Impacts arising from MRC supported institutes and major investments

A selection of recent research impacts from MRC supported institutes and long-established major investments

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November 2023

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Executive Summary

This report highlights a selection of recent research impacts from MRC supported institutes and long-established major investments. Although the research impacts included in this report arose between 2020 and 2023, the underpinning knowledge that contributed to these impacts often spanned decades of discovery science carried out by academic researchers funded by MRC.

As these institutes and major investments do not report impacts from their research to the Research Excellence Framework (REF) assessment, impacts from this part of MRC's portfolio did not feature in our Analysis of MRC-funded non-academic impacts submitted to REF2021 report, published in June 2023.

The MRC supports five Institutes that together study biological mechanisms and disease processes from molecules, through cells to individuals and populations. In addition to these major investments, MRC also provides long-term sustained support for critical UK biomedical research infrastructures.

This report addresses that gap, providing an overview of breadth of impacts arising from MRC funded research with exemplar case studies from these institutes and major investments.

Introduction

MRC funds research at the forefront of science to prevent illness, develop treatments, and improve human health and wellbeing. To achieve this, MRC funded research focuses on discovery science that uncovers the processes of life and how they contribute to health and disease. Curiosity-driven discovery science provides the fertile ground upon which novel technologies for improving human health are developed; historical examples include the development of DNA sequencing, X-ray and MRI scanning techniques, antibiotics, monoclonal antibodies, and many others. Improving our understanding of fundamental biological processes is essential for developing preventive, diagnostic and therapeutic interventions, that will go on to have wider benefits to the economy and society.

MRC supported Institutes adopt broad multidisciplinary approaches to address major challenges in health-related research, often developing ground-breaking methodology and technology in the process. They are provided with sustained support, state-of-the-art facilities, and a critical mass of collaborative expertise. This allows the use of highly innovative and risky approaches across a flexible range of disciplines, that would not be feasible in a university setting, to tackle crucially important and complex issues over long periods of time. These Institutes attract and develop outstanding students and early career scientists from the UK, and internationally, providing in-depth, advanced research training and a wide-ranging multidisciplinary research environment.

Exterior view of Francis Crick Institute building. Credit: Francis Crick Institute

The five MRC supported Institutes, listed below, are a key component of MRC's portfolio, accounting for 20% of our annual spend. Although these are independent research-focused organisations outside of UK higher education institutions (HEIs), they collaborate closely with all parts of the UK research landscape.

The MRC supported institutes included in this report are:

- Laboratory of Molecular Biology
- Laboratory of Medical Sciences (formerly London Institute of Medical Sciences)
- Health Data Research UK
- UK Dementia Research Institute
- The Francis Crick Institute

These institutes are comprehensively reviewed by MRC and relevant funding partners every five to seven years. As emphasised in the Nurse Review published in June 2023, these institutes '*provide long-term capabilities supporting a critical mass of diverse expertise and knowledge, technologies and equipment to help fulfil scientific and innovation objectives*'.

Alongside these institutes, MRC provides long-term support for critical UK biomedical research infrastructures that represent major investments for MRC.

The long-established MRC major investments included in this report are:

- The MRC Centre for Macaques
- The Mary Lyon Centre at MRC Harwell
- UK Biobank

MRC Laboratory of Molecular Biology (LMB)

The MRC Laboratory of Molecular Biology (MRC LMB)'s overarching mission is to provide knowledge needed to solve key problems in human health through a better understanding of biological processes at the molecular level. The LMB's work employs diverse methods of biology, chemistry, physics, and more recently, machine learning. The emphasis is on areas that are of fundamental biological importance, providing major challenges best addressed in a multidisciplinary environment with long-term support.

The LMB's focus also includes areas where detailed molecular studies offer opportunities for paradigm shifts in our understanding, medical benefits, or major technical innovation.

The LMB is one of the birthplaces of molecular biology and throughout its 70-year history it has consistently made major contributions, providing deep insights and powerful technologies that have transformed biology, medicine, and society. This is most notably evident from the 12 Nobel prizes shared among 16 LMB scientists between 1958 and 2018, establishing the moniker of The Nobel Prize Factory and providing an inspiring role model for research institutions worldwide.

Exterior view of LMB building from south west looking towards Addenbrooke's Hospital.
Credit: MRC Laboratory of Molecular Biology

Synthetic biology and reprogramming the genetic code

MRC LMB researchers have entirely re-engineered the genetic code of the gut bacterium, E. coli, creating a living organism with the largest synthetic genome to date. These cells, with capabilities unlike anything in nature, could be turned into programmable micro-factories that produce a wide range of molecules with novel properties, creating new classes of enzymes, drugs and biomaterials. The bacteria produced in this way are also virus-resistant and provide a new approach for the generation of organisms that cannot exchange genetic information with natural life. In 2022, the Cambridge-based spin-out company constructive.bio was launched to commercialise the opportunities presented by this ground-breaking synthetic biology research.

Most life on earth is encoded by the DNA in its genome, which is composed of four bases; A, T, G, and C. Triplets of these bases, known as codons, encode each of the amino acid building blocks in proteins. The order of triplet codons in DNA corresponds to the order of amino acids, which are joined into long chains to make a given protein. Proteins are the major component of cells of all living species and are assembled by complex cellular machinery within the cell according to a genetic code.

Because the genetic code is read in triplets of bases, there are 64 possible combinations of the four bases in different sets of three, i.e. there are 64 codons (4^3= 64). But in nature, only 20 common amino acids are used by the genetic code. As a result, most amino acids are coded for by more than one codon; different codons that are used for the same amino acid are known as synonymous codons.

The synonymous codons found in nature's genetic code presented an opportunity for LMB researchers to redesign it. The researchers designed a compressed genetic code that used fewer synonymous codons to make the same proteins. In 2019 the researchers published that they had computationally designed and experimentally built a genome for *E. coli* that used this compressed genetic code.

In 2021 and 2022 the team engineered the genetic code in the synthetic *E. coli* cells, creating genetically isolated organisms which cannot exchange genetic information with the environment. This 'genetic firewall' both protects the valuable engineered organisms from natural invaders such as viruses and safeguards the natural world from engineered genetic material.

The synthetic strain of *E. coli* also provides the starting point for genetically-encoded synthesis of new molecules. The researchers showed that they could reprogramme the synthetic *E. coli* cells to assemble complex molecules from both naturally occurring and synthetic building blocks. This new approach allows the team to harness cells for creating programmable micro-factories to produce novel molecules.

The applications made possible by this discovery are vast; by unlocking the potential of the cellular machinery, researchers could in theory produce biodegradable plastics, biomaterials, and new classes of drugs. The building blocks for these molecules go well beyond the 20 common amino acids found in nature that are used to make proteins.

In 2022, the Cambridge-based spin-out constructive.bio was launched to capitalise on this commercialisation opportunity to re-engineer biology, creating new classes of drugs and biomaterials. Potential applications include novel therapeutics and antibiotics, enhanced agriculture, manufacturing and materials, and polymers that can be programmed to be biodegradable.

## Discovery of new immune cells and potential for treating asthma

A novel type of immune cell discovered by MRC LMB researchers has advanced our knowledge of how the immune system is involved in allergic asthma. These cells, named type-2 innate lymphoid cells (ILC2) secrete large amounts of chemical messenger molecules that trigger a reaction in asthma patients. Therapeutic targeting of these molecules represents a new avenue for tackling inflammation. In 2019, a clinical candidate antibody was developed by the team in collaboration with LifeArc researchers to harness this knowledge, leading to the launch of a phase 1 clinical trial in 2022 that will test if the therapy is safe for treating allergic asthma. There are also indications that this approach could also be used to treat colorectal cancer.

Type-2 innate lymphoid cells (ILC2) are immune cells located on the inner surfaces of airways and are involved in regulating the immune response to allergic asthma. The cells, discovered by MRC LMB researchers in 2010, were shown to secrete large amounts of an inflammatory molecule called interleukin-13 (IL-13). IL-13 plays a central role in asthma; too much IL-13 was shown to trigger a reaction in asthma patients. IL-13 is activated by another related molecule called IL-25, which presented an opportunity for the team to develop therapies to halt its action.

Following these discoveries at the cellular level, identifying the mechanisms behind allergic asthma activation, the team collaborated with scientists at LifeArc to develop an antibody candidate that could block the IL-25 receptor. Blocking the IL-25 receptor in this way would prevent it from activating IL-13, which triggers an asthma reaction. The antibody candidate, named SM17 was licensed to SinoMab Therapeutics and a phase 1 clinical trial was launched in 2022. If this clinical trial proves that SM17 is safe and well-tolerated in healthy volunteers, it could be a valuable tool for treating asthma.

Through a similar molecule mechanism, but addressing an entirely different disease, SM17 could also be used to treat colorectal cancer. In 2022, the LMB team showed that cancer cells in a tumour recruit ILC2 cells to suppress the immune response, thereby preventing the immune system from destroying the cancer cells. But in mice treated with SM17 to block the action of IL-25, the immune system was able to eliminate the tumour. As a result, SM17 could potentially be used as a novel first-in-class IL-25 inhibitor to treat both allergic asthma and colorectal cancer.
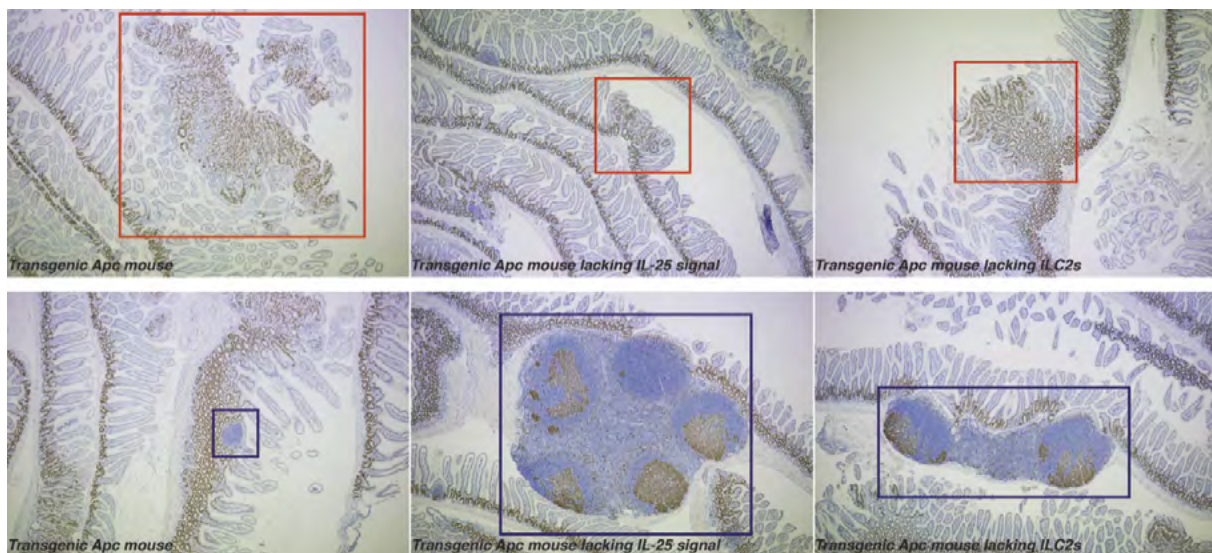
Microscope images of a mouse intestine showing smaller cancers and a more active immune response when ILC2 immune cells are blocked or removed. Credit: MRC Laboratory of Molecular Biology

Understanding the mechanisms of behaviour from insect larval brain map

MRC LMB researchers have built the first ever detailed wiring map of an insect larval brain, revealing deep insights into how a brain can learn and generate behaviour. Published in 2023, the team mapped each one of the 3016 neurons in the fruit fly larvae, and the 548,000 connections between them, using computer-assisted reconstruction from high resolution electron microscopy imaging. This complete brain connectome is a landmark achievement, with techniques that can be applied to analyse connectomes in other more complex animals while also providing intriguing insights into the future development of biology-inspired artificial neural networks.

