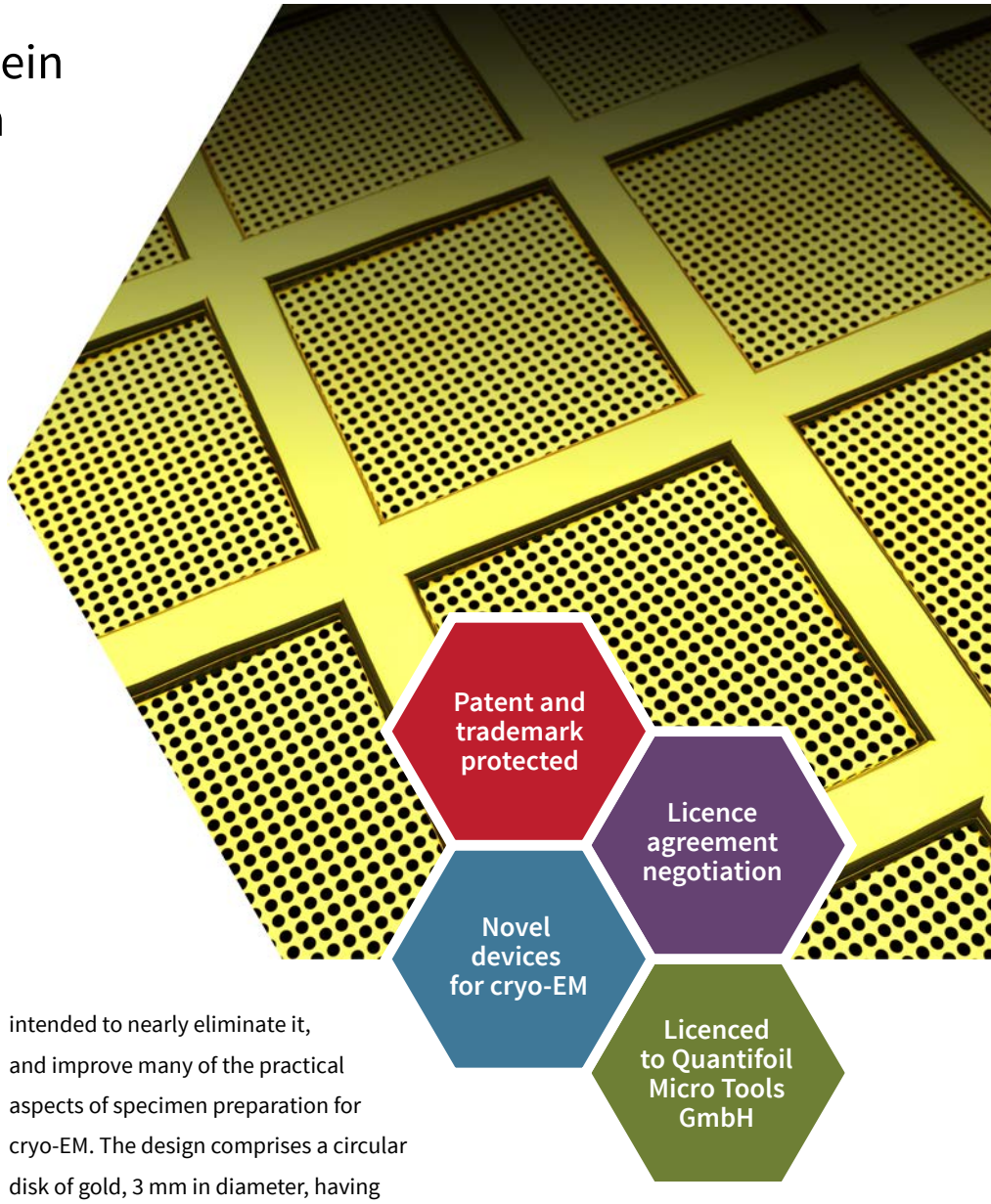
Partnering with industry

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.

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.

Gold supports for the determination of protein structures by electron cryomicroscopy (UltrAuFoil®)



MRC Laboratory of Molecular Biology

Dr Lori Passmore and
Dr Chris Russo

Many protein structures are difficult to solve using electron cryomicroscopy (cryo-EM) because the specimens move in the microscope while they are imaged. Although it has long been known that radiation-induced specimen movement can severely impact the quality of electron cryomicrographs, it was only recently appreciated what role the specimen support had in this degradation. The new gold supports nearly eliminate this motion resulting in improved image contrast and quality of electron cryomicrographs.

The gold supports were developed at the MRC Laboratory of Molecular Biology by Dr Lori A Passmore and Dr Christopher J Russo and are described in Science (2014) Dec 12;346 (6215):1377-80.

