UCL’s School of Life and Medical Sciences encompasses arguably the greatest concentration of biomedical science and population health expertise in Europe. Our performance in the UK’s last Research Assessment Exercise was outstanding, and for most key measures the School comfortably tops UK league tables.

In part because of UCL’s size and organisational complexity, the scale of the School’s achievements is not always apparent. This publication, one of six, seeks to address this. Our recent reorganisation, with the creation of four new Faculties, has been designed to create a more coherent structure. But the School’s restructuring has also placed great emphasis on cross-Faculty interactions and interdisciplinary research – and indeed on interactions with UCL departments outside the School. Such interdisciplinary endeavour is promoted through ‘Domains’, inclusive strategically led fluid networks.

Moreover, UCL is acutely aware that scientific advance of real relevance to society is aided not only by an interdisciplinary approach but also through collaborative strategic alliances with other research-intensive institutions with complementary strengths. Our founding partner status in the new Francis Crick Institute engages us in what will be the European powerhouse of biomedical research expertise. Our links with our London Academic Health Science Centre partners also include our joint engagement together with the Medical Research Council in a new imaging company, Imanova, and our highly productive links to the health service, through UCL Partners, provides access to unmatched clinical expertise and large patient groups.

We are fortunate to be partners in three National Institute for Health Research (NIHR) Biomedical Research Centres and an NIHR Biomedical Research Unit in dementia, the principal focus of which is experimental medicine.

The breadth and quality of our research is one in which intellectual curiosity can prosper, while a high priority is also given to the practical application of knowledge to improve health and quality of life. This can take many forms, including commercialisation of new products as well as developing and informing health and social policy, and engaging with important stakeholders, including the public. UCL’s wholly owned subsidiary, UCL Business, ensures that discovery really does lead to new treatments and diagnostics and that our translational endeavour supports the UK’s Life Sciences Strategy.

This publication, one of six (see right), showcases some of the enterprising work being carried out within the School and in collaboration with external partners. It is impossible to be comprehensive, but the stories give a flavour of the breadth, quality and impact of the School’s work in this area. Looking forward, our aims are to enhance and expand our research to ensure we remain a global leader, and to see more people benefit from the groundbreaking research being carried out across the School.

Sir John Tooke
Vice-Provost (Health) and Head of the UCL School of Life and Medical Sciences.
Overview: Enterprise
Capitalising on intellectual assets to improve the world.

Section 1: Drugs of the future
Using greater biological understanding to develop a new generation of pharmaceutical interventions.
Feature: Translation by numbers

Section 2: Diagnostics and imaging
The detection and characterisation of disease has an increasingly important role to play in modern medicine.

Section 3: Repair and regeneration
Advances in multiple disciplines are combining to create a new wave of replacement body parts.
Feature: Clinical infrastructure

Section 4: Innovative therapies
Genes, cells and neuropsychology are all being used as the basis for innovative new therapies.

Section 5: Using knowledge
The ideas, expertise and knowledge of UCL researchers are being put to a wide variety of good uses.
Feature: The ABC of UCL Enterprise

UCL institutes, support services, partners, funding and sponsors.
Enterprise is a ‘win–win–win’ activity, benefiting host institutions, researchers and, most importantly, people and society.

Alongside research and education, enterprise is a core activity of UCL. Enterprise has close links to impact – it is one of the most important routes by which intellectual endeavour can influence the world outside academia. In the life and medical sciences, that generally means enhanced health and wellbeing.

Enterprise brings a financial perspective to research. Universities have traditionally set great store on ‘research income’ as an indicator of research strength. Yet, although it is also widely recognised that investment in research delivers economic benefits, only recently have universities begun to pay more attention to the financial returns that research can generate. Such income streams can, of course, support the core activities of research and education, and enable an institution to achieve yet more.

The UCL approach to enterprise is to capitalise on its intellectual strengths – individuals whose ideas have the potential to make a real difference to the outside world. The aim is not to provide a high-tech support service for industry but to work jointly with commercial partners to develop ideas and products. It recognises that to achieve lasting impact, medical advances typically need to be developed and packaged in a way compatible with health service delivery or other social structures. Commercial engagement is likely to be the route by which this is achieved.

UCL is unusual in having a well-established enterprise strategy and an institutional office dedicated to promoting enterprise activity. The UCL School of Life and Medical Sciences’ enterprise strategy complements this institutional approach, and considers how it can best be applied in health and life science fields. There is a strong emphasis on engagement with the pharmaceutical industry and biotech sector, both thriving areas in the UK, though there are increasingly opportunities for application in other domains.

Medical device development is another area of strength, reflecting close links with the UCL Faculty of Engineering. Indeed, a recurrent theme in translation and enterprise is the importance of interdisciplinary interactions. A further important factor in clinical translation is the close relationship with NHS bodies achieved through UCL Partners, its associated clinical research infrastructure providing unmatched opportunities for experimental medicine and first-in-human studies.

A changing landscape

The drive to enhance translation and boost enterprise activities reflects a radically changing life science innovation landscape. Funding for translational activities has increased markedly, from government, charity and European sources. Clinical research infrastructure has been established to enhance opportunities for research on patients.

Notably, the pharmaceutical industry has made significant changes in its approach to research, with recognition that a lack of understanding of biological mechanisms is a major obstacle to the development of new medicines. Increasingly, it is looking to establish collaborations with academic partners, and to operate in pre-competitive space in ‘open innovation’ partnerships. Biotech companies occupy an important niche, often serving as the sites in which emerging technologies can be developed and moved towards market, with government and European funding specifically encouraging academic–company link-ups.

UCL in general and the UCL School of Life and Medical Sciences in particular have been at the forefront of activities in this changing landscape. It has strong partnerships with numerous world-leading pharmaceutical companies and with innovative small and medium-sized enterprises.
Within the UCL School of Life and Medical Sciences, an important role is played by the Translational Research Office, which includes staff with industry expertise and coordinates interactions with the life science industry, manages a substantial portfolio of translational projects, and runs the School’s translational grants schemes.

Imagination and innovation

Therapeutic development remains central to modern medicine. Through high-quality research into basic biological mechanisms, UCL researchers have identified myriad opportunities for therapeutic intervention. Many are now actively involved in translation of these findings, developing new small-molecule and biological interventions in-house and with industry partners.

The UCL School of Life and Medical Sciences also has an outstanding track record in the development and application of innovative forms of therapy. It has run world-leading trials in gene therapy and cell-based treatments, and pioneered new approaches in regenerative medicine. It is also highly active in the areas of diagnostics and medical devices.

One common theme is that enterprise is not an individual activity. Capitalising on ideas, and seeing them make a practical difference in medicine or in society, depends on coordinated teams, each team member bringing different attributes and expertise to the table. Often these skills lie outside the academic world, requiring relationships to be built with clinical colleagues and those in industry. It is this collective action that ultimately leads to success.

Furthermore, translation is rarely a ‘quick win’. As well as a smart idea and team-working, successful translation requires a dogged determination, a commitment to patients not just the next paper, and the ability to adapt when initial plans do not work out.

Universities have the intellectual firepower to change the world. Being enterprising – thinking creatively, identifying how change can be achieved, working with others towards common goals, making things happen – is a critical way in which this potential can be realised. Ultimately that is good for the university, for patients and people globally, and for the people that make it happen.
Greater biological understanding is paving the way to a new generation of pharmaceutical interventions.
It is widely recognised that greater biological understanding will lie at the heart of future pharmaceutical development – and that institutions such as UCL carrying out high-quality research will be fundamental to this endeavour. Accordingly, the pharmaceutical industry has moved to increase its engagement with the academic sector. Industry is now more focused on partnerships with academic teams, even in ‘pre-competitive’ space and through the principle of open innovation – contributing to and drawing upon global pools of knowledge rather than just in-house expertise. Also critical to this new landscape is the biotech sector, with SMEs often undertaking the first stages of drug development with academic partners.

UCL has been an enthusiastic contributor to this new model. It has established large-scale partnerships with several pharmaceutical companies, set up its own spinout companies and worked with many SMEs in the UK and internationally.

One of the most notable is a pioneering partnership between UCL and the Eisai pharmaceutical company, driving forward the development of novel therapeutics for neurodegenerative diseases. While UCL provides unmatched scientific expertise and numerous leads for the development of new therapeutics, Eisai brings the experience and expertise of drug development, including assay development and medicinal chemistry as well as regulatory and clinical expertise, that will be required to bring new products to market.

The Leonard Wolfson Experimental Neurology Centre, funded through a £20m award from the Leonard Wolfson Foundation, provides an ideal facility in which the most promising can be tested in proof-of-concept trials in patients. Unusually, the initiative will see interdisciplinary teams of academic and industry researchers put together to work on promising areas of translational research. Over time, a portfolio of development projects will be established. In line with commercial principles, projects will be subject to ‘go/no-go’ decision-making, with researchers redeployed to alternative projects if a project is terminated. One of the first projects being developed through this partnership is being led by Professor Michael Duchen (see page 6).

The School has also established several joint initiatives with GlaxoSmithKline. For example, a partnership has been established between GSK and Pentraxin Therapeutics Ltd, a UCL spin-out company that holds intellectual property relating to the research of Professor Sir Mark Pepys. Professor Pepys has been developing agents to treat rare forms of amyloidosis, build up of abnormal protein aggregates in body tissues.
GSK is also collaborating with Professor John Collinge, Director of the MRC Prion Unit at UCL, on possible therapeutics for prion disease. Professor Collinge has established that preventing the conversion of cellular prion protein to a toxic and transmissible form could slow or prevent the onset of prion diseases such as Creutzfeldt–Jakob disease. With GSK, he is exploring the potential of small-molecule ‘chaperones’ that protect the natural cellular protein.

GSK has also been working for several years with Professor Rachel Chambers and colleagues in the CRAFT consortium, developing potential new therapies for lung fibrosis (see page 7). Professor Chambers is also leading a pioneering project being established at the Stevenage Bioscience Catalyst. Through this innovative partnership also involving the University of Cambridge, therapeutic development projects arising from university research are being established at the Stevenage Bioscience Catalyst, an open innovation campus where researchers will be able to gain access to a wide range of technical and business support, and network with other teams engaged in translational research.

Stevenage Bioscience Catalyst provides an environment in which the commercial development of projects can be accelerated. It will also provide academic researchers with invaluable exposure to the translational environment. As well as Professor Chambers’ project, another project based on a polymer developed by Professor Alex Seifalian will also be based at Stevenage.

One of the great strengths of the School of Life and Medical Sciences is the breadth of its high-quality research. To take advantage of this critical mass and to facilitate industrial collaboration, the FLARRE (Inflammation, Tissue Repair, Scarring and Fibrotic Disease) consortium has been established by Professor David Abraham to promote translational research in this area of growing pharmaceutical interest (see page 7).

**Developing ideas**

In-house support for translation is available through the Translational Research Office (see page 44), including MRC ‘Confidence in Concept’ target validation in drug development, one of these was chosen among the first UCL researchers to team up with Professor Michael Duchen and Dr Gyorgy Szabadkai to discuss with Dr David Miller in the Translational Research Office about the possibility of launching drug development work. The two strands came together, with Professor Duchen being selected to lead one of the first three projects to be progressed through the new partnership with Eisai.

During the course of his research, Professor Duchen has identified several possible targets for intervention. Through extensive discussions with Eisai, which brought its expertise in target validation in drug development, one of these was chosen as the basis of the new project. The critical pathway is one that, when activated, triggers a cascade of events that eventually leads to the death of the cell. It has been implicated, to varying degrees, in a range of conditions, including Parkinson’s disease, Alzheimer’s disease and multiple sclerosis, as well as tissue damage caused by oxygen deprivation.

The first stage of the project, says Professor Duchen, is to refine their assay of mitochondrial function. Using existing departmental high-throughput screening equipment, they will then screen an Eisai compound library to identify hits affecting their process of interest. Follow up of these hits will help to identify their specific molecular targets, while their effects in different disease models will guide decisions about potential conditions to be targeted.

Two newly appointed postdoctoral researchers will join the project. It will be run along industry lines, with clear milestones and ‘go/no-go’ decision points. In the event of a ‘no-go’, the two translational researchers will be moved onto other projects in the UCL–Eisai portfolio.

Professor Duchen is naturally hoping for a successful outcome but, he suggests, the project will also provide other benefits along the way. Because they will be using a cell-based assay, the screen will pick up hits in multiple pathways affecting the function of their molecular target, potentially generating a range of useful experimental tools.

Although he considers himself principally a basic scientist, Professor Duchen has a clinical background. He left medicine, he says, dismayed by the lack of options available in neurology. Twenty years on, he believes the understanding of mitochondrial biology has progressed to the stage where therapeutic strategies can be envisaged for a range of diseases. The partnership with Eisai is a major step towards this goal, for neurodegenerative disease and potentially other conditions.
Academic–industrial partnerships are kick-starting the development of new agents for respiratory disease.

Respiratory disease is the third biggest cause of death after circulatory diseases and cancer. It is responsible for some 70,000 deaths each year in the UK alone, and death rates have hardly changed over the past decade. The development of new treatments, in particular for interstitial lung disease, has been hampered by a poor understanding of key disease mechanisms. By working closely with industry, Professor Rachel Chambers and colleagues are generating new insight into disease processes and opening up promising avenues for drug development.

Professor Chambers has two main areas of interest: acute lung injury, typically leading to acute respiratory distress syndrome (ARDS), and chronic lung conditions leading to lung fibrosis. Encouraging progress is being made in both areas.

Fibrosis, the build up of fibrous connective tissue, is associated with repetitive tissue injury and inflammation in many organ systems. Until recently, fibrosis was considered to be driven by the underlying inflammatory response, with most therapeutic strategies focused on dampening inflammation. Now, however, there is growing awareness that there may be a point of no return where fibrosis develops independently of inflammation and is self-perpetuating. Therapeutic strategies will therefore need to focus on tackling fibrotic rather than inflammatory responses, not just in the lung but in many other organ systems, including the kidney and the liver.

Fibrosis is seen in a range of lung diseases, most of which lack effective treatments. One of Professor Chambers’ long-standing interests has been idiopathic pulmonary fibrosis (IPF). As its name suggests, the causes of IPF are unclear; some 5000 cases are diagnosed each year in the UK and most patients die within five years.

Under the umbrella of the multicentre public–private CRAFT consortium, which includes GSK, UCL, the Royal Brompton Hospital, and the Universities of Nottingham, Newcastle and McMaster, Professor Chambers has been leading a target discovery and validation group aimed at identifying new treatment paradigms for IPF.

A major focus of her team’s work, as part of the CRAFT consortium, has been focused on the role of one particular intracellular signalling pathway. Professor Chambers’ team established the scientific rationale for this approach, and successful preclinical studies paved the way for a proof-of-concept trial currently jointly being run at the Royal Brompton Hospital and UCL’s Institute of Nuclear Medicine. The close working relationship with GSK, which has seen secondments for both GSK and UCL staff, is currently being expanded to include other fibrosis teams at UCL.

