

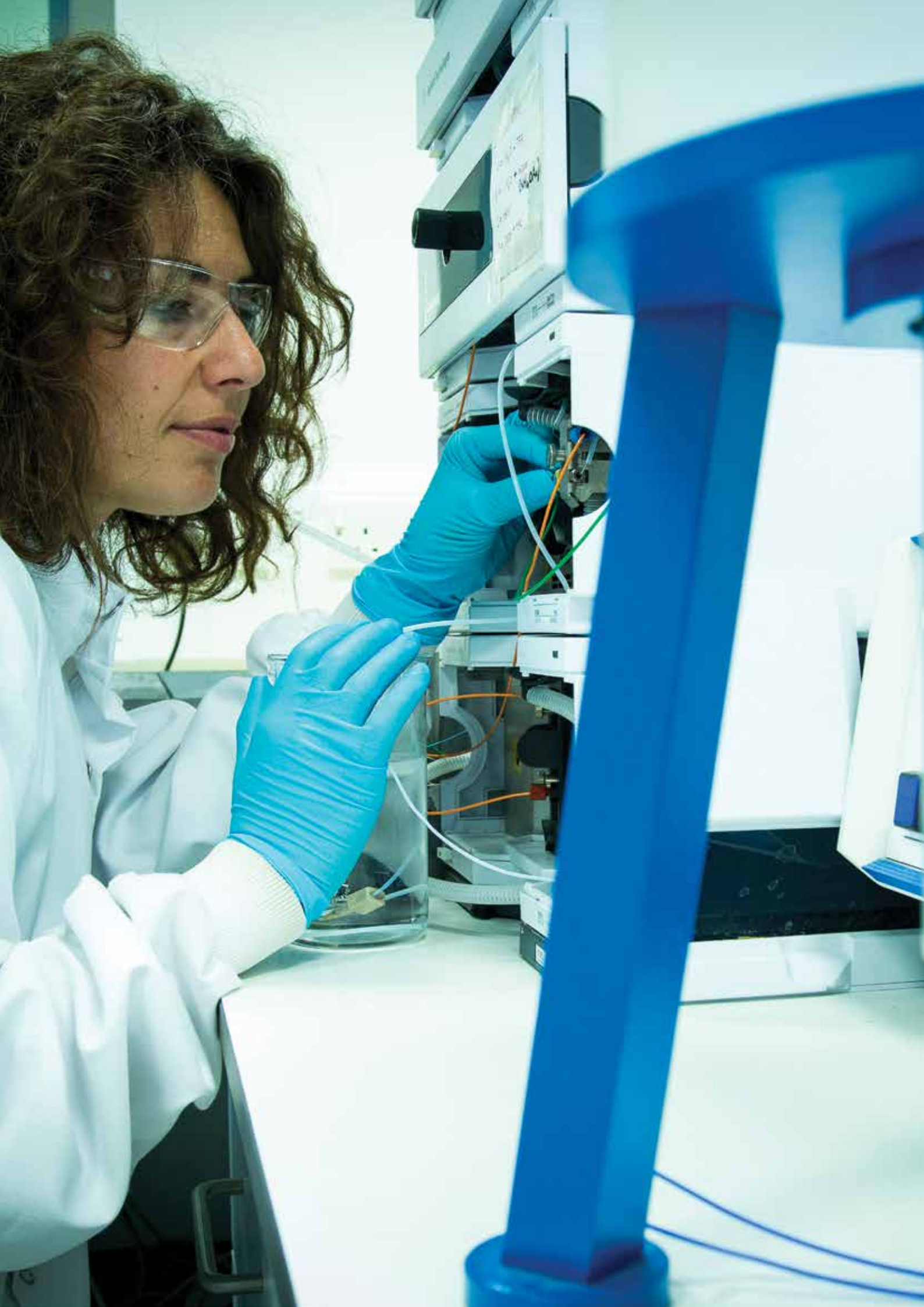
University College
London Hospitals
Biomedical Research Centre

NHS
*National Institute for
Health Research*

Building research infrastructures

Highlights of our 2007–2011 funding





Introduction from Professor Bryan Williams

It is a pleasure to introduce this brochure highlighting the impact of our National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre (BRC). This brochure focuses on the impact of our 2007–11 investments in research infrastructure.

The NIHR provides funding to us as a leading university and NHS hospital partnership to drive the translation of world class clinical research into new diagnostics, technologies and treatments to improve the care and outcomes of our patients.

There is also huge untapped potential to commercialise biomedical innovation in our universities by partnering with small to medium enterprises and creating new businesses to reinvigorate the life science economy of the UK.

In order to create health and wealth, we have needed to focus on a number of areas including:

- building our research infrastructure at the interface between fundamental research at UCL and clinical translation in our hospitals
- creating a platform of specialised research estate and equipment, imaging and informatics, that will facilitate a step change in our capacity to deliver clinical translation
- building our cadre of clinician scientists to help bridge the boundaries between fundamental discovery research and clinical practice to lead clinical translation.



We have been working hard to cultivate stronger links with the huge strengths UCL has in the physical sciences, chemistry, mathematics, engineering, nanotechnology, computing and informatics. We have also been working hard to embed a culture of innovation and enterprise in our biomedical research.

We have made incredible progress but there is still so much more to be done and ultimately we will be judged, not by the magnificence of our new infrastructure, but rather by its impact on our research. I hope this brochure will capture the scale of the progress our BRC is making.