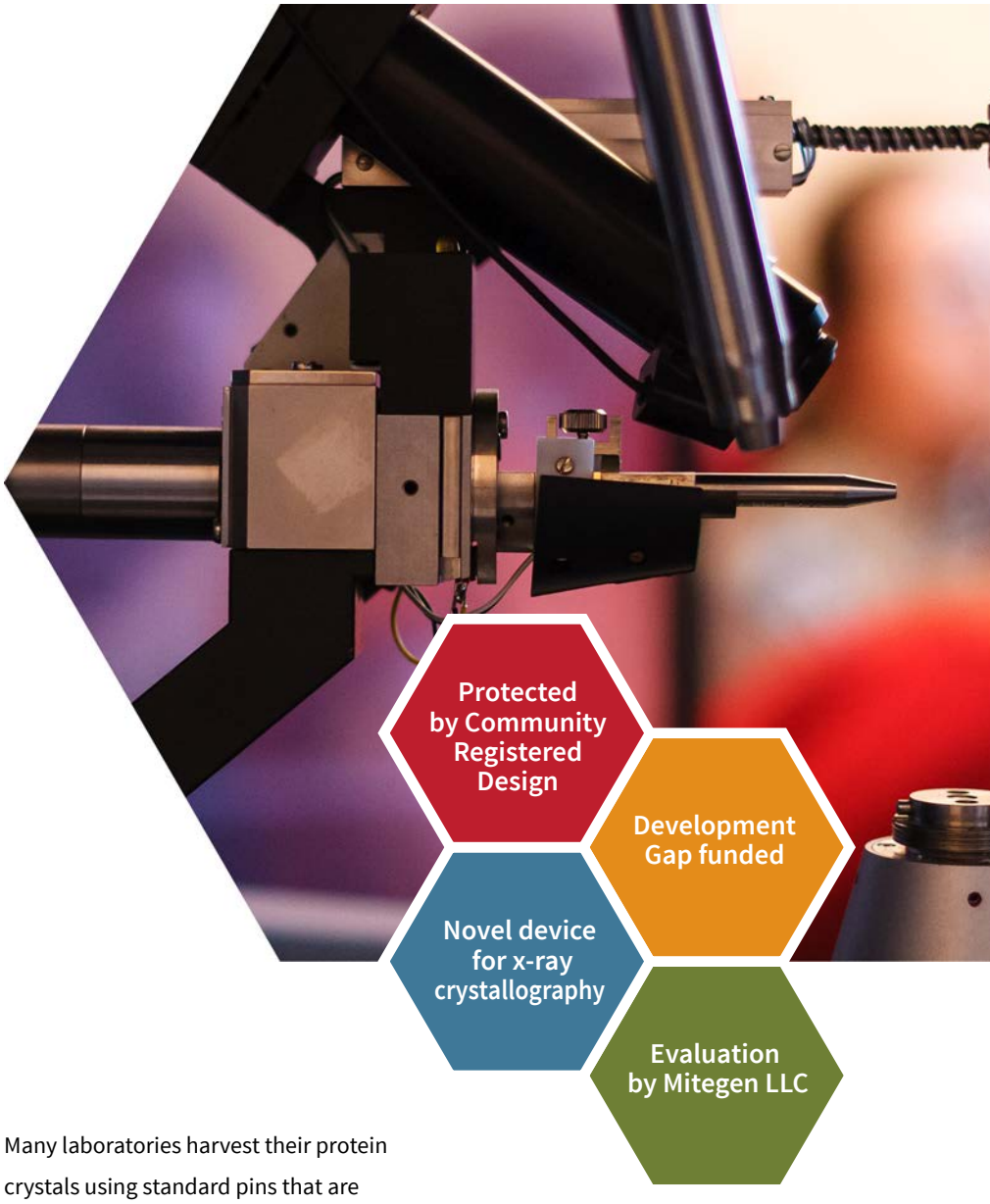
The inventors demonstrated that much of the particle motion in cryo-EM is due to movement of the support: upon irradiation, supports with a perforated carbon foil over a metal mesh grid move by a surprising amount: 200–400 Å in the direction parallel to the electron beam. By carefully analysing the origins of this the inventors designed a support intended to nearly eliminate it, and improve many of the practical aspects of specimen preparation for cryo-EM. The design comprises a circular disk of gold, 3 mm in diameter, having a mesh pattern on which is suspended a thin, polycrystalline gold foil with a regular array of micrometer-sized holes.

Making the support entirely from gold improves image quality in at least three ways: (1) The differential contraction of different materials (e.g. carbon on copper) during cooling is eliminated. (2) The foil is highly conductive at all temperatures of interest and does not accumulate static or semi-mobile charge that can potentially distort the images. (3) Irradiating the gold adjacent to the suspended ice generates secondary electrons close to the suspended ice which may neutralise accumulated positive charge in the specimen.