Brains consist of neurons that are connected to each other, with information in the form of chemical signals passing from one neuron to another through these contact points. In order to understand how a brain can generate behaviour, it is vital to first develop a 'connectome'; a map of all neurons and all connections between each other. Building a connectome is akin to drawing a road map from satellite images, except in three dimensions. To do this, the MRC LMB team used high resolution electron microscopy images of serial sections of a whole larval fly brain. Previously, only three organisms have been mapped to show complete connectomes, but these animals were far simpler. In contrast, the fruit fly larval brain consists of 3016 neurons, with over 548,000 connections between them. Published in 2023, it is the most complex connectome determined to date and represents a key milestone in our quest to understand information processing in animal brains.

Many of the techniques and computational tools built by the team to study the fly larval connectome can be directly applied to analyse more complicated connectomes. For example, the adult fruit fly brain consists of approximately 100,000 neurons making an estimated 100 million connections. Understanding the differences in connectomes between larval and adult brains of the same organism offers intriguing possibilities into how a brain changes as it develops. As scientists map more connectomes in other species, it will be possible to identify circuit architecture

Image showing morphology of all neurons in a larval fruit fly brain.
Credit: MRC Laboratory of Molecular Biology

that they have in common, for example for learning, memory or movement.

Analysis of the connectome also provided a fascinating insight into machine learning architectures. The team showed that some of the features observed in the connectome, such as 'multilayer shortcuts' or 'prominent nested recurrent loops' are also found in artificial neural networks.

For example, nested loops are a powerful programming concept that allows software developers to implement complex iterations and repetitive tasks, while multilayer shortcuts are commonly used in artificial neural network design to facilitate their training. Analysing the differences between connectome maps and artificial neural networks could therefore help identify and inspire new approaches to developing novel machine learning and artificial intelligence (AI) concepts.

MRC Laboratory of Medical Sciences (LMS)

The MRC Laboratory of Medical Sciences (formerly the MRC London Institute of Medical Sciences) is a biomedical research institute where scientists and clinicians collaborate to advance the understanding of biology and its application to medicine. It takes a challenge-based transdisciplinary approach to tackle major questions of relevance to human health and disease with a strengthened focus on human studies.

The LMS is located in a newly constructed state-of-the-art facility on the Hammersmith Hospital campus of Imperial College London, thereby aiming to enhance its position as a national hub for clinician scientists in training. The LMS is fully supported by MRC, with funding for its core research, staff, and facilities.

Exterior view of newly built LMS building.
Credit: MRC Laboratory of Medical Sciences

Interleukin-11 and its role in disease

MRC LMS researchers, in collaboration with researchers in Singapore, have shown that inhibiting a chemical messenger molecule called interleukin-11 could be a promising approach to treating a range of diseases. The team showed in 2017 that interleukin-11 enhanced inflammation and was therefore involved at a key stage in a group of diseases linked to dysregulated tissue repair and healing, known as fibro-inflammatory diseases. The discovery led to significant private sector investment and the founding of a spin-out company Enleofen, whose IL-11 platform was subsequently acquired by Boehringer Ingelheim in 2019. The agreement could see Enleofen receive in excess of $1 billion per product in upfront and success-based development and commercialisation milestones. Successive research and development since led to first-in-class antibody therapeutics targeting interleukin-11, and to the launch of a phase 1 clinical trial in 2023.

Interleukin-11 (IL-11) was identified and characterised in the 1990s but was misclassified as an anti-inflammatory molecule, with few studies and publications since. However, in 2017 researchers at LMS and Duke-National University of Singapore identified IL-11 as a major cause of heart and kidney fibrosis. The team showed that IL-11 is upregulated in a wide variety of fibro-inflammatory diseases such as systemic sclerosis, rheumatoid arthritis, inflammatory bowel disease, pulmonary fibrosis, kidney disease, drug-induced liver injury, and nonalcoholic steatohepatitis. Detailed study of the inflammatory cell signalling pathways involved in these diseases showed that IL-11 is indeed the master switch for driving tissue pathology, while also inhibiting tissue regeneration.

The discovery of IL-11's role in driving fibrosis and tissue pathology was a radical shift, providing new directions for researchers to expand their knowledge and understanding. For example they focused on better understanding the structural and biochemical mechanisms at the cellular and organ-level underlying IL-11 dysfunction.

The researchers went on to show that neutralizing IL-11 antibodies can prevent and reverse fibrosis in mouse models of human heart, lung, and liver disease. In the years that followed, the researchers were granted over 10 patents relating to IL-11 biology, enabling the launch of a Singapore-based spin-out company Enleofen. In 2019, Boehringer Ingelheim acquired worldwide exclusive rights to Enleofen's preclinical IL-11 platform to develop first-in-class therapies across a broad range of fibro-inflammatory diseases. In May 2023 a Phase 1 study was launched to progress the clinical development of its first-in-class IL-11 inhibitor antibody to assess the safety, and tolerability in healthy volunteers.

Discovering the genetic drivers of premature aging in the heart and circulation

A novel artificial intelligence (AI) tool, collaboratively developed by MRC LMS researchers with support from the British Heart Foundation and Bayer Pharmaceuticals, has been shown to predict 'Heart Age'. AI was used to analyse moving magnetic resonance (MR) images of the beating heart and circulation in 40,000 participants of UK Biobank alongside electrocardiogram (ECG) traces and genetic sequencing. Over 100 different measurements were then used to train the algorithm to model healthy aging and predict an 'age gap' quantifying the deviation in years from healthy ageing. The study showed that premature aging was an important risk factor for cardiovascular diseases, and identified genetic variants associated with premature aging. This work shows how AI can make effective use of large-scale health data to understand mechanisms that drive aging and multimorbidity.

The research team expect that this AI tool can identify genetic and environmental risk factors that regulate the processes of aging and support research into treatments to combat age related disease. The study, published in 2023, showed that aging is characterised by changes in the mechanical properties of the heart and circulation – with the heart muscle and major blood vessels becoming progressively stiffer with age. This loss of elasticity across different tissues can be assessed with MRI as well as measuring the underlying tissue fibrosis, which is a key mechanism of aging.

The study found that, PLCE1, a gene that regulates how the heart muscle responds to stress over time could be important in how people age differently. ELN, a gene that produces elastic fibres throughout the body, was also implicated in aging progresses. The study also identified variants in a gene called TREM2 which regulates immune responses in the heart, adding to evidence for the role of 'inflammageing' in cardiovascular aging. Inflammageing is defined as an age-related increase in levels of these pro-inflammatory biomarkers in blood and tissues and is a strong risk factor for multiple diseases that are highly prevalent and frequent causes of disability in elderly individuals. Environmental risk factors were also important for aging – with hypertension being the strongest predictor.

The study found that 'latent' features in routine ECGs could also accurately predict cardiovascular age using machine learning algorithms that analyse the traces.

This revealed associations with genetic variants in genes that regulate heart rhythm and influence how fibrosis develops in the atrium (the chamber of the heart that receives blood from the circulatory system). As advanced imaging is not widely available, the use of ECG traces to assess age-related disease offers a simple and inexpensive tool for future research on heart aging.

The introduction of this innovative AI tool marks an important step in understanding the drivers of aging – which is a leading risk factor for cardiovascular disease. Cardiovascular ageing was found to be significantly associated with variants in genes regulating muscle contraction, immune responses, and how tissues adapt to chronic stress. Such partnerships between academia and pharmaceutical companies will accelerate the assessment of potential molecular targets to reduce the impact age-related processes.

Left ventricular wall thickness

| 50 - 59 years | 60 - 69 years | 70 - 79 years |
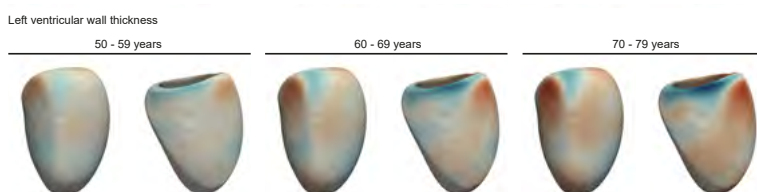
Three dimensional models of how the human heart ages between 50 - 79 years. Data collected from cardiac MRIs in almost 40,000 UK Biobank participants.
Credit: Professor Declan O'Regan

Genetic analysis could improve heart muscle disease diagnosis and management

New understanding of the genetics that contribute to heart muscle diseases could help clinicians improve diagnosis and predict the severity of the disease. Researchers are already aware of the rare mutations that affect the heart muscle and disrupts the contractions but many more common mutations in the genome appear to act in combination to influence susceptibility to heart disease. Both hypertrophic (HCM) and dilated cardiomyopathies (DCM) were thought to be single gene disorders, but new research from the MRC LMS shows otherwise. The results, published in 2021, could have an impact on how these patients are monitored, aiding the calculation of diagnostic risk scores. This will help patients and clinicians better manage the disease, and the team are currently testing these scores in the clinic to understand whether they can be useful to inform patient assessments routinely in cardiomyopathy clinics.

Hypertrophic (HCM) and dilated cardiomyopathies (DCM) are the leading causes of sudden death in young people who are otherwise healthy. Both these diseases involve defects in the part of the heart muscle cell that makes it contract, known as the sarcomere. Defects in the sarcomere makes it difficult for these hearts to pump blood around the body, leading to disrupted heart rhythm or even heart failure. Intriguingly, genetic testing has shown that nearly half of those with the condition don't have any mutations in genes involved in the development of the sarcomere. In addition, not all family members with the same inherited mutation go on to develop the disease, and if they do, the severity of the disease can also vary. These variations make it very difficult for clinicians to manage treatment and makes it worrying for the families that are affected by this condition.

Researchers at the MRC LMS studied the genomes of 1733 patients with HCM and compared them to a group of healthy individuals to assess which mutations would contribute to HCM risk. They then compared this with data from 5,521 patients with DCM, and almost 20,000 people from the general population who had their hearts assessed using cardiac MRI scans. The results of the analysis, published in 2021, indicate that HCM and DCM are not single gene disorders; rather, a complex interplay of multiple genes can influence how the disease develops and progresses. The team are working on developing diagnostic risk scores that could be used to identify more vulnerable family members and calculate the severity of the disease to predict those who may need closer monitoring and advanced treatment.

Health Data Research UK (HDR UK)

Health Data Research UK (HDR UK) was established in 2018 to address the most pressing health research challenges facing the public by delivering cutting edge health data intensive research programmes and establishing UK-wide data research infrastructure capabilities and services, enabling the use of health-related data at scale for research and innovation. HDR UK is an independent charitable company, supported through a joint investment led by MRC, together with National Institute for Health and Care Research (NIHR), British Heart Foundation, Cancer Research UK, Economic and Social Research Council (ESRC), Engineering and Physical Sciences Research Council (EPSRC) Health Care Research Wales (HCRW), Health and Social Care R&D Division, Public Health Agency Northern Ireland (HSC PHA NI), and Chief Scientist Office Scotland (CSO Scotland). MRC contributes 70% of the core funding.