Professor Bryan Williams

Director of the National Institute for Health Research University College London Hospitals Biomedical Research Centre



Here at the National Institute for Health Research University College London Hospitals Biomedical Research Centre (BRC) we are delighted to see the incredible impact our investments are having on the biomedical research infrastructures at University College London Hospitals NHS Trust and UCL.

The following pages focus on just some of the highlights of our work.

What is particularly exciting is to not only see the groundbreaking research taking place but to recognise the key role our BRC has had in making this happen.

As you can see, our work extends from investing in the kind of person power we need to be at the cutting edge of experimental research, to making sure our researchers have access to high-tech facilities.

Whether you are one of our stakeholders or a lay person interested in research, we hope that over the following pages we can share some of our excitement with you.

Nick McNally

Chief Operating Officer



Debbie Hughes, research assistant, in front of the next generation sequencer at UCL

Access to next generation sequencing

The use of next generation sequencing technology to decipher DNA sequences has revolutionised biomedical research.

Investment by our biomedical research centre (BRC) has made sure researchers at UCL and UCLH have had access to this technology soon after its development. The result is groundbreaking research into a range of human diseases, allowing a much greater understanding of the genetic causes, mechanisms and progress of disease.

In 2010 a BRC award of £339,000 leveraged a further £661,363 from the Wellcome Trust to enable researchers to purchase a next generation sequencer (NGS) housed at the UCL Institute of Neurology. The researchers run the next generation sequencer as a non-profit concern to benefit all UCL researchers.

The team of researchers, led by Professor Henry Houlden, mainly use the sequencer for exome sequencing. In this process, a person's blood is taken, DNA is extracted, certain sequences are enriched and, over a 7-10 day period, all protein encoding genes are sequenced. The data is then analysed using a bioinformatic pipeline.

The team works closely with research groups across UCL and UCLH and is able to offer them a supplemented service that is very cost effective. In the future, sequencing is likely to become a part of diagnosing disease. The team is also looking to develop new techniques to answer further important questions about DNA and RNA.

Professor Houlden said: "We have sequenced over 1,100 exomes for many groups across UCL and results from the NGS have allowed us to unravel the genetics of common disease, such as Alzheimer's disease, and also rare diseases such as inherited ataxia and dystonia, with a major impact on diagnosis and the identification of pathogenic pathways."

Professor Houlden added: "The NGS has worked very well. This is down to an excellent technical and analytical team in place that has not only benefited neurology, but also many diseases across UCL, particularly in child health and cancer. The NGS exome sequencing has provided a benchmark for high throughput sequencing, and hopefully in the next few years this will become part of the diagnostic service."

He concluded: "The next step is to add extra research capability and techniques to the sequencing facility so that we can offer techniques such as transcriptome and methylome sequencing to research groups at UCL".

What is next generation sequencing?

Next generation sequencing is a technique that allows researchers to look very quickly and cost effectively at each individual part (bases) of the DNA molecule in all of the genes (whole exome) or genes and non-coding gaps (whole genome).

Before NGA technology, biomedical researchers used the Sanger sequencing technique which was expensive and slow.

In the Sanger sequencing method bases are sequentially identified from signals emitted from each fragment of DNA. However, NGS extends this across millions of reactions in parallel rather than being limited to just a few DNA fragments.

The new techniques called exome and genome sequencing have accelerated our knowledge of genes and have advanced research into the genetic risks of disease. The aim is to develop further techniques for sequencing RNA and methylated DNA, which will allow researchers to investigate other aspects of the disease process and mechanisms.

Scientists and clinicians working together on genetics

Research into the genetics of disease has made it vital for scientists and clinicians to work together.

Our biomedical research centre (BRC) has been fundamental to the development of the UCL Genetics Institute where researchers look at the genetics of complex diseases using biostatistical and bio-informatics approaches. A key emphasis is on clinical and human population genetics including the effect of genetic factors on reactions to drugs (pharmacogenetics).

Recognising the vast potential of this work, the BRC invested £2.15m to refurbish space to house and develop the institute. The result is an environment where basic science and clinical research in genetics are combined and researchers can work together to speed up the pathway from scientific discovery to treatments that benefit patients. The institute has nurtured some of the most fruitful multi-disciplinary research collaborations.

The research

The institute has brought together basic scientists, statisticians, bioinformaticians, computational biologists, and clinicians. The work led by investigators at the institute has to date attracted a further £6m in funding.



Predicting inherited cardiac conditions

Professor David Balding and his team have been collaborating with the NIHR Cardiac Biomedical Research Unit at the Royal Brompton & Harefield NHS Foundation Trust to develop risk prediction models for inherited cardiac conditions such as Long QT Syndrome, Brugada Syndrome and Hypertrophic Cardiomyopathy.

Rare genetic disorders

Dr Vincent Plagnol and his research group have made a major contribution to the methodology and data analysis of sequence data from patients with undiagnosed rare conditions in several fields including ophthalmology. Their work has enabled collaborations with biomedical research centres at Moorfields Eye Hospital and Great Ormond Street Hospital, and with the University of Cambridge and Queen Mary, University of London.

Familial Hypercholesterolemia

Director of the institute, Professor Steve Humphries, leads a team looking at the early heart disease familial hypercholesterolemia (FH) which is a monogenic disease caused by a variation in a single gene. The team has discovered a substantial proportion of people diagnosed with FH inherit a combination of small-effect changes in several genes (polygenic). With implications for national guidelines, this suggests screening should be restricted to the relatives of only FH patients with an autosomal dominant mutation (where possession of the mutation in just one of copy of a gene is sufficient to inherit the disease).