A US provisional patent application claiming the gold supports was filed on 13 August 2013 and patent applications are currently pending in Europe, Japan, China, Canada, Australia, Israel, United States, Singapore and South Africa. A trademark application for UltrAuFoil® was filed on 25 November 2014 and is now registered in Europe and Australia and pending in Canada, Japan, China, Singapore, Israel, Korea and United States.

MRC Technology negotiated an exclusive licence for ultrastable gold supports with Quantifoil Micro Tools GmbH (Quantifoil). Under this licence, Quantifoil will manufacture and market the gold supports (UltrAuFoil®).

CombiPuck™ for X-ray crystallography



MRC Laboratory of Molecular Biology

Dr Andrew Leslie and
Dr Minmin Yu

MRC has designed and built a prototype cryopuck (CombiPuck™) and related tools for the cryogenic storage, transport and robotic handling of mounted crystals used in X-ray diffraction studies to determine molecular structures.

Macromolecular crystals grown in the laboratory need to be transported in liquid nitrogen at cryogenic temperatures to synchrotrons for both screening to identify crystals of a suitable quality, and collection of X-ray diffraction data used for structure determination.

Shipping the crystals is generally carried out by commercial carriers and therefore a robust way of storing the crystals in the shipping dewars is required. Once at the synchrotron, the crystals are placed in staging dewars of liquid nitrogen at the beamline and then individually mounted by robots for exposure to X-rays, and this also requires a standard and robust way of handling the crystals. Both of these requirements are met by the use of standardised pucks that completely enclose the crystals during shipping, but allow access to the crystals when placed in the robot dewar.

Many laboratories harvest their protein crystals using standard pins that are placed in standard magnetic cryovials in order to protect the crystals. These vials are then placed in canes and stored in liquid nitrogen. Most commercially available pucks do not accommodate these vials and so additional steps are required in order to transfer the crystals from the vials to the pucks, increasing the risk that the crystals (or the crystal mount) will be damaged.

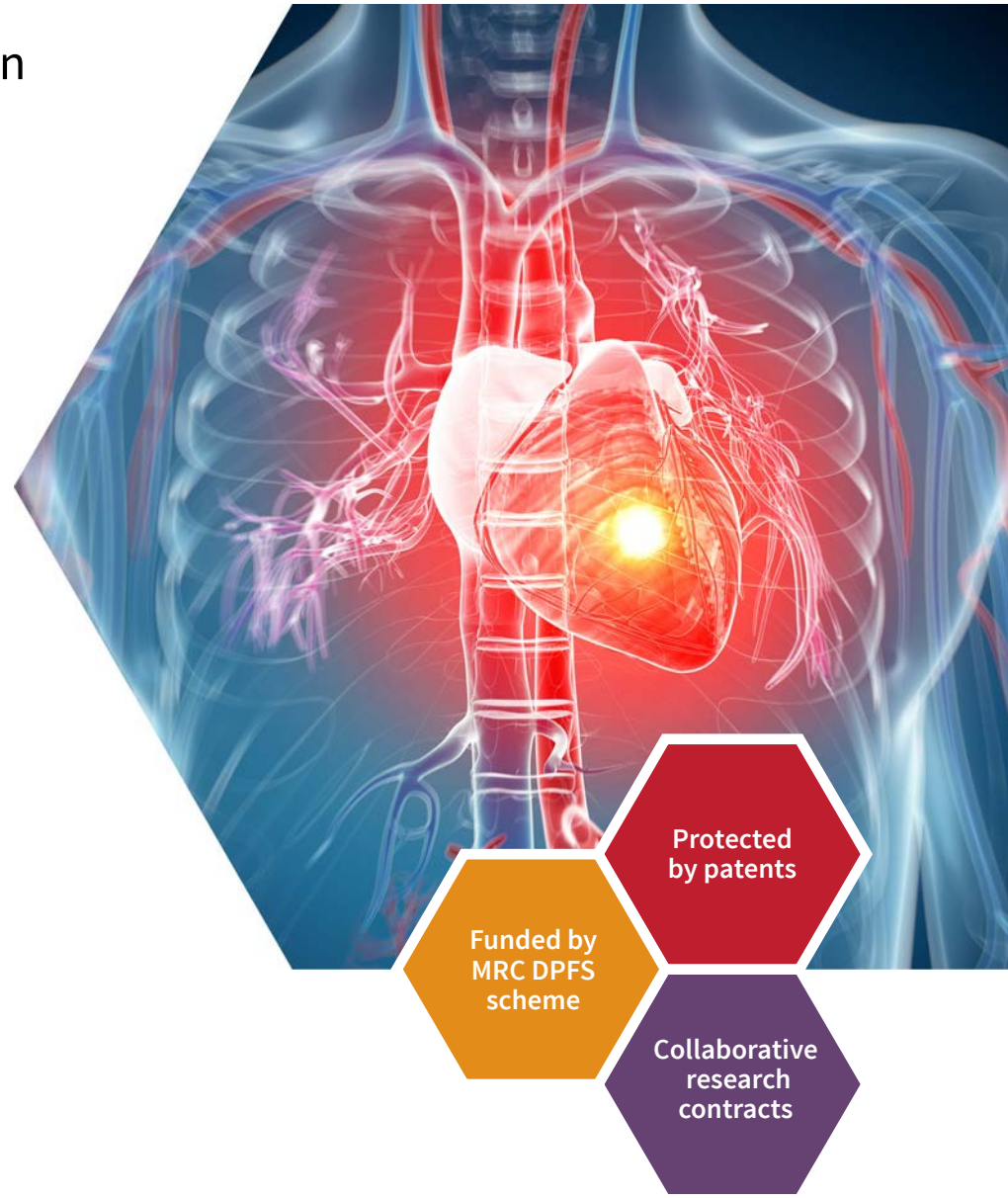
CombiPuck™ overcomes this problem as it is able to accommodate the cryovials directly, reducing the risk that the samples will be damaged. In addition, CombiPuck™ makes it much simpler to recover unused samples from the Unipuck base so that they can be stored for later use.