Streamlining accessibility to COVID-19 data across the UK with Trusted Research Environments

Providing policymakers with timely information from across the UK during the course of the COVID-19 pandemic was a key priority for those at the forefront of the COVID-19 research response. This was essential for ensuring that robust data and evidence were used to inform social and health policy in response to the rapidly unfolding global emergency. The national Trusted Research Environment (TRE) networks, brought together by HDR UK have been instrumental in making a range of datasets accessible to policymakers. It required streamlining access to high priority health, administrative, molecular, and behavioural data assets for researchers working on COVID-19. Making these datasets accessible across the whole of the UK population was a unique success of Data and Connectivity National Core Studies programme, led by HDR UK. As of January 2023, 70 datasets have been provisioned for users in 26 research institutions, enabling COVID-19 researchers to conduct statistically powerful population scale research.

Trusted Research Environments (TREs) are highly secure computing environments that provide remote access to health data for approved researchers. These include routinely collected, de-identified, linked health data that includes primary and secondary care, registered deaths, medication data, COVID-19 laboratory and vaccination data and cardiovascular specialist audits.

Prior to the COVID-19 pandemic, researchers could not access these linked health datasets across the whole UK population. Recognising the need to make these datasets accessible, HDR UK led efforts to streamline access to high priority health, administrative, molecular, and behavioural data assets for researchers working on COVID-19. Analysing these datasets would provide researchers information on health service burden, potential impact of vaccines and treatments, and the effects of new variants of concern from across the four nations of the UK. The information could then be used to provide evidence and inform policy decisions in response to the evolving pandemic.

The team at HDR UK worked closely with other TRE delivery partners such as SAIL Databank (Wales), Public Health Scotland/ EPCC (Scotland), Health and Social Care Honest Broker Service (Northern Ireland),

and the Office for National Statistics and OpenSAFELY to make these vital datasets available across the whole UK. As a result, remote secure access is provided in a new NHS Digital TRE for England, which holds about 4.9 billion records and covers 96% of the population of England (>54m people), with similar linked data made available in TREs for Scotland and Wales (>8m people).

These linked datasets have already provided vital insights for policymakers, such as the results from a study of 46 million adults in England, published in March 2022 which demonstrated evidence for a lower incidence of myocarditis after COVID-19 vaccination. The study contrasted with previous reports emerging from the United States of America and Israel in which small numbers of patients reported these adverse events following vaccination. The large dataset enabled population-scale research, showing that the benefits of COVID-19 vaccination outweighed the risk of myocarditis. Another study of 48 million adults in England published in September 2022 identified that COVID-19 infection is associated with a serious risk of blood clots, even after 49 weeks following infection. The results provided clear support for policies to prevent severe COVID-19 by means of vaccines, and use of secondary preventive agents in high-risk patients.

Machine learning improves detection of heart damage using cardiac magnetic resonance (CMR) scans

Machine learning techniques have made progress in simplifying the detection of damage caused by myocardial infarction (MI) using cardiac magnetic resonance (CMR) scans. Researchers part-funded by HDR UK have developed artificial intelligence algorithms to analyse large amounts of data, learn from the insights, and then predict which scans show heart tissue damage. The approach, published in 2022, could lead to detecting scarred heart tissue more quickly, cheaply, and without the use of contrast agents.

Cardiovascular diseases caused approximately 18.6 million deaths (31% of all deaths) in 2022 according to the World Heart Federation. Many of these resulted from MI – myocardial infarction – which can lead to the loss of contraction of the damaged portion of the heart muscle. A type of imaging technique known as a cardiac magnetic resonance (CMR) scan is effective for diagnosing MI, while showing the presence, location, and extent of scarring on the heart tissue. The patient requires an initial scan, after which contrast agents are administered and a second scan is performed. The scans are then compared and used for diagnosis.

The research team set out to see if machine learning techniques could be used to analyse the first scan and accurately predict what the second would show. This could lead to quicker scans, simpler diagnosis, shorter appointments, and lower costs. It would also extend the use of CMR to patients, such as those with severe kidney disease, for whom contrast agents are unsafe.

The team studied 272 retrospectively selected CMR studies, with 108 showing MI and 164 healthy controls. They applied algorithms to study the scans and classify them, to discover the extent and location of any scars. Using a radiomics approach, where a large number of features are extracted from the scans using data-characterisation algorithms, the team captured complex data patterns.
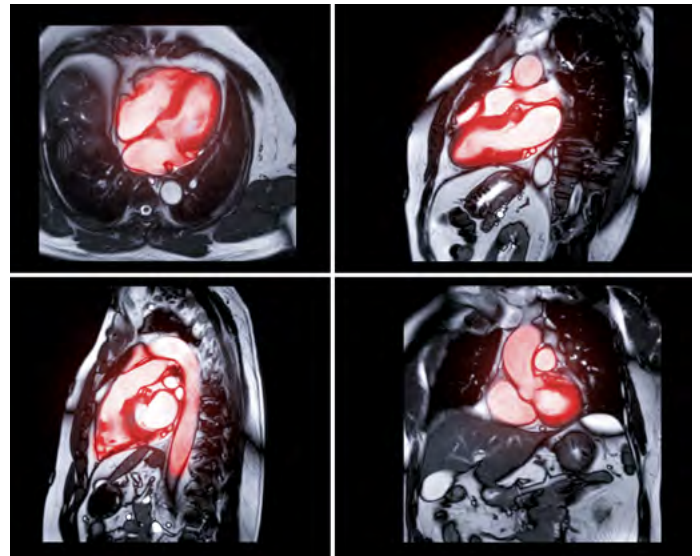
MRI magnetic resonance imaging of the heart for diagnosis heart disease. Credit: Getty Images

These were used to develop predictive models that would allow pre-contrast scans to predict what would be found using post-contrast scans.

The results published in 2022 suggests that sufficient information could be available from pre-contrast CMR scans to identify MI damage. In addition, the research presents new parameters (such as rate of myocardial area change, optical flow and radiomics parameters) that could be considered biomarkers for the mechanics of myocardial disease. Overall the team successfully developed promising techniques that, with further work could lead to practical and inexpensive methods for using machine learning to diagnose MI effectively but in a less invasive and more efficient manner.

Home adaptation interventions reduce emergency fall admissions for older people

Falls are a significant concern for older people and come with a high cost to the NHS. Although there are services available to make adaptations for older people who wish to continue living at home, there is little evidence demonstrating the effectiveness of these services at reducing the amount of falls that older people experience. HDR UK researchers have created a new dataset to study fall outcomes following home adaptation interventions, which has shown that these interventions are indeed effective while identifying the population that are more likely to have falls. The work, published in 2022, strengthens the evidence base for providing falls prevention services and could lead to policy implications for providing these interventions pro-actively.

Falls in older people can have devastating consequences, and have significant financial impact, costing the NHS more than £2.3 bilion per year. A third of people over 65, and half of people over 80, fall at least once a year, and it is the most common cause of death from injury in the over 65 age group. However, as many older people prefer to remain living in their own homes for as long as possible, home adaptation services could be used to make continuing to live at home safer and more comfortably. These include modifications such as fitting in a stairlift, adding a bath lift or a grab-rail for the shower, widening doorways, lowering kitchen countertops and installing an outdoor ramp. However, until now there have been no evaluation of these adaptations

to see if they indeed reduced the falls experienced by older people.

To check if these adaptations make a difference, HDR UK researchers created a dataset to study fall outcomes following home adaptation interventions. To do this, they looked at older people who had been supported by Care & Repair Cymru (C&RC), a charity in Wales that provides home adaptation services. The team looked at electronic health records of over 600,000 older people in Wales, of whom 120,000 had received a home adaption service. Over the period covered by the data, they analysed if a fall occurred at home that required an emergency department or hospital admission.

The results, published in 2022, showed that the people who used C&RC were almost twice as likely to have a fall compared to the control group. This demonstrates that C&RC reaches those who are at higher risk, many of whom had had a fall just before using the service. After the home adaptation, falls of C&RC clients decreased by 3% per quarter. The study also found that falls were more likely in people who were older, frailer, living in more deprived areas and female. The data may inform targeting this population proactively to reduce falls. The team will study the data further to understand the effects of the local environment on fall risks, and hope that it can influence policy to provide home adaptation interventions proactively for older people living at home.

UK Dementia Research Institute (UK DRI)

The UK Dementia Research Institute (UK DRI) was established in 2017 with funding from MRC, Alzheimer's Society and Alzheimer's Research UK. It forged the way for a new type of distributed institute that joins together the very best leadership, expertise, tools, and resources from across the UK. The UK DRI aims to better understand the underlying mechanisms of neurodegenerative diseases, drive early-stage development of diagnostics and treatments, and develop innovative technologies for assisted living. It carries out research relevant to all dementias and neurodegenerative diseases, including Alzheimer's disease, Parkinson's, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS, the most common form of motor neuron disease), vascular dementia, Huntington's disease and beyond. The UK DRI has been established as an independent charitable company; MRC provides 90% of the institute's core support. The UK DRI Hub is based at University College London, and its six Centres are hosted at University of Cambridge, Cardiff University, University of Edinburgh, Imperial College London (two centres), and King's College London.

New insights into genetics of Alzheimer's disease and related dementias

An [international study involving UK DRI researchers](#) has identified 75 genes associated with an increased risk of developing Alzheimer's disease. The study analysed the genomes of 111,326 people diagnosed with Alzheimer's disease and 677,633 genomes from healthy people, making it the largest genetic study of Alzheimer's disease to date. The data from the study identified 42 new genes that had not previously been implicated in increasing risk of Alzheimer's, providing valuable insights into how disruption of the brain's immune system is involved in the disease. The researchers used this information to develop a new genetic risk score that could predict which patients with cognitive impairment would, within three years, go on to develop Alzheimer's. The score could be used when recruiting patients for clinical trials aimed at treating the early stages of the disease.

Alzheimer's disease is the most common cause of dementia, which affects around 900,000 in the UK. Despite the huge burden of the disease, there have been no new drugs approved for it in the UK for the past two decades. Defining the molecular and cellular mechanisms responsible for the early stages of the disease is therefore essential; both for developing novel biomarkers to identify people who are at risk, and for identifying drug targets that can help tackle the disease process at its earliest stages.

Previous research has shown that while lifestyle factors such as diet and smoking can influence the risk of Alzheimer's disease, 60% of the risk is based on genetics. Therefore identifying the genes involved and understanding how they contribute to disease is key. This study showed the involvement of a cellular signalling pathway known as the TNF alpha pathway, which is related to inflammation, as it involves key components of the immune system. In addition, the results highlighted genes that affected the function of microglial cells, known as the immune system of the brain. Microglia function to clear away damaged or inflamed bits of cells and clumps of proteins, thereby preventing them from damaging healthy neurons.

The data from the study allowed the team to develop a new genetic risk score incorporating these new genes. Although the score is not so far intended for clinical use in diagnosing patients, it could be used in clinical trials for recruitment and stratification, to test for efficacy at early stages of the disease where treatments are most likely to be beneficial and the damage to the brain caused by the disease is minimal.