Epilepsy and dementia

Researchers, including Professor Nick Wood and Professor Sanjay Sisodiya, have been able to analyse complex data from a range of neurological conditions, such as Parkinson's Disease, the epilepsies, and dementias. UCLH clinicians also have tremendous expertise in rare genetic disorders and the institute's co-ordinated approach means research groups are more able to interrogate sequencing data and draw meaningful conclusions.

Looking to the future

- With such a strong and established base in computational biology and genetics, the institute is setting up a pharmacogenetics unit.
- The institute works hard to cultivate new scientists and runs masters courses, including an MSc in Pharmacogenetics and Stratified Medicine, with an MSc in Computational and Genomic Medicine due to start in 2014.

Professor Andres Ruiz-Linares and Professor Steve Humphries pictured at the UCL Genetics Institute

Culturing cells for nerve repair research

A small box-like room could be crucial in finding ways to repair damaged nerves in the spine.

Our biomedical research centre (BRC) awarded £670,000 to David Choi to build a state-of-the-art clean room to culture cells for human application. The result is researchers are now one step closer to being able to start phase 1 studies in patients of a revolutionary way of regenerating nerve cells.

David Choi, Reader in Neurosurgery, Brain Repair & Rehabilitation, is researching the use of cells from the lining of the nose to repair damaged nerves in the spinal cord.

The aim is to use olfactory ensheathing cells (OECs) from the lining of the nose to improve the surgical repair of brachial plexus avulsion, an injury common in motorcycle accidents when the nerve roots are pulled out of the spinal cord and the arm is left paralysed and senseless. In animal models, when OECs are transplanted to the site of nerve root injury, dramatic improvements are seen in walking and forelimb activity.

The clean room will be used to culture OECs under controlled conditions so that human trials can start. This phase I study will be to check proof of principle and will involve a relatively small number of patients – 15 patients undergoing treatment and 15 as controls. It is possible that an improvement might be found of around 10-20%.

Why researchers are looking at cells from the nose

Researchers are investigating the possibility of regenerating the central nervous system following brachial plexus avulsion.

The central nervous system does not generally encourage nerve cells to grow, but instead forms a barrier in response to injury in an attempt to prevent seepage of axons and loss of cytoplasm.

The effect of this is the prevention of regeneration across the peripheral-central nervous system.

However, regeneration does occur in the region at the top of the nose and bottom of the brain. By obtaining cells called olfactory ensheathing cells and transplanting them to the site of injury it may be possible to regenerate nerve cells from the peripheral to central nervous system.

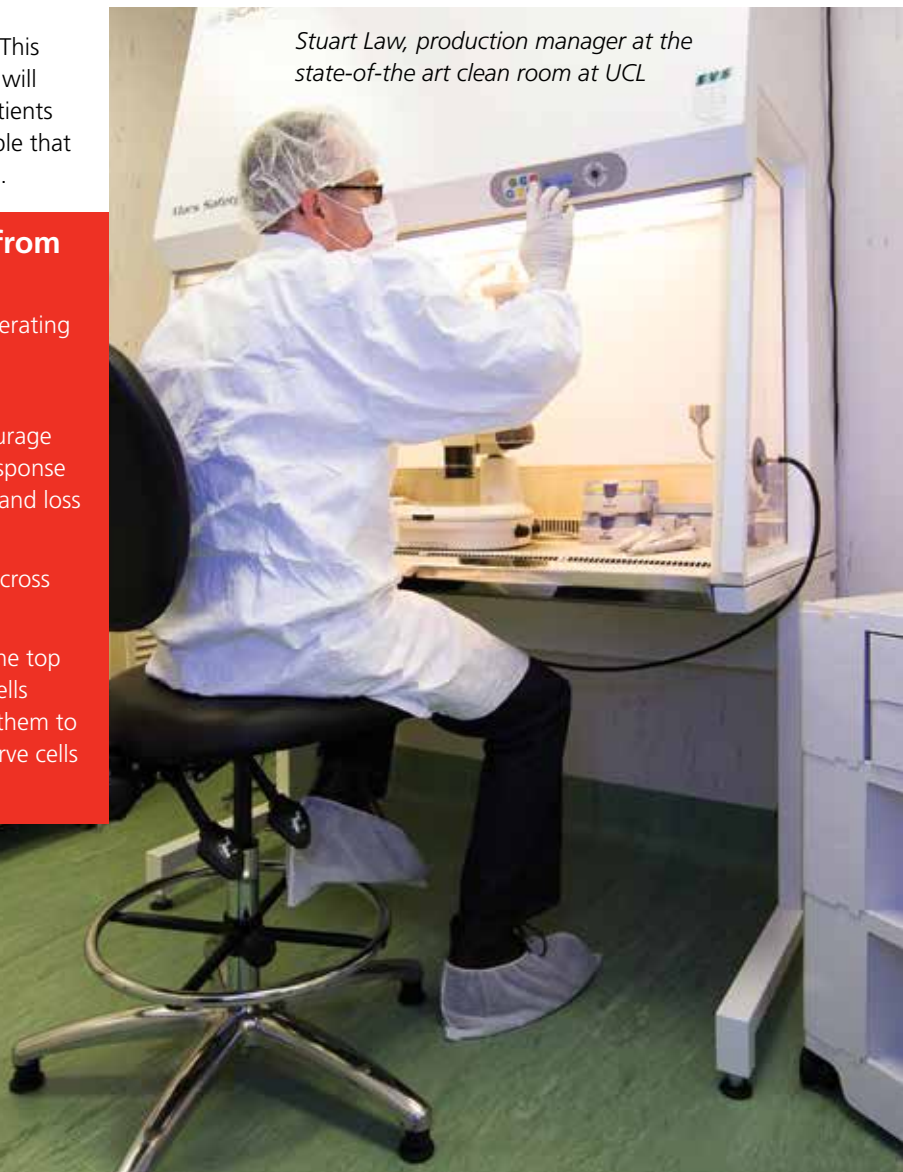
The role of the clean room

As these cells are classified as an Advanced Therapy Medicinal Product (ATMP) by the Medicines and Healthcare products Regulatory Agency (MHRA), the clean room must be a pharmaceutical level cell culture facility for cell production and meet Good Manufacturing Practice (GMP) regulations.