CombiPuck™ has been developed and tested in collaboration with Diamond Light Source in Oxfordshire, the UK's main synchrotron facility.

Dr Andrew Leslie obtained a Development Gap Fund award via MRC Technology to work with Mitegen LLC to further evaluate CombiPuck™ and produce a dependable manufactured product.

CombiPuck™ is protected by a Community Registered Design (EP) filed on 9 Dec 2014 and by registered design rights in Australia, Canada, China and Japan. A design right application is currently pending in the United States.

Novel therapeutic for Ischaemia-reperfusion injury



MRC Mitochondrial Biology Unit

Dr Mike Murphy

Ischaemia-reperfusion (IR) injury underlies many clinically important conditions such as heart attack and stroke. Ischaemia occurs when the blood supply to an organ is interrupted. If the blood supply is restored the tissue can recover, however, reperfusion of the ischaemic organ with oxygenated blood leads to extensive tissue damage that worsens long-term prognosis.

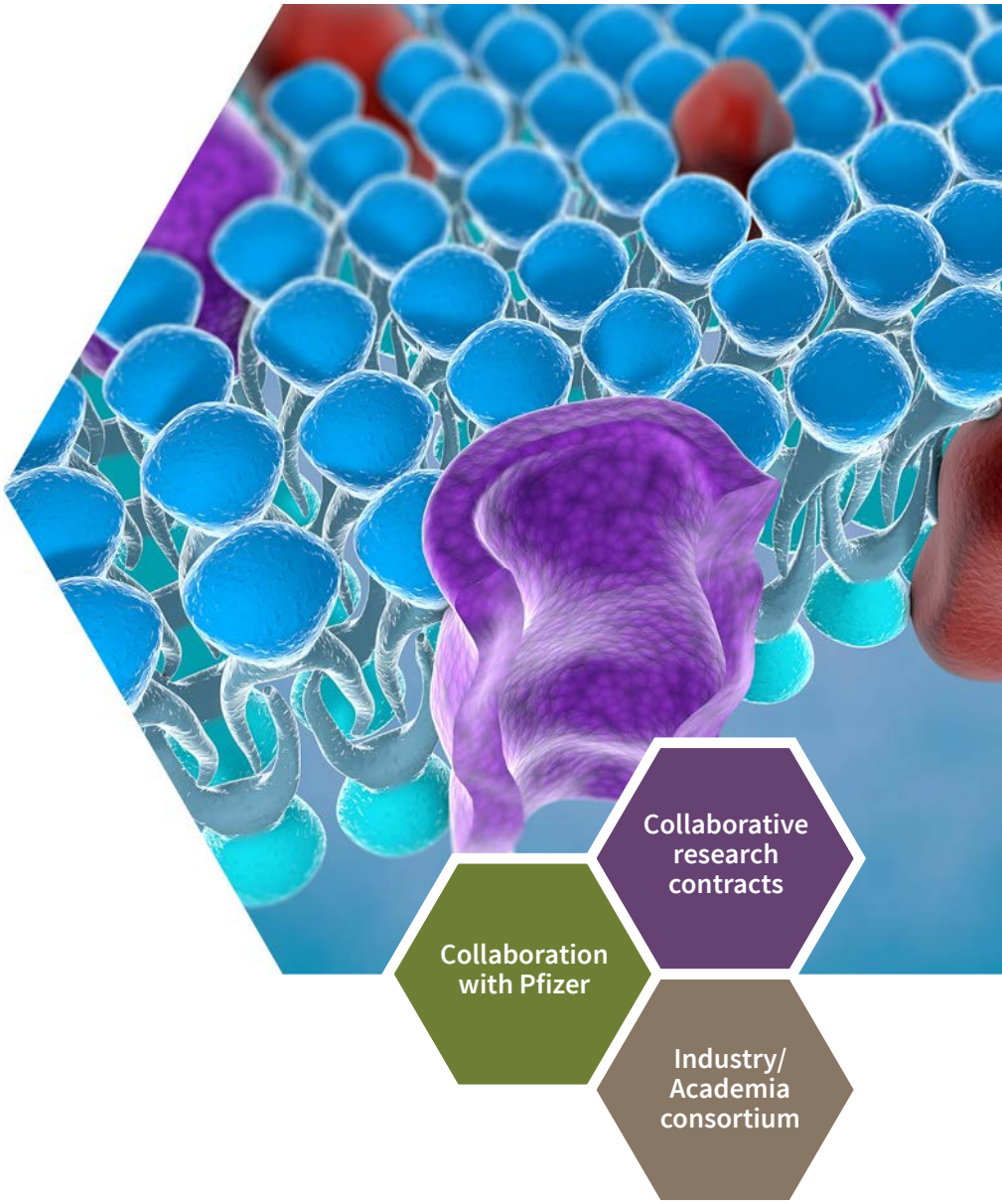
This injury is initiated largely by the production of damaging free radicals from mitochondria during reperfusion that initiates a series of damaging events, including cell death and inflammation.