Brain inflammation with microglia that fail to clear debris, causing astrocytes to react.
Credit: National Institute on Aging, National Institutes of Health
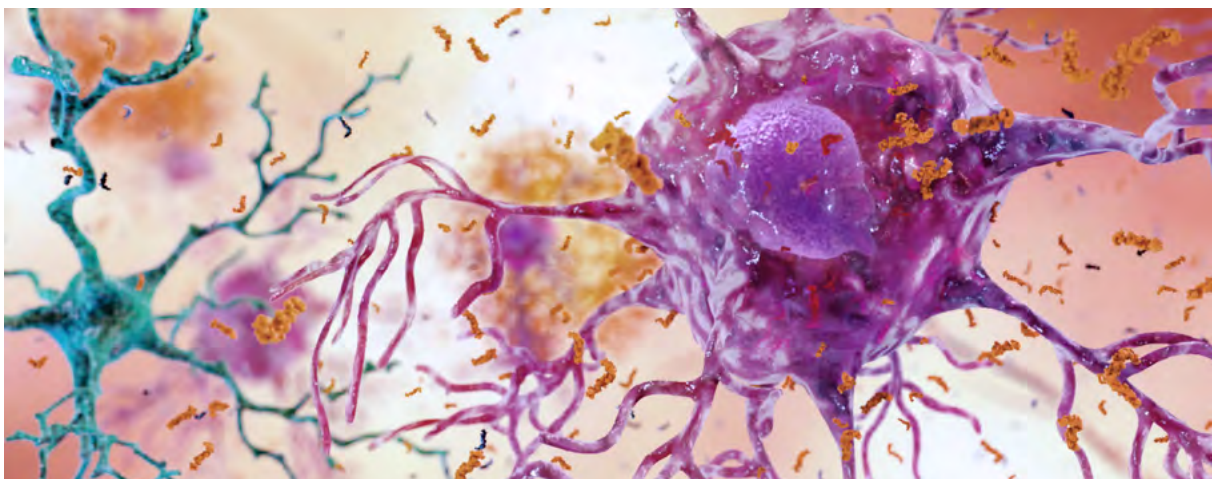
Repurposed drugs potential for treating strokes linked to dementia

A clinical trial led by UK DRI researchers and funded by the British Heart Foundation has shown early results that indicate how two cheap and commonly used drugs could be repurposed to treat the effects of lacunar stroke, a type of stroke linked to dementia. The Phase II LACI-2 trial involved 363 patients who had experienced a lacunar stroke and tested the effectiveness of two drugs. After one year, results published in 2023 showed that participants that took both drugs were nearly 20% less likely to have problems with their thinking and memory compared to the group that did not take either drug. The team will next test the drugs in a larger four-year clinical trial, expected to start by the end of 2023.

Lacunar strokes affect the small blood vessels deep inside the brain. These were first described in post-mortem examinations in the 1950s, when 'lacunae', or empty spaces, were spotted in the brain. Lacunar strokes accounts for about a fifth of strokes – more than 25,000 a year in the UK and are linked to nearly half of all dementias. They can have distressing effects as people may develop problems with their thinking, memory, and movement. It is thought that these strokes are caused by damage to endothelial cells, which line the blood vessels. There are currently no effective treatments.

In the LACunar Intervention (LACI-2) Trial-2 (LACI-2) clinical trial, the team tested two drugs known to act on endothelial tissue. The first drug - isosorbide mononitrate – belongs to a group of drugs called nitrates, which are used to treat angina while the second drug – cilostazol - is used as an antiplatelet drug linked to improving endothelial function. Funded by the BHF, the LACI-2 trial involved 363 lacunar stroke patients who took standard stroke prevention treatment as well as either isosorbide mononitrate or cilostazol individually, both drugs together, or neither, for one year.

Results published in July 2023 showed that after one year, participants that took both drugs were nearly 20% less likely to have problems with their thinking and memory compared to the group that did not take either drug. They were also more independent and reported a better quality of life. Those who took isosorbide mononitrate were less likely to have had further strokes at one year than those who did not take the drug. Individually, isosorbide mononitrate also improved thinking and memory skills, and quality of life, while cilostazol improved independence and mood. But these effects were strengthened when the two drugs were taken together.

The results are promising and will need to be confirmed in a larger trial expected to start by the end of 2023. As these drugs are already available for treating other circulatory disorders, and are not expensive, they would be ideal candidates for treating patients vulnerable to lacunar strokes.
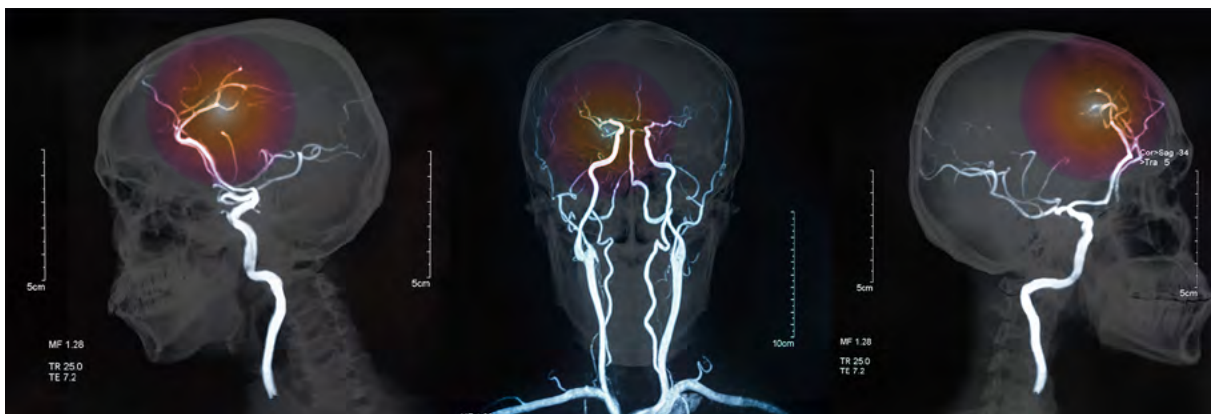
Progress towards gene therapy treatments for neurodegenerative diseases

Improved understanding of the underlying genetic causes of certain types of neurodegenerative diseases has opened up the possibility of developing new treatments using gene therapy. UK DRI researchers have been at the forefront of these efforts, tackling both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD); two closely related neurodegenerative conditions with significant overlap in both clinical and genetic characteristics. The research has led to a significant £2 million investment from UK DRI in 2019 into establishing a gene therapy core facility targeting development and refinement of gene therapies to translate into patient benefit. Subsequent developments in the project led to the launch of a new gene therapy spin-out company AviadoBio in 2021, with a novel single treatment gene therapy candidate AVB-101 currently in pre-clinical development for treating frontotemporal dementia.

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two devastating neurodegenerative diseases. Although ALS primarily affects movement while FTD affects behaviour and personality, there are several shared genetic contributors and significant overlap in their underlying biology. A key goal of the UK DRI research team is to develop a new gene therapy for patients with a type of FTD that is caused by sequence errors in a specific gene called GRN. GRN encodes a protein called progranulin, which is defective in about 20% of patients affected by FTD. It is hoped that the gene therapy can restore levels of the functional progranulin protein, with a single infusion of the corrected gene to replace the faulty copy of the gene.

The team hope to develop and refine a gene therapy delivery system called the adeno-associated virus (AAV) platform which has already been used to develop gene therapies for other genetic diseases. The AAV gene therapy platform has recently proven successful in another gene therapy clinical trial, developed for treating type 1 spinal muscular atrophy (SMA). Given the promise of AAV therapies, UK DRI established a core-funded facility in 2019 to develop the AAV platform across the institute for the design and pre-clinical validation and clinical trials of AAV vectors. The core facility supports UK DRI researchers with designing AAV gene therapy vectors for tackling a range of neurodegenerative diseases.
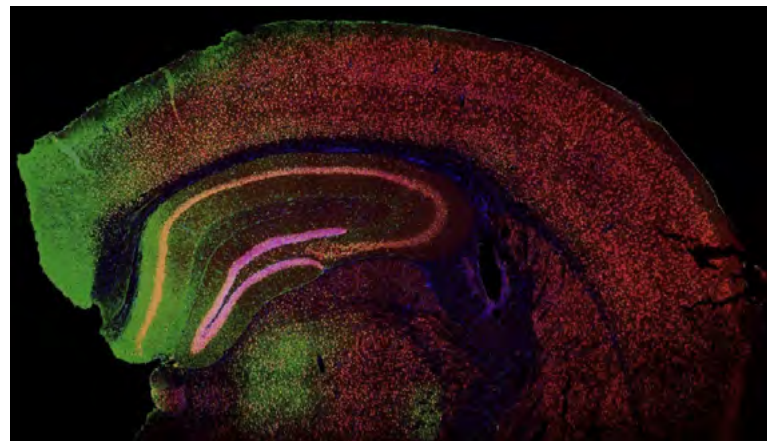
Image of green fluorescent protein (GFP) expression in the mouse brain cortex following adeno-associated viral (AAV) vector injection.
Credit: Shaw Lab, UK Dementia Research Institute

The UK DRI gene therapy core facility allowed the team to refine their AAV gene therapy candidate for treating FTD. Two years later, their research led to the launch of a spin-out company AviadoBio in 2021 and their gene therapy candidate was named AVB 101. The UK DRI gene therapy core facility provided the infrastructure to demonstrate the progress from proof of concept towards first in human research. AviadoBio is investigating AVB-101 gene therapy, aimed at supplying a corrected copy of the GRN gene using an AAV vector currently in pre-clinical studies. Similar gene therapies for ALS are also in the discovery phase of the clinical development pipeline.

The Francis Crick Institute (FCI)

The Francis Crick Institute is a unique partnership between MRC, Cancer Research UK and Wellcome, supported by the three other founder partners University College London, Imperial College London, and King's College London. It operates as an independent, charitable company, and MRC provides 42% of its core funding.

The Crick's mission is 'discovery without boundaries; to carry out world-class discovery research to understand how living things work and to drive benefits for human health'. The Crick explores biological mechanisms at all scales from molecules through cells to organisms.

Its discoveries aim to enhance our understanding of the fundamental processes of life, and have the potential to transform the prevention, diagnosis, and treatment of human disease, with an emphasis on cancer, human developmental and neurodegenerative conditions.

