University College
London Hospitals
Biomedical Research Centre

NHS
National Institute for
Health Research

Research with impact

Highlights of our successes

Research with impact

A key mission of our Biomedical Research Centre at UCLH is to drive the clinical translation of discovery science for patient benefit and ultimately the life sciences economy of the UK. Thus, our focus is to identify and support novel science that is on the cusp of clinical translation and ensure that translation happens. This has a number of key elements, including: the provision of the infrastructure for translation via our clinical research facilities for early phase trials, fostering links between clinical academics and other disciplines such engineering, physical sciences, mathematics, computer and data science, as well as creating enabling platforms in genomics, other omics, devices, biomarker discovery and advanced imaging.

Another important element has been BRC support for dedicated expertise in the design of early phase trials, regulatory aspects, business partnerships, contracting, investment and licensing. Thus, our impact is determined by our success in fostering partnerships at multiple levels, as well as ensuring that the key partnership between UCLH and UCL is strong and aligned to the mission. The value of what we do is defined by the impact of what we deliver for patients, the life sciences economy and in training and inspiring the next generation of discovery and translational scientists.

Professor Bryan Williams, Director, NIHR University College London Hospitals Biomedical Research Centre

Trialling drugs to prevent Alzheimer's

BRC funding has been essential in the UK's first clinical trial of drugs to prevent Alzheimer's disease before symptoms emerge. The landmark study, at UCLH, has published interim results showing promising results that immunotherapy drugs can prevent the onset of symptoms in people with high risk of developing Alzheimer's.

BRC-supported Dr Cath Mummery, a consultant neurologist and head of clinical trials at Queen Square's Dementia Research Centre, leads the UK arm of the pioneering international collaboration.

The study is the first of its kind in the UK, as it looks at people who have a mutation that causes inherited Alzheimer's, but don't have symptoms. Up until now, studies have only trialled treatments in patients already suffering from dementia.

The trial has found a marked reduction in amyloid load using PET scans and confirmed the drug removed amyloid from brains of people with Alzheimer's disease.

One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques. Amyloid is a protein that is generally found within the body. However, it can aggregate to form plaques. The two immunotherapies being looked at in this study eliminate amyloid in the system, to prevent onset of Alzheimer's.

The collaboration has recruited 200 people who have a 50-50 chance of carrying a rare genetic mutation. Carriers will develop the disease early in life (30s and 40s). The research team will continue to monitor the effect of the drugs by looking for early signs of the disease. The development of Alzheimer's is by looking at imaging changes in the brain, cognitive performance and spinal fluid.

Revolutionary drug gives hope of Huntington's treatment

BRC support has been fundamental in developing a revolutionary drug that targets the known cause of Huntington's disease.

The drug (IONIS-HTTRx) targets the product of the HTT gene, including the mutated version, which is responsible for damaging neurons in the disease. Reducing the production of the mutated protein means that the drug has the potential to change the course of the disease.

Professor Sarah Tabrizi, who was lead researcher on the trial, said: "For the first time we have the potential, we have the hope of a therapy that one day may slow or prevent Huntington's disease. This is of ground-breaking importance for patients and families."

This major breakthrough followed development at UCLH of the first blood test that can predict the onset and progression of Huntington's disease. This was the first time a potential blood marker had been identified to track the disease so strongly.

Dr Edward Wild, supported by the BRC and senior author on the paper, led UCL scientists in collaboration with colleagues in Sweden, USA, Canada, France and the Netherlands. Neurofilament levels were measured in the blood. Neurofilament light chain is released when damage to the brain occurs and has been linked to many brain diseases. Individuals carrying the Huntington mutation were found to have significantly elevated levels of neurofilament.

This biomarker reflects how quickly the brain is changing and so could help to track the progression of Huntington's disease for over a decade.

Immune cell therapy breakthrough in cancer treatments

Cellular Immunotherapy

BRC funding has enabled researchers to take the development of CAR T-cell therapies to the point where therapies are now entering clinical trials and attracting large-scale investment from industry.

The therapies, that enable the patient's own immune system to fight cancer could revolutionise the way cancer is treated.

The BRC has funded the groundbreaking work of Dr Martin Pule, which attracted an initial £30m Series A investment in 2015 from Healthcare technology investment company Syncona to set up the 'spin out' company Autolus. Autolus aims to develop and commercialise next-generation engineered T-cell therapies for haematological and solid tumours. Since 2015 additional investment totalling £109m from Woodford Investment Management, Arix Bioscience, Cormorant Asset Management, Nextech Invest and others has augmented Syncona's initial investment in Autolus.

Trials have begun into CAR ~T-cell therapy for patients with T multiple myeloma, a bone marrow cancer, and patients with relapsed or non-responsive B cell lymphoma, with UCLH recruiting the first global patients.

BRC-funding has also been key to a collaboration between UCL and a company that develops, manufactures and markets personalized immunotherapeutics for cancer and infectious disease, Cell Medica. Cell Medica is leading pioneering research in modified T cell receptor products which can recognise and destroy leukaemia cells over-expressing tumour associated proteins. UCL has provided Cell Medica with an exclusive license to its novel T cell receptor (TCR) technology to generate leading-edge modified TCR products.

TCR technology exploits the ability of TCRs, which are molecules on the surface of T cells and which recognise antigens expressed by cancer cells, to target both intracellular and cell surface antigens. The engineered T-cells have been likened to small programmable robots which could directly destroy the tumour and survive in the patient, patrolling for years and protecting against relapse.

Professor Emma Morris, who founded the innovative treatment being taken forward by Cell Media, said: "As a clinician treating patients with blood cancers, I am aware of the urgent need to develop more effective and less toxic therapies. Immunotherapy with gene-modified immune cells has enormous potential to transform the lives of cancer patients."

Tumour Heterogeneity

BRC funding has been key to groundbreaking research into treatment of lung cancer. Research by Professor Charlie Swanton looks to harness the patient's own immune system to destroy lung cancer cells. BRC-supported scientists were part of a team that first discovered the unique flags (neo-antigens) on cancer cells that trigger the immune system. The discovery of such neo-antigens underpins Swanton's work.

This work secured over £13 million by Healthcare technology investment company Syncona and commercialisation company Cancer Research Technology (CRT) to establish a new UCL 'spin out' company called Achilles Therapeutics to design therapies targeting truncal tumour neo-antigens. These neo-antigens which are present on all cancer cells in an individual patient's tumour are not present on healthy cells and so scientists are able to target and destroy tumours without harming healthy tissues.

Swanton also leads the TRACERx study for people with non-small lung cancer. The neo-antigen technology helps Achilles Therapeutics to track cancers over time and monitor response to treatment. The study receives infrastructure support from the BRC and is being carried out at the UCLH Clinical Research Facility on Tottenham Court Road.

Professor Swanton said: "Our research could provide a truly personalised approach to lung cancer therapy by targeting cell surface markers that are specific to each patient and present on all cancer cells rather than just a subset of cells."

Using light to battle gum disease

- BRC funding contributed to UCL Eastman Dental Institute staff being able to undertake clinical trials that helped establish light-activated antimicrobial agents (LAAA) as a means of treating periodontal disease.
- LAAAs are drugs that have no antimicrobial activity in the dark but can be activated by light of an appropriate wavelength – they are quick, simple and help to reduce antibiotic use.

Gene therapies

BRC investment has been key in the development of a gene therapy for haemophilia, bringing significant potential savings for the NHS.

Professor Amit Nathwani's team collaborated with St Jude's Children's Research Hospital in Tennessee to develop gene therapy for the haemophilia A and B. This single-dose treatment, which delivers normal copies of a defective protein and restores the blood clotting process, means patients no longer need regular injections.

This Haemophilia B therapy has been successfully used to treat severely affected patients, and has proved to have a dramatic effect on patient's lives. One patient said: "I have not needed any of my normal treatment, either preventative or on-demand as a result of an injury. Previously, I used to infuse at home three times a week …. I play football, run and take part in triathlons – and previously I might have had to infuse both before I took part and possibly after as well. Not having to do that has been absolutely brilliant."

Following Professor Nathwani's success, UCL launched a new 'spin out' company called Freeline Therapeutics, which was created following a £25 million investment. Freeline develops next generation gene delivery technology to enhance therapeutic potential and efficacy.

Haemophilia A and B are inherited genetic diseases caused by the absence of or production of a defective protein, which prevents blood from clotting properly. Over 3,500 people are affected every year in the UK and severely affected patients suffer from frequent, often life-threatening, bleeding episodes that occur without any apparent injury.

The standard treatment for the condition is to inject normal clotting proteins every two or three days; however, this is both inconvenient and invasive. It is also very expensive (£150,000 per year) meaning it is only available to patients living in high-income countries, leaving 80% of the world's haemophilia patients untreated. A trial with six patients could save the NHS £1.5m in the first few years. In a significant proportion of patient's antibodies in the blood destroy the clotting factor before it has a chance to work and so the treatment is unsuccessful.