Exciting progress is also being made by Professor Chambers’ team in identifying novel targets to interfere with neutrophilic inflammation in ARDS. Development of a novel therapeutic antibody against a target chemokine is currently being taken forward by a small team based at the Stevenage Bioscience Catalyst, which provides an open-innovation environment tailored to commercial translation.

Fibrosis, build-up of fibrous connective tissue, affects multiple organ systems and contributes to many diseases. Recent years have seen a resurgence of interest in fibrosis, with several pharmaceutical companies launching fibrosis programmes. To capitalise on this renewed interest, Professor David Abraham has established the FLARRE (Inflammation, Tissue Repair, Scarring and Fibrotic Diseases) consortium to promote joint ventures with industry.

Inflammation is an immune-mediated process designed to combat infection and promote tissue repair. Though generally beneficial in the short term, chronic activation of inflammatory systems leads to a wide range of conditions. Similarly, scarring and fibrosis are part of normal tissue repair, but excessive build up of fibrotic tissue can be highly damaging.

Inflammation and fibrosis can affect multiple tissues, including the lungs, liver, kidneys, muscle, skin and intestine. Although the specific features of disease vary according to the organ system involved, there are many commonalities. There is thus great value in fostering collaborations across disease areas, and to explore with industry the potential to translate insights from research into therapies that benefit patients.

Following a successful bid for Knowledge Transfer Champion funding, Professor Abraham set out to create a ‘one-stop shop’ enabling industry to access the wide-ranging excellence of UCL research across multiple disease areas. As well as all organ systems, UCL researchers have expertise in key technologies relevant to pre-clinical development, as well as access to clinical populations and experience of clinical trials. Through a single point of contact, industry can access the skills and experience of 20 or so world-leading groups.

A further aim has been to raise awareness of industry engagement among early-career researchers. Events with industry speakers and other initiatives are encouraging such researchers to consider how they might begin translating their research or developing links with industry.

Over the past year, Professor Abraham has been recruiting UCL groups to FLARRE, establishing a steering group, developing a web portal and setting out plans for an ‘investors’ day’. As well as enabling groups to showcase their research in short presentations, the investors’ day will also provide opportunities for networking and informal discussions about collaboration, for example through joint studentships or larger collaborations.

The consortium has already been developing a joint bid for MRC funding and Professor Abraham is hopeful that the investors’ day will trigger new collaborations. One area of particular interest, promoted by Professor Patricia Woo, is drug repurposing. FLARRE could be a platform for assessing new uses of existing drugs, accelerating the introduction of new medicines. Professor Abraham is also discussing the possibility of extending the consortium to other international centres. In addition, he suggests, the model could be adopted more widely to facilitate interactions with industry in disease-spanning areas sharing an underlying biology.
AN IMPRESSIVE CATCH
What began as a ‘fishing exercise’ has hooked Professor John Greenwood and Professor Steve Moss one of cell biology’s biggest fish.

In 2005, Professor John Greenwood and Professor Steve Moss had the unusual opportunity to choose a way to tackle a rare eye condition, thanks to the generosity of a philanthropic foundation. The project afforded the rare chance to undertake the kind of ‘fishing exercise’ frowned upon by funding agencies wedded to hypothesis-driven research. However, a search for genes showing abnormal expression in affected blood vessels in the eye threw up a host of interesting hits – leading not just to a Nature article but also to the beginnings of an extensive drug development programme.

The initial study led to the identification of LRG1, a potent stimulator of new blood vessel formation. Notably, though, it seemed to have a more important role in the disorganised blood vessel growth seen in disease than in the carefully orchestrated formation of blood vessels during development.

Following successful project grant funding from the MRC, these effects turned out to reflect LRG1’s action on the well-characterised TGF-β signalling pathway. TGF-β has been implicated in many cellular processes, and its action is highly context-dependent. LRG1 may be one of many factors influencing its action, tilting it in favour of pathogenic angiogenesis.

Aberrant blood vessel formation is seen in several conditions, including the wet form of age-related macular degeneration, the most common form of blindness in older people, and proliferative diabetic retinopathy. Angiogenesis is also a target of several cancer therapies, which block the formation of new blood vessels that tumours need to grow.

With translational funding from the MRC, Professor Greenwood and Professor Moss are generating a ‘humanised’ LRG1-blocking monoclonal antibody. In addition, with Proof of Concept funding from UCLB, they have been collaborating with Professor Dave Selwood, screening a chemical library to identify small molecule inhibitors of LRG1. Several interesting hits are being further characterised.

Professor Greenwood sees the work as an archetypal ‘bench to bedside’ project. The key aim is to identify basic mechanisms of disease, to assess the potential to intervene in critical pathways, and to develop targeted interventions. This has the twin benefits of shedding light on critical biological processes – in this case how new blood vessels are formed – while also generating potential new therapeutic agents. It is an approach he suggests is embedded within the Institute of Ophthalmology, and one that can be readily adopted by researchers whose primary interest is basic research.

The project generated a Nature article in July 2013 and has sparked considerable interest from the pharmaceutical industry. With UCLB, Professor Greenwood and Professor Moss are now considering which route to pursue for further commercialisation. The work has also generated a wealth of opportunities for further research, into the mechanisms of blood vessel formation and the action of one of cell biology’s most pivotal signalling pathways.

BREATHING LIFE INTO DRUG DISCOVERY
Driven by a passion to deliver new medicines, Professor Margaret Ashcroft takes a hands-on approach to academic drug discovery.

After identifying a target, some may want to leave translation to others, perhaps maintaining an arm’s-length role as an adviser. Professor Margaret Ashcroft, however, has the skills and experience to tackle the challenges of drug discovery and development within an academic setting.

Professor Ashcroft’s main interest is the cell’s response to hypoxia, shortage of oxygen. Hypoxia triggers a wide-ranging adaptive response coordinated by a transcription factor, HIF (hypoxia-inducible factor). The pathway is of obvious interest in conditions where blood flow and oxygen supply to tissues is compromised, such as stroke or injury, but it is also central to cancer. As solid tumours grow, cells typically become starved of oxygen, triggering a hypoxia response which renders them more resistant to cancer treatments. Elevated levels of components of the HIF pathway are associated with cancer progression and poor prognosis.

One of Professor Ashcroft’s aims is to understand the biochemical mechanisms underlying a cell’s response to hypoxia. Recently, she and her team discovered a novel protein family, encoded by the human CHCHD4 gene, that may act as a link between mitochondrial respiration and the HIF pathway – providing a mechanism for oxygen use to be dialled down at times of hypoxia. Notably, increased levels of CHCHD4 were associated with tumour progression and poor survival.

The work illustrates how research into fundamental mechanisms goes hand in hand with an assessment of clinical relevance. Indeed, Professor Ashcroft is committed to a science-driven approach to academic drug development, with basic research on biological understanding continually informing therapeutic development. Furthermore, the reverse is also true, with drug development generating tools to probe biological pathways and enhance understanding of biological processes.

Professor Ashcroft arrived at UCL having identified a set of lead compounds targeting the HIF pathway. As well as funding from CRUK’s technology transfer division, she has obtained support from UCL’s own internal funding streams to continue chemical refinement of lead compounds.

Drug development is a multidisciplinary team endeavour, she suggests. It is essential that members of the project team appreciate each other’s workload and see the value in each other’s contributions. Professor Ashcroft provides the glue, and the essential strategic leadership.

With funding and expertise in areas such as medicinal chemistry in place, Professor Ashcroft suggests it is now entirely possible to carry out drug development in an academic setting, with interdisciplinary input from academic, clinical and industrial partners. Indeed, she argues, preclinical drug development may best be carried out in such settings, where in-depth biological expertise and understanding is greatest, and can be channelled to underpin and add value to the drug development process.
funds and the TRO’s own Therapeutic Innovation Fund. Recipients of such funds include Professor Stephen Neidle at the UCL School of Pharmacy (see right) and Professor Margaret Ashcroft (see left). UCL Business (UCLB) also provides Proof of Concept funding for projects. Various forms of support are available, depending on the development needs of the project. This funding enabled Professor John Greenwood and Professor Steve Moss to carry out the research underpinning a patent on a novel anti-angiogenesis target (see page 8).

The MRC Laboratory of Molecular Cell Biology at UCL includes a small-molecule screening facility led by Dr Robin Ketteler. As well as Confidence in Concept and Therapeutic Innovation Fund support, Dr Ketteler has also received BBSRC funding to study the control of autophagy – disposal of cell components, a process implicated in multiple diseases. A second arm of the facility is based in the Wohl Virion Centre and enables screening to be carried out in biosafety level 3 facilities. Run by Dr Ariberto Fassati, the facility is being used to identify potential therapeutics for pathogens such as hepatitis viruses and HIV.

**Licensing and spinouts**
Managed through UCLB (see page 44), the School has many examples of successfully licensed technology, including a drug developed by Professor Rajiv Jalan to treat toxic ammonia build up in liver failure (see page 10) and light-activated antimicrobial technologies developed by Professor Michael Wilson at the Eastman Dental Institute in collaboration with Professor Ivan Parkin in the Department of Chemistry, being jointly marketed by UCLB and Ondine Biomedical Inc. In the Periwave treatment for periodontal disease, photosensitive dyes activated by light of particular wavelengths release bacteriocidal free radicals. Ondine is also collaborating on a project to incorporate photosensitive dyes into catheters, to prevent the establishment of infections.

Several start-up companies have been established on the back of the School’s research. Professor John Hartley’s research on anti-cancer DNA-binding agents lies at the heart of technology being developed by Spirogen, with agents currently in clinical trials in the USA and the UK. In October 2013, Spirogen was bought by the AstraZeneca Pharmaceutical company, which thwarted further work on MRSA.

Through Professor Mann, Professor Neidle was put in touch with a small biotech company, Summit, which was better placed to do the chemical optimisation necessary to turn a promising hit into a genuine drug. One immediate hurdle was a patent held by a pharmaceutical company, which thwarted further work on MRSA. However, the compounds also turned out to have activity on another important pathogen, Clostridium difficile. With translation funding from the Wellcome Trust, Summit recently completed highly positive phase I trials on its lead compound, SMT19969.

The development of SMT19969, Professor Neidle points out, goes against much of the current thinking in drug discovery. The modern paradigm is to identify molecular targets then to develop agents that act on them as specifically as possible. Conceptually neat though this approach is, and despite some success stories, it has not been as successful as many hoped.

Indeed, suggests Professor Neidle, the field may be undergoing a paradigm shift, with a return to functional or cell-based screens. The cellular targets of the antibacterial compound in C. difficile are still unknown, for example, but are unlikely to be the DNA structures originally targeted. Furthermore, it may be advantageous to hit multiple targets inside the cell.

Meanwhile, Professor Neidle is continuing his major projects targeting unusual DNA structures, quadruplexes, found in a number of growth-control genes, an approach he is interesting in applying to pancreatic cancer. Through funding from the Pancreatic Cancer Research Fund and a successful bid for MRC Confidence in Concept support, he has generated encouraging findings in animal models with a novel experimental drug.
Clinician scientist Professor Rajiv Jalan has seen an intervention he pioneered proceed to phase II clinical trials, his compound (OCR-002) being a key component of the portfolio of US biotech company Ocera Therapeutics. The experience is shaping ambitious plans in which his own company – Yakrit, Sanskrit for ‘liver’ – will play a more prominent role in developing a suite of medicinal products.

Professor Jalan’s main interest is liver failure, particularly the rapid build up of ammonia in acute liver failure, which can lead to coma and death. Received wisdom was that the ammonia originated from gut bacteria, but Professor Jalan discovered that the more likely source was a host enzyme, glutaminase. Curiously, while ammonia was generated in the gut, it seemed to be used up in muscle, due to the action of a second enzyme, glutamine synthetase, creating a kind of futile cycle.

Spotting the opportunity offered by muscle glutamine synthetase, a drug company developed a treatment for excess ammonia, L-ornithine-L-aspartate (LOLA) – ornithine being a precursor of glutamate. Yet Professor Jalan’s work suggested that the newly formed glutamate would simply be converted back to glutamate in the gut, re-releasing ammonia.

While working in India, Professor Jalan discovered that some acute liver failure patients had surprisingly low blood ammonia levels, because glutamine was being removed by dialysis. Hence, he reasoned, LOLA could be useful if the glutamine produced by muscle glutamine synthetase could be captured and excreted. And, fortuitously, a drug already existed that could do this, sodium phenylbutyrate.

With UCLB Proof of Concept funding, he was able to show that the two compounds given together could lower ammonia levels. And with Norwegian collaborators, he obtained good evidence that ammonia metabolism was altered as predicted in animal models.

At this point, the idea was licensed to Ocera Therapeutics, which began developing a single formulation of the two compounds. In the summer of 2013, Ocera joined forces with Tranzyme Pharma and announced major funding of phase Ib clinical studies of OCR-002. Something of a serial inventor, Professor Jalan and UCLB have now established a new company, Yakrit, to provide a vehicle for the development of five new diagnostics and devices. These range from a new liver dialysis machine – awarded funding from the MRC – to the use of carbon to manage the microbiological environment of the gut and prevent inflammatory damage to the liver.

This new model has many advantages, he suggests. The company maintains strong links with UCL, but opens up access to revenue streams that require a commercial partner. Moreover, he adds, it makes sense for academic groups, who have a deep understanding of human biology, to lead early development. And by continuing to generate data, the technology becomes increasingly valuable – particularly once data in humans have been gathered.

A CYCLE OF INVENTION
Having developed an innovative therapeutic now in phase II trials, Professor Rajiv Jalan has established a spin-out company to develop a suite of liver-related products.

Based on research on the molecular constituents of gap junctions, Professor David Becker has developed a highly promising RNA-based therapy, nexagon, for hard-to-heal ulcers and wound healing. With a positive phase Ib study completed, development of nexagon is being taken forward by CoDa Therapeutics.

Less advanced but with significant potential, the Canbex Therapeutics Ltd spinout has been established to support development of a small-molecule agent, VSN16R, to treat spasticity in multiple sclerosis (see page 11). Developed by Professor Dave Selwood, phase I trials of VSN16R were launched in November 2013. Professor Selwood was also the founder of an earlier spinout company, NCE Discovery, which merged with Domainex (UCLB retains a stake in the merged company).

Drug delivery platforms
While much attention focuses on novel targets and interventions, drug development can also benefit from innovations in drug delivery and production technologies – additional areas where UCL has great strengths.