Exterior view of Francis Crick Institute building.
Credit: Francis Crick Institute
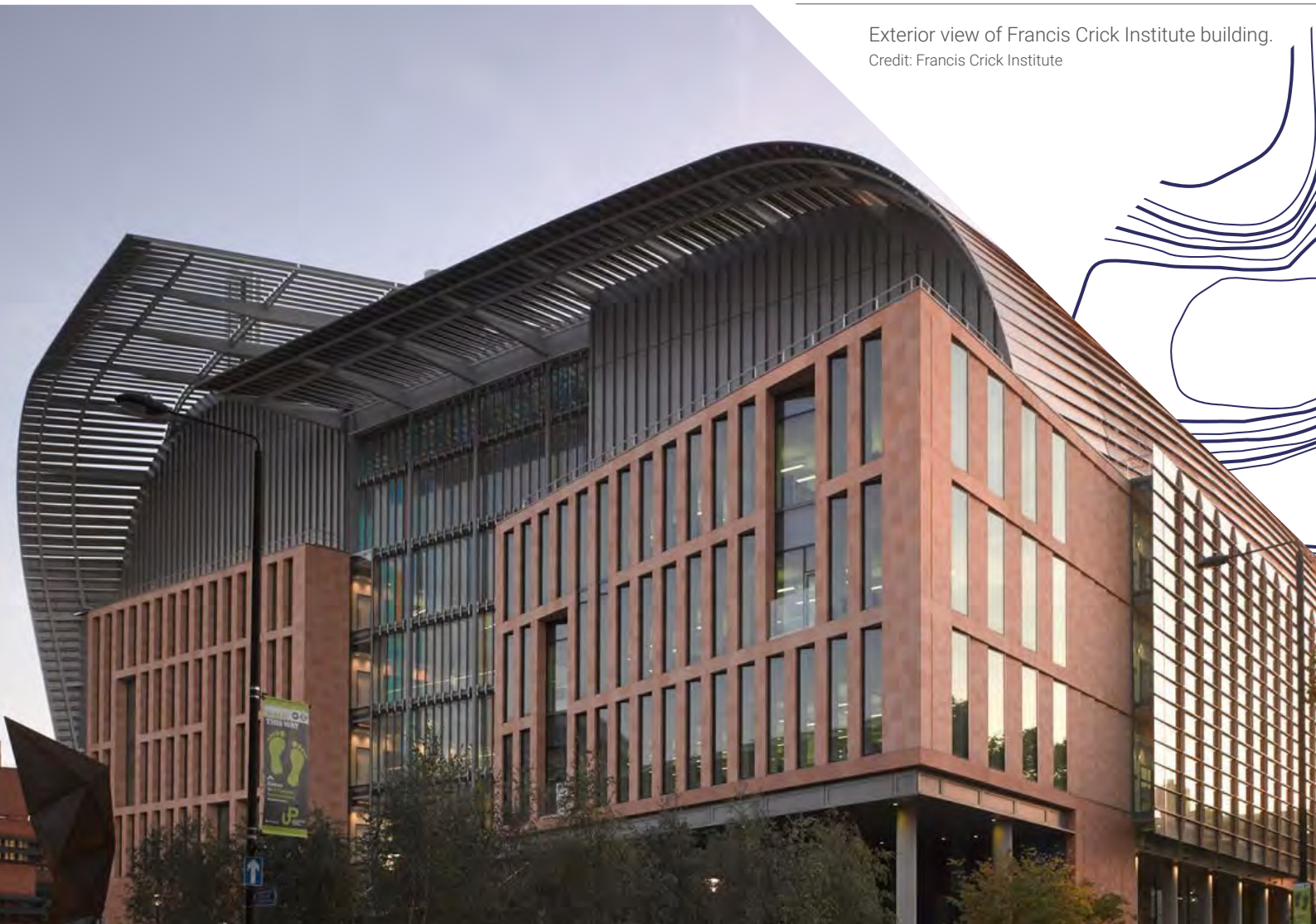
Cancer immunology provides new insights into therapies

Insights into the mechanisms behind how cancer cells interact with the immune system have led to new avenues for developing therapies. Researchers at the Francis Crick Institute have identified several unique cellular processes, advancing our knowledge of cancer immunology in unprecedented detail. This has led to promising commercialisation opportunities via the launch of several spin-out companies that include Achilles Therapeutics, Adendra Therapeutics, and GammaDelta Therapeutics. In 2021, these spin-out companies were collectively valued at £54.4 million and employed 326 people, with several therapeutic candidates in phase I/II trials for melanoma, solid cancers, and leukaemia.

Cancer cells within a tumour are surrounded by many components such as immune cells and signalling molecules – collectively known as the tumour microenvironment. The tumour and its surrounding microenvironment interact constantly, and recent research has shown how cancer cells can co-opt these immune cells into driving forward cancer growth. Several research groups at the Francis Crick Institute have helped refine our understanding of these oncogenic processes, providing unique opportunities to develop targeted therapies aimed at disrupting them.

Neoantigens and personalised immunotherapies

The ground-breaking TRACERx study launched in 2014 and funded by Cancer Research UK was pivotal for understanding the clonal evolution of cancer cells. The study sequenced the genomes of lung cancer patients and followed them all the way from diagnosis through to either disease relapse or cure after surgery, tracking and analysing how their cancer developed. Now at the Crick, data from TRACERx continues to provide fascinating insights into how tumours evolve and evade treatment.
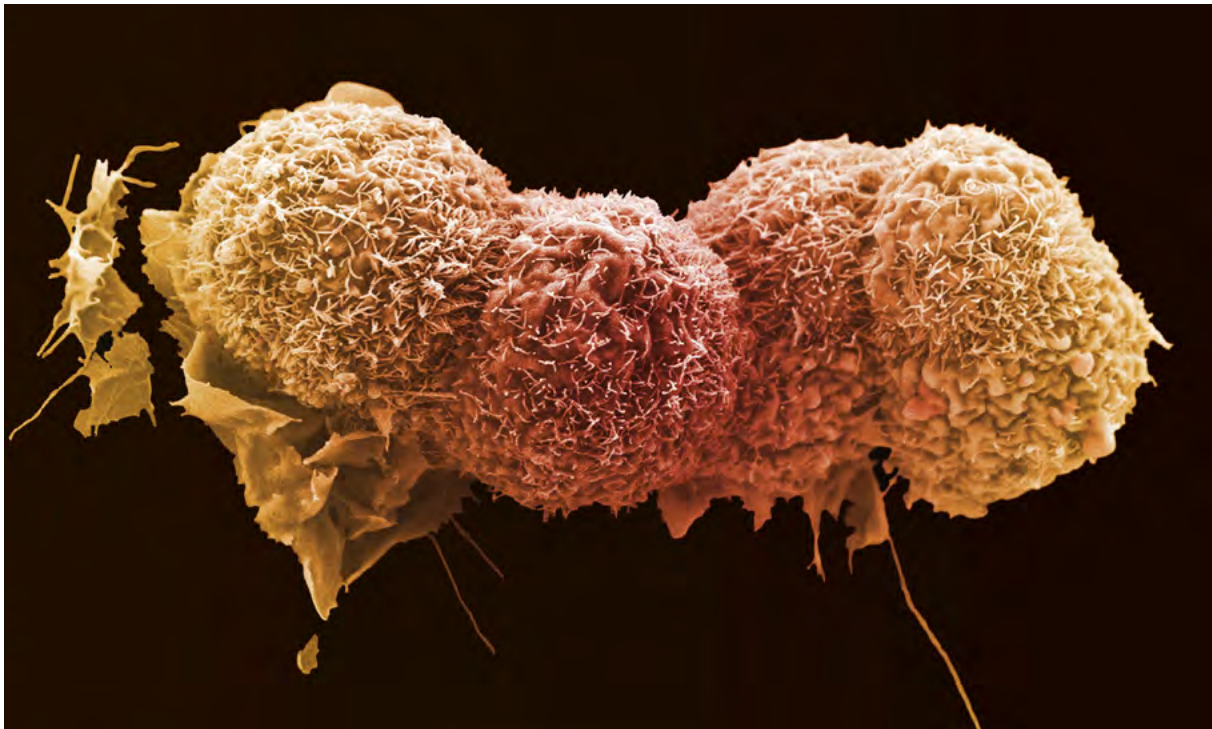
False coloured scanning electron micrograph of a cell cultured lung cancer cell.
Credit: Anne Weston, Francis Crick Institute. Attribution-NonCommercial 4.0 International (CC BY-NC 4.0). Source: Wellcome Collection.
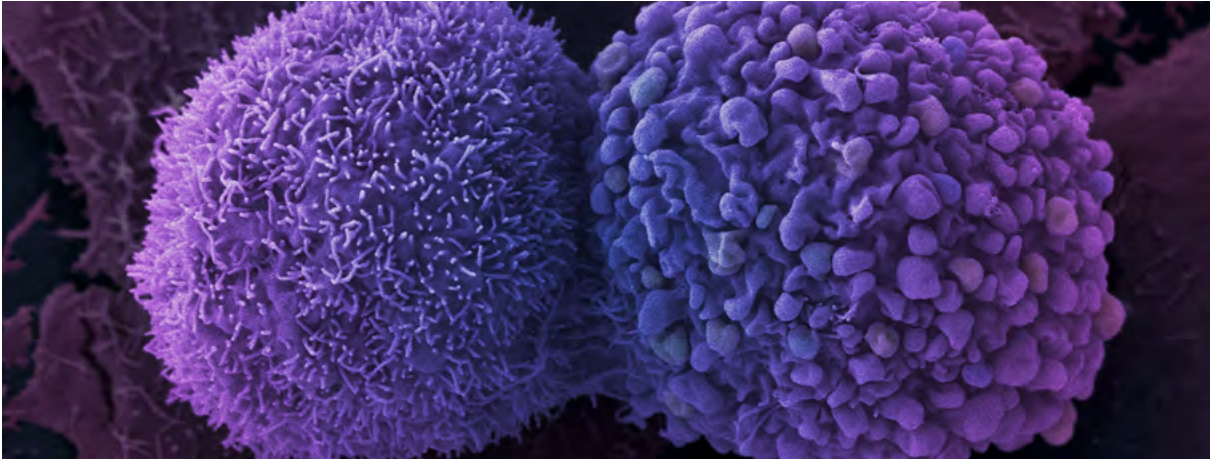
Lung cancer cells. Credit: Anne Weston, Francis Crick Institute. Source: Wellcome Collection.

One of these is the discovery of neoantigens, which are mutated proteins that are displayed on the surface of cancer cells. They are not found on the surface of normal healthy cells, so are a useful way to identify which cells are normal and which cells are cancerous. As a result, these neoantigens provide an incredibly valuable target for directing immunotherapies to identify and destroy all cancer cells with that specific neoantigen, regardless of where they are in the body. With the launch of Achilles Therapeutics, the researchers have developed modified, personalised T lymphocytes that could infiltrate tumours and target all cancer cells in a patient. The approach has led to the launch of a phase I/II clinical trial for patients with melanoma in 2019.

Harnessing dendritic cells for cancer therapy

Dendritic cells are a specialised type of immune cell responsible for alerting the immune system in response to disease. Dendritic cells process antigens from diseased cells (such as cancer cells) and migrate to the lymph nodes where they present these antigens to B and T cells, leading to a specific immune response directed against any cells that contain these identifying antigens. High concentrations of dendritic cells in tumour sites have been associated with better clinical outcomes, demonstrating the opportunity to harness dendritic cells in cancer therapy.

Researchers at the Crick have identified the complex molecular signalling processes involved in activating dendritic cells in response to cancer. Exploiting this new understanding, they have launched Adendra Therapeutics in 2021 to discover and develop treatments for solid cancers.

Gamma Delta T cells and cancer

Specialised immune cells known as gamma delta T cells are responsible for a type of cellular surveillance that identifies dysregulated cells, such as cancer cells. Developing these cells into a treatment, so they can recognise and destroy cancer cells present a novel approach for harnessing the power of the immune system for cancer therapy. With significant funding from Cancer Research UK over several decades, the researchers built their knowledge of gamma delta T cells and avenues for translating it into treatments. In 2014, MRC supported a project to develop a GMP protocol for the isolation and culture of these gamma delta T cells from human blood. The project led to the launch of a spin out company Gamma Delta Therapeutics established by the Francis Crick Institute, Kings College and Cancer Research UK. In 2021, Gamma Delta Therapeutics was acquired by Takeda Pharmaceuticals, and in 2023 a phase I/II clinical trial testing transplanted gamma delta T cells in acute myeloid leukaemia (AML) patients was initiated.

Specialised heart cell culture methods

A novel method for growing a specialised type of heart cell in the lab using stem cells has led to new opportunities for understanding heart disease, with applications in drug screening and potential development of new treatments. Research from the Francis Crick Institute, building on decades of MRC funded discovery science, enabled the development of this method now licensed to Axol Bioscience. The agreement to commercialise the protocol will allow more labs across the world to use these specialised heart cells in their own research, particularly in cardiotoxicity assays and drug screening programmes.