Involving patients in setting BRC strategy

IN a bid to ensure patients and the public are true partners in the BRC's work, the BRC held several events to engage with lay people and get their input into the strategy and direction of the BRC for its third term. Fourteen patients and members of the public met with BRC directors and steered the direction of public involvement. Directors also met with 'A' level students and medical students to discuss priorities and funding emphasis.

Computational imaging set to revolutionise work of clinicians and researchers

BRC funding has enabled UCL and UCLH researchers to work together to develop state-of-the-art imaging that is breaking new ground in the diagnosis and treatment of disease and providing powerful tools for researchers.

Researchers have extensively developed computational imaging techniques, which bring together mathematics, optics, electronics and high performance computing to give unprecedented access to information of the body.

The combination of knowledge within image acquisition, reconstruction processing, computational modelling and image-guided surgery, will allow for effective and powerful application of research to patient care. Advanced imaging is key in disease prevention, experimental medicine, evaluating disease progression and analysing effectiveness of new interventions.

Examples of this work and its effect on treatments and diagnosis include:

Developing imaging to diagnose dementia

The spin out company Brainminer was awarded £1 million by NHS England's Small Business Research Initiative for Healthcare. The team, which includes BRC-supported Professor Sebastian Ourselin, develops revolutionary software to improve dementia diagnosis. The software automatically and intelligently analyses magnetic resonance imaging (MRI) scans to help diagnose dementia and Alzheimer's disease. Brainminer software also enables scans to be read quicker than the current standard assessment and so is a more cost-effective method.

BRC Director Professor Bryan Williams said: "This is a great example of how our BRC can help rapidly translate truly innovative technology for patient benefit for the whole of the NHS."

Guided surgery

Professor Ourselin is collaborating with Innersight labs to develop a surgery planning tool that can generate a patient specific 3D anatomical model. This tool uses medical imaging and machine learning algorithms in order to make better treatment decisions and personalised surgery plans.

In the future the platform will enable clinicians to manipulate interactive 3D models on screen and merge them with more quantitative information, such as tumour size.

A good example of the effect on surgery includes the development of EpiNavTM software, which is able to identify the source of epilepsy and determine whether this may be treated with surgery. EpiNavTM will greatly improve the accuracy of, and speed up the process; increasing the number of patients suitable for epilepsy surgery and may enable the possibility of surgery in circumstances that were previously considered too risky.

EpiNavTM technology, combines information from many different imaging technologies to provide an integrated 3D image of multiple brain structures and functions. The software has enabled neurosurgeons to plan the best operative approach for patients.

Fetal surgery

UCL groups and KU Leuven in Belgium are now working together to develop novel low risk imaging tools and techniques for the diagnosis, treatment and therapy of unborn babies with severe birth defects. Tools are used before and during surgery, allowing surgeons to better plan and perform procedures on unborn babies with a range of abnormalities.

The GIFT-Surg (Guided Instrumentation for Fetal Therapy and Surgery) project has recently marked the halfway point (3.5 years). The first half of the project had focused on engineering and imaging elements such as:

- developing mosaicking technology and miniature flexible instruments
- motion correction in MRI for fetal scans
- motion stabilisation devices to be used during surgery
- developing software to track surgical tools in real-time
- developing software that automatically segments organs of interest from fetal MRI
- establishing GIFT Cloud for end to end automatically anonymised data sharing across institutions
- preclinical testing for all optical ultrasound capabilities in 1mm needle tip.

In the next 3.5 years of the project, the team will be concentrating on moving to preclinical and clinical trials. They aim to integrate the various technological elements by implementing:

- Quality Management Systems to ensure developments can move forward quickly.
- clinical testing for all optical ultrasound needles
- expanding clinical treatments available at UCLH.

Improving surgery for epilepsy to reduce the risk of loss of sight, language or limb control

BRC funding provided salary support to a team that pioneered advances in brain scanning at the UCL Institute of Neurology, underpinning major improvements in the surgical treatment of epilepsy and reducing the risk of loss of sight, language or limb control.

Researcher Professor John Duncan and consultant neurosurgeons Dr Anna Miserocchi and Mr Andrew McEvoy, obtained a Wellcome Trust innovation grant with Professor Sebastien Ourselin to further develop image-guided neurosurgery. These advances are now used in epilepsy surgery at the National Hospital for Neurology and Neurosurgery and being rolled out elsewhere.

BRC support also contributed towards the salary of MRI physicist Dr Sjoerd Vos, who supports the epilepsy imaging programme.

Epilepsy is one of the most common serious brain disorders, affecting over 450,000 people in the UK. One third of these individuals continue to have seizures despite anti-epileptic drug treatment. For those in whom the source of epilepsy can be pinpointed in the brain, neurosurgical treatment can be curative. Over the last 20 years, research led by Professor Duncan has optimised brain imaging applied to epilepsy surgery and the clinical utilisation of functional magnetic resonance imaging (fMRI) and tractography to visualise brain activations related to language, motor and sensory functions, memory and critical nerve pathways in the brain.

The fMRI and tractography approaches pioneered at UCL are now used by neurosurgeons throughout Europe to identify the risks of surgery in individuals and to plan the surgery so that risks may be reduced. Surgeons use tractography to visualise pathways of white matter fibre pathways in the brain in the pre-operative MRI scans, helping them to avoid damaging nerve fibres in these critical pathways, which otherwise would lead to visual impairments that would, for example, prevent driving. The system is used on roughly one patient a week and has been fully operational since 2012.

As well as informing decisions about whether to undertake surgery or not, scans are also used in the interventional MRI operating theatre during surgery. A three-dimensional map of critical brain areas can now be visualised and presented to the surgeon as the operation proceeds, to enable the guiding of the surgery away from critical areas that must be avoided. This enhancement is already used in clinical practice at the National Hospital for Neurology and Neurosurgery, resulting in safer surgery with reduced risk of causing new visual impairments.

An early evaluation of the system demonstrated its impact in 21 patients undergoing anterior temporal lobe resection compared to a control group who underwent the same surgery without the system. None of those who had their visual pathway displayed to the surgeon via the tractography system were left with a visual impairment that would prevent driving, compared to 13% in the control group.

The use of fMRI to identify the side of the brain responsible for this function has entirely replaced the carotid amytal test at the National Hospital for Neurology and Neurosurgery, with benefits to patients and health providers. The old, more expensive test could be dangerous, involved radiation and required a two-day hospital stay. The hospital used to carry out around four such procedures per month, but have done none since 2004. The fMRI method has been widely adopted in epilepsy surgery centres around the world.

New way of assessing Alzheimer's disease progression becomes industry standard in trials

BRC funding has been pivotal in the development of a technique for assessing atrophy progression in Alzheimer's disease that has become the industry standard. UCL's Boundary Shift Integral technique has changed the way pharmaceutical trials in Alzheimer's disease are conducted, bringing greater efficiency and precision. These methods are more accurate than the previous manual measures they have largely replaced, and have as a result enabled researchers to develop more efficient clinical trials and brought significant benefit to the UK economy.

Since the mid-1990s, research at the UCL Institute of Neurology led by Professors Nick Fox and Martin Rossor has focused on improving diagnosis and measurement of disease progression in Alzheimer's disease and related disorders. The researchers began by describing brain changes to improve diagnosis. For instance, cerebral atrophy had long been a recognised characteristic of Alzheimer's and research showed that certain regions such as the hippocampus were reduced in volume very early in disease progression.

Professor Fox and colleagues went on to develop a novel technique (called the Boundary Shift Integral technique) of quantifying these changes in brain volume from rigid-body registration of serial magnetic resonance imaging (MRI). They were able to show that the method had a very high level of precision – ten times greater than previous methods.

The hope was that what had initially had been a better diagnostic tool for clinical use would be a technique that would actually help researchers identify which potential treatments showed the most promise and so could go into larger clinical trials.

In a decade of subsequent research, this novel technique was developed and validated in collaboration with Dr Kelvin Leung and Professor Sebastien Ourselin. These new methods and techniques were adopted for use in monitoring disease progression and were shown to be clinically useful – individuals with very early Alzheimer's disease show increased rates of brain atrophy relative to healthy controls.

The Boundary Shift Integral method has provided a precise, regulatory-compliant means of assessing whether a potential treatment for Alzheimer's disease could modify the disease course by slowing the rate of atrophy. These techniques have also brought economic benefits for the pharmaceutical industry. Image analysis allows trials to be conducted using far fewer subjects than would have been needed to power a study using clinical outcomes, effectively reducing the cost of clinical studies.

It has therefore had a significant impact on clinical trial protocols by reducing the number of patients needed and reducing patient exposure to potential side effects.

The Boundary Shift Integral has become the most widely used method of analysing brain atrophy in trials in Alzheimer's disease and in related disorders. Previously trials relied on manual methods to monitor atrophy. These were both labour intensive and error prone. The image analysis methods, developed at UCL, removed the need for these manual measurements and greatly improved both precision and reliability. This has led to the Boundary Shift Integral being the method of choice for many Alzheimer's disease trials (and now other diseases). Trials using UCL's techniques include some of the largest international immunotherapy trials in Alzheimer's disease.