Dr Mike Murphy and his collaborators have developed a novel small molecule called MitoSNO that offers cardioprotection from IR injury. In mice, injection of MitoSNO just prior to reperfusion reduces infarct size. The cardioprotective mechanism offered by MitoSNO is due to S-nitrosation of Cys39 of the ND3 subunit of mitochondrial respiratory complex I which only becomes susceptible to modification during ischemia. This reversible S-nitrosation of complex I slows the reactivation of mitochondria during the critical first minutes of reperfusion of ischemic tissue, thereby decreasing oxidative damage and tissue damage. As the same mechanism of IR injury also occurs in stroke and during organ transplantation, MitoSNO is also showing promise as a potential therapeutic in these situations.

Recently the project team have been awarded funding from the Biomedical Catalyst: Developmental Pathway Funding Scheme (DPFS). The DPFS funding will be used to carry out a pilot scale synthesis of MitoSNO that can later be scaled up to produce clinical standard MitoSNO for human studies. This preparation will then be tested in mice and to demonstrate whether MitoSNO is protective against cardiac IR injury in mouse models with co-morbidities, such as diabetes and metabolic syndrome, which are likely to be found in heart attack patients undergoing coronary angioplasty. After this, the efficacy of MitoSNO against cardiac IR injury will be tested in a pig model, which is the standard large animal model to assess a cardiovascular drug prior to translation into humans.

MitoSNO and related compounds are protected by granted patents in Europe, United States, Canada and Australia. MRC Technology manages this patent family, assisted in completing the DPFS application form and is negotiating the associated collaboration agreement.

Ion channel structure determination by electron cryomicroscopy



MRC Laboratory of Molecular Biology

Dr Chris Tate and
Dr Sjors Scheres

Electron cryomicroscopy (cryo-EM) is a form of transmission electron microscopy where the sample is studied at cryogenic temperatures. Cryo-EM allows the imaging and structure determination of protein molecules in solution, in contrast to X-ray crystallography that requires crystallising the sample, which is not always possible.

A thin film of an aqueous solution containing the protein sample is rapidly frozen on a support grid, so rapidly that the water has no time to crystallise. The vitrified sample is then placed in the high vacuum of the electron microscope, where it is maintained at −180°C with liquid nitrogen. Projection images of multiple copies of the molecule suspended in random orientations in the vitrified film are recorded and the structure of the molecule is determined by 3-D reconstruction of the cryo-EM images.

Cryo-EM has been gaining increasing popularity in structural biology. Recent advances in electron detection technology and image processing algorithms have seen resolutions steadily improve with some protein structures resolved at near atomic resolution.

Dr Chris Tate and Dr Sjors Scheres have entered into a collaboration with Pfizer to determine the structures of various ion channels by cryo-EM. These structures will provide detailed insights into the biology of the channels and will also potentially be useful for structure-based drug design. Under the terms of the collaboration agreement, which was negotiated by MRC Technology, Pfizer will fund four postdoctoral scientists working at the Laboratory of Molecular Biology for a three-year period.

LMB crystallisation screen for protein crystal production

MRC Laboratory of Molecular Biology

Dr Fabrice Gorrec

Protein crystallisation is essential for structural analysis by X-ray crystallography with the resulting structures often used for rational drug design. For most of the 20th century progress in determining protein structures was relatively slow due to the difficulties in obtaining suitable protein crystals. Despite this, the protein data bank now holds over 100,000 structures with the majority of them having been elucidated by X-ray crystallography.