Although clean rooms are common in pharmaceutical research, they are not common in healthcare settings. The room at UCLH/UCL, which has two culture hoods, opens up the possibility of other groups using it to culture batches of cells.

David Choi said: "There is much work looking at how to grow and perpetuate cells, how to make them pure and remove those that are not required. Clinical work will move in parallel, by applying those technologies and pushing the frontiers of experimental medicine."

Stuart Law, production manager at the state-of-the-art clean room at UCL



Post doctoral research associates Dr Eva Galante and Dr Kerstin Sander in the radiochemistry lab at UCL

Radiochemistry lab for research

A state-of-the-art radiochemistry facility at UCL has enabled researchers to develop important new ways of manufacturing the radiotracers that researchers and clinicians use in nuclear imaging of the body.

Nuclear imaging of the body is key when researchers are looking at drugs at a very early stage of their development or studying how diseases operate. It is also key when monitoring the effects of gene therapy.

BRC funded lab

The radiochemistry facility was built at the UCL Campus in 2010 with funding from the biomedical research centre (BRC) and the Higher Education Funding Council for England (HEFCE). The facility houses the UCL radiochemistry group, which is a collaboration between the Department of Chemistry and Division of Medicine at UCL and University College London Hospitals NHS Foundation Trust.

The aim is to bridge expertise across chemistry, biological sciences and medicine to develop methods for labelling and coupling molecules (bioconjugation), to support preclinical imaging and translational studies and to develop tracers for diagnostic imaging.

The new lab meant the chemists and biologists could work together to develop new compounds in the laboratory and show how they could be quickly and efficiently manufactured. Importantly, the investment has leveraged further funding to establish facilities at UCL to manufacture radioactive compounds for use in imaging.

Groundbreaking work on radiotracers

Researchers have been developing radiotracers – small amounts of radioactive material – for use in diagnostic imaging. The team recently developed a method for producing tracers that is technically straight forward, but high yielding and robust. The method allows rapid access to highly functionalized tracers.

This speed is crucial. Radiotracers are designed to accumulate in the body and visualize the disease processes happening. Once the tracer has been administered, a specialized (gamma) camera is used to detect the radiation throughout the body. Distribution of the radiation gives information about disease.

However, because the radioactivity decays quickly it is important that the tracers are synthesized rapidly and used immediately. The efficient preparation of radiotracers with the right biological properties is challenging.

Work on tracers at the lab – the science

Researchers recently developed a high-yielding method for producing tracers. What they did was develop a novel three-component labelling reaction for the formation of trisubstituted iodotriazoles directly from aqueous radioactive iodide, and the parent azide and alkynes.

They used the method to prepare dual optical and nuclear labelling reagents, and demonstrated imaging of antibody distribution from the cellular level to the whole body (multiscale imaging).

The group has also made progress on new ^{18}F chemistry, which is currently implemented for development of metabolic tracers for imaging of drug efflux pumps. They are also working on tracers for imaging of voltage-gated sodium channels, the development of novel analgesics, and multimodal (SPECT/MR) imaging agents for inflammation.

Recent publications include:

- Yan R, El-Emir E, Rajkumar V, Robson M, Jathoul AP, Pedley RB and Årstad E*. One-pot Synthesis of a ^{125}I -labeled Trifunctional Reagent for Multiscale Imaging with Optical and Nuclear Techniques. *Angewandte Chemie Int Ed.* 2011; 50(30): 6793-6795.
- Yan R, Sander K, Galante E, Rajkumar V, Badar A, Robson M, et al. A one-pot three-component radiochemical reaction for rapid assembly of ^{125}I -labeled molecular probes. *J Am Chem Soc.* 2013 Jan 16;135(2):703-9.

Filed patent applications with UCL Business plc:

- Arstad E, Yan R (2012) Processes for producing radiohalogenated bioconjugates and products thereof, WO2012022932 (A1).
- Arstad E and Sander K (2012) Light Activated Fluorination, GB 1218352.1

Grants/leveraged funding:

- New project grant income of approximately £8 million



Dr Marios C. Yiannakas looking at scans at the NMR Research Unit, UCL

Innovative imaging in MS research

Imaging is a key tool for understanding, diagnosing and treating multiple sclerosis (MS) and funding from our biomedical research centre (BRC) has enabled researchers to look at groundbreaking new ways of using imaging in research.

MS is the most common disabling neurological disease of young adults in the UK, affecting 1 in 800 of the population, and is associated with very large health and socioeconomic costs.

A capacity building award of nearly half million pounds was made to Professor David H. Miller to work on the use of magnetic resonance (MR) imaging to help identify disease modifying treatments and to improve early diagnosis in MS.