Introduction of UCL techniques has also had a significant benefit to the UK economy, through the provision of image analysis services to overseas companies. For example, the image analysis unit at the Dementia Research Unit provided £5m in image analysis services to clinical trials between 2008 and 2013. IXICO (a company providing imaging services for clinical trials) uses the Boundary Shift Integral technique under licence and has attracted a number of large contracts. These techniques are also used in a large number of studies by image analysis companies in the United States.

Giving us the tools to identify inherited heart disease and save lives

Infrastructure funding from the BRC has enabled clinicians to work closely with UCL scientists to carry out basic molecular genetic research. This has had a major impact on screening for people with an inherited risk of early heart disease, with the potential to save thousands of lives as well as to save the NHS millions of pounds that would be otherwise needed to treat people who have heart attacks as a result of inherited cardiovascular disease.

The BRC invested over £2m to refresh space to house and develop the UCL Genetics Institute where researchers look at the genetics of complex diseases using biostatistical and bio-informatics approaches. Established in 2008, the institute looks at clinical and human population genetics, focusing in particular on cardiovascular and neurological diseases and cancer, including looking at the effect of genetic factors on reactions to drugs (pharmacogenetics). The result is an environment where basic science and clinical research in genetics are combined.

Research over the last 20 years by Professor Steve Humphries, the director of the UGI from 2005 till 2016, and the head of UCL Cardiovascular Genetics, has had a significant impact on the identification and treatment of patients with familial hypercholesterolaemia (FH), particularly by developing new DNA tests and diagnostic protocols now in wide use across the UK.

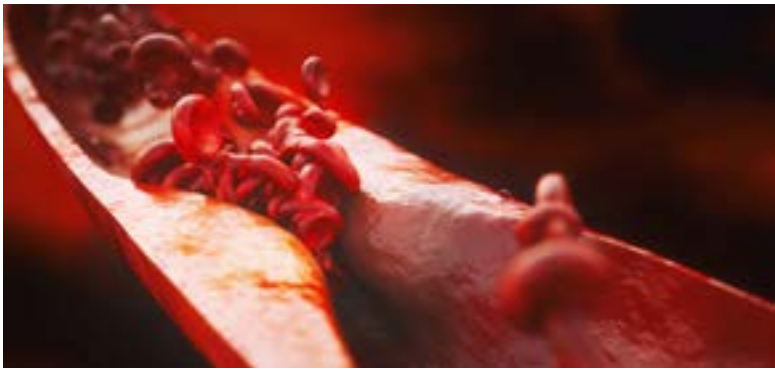
About one in every 250 members of the UK's general population – or approximately 200,000 people – have the inherited disorder FH. People with FH have very high levels of cholesterol in the bloodstream from birth and are at extremely high risk of developing early heart disease. Without treatment, half of men with FH will suffer a heart attack before the age of 55, as will one-third of women by age 60. First-degree relatives of people with FH have a 50:50 chance of having inherited the defective gene that causes FH.

However studies coordinated from UCL have shown that treatment with cholesterol-lowering statins is highly effective, and that if someone with the gene is identified early in life and treated with statins they will have a full life expectancy. Despite this, only around 15,000 people with FH have been identified to date and are being adequately treated. It is estimated that around 180,000 people in the UK have undiagnosed FH – around four to five families in a typically sized general practice. Studies coordinated from UCL have shown that the most cost effective way of finding more FH patients is by testing the children and brothers and sisters of patients known to have FH, as on average half of the tested relatives will also have FH. This process, called cascade testing, has been funded UK-wide by the British Heart Foundation (BHF), based on the findings from the UCL team, who are actively involved in supporting the FH Nurses in their work.

Population screening for FH is not practicable but tracing of close relatives of those diagnosed could pick up a sizeable number of those at risk. Professor Humphries has led pilot studies demonstrating the feasibility of cascade testing. These studies have also shown that, although incurring costs during implementation, a testing programme would generate savings within three years because of the reduced numbers of heart attacks. The evidence was compelling enough for the National Institute for Health and Clinical Excellence (NICE) to recommend cascade testing in 2008 and early treatment with high-intensity statins. In 2017, these cost estimates have been revisited using the actual data available from the BHF FH Nurses, and have once again clearly demonstrated how very cost effective this approach is.

In 2009/2010, Professor Humphries carried out a series of audits for the Royal College of Physicians. These showed that DNA and cascade testing had been implemented well in Scotland, Northern Ireland and Wales but almost not at all in England, where just 5% of families were being tested. It is estimated that as a result one undiagnosed FH patient suffers a heart attack every day.

Since the report was published, Professor Humphries has continued to campaign on this issue, from policy to ground level. He has worked with the National Screening Committee to include FH criteria in the NHS Vascular Checks programme to help identify further FH patients as index cases for cascade testing. He is a member of the 2017 NICE FH Guideline group, which will be updating the 2008 document based on new evidence, with several key papers from UCL contributing to the changes in recommendations for patient finding and management. Finally, he is the Director of the Children's FH UK Register, which is collecting data on all identified children with FH, to monitor their growth rate and to check that there are no side effects from treating children with statin from an early age.



Genomics medicine helps researchers to understand disease and speed translation

BRC funding has been fundamental in enabling researchers to develop the use of genomics, to understand disease better, personalise medicine and dramatically accelerate drug development.

For instance, BRC funding enabled researchers to collaborate with SomaLogic to use SomaLogic's SOMAscan assay to accelerate protein biomarker discovery. Protein levels are measured in the blood and body tissues, allowing molecular processes of health and disease to be understood in greater depth.

The assay provides researchers with unprecedented power for protein biomarker discovery, diagnostics development, and pharmaceutical discovery and development. SOMAScan is able to detect the proteins in the body and so biological processes can be captured, as well as identifying diagnostic markers and therapeutic targets. The assay provides an expansive view and is able to measure thousands of proteins at the same time. Profiling these proteins will improve understanding of drug resistance mechanisms, helping researchers to find the best combination therapy and drugs suited to an individual and their particular disease.

The information on how patients respond to certain drugs will allow drug mechanisms to be understood much quicker. This may mean that therapies are able to progress through to clinical trials at a much faster rate, giving patients quicker access to new procedures and medication.

Director of the BRC Cardiovascular theme Professor Aroon Hingorani said: "We are excited to apply this cutting edge technology to the many disease areas being studied here at UCL."

Another example of BRC support in genomics medicine research is UCLH's participation in the 100,000 Genomes project. UCLH is lead recruiter of patients with rare neurological diseases to the project.

The national project aims to sequence 100,000 genomes from around 70,000 NHS patients with a rare disease, plus their families, as well as patients with common types of cancer.

The aim is to create a new genomic medicine service for the NHS – transforming the way people are cared for. Patients may be offered a diagnosis where there wasn't one before. In time, there is the potential of new and more effective treatments. The project will also enable new medical research.

Although genomic medicine for cancer already exists within the NHS, this project will develop the evidence so that genomic medicine can be expanded. For individuals with rare diseases, this also presents as an opportunity for clinicians to better understand their disease and produce personalised treatment plans, if possible.

Genomes of patients with the same diseases can also be compared to help identify patterns in DNA changes. These patterns may help to identify whether patients will become ill and how severe their illness is likely to be.

Open day puts research on the map

Since 2014, the BRC has run a research open day in the main atrium of UCH. With the emphasis on interactive stalls, with researchers engaging with members of the public, patients and staff, the open day has grown from 20 stalls to 50 stalls. Each year 40-60 school children are given a tour of stalls and talks from researchers on research careers. Supported by the chief executive and chairman of UCLH, the open day has become a recognised date in the trust's diary of events and has been successful in enlisting lay people to get actively involved in research and raising the profile of the hospital as a research hospital among both the public and trust staff. Advertised in the local press, the day was key to engaging with local communities, and expanding the number of people interested in our PPI, as well as recruiting participants to the UCL BioResource.

How funding doctors to carry out research changed national guidelines on treating lower urinary tract symptoms in men

BRC funding to free up a busy surgeon's time for research has enabled UCLH clinicians to devote time to evaluating self-management interventions to help men with lower urinary tract symptoms (LUTS). The result is they discovered self-management interventions are more effective than drugs and as effective as surgery, saving the NHS an estimated £20million a year and cutting down on secondary care referrals.

As a direct result of this research nearly all evidence-based practice guidelines now recommend self-management as the initial form of therapy for men presenting with LUTS.

BRC funding was crucial because it allowed clinicians to use their experience and observations to pursue highly focused and relevant research.

A third of men over 60 suffer significant impairment of quality life as a result of lower urinary tract symptoms. Until recently, these symptoms were managed in the NHS by a step-up regimen of drugs and surgical interventions.