Proteins vary greatly in their physicochemical characteristics and hence crystallisation of a particular protein is rarely predictable. Determination of appropriate crystallisation conditions for a given protein requires empirical testing of many conditions before successful crystallisation conditions are found.

High-throughput methods have been implemented to help streamline the large number of experiments required to explore the various conditions (precipitants, buffers and additives) that are necessary for successful crystal growth, such as the ones developed at the Laboratory of Molecular Biology (LMB)'s crystallisation facility. There are also numerous commercials kits available to increase the likelihood of successful crystallisation.

Dr Fabrice Gorrec has analysed crystallisation data generated at the LMB using a large initial screen of 1440 commercial conditions. The analysis included over four million crystallisation experiments that were necessary to solve protein structures at the LMB over a seven year period. Subsequently the LMB crystallisation screen, a sparse matrix composed of 96 optimised conditions was formulated. The LMB crystallisation screen was licensed to Molecular Dimensions Ltd in 2015 and will soon be available for purchase.

Accelerating our understanding of how genes contribute to disease

MRC Harwell

MRC Harwell is at the international forefront of mouse genetics, helping scientists study the relationship between genes and disease. Harwell has an enviable track record for making mouse models for MRC researchers, but has also made significant contributions to the International Mouse Phenotyping Consortium (IMPC - www.mousephenotype.org), which aims to generate and phenotype knockout mice for each of the 20,000 genes in the mouse genome.

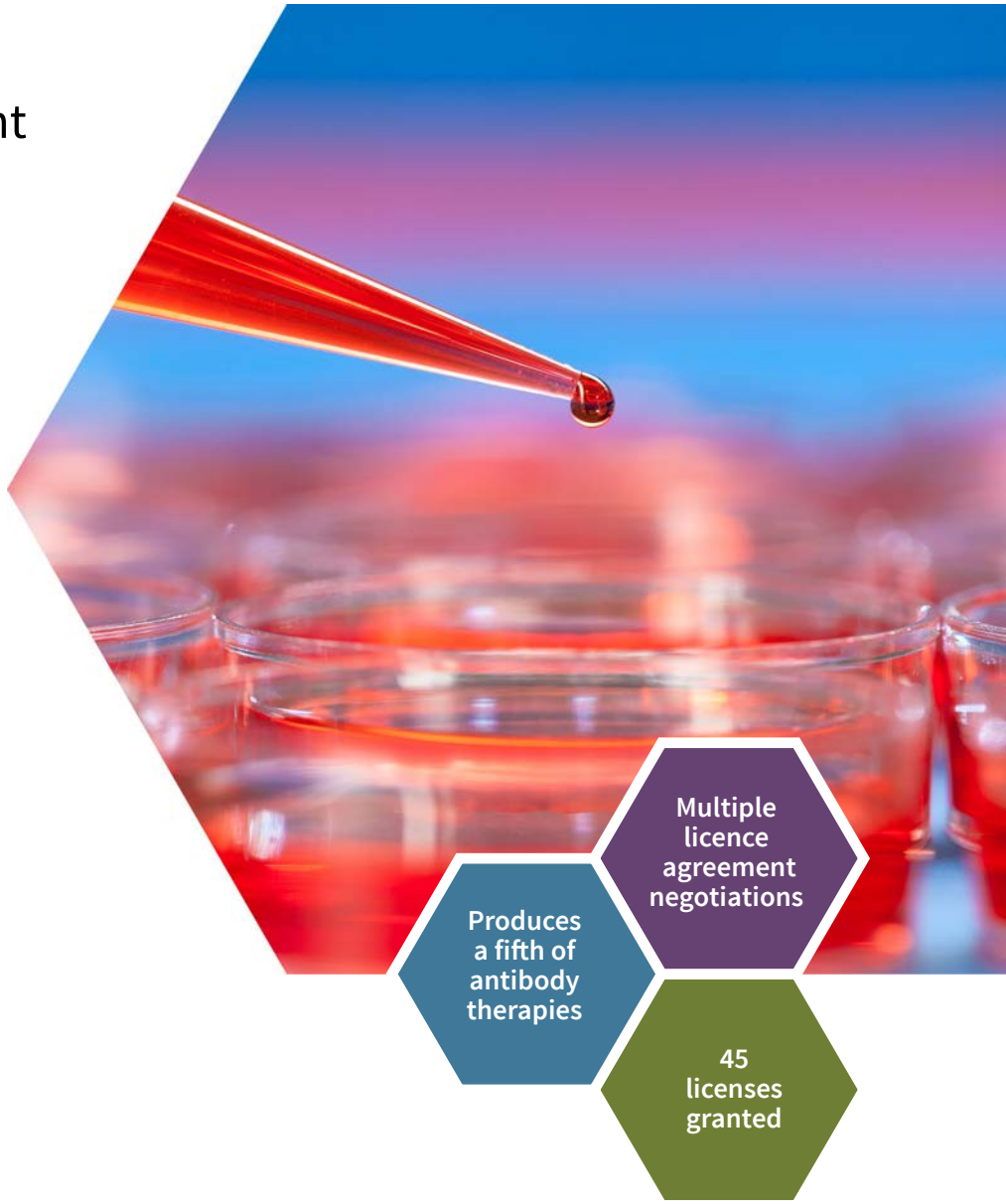
It successfully established the use of CRISPR/Cas-9 genome engineering technology, ensuring precision gene-editing can be delivered quickly and efficiently. This technology is at the centre of two exciting new projects, the second phase of the IMPC and Genome Editing Mice for Medicine (GEMM), both of which will deliver mouse models to support human genomics projects.