Professor Miller's research has helped the MS imaging group at UCL's Institute of Neurology advance international progress in the field. For instance, a team of clinicians, physicists and a statistician have been developing sensitive methods of imaging the effects of MS during its evolution. Imaging measures have already provided a useful tool for researchers when trialling experimental treatments to prevent inflammation.

Current research is focused on developing imaging techniques to detect treatments that protect and repair nerves (neuroprotective and reparative treatments).

New proof-of-concept trial designs have been developed that use imaging measures to detect neuroprotection. Metabolic imaging techniques have been used to measure sodium and perfusion. These techniques may enable clinicians to identify pathophysiological events at an early stage when interventions are likely to benefit patients the most.

The capacity building funding has enabled researchers to leverage new grants from funders such as EPSRC, the National Institute for Health Research, the MS Society and industry partners.

Researchers also worked closely with members of the MS Society who helped appraise research proposals.

Commenting on the completion of the award, Professor Miller said: "The award set in place a process whereby a number of researchers could engage with new approaches in MR imaging especially of relevance to neuroprotection and repair in MS."

Transforming neuromuscular experimental medicine

Funding from our biomedical research centre (BRC) has been key to bridging the gap between basic science and clinical outcomes for some of the most serious muscle wasting neurological diseases such as muscular dystrophy and peripheral neuropathies.

Investment by the BRC into the MRC Centre for Neuromuscular Disease at UCL has enabled researchers to build up an invaluable research infrastructure, a tissue bank, patient cohorts and education and training.

Although diseases like muscular dystrophy, muscle channelopathies, mitochondrial diseases and peripheral neuropathies are individually rare diseases, together they affect over 100,000 people in the UK causing life-long disability or premature death.

BRC investments

The BRC originally invested half a million pounds five years ago and with this funding Director of the Centre Professor Mike Hanna and his team were able to raise a further £1.5m to establish a world class neuromuscular experimental trials facility. The facility, which opened in 2009, includes state of the art equipment to accurately assess and measure muscle function and neuromuscular phenotypes in neuromuscular disease patients.

The cohorts of patients studied in the centre have subsequently been involved in a range of natural history studies and experimental trials over the last 5 years.

More recently the BRC has awarded over £350,000 contingent on renewal of the MRC Centre for five years from 2013. With over £3million of new MRC funding, this joint UCL Newcastle Centre is one of the MRC's flagship translational research centres.

How the centre has enabled a step change in neuromuscular disease research

- The number of patients in experimental clinical trials of new gene therapies and repurposed drug therapies rose from just 20 to over 250.
- Two experimental trials centres were set up in the north (Newcastle) and south (UCL) of England.
- Researchers have been able to establish national cohorts of patients for experimental medicine and natural history studies. These cohorts are classified (stratified) according to clinical and genetic features. The number of people in these national cohorts has shot up from a mere 240 in 2008 to over 3,000 in 2013.
- A national neuromuscular tissue biobank has been developed giving translational scientists nationally and internationally access to over 1,800 human muscle cell lines for preclinical therapy evaluation.
- The centre has developed a bespoke four year translational research PhD programme with 16 students so far graduating with PhDs.
- The centre's MRI biomarker programme has been shown to be a reliable and sensitive method of identifying early disease stages and assessing disease progression and treatment responses. Over £1m in industry support has been leveraged for joint biomarker studies.

Professor Hanna said "The BRC support linked to the MRC Centre award has enabled a genuinely national experimental medicine strategic approach to be developed in neuromuscular diseases."



L-R Research nurse Iwona Skorvpinska and physiotherapist Magda Dudzic at the MRC Centre for Neuromuscular Disease at UCL

Experimental medicine highlights of the centre include:

- An international randomised control trial repurposing a cardiac drug in patients with genetic muscle channelopathies had strikingly positive patient reported outcome results, leading to a successful European Medicines Agency orphan status application for the use of this drug in this rare disease patient group. *JAMA* 2012 with editorial commentary *A triumph of rare diseases research JAMA* 2012
- First in human studies led by Professor Francesco Muntoni using antisense oligonucleotides to successfully correct dystrophin deficiency in Duchenne Muscular Dystrophy *Lancet* 2011 – paving the way for larger scale clinical trials.

L-R Jo Williams and Saadia Rahman of the Clinical Infection Research Team with MB PhD student Lucy Bell

Investing in human infrastructure

The ability to respond quickly to research developments depends on having people capacity at the ready. No amount of equipment and financial resources will work if the human infrastructure – people – is not there too.

In infection and immunity research, a capacity building initiative by our biomedical research centre (BRC) has given UCL and UCLH researchers the flexibility to go that one step further – including solving one of biomedicine's more recent cases of mistaken identity.

The BRC invested £450,000 to set up the Comprehensive Infection Research Centre for Investigation, Translation and Training (CIRCITT). The aim of the centre is to help develop individual researchers and research teams.

One of the first things the centre did was establish a post doctoral research post which was not tied to a specific research project. Eleanor Gray, whose post was embedded in clinical services, worked on a range of projects including looking at the host proteins preventing HIV activation in humans and studying chlamydia.

Solving the mystery of mistaken identity

It was the unusual flexibility of her post that meant Eleanor could respond quickly when the world of retrovirology was rocked in 2010 by a convoluted tale of mistaken identity.

US researchers claimed to have discovered that the xenotropic murine leukaemia virus-related virus (XMRV) was the cause of chronic fatigue syndrome (CFS). The implications were huge, especially if it was concluded antivirals could be used to treat CFS patients.