Professor Mark Emberton, a urological surgeon, had noticed that many men were adopting informal strategies rather than pharmacotherapy to 'manage' their symptoms. He observed that men tended to work out these strategies by trial and error, or found out about them from the informal network of men with similar symptoms. Sometimes, they learnt strategies from the growing number of continence advisors and nurse specialists. Self-management strategies included: fluid management, caffeine avoidance, timed toileting, urethral milking, double voiding and bladder re-training.

When Professor Emberton surveyed professionals working in the field of incontinence, he discovered that many would recommend these strategies, but there was a wide variation in their use, and no supporting evidence base.

Professor Emberton then set up a programme of rigorous research to address this gap in knowledge, defining an intervention, piloting it, and then undertaking a randomised controlled trial to compare the intervention to standard care.

For the first time, this study provided an evidence base for the efficacy of self-management. What the research demonstrated was that self-management was as good as surgery at reducing symptoms and ultimately reduced the need for medical and surgical treatment.

These results have informed treatment guidelines, and as a result, fewer patients now require drug therapy, and those receiving therapy may find it to be more effective. Data from the trial suggested that men using self-management have a three-fold reduction in risk of requiring therapy or progressing symptomatically. The estimated cost saving to the NHS is around £20 million annually.

Research changes national chlamydia screening

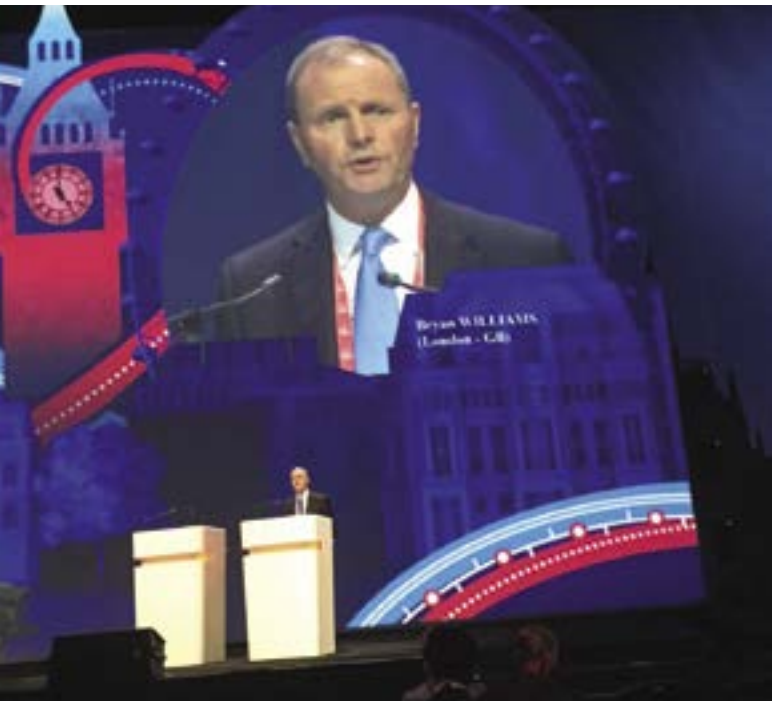
- Research by the UCL Institute of Women's Health into the effectiveness of chlamydia screening resulted in changes to the National Chlamydia Screening Programme in England.
- This review of chlamydia control in the UK was part of a systematic survey of chlamydia control activities in 29 European countries.

Helping researchers to involve harder-to-reach groups

The BRC runs a PPI bursary fund to support effective PPI and with the aim of ensuring PPI has an impact on biomedical research. To date, over £36,000 has been distributed among a range of projects. The fund provided support for researchers seeking to involve harder-to-reach groups including working with: over 75 older people to identify research priorities; which UCL School of Pharmacy researchers are now taking up; people with learning difficulties to develop weight management research; people with Down syndrome to look at attitudes to brain imaging in Alzheimer's disease research; and young people with Irritable bowel disease. One large project involved work with over 80 young people looking at adolescent rheumatology research studies proposals, advising on things like data collection and designing of a website – 17 focus groups were held per an 18 month period and five science days held for local sixth formers.

Repurposing – finding new ways of using known drugs

BRC support for researchers at UCLH/UCL has enabled dramatic progress in one of the most exciting approaches in translational research – the repurposing of drugs to treat new diseases. Repurposing is the application of known drugs and compounds that have been licensed for treating certain diseases to treat new or different diseases. One of the attractions of repurposing is that it carries the potential of getting new treatments to patients quicker as drugs have already gone through important safety trials. Recently published study results from UCLH/UCL show promising developments of drugs to treat symptoms and conditions previously regarded as almost untreatable.



Repurposing a 50-year old medicine provides modern treatment for resistant hypertension

Research conducted by a consortium of investigators across the UK identified that repurposing a drug that is over 50 years old (spironolactone) is the most effective treatment for difficult to treat high blood pressure, so called "resistant hypertension". The finding was published in the Lancet (2015) and lead author Professor Bryan Williams (NIHR UCLH BRC Director) commented: "This was a dramatic and convincing result that is already leading to changes in international treatment guidelines across the world and will improve the treatment and clinical outcomes for millions of patients globally."

High blood pressure is the leading preventable cause of death globally and affecting over 25% of adults in the UK. Most patients can be treated very effectively with lifestyle interventions and medication. However, there is a subset of patients whose blood pressure is resistant to control with existing medications and these are termed "resistant hypertension". It is estimated that up to 500,000 people in the UK and 100 million people world-wide have resistant hypertension globally. Importantly, because these patients have chronic elevations in blood pressure despite treatment, they are a group of patients at highest risk of premature cardiovascular disease, stroke and death. The optimal treatment strategy for resistant hypertension was identified by NICE in 2011 as a key gap in evidence that required further research.

The PATHWAY-2 study was a randomised clinical trial that recruited patients with well-characterised resistant hypertension and randomized to treatment with three different types of drugs that were designed to target

different pathways that might contribute to treatment resistance. One of these drugs was spironolactone, an aldosterone receptor antagonist which provided further diuretic therapy to counteract what the investigators hypothesised was the principal cause of resistant hypertension, notably, sodium retention that was resistant to conventional diuretic therapy. Thus, in addition to testing this hypothesis, the research team also included a series of detailed mechanistic experimental medicine studies to evaluate mechanisms of drug benefit. Professor Williams commented: "The results were remarkable and provided unequivocal evidence that spironolactone was the most effective treatment at lowering blood pressure, in many cases, controlling blood pressure for the first time in these patients. What was particularly interesting is that the benefit was seen in almost every patient, supporting our hypothesis that resistant hypertension was predominantly a salt retaining state." Work is now ongoing to try and identify the mechanism for salt retention in these patients which might provide additional novel avenues for treatment. In the meantime, the research has had an immediate impact globally, providing a simple, cheap and effective treatment. Professor Williams commented: "Based on what we know about the benefits of blood pressure treatment on clinical outcomes, especially in this high-risk group of patients, there is no doubt that the rapid implementation of the findings from this study will save many lives." The PATHWAY-2 study was funded by a British Heart Foundation special programme grant and the NIHR comprehensive research network.


Back to the future in resistant hypertension

Spironolactone 'overwhelmingly' the most effective

HOT LINE SESSION RESULTS

Professor Bryan Williams presents the results of the PATHWAY2 study at the Hotline session of the European Society of Cardiology meeting – London 2015

Diabetes drug could hold key for Parkinson's patients

BRC supported researchers have found that a diabetes drug could be a disease-modifying therapy for Parkinson's disease.

The findings by the UCL-led study paves the way for further research into the therapy's efficacy and safety in treating Parkinsons.

The study, published in The Lancet and funded by The Michael J. Fox Foundation for Parkinson's Research (MJFF), found that people with Parkinson's who injected themselves each week with exenatide for one year performed better in movement (motor) tests than those who injected a placebo.

"This is a very promising finding, as the drug holds potential to affect the course of the disease itself, and not merely the symptoms," said the study's senior author, Professor Tom Foltynie "With existing treatments, we can relieve most of the symptoms for some years, but the disease continues to worsen."

The researchers followed 60 people with Parkinson's disease at the National Hospital for Neurology and Neurosurgery (NHNN) as they used either a once-weekly injection of exenatide for 48 weeks, or a placebo, in addition to their regular medications.

They found that people who used exenatide had better motor function at 48 weeks when they came off the treatment, which persisted after the 12-week follow-up. Those who had injected the placebo showed a decline in their motor scores at both the 48- and 60-week tests. The advantage of 4 points, on a 132-point scale of measures such as tremors, agility and speech, was statistically significant.

Discovering that two older drugs could fight multiple sclerosis

BRC funding has been key to repurposing existing treatments, already shown to be clinically effective in other diseases, to help alleviate symptoms of multiple sclerosis (MS).

Researchers Dr Jeremy Chataway and Professor Raj Kapoor have carried out separate studies exploring the benefit of statins (Chataway) and epilepsy drug phenytoin (Kapoor) to treat MS. Both Dr Chatway and Professor Kapoor hold very busy clinical positions as consultant neurologists, however BRC investment funded valuable time each week allowing them to focus on their pioneering research.