In a growing embryo, the heart develops from a layer of tissue known as the mesoderm. Stem cells in the mesoderm specialise into different types of cells that go on to form the different organs including the different structures of the heart, in a process known as differentiation. Stem cell differentiation is an exquisitely controlled, complex process, involving various chemical signals and pathways that activate and suppress different genes in the right amounts, at the right locations, at precisely the right time.

The stem cells that form the left ventricle of the heart differentiate early on during this process and coordinated contraction of the heart muscle cells provides the force to pump blood around the developing body. As such, these cells are important during embryonic development, and defects in these cells are linked to heart disease and heart attacks, as well as being sensitive to the cardiotoxic effects of certain drugs. Being able to study these cells in the lab so researchers can understand how they develop and what can go wrong with them is therefore essential. Using these cells in drug assays and toxicity screens can also help evaluate the safety profiles of drugs and ensure they are safe, before proceeding further into pre-clinical studies and clinical trials.

Nearly three decades of developmental biology research from the MRC National Institute for Medical Research (NIMR), one of the Crick's founder institutes, helped advance our understanding of stem cell differentiation processes. These incremental knowledge advancements enabled Crick researchers to recreate the left ventricle heart cell differentiation process in the lab. The researchers provided the stems cells with the correct chemical signals at the appropriate stage of development, eventually leading to a near uniform population of left ventricular heart cells that beat in synchrony. The methods developed by the researchers were licensed to Axol Bioscience, so that the translational potential of this research could be applied to developing therapies in the future.

Heart muscle cells derived from neural stem cells that have been reprogrammed. Credit: Jose Silva. Attribution 4.0 International (CC BY 4.0). Source: Wellcome Collection.
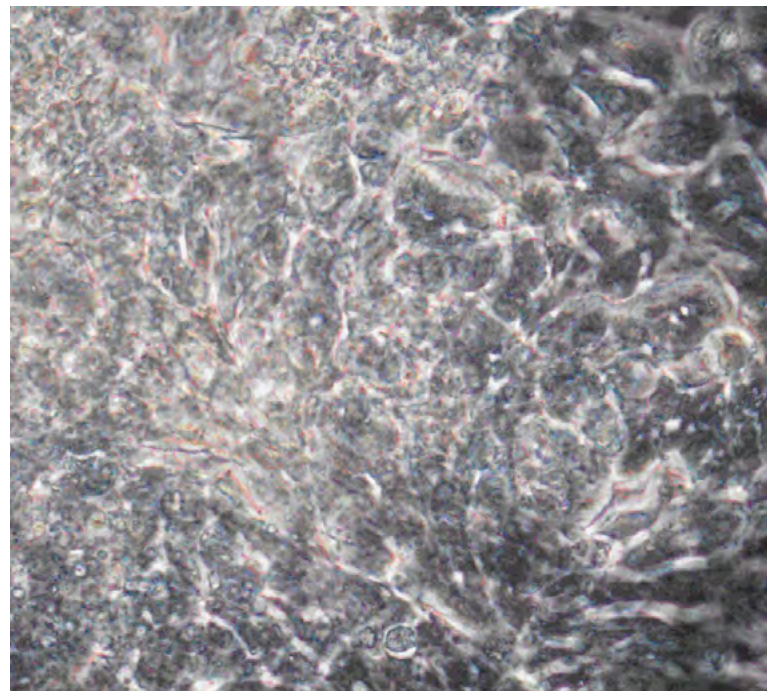
National COVID-19 treatment guidelines influenced by virology insights

A study analysing over 400,000 coronavirus samples has influenced new national COVID-19 treatment guidelines. The Legacy Study led by researchers at the Francis Crick Institute utilised a unique bank of coronavirus samples gathered as part of the Crick's testing partnership with London healthcare facilities. The study showed that antibodies generated by the monoclonal therapy sotrovimab were able to block entry of the virus into cells and offer protection and were still effective against newer strains of the virus. The data led to a change in the treatment guidelines in February 2023 to support the ongoing use of sotrovimab for treating patients at high risk from COVID-19.

Sotrovimab is a monoclonal antibody therapy that was one of the first to be licensed for the treatment of COVID-19. Antiviral therapies such these were developed at speed in 2020 through 2021 in parallel with vaccines and were an essential defence against the virus for those people who have a poorer response to vaccination. These include some older adults, people with significant pre-existing health conditions and immunocompromised people who are at higher risk of serious illness if they become infected with the virus. There are currently 3.7 million adults in the UK who are considered clinically extremely vulnerable.

In 2022, some preliminary laboratory studies indicated that sotrovimab may no longer be effective at responding to specific Omicron sub-variants such as BA.2 and BA.5. In response the WHO recommended that sotrovimab should no longer be used to treat clinically vulnerable people with COVID-19 until more trial data could be made available. However, these laboratory studies had significant limitations, and effective clinical trials were becoming more difficult to run as the numbers of patients that could be recruited were continuing to fall with the drop in COVID-19 infections.

In response, Crick and UCL researchers turned to the Legacy Study, launched in 2021 with coronavirus samples that had been collected since 2020. The team tested a variety of therapies, including sotrovimab, to see if they were still effective against the newer SARS-CoV-2 sub-variant of Omicron BA.2 and BA.5. They showed that antibodies generated by sotrovimab were still able to block entry of the virus into cells and therefore offer protection. The data was shared with NHS England policymakers and the National Institute for Health and Care Excellence (NICE) to support the ongoing use of sotrovimab as the SARS-CoV-2 virus continued to evolve. As a result the NICE guidelines issued in February 2023 advises that sotrovimab can still be used for early COVID-19 treatment for clinically vulnerable adults.

The Centre for Macaques (CFM)

The Centre for Macaques (CFM) was established at Porton Down, Wiltshire in 2003 with the mandate to protect and support the national capability to carry out academic primate research within the UK. The primary objectives of the unit were to secure the supply of rhesus macaques, to establish a centre of excellence in primate welfare and care, and to provide a resource centre for the academic community. Since 2010, the centre has been wholly managed by MRC with an annual financial contribution from Wellcome. It is a requirement of researchers with programmes that include rhesus macaques to source their animals from CFM if they are funded by UKRI or Wellcome. Although the primary function of CFM is to supply non-human primates (NHPs) to UK academia, the centre also has a significant role in scientific and welfare research and distributes tissue for both commercial and academic *ex vivo* use.

A group of macaques housed at the MRC Centre for Macaques.
Credit: MRC Centre for Macaques

Using light to modify brain waves has potential for developing new treatments for epilepsy

Researchers at Newcastle University have developed a system that uses light stimulation to modify brain activity. The team engineered a small implant containing LEDs which was surgically placed inside the brains of two anaesthetised non-human primates, to deliver light directly to the brain. The cells within the brain were altered using gene therapy to make them receptive to the light. The results published in 2022 showed that this technology successfully supressed abnormal brain waves that resembled epileptic seizures. The approach opens up new avenues to explore for possible treatment of conditions such as epilepsy, Parkinson's, and migraine.

In the brain, nerve cells generate rhythmic activity or 'brain waves'. These rhythms are disrupted in many neurological diseases, producing abnormal patterns of activity. For example, in epilepsy, abnormal activity can often be localised to a small 'focus', which then spreads causing a seizure.

To study this process more closely, the researchers altered some brain cells in two non-human primate brains using a type of gene therapy called optogenetics to make them sensitive to light. They then embedded a surgical implant in the brain which then continuously monitored brain waves through electrodes and provided precisely timed stimulation by activating the LEDs. Since light does not interfere with sensitive electrical recordings, the researchers were able to develop a 'closed-loop' control of

brain activity where the patterns of activity were continuously monitored, controlling the delivery of the precisely timed light to the brain in a continuous feedback loop. Through this method the researchers were able to modulate the intensity of an abnormal brain wave pattern, i.e. reduce the severity of a seizure.

The results, published in 2022, showed that it was possible to effectively modify local brain activity in a non-human primate using implanted LEDs. This is an important experiment for showing that the approach was effective, before attempting to do this in humans. Using a small implant to modulate abnormal activity in the brain opens up a possible alternative treatment for epilepsy, particularly for types of epilepsy that are resistant to treatment using drugs.

'Mindreading' neurons provide insights into predicting decisions of social partners

Researchers from the University of Cambridge have identified a previously unknown type of neuron in the amygdala region of primate brains that can simulate decision-making processes occurring in others. The process effectively allows one rhesus monkey to reconstruct the state of mind of another and predict their intentions. The research published in 2019, in collaboration with a team in Spain, suggest that dysfunction in such 'simulation neurons' may be linked with social difficulties experienced by people with conditions such as autism and social anxiety.

The ability to simulate decisions made by others is a sophisticated cognitive process that is rooted in social learning. For example, primates observe the choices made by other members of their group to learn about the reward value of objects. Psychologists reason that humans also use simulation as a mechanism to help understand each other's minds, but the neurological workings that underpin this complex process are not well understood. It is thought that the amygdala, which plays diverse roles in social behaviour, and has also been implicated in autism, might be involved in this process. However, it is not known whether neurons in the amygdala may also contribute to more advanced social cognition, such as simulating others' decisions.

The team recorded the activity of individual amygdala neurons in rhesus monkeys, in a social context, which involved placing the monkeys in a situation in which they observed and learned from each other's reward-based choices. The animals were sat facing each other with a touch screen between them and took turns making choices to obtain a fruit juice reward. To maximise the reward the animals needed to learn and track the reward probabilities linked to different pictures displayed on the screen. One animal was allowed to observe its partner's choices and learn the reward values of the pictures displayed to them. When the roles were reversed, the animal that had previously been the 'observer' was able to use what it had learned to inform its own choices. The results, published in 2019, indicated that a specific type of
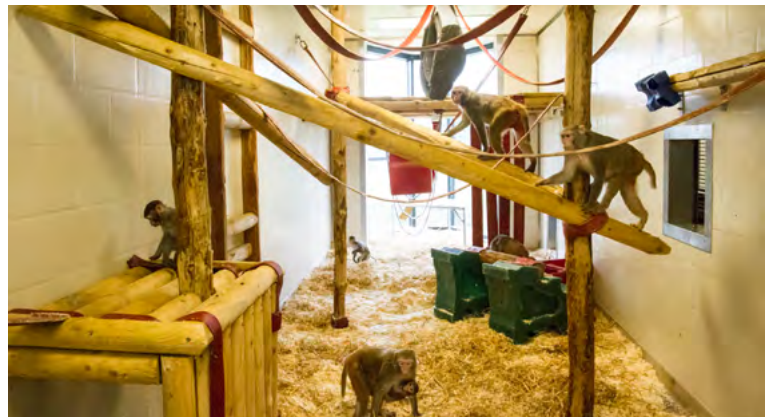
A room at the MRC Centre for Macaques showing the environmental enrichment. Credit: MRC Centre for Macaques

neuron in the amygdala of an observing animal could actively simulate the partner's decision-making processes. The observer's amygdala neurons were effectively carrying out decision computations, first comparing the reward values of the partner's choice options and then signalling the partner's likely choice.

These results link prior findings on the functions of amygdala neurons in decision making to the amygdala's well-known role in social behaviour and implicated role in autism and other conditions characterised by atypical social cognition, such as social anxiety. Dysfunction of the simulation neurons or their inputs could hamper social behaviour by reducing an individual's ability to relate to the mental states of others. Conversely, hyperactivity of the amygdala neurons might exaggerate spontaneous simulation of others' mental processes, which could lead to symptoms typical of social anxiety.