Eleanor and her colleague Dr Stephane Hue, a phylogeneticist, were able to respond quickly using reagents designed to identify XMRV in samples from patients in the US. In what has been described as an 'elegant' study, the researchers showed that the sequences of XMRV found by their US colleagues were actually consistent with laboratory contamination.

The publication from Hue, Gray et al is the 14th most accessed publication for the journal *Retrovirology* and an important contribution to the body of evidence against the inappropriate treatment of patients.

Research nurses to the ready

CIRCITT has also set up a Clinical Infection Research Team. This team provides cross-cover for clinical infection and immunity research, and includes a coordinator to help with ethics and governance applications.

The team is now a self-sustaining resource and supports 15 UK Clinical Research Network (UKCRN) Portfolio registered projects on topics ranging from the influence of worm co-infection on TB, to the effects of aging on the skin immune system.

The team also recruits patients and collects samples for the Fever at the Front Door collaboration which is being extended in an initiative called 'NIHR Bioresource Adult Infectious Diseases: BioAID' across five biomedical research centres. The aim is to build up a massive research databank of samples from patients with infectious diseases.

CIRCITT has also supported a new research team set up by infectious disease clinician Dr Ravi Gupta to look at whole genome sequencing strategies in HIV.

Four new clinical research posts have been created by leveraging external funding:

- Dr Gabriele Pollara received a Wellcome Trust post-doctoral clinical fellowship to investigate how an individual's immune system determines whether or not they are protected from TB in its active disease form.
- Dr Jennifer Roe was awarded an MRC clinical training fellowship to investigate the potential for vitamin D treatment to enhance immune defense against TB infection.
- Dr Rachel Byng-Maddick is the recipient of an Arthritis UK clinical research fellowship researching whether one group of immune cells weakens people's defense against TB.
- Dr Jimstan Periseleris received an MRC clinical research training fellowship to investigate the importance of the inflammatory response generated by the outer layer (capsule) of the bacteria causing pneumonia and meningitis *S. pneumoniae*.

State of the art scanner time for research

An MRI scanner may not be unusual in a hospital trust. But a scanner with 50% of its usage devoted to research is special.

Investment by our biomedical research centre (BRC) in a 3T MRI research facility at UCLH has meant researchers and clinicians have been able to set up some of the most innovative research into tracking the progression of disease and predicting how patients will respond to different kinds of treatment. The MRI scanner provides a more sophisticated understanding of the effect treatments have on diseases such as cancer.

The UCLH 3T MRI Research Facility scanner was installed in April 2011. The BRC funded 50% of the purchase and installation costs and a tapered grant to cover running costs for a period of three years. Half of the scanner usage is devoted to research.

The five ton scanner provides detailed, high definition images of tissue – without the patient being exposed to radiation. The ability to image the microstructure and function of tissues using the scanner enables research into ways of improving diagnosis and management of disease.

For instance researchers can study the tiny changes to the structure and function of tissue which precede larger more obvious macroscopic changes to the anatomy.

The facility has been pivotal in developing research projects focusing on scanning techniques which are not routinely available but show promise or have been successful in pre-clinical models.

The 3T MRI scanner at UCLH

Research using the scanner

Multi-parametric (mp) MRI is a technique that uses a combination of images to show tissue anatomy together with cells and vessels (cellularity and vascularity). Using mp MRI could enable clinicians to accurately stage patients newly diagnosed with prostate cancer, as well as guiding biopsy and indicating where a biopsy isn't necessary.

The addition of new functional MRI techniques such as diffusion and dynamic contrast enhanced imaging can give a more accurate assessment of where prostate cancer is located and the benefits to patients of this technique are being investigated as part of an ongoing multi-disciplinary study ('PICTURE' study).

The team is extending this approach to develop multi-parametric whole-body MRI techniques to stage and assess treatment response of metastatic disease ('MASTER' study). The technique is being evaluated for multiple myeloma, lymphoma and prostate cancers.

Researchers are exploring the development of novel types of imaging techniques. Projects include:

- **Assessing functional MRI techniques in cancer staging, treatment follow-up and prognostication**
Initial work is looking at the use of MRI as a biomarker of response to treatment novel therapies. Simply measuring changes in the size of a tumour is not a sensitive way to assess treatment response. Investigators are looking at techniques like 'perfusion MRI' (dynamic contrast enhanced MRI) and arterial spin labeling (perfusion imaging without the need for contrast agent).
- **Measuring extra-cellular volume using equilibrium (EQ) MRI**
Changes in what is called the extracellular volume fraction (ECV) of tissue can be indicative of pathology and have been shown to influence tumour aggressiveness and treatment response. Researchers are developing EQ-MRI to allow ECV measurement of tumours.

Revolutionary technique for studying virus DNA

Sometimes trying to deal with the practical challenges posed by research in one area can lead researchers to find new techniques that have widespread application with dramatic and far reaching results.

This is what happened when Professor Judy Breuer, with a grant from our biomedical research centre (BRC), tackled the particular problems of studying the varicella zoster virus or VZV. Professor Breuer and her team ended up developing a powerful new tool that could bring about a new era in patient diagnosis and infection control.

The problem of a small virus

Professor Judy Breuer is a clinical virologist looking for ways of preventing people from getting infected with the virus that causes chicken pox and shingles, and stopping the nerve pain associated with shingles.

The work of virologists like Professor Breuer depends on being able to collect the virus from an infected person and looking at what is called the whole viral population in the laboratory. Like the human population, the viral population is made up of individual viruses each of which can be slightly different to the others. Sometimes only a proportion of the population is responsible for a particular effect.