Dr Chataway's trial, now in its third phase, will test simvastatin, a cheap cholesterol lowering drug, in people with the secondary progressive form of MS.

More than 120,000 people in the UK have MS, which attacks the central nervous system. Symptoms usually start when a person is in their 20s and 30s and it affects almost three times as many women as men. Most of those diagnosed have relapsing MS and about 65% of these cases develop secondary progressive MS, usually within 15 years. There are currently no licensed treatments that can slow or stop disability progression in people with this type of MS.

Dr Chataway previously led the phase 2 trial into simvastatin that found those taking high doses of the drug had a significant reduction in the rate of brain atrophy (brain shrinkage) over two years and also had better disability scores at the end of study.

Dr Chataway said: "This drug holds incredible promise for the thousands of people living with secondary progressive MS in the UK, and around the world, who currently have few options for treatments that have an effect on disability. This study will establish definitively whether simvastatin is able to slow the rate of disability progression over a three year period, and we are very hopeful it will."

This phase of the trial will involve more than 1,000 people with MS throughout the UK.

Professor Kapoor's trial, which has completed its second phase, found the anti-convulsant drug phenytoin protected neural tissue in patients with optic neuritis. Optic neuritis is a symptom of MS which causes the nerves carrying information between the eye to the brain to become inflamed and damaged.

The findings bring researchers one step closer to establishing neuroprotective drugs for people with MS – currently there are none.

In the study, 86 people with acute optic neuritis received either phenytoin or a placebo for three months. OCT (Optical Coherence Tomography) was used to measure the thickness of the retina and the light sensitive nerve layer at the back of the eye. At the end of the trial the group who had taken phenytoin had on average 30 per cent less damage to the nerve fibre layer compared with those who received the placebo.

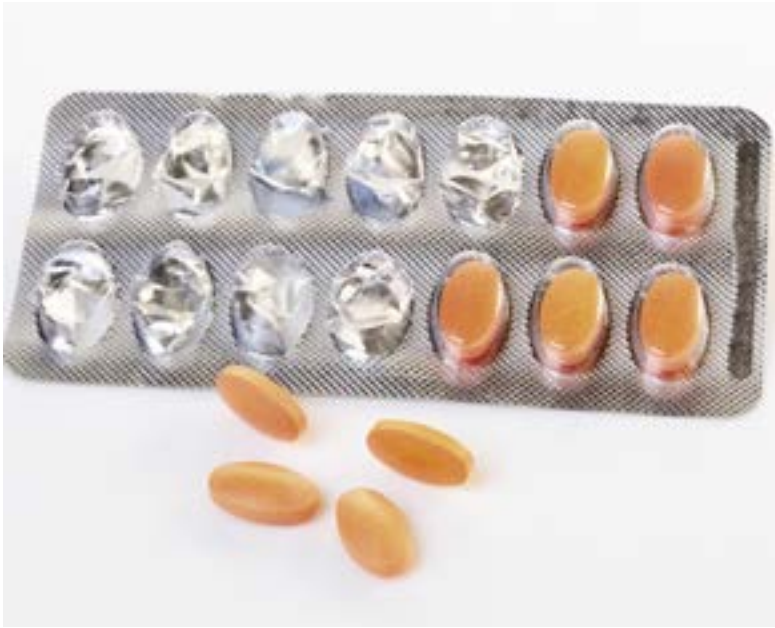
Professor Kapoor and his team had been focusing on the sodium channel as part of their research into neuroprotection. In inflamed areas, the axons of nerve cells get flooded with sodium, which causes an influx of calcium and in turn causes cell death. If sodium entry into the cell can be blocked there is potential to prevent this.

Professor Kapoor said: "We wanted to find out if the theory that blocking sodium currents, which we developed in basic work over many years, actually served to protect neural tissue – a test-bed to see if we can achieve neuroprotection."

Optic neuritis, which is often the first symptom of MS, gave the researchers a window of opportunity to study active inflammation early on in the disease process. Changes or damage to the nerves in the eye and the optic nerve are easy to measure.

Professor Kapoor said: "These are promising results that could lead to a new treatment that protects nerves from the damage caused both in optic neuritis and throughout the central nervous system in other attacks of MS."

As these studies look at repurposing an existing treatment already shown to be clinically effective, the use of phenytoin or simvastatin for MS could potentially have patient benefit in a much shorter timescale than usual.



Patients input into research strategy

BRC-supported ENT researchers at UCL have for some time now been leaders in PPI and engagement. The evidENT team at the UCL Ear Institute is a multidisciplinary team specialising in designing and facilitating a wide range of research activities within ENT hearing and balance, and has a dedicated PPI lead as well as a wide patient database of ENT patients and carers interested in research. The evidENT team recently developed the UK National Research Agenda for ENT, Hearing and Balance, a partnership of patients, the public, clinicians, researchers, industry, funders and health policy-makers which identified research priorities for ENT, Hearing and Balance care for the next decade.

Over 1,500 research ideas were gathered through an online survey and five focus groups meetings.

An expert forum identified questions that could be removed because they were already answered, were currently being researched or could be answered using knowledge from other fields. As a result 99 research ideas across six topic areas were presented to participants at the Consensus Conference.

Their discussion identified 21 priorities with research questions around hearing loss, tinnitus and ageing featuring high on the agenda. Examples of priorities identified include the underestimated impact of tinnitus and lack of evidence for current management of the condition; and the need for better understanding of why age-related hearing loss develops.

Improving the management of an autoimmune disease of the connective tissue

- A senior clinical fellow was funded by the BRC to research sclerosis, an autoimmune disease in which there is abnormal growth of connective tissue.
- Researchers at the UCL Centre for Rheumatology & Connective Tissue Disease defined the importance of regular proactive screening for lung fibrosis and pulmonary hypertension – both symptoms of sclerosis.

Innovative collaboration between academia and industry leads to ground breaking drug development

BRC investment has led to exciting progress in drug development in the last few years with one commercial phase 1 trial completed, demonstrating unprecedented positive results, and two phase 2b clinical trials just starting now, one commercial and one a UCL sponsored academic study.

The BRC has invested over £5.5m (£1m core support 2011-17; £1m for DESPIAD preparation; £2.75m for DESPIAD itself; £1m for core support 2017-20) in the UCL Wolfson Drug Discovery Unit, established and directed by Professor Sir Mark Pepys FRS. He has invented new potential drugs intended for treatment of systemic amyloidosis, a rare fatal disease, and for Alzheimer's disease, the very common cause of dementia in the elderly. Although there is no relationship at all between amyloidosis and Alzheimer's disease, they share some pathological and biochemical features on which Pepys has been working since 1974. His research led to the discovery of new therapeutic targets and then to invention of new treatments. GlaxoSmithKline (GSK) has licensed some of his patents and has pioneered a novel approach to the relationship between pharma and academia in developing them for clinical testing. Instead of just acquiring the intellectual property and developing the drugs themselves, GSK has collaborated and interacted closely with UCL's academic team, enabling a powerful synergy between UCL's scientific expertise and well-characterised clinical populations on the one hand and the resources and drug development capabilities of the company on the other. The BRC's core support for the Wolfson Drug Discovery Unit since 2011 has enabled delivery of its component of the collaboration.

Amyloidosis and Alzheimer's disease are very different clinical conditions but in both cases the tissues contain deposits of abnormal protein fibres, called amyloid, together with a normal blood protein called serum amyloid P component (SAP). Pepys discovered in the 1970s why SAP was always associated with amyloid fibres and in the 1980s he invented the use of radiolabelled SAP for detecting and quantifying amyloid in the tissues. This technique, using gamma camera imaging of the whole patient, is called SAP scintigraphy. It provides unique invaluable clinical information that has transformed understanding of the disease, leading to Pepys's establishment of the NHS National Amyloidosis Centre in 1999 when he joined UCL.

Accumulation of amyloid disrupts the structure and thus the function of tissues and organs, causing the disease of systemic amyloidosis. This rare but serious condition is usually fatal and is responsible for about one in a thousand deaths in developed countries. There are about 6,000 systemic amyloidosis patients in the UK. Treatments exist for only some forms of systemic amyloidosis and the therapies are toxic, expensive and often of limited efficacy. Crucially no existing intervention directly targets amyloid itself. Abnormal debris in the tissue is normally cleared rapidly and efficiently but this does not happen with amyloid. In the 1990s Pepys discovered that SAP contributes to the unusual persistence of amyloid and he invented a high throughput screening test for compounds that could block the binding of SAP to amyloid. In collaboration with Roche, this test was used to create a novel small molecule drug intended to remove SAP from amyloid deposits and thus promote the removal of amyloid deposits from tissues.