Research on drug delivery is a noted strength of the UCL School of Pharmacy. Several groups are working on ways to enhance the delivery of pharmaceuticals, while others are exploring the potential of novel technologies. Professor Ijeoma Uchegbu and Dr Andreas Schatzlein, for example, are developing nanoparticles to deliver a wide range of therapeutics (see page 11).
Broadly speaking, drug discovery takes two forms. One approach is to screen large chemical libraries, to find “hits” that interfere with a biological process of interest and can form the basis of a drug development programme. An alternative strategy is to build compounds specifically to target known structures. This “structure-based” approach is the one favoured by Professor Dave Selwood, and led to the development of VSN16R to treat involuntary muscle contraction in multiple sclerosis.

Professor Selwood’s career has spanned industry and academia. Formerly employed by the Wellcome Research Laboratories, in 1995 he moved to the Wolfson Institute for Biomedical Research at UCL, to establish a medicinal chemistry group – still a rarity in UK academia.

His usual approach to drug design is to exploit the power of modern computing and advances in structural biology. Starting with the structure of a target, his aim is to design compounds that will bind to an active site, to inhibit activity or to mimic the activity of a natural signalling molecule. In the latter case, the challenge is to design a chemical analogue that retains the required biological properties, is metabolised more slowly than natural biological mediators, and can be synthesised in the lab.

Development of VSN16R followed precisely this route. It is based on a naturally occurring lipid signalling molecule, anandamide, which showed interesting properties in animal models of multiple sclerosis, work carried out in collaboration with Professor David Baker. VSN16R targets spasticity, an involuntary prolonged muscle contraction commonly experienced by multiple sclerosis patients. Although some drugs are available to treat spasticity, they do not work for everyone and have severe side-effects, including sedation and cognitive dysfunction, so there is a great need for alternatives. VSN16R has been designed to act on a receptor not targeted by existing treatments.

With promising pilot data, Professor Selwood was able to obtain translational funding from the Wellcome Trust, and later substantial Technology Strategy Board funding to complete the preclinical development of their neuropeptide painkiller, METDoloron. The company has also established alliances with two US companies, which are evaluating the company’s technology as a delivery mechanism. Indeed, more generally the technology may be able to ‘rescue’ drugs that have demonstrated biological activity but cannot, because of their physico-chemical properties, cannot get to locations in the body where they might act. Their initial hopes, however, are pinned on delivery of an innovative painkiller into the brain.

For more than a decade, the pair have been working on a family of polymers that spontaneously assemble into nanoparticles. Most usefully, the polymers can wrap around and protect drug molecules, while their natural ‘stickiness’ enables them to adhere to tissues and cells, promoting take up into the body and delivery of their cargo into cells.

Professor Ijeoma Uchegbu and Dr Andreas Schatzlein initially planned to use their nanoparticles to deliver therapeutic RNAs to cancer cells. Despite promising data in animal models, they were hit by waning enthusiasm for RNA therapeutics. However, work on a modified form of a naturally occurring peptide with painkilling properties, enkephalin, has blossomed. Although acute pain is generally well catered for, there is an urgent need for new agents for chronic pain and alternatives to drugs such as morphine, which has numerous drawbacks, for severe pain.

Enkephalin is far from ideal as a drug – being a peptide, it would be digested if given orally; even if it got as far as the bloodstream, it cannot cross the blood–brain barrier to reach its receptors in the brain. However, by chemically modifying the peptide and combining it with their self-assembling polymers, Professor Uchegbu and Dr Schatzlein have been able to create nanoparticles that are taken up by the gut, stick to blood vessels in the brain, and deliver the peptide across the blood–brain barrier. The pair established the Nanomerics spinout to commercialise their work in 2011, and have obtained Technology Strategy Board funding to complete the preclinical development of their peptide across the blood–brain barrier. The pair established the Nanomerics spinout to commercialise their work in 2011, and have obtained Technology Strategy Board funding to complete the preclinical development of their peptide across the blood–brain barrier. The pair established the Nanomerics spinout to commercialise their work in 2011, and have obtained Technology Strategy Board funding to complete the preclinical development of their neuropeptide painkiller, METDoloron. The company has also established alliances with two US companies, which are evaluating the company’s technology as a delivery mechanism. Indeed, more generally the technology may be able to ‘rescue’ drugs that have demonstrated biological activity but cannot, because of their physico-chemical properties, be turned into pharmaceutical agents. Professor Uchegbu and Dr Schatzlein wrote their first business plan in 2002. The translational road has not been straightforward, requiring considerable investment in time (and, at one point, personal finance) and flexibility to adapt in a changing commercial landscape. The result, though, is the potential launch of a drug that could make a real difference to patients’ lives.
Translation and enterprise are large and growing aspects of the UCL School of Life and Medical Sciences.

## TRANSLATION BY NUMBERS

### SCHOOL

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### UCL BUSINESS

**TOTAL LICENSES**

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**EQUITY HOLDINGS**

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**TURNOVER**

- **2012/13**: £9.3m

**VALUE OF INVESTMENTS**

- £80-110m

**PATENT FAMILIES**

- 2010/11: 295
- 2011/12: 360
- 2012/13: 306
DIAGNOSTICS
AND IMAGING

The detection and characterisation of disease has an increasingly important role to play in modern medicine.
Diagnosis is central to medical practice. In past centuries, doctors relied primarily on their own experience and judgement to make diagnoses, but now they are aided by multiple technologies, including biochemical tests, genetic diagnostics and advanced imaging.

Cancer is one area in which diagnosis is critical. One aim is to catch disease early, to increase the likelihood that treatment will be successful. Molecular diagnostics can also guide the choice of treatments, which are increasingly tailored to the precise genetic causes of disease.

Dr Kai Stoeber and Professor Gareth Williams have established an impressive track record in translating basic research findings in cancer, helping to develop a range of diagnostic tests and therapeutic compounds. Their research has been based on understanding the mechanisms controlling DNA replication, which has revealed excellent biochemical biomarkers of actively dividing cells. These markers have formed the basis of a range of diagnostic products, including an application in cervical screening developed by BD Diagnostics being considered for US Food and Drug Administration approval. Dr Stoeber and Professor Williams are collaborating with biotech companies on other promising diagnostic technologies (see page 16).

With their reputation for achieving translation of cell cycle research, the pair were also invited to join the £8m European MitoCheck consortium, which undertook a systematic screen for genes controlling mitosis. A technical tour de force, the consortium identified some 600 genes involved in one of the four stages of mitosis. Dr Stoeber and Professor Williams discovered that one of these genes – coding for a protein known as PAPPA (pregnancy-associated plasma protein A) – was responsible for stalling cell division in some breast cancer cell lines. This stalling appears to allow a tumour the opportunity to develop clinically highly damaging characteristics. Hence PAPPA may provide a way to identify the potentially most dangerous early breast cancers.

Genetic characterisation of cancers is becoming an increasingly common approach for targeting therapeutics, to avoid unnecessary use of expensive agents and to...
BREAKING THE CYCLE

Dr Kai Stoeber and Professor Gareth Williams have become the ‘go-to’ people for translation of cell cycle research.

Clinical translation often involves interplay between medicine and laboratory science, as exemplified by the long-lasting partnership between basic researcher Dr Kai Stoeber and clinical scientist Professor Gareth Williams. Over the past decade, their fruitful collaboration has led to a succession of translational spin-offs rooted in the basic science of cell division.

Their primary aim was to understand the protein machinery coordinating DNA replication in dividing cells. DNA synthesis is initiated simultaneously at multiple sites across the genome, which is made possible by pre-assembled replication complexes, so-called ‘replication licensing complexes’. These complexes, the pair discovered, are jump-started by cell cycle kinases. Dr Stoeber and Professor Williams realised that components of this licensing complex, particularly a protein known as Mcm5, had potential as biomarkers of actively dividing cells. Possible applications in cancer detection were immediately apparent.

The Mcm5 approach was licensed to the US company Becton Dickinson, which has developed systems to integrate Mcm5 detection with standard cervical screening. Dr Stoeber and Professor Williams have also developed methods to detect Mcm5 in genito-urinary tract and other body fluids, as the basis for diagnostic tests for bladder, prostate and other cancers. The pair have been working with a Cambridge-based start-up, Urosens Ltd, on a urine cancer test which won the 2008 Medical Futures Innovations Award and in 2012 received European approval for CE marking, a step on the road to testing in clinical trials.

A further spin-off from their research has been a drug discovery programme focused on one of the kinases that jumpstart the replication licensing complex, CDC7, in partnership with CRUK’s own drug discovery lab. Early in 2014 promising lead compounds were licensed to a major biopharma company for further development.

With their reputation for translating cell cycle research, the pair were also invited to join the £8m European MitoCheck consortium, which was undertaking a systematic screen for genes involved in mitosis. Remarkably, Dr Stoeber and Professor Williams have discovered that one of the genes identified by the MitoCheck consortium – coding for a protein known as PAPP/ (pregnancy-associated plasma protein A) – is switched off in breast cancer causing a distinctive delay in progression through mitosis and rendering breast cancer cells more invasive.

As imaging reveals ever more lesions of uncertain medical significance, the discovery may provide a way to identify the potentially most dangerous early breast cancers. This work is also leading to new therapeutics managed through Sarah Cannon. Hence the bank of mutations included in the test will continually be expanded, to include genes associated with approved therapies but also those that could guide entry into clinical trials of new anti-cancer treatments.

New cancer drugs are typically both powerful and expensive, so there are good clinical and financial reasons why they should be given only to those likely to respond. Building on UCL-AD’s existing genetic diagnostic service in cancer, the new approach has two key advantages.

First, the new method screens for mutations in multiple genes implicated in cancer – 11 initially but with another 20 or so to be added in the near future. Traditionally, genetic tests have been restricted to individual genes, but for the same cost UCL-AD’s new test will screen an array of genes for which genetic information can guide choice of therapy.

The second significant advantage is that the UCL-AD approach uses standard biopsy material gathered in routine clinical practice, ‘formalin-fixed paraffin-embedded’ tissue. UCL-AD researcher Dr Rifat Hamoudi has developed new amplification methods to handle the tiny amounts of degraded material present in such samples. Other tests typically require fresh or frozen samples from patients, but the use of standard materials means that the genetic profiling can be readily integrated into existing pathology work practices and patients will not have to undergo additional invasive biopsies for genetic profiling.

As well as the detection technology – which works with as little as 1 ng of degraded DNA – Dr Hamoudi has developed a supporting bioinformatics and reporting pipeline. Within seven working days, doctors receive a user-friendly report, which they can use to guide their choice of treatment. UCL-AD is able to analyse at least 10,000 samples a year, from UCL-associated hospitals, other UK clinical centres and even internationally.

The new service, to be run by Professor Adrienne Flanagan, has been developed with the Sarah Cannon Research Institute, which manages a range of clinical trial facilities in the UK. A significant advantage of this arrangement is that genetically profiled patients will be able to enter clinical trials of experimental new therapeutics managed through Sarah Cannon. Hence the bank of mutations included in the test will continually be expanded, to include genes associated with approved therapies but also those that could guide entry into clinical trials of new treatments, including those developed at UCL. As additional genetic markers are added, they may also reveal factors associated with success or failure of targeted therapies.

GETTING PERSONAL IN CANCER DIAGNOSIS

Technological innovations are underpinning a new cancer profiling service at UCL Advanced Diagnostics.

As anti-cancer drugs increasingly target specific mutations, genetic profiling is rapidly becoming the standard way to characterise tumours. Taking advantage of advances in DNA sequencing technology, researchers at UCL Advanced Diagnostics (UCL-AD) – a cancer diagnostics service embedded within the UCL Cancer Institute – have teamed up with the Sarah Cannon Research Institute to offer a rapid and convenient new DNA-based cancer-profiling service. As well as helping doctors choose the most appropriate therapies, the service will also provide a gateway for patients to enter clinical trials of new anti-cancer treatments.

The new service, to be run by Professor Adrienne Flanagan, has been developed with the Sarah Cannon Research Institute, which manages a range of clinical trial facilities in the UK. A significant advantage of this arrangement is that genetically profiled patients will be able to enter clinical trials of experimental new therapeutics managed through Sarah Cannon. Hence the bank of mutations included in the test will continually be expanded, to include genes associated with approved therapies but also those that could guide entry into clinical trials of new treatments, including those developed at UCL. As additional genetic markers are added, they may also reveal factors associated with success or failure of targeted therapies.
spare patients from treatment that will offer no benefits. Part of the UCL Cancer Institute, UCL Advanced Diagnostics has been offering a range of cancer-profiling services to research institutes and hospitals. In 2013, UCL Advanced Diagnostics teamed up with Sarah Cannon Research Institute, the cancer arm of HCA International, to provide access to new methods of mutation detection developed by Dr Rifat Hamoudi at UCL (see page 16). As well as supporting more personalised medicine in cancer, the technology will also enable more patients to be entered into clinical trials of targeted anticancer therapeutics.

A major new academia–industry partnership funded through the EU Seventh Framework Programme, EpifemCare, aims to transform screening, diagnosis and treatment of ovarian and breast cancer. Led by Professor Martin Widschwendter, the EpifemCare consortium is using epigenetic and genetic methods to develop blood-based tests to detect cancer and predict responses to treatment. Although less common than breast cancer, ovarian cancer is often diagnosed late, when it has already spread to other areas of the body; more than 60 per cent of ovarian cancer patients die within five years of diagnosis. Funded through a €5.8m award, the consortium encompasses six industrial and academic partners in five European countries.

Cancer is also the focus of Professor Quentin Pankhurst, who aims to exploit the potential of magnetic nanoparticles in both diagnostic imaging and therapy. Professor Pankhurst established a spinout company, Endomagnetics, which has developed a technology to locate sentinel lymph nodes without the use of radioactive tracers. This makes breast cancer scans available to a wide audience of clinicians and patients in a highly cost-effective manner. With Professor Kerry Chester and others, he is also examining the potential use of nanoparticles in thermal ablation of tumours.

Advances in medical imaging are providing numerous ways to characterise disease and guide treatment. As well as new imaging technologies, progress in software development is transforming the ability to visualise the body non-invasively. UCL’s Centre for Medical Image Computing, which draws together computer scientists, engineers and biomedical scientists, is a world leader in this field. As well as multiple Technology Strategy Board grants and EU funding, the Centre has also launched two start-up companies, including IXICO plc. Established by Professor David Hawkes with colleagues from King’s College London and Imperial College, IXICO provides clinical trial services and disease diagnostic tools with a particular focus on dementia.

Professor Hawkes and Professor Brian Davidson have received support from the Health Innovation Challenge Fund (HICF) – a partnership between the Department of Health and the Wellcome Trust – to develop new imaging systems for keyhole surgery of liver cancer. Although keyhole surgery has several advantages, it is rarely used because of difficulties in identifying blood vessels in the liver and vessel and tumour movement during surgery. The project is using a pre-surgery CT scan to build a computer model of the tumour and surrounding liver tissue, including blood vessels, to provide a guide during surgery.