In this instance Professor Breuer wanted to find out if some viruses were responsible for causing pain in people with shingles. However, VZV is difficult to study. Firstly because the viral particles are very tightly associated with human cells, so it is difficult to isolate viral DNA without 'contamination' by the person's own DNA.

The other problem is VZV particles are extremely small – you could fit 100 of them lined up on the surface of a single grain of talcum powder – and so the viral DNA only makes up a tiny proportion of the total sample and is difficult to separate from the rest.

Although virologists may amplify the virus, the techniques create problems – synthetic copies introduce 'mistakes' and viruses cultured in the laboratory are artificial and so may favour one population over another.

Finding a better solution

Professor Breuer and her team looked at ways of overcoming the limitations to studying VZV. They began by cutting up all of the DNA in samples of blood, saliva and the fluid from chicken pox rash spots. Then they used a set of virus-specific tags that work like miniature stretches of 'Velcro' to pull pieces of viral DNA out of the clinical samples, leaving the human DNA behind.

The researchers combined this targeted 'fishing' approach with the high throughput next generation sequencing technique for DNA analysis and developed computer software to analyse the data. They found they could build up a picture of exactly what the viral population looks like in a clinical sample.

This breakthrough was exciting because the technique has clinical applications for other pathogens, such as the organisms that cause TB, Influenza A and norovirus.

Next steps

Researchers are now building on this initial proof of concept work and developing the technique. The implications are exciting and far reaching.

Professor Breuer is leading a European project to develop the technique for clinical application. The aim of the €7m 'PATHSEEK' project is to develop the system for rapid isolation and sequencing of pathogens from clinical samples within 24-48 hours.

This kind of system will not only give clinicians all the information they need to make a diagnosis, but also provide information on drug resistant mutations.

On a wider scale, this will help public health initiatives by determining the relationships between infections from different patients, so that community clusters of disease can be identified, and chains of person to person transmission broken.





Scanning during brain surgery

Funding from our biomedical research centre (BRC) has not only helped put UCLH and UCL researchers at the forefront of research into imaging in brain surgery but has had a direct impact on improving patient outcomes.

The BRC awarded £900,000 to enable the creation of the Angio MR Interventional Suite (AMRIS) by converting an MR suite at UCLH/UCL into a fully functioning operating theatre.

AMRIS is an internationally unique facility combining within the same operating theatre room, an MRI scanner, an x-ray system to examine blood vessels and a computer system with display of imaging data for the surgeon. The suite enables brain scans to be performed during brain tumour surgery. Over the past three years, patients with intracerebral tumours, epilepsy and movement disorders have all been operated in this suite.

What makes AMRIS so special

The combination of advanced medical imaging to guide surgery is commonly referred to as neuro-navigation and is increasingly used as a standard supporting technology for brain tumour surgery to accurately identify the edges of tumours and other functionally crucial brain regions which must be avoided during surgery.

However, these techniques usually rely on brain images obtained before the operation – they do not take account of changes in the shape of the brain which occur during and as a result of the surgery. The AMRIS facility enables brain scans to be performed as surgery proceeds so these changes can be taken into account.

Improving patient outcomes

As might be expected patients undergoing surgery to remove brain tumours benefited from this environment. Reimaging the patients during surgery allowed the neurosurgeon to assess if and how much tumour still needed to be removed. This meant the neurosurgeon could be as radical as possible in removing the tumour while preserving the functional status of the patient.

In epilepsy patients with the condition hippocampal sclerosis, which involves severe loss of neuronal cells, the classic surgery aims to remove the cause of the epilepsy while preserving the vision, which could be affected by the intervention. Researchers and surgeons using AMRIS have now shown that to preserve vision, it is important to visualize the relevant optic pathways. The effect of the movement of the brain (shift) during surgery is less relevant. This finding is important as it suggests that to improve outcomes, it is important to disseminate specific advanced imaging techniques (tractography) and that it is not necessary to carry out intraoperative MRI.

For patients with movement disorders, undergoing deep brain stimulation, AMRIS had a significant impact as it allowed a doubling of the number of patients having this treatment.

In terms of current research activities, researchers are in the process of establishing an intraoperative imaging protocol to perform fMRI and tractography in the AMRIS – which should further improve surgical outcome in patients with tumours.

Commenting on the award, Professor Tarek Yousry, of the Brain Repair and Rehabilitation Department at UCL, said: “The BRC grant was vital as leverage in part of a larger UCL/UCLH ‘Joint MR Project’ totaling around £15m involving the National Brain Appeal, the Wolfson Foundation, and the DRG”. He went on to say: “This project has consolidated the leadership role our institution plays in MR research.”

Translating new science into therapies

It is all very well having fantastic science happening in laboratories, but the challenge is to make sure these scientific innovations and discoveries are quickly translated into therapies and treatments that have a direct benefit for patients.

Our biomedical research centre (BRC) has played a key role in drawing attention to research that translates scientific breakthroughs into patient benefit and in leveraging badly needed funds for this crucial research at UCL and UCLH.

Filling a funding gap and attracting more money

In 2010 the BRC committed up to £500,000, in two tranches, to establish the UCL Therapeutic Innovation Fund (TIF), which aims to stimulate the development of a pipeline of high-quality therapeutic projects.

The fund has played a pivotal role in the development of UCL's translational pipeline. Over 100 Principal Investigators have applied to the fund and several of these are now being actively supported in developing their translational research and seeking further funding.