The drug, originally called CPHPC but lately given its WHO International Nonproprietary Name, miridesap, removes SAP from the blood but cannot remove all SAP from systemic amyloid deposits. Although miridesap is safe and well tolerated, it does not produce clearance of amyloid. However, depletion of SAP from the blood uniquely enables antibodies against SAP to be safely administered. These antibodies target the residual SAP in the amyloid deposits in the tissues and trigger the body's normal efficient clearance mechanisms to remove the amyloid. Pepys invented this approach in 2005, showing dramatic elimination of amyloid deposits from vital organs in experimental models and in 2009 GlaxoSmithKline licensed his patents for clinical development.

The comprehensively characterised and monitored patients of the National Amyloidosis Centre enabled GSK to conduct a decisive first in human phase 1 clinical trial of miridesap plus anti-SAP antibody. The treatment was well tolerated and has produced unprecedented reduction in amyloid deposits in vital organs, associated with improvement in organ function. Initial results were published in the New England Journal of Medicine in 2015 and the full report will be published shortly. A phase 2 trial in the UK and USA, focussed on cardiac amyloidosis, started in August 2017. The ability to remove amyloid is a potentially powerful new approach to the treatment of this debilitating and usually fatal disease.

In contrast to systemic amyloidosis, the amyloid deposits in the brain in Alzheimer's disease are microscopic and it is not known whether they cause the disease or not. However, there is good evidence that SAP itself is bad for the brain and the presence of amyloid in the brain increases the amount of SAP there, potentially causing dementia. In a preliminary experimental clinical study, Pepys and Professor Martin Rossor, Director of the Dementia BRU, previously showed that miridesap treatment removed all the SAP from the cerebrospinal fluid in patients with Alzheimer's disease. The Wolfson Drug Discovery Unit team has also shown that miridesap removes all SAP from brain amyloid in experimental models of Alzheimer's disease. There is therefore compelling evidence to support a clinical trial of miridesap in Alzheimer's disease. The preparations for the trial, 'DEpletion of Serum amyloid P component In Alzheimer's Disease' (DESPIAD), have been funded directly by the BRC. DESPIAD itself, a double blind placebo controlled trial of miridesap in 100 patients, is funded by the NIHR via additional funds for the BRC and is due to start soon. It is an entirely academic study although GSK have provided enormous pro bono support and technical assistance. The trial will run for three years, will establish safety and tolerability of miridesap in Alzheimer's disease, and should detect any appreciable disease modifying activity.

Professor Sir Mark Pepys said: "Development of new medicines is one of the slowest, most complex and most expensive of human activities. It is clearly beyond the skills and resources of a university, although the scientific and clinical knowledge, which identifies targets for new medicines, resides mostly in academic institutions. Bringing together the disparate resources and capacities of academia and big pharma productively is currently an evolving process with deployment of different strategies by different companies. Our collaboration with GSK has been exhilarating, especially after decades of working on amyloidosis, a rare but terrible disease for which effective treatments are very limited and challenging. There is no greater reward than testing our ideas in patients and seeing them produce clinical benefit. It is also a reward for the taxpayer as my research has been funded by the MRC without interruption since 1969, along with generous support from the Wolfson Foundation, The Wellcome Trust and other medical charities. The NIHR, via the BRC, is now being wonderfully supportive and there are grounds for optimism that one or more new medicines may eventually emerge."

Tracking the stealth virus – diagnosing and treating CMV infection

- BRC funding helped researchers to develop assays to measure CMV (cytomegalovirus – a common virus that belongs to the herpes family of viruses) DNA in infected humans.
- The assays allow rapid diagnosis of CMV viral load, inform the initiation of pre-emptive therapy in transplant patients; and have been licensed to Public Health England.

Transforming European cardiology guidelines

Professor Perry Elliott, a member of the BRC Cardiometabolic programme faculty, has been instrumental in creating a UCL risk model which has changed European cardiology guidelines and helped diagnose and treat patients with inherited cardiomyopathies.

Cardiomyopathies are diseases of the heart muscle, which are usually inherited. They cause a variety of clinical syndromes, including sudden death in apparently healthy young people, heart rhythm disturbances in later life, that cause stroke, and debilitating heart failure that reduces the quality of life and causes premature death.

Basic molecular and clinical research undertaken by researchers at the UCL Institute of Cardiovascular Science has resulted in significant improvements in the identification and treatment of patients with cardiomyopathies, underpinning development of the largest inherited cardiovascular disease service in the UK at UCLH and Great Ormond Street Hospitals, which sees more than 20% of the national caseload. Genes identified by the research are now regularly tested for across the UK and around the world.

The UCL risk model is being employed in guidelines from The European Society of Cardiology guidelines. Professor Elliott said: "These recommendations for sudden death prevention are likely to spark considerable interest and debate as they provide advice based on real estimates of risk rather than relative risks as in all previous guidelines. This will bring into focus the balance between clinical efficacy on the one hand and the potential risks and costs of therapy to individual patients and health-care economies on the other."

In hypertrophic cardiomyopathy (HCM), which is the most common inherited cardiac disease, the team have identified new mutations in patients with this condition and established a new method for the classification of genetic variants. The data collected in the clinical HCM programme at UCL have been used to develop and validate new risk prediction models that have been incorporated into European guidelines for treatment with implantable cardioverter defibrillators, which prevent sudden cardiac death by sensing heart rhythm disturbance and restoring normal rhythm. Around 400 patients have already undergone ICD implantation using the risk tools developed by the group.

In arrhythmogenic right ventricular cardiomyopathy (ARVC), which commonly presents with heart rhythm disturbance and sudden cardiac death in young, previously well individuals, researchers have undertaken a systematic evaluation of families with ARVC using MRI scanning, which has revealed previously unrecognised sub-clinical forms of the disease. Detailed work examining the relationship between genetic mutations and clinical presentation has led to a new European classification for cardiomyopathies and a clinically based approach to diagnosis that emphasises disease specific presentations and outcomes.

Since 2011, a pan-European study (the INHERITANCE Consortium) has investigated the laminopathies – a group of diseases caused by mutations in the gene coding for a protein called Lamin AC that accounts for 5–8% of unexplained heart failure and also leads to sudden cardiac death. This work showed that for most people who inherit the gene, the disease follows a predictable course. By recognising these characteristic stages of disease, patients and families can be identified much earlier, and preventative treatment can be started. A number of families have already been identified through the UCL screening clinic, and are benefiting from early treatment.

Funding for neuromuscular disease centre leads to UK's first diagnosis centre for channelopathies

BRC funding of £850,000 towards a special centre for neuromuscular diseases has been key to the delivery of rapid and reliable diagnostics for rare but disabling muscle conditions.

As a result of their expertise in this field, Professor Michael Hanna's team was commissioned by NHS Highly Specialised Services to provide the UK's only diagnostic and treatment centre for channelopathies – rare but disabling disorders that result in debilitating episodes of muscle paralysis and/or severe stiffness; over time, permanent muscle weakness can result in significant disability. The centre received a capital funding award from the BRC of £500,000 for refurbishment of the centre; followed by an additional award of over £350,000.

Because they are so rare, accurate diagnosis of these episodic conditions is difficult. It requires specialist clinical, genetic and electrophysiological assessment, the latter involving detailed measurement of the electrical properties of relevant cells and tissues. In the absence of these highly specialised assessments misdiagnosis is common. Consequently, patients often experience a long delay before a correct diagnosis is achieved and effective treatment instituted.

World-leading collaborative research established and led by Professor Hanna has helped to redress this problem by elucidating the genetic architecture and identifying new disease mechanisms for genetic muscle channelopathies. By significantly progressing fundamental understanding of the pathophysiology of such diseases, it has resulted in the development of new tests supporting faster diagnosis and better patient outcomes.

Professor Hanna, Director of the Centre, said: "The invaluable BRC support has enabled a genuinely national strategic approach to be developed. Specifically, the award will help us to bring the UK neuromuscular scientific and clinical community together, as we focus our research programmes on taking on the most mature preclinical science and applying it in experimental medicine settings to develop new treatments for patients with these often devastating muscle wasting diseases."

As well as diagnostic services, the centre also offers a clinical service which provides one-stop, same-day assessments and subsequent electrophysiological testing for more than 2,000 patients. The clinical service provided here has defined best practice in treating patients with these rare conditions: by providing accurate individual diagnoses it ensures that they receive the most effective medications for their particular condition, often significantly improving their quality of life.

Making sure research careers are open to all

The BRC is the main funder of the in2science scheme which provides lab placements to 'A' level students from disadvantaged backgrounds. The scheme has had astounding results in helping to develop students' careers, with 58% of in2 science students going on to Russell group universities compared to just 5% (national figures Dfe) of students on free school meals. 83 % of in2science students go on to university, largely to study STEM subjects, compared with 44% of students who go to university according to national figures.

"I now want to study a scientific research-related subject at university. The placement has changed my perceptions of science."

Non-invasive method of investigating the large bowel replaces standard barium enema

BRC funding, which aided the investigation of the role of CT colonography (a relatively novel and non-invasive method of investigating the large bowel using an X-ray scanner), has led to this examination replacing the standard radiological alternative of barium enema in the UK National Bowel Cancer Screening Programme and for symptomatic patients in the NHS.