An imaging-related HICF grant has also been awarded to Professor John Duncan and Dr Sebastian Ourselin, who have developed methods to visualise in 3D areas of brain function, connections and blood vessels. The system is being developed, in conjunction with Medtronic, to provide a practical tool to guide epilepsy surgery. A third HICF grant has been awarded to Professor Mark Emberton and Dr Dean Barrett, whose ‘SmartTarget’ approach aims to combine detailed MRI pictures of prostate cancer with ultrasound that is typically used to guide biopsies and treatment delivery in order to deliver improved diagnosis and treatment outcomes.

Medical imaging typically depends on large pieces of equipment, such as MRI, CT and PET scanners. As a result, patients have to visit specialist facilities for treatment or to take part in research, limiting their application. Professor Clare Elwell and colleagues have been developing a more portable optical imaging-based approach, which is opening up new opportunities in both medicine and research (see page 18). Optical imaging technology is both relatively cheap and practical to use. It provides a way to monitor various aspects of metabolism, including oxygen use, and has been used to assess brain function in neonatal intensive care and, more recently, adult critical care.

Other groups have been keen to use the technology, and a colleague of Professor Elwell, Dr Nick Everdell, has built several machines for other labs to use. With demand increasing, he has established a spinout company, Gower Labs, to produce equipment commercially. Professor Elwell has also obtained a large EPSRC grant to develop wearable detectors, which will further extend the range of situations in which the technology can be used.

While imaging and other diagnostic tools have obvious value in clinical practice, their importance to clinical trials should not be underestimated. Trials are heavily dependent on biomarkers which can be used to track disease progression reliably and over practical timescales. Alongside brain imaging, a technology for identifying dying cells in the retina, developed by Professor Francesca Cordeiro, may be applicable in dementia, as well as in eye diseases such as glaucoma (see page 19).

Nanotechnology lies at the heart of an ambitious programme being led by Professor Rachel McKendry, who holds a joint position at the London Centre for Nanotechnology (a partnership between UCL and Imperial College) and in the UCL School of Life and Medical Sciences. With funding from the EPSRC, Professor McKendry has established a public–private interdisciplinary research consortium developing handheld diagnostic devices for a range of important infectious diseases (see page 19). The consortium is also developing new tools to mine internet data and capture advance warning of emerging infections and epidemics.
RULES OF ATTRACTION

Magnetic nanoparticles may have many medical applications, says Professor Quentin Pankhurst.

Convinced of the potential of magnetic nanoparticles, Professor Quentin Pankhurst sought government funding for groundbreaking applications in cancer. He was awarded £15,000 to clarify his thinking, and went on to establish a successful spinout company, Endomagnetics. Now he hopes to make use of this experience in a new wave of commercial ventures.

Although based in UCL’s Faculty of Engineering, Professor Pankhurst collaborates extensively with life scientists and clinicians. His first foray into commercialisation came when he applied for funds from the then Department for Trade and Industry (DTI). The DTI was impressed with his technology, but unconvinced of the business case. It awarded him £15,000 – 10 per cent of what he had asked for – to investigate the actual clinical need.

It was a key turning point. A series of contacts led to a collaboration with breast cancer surgeon Mr Michael Douek, and the development of a tool to visualise sentinel nodes – enabling biopsies to be taken to check for the spread of disease without the need for radioactive tracers.

Professor Pankhurst led Endomagnetics through its early years, obtaining funds from the DTI and the Technology Strategy Board, before handing over to a full-time CEO. As of late 2013, Endomagnetics has grown to six full-time staff, signed a distribution agreement, and seen its products used to treat more than 1000 patients.

Despite its success, Professor Pankhurst believes development could have been quicker, particularly if more attention had been given to adoption pathways and clinical take up. These ideas have fed into the ‘MedTech Accelerator’ adopted by the cross-Faculty Institute of Biomedical Engineering for developing new commercial opportunities (see page 23).

Having taken a step back from Endomagnetics, Professor Pankhurst is now working on new applications for magnetic nanoparticles. In one promising line of research, particles are targeted to tumours and a ‘magnetic microwave oven’ is used to heat the particles and destroy the tumour. This ‘thermal ablation’ approach is being developed for brain cancer in collaboration with Professor Mark Emberton, neuroanaesthetist Professor Martin Smith, brain-injured adults on the centre of a spider’s web of collaborations with clinicians and scientists at UCL and beyond.

Over the past 25 years, optical imaging has emerged as a valuable technique for monitoring physiological processes, including brain function, non-invasively and with relatively simple equipment. Much development has been carried out at UCL’s Department of Medical Physics and Bioengineering, where Professor Clare Elwell sits at the centre of a spider’s web of collaborations with clinicians and scientists at UCL and beyond.

Optical imaging uses light to gather information about metabolic processes such as oxygen consumption. The same approach is used in functional MRI, but optical imaging is cheaper, easier to use and portable. An early application, developed in collaboration with neonatologists at UCLH, was monitoring of blood flow in the brains of neonates in intensive care. Systems have also been used to monitor infants and children at Great Ormond Street Hospital and, through a long-standing collaboration with consultant neuroanaesthetist Professor Martin Smith, brain-injured adults on the neurocritical care unit at the National Hospital for Neurology and Neurosurgery.

But scientists have also been attracted to the technology. For example, Professor Elwell collaborates with Professor Mark Johnson’s team in the ‘baby lab’ at nearby Birkbeck, who are interested in infant brain development. Professor Elwell helped to design a headpiece suitable for young infants, which has generated highly significant findings, including marked abnormalities in how four-month-old infants at risk of autism respond to social stimuli.

Furthermore, in collaboration with nutritionists at the London School of Hygiene and Tropical Medicine, and with pilot funding from the Bill and Melinda Gates Foundation, her team developed a stripped down version of the technology for use in a rural field station in The Gambia. Remarkably, the equipment was up and running and generating results on the day of arrival.

Professor Elwell admits to being a late arrival to the field of commercial exploitation. Her aim has been to encourage wider use of her technologies, which she has seen picked up and used by others (including companies). Applying for a technology development grant, however, has encouraged a change in mindset and a greater appreciation of the challenges involved in broadening the use of technology, and of the internal support available for translational research. She is hoping to build on the work in the adult neurocritical care unit, aiming to make the results generated by the technology easier for clinicians to digest.

Her group’s work may also generate further commercial spinoffs. Her colleague Dr Nick Everdell has built several optical imaging set-ups for other groups, on a bespoke basis. With demand increasing, he is now setting up a spinout company, Gower Labs, to commercialise production of equipment. Additional opportunities may arise from the development of more portable wearable systems, which could extend still further the range of possible applications.
THE DARC SIDE
Visualising cell death in the retina may provide a way to diagnose not just eye disease but also neurodegenerative conditions such as Alzheimer’s and Parkinson’s disease.

Combining research with clinical practice as a consultant ophthalmologist at the Western Eye Hospital has given Professor Francesca Cordeiro a clear view of clinical priorities. The need for a simple diagnostic for glaucoma, for example, prompted work on labelling of dying cells in the retina. The resulting technology, however, has turned out to be of wider application.

Glaucoma, raised fluid pressure in the eye, is a common cause of sight loss. However, it is challenging to assess clinically, and its impact is monitored through changes in vision, which are difficult to measure sensitively and a sign that considerable eye damage has already occurred. A tool that could detect early signs of glaucoma would therefore be clinically useful. But it would also greatly aid clinical trials assessing the impact of new interventions.

Glaucoma leads to the death of retinal ganglion cells (RGCs). RGCs undergo a controlled process of programmed cell death, which leads to the appearance of particular lipid molecules on the cell surface. These lipids are bound by a specific protein, annexin 5. Professor Cordeiro realised that fluorescently labelled annexin 5 would provide a way to identify apoptosing cells and hence the onset of glaucoma.

During the past five years, Professor Cordeiro has been developing the technology – known as DARC, or detection of apoptosing retinal cells – for use in humans. A key advantage of the technology is that it can be used with minor modification of standard ophthalmological equipment. With safety and toxicity studies completed, phase I studies for glaucoma are scheduled for 2014.

Furthermore, RGC apoptosis is also a feature of neurodegenerative diseases such as Alzheimer’s disease – another area where there is a great need for a reliable and simple diagnostic test. Alongside the work on glaucoma, Professor Cordeiro has also been exploring the potential use of DARC in neurodegeneration, showing in various animal models of disease that the degree of eye damage picked up by DARC corresponds well with damage to the brain. If the glaucoma phase I trials go according to plan, Professor Cordeiro hopes to extend phase II studies to include Alzheimer’s disease as well as glaucoma patients.

The glaucoma studies have provided a further spinoff opportunity. The label is currently delivered to the eye by injection, but Professor Cordeiro has been working on a new non-invasive delivery system, which again she hopes to rollout in phase II studies. Furthermore, the delivery system could itself be a valuable platform technology for delivery of drugs to the eye. UCLB is currently discussing with Professor Cordeiro the possibility of establishing a spinout company to commercialise the drug delivery technology.

DIAL-A-DIAGNOSIS
By combining nanotechnology with the power of ‘big data’, Professor Rachel McKendry is generating new tools to diagnose infectious disease in individuals and to track outbreaks in populations.

Professor Rachel McKendry has a background in chemistry, but not a conventional one. Her PhD was sponsored by the pharmaceutical company Zeneca and involved work on one of the UK’s first atomic force microscopes, analysing the interactions of individual molecules at the nanoscale. Still impossible to pigeonhole, and with positions in both the London Centre for Nanotechnology and UCL’s Department of Medicine, she is now leading an innovative interdisciplinary consortium tackling the very real threat posed by emerging infections.

Surface chemistry is the thread that links Professor McKendry’s diverse research interests. One strand of research has examined interactions between antibiotics and the cell wall of MRSA. A better understanding of these interactions underpinned chemical modifications that enhanced antibiotic efficacy by several orders of magnitude – breathing new life into old drugs whose patents had expired. In recognition of this work, Professor McKendry was awarded the Institute of Physics’ Paterson medal and prize in 2009.

The other main theme of her work is diagnosis of infectious disease. With funding from the NHRI i4i programme, and in collaboration with UCL virologists Professors Robin Weiss, Vince Emery, Deenan Pillay and Dr Eleni Nastouli, she is working with OJ-Bio Ltd to develop diagnostic tools for HIV, adapting sensors present in mobile phones. As well as rapid point-of-care diagnosis, information will be rapidly transmitted to a central data store.

Building on this project, Professor McKendry has recently put together an interdisciplinary research consortium, with academic and commercial partners, to extend the concept across HIV, MRSA and emerging strains of influenza. With £11m funding from the EPSRC, the consortium aims to develop low-cost point-of-care mobile diagnostics and web-tracking systems to identify outbreaks of deadly strains much earlier than is now possible.

The approach will support more rapid diagnosis and treatment for individuals, but the aggregated data will provide invaluable epidemiological data on disease outbreaks and the effectiveness of control programmes. Complementing this latter aim, Professor Ingemar Cox (UCL Computing) and Professor Anne Johnson are leading a strand of work aiming to extract epidemiologically useful information from the ‘big data’ being generated by internet searches and social media messages. Notably, these patterns emerge well before similar trends are seen in healthcare data.

Professor McKendry career has spanned industry and academia, and she encourages an outward-looking and entrepreneurial spirit in her group. Her own motivation has been to use her specialist knowledge to tackle some of the greatest threats to society in ways that benefit people, particularly in developing countries. The best way to do this, she suggests, is through the kind of interdisciplinary approach underpinning her new consortium, where each partner brings specific expertise that enables the group to achieve what none could individually, for the common good.
REPAIR AND REGENERATION

Advances in materials science, stem cell biology and engineering are combining to create a new wave of replacement body parts.
Replacement body parts have been one of medicine’s holy grails. Transplantation has provided one route to repair, but is inevitably limited by the shortage of donor organs and by recipients’ need for lifelong immunosuppression. In recent years, however, the prospect of ‘home-grown’ organs has gone from pipe dream to reality, with UCL researchers responsible for a range of world firsts.

Developments in two areas in particular have been responsible for this rapid progress. The first has been the harnessing of the potential of stem cells, particularly a patient’s own cells, which create the living tissue necessary to build a new organ. The second key factor has been new biocompatible materials that have excellent physical properties – strength, flexibility, resilience – but also create highly supportive environments to which cells can attach and develop.

Some of the most successful materials have been developed by Professor Alex Seifalian (see page 22). His polymers have been used to create a range of artificial organs, including a windpipe, bile duct, tear duct, ear and nose. They have been incorporated into an artificial heart valve developed by Professor Gaetano Burriesci (see page 22), while Professor Seifalian is also developing artificial blood vessels which could transform heart bypass surgery and treatment of limb blood vessel damage in diabetes. Professor Seifalian won the prestigious Cardiovascular Innovation Award for Medical Futures 2007, one of the UK’s most sought after accolades for healthcare innovation.

Through a UCLB-supported project, Professor Seifalian is also developing an artificial stent, as an alternative to current artificial devices which have a tendency to narrow or become blocked.

Professor Seifalian worked with Professor Martin Birchall on synthetic tracheas. Professor Birchall has previously been involved in transplants in which a donor trachea was stripped back to a cartilage matrix, ‘de-cellularised’, before being repopulated with a recipient’s own stem cells. The approach was used successfully to treat a child with a potentially deadly trachea abnormality. Professor Birchall is now exploring the use of de-cellularised and artificial grafts in trachea and larynx transplantation, as well as possible replacement of the oesophagus and bladder. As well as laying the ground for clinical trials, these projects are also modelling the economic implications of introducing such technology more widely.
**SPARE PART GENERATOR**

Professor Alex Seifalian has created the materials used in pioneering replacement surgery for the trachea, nose and ear – and has his eyes set on a range of other applications.

Until recently, artificial organs lay in the realm of science fiction. But the biocompatible nanocposite polymers developed by Professor Alex Seifalian have helped turn vision into reality. His materials have been used in a range of world firsts, including transplants of trachea, nose, ear and tear duct. Now, they are poised to find application in artificial blood vessels, opening up potentially vast markets.

Over the past two decades, with funding from the EPSRC and Wellcome Trust, and drawing inspiration from natural structures such as butterfly wings, Professor Seifalian has developed a new generation of polymers suitable for use in human patients. Strong, flexible and highly biocompatible, his polymers have been taken up widely. Professor Seifalian’s own work has focused primarily on artificial blood vessels.

There is an urgent need for artificial vessels, for example to replace limb vessels damaged in diabetes or for use in heart bypass procedures. In the latter case, almost a third of patients have no suitable vessel that could be grafted. Artificial alternatives are not ideal – with the most commonly used, PTFE, 75 per cent of vessels are blocked within five years, and they are suitable only for limb surgery; there is no alternative for the heart.

As well as their attractive innate properties, Professor Seifalian’s polymers can also be chemically modified to add biologically useful functionality. Hence his vessels incorporate antibodies that snare circulating stem cells, which generate a layer of endothelium around the vessel – effectively integrating it into the body.