The Diabetes Research Group at Harwell provides an example of the power of gene manipulation; they selected candidate genes involved in type II diabetes, supported by data from human genetics collaborators, generating point mutants, conditional over-expressers and conditional knockouts. Systematic analysis allowed the team to validate genes such as FTO, discovering that reduced function of the gene led to lean mice, whereas overexpression resulted in overeating and obesity.

Alongside the Wellcome Trust Sanger Institute and the Helmholtz Zentrum München, Harwell has entered into a licensing arrangement with GenOway to enable industry to access the large numbers of knockout mice it has generated under the European Conditional Mouse Mutagenesis program (EUCOMM). Under this landmark agreement, which MRC Technology was integral in negotiating, GenOway will act as a conduit, enabling industry to access these well characterised animal models, avoiding duplication of efforts and reducing the overall numbers of animals required.

Harwell offers a range of other services to the scientific community including mouse husbandry and phenotyping, archiving and distribution, pathology and bioimaging, gene expression studies and model generation. For further information see www.har.mrc.ac.uk/.

Continued success: The NS0 cell line in antibody development and production



MRC Laboratory of Molecular Biology

Professor Sir César Milstein

Monoclonal antibody technology was invented by César Milstein and Georges Köhler in 1975 at the MRC Laboratory of Molecular Biology (Nobel Prize in Physiology or Medicine, 1984).

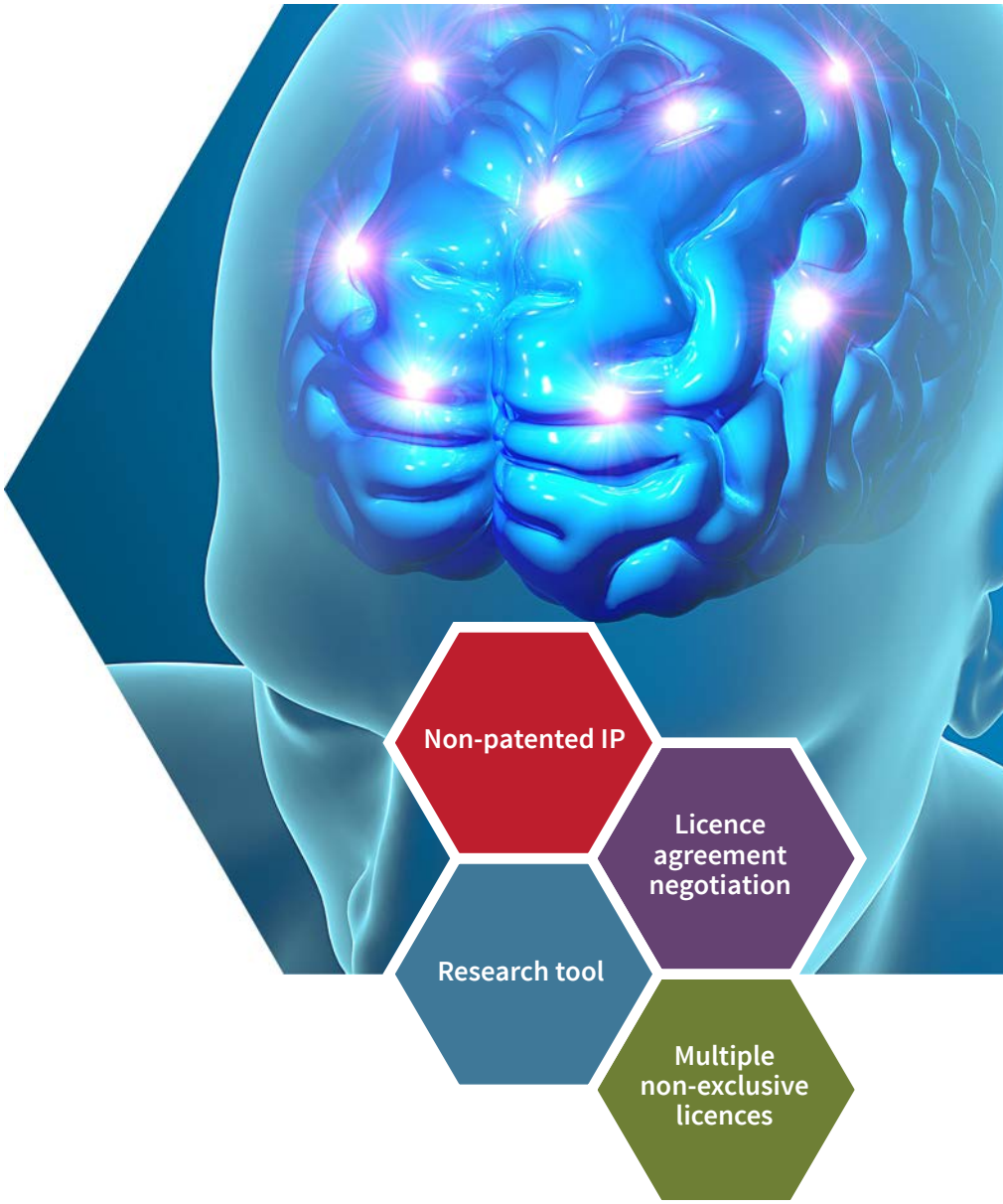
The process involves the generation of a hybrid cell (hybridoma), consisting of the desired antibody-producing B cell and an immortalised fusion partner. It requires a fusion partner that can act as a 'blank canvas' for the expression of monoclonal antibodies, and myeloma cell lines were highlighted as ideal candidates. As immortalised B-cell cell lines they display many desirable features, being inherently adapted to high levels of antibody production as well as growth in suspension.