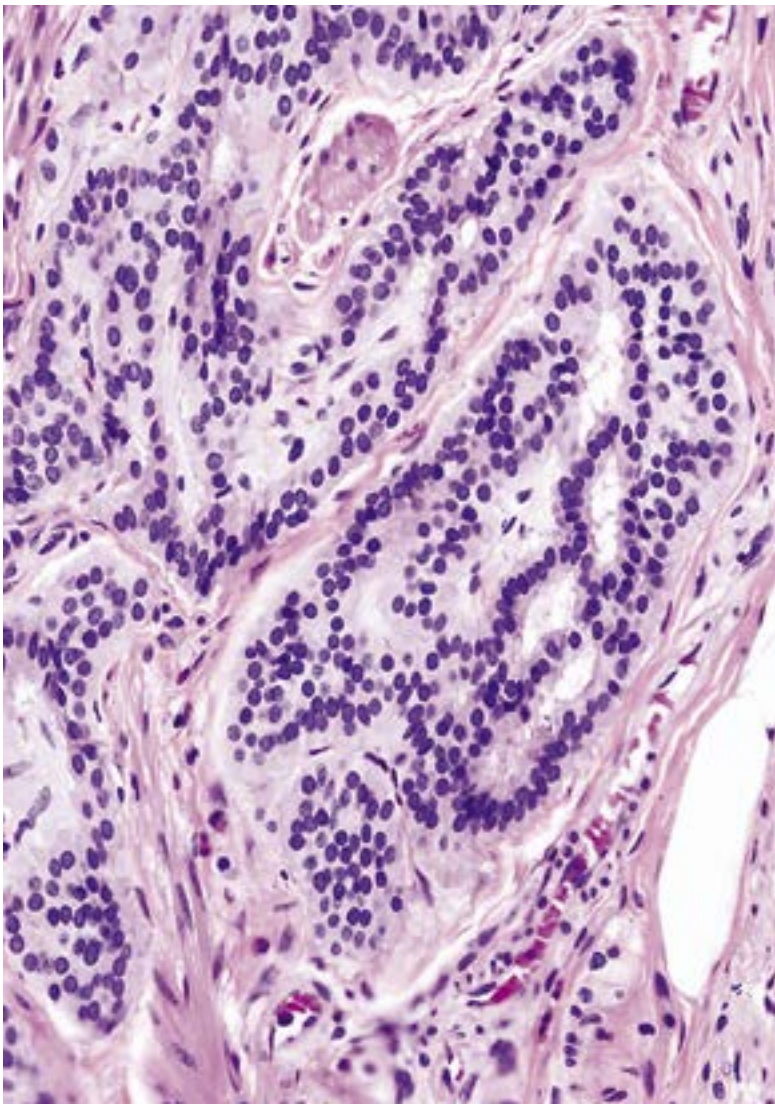
Every year in the UK over 700,000 patients with bowel symptoms undergo diagnostic investigations to see if they are caused by bowel cancer. Previously, investigation was typically by either barium enema (an x-ray) or colonoscopy (where a camera is inserted into the large bowel). CT colonography (CTC) offered theoretical advantages over either of these techniques, but there was no high-level research evidence to support its use.

Together with collaborators at Imperial and Birmingham, researcher Professor Steve Halligan first undertook a systematic review and meta-analysis that suggested CTC was as sensitive as colonoscopy for detection of bowel cancer. As a result, further research was commissioned by the NIHR Health Technology Assessment programme.

Two parallel multi-centre randomised controlled trials compared CTC with either barium enema or colonoscopy in symptomatic patients. 5,448 patients were randomised overall across 21 NHS hospitals in England. The results were published in The Lancet in 2013 and found that CTC was more sensitive than barium enema for the diagnosis of colorectal cancer and large polyps. There was no significant difference between CTC and colonoscopy, but CTC was better perceived by patients. Subsequent studies found CTC more cost-effective than barium enema and as cost-effective as colonoscopy.

The results of these trials led to a change in the NHS Bowel Cancer Screening Programme, which immediately discontinued barium enema and replaced it with CTC as the preferred method for radiological examination. Professor Halligan was asked to join the Bowel Cancer Screening Advisory Panel to advise on the subsequent national implementation.

Diagnostic services for symptomatic patients also changed as a result of the trials: English NHS hospitals rapidly started to replace barium enema with CTC. In Wales a Ministerial 'Task and Finish' group recommended that all barium enemas cease by March 2015. CTC is also helping alleviate pressure on endoscopy services generated by both the



symptomatic service and the screening programme. Since publication, the trials have been quoted widely and have appeared in international guidelines for management of symptomatic colorectal cancer.

At present Professor Halligan and his group are funded to investigate the effect of a dedicated training programme applied to radiologists reporting CTC in the National Bowel Cancer Screening Programme. A rigorous Quality Assurance is in place for mammography in the breast screening programme and this research seeks to implement the same for CTC and bowel cancer screening.

Blood test for early diagnosis of vCJD prion infection

BRC funding has enabled the MRC Prion Unit at UCL to play a key role in addressing the public health issues raised by 'mad cow disease' and its human variant, by developing blood tests for early diagnosis and to screen donated blood and organs for transplantation.

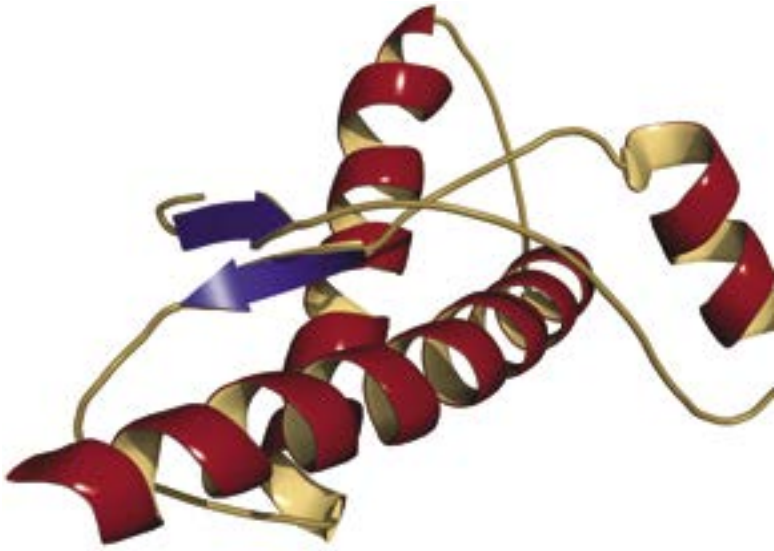
Bovine spongiform encephalopathy (BSE), popularly known as 'mad cow disease', is related to variant Creutzfeldt-Jakob disease (vCJD) in humans. This degenerative neurological disorder is invariably fatal, and a study by the Health Protection Agency (HPA) estimates that one in 2,000 UK citizens are carriers – clearly alarming when coupled with the known potential for transmission via blood transfusion.

The MRC Prion Unit at UCL was set up in 1998 to address this national public health issue, with the key priority of creating a validated blood test for vCJD. The UCLH BRC has provided support towards the National Prion Monitoring Cohort study.

Without a validated blood test, clinicians can only use existing World Health Organization diagnostic criteria for vCJD, to classify the disease as 'probable' in the presence of significant neurological deficits and to confirm it as 'definite' using neuropathological examination. These disorders are relentlessly progressive and have a devastating prognosis, but getting a firm early diagnosis is crucial. It removes distressing uncertainty and helps to identify potentially reversible conditions. Patient care plans can be established, patients and families counselled and appropriate infection control measures implemented. A sensitive and specific blood-based molecular diagnostic test for prion disease facilitates entry into therapeutic trials. In addition, such a test has obvious applications in reducing transmission, screening of blood products for transfusion, food and medicinal products.