At the development of artificial organs relies on multiple forms of expertise, including materials science and nanotechnology, cell biology, cardiovascular science, animal studies, and surgery, alongside business and commercial support. While Professor Seifalian has been able to tap into networks at UCL and beyond, he also has a remarkably diverse background, having at various times studied physics, medicine, polymer chemistry, tumour biology, transplantation, surgery and cardiovascular medicine. Interdisciplinarity thus comes naturally, enabling him to converse with a wide range of collaborators and see his technologies applied in multiple medical contexts.

**THE HEART OF INNOVATION**

Dr Gaetano Burriesci has swapped commerce for academia, but still aims to bring a new medical device to market.

By exploiting innovations in different areas of materials science, Dr Gaetano Burriesci aims to generate a new generation of cardiovascular implant. Having joined UCL from a medical device company, he appreciates having more freedom to pursue his own ideas – but his goal is nonetheless to develop successful products to meet unmet medical needs.

His most advanced work is on an artificial heart valve, to treat patients whose own valves have become calcified and are failing to operate efficiently – a common complaint of old age. Artificial heart valves have been used for some time, but around one-third of patients are too frail to undergo conventional surgery to have them fitted.

This fact has driven increased use of ‘transcatheter implants’, a minimally invasive approach in which valves in metal frames are inserted in a catheter through a blood vessel in the groin and manoeuvred to the heart.

Worldwide, several thousand such valves have been implanted. Although largely successful, this initial use has revealed some significant issues. One of the most serious is that implants cannot be repositioned, so if a valve moves or is positioned poorly, patients have to undergo surgery – despite being a high-risk group. Other issues include a less-than-perfect seal leading to some backflow of blood, and a tendency for valves to exert excessive pressure on the walls of the heart and interfere with the electrical signals that coordinate heart contraction.

Dr Burriesci’s new device addresses all these limitations. Like some existing devices, his supporting frame is made of nitinol, a nickel titanium alloy that is both highly elastic and has shape memory. This is inserted in a collapsed form, and springs to normal size when positioned. However, his frame incorporates miniature springs, which dramatically reduce stresses but also enable valves to be ‘re-hooked’ and repositioned. The design also significantly reduces radial stress on the heart walls. A further innovation has been the choice of material for the ‘leaflets’ that make up the moving part of the valve, which are based on novel biocompatible polymers developed by Professor Alex Seifalian (see left).

Indeed, the project has depended on a faculty-spanning interdisciplinary team. Alongside engineers and material scientists, Dr Burriesci has worked closely with cardiologist Dr Mike Mullen and cardiac surgeon Mr John Yap, who have provided key insight into clinical needs and the practicalities of surgical application.

With translation funding from the Wellcome Trust, Dr Burriesci has developed three sizes of artificial valve, which have undergone extensive evaluation in an experimental set up mimicking the pumping of the heart, and show significantly better performance than existing products. The next steps include durability testing – monitoring how well the artificial valve performs after 200 million contractions – and studies in suitable experimental animals. Through UCLB, discussions are also being held with potential commercial partners.
Tissue engineering is also the focus of Professor Robert Brown, who has pioneered the use of a collagen-based artificial 3D tissue (see page 25). Much of this work has been carried out with TAP Biosystems, which was awarded UCL’s SME Partner of the Year Award 2012. TAP licensed the technology developed by Professor Brown, and a portfolio of patents from UCLB. With TSB funding, TAP, Professor Brown and Professor Julie Daniels of the UCL Institute of Ophthalmology are layering thin strips of the tissue and incorporating corneal stem cells to create corneal implants. Many other applications could be envisaged, not just in tissue repair – including mini-tissues now being used in toxicology testing.

Professor Brown has worked with a range of innovative SMEs. With Lein Advanced Diagnostics, for example, he has received TSB funding to evaluate a laser-based technology for tracking the position of labelled molecules or cells within the 3D tissue.

The ‘innovation spiral’ guides researchers’ thinking about translation.

Dr Gaetano Burriesci with his artificial heart valve.

The medical technologies sector is sizeable and highly dynamic, characterised in the UK by a large number of small companies.

Professor Brown is based at the UCL Institute of Orthopaedics and Musculoskeletal Science, which works closely with the Royal National Orthopaedic Hospital at Stanmore. The Institute and its Director, Professor Gordon Blunn, are strongly focused on practical application, having developed a range of innovative regenerative medicine technologies (see page 24). These have included novel prosthetics that attach directly into a recipient’s bone – an approach used successfully in both human and animal medicine – and an innovative bone prosthetic for children that can be extended non-invasively as children grow. The Institute is also exploring the use of stem cells to repair tissues such as tendon and bone. A successful spinout company from the Institute, Stanmore Implants Worldwide, now run independently, provides one route by which its advances can be commercialised.

Stem cells are not the only route to artificial organs. Dr Clare Selden is developing a bioartificial liver based on a liver cell line encapsulated within an alginate scaffold (see page 26). The bioartificial liver would temporarily take over the function of a recipient’s liver, buying time for the liver to repair itself or for a donor organ to be found. One of the most successful assistive devices is the cochlear implant. Researchers at the UCL Ear Institute are working with cochlear implant manufacturers to improve their devices. Notably, Professor David McAlpine is leading a €4m academic–industrial collaboration to develop a radically improved ‘binaural’ design, sending integrated signals to the brain from both ears, which would greatly enhance users’ hearing experience (see page 26).

The interface between engineering and biomedical science is particularly fertile ground for innovation. The medical technologies sector is sizeable and highly dynamic, characterised in the UK by a large number of small companies. At UCL, an important focus for this activity is the cross-faculty Institute of Biomedical Engineering (IBME), led by Professor Quentin Pankhurst. IBME acts as a bridge between physical science and life science faculties and UCL-associated hospitals, promoting interdisciplinary work on a wide range of diagnostics, imaging, and assistive and other devices. IBME encompasses more than 150 staff spanning 35 UCL departments, institutes and centres.

The IBME has pioneered the use of a ‘MedTech accelerator’ to guide the development of new innovations. The accelerator is based on a concept of an ‘innovation spiral’ (see above) rather than the traditional linear view of bench-to-bedside translation, that roots development in patient benefit and repeatedly crosschecks a technology’s likely commercial viability, technical feasibility and clinical relevance. By simultaneously addressing these three criteria – all of which will need to be satisfied in order to achieve commercial success – the viability of projects can be assessed more readily and progress accelerated.
REBUILDING WORK
Academic and clinical teamwork has underpinned a series of world firsts in regenerative medicine, says Professor Martin Birchall.

Dismayed by the lack of options available for patients with damaged tracheas (windpipes) and larynxes (voice boxes), Professor Martin Birchall set out to develop some alternatives. His research, initially at Bristol and lately at UCL, has underpinned a series of world-first life-saving procedures providing patients with replacement organs. His aim now is to build on this foundation and widen the use of these innovative treatments.

Professor Birchall initially pinned his hopes on transplantation, an approach hampered by the immunological reactivity of the trachea and larynx. However, work in the USA suggested a possible alternative – ‘decellularised’ grafts, in which donor organs are stripped of cells, leaving a cartilage scaffold that can be repopulated with a recipient’s own stem cells. Professor Birchall began testing this approach in animal models, with promising results.

In 2008 Professor Birchall and collaborators in Spain had an opportunity to test the approach clinically, replacing the trachea of a patient whose airway was acutely obstructed. The procedure, the first ever stem cell-based organ transplant, was a great success – and five years on the patient remains well.

Soon after, Professor Birchall moved to UCL, inspired by the prospect of working with world experts in a range of scientific and clinical fields, and the chance to establish a specialist clinic at the Royal National Throat, Nose and Ear Hospital. In 2010, he was presented with another medical emergency – a young boy with a defective trachea and a failing replacement metal stent. A cell-based transplant again proved successful. In addition, at the invitation of colleagues at the University of California Davis, Professor Birchall assembled an interdisciplinary team that successfully carried out a laryngeal transplant – the world’s second – on a woman suffering from end-stage laryngeal disease.

These success stories have underpinned an extensive translational research programme, drawing on interdisciplinary teams of scientists, chemists, business experts and clinicians. With MRC funding, Professor Birchall is working towards clinical trials of laryngeal transplants based either on decellularised scaffolds or nanocomposite materials developed by Professor Alex Seifalian. He has also secured Technology Strategy Board funding for work on tracheal transplantation, in partnership with Vidergen, a start-up company specialising in decellularisation. With Dr Paolo de Coppi and colleagues at Great Ormond Street Hospital, he is also helping to develop new approaches for oesophagus and, with MRC funding, bladder transplantation.

Beyond the scientific and technical challenges, Professor Birchall is conscious of the need to consider how such innovative approaches could be integrated into the health service. As part of the MRC programme, Professor Chris Mason is examining the health economic implications of personalised, one-off treatments providing long-term health benefits – an analysis likely to reveal benefits all round. Recurrent treatment costs can amount to half a million pounds per patient, while a transplant might cost one-tenth that sum.

REPAIRING BODIES, RE-BUILDING LIVES
Life-changing prosthetics are just one of the medical innovations being developed by Professor Gordon Blunn and colleagues.

Based at Stanmore, the UCL Institute of Orthopaedics and Musculoskeletal Science shares grounds with the Royal National Orthopaedic Hospital. This juxtaposition is critical, says Institute Director Professor Gordon Blunn, providing a focus on clinical needs and clinical expertise which is underpinning the development of a new generation of prosthetic devices and regenerative therapies.

In 2008, Professor Blunn was an inaugural winner of UCL Enterprise’s Business Award. The award recognised Professor Blunn’s role in integrating commercial activities at the Institute, particularly through spinout company Stanmore Implants Worldwide. The company is now independently run but maintains close links with the Institute.

Stanmore Implants has been a route through which the Institute’s innovations have achieved global take up. One of the most notable is a remarkable implant for children who, because of cancer, have lost large parts of leg bones, including growth plates. Hence, the prosthetic has to ‘grow’ to keep pace with the uninjured leg. The solution is a prosthetic containing a tiny motor and gearbox. Every three or four months, patients undergo a short session, in outpatients, where the motor is activated by an external magnetic field, extending the prosthetic by a few millimetres. Although childhood bone cancers are rare, the device has made a huge difference to the children affected. It has been a commercial success, with more than 500 sold through Stanmore Implants.

A further strand of innovation has focused on limb prostheses. Although traditional stump–socket devices are often effective, they can be awkward and uncomfortable, particularly when much of the limb has been lost. Inspired by the biological example of antlers, Professor Blunn has developed an alternative in which the prosthetic is fixed directly into bone.

Prototypes have been used in both clinical and veterinary medicine. Human recipients include a victim of the London 7/7 bombing and a man who lost a leg but has since climbed Mount Kilimanjaro and completed long-distance walks. This pioneering work has revealed some teething problems, including recurrent infections at sites of insertion. An antibacterial silver coating is now being tested in a clinical trial, while other research, funded by the Wellcome Trust, is examining how to improve the seal between implant and body tissues. As well as this ‘hard’ engineering work, other projects are exploring the potential of stem cells in repair of tendon and bone.

Enterprise, suggests Professor Blunn, is an integral part of the Institute. The clinicians provide a constant source of medical issues and the bioengineers, working with many collaborators throughout UCL, are adept at coming up with solutions. Stanmore Implants and other commercial partners provide a way in which these innovations can be made more widely available.

Hospital and research institute therefore go hand in hand. Both will soon be occupying expanded new facilities, as major development work begins on the Stanmore Campus.
In practical terms, the MedTech accelerator provides a framework within which researchers with a promising technology can begin to think about and plan a translational pathway. As well as expert guidance on translational processes, it can also help researchers identify suitable technical, clinical or industry partners. By putting patient benefit and clinical need at the heart of the process, the approach relies on input from clinicians who identify the technical obstacles limiting patient care. As well as working with numerous clinical academics, the IBME also holds ‘consultants meet the engineers’ events to establish contacts and brainstorm potential solutions. The IBME also has a dedicated industry liaison programme, providing potential external partners with access to an unrivalled range of expertise across UCL.

One area in which the MedTech accelerator is being extensively used is the Yale–UCL Medical Technologies Collaborative, part of a wider strategic alliance between Yale and UCL. Following a series of workshops in areas such as imaging and sensing, biomaterials and drug delivery and vascular engineering, seven flagship projects including researchers from both the USA and UK are being progressed through the accelerator.

As well as bringing together complementary expertise, the partnerships are exploiting the strengths of each location in different areas of translation. A wide variety of innovative projects are being pursued, including development of imaging agents for MRI in cancer and use of amniotic stem cells in regenerative medicine.

Solutions of collagen, the main structural protein of connective tissue, show a natural tendency to form gels. And if the solution also includes cells, the gelling collagen encapsulates them in a mesh. Professor Robert Brown has taken advantage of these innate properties to develop three-dimensional artificial tissues, working with industrial partner TAP Biosystems on a range of promising applications.

The drawback of collagen gels is that they are rather weak – not surprisingly, as they are 99.8 per cent water. However, in 2004 Professor Brown discovered that compressing the gels to squeeze out water created thin films that were more robust yet still provided an environment in which cells could thrive.

The discovery provided a way to make a simple but highly physiological artificial tissue. The basic ingredient is collagen, but all kinds of cells can be added to the mix (or even biomolecules or nanoparticles – anything big enough to be trapped within the collagen mesh).

One application has been in tissue implants. Working with Professor Brown and TAP Biosystems, Professor Julie Daniels of the UCL Institute of Ophthalmology has layered individual sheets impregnated with epithelial stem cells to create corneal implants. Funding has been obtained for first-in-human studies of this new approach.

A second promising approach, now being marketed by TAP Biosystems, is in toxicology screening. The 3D tissues are more complex than cell lines but simpler than animals, allowing for rapid and effective screening of the effects of drugs and chemicals.

A third use is in delivery of cell therapies. Instead of being injected at sites of interest, stem cells can be encapsulated in 3D tissues and pasted into place like a kind of cellular ‘wallpaper’.

Professor Brown is also investigating other potential applications. One interesting idea is to culture ‘tumouroids’ – 3D mini-tumours cultured directly from patient cancer samples – which could be tested for susceptibility to different cancer drugs.

It is also possible to impress patterns into the surface of the films, creating pathways to guide new blood vessel growth or even nerve cell development.

Finally, work with physical scientists on the way that physical forces control tissue repair has led to a further novel application. The physical stresses of pregnancy often lead to subclinical scarring – stretch marks. With Dr Stephen Barker, Professor Brown helped to develop a garment device with rubbery patches that redistributes the skin forces imposed by pregnancy, which is now available commercially. As well as this cosmetic use, suggests Professor Brown, similar principles could be applied in more clinically serious situations, such as hernia development or blood vessel aneurysms.
Although several artificial organs have been developed, from kidney dialysis machines to heart bypass devices, no one has yet come up with an artificial liver. The reason, says Dr Clare Selden, is the liver’s metabolic complexity. Any solution, she suggests, will have to be based on living liver cells – and since the mid-1990s, her goal has been to develop just such a bioartificial organ.