Around one third of the applications focussed on small-molecule discovery and this high demand for support was key in helping us to secure further funds from the Wellcome Trust Institutional Strategic Support Fund to recruit two medicinal chemists into the Translational Research Office.

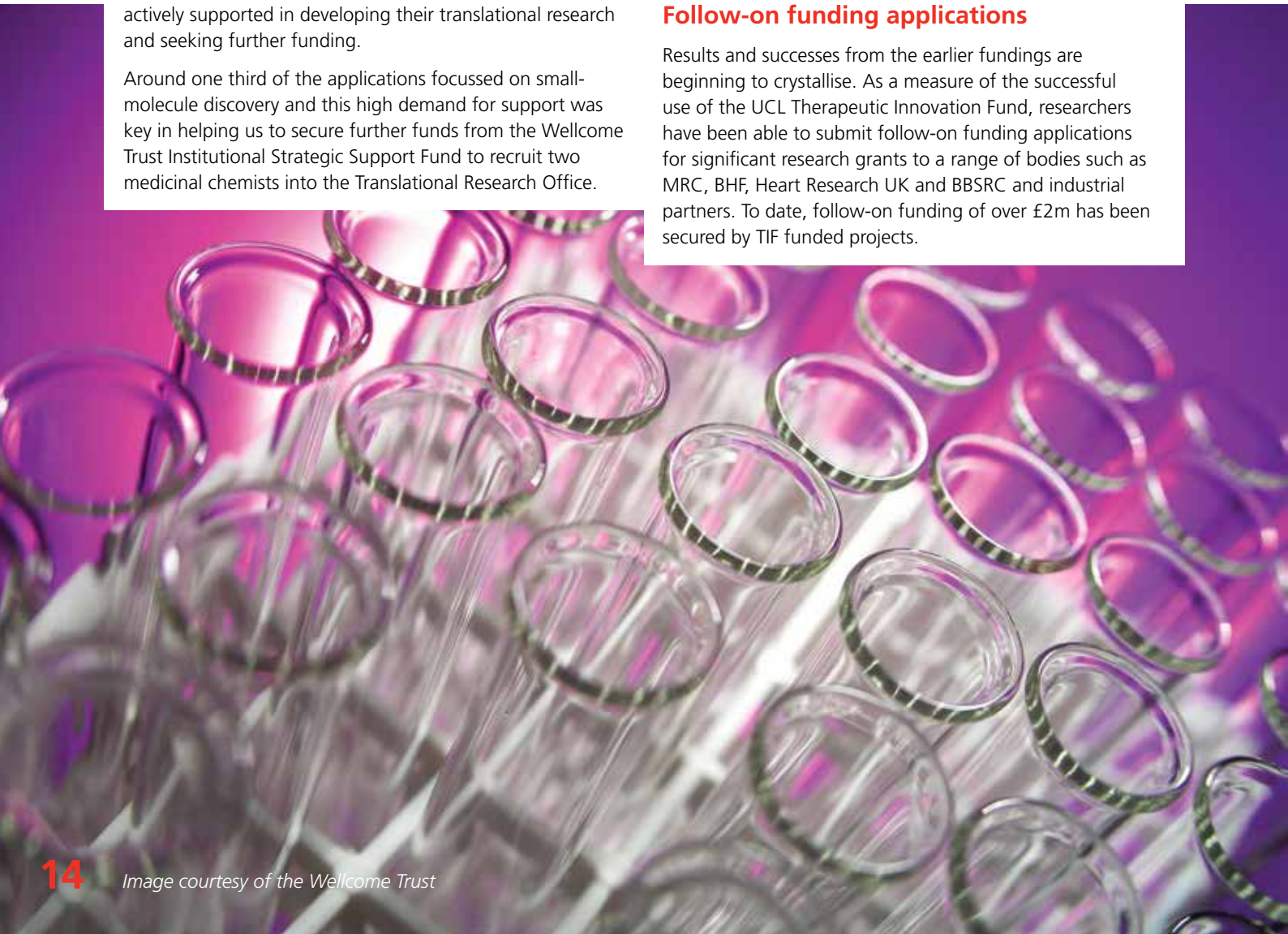
Moreover, as a result of the leverage provided by the BRC contribution, additional funds were secured for the fund from the NIHR Specialist Biomedical Research Centre for Ophthalmology, the Wellcome Trust, the Rosetrees Trust medical charity and UCL Business. This enabled a third call and six more projects were awarded funding to start in 2012. In total, 16 projects have been funded at a cost of almost £800,000.

The establishment of the UCL Therapeutic Innovation Fund was in the vanguard of responding to the gap in funding available to the early stages of moving from discovery into translation. Other institutions and funding bodies are now waking up to this need. For example, in 2012, Imperial College launched its Therapeutic Primer Fund with support from the Imperial NIHR Biomedical Research Centre and Imperial Innovations. More recently, the MRC has launched its 'Confidence in Concept' scheme.

UCL's experience with the UCL Therapeutic Innovation Fund stood it in excellent stead in successfully applying for a £700,000 fund to operate alongside the TIF, following much the same operational principles.

Follow-on funding applications

Results and successes from the earlier fundings are beginning to crystallise. As a measure of the successful use of the UCL Therapeutic Innovation Fund, researchers have been able to submit follow-on funding applications for significant research grants to a range of bodies such as MRC, BHF, Heart Research UK and BBSRC and industrial partners. To date, follow-on funding of over £2m has been secured by TIF funded projects.







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