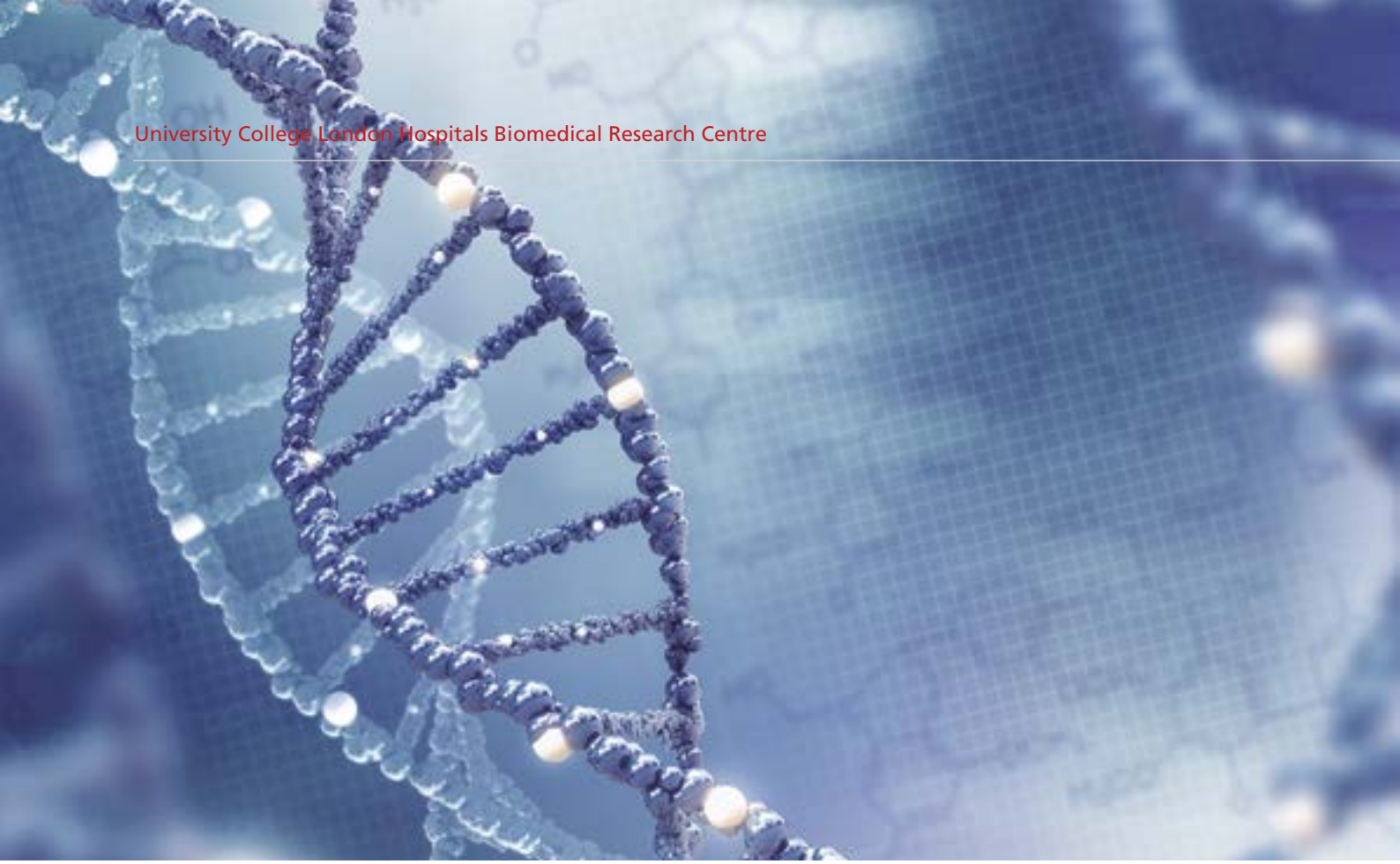
The MRC Prion Unit at UCL, led by Professor John Collinge has identified new methods for the specific detection of abnormal forms of the prion protein PrP. These methods are used in conjunction with monoclonal antibodies developed by the Unit to detect the presence of disease-associated forms, to develop sensitive methods capable of diagnosing prion infection from blood, and biopsies of neural or tonsillar tissue. These are crucial breakthroughs for both individual patients and public health services.

The UCL blood test is now in use at the National Prion Clinic (NPC) – the national referral centre for prion disease based at the National Hospital for Neurology and Neurosurgery – to allow diagnosis of vCJD. Over a hundred patients have been tested so far through the clinic. The blood test has been demonstrated to detect infection in over 70% of patients with vCJD with, to date, 100% specificity.



Training helps researchers involve patients

The BRC has developed an extensive programme of training for researchers on involving patients and the public in their work. The BRC is now recognised as a centre for excellence in PPI training and in 2016 our programme was awarded the Hencel award for work in "education and training that has been innovative in putting patients and/or carers at the centre of the programme" and received £10,000 towards the next programme. Over 50 workshops have been delivered across multiple sites and to date 640 researchers have been trained. Evaluation and feedback has revealed the training triples researchers' confidence in carrying out PPI. Six months after a workshop, 64% had carried out PPI with 75% saying the training helped them. Over 50% had involved people in identifying research topics.



A genetic test for Parkinson's disease

BRC funding was instrumental in the development of a new genetic test for Parkinson's disease (PD), now available to patients and their families.

The test was created after research carried out in the laboratory of BRC researcher Professor Nick Wood revealed some of the genetic causes of PD; it is the most common single mutation accounting for PD and is now implemented in many laboratories world-wide.

This is the first time in PD that tests have been widely available and have been useful to a large number of potential sufferers. The test works by revealing whether or not an individual has mutations in the LRRK2 gene.

Discovered in 2004, the LRRK2 gene is a known genetic contributor to PD. This represented a significant shift in understanding of an apparently sporadic condition that had, for many years, had been taught to medical students as the prime example of a non-genetic disease. Furthermore, the discovery in 2005 of the so-called common mutation (G2019S) in this gene showed for the first time that a relatively rare genetic variant could not only cause familial PD, but could also play a significant role in sporadic PD.

The test gives patients a precise diagnosis and understanding of the risk of disease to relatives. Prenatal testing is also a possibility. It also provided insights into patterns of PD in particular ethnic groups and generated industry research leading to new drug candidates.

The UK Genetic Testing network approved an evaluation of the test for LRRK2 as a genetic test for the NHS Service Gene Dossier in 2011.

Approximately 200,000 people in the UK suffer from PD, and the lifetime risk of developing PD in the UK is now 4%, making it the second most common neurodegenerative disease in the country.

Parkinson's Disease – recognition, quantification and treatment of non-motor features

- UCL research has supported the production of new scales for the identification and quantification of non-motor symptoms and signs in Parkinson's disease.
- These have been incorporated as end points in international clinical trials and introduced by specialist societies and NHS commissioners as a standard of care for Parkinson's patients.

Natalizumab: the first MS treatment with unequivocal effect in preventing disability

BRC investment in programmed activities of Professor David Miller and in the imaging facility at UCL Institute of Neurology that undertook centralised MRI analysis for assessment of MS trials was key to the development and licensing of natalizumab – the first NICE-recommended disease- modifying treatment for MS available via the UK NHS.

Natalizumab (Tysabri) s a potent treatment for highly active relapsing remitting multiple sclerosis and has been shown to reduce relapse rate by two-thirds and relapse-related disability by 50%. Indeed, it is the first treatment for MS to show a large and unequivocal effect in preventing disability. Moreover, a substantial number of natalizumabtreated patients actually experienced a reduction in existing disability.

By 2013, over 115,000 patients had received natalizumab. MS is the most common disabling neurological disease of young adults in the UK, affecting one in 800 of the population and associated with high healthcare and socioeconomic costs and a markedly reduced quality of life. The first available disease-modifying treatments – beta interferon and glatiramer acetate – were introduced in the 1990s, with limited usefulness in preventing relapses and reducing disability and deemed by a NICE appraisal as not cost effective for NHS.

Natalizumab is a monoclonal anti-adhesion molecule antibody shown to prevent trafficking of mononuclear white blood cells from blood to brain. Serial magnetic resonance imaging (MRI) studies conducted at the UCL Institute of Neurology identified that the break down of the blood-brain barrier (BBB) was a key early event in new lesion formation in relapsing remitting MS. As well as playing an important role in defining protocols for MRI in proof-of concept trials of potential new disease modifying treatments, this discovery provided a rationale for investigating natalizumab.

Under the leadership of Professor David Miller, the UCL Nuclear Magnetic Resonance Research Unit investigated the efficacy of natalizumab by performing central MRI analysis of multicentre Phase 1/2a and Phase 2b placebo-controlled trials in relapsing MS, using MRI lesion activity as the primary outcome measure. The large phase 3, multicentre, placebocontrolled trial that followed showed that, compared with placebo, natalizumab:

- reduced relapse rate by two thirds, and by 81% in a subgroup of patients with highly active relapsing remitting MS
- reduced the rate of hospitalisations by 64% and the need for steroid treatment for relapses by 69%
- reduced by 50% (and by 64% in the subgroup with highly active disease) the development of irreversible disability; with a substantial number of natalizumabtreated patients actually experiencing a reduction in disability
- reduced by 43% the risk of a confirmed worsening of cognitive function
- significantly improved both physical and mental healthrelated quality of life.

The phase 3 trials also identified a rare but serious adverse effect of natalizumab: progressive multifocal leucoencephalopathy (PML), a severe and sometimes fatal viral brain disease. As a result, natalizumab is largely used as a second-line treatment in highly active MS. Professor Tarek Yousry from the UCL Institute of Neurology led an international group that initially defined the risk for PML and he and Professor Miller have since contributed to guidelines relating to the monitoring of natalizumab-treated patients for early detection of PML.

This pivotal phase 3 trial led to a full NICE technology appraisal of natalizumab in 2007. The drug was also approved by regulatory authorities for the treatment of active relapsing remitting MS in many other parts of the world, including in the United States, European Union, Canada and Australia.

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