Such a device could be used as a ‘bridge’ for patients awaiting a transplant. But the liver also has an extraordinary ability to regenerate after damage – so external support could buy time to allow the liver to heal itself. With demand far outstripping supply of donor organs, such an assistive device could have a major impact.

Dr Selden began work with Professor Humphrey Hodgson, whose clinical experience complemented Dr Selden’s background in hepatic cell biology. Dr Selden has based her device on an established tumour cell line, which maintains most liver functions. However, under standard culture conditions, the cells neither grow nor behave much like bona fide liver cells.

The solution was to provide cells with a more physiologically congenial environment, using a 3D biocompatible scaffold. Best results were obtained with alginate, a glutinous substance obtained from seaweed. Other groups encase alginate in porous membranes – can readily diffuse. The core of her bioartificial liver is based on alginate beads some 0.5 mm in diameter, packed full of functioning liver cells.

Work on surgically treated pigs has shown that a device containing 1–4 x 10^6 cells can provide high levels of liver function. With translational funding from the Wellcome Trust, Dr Selden is now scaling up further, to generate devices containing up to 1 x 10^8 cells for human use, and to prepare the regulatory documentation required for human trials.

However, it takes several weeks to grow this number of cells. To meet acute needs, Dr Selden has obtained funding from the Technology Strategy Board to work with Professor Barry Fuller and a biotech company, Asymptote, on a cryopreservation system. A cryopreserved bioartificial liver could be shipped to a hospital and defrosted locally for use within days.

As is often the case in translation, the project has taken longer than Dr Selden ever imagined. But by concentrating on short- and medium-term goals, she has been able to maintain steady progress towards a practical and effective device. Ultimately she hopes to see her invention through to first-in-human studies, when, if all goes well, it should be an attractive opportunity for commercial investment.

PATIENTS AND PERSEVERANCE
A desire to help patients, combined with formidable commitment, has kept Dr Clare Selden in pursuit of a bioartificial liver for 20 years.

Cochlear implants have had a huge impact on the quality of life of people with severe hearing loss. Yet there is room for improvement, particularly to enhance perception of the spatial origins of sound. This is the goal of a €4m EU Framework Programme 7 grant, Advancing Binaural Cochlear Implant Technology (ABCIT), to Professor David McAlpine and colleagues at Oldenburg University, Germany (and their technology spin-out group HoerTech), and the French cochlear implant company Neurelec. Professor McAlpine is a world expert on the brain’s ability to analyse auditory input and build three-dimensional soundscapes, enabling us to pinpoint precisely the origins of sounds in space. This ability relies on the fact that we have two ears: by analysing differences in the time taken for signals to travel from each ear to auditory processing centres, the brain can calculate the sound’s origin in space.

Until recently, cochlear implants have not been able to support such complex processing. Usually, only one is implanted. Even when two are used, independent signals to each ear cannot be integrated to provide three-dimensional information. Recently, however, Neurelec has developed technology that creates a genuinely binaural experience. Signals from left and right microphones pass through a single processor, enabling spatially important sound cues to be extracted and synchronised electrical pulses sent to the brain.

The new grant is enabling Professor McAlpine to apply his expertise in sound processing to the development of these innovative new devices. As well as 3D localisation, they will also improve the perception of sound signals such as speech in noisy environments – enhancing so-called ‘cocktail party’ listening. By the end of the three-year EU funding, the ABCIT team plans to have developed prototype devices for evaluation.

Professor McAlpine is Director of the UCL Ear Institute, which is strongly committed to translation and enterprise, to benefit those with hearing loss. Improving the design of cochlear implants is one important theme, but the Institute is also exploring other potential interventions. It maintains strong links with Autifony Ltd, a start-up company spun out of GSK in 2011. Professor McAlpine is a member of the company’s Scientific Advisory Board, and he and Dr Jennifer Linden have worked with the company on a promising pharmacological treatment for tinnitus, now in phase I trials.

To support enterprise-related research, the Institute has also appointed a resident technology transfer specialist, Dr Denise Goldman, who provides an important link to the TRO and UCLB. Dr Goldman offers advice and support to the Institute’s researchers interested in translating their work and develops and manages relationships with commercial partners. The Institute also benefits from its close links with the Royal National Throat, Nose and Ear Hospital, and associated capacity for clinical research and trials.

THE ABC OF BETTER COCHLEAR IMPLANTS
Working with commercial and academic partners in Germany and France, Professor David McAlpine is hoping to increase significantly the numbers of people benefiting from binaural cochlear transplants.

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AN EYE ON INNOVATION

Professor Sir Peng Tee Khaw is one of the UK's leading proponents of translation. His ambitious goal now is to transform treatment of an eye disease affecting millions worldwide.

In 2012, Professor Sir Peng Tee Khaw had the rare honour of being invited to take part in the 'Audacious Goals' initiative being run by the National Eye Institute, part of the US National Institutes of Health. To start with, researchers had just one page to make a compelling case for a groundbreaking programme. Professor Khaw came up with the '10:10:10' challenge in glaucoma: to reduce fluid pressure in the eye to 10 mmHg for 10 years in an operation lasting 10 minutes. If successful, the programme could save the sight of millions of people worldwide. It is the kind of ambitious thinking that has made Professor Khaw and the UCL Institute of Ophthalmology world leaders in both research and translation.

To lower eye pressure, Professor Khaw improved surgical interventions that, in effect, created new drainage channels from the eye. Unfortunately, scarring severely reduced the effectiveness of the treatment, driving Professor Khaw back to the lab to understand more about the processes involved in scarring and how they might be counteracted.

In a hallmark of Professor Khaw's approach to translation, the work drew on an interdisciplinary collaboration encompassing surgery, biomechanics and fluid mechanics as well as cell biology. The resulting 'Moorfields Safer Surgery System' has been shown to result in better outcomes and has been widely adopted around the world.

Yet, he argues, there is more to be done. Even with his innovations, surgery is complicated. The vision of the '10:10:10' challenge is of a more simple procedure that has lasting and profound benefits.

To turn this audacious goal into reality, he has pulled together an interdisciplinary team spanning clinicians, biomaterials researchers, flow engineers, polymer specialists, pharmacists, and cell and molecular biologists (as well as the unsung heroes, such as project managers who ensure everyone stays on track). His team has drawn in world-leading experts from UCL but also industrial experts and partners, who bring invaluable technical skills and experience of regulatory pathways and product delivery.

Professor Khaw has a remarkable track record in innovation. As well as surgical systems and anti-scarring therapeutics, he has redesigned instruments for eye surgery and developed novel approaches for drug delivery to the eye. This strong emphasis on translation is reflected in the close integration between the UCL Institute of Ophthalmology and Moorfields Eye Hospital, including a shared research strategy strongly informed by clinical need. Another essential ingredient is clinical research infrastructure, particularly the NIHR Biomedical Research Centre uniting research institute and hospital and its associated Clinical Trials Facility.

He has, he suggests, lived through a sea change in attitudes to translation. His message to young clinical academics is that, with funding and facilities in place, the opportunities for translation have never been greater.

A CELLULAR SUCCESS STORY

UCL has led the world in its use of cell-based therapies. Much has depended on the cell medicines facility developed by Dr Mark Lowdell.

There is growing interest in the use of cells as therapeutic agents, particularly immune cells in cancer treatment and stem cells in regenerative medicine. With a background in bone marrow transplantation, Dr Mark Lowdell has been ideally placed to respond to the changing status of cellular therapies in medicine and contribute to pioneering studies in multiple disease areas.

Based at the Royal Free Hospital, Dr Lowdell joined UCL in 1994, taking on responsibility for a facility producing cells for use in treatment of haematological cancers. In the late 1990s, regulations began to be introduced to cover the use of cell therapies. Anticipating these changes, Dr Lowdell established the first UK laboratory capable of manufacturing human cells as medicines, working to full pharmaceutical standards – enabling UCL researchers to take a lead in the development of cellular therapies.

One example emerged from Dr Lowdell's own research on acute myeloid leukaemia, examining why only some patients mounted immune responses to their cancers after treatment. This turned out to reflect the capacity of the leukaemia to trigger a natural killer (NK) response, a discovery that enabled Dr Lowdell to develop a method to stimulate anticancer NK cells. This technology is being commercialised by Coronado Biosciences, with Dr Lowdell contracted as a consultant.

Thanks to his background, Dr Lowdell has been able to gain formal recognition as a 'qualified person', enabling him to sign off pharmaceutical agents for clinical trials. This greatly facilitates the planning and organisation of clinical trials. He is now involved in multiple trials of cellular therapies, including mesenchymal stem cell therapies, a dendritic stem cell vaccine for neuroblastoma and Professor Martin Birchall and colleagues' pioneering trachea and larynx transplants (see page 24).

His facility has also established a close relationship with a UK biotech company Cell Medica. The company is working with Professor Waseem Qasim on a T-cell-based therapy against adenovirus in children receiving a stem cell transplant, funded by the Technology Strategy Board, and with Dr Karl Peggs on a similar approach for cytomegalovirus, funded by the Wellcome Trust.

Dr Lowdell is a member of Cell Medical's Scientific Advisory Board, alongside other UCL researchers.

Dr Lowdell suggests that a new era of cell-based therapies is dawning. However, the translational pathway is likely to be more complex than the traditional biopharmaceutical route, calling for extended developmental stages in which researchers, clinicians and translational specialists refine technologies in collaboration with commercial partners. These collaborations will ensure that, as well as generating a landmark paper, a technology can also provide benefits to patients.
Work with clinical populations is essential to successful translation – and through its health service partners UCL has outstanding access to patients.

A critical step in the translation of new therapies is initial testing in human subjects. If therapies appear safe for human use, larger studies can be envisaged to demonstrate clinical efficacy. Through close associations with specialist and general hospitals, UCL has unrivalled access to patients and excellent facilities in which to test the impact of new medicines in people.

Central to the integration of clinic and lab are the Biomedical Research Centres and Biomedical Research Unit supported by the National Institute for Health Research (NIHR).

Uniquely, UCL has three NIHR Biomedical Research Centres and one Biomedical Research Unit:
- UCLH Biomedical Research Centre (specialising in cancer, infection and immunity, cardiometabolic conditions and neuroscience),
- Great Ormond Street Hospital–UCL Biomedical Research Centre (paediatrics and child care),
- Moorfields Eye Hospital–UCL Biomedical Research Centre (eyes and vision),
- UCLH–UCL Dementia Biomedical Research Unit.

Each hospital site includes state-of-the-art clinical research facilities in which studies on humans can be carried out. A recent addition to these facilities is the Leonard Wolfson Experimental Neurology Centre, located within the National Hospital for Neurology and Neurosurgery in Queen Square. Opened in 2013, research at the Leonard Wolfson Centre focuses on further characterisation of dementia and other neurodegenerative conditions but, importantly, it is also a much-needed site at which first-in-human studies of experimental therapies can be carried out. In time, these will include agents developed through UCL’s partnership with the Eisai pharmaceutical company.

An umbrella for interactions with clinical populations is provided by UCL Partners. A partnership between UCL, UCLH and other academic and health service organisations, UCL Partners has been established to integrate clinical practice and research, to drive forward research of relevance to patients, and promote the uptake of innovative new treatments into the health service.
UCL Partners encompasses some 100,000 health professionals and academics, across 13 higher education institutions and research networks, 24 acute, community and mental health providers, and 20 Clinical Commissioning Groups, serving a population of six million people in north and west London and surrounding areas.

UCL Partners is one of five accredited Academic Health Science Centres (AHSCs) in the UK. UCL Partners also acts as an Academic Health Science Network (AHSN), developed to accelerate the uptake of innovative therapies within the NHS. Based on a model of collaboration across healthcare, academia and industry, the AHSN aims to improve health and generate wealth by driving forward the adoption of emerging and proven therapies and medical technologies.

Collectively, these structures provide a wealth of opportunities to engage both clinicians and patients in research, carry out first-in-human and other early-phase trials, and assess implementation within the health service.

New opportunities

Major new developments at UCL will provide additional opportunities for translation and enterprise:

Institute of Immunity, Infection and Transplantation: This new centre at the Royal Free Hospital will provide a critical new site for translational research in vaccination, gene therapy and cell therapy, as well as conventional treatments, across a wide range of disease areas.

Bloomsbury Research Institute: A joint initiative between UCL and the London School of Hygiene and Tropical Medicine, the Bloomsbury Research Institute will focus on the major global infectious diseases such as HIV, TB and malaria. As well as work on diagnostics and therapies, the Institute will play an important role in global health policy.

Francis Crick Institute: UCL is a founding academic partner in the Francis Crick Institute, a European powerhouse in research due to open in 2015. UCL’s research expertise, facilities and access to partner specialist hospitals will be an important route by which research at the Crick Institute will ultimately benefit patients.

King’s Cross: Planned new facilities for the UCL Institute for Ophthalmology and Moorfields Eye Hospital near King’s Cross will include incubator space for development of new spinoffs. Commercial incubator space is also being developed at the UCL Institute of Cognitive Neuroscience.

Institute of Orthopaedics and Musculoskeletal Sciences: Redevelopment of the Stanmore Campus, with new facilities for both the Institute of Orthopaedics and Musculoskeletal Sciences and the associated Royal National Orthopaedic Hospital, will enable the Institute to develop further its world-leading translational research (see pages 24, 25).
INNOVATIVE THERAPIES

Genes, cells and neuropsychology are all being used as the basis for innovative new therapies.
Gene therapy has held great promise for many years. Now that promise is beginning to be realized, with successful trials in a range of diseases. UCL researchers have been world leaders in this area.

A major challenge now is not just to improve the efficiency of gene therapy, and to expand the range of conditions to which it can be applied, but also to establish mechanisms by which it can be introduced more widely into clinical practice.

Researchers at the UCL Institute of Child Health, led by Professor Bobby Gaspar and Professor Adrian Thrasher, were among the first to use gene therapy to treat inherited immunodeficiencies (see page 32). Having shown long-term success with gene therapy, the team is now testing new, safer vectors and discussing with potential partners how the technology could be introduced into other centres.

Another successful application has been in haemophilia, where Professor Amit Nathwani and colleagues have successfully treated adults with haemophilia B, caused by mutations affecting the blood clotting protein factor IX (see page 32). A similar treatment has been developed for the more common haemophilia A, caused by abnormal factor VIII. This technology has been licensed to the US biotech company Biomarin, which is scaling up production for clinical trials and possible clinical use.

The haemophilia example also illustrates an important aspect of novel therapies for inherited disease. It currently costs £140,000 a year to provide a haemophilia B patient with the protein they are missing and £100,000 a year to treat each haemophilia A patient. In trials, in several cases a single round of gene therapy has been sufficient to eliminate the need for routine blood-clotting injections. To date, Professor Amit Nathwani estimates that the haemophilia B trial has saved around £2m in health service costs. Hence, as well as a huge commercial opportunity, the new technology could also be economically beneficial to the health service.