Non-human primate tissue bank provides new insights into vision

For many years, a project licence from the UK Home Office has been in place to authorise the supply of primate blood and prepared tissue to academic and commercial collaborators. Since then, the Centre for Macaques (CFM) has supplied over 900 tissue and blood samples to 19 academic, two governmental and four commercial partners. In 2020, the CFM established a quality controlled biobank with tissues from 48 animals, covering both sexes and a range of ages, with over 40 different types of tissue available. It is envisaged that this will be particularly attractive for those studying comparative gene expression. In addition to the snap frozen tissue, the biobank also houses formalin fixed tissues including whole brains and pituitary glands that can be readily sectioned into microscopic slides for further analysis. For example, in 2019 these tissues provided useful insights into retinal ageing in primates that can extrapolate to humans, highlighting the valuable resource provided by the CFM biobank for advancing medical research

The specialised cells in the eye, known as photoreceptors, convert light into electrical signals that are sent to the brain. These cells have a high metabolic demand and age rapidly, so over time this ageing leads to loss of vision. Our understanding of this process is based mainly on the study of ageing mice, where elevated inflammation and the loss of cone and rod cells from the retina are observed. Ageing mice also develop a build-up of a protein called amyloid beta in their retinas. However in ageing primates, the amyloid beta build-up is not seen in the retina, with less inflammation, and their cone cells remain present – although they decline in function.

This indicates that primates age differently to mice and studying retinal ageing in primates could provide insights that would not be possible in mouse studies. The researchers showed that ageing primate retinas have reduced levels of a molecule called adenosine triphosphate (ATP), which is used as a fuel by all cells to derive energy from glucose for metabolism.

This finding seems to indicate that cone cell functionality could be restored if they could be fuelled appropriately, to potentially restore vision. Cone cells are responsible for colour vision and high spatial awareness, and as humans we rely more on cones for vision. The limited amount of age-related inflammation and amyloid beta build-up that was observed may also explain the lack of success in clinical trials in humans for macular degeneration that aim to tackle inflammation in the retina.

Mary Lyon Centre at MRC Harwell (MLC)

The Mary Lyon Centre (MLC) at MRC Harwell is the UK's national facility for mouse genetics and the use of mouse models for the study of human disease. It offers a wide range of services to researchers around the world. Services include free archiving of mouse lines to protect them for future use, distribution of mouse lines, breeding and phenotyping of genetically altered mice, and genome engineering services to generate new mouse models. The MLC is proactively committed to implementing the 3Rs – the replacement, refinement, and replacement of the use of animals in research, and are leading the field in the development on new technologies and innovations such as home cage monitoring systems.

Exterior view of Mary Lyon Centre building, located at the MRC Harwell campus.
Credit: Mary Lyon Centre at MRC Harwell

Mouse genome editing resource provides improved understanding of complex diseases

Genetically altered mouse-lines are a valuable resource for answering research questions that cannot be answered through alternative systems such as in vitro cell and tissue culture systems. These mouse models, produced through specialised genome-editing technologies such as CRISPR/Cas9, are useful for understanding more about complex diseases such as those that impact multiple organs. Since its inception in 2017, the Genome Editing Mice for Medicine programme at the Mary Lyon Centre (MLC) has generated 112 novel mouse lines and sets a world-leading example of a mouse genome-editing programme that synergises directly with the human genomics community. The mouse lines generated from this initiative have helped researchers across the UK to better understand diseases or to test potential future therapies for a range of diseases, such as pulmonary arterial hypertension, ciliopathies, and diabetes.

The Genome Editing Mice for Medicine (GEMM) programme at the Mary Lyon Centre (MLC) was launched in 2017 to create novel mouse lines for preclinical studies and to improve existing models. The UK academic research community nominate mouse lines for production using CRISPR/Cas9 technologies, which are reviewed by an expert panel for their value to research hypotheses or clinical diagnosis and their impact and utility for the wider research community.

The programme provides support for generating mouse models in a timely and cost-effective way for mechanistic studies of human genetic disease, whilst building a public collection of mouse lines to be used for future pre-clinical studies by the UK and international research communities. These mouse lines have been used by 77 research groups across the UK as of August 2023, and helped refine our understanding of disease mechanisms, providing unique opportunities to develop future therapies.

A single-celled pre-implantation mouse embryo being microinjected. Credit: Mary Lyon Centre at MRC Harwell

Mouse embryos and sperm are stored in liquid nitrogen as part of the cryopreserved archiving service.
Credit: Mary Lyon Centre at MRC Harwell

A novel model of pulmonary arterial hypertension

Researchers from the University of Cambridge have identified a mutation from a patient diagnosed with pulmonary arterial hypertension (PAH) at the age of 33. The mutation, found in a protein called ATP13A3 is caused by a single letter deletion in the DNA code. The deleted letter results in the encoded ATP13A3 protein being shorter than normal, thereby preventing it from carrying out its normal cellular function. The team successfully worked with MLC scientists to create a mouse model that had the same mutation in the same protein, to explore whether this mutation was significant and could be used as a preclinical model for PAH.

The researchers studied the mouse model created by MLC and as expected, found reduced levels of ATP13A3 protein. However, they also found that these mice had elevated right ventricular systolic pressure, which is an indicator of increased blood pressure in the lungs. The mice also had right ventricular anterior wall thickening, a sign that the right side of the heart is having to work harder than normal. Together, these findings showed that this mouse provides a good model of human PAH and further insights into how ATP13A3 function might be linked to the development of the disease. More information about this research can be found here.

Testing genetic therapies for ciliopathies

Cilia are tiny thread-like projections found on the surface of cells and are important for many cellular processes such as cell signalling, cell motility, and extracellular fluid movement. This means that their dysfunction can result in a range of complex disorders, collectively known as ciliopathies, that affect many different organ systems. There are many gene mutations that can cause ciliopathies, but the mutation of a gene called CEP290 is the most common. For example, a ciliopathy known as Joubert syndrome affects multiple systems, including the retina, brain, and kidneys, and currently has no cure; treatment of symptoms is the only option. Typically the disorder progresses to kidney failure within the first two decades of life.

The CEP290 gene mutations in ciliopathies could be addressed by drugs known as 'exon skipping drugs' that instruct the protein translation machinery in the cell

to 'skip' the defective bit of the gene. The resulting CEP290 protein is very similar to the normal CEP290 protein, so it can fulfil the same function in the cell, leading to the development of normal cilia.

A research team from the University of Newcastle used this approach in a cell culture system, using cells isolated from a patient with Joubert syndrome. The team showed that when these cells were treated with an exon skipping drug, levels of CEP290 protein returned to normal and defects in cilia were rescued.

Joubert syndrome affects multiple organ systems and causes a range of problems across these systems. The team were keen to see whether using an exon skipping drug to restore CEP290 protein levels, to address the defects in the cilia would indeed ease these symptoms of Joubert syndrome. To do this they worked closely with the MLC team to develop a genetically modified mouse carrying the mutation on the mouse CEP290 gene. The MLC scientists did this by injecting gene editing reagents into a microscopic single-celled pre-implantation mouse embryo, which required expertise in micro-injection techniques. The resulting mouse line was successfully used to demonstrate that exon skipping drugs were indeed able to restore the defects in cilia, and rescue Joubert syndrome symptoms. The mouse line will also be a valuable resource for testing other gene therapy strategies for treating ciliopathies that involve CEP290 mutations. More information about this research can be found here.

Insight into diabetes mechanisms

Diabetes is characterised by chronic elevation of the blood glucose concentration, which increases the risk of heart disease, stroke, blindness, and kidney failure. There are many different types of diabetes, but impaired release of insulin from the pancreas is something they all have in common. Because diabetes is so complex and affects many different organs, mouse models for diabetes are incredibly valuable in helping us improve our understanding of disease mechanisms and treatments.

Neonatal diabetes is a rare type of inherited diabetes that can occur within the first six months of life. Researchers have identified a gene called KCNJ11, where mutations in the gene are shown to cause neonatal diabetes. Intriguingly, a different form of the KCNJ11 gene found in 40% of the population has been shown to cause a small increase in the risk of developing the more common type 2 diabetes. Although researchers have known for a long time that this variant of the KCNJ11 gene is involved in type 2 diabetes, the exact mechanism behind how it enhances the risk has not been clear.

To clarify KCNJ11's role in diabetes, a team of researchers at the University of Oxford applied to the MLC to create a mouse model carrying this mutation. In a recent study using this mouse model, the researchers showed that the KCNJ11 variant indeed impairs glucose-induced insulin secretion, with an increased risk of diabetes when mice were fed a high fat diet. The mouse model therefore helped the researchers gain a deeper understanding of the cell signalling pathways involved in the process and how the KCNJ11 is involved. It will be valuable for future studies of type 2 diabetes as well. More information about this research can be found here.

# Home cage monitoring – an innovation that improves animal welfare

Researchers at the MLC have pioneered the development and use of home cage monitoring (HCM) systems for the phenotyping of mice, to improve both the sensitivity and accuracy of observations and to improve the welfare of the animals by reducing handling and operator-induced stress. The initial project was funded by the National Centre for the Replacement Reduction and Refinement of Animal Research (NC3Rs). MLC researchers are now developing an algorithm to automatically annotate behaviours of animals undisturbed by humans. This approach will extract vast amounts of data from a single experiment by harnessing the power of automation. The sector-leading work carried out by MLC on home cage monitoring systems is built on interdisciplinary collaborations and platforms for knowledge exchange between multiple communities across the world that bring together diverse expertise to deliver user-driven technologies.

A technician checking a mouse. Credit: Mary Lyon Centre at MRC Harwell

Measuring the activity and behaviour of laboratory animals provides key information in preclinical research, such as the progression of disease symptoms and whether a new treatment is safe and effective. Typically, these measurements are taken by either monitoring the behaviour of individually housed mice in tasks such as wheel running or removing the animals from their home-cage to study behavioural indicators in specific tests that can expose a potential scientific effect. These approaches have been standard practice for many years but have significant limitations, such as causing stress to the animals, which in turn can affect behaviour and impact the quality of the results, while also impacting welfare.
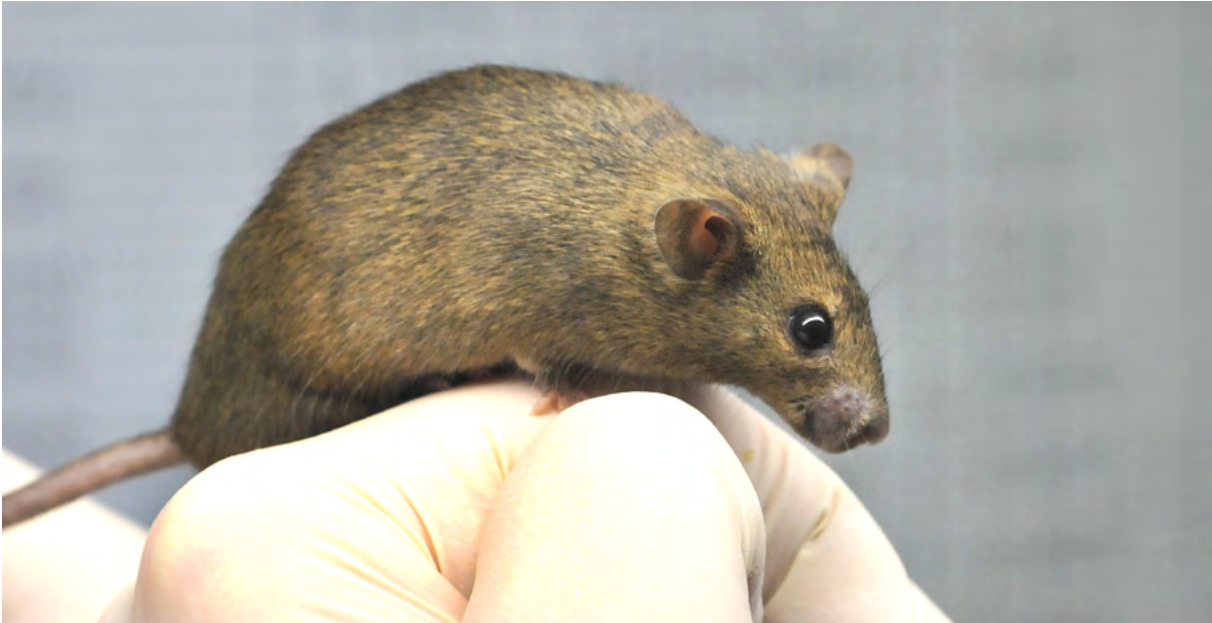
A technician checking a mouse. Credit: Mary Lyon Centre at MRC Harwell

Mice are also typically active at night, so studies that take place during researcher working hours in the daytime may not provide an accurate reflection of mouse behaviour.