One issue that remained however is that myeloma cells normally continue to produce antibody, making the separation of desired antibody from background antibody difficult. The NS0 cell line was developed in 1980 in the Milstein lab as a solution to this problem. NS0 is a non-secreting mouse myeloma cell line and has become a popular fusion partner for the generation of hybridomas.

The true potential of NS0 became apparent upon the development of antibody humanisation by Sir Greg Winter at the MRC Laboratory of Molecular Biology in 1986. Cell lines were needed to express these recombinant antibodies and cells like NS0, which are adapted to high levels of antibody secretion, made a logical choice. Humanised antibodies were first approved for therapeutic use in 1996, and the first approval of an NS0 produced antibody followed rapidly in 1997. NS0-produced therapeutic antibodies now represent a fifth of all antibodies on the market.

MRC Technology manages the commercialisation of NS0 and has completed 10 commercial agreements for the development of therapeutic antibodies, as well as a further 35 agreements for other industry activities. The NS0 cell line demonstrates the potential value of research materials and highlights the importance of research output beyond patented intellectual property in commercialisation.

Continued success: Transgenic mice expressing human P301S tau protein



MRC Laboratory of Molecular Biology

Dr Michel Goedert

The build-up of Tau protein within neurones (Tau tangles) constitutes a defining characteristic of a number of neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).

Discovery of mutations in both coding and non-coding regions of the Tau gene has firmly established that dysfunction of tau protein can cause neurodegeneration and dementia. The age of onset of disease and the magnitude of the functional effects produced varies, depending on the Tau mutation. Mutation P301S in exon 10 of the Tau gene causes an early onset of clinical signs and has strong functional effects, leading to a reduced ability to promote microtubule assembly and an increase in aggregation.

Dr Goedert and his team generated and characterised a line of transgenic mice that constitutively express human tau with the P301S mutation (The Journal of Neuroscience, 2002, 22(21):9340). At five to six months of age, homozygous animals develop motor symptoms characterised by severe lower limb paralysis

The transgenic mouse line exhibits the essential features of a human tauopathy, including the formation of abundant filaments made of hyper-phosphorylated tau protein and nerve cell degeneration.

This mouse line expressing human mutant tau is of great value for elucidating the molecular mechanisms by which mutant tau protein causes the dysfunction and death of nerve cells. This may in turn lead to the design of new therapeutic strategies aimed at preventing tau dysfunction. Since characterisation of this mouse line was first published in 2002, the pharmaceutical industry has shown strong interest in utilising this unpatented research tool to enable in-house research and development efforts, such as testing new potential therapeutic entities for prevention, delay or amelioration of neurodegenerative disorders.

A number of big pharma and smaller biotech companies (Esai, Eli Lilly, Voyager Therapeutics, Roche, Pharma Eight Co, reMYND, Crucell Biologics, MedImmune) have acquired the mice under non-exclusive licenses, negotiated by MRC Technology, for the purposes of *in vivo* efficacy testing of proprietary compounds and biological agents, generating significant income over the years for the MRC in the form of upfront fees and annual licence fees.

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 medical research charities and organisations.

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 Centres on a revenue share basis. The Centre for Therapeutics Discovery (CTD) which has world-class skills in antibody humanisation and small molecule discovery and development, while the Centre for Diagnostics 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 in 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

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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