Gene therapy has also been applied to inherited eye diseases. Professor Robin Ali, Dr James Bainbridge and colleagues pioneered the use of gene therapy to treat an inherited form of sight loss, Leber congenital amaurosis (LCA). The clinical success of this trial is now leading to a range of programmes focused on other forms of LCA, and other inherited eye diseases such as retinitis pigmentosa and achromatopsia. The group is also exploring the
IN SEARCH OF THE LIFELONG CURE

‘Cure’ is a dangerous word to use, but in paediatric gene therapy, the signs are that the pioneering work of Professor Bobby Gaspar, Professor Adrian Thrasher and colleagues is leading to genuine lifelong cures.

Gene therapy has had its fair shares of ups and downs. But, argues Professor Bobby Gaspar, that is only to be expected of a new medical technology. With researchers and clinicians at the UCL Institute of Child Health and Great Ormond Street Hospital, Professor Gaspar, Professor Thrasher and colleagues have pioneered the use of gene therapy in children with inherited immunodeficiencies – running two of the world’s first four successful clinical trials. Now, a major challenge is to find ways to establish gene therapy as a routine treatment.

Conceptually, gene therapy is very simple: a new gene is inserted into a patient’s cells to restore missing or abnormal function. For one class of patients, the approach seemed very attractive. Children with inherited forms of severe combined immunodeficiency (SCID) can be treated by bone marrow transplantation, but if the match between donor and recipient is poor, the likelihood of success is greatly reduced.

The first two gene therapy trials, in 2001 and 2003, were for two forms of SCID, caused by mutations in different genes. They were remarkably successful, with the children treated now at school and living essentially normal lives.

One issue did emerge, however. The viral vector used to deliver the gene to a patient’s cells had a tendency to activate growth-control genes close to points of insertion, leading to proliferation of some forms of blood cell. The effect was seen in all early trials; one UK patient was affected (but successfully treated).

As a result, the vector has been newly engineered so that it cannot activate genes close to insertion sites. New trials are now underway for SCID and also for other conditions affecting bone marrow cells, including Wiskott–Aldrich syndrome and chronic granulomatous disease. In addition, some patients are being treated on compassionate grounds, outside the context of a clinical trial.

The technology is entirely ‘homegrown’, having been conceived, developed and first used locally. Professor Gaspar and Professor Thrasher pay tribute to the many individuals that have contributed to its success – laboratory scientists, translational researchers, clinicians, clinical research facility staff and many others.

Now, having solved numerous technical issues, the team faces a new challenge – ensuring others can benefit from the technology. Discussions are underway with potential commercial partners with a view to making the technology more widely available. The diseases are rare, and there are no precedents for the commercialisation of gene therapy, so Professor Gaspar and Professor Thrasher are again breaking new ground. Although very different from the scientific challenges, solving them will help to ensure many more patients gain access to life-changing treatment.

AN END TO INJECTION

Professor Amit Nathwani has seen gene therapy for haemophilia go from dream to reality.

In 1999, Professor Amit Nathwani took time out from his haematology training to work on a PhD. His main aim, he admits, was to learn new techniques in cell and molecular biology which might be useful in studies of blood disorders. It turned out to be the beginning of a journey that led to the world’s first successful gene therapy for haemophilia.

During his PhD, it struck Professor Nathwani that single-gene blood disorders were ideal candidates for gene therapy. After an abortive attempt at haematopoietic stem cell modification for sickle cell disease, he settled on haemophilia B, caused by lack of a clotting protein, factor IX.

Although not the first to attempt gene therapy for haemophilia, Professor Nathwani and his US mentor and collaborator Professor Art Nienhuis made a number of key innovations. These included introducing a new strain of viral vector, developing more reliable animal models, targeting injection to the liver, and sophisticated engineering of the factor IX expression cassette. These innovations came together in a clinical trial which generated, for the first time, clinically significant expression of factor IX in haemophilia B patients.

For some trial participants, the therapy has been life-changing. Even low-level expression – 2 per cent of normal – can do away with the need for regular injections of protein IX. And as treatment is so expensive – £140,000 a year per patient – the trial itself has provided healthcare savings of around £2m.

Heartened by this success, Professor Nathwani has adapted his technology for the more common haemophilia A, linked to abnormal factor VIII. This is technically more challenging – factor VIII protein has a shorter half-life while the factor VIII gene is larger and not a good fit for the viral vector his group uses. Nevertheless, with more engineering, Professor Nathwani has generated vectors showing excellent performance in animal models.

On the back of these encouraging developments, UCLB and Professor Nathwani have negotiated a major agreement with a US biotech company, BioMarin, which is scaling up production for clinical trials. With treatment currently costing £100,000 per patient per year, and the global market worth £8bn, there are rich rewards to be reaped – but also the prospect of greatly reduced healthcare costs.

As well as advising BioMarin, Professor Nathwani is also looking at other potential applications of his technology. Alongside other single-gene blood and metabolic conditions, he has also developed a vector targeting liver cancer, which is switched on in cancer cells, producing a cytotoxic protein, but inactive in normal cells.

Gene therapy has been in turn hyped and written off. In reality, says Professor Nathwani, its development has not been too dissimilar from other novel therapeutic approaches – and its safety record has been superior to that of other experimental treatments now seen as routine.
potential of gene therapy to deliver growth factors or other biomolecules into the eye, to prevent cell loss and preserve sight. The group is engaged in discussions with potential commercial partners to establish routes towards large-scale clinical trials and ultimately clinical application.

As well as DNA-based therapies, some research teams are exploring the potential of RNA-based therapies. One of the most notable is the ‘exon-skipping’ approach being applied by Professor Francesco Muntoni and colleagues to Duchenne muscular dystrophy, caused by mutations affecting the muscle protein dystrophin. Using RNA-like therapeutics, the team aims to eliminate a mutation-containing coding region, or exon, during RNA splicing, so a shorter but still partially functional protein is produced. Clinical trials have shown that the technique is safe and significantly increases dystrophin levels in muscle. The work is being extended through a £4.4m EU Health Innovation grant, supporting a European consortium that also includes Sarepta Therapeutics in the USA, which will target a second mutation-containing exon.

The exon-skipping approach has also been adopted by Dr Bernard Khoo and colleagues, to treat familial hypercholesterolaemia, an inherited condition characterised by dangerously high cholesterol levels. A significant advantage of Dr Khoo’s approach is that exon skipping, applied to the apolipoprotein B gene, generates an alternative form of the protein with known cholesterol-lowering properties.

One of the first commercial applications of gene therapy was pioneered by Professor John Martin. Back in 1997, Professor Martin came up with the idea of gene therapy to prevent blockage of ‘haemodialysis access loops’ – vessel grafts used in patients undergoing long-term blood dialysis, which are susceptible to ingrowth of the arterial wall. Having written his own patent application, Professor Martin went on to secure venture capital to develop a business plan and set up a company that later morphed into Ark Therapeutics. In 2004, Ark Therapeutics was floated on the London Stock Exchange. Ark Therapeutics has gone on to follow its own commercial pathway. While maintaining some links with the company, Professor Martin has also been exploring alternative routes of translation – including an imaginative new venture, Magnus, which has attracted substantial private equity funding.

Professor Martin has brought together five innovative technologies under the umbrella of Magnus, securing some £15m in equity funding to drive forward translation through phase I studies.

A second Magnus project is using gene therapy technologies, to tackle the devastating consequences of fetal growth restriction. The project, being led by Dr Anna David, has been awarded €6m EU Framework Programme 7 funding (see page 34). Most of the projects draw on Professor Martin’s own inventions and have already secured substantial translation funding. One project is based on a biodegradable magnetic stent. Commonly used to treat narrowed arteries, stents are themselves prone to narrowing or becoming blocked, requiring replacement. Funded through the EU Framework Programme 7, the BIOMAGSCAR consortium aims to overcome this problem through use of a biodegradable magnetic stent and stem cells tagged with magnetic nanoparticles. The stem cells will be attracted to the stent and seed the formation of a new vessel, which will remain when the stent disappears. The project is being led by Professor Martin and his colleague Professor Anthony Mathur.

Brain training’ may be able to mitigate the effects of neurodegeneration.

Gene therapy is showing promise in a range of conditions.
A VISION OF TRANSLATION

Professor Robin Ali has put together a team of scientists and clinicians that is making ground-breaking progress in both gene and cell therapies for eye diseases.

A geneticist by background, Professor Robin Ali has spent 20 years pioneering gene therapy for inherited retinopathies, achieving some of the world’s first positive results in any kind of gene therapy. With a complementary highly promising cell therapy research programme, he and his colleagues have generated a translational research portfolio of remarkable breadth, spanning rare and more common diseases of the eye.

Over the past decade, gene therapy has begun to realise some of its immense potential, with a string of successful applications. One of the most notable was work carried out by Professor Ali, Professor James Bainbridge and colleagues on Leber’s congenital amaurosis (LCA), published to some acclaim in 2008. Further LCA patients have now been treated, with similarly positive results. However, LCA is just one of a range of conditions that Professor Ali’s team has been targeting. In proof-of-concept studies, Professor Ali has shown that gene therapy is a feasible approach for around a dozen inherited retinal conditions. Moreover, the approach may also be a way to deliver therapeutic molecules to treat other, more common conditions.

Although less advanced, exciting progress is also being made in cell transplantation. In a series of landmark papers, Professor Ali and colleagues have shown that early retinal progenitor cells – from a narrow developmental window – can integrate into the mouse retina, wire up with existing cells and improve vision. His group has also shown that such cells can be grown from embryonic stem cells in culture. However, more work will be needed before clinical trials can be considered.

Nevertheless, Professor Ali’s team has begun to gain experience of clinical application, in a trial being carried out in partnership with the US company Advanced Cell Technology, Inc (ACT) and led by Professor Bainbridge. ACT has developed a way to generate one type of retinal cell, retinal pigment epithelial cells, from embryonic stem cells, which are being tested as a possible therapy for the inherited retinopathy Stargardt disease.

Back in the laboratory, Professor Ali is also making exciting progress in cone transplantation. Responsible for colour vision, cones are an even greater challenge, but would offer additional visual benefits.

Both gene therapy and cell therapy are attracting commercial interest, particularly the former. Professor Ali is in discussion with UCLB and potential investors to identify routes of commercialisation, potentially through a new spinout company. Part of the challenge is to identify the business models that will make gene therapy economically sustainable – requiring extensive discussion with regulators on possible pricing arrangements. Resolving these issues, and finding commercial investors willing to fund late-stage clinical development, will be essential if gene therapy for the eye is ultimately going to move from experimental to mainstream treatment.

A MAN WITH AN AMBITIOUS PLAN

Professor John Martin is a fervent believer in the power of universities to shape society – and has persuaded others to invest millions in an ambitious plan to rewrite the rules of commercial translation.

In 1997, Professor John Martin set up a company that went on to become Ark Therapeutics, initially to commercialise a gene therapy technology. Fast forward 16 years and he is pioneering an entirely new approach to translation, having secured £15m of private equity funding to support work on a basket of innovative therapeutics.

Professor Martin adheres to the idea that universities, uniquely, have the intellectual capacity to understand disease and to come up with innovative new approaches to treatment. Furthermore, the NHS provides access to the clinical populations in which these treatments can first be applied. In particular, with its formidable intellectual expertise, therapeutic development resources, and outstanding links to NHS infrastructure, UCL has an unmatched opportunity to pursue therapy development from concept to validated product.

The key ingredient that is missing is the financing. In particular, while translational funding is now more widely available to progress promising laboratory studies, it still remains difficult to cross the ‘valley of death’ – to reach the point at which an agent has demonstrated safety and efficacy in patients.

Professor Martin has pinned his hopes on a novel source of funding – private equity. He has established a new company, Magnus Life Science, which will hold intellectual property on five innovative health technologies, four of which were initiated by Professor Martin, and has secured £15m in private equity funding to drive each through to completion of phase I studies.

The five projects are being led by colleagues of Professor Martin at UCL. Professor Mervyn Singer is leading a project that aims to mimic the effects of hibernation, to improve mitochondrial activity after a heart attack and protect heart muscle. Professor Anthony Mathur is heading a project developing a biodegradable magnetic stent, which will attract stem cells tagged with metallic nanoparticles and seed formation of a new blood vessel. Dr Anna David is using gene therapy to boost the growth of placental blood vessels in mothers at risk of delivering abnormally small infants. Professor Ian Zachary is targeting the neuropilin pathway to develop new diabetes treatments. And Professor Dave Selwood is developing a new agent for melanoma, again by targeting neuropilin.

Each project is innovative, addresses a significant unmet medical need, and has the potential to make a major difference to people’s lives. Assuming they generate positive safety and efficacy data, they are likely to be immensely valuable and highly attractive to companies able to complete commercial development and launch products. If the approach succeeds, says Professor Martin, it is a model that could profoundly change the commercialisation landscape in universities.
A project being led by Professor Mervyn Singer aims to protect heart muscle after a heart attack, by mimicking the effects of hibernation, which leads to increased efficiency of mitochondrial activity and energy use. Two further projects are based on more conventional pharmaceutical development. Professor Dave Selwood is targeting neuropilin (a vascular endothelial growth factor receptor) to develop new melanoma treatments, while Professor Ian Zachary is working on the same target to modulate fatty acid metabolism in diabetes.

The cellular route

Cell-based therapies are a further area of intense interest, and one in which UCL has world-leading expertise – not least in regenerative medicine, where stem cells and new materials are being put to therapeutic use (see pages 20-25).

Eye repair is a further area where cell therapies are showing great promise. In the London Project to Cure Blindness, a collaboration between Professor Pete Coffey at the UCL Institute of Ophthalmology and Dr Lyndon da Cruz from Moorfields Eye Hospital, embryonic stem (ES) cells are being tested as a way to treat age-related macular degeneration, the most common form of blindness in later life. This work is being progressed in partnership with Pfizer.

Also at the UCL Institute of Ophthalmology, Professor Robin Ali and colleagues are exploring the potential for cell transplantation therapies for inherited conditions, particularly for situations in which many cells have been lost and hence gene therapy is unlikely to be effective. In landmark animal studies, Professor Ali and colleagues have shown that transfer of immature photoreceptor cells can integrate into the eye and improve vision. Recent work has explored the potential of generating human precursor photoreceptor cells from ES cells.

Although not as advanced as his gene therapy research, Professor Ali has begun to lay the foundations of clinical application, for example in a clinical trial being undertaken on behalf of the US company Advanced Cell Technology, which is testing the ability of retinal pigment epithelial cells derived from ES cells to treat Stargardt macular dystrophy.

As well as these constructive uses of cells, other researchers are exploiting their destructive powers, for example to treat infections or cancer. A common starting point is the T cell, which has the power both to orchestrate immune responses and to kill cells directly. Sophisticated T cell manipulations are being used in bone marrow transplantation, to improve clearance of blood cancer and prevent opportunistic infections. Further advances may come from the innovative combination of genetic and cellular approaches.