Home cage monitoring (HCM) systems offer an alternative, where the animals remain in their 'home cage' in groups, and their activity and behaviour are measured using minimally invasive methods. It requires systems that can combine video and spatiotemporal data and identify individual animals under group-housed conditions. In addition to the welfare advantages offered by this approach, the ability to track multiple animals within a single home-cage has enabled the investigation of biologically relevant, non-evoked, voluntary social interactions. For example, the use of ultrasonic vocalisations (USVs) recorded over 24 hours within a home-cage, can provide useful information on the social behaviour and welfare of mice and lead to the earlier prediction of adverse effects including disease onset.

Researchers at MLC have pioneered the development, dissemination, and advocacy of HCM systems by bringing together interdisciplinary teams that have worked together to develop advances in relevant technologies. For example, machine learning techniques for image analysis have become more widely available, leading to a radical improvement in the design of behavioural tests and allowing image analysis to be applied to voluntary behaviours, with broad applications in the field. The ability to process large amounts of information using artificial intelligence has reduced the time between data capture in passive monitoring studies and the analysis and interpretation of biologically meaningful data.

In 2021, researchers at MLC and the University of Helsinki won a European Cooperation in Science and Technology (COST) Action award that was funded by the European Commission. This international effort aims to extend the use of HCM systems by sharing information and data with an expanding network of scientists from 27 countries. One of its primary goals is to expand the initiative to a network of 500 behavioural research scientists, manufacturers, bioinformaticians and experts in machine learning to form a collaborative, multidisciplinary consortium.

UK Biobank (UKB)

UK Biobank (UKB) is the most comprehensive population-scale source of health data. It has been following the health outcomes of 500,000 volunteer participants, aged 40-69, who were recruited between 2006 and 2010. UK Biobank was established by MRC and Wellcome (with additional support from other funders) to enable approved researchers to improve our understanding of the prevention, diagnosis, and treatment of a wide range of serious and life-threatening illnesses.

UK Biobank encompasses a huge breadth of information, including biological samples, genetic and proteomic data, body and brain imaging, hospital and GP records, physical measurements, bone density, eye scans, activity tracking, questionnaires, environmental data, lifestyle data and more. UK Biobank's combination of detailed characterisation of a very large number of individuals with prolonged follow-up of their health outcomes (15 years already) makes it uniquely valuable for studying the determinants of disease.

UK Biobank has gone to great lengths to ensure that the database is accessible to all approved researchers and that all research conducted using UK Biobank data must be made publicly accessible. Since UK Biobank was opened for research use in April 2012, more than 50,000 researchers from 100 countries have registered to use it. Recent years have seen an exponential increase in publications, citations and patents based on UK Biobank data: over 11,000 peer-reviewed papers have been published – in 2022 alone, there were over 2,200 peer-reviewed publications (over 800 from the US), and a further 70,000 citations.

UK Biobank participant undergoing a brain scan as part of the UK Biobank COVID-19 Repeat Imaging study.
Credit: UK Biobank

Evidence of physical changes to brain structures following Covid-19 infection from UK Biobank scans

Brain scans from UK Biobank participants have provided a unique insight into how even mild SARS-CoV-2 infection can cause physical changes to brain structures, with tissue damage and greater shrinkage in brain areas related to smell. UK Biobank is a large-scale biomedical database and research resource, providing researchers with an invaluable opportunity to conduct statistically robust studies at the population level. The longitudinal clinical brain images used in UK Biobank's COVID-19 Repeat Imaging study, with results published in 2022, makes this the only study in the world to be able to demonstrate 'before vs after' changes in the brain associated with SARS-CoV-2 infection.

UK Biobank's imaging data provides an unparalleled opportunity to answer this question, as the database has brain scans of participants taken before the pandemic. Previous research on hospitalised patients with severe disease has already shown that COVID-19 may cause brain-related abnormalities. However, these studies have been limited to post-infection data, without the ability to compare what the patient's brains would have looked like prior to infection. This limits the ability to attribute a COVID-19 infection as the cause of the brain changes seen on a scan taken after an infection. Additionally, UK Biobank data showed the effects of SARS-CoV-2 on the brain in milder (and more common) cases which were previously undetected. Investigating these cases could reveal possible mechanisms that contribute to brain disease or damage.

The research team used data from the UK Biobank COVID-19 Repeat Imaging study to investigate changes in the brains of 785 participants. These participants were aged 51–81 and underwent two brain scans, on average 38 months apart, as well as cognitive tests. A total of 401 participants tested positive for infection with SARS-CoV-2 between their two scans, of whom 15 were hospitalised. The remaining 384 individuals, who did not get infected, were similar to the infected group in age, sex, and many risk factors, including blood pressure, obesity, smoking, socio-economic status, and diabetes.

The results of the COVID-19 Repeat imaging study published in 2022 showed that UK Biobank participants who had COVID-19 had a greater reduction in grey matter thickness in the regions of the brain associated with smell, and a reduction in whole brain size compared to uninfected participants. These effects ranged from 0.2% to 2%, compared with uninfected participants. On average, the participants who were infected also showed greater cognitive decline between their two scans, associated with a reduction of a specific part of the brain linked to cognition. To rule out whether these changes were generic effects of a respiratory virus, the researchers studied people who developed pneumonia not related to COVID-19 and did not see similar change in the brain scans.

Further investigation into the impact of vaccines and understanding whether these brain structure changes are reversible over time will be important. UK Biobank will continue to be a vital resource for providing researchers with the data needed to conduct statistically rigorous large-scale population research.

Activity trackers and UK Biobank data for early Parkinson's diagnosis

Data from UK Biobank participants has been instrumental for furthering our understanding of neurodegenerative diseases such as Parkinson's, whilst showing promising approaches for earlier detection. Early detection is a key priority for researchers working in this field, as by the time symptoms appear, the disease has unfortunately already advanced to a stage that is hard to treat. UK Biobank collected a wealth of information on exposure, sociodemographic, lifestyle, environmental and health data, along with a range of physical measures and cognitive tests, when participants entered the study. Participants also had their genomes sequenced, along with repeat cognitive testing, dietary questionnaires and multimodal imaging including whole body MRI. Some of these participants have gone on to develop Parkinson's. Use of their data allowed researchers to explore the different risk factors involved in Parkinson's, and how they interact with each other, to improve early detection. The approach is already showing promising results for diagnosing Parkinson's up to seven years before symptoms begin to show.

Parkinson's is the fastest growing neurological condition in the world, and currently there is no cure. Around 145,000 people live with a Parkinson's diagnosis in the UK in 2020. Unfortunately, current treatments can only alleviate symptoms; they do not slow down or modify the course of the disease. Parkinson's disease affects cells in the brain called dopaminergic neurons, located in an area of the brain known as the substantia nigra. Loss of these cells eventually causes motor symptoms such as tremor, stiffness, and slowness of movement. By the time these hallmark symptoms of Parkinson's begin to show, and a clinical diagnosis can be made, more than half of the cells in the substantia nigra will already have died. However, it may be possible that treatments could be more effective if they were made available to patients at an earlier stage before the disease causes extensive damage to the brain.

Researchers at the UK Dementia Research Institute (UK DRI) analysed data collected from 103,712 UK Biobank participants who wore a medical-grade activity tracker for a 7-day period in 2013-2016. The devices measured average speed of movement continuously over the week-long period. Previous MRC-funded studies have pioneered the use of wrist-worn accelerometers to continuously measure activity, for example a study published in 2020 by researchers at MRC Epidemiology Unit in Cambridge also used UK Biobank participants. The UK DRI researchers in this study compared data from a subset of participants who had already been diagnosed with Parkinson's, to another group who received a diagnosis up to seven years after the activity tracker data was collected. These groups were also compared to age- and sex-matched healthy people.

The results published in 2023 showed that, using AI approaches to analyse subtle patterns in the huge amount of data gathered, it is possible to predict and identify participants who will go on to develop Parkinson's disease, up to seven years before hallmark symptoms appear and a clinical diagnosis can be made. The approach was also more accurate in predicting whether someone would develop Parkinson's disease than any other known risk factor or recognised early symptoms. Using real-world data in this manner could improve recruitment into clinical trials and allow people living with Parkinson's to access treatments at an earlier stage when they are available.

Shared genetics of endometriosis identified from UK Biobank data

A global study published in 2023, which includes data from UK Biobank participants, is the largest study to date on the genetic basis of endometriosis. The global collaboration involved 25 academic and industry groups across the world published evidence of a shared genetic basis for endometriosis and other types of pain including migraine, back pain, and multi-site pain. The study has also revealed that ovarian endometriosis has a different genetic basis from other types of endometrioses. This is an under-researched area of human health, and data from UK Biobank participants provided a vital resource for enabling these results which provide novel insights into the genes involved in endometriosis. The findings can open new avenues for designing novel medical treatments targeting subtypes of endometriosis, or even the repurposing of existing pain treatments for endometriosis.

Endometriosis is a disease that affects about 10% of women of reproductive age (190 million globally), with enormous implications on quality of life as it can cause constant and intense pelvic pain, fatigue, depression, anxiety, and infertility. It is characterised by the presence of tissue that resembles the lining of the uterus (known as the endometrium) outside the uterus. These tissue deposits occur primarily on organs within the pelvis such as the ovaries, bowel, or bladder. The causes of endometriosis are unknown, with currently no cure. Treatment is often limited to managing symptoms with repeated surgeries, and hormonal therapy with many side-effects.

The study published in 2023 included participants from UK Biobank who were subsequently diagnosed with endometriosis. The study analysed the DNA from these women and others from similar population cohorts, totalling 60,647 women with endometriosis and 701,926 without. The researchers found 42 areas across the genome which harbour variations in genes that increase risk of endometriosis. Large scale data resources such as UK Biobank allow researchers to conduct statistically robust population studies that can identify novel genes which might be associated with a particular condition, and this study identified 31 genes that had not previously been linked to endometriosis. By linking these genes to the profiles of molecules in endometrium and blood, the team identified a range of genes that were differently expressed in these tissues and therefore had a likely role in disease development.

The researchers also observed that many of the genes were involved in pain perception, thereby linking endometriosis to a range of other conditions that involve chronic pain such as migraine and back pain. The results could lead to new approaches for treating endometriosis such as designing new pain-focused non-hormonal treatments or repurposing existing pain treatments.

Blood samples from UK Biobank participants being analysed.
Credit: UK Biobank

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