Dr Martin Pule, for example, has developed techniques to re-engineer T cells so that they specifically target cancer cells (see page 36). He is working with the biotech company Cellectis, which has developed innovative ways to precisely engineer the human genome, opening up new ways of adapting T cell behaviour. T-cell engineering is also being developed by Professor Hans Stauss, head of a new Institute of Immunity, Infection and Transplantation at the Royal Free Hospital, and Dr Emma Morris. In addition, modification of regulatory T cells, which act to dampen down immune responses, may be a way to limit reactions to specific antigens driving autoinflammatory responses.

Modifying brains

One of the most remarkable properties of the brain is its plasticity – its capacity to change with experience. From a therapeutic point of view, neural plasticity means that brain function can be modified by brain use, which underlies approaches such as neurorehabilitation.
An ultrasound scan mid-pregnancy usually provides assurance that all is going well. But for a small number of mothers, it can bring bad news, revealing abnormally slow fetal development – fetal growth restriction. With no treatment available, mothers will inevitably give birth to a severely underdeveloped baby. To address this serious problem, Dr Anna David is preparing to treat pregnant mothers by gene therapy to boost blood supply to the uterus and placenta to promote fetal growth – the first programme of its kind anywhere in the world.

Dr David’s programme is one of five within Professor John Martin’s Magnus initiative (see page 34). Indeed, its origins lie in a conversation between Professor Martin and her then boss, Professor Charles Rodeck, in 2005. They came up with the idea of using gene therapy to enhance levels of vascular endothelial growth factor (VEGF) in the uterine artery. Known to be critical to normal placental development, VEGF has several potentially useful properties, including the ability to promote new blood vessel growth.

Thanks to her clinical training in obstetrics and gynaecology, and a PhD in fetal gene therapy, Dr David was well placed to explore this imaginative idea. Dr David began with normal sheep, achieving both short-term and long-term VEGF expression, before collaborating with a group in Aberdeen to test the technology in a sheep model of fetal growth restriction. She has also introduced a guinea-pig model of fetal growth restriction to UCL. Collectively, the results have shown that the technology works, leads to changes in uterine artery blood vessel structure and function, leads to larger offspring, and appears to have no detrimental effects on either mother or infant.

These positive results helped Dr David secure £6m funding from the EU Framework Programme 7 for a six-year programme to apply the technology clinically. Funded through the Health 2012 initiative, the programme was one of just four funded in the ‘gene medicines’ stream.

Other consortium members include FinVector, which will be manufacturing the gene therapy vector used in the trial, and a new company, Magnus Growth, part of Professor Martin’s wider Magnus initiative, which will handle the innovation and exploitation aspects of the programme. This will include managing IP issues and dealing with regulatory affairs in preparation for phase I and, if all goes well, later phase II trials.

Dr David’s main aim is to buy time – to enable the fetus to develop for an additional four weeks in the uterus. Currently, babies are delivered very early, to avoid stillbirths, at the very limits of their survival potential and at high risk of many developmental abnormalities. Moreover, given the high cost of neonatal intensive care, effective treatment could have a substantial economic impact, potentially saving the EU around €50m a year.

The idea of using the body’s own defences to tackle cancer is far from new. But despite enormous effort, conventional cancer vaccines have mostly been a disappointment. Use of specific types of T cell has been more encouraging, but has been limited to special cases. Now, says Dr Martin Pule, innovative forms of genetic manipulation are greatly expanding the therapeutic potential of T cells.

T cells are excellent ‘killing machines’. The challenge has been how to direct their firepower at the right target – which is where the genetic manipulation comes in. The idea, says Dr Pule, is to engineer a patient’s own T cells so they recognise and attack cancer cells.

Dr Pule’s take on this approach is the ‘chimeric antigen receptor’ (CAR), which combines the recognition region of an antibody with the intracellular signalling domain of a T cell receptor. These are ultimate smart weapons, he suggests: they can move under their own steam, divide and signal to other cells. Within UCL, a clinical trial is already underway to treat acute lymphoblastic leukaemia, a second is opening soon for neuroblastoma, and a suite of others are in development.

Conceptually appealing though the approach is, however, it has a significant drawback. Treatment has to be tailored to each individual patient, making wider rollout difficult.

However, there may be a way to expand the application of CARs. Dr Pule has teamed up with the French company Cellectis, which has developed an innovative genome-editing technology known as ‘TALENs’. This technology can, specifically and with high efficiency, modify or disrupt any gene in the human genome. Dr Pule is working with the company to engineer generic donor T cells so that they do not attack the recipient (except the cancer cells they are engineered to recognise) and are not themselves attacked by the recipient’s immune system.

Such ‘universal’ CAR T cells could be used as an off-the-shelf product, eliminating the need to modifying a patient’s own cells. The first universal cells will be targeted at a B-cell marker, for treatment of leukaemias such as chronic lymphocytic leukaemia (CLL).

Dr Pule is excited at the potential of combining UCL’s cell engineering and early clinical trial expertise with Cellectis’s technology, in a genuine industry–academia collaboration. With the first clinical success stories appearing, the field has gone from a cottage industry to one attracting hundreds of millions in investment. He is excited by the opportunities arising from the influx of industrial expertise and funding, without which it would be difficult to be internationally competitive.

More generally, he remains a strong advocate for the burgeoning field of therapeutic cell engineering. The increasing complexity of genetic engineering possibilities, he suggests, has the potential to create treatments far much sophisticated and subtle than can be achieved with small chemicals.
THE MAN BEHIND THE AVATAR

Dr Julian Leff has developed a remarkably successful avatar-based therapy for people with schizophrenia who hear voices – in some cases, with genuinely life-changing results.

After a distinguished career in psychiatry, in retirement Dr Julian Leff had an idea about how new technologies might be able to help those whose lives are blighted by abusive voices. And with help from colleagues in UCL, he has been able to demonstrate that his approach actually works – findings that helped to secure major translational funding from the Wellcome Trust.

The voices experienced by people with schizophrenia are often persecutory and can greatly disrupt patients’ lives, making it impossible for them to hold down a job or form social ties. Notably, patients tend to hear the same voice repeatedly, and it is constantly talking at patients rather than taking part in conversations. However, some patients can establish a dialogue of sorts with their voices, and feel more in control as a result. This led Dr Leff to think about how such dialogue with internal demons could be encouraged – and came up with the idea of avatars.

His idea was to enable patients to create an avatar that personified the voice afflicting them – either a real person or an abstract personification, such as a red devil. Based in a separate room, the voice encouraged – and came up with the idea of avatars.

To create such a system, Dr Leff enlisted the help of two UCL researchers – Dr Mark Huckvale, an expert in voice morphing, and Dr Geoffrey Williams, who had already begun designing avatars to help deaf people learn to lip-read. With a team assembled, Dr Leff managed to secure a small grant to test the idea.

The results greatly exceeded Dr Leff’s expectations. Patients spent the first session creating their avatar’s physical form and voice, and 24 out of 26 patients confirmed that their avatar truly represented the source of their voices. Soon, it became clear that patients were responding – one even declared himself cured at the end of his third session. And formal analysis of the intrusiveness and unpleasantness of voices showed statistically significant falls compared with control groups at the end of therapy and at three-month follow-up. Moreover, at follow up, significant differences were also seen in depression levels.

These remarkable effects laid the foundations of a successful £1.3m bid to the Wellcome Trust, to test the approach on larger numbers of patients. Dr Leff is training other therapists to use the approach, while the software is being enhanced.

Dr Leff and his colleagues are also working with UCLB to protect the intellectual property associated with some of the newly developed software, and to consider other possible innovative applications of his approach.

POSITIVE FEEDBACK

Might a form of ‘brain training’ help to stave off the effects of neurodegeneration?

Early in her career, neuroscientist Dr Marina Papoutsi became excited by the prospect of ‘neurofeedback training’ as a way to harness the brain’s capacity to compensate for brain tissue damage. Through a major new translational award from the MRC, she and Professor Sarah Tabrizi are now putting the theory into practice.

Neurofeedback therapy relies on an effect known as ‘neural compensation’, through which the brain recruits additional regions to perform tasks previously carried out by damaged tissue. It is in effect a form of brain training, as subjects receive visual information about levels of brain activity and, with training, learn to enhance this activity and boost brain performance.

Since 2011, Dr Papoutsi has been working with Professor Tabrizi on the TrackOn-HD project, which has been characterising brain and other changes in a cohort of Huntington’s disease gene carriers, to identify markers of neurodegeneration. This population is well suited to neurofeedback therapy, as patients can be identified by genetic testing and treatment begun early in disease.

Furthermore, UCL researchers such as Dr Nikolaus Weiskopf, one of the pioneers of the technique, and Professor Geraint Rees had been using neurofeedback in basic studies, and will be contributing to its clinical application.

During neurofeedback, participants receive real-time visual feedback on brain activity in motor areas while they are undergoing an fMRI scan. They are then encouraged to imagine some form of movement, in order to increase activity in these areas. After three or four training sessions, participants learn to enhance activity even without visual feedback.

Pilot studies have shown that the approach is practical, that early-stage Huntington’s disease patients can learn how to modulate brain activity, and that performance on behavioural tasks improves as a result. The MRC-funded study will extend this preliminary work, in a controlled trial of 32 patients that will test patients’ ability to regulate activity in a specific area of the brain as well as a neural pathway affected in early disease.

The project also incorporates an important aspect of technology development. Huntington’s disease patients often show involuntary head movements, which is an issue for fMRI. Through use of a high-speed motion detection camera, Dr Weiskopf will be developing techniques to adjust data recordings in real time to take account of patients’ movements, with wider implications for fMRI use and clinical application.

The neurofeedback approach has several appealing features. Because it is non-invasive, it is safe and could easily be used in presymptomatic as well as patients early in disease. Furthermore, it could in principle be applied to other neurodegenerative conditions, such as Alzheimer’s disease.
SECTION 5

USING KNOWLEDGE

The ideas, expertise and knowledge of UCL researchers are being put to a wide variety of good uses.
The fruits of life science researchers’ labour may feed into the development of new therapies, diagnostics or medical products. But universities are home to large numbers of bright, creative thinkers whose specialist expertise could be applied in a wide variety of domains. Indeed, UCL researchers have established numerous external collaborations to apply their knowledge outside academia, often working with commercial partners.

An understanding of brain and behaviour, and how people respond to specific sets of circumstances, is potentially valuable in many spheres of life. Professor Nilli Lavie, for example, who studies the impact of attention and information load on perception, has found several outlets for application of her research and expertise (see page 41). She has established an agreement with the carmaker Toyota to investigate brain function in drivers under high information loads, and is also working with the UCL Centre for Space Medicine on information processing by astronauts.

Similarly, Professor Vincent Walsh has developed neuroscience and sport workshops applying principles of cognitive neuroscience to the challenges faced by sporting elites. His expertise has been drawn upon by, among others, the English Rugby Football Union, the English Hockey team, Team GB canoeing and the English Cricket Board. Professor Walsh was a scientific advisor to the RFU’s two-day Talent Symposium, held at the Royal Society, and he is now an official special advisor to the English Institute of Sport and cognition advisor to the GSK Human Performance Laboratory, a facility built to examine and promote elite performance.

In the world of medicine, many researchers draw on their expertise to advise small biotech or large pharmaceutical companies. This is particularly true of individuals whose technology has been licensed or incorporated into a spinout company, who often continue to act as scientific advisers.

A notable example is Dr Mark Lowdell, who runs the cell therapy facilities at the Royal Free Hospital and has played a central role in many of the cell-based therapies developed at UCL. Dr Lowdell maintains close ties with Coronado Biosciences, Inc., a company that licenses a cellular therapy for acute myeloid leukaemia developed by Dr Lowdell, based on activated natural killer cells. This therapy is being tested in clinical trials in the UK and the USA.

Acting as a consultant, Dr Lowdell continues to devote considerable time to the development of the product – a reminder
that clinical application of complex cellular therapies is not straightforward and relies on input from their originators. Scaling up from proof of concept to larger trials and, ideally, clinical adoption raises a host of practical issues. Addressing these challenges is essential if a promising new technology is to achieve its full potential.

The power of data

Biomedical research generates data, which may itself be of value to the development of diagnostics and therapeutics. One highly successful example is Abcodia, a company that has grown out of the UKCTOCS trial of screening for ovarian cancer, run from UCL. As part of this programme, serum samples were collected from more than 200,000 women volunteers. Abcodia grew out of the realisation that these samples were an invaluable resource for exploring the development of cancer, and in particular the development of biomarkers associated with particular forms of cancer (see page 41).

Unusually, the UKCTOCS samples are from presymptomatic women, rather than those already with a clinical diagnosis. Through analysis of these samples, it may therefore be possible to identify diagnostic biomarkers. Abcodia works closely with the Gynaecological Research Centre at UCL and commercial and other academic partners to use the data for health benefit. Such work should accelerate the development of tests to diagnose cancer at early stages and promote more tailored treatments.

Data from patient and clinical populations may also be of value in drug development. Professor Aroon Hingorani, for example, is exploring the potential of ‘Mendelian randomisation’ to shed light on disease mechanisms and the validity of potential drug targets (see page 42). The approach exploits the natural genetic variation in populations, assessing whether variation affecting potential target processes influences disease risk.

Health data may also contain trends important to commercial bodies. Professor Rosalind Raine has worked with Legal & General on socioeconomic modelling of inequalities in cardiovascular health. Other important work in this area has included a range of pharmacovigilance studies and other collaborations with pharmaceutical companies.

Data management is also at the heart of the work of Helicon Health, a spinout company drawing on software tools developed by the UCL Centre for Health Informatics and Multi-professional Education (CHIME) in collaboration with Professor David Patterson. Helicon Health works with commissioning groups to develop integrated community-based care packages for patients with long-term health conditions – benefiting patients but also generating savings to the health service. Its Helicon Heart package, for example, has been developed to guide anticoagulant and atrial fibrillation services and minimise stroke risk in heart disease patients. Developed over an eight-year pilot with the Whittington Hospital, it has already been implemented in north London and is being made more widely available through the Helicon Health spinout.

Much research has the potential to feed into policy making. While published papers provide one potential route of influence, there are other more proactive ways in which researchers can contribute to the policy-making process. One of UCL’s most active areas in policy is the UCL Institute of Health Equality, led by Professor Sir Michael Marmot – responsible for such landmark works as ‘Fair Society, Healthy Lives’ (‘the Marmot Review’, commissioned by the Secretary of State for Health and published in 2010) and ‘Closing the Gap in a Generation’, the influential report from the World Health Organisation’s Commission on the Social Determinants...
PAYING ATTENTION IN A WORLD OF INFORMATION OVERLOAD

Having developed an influential theory on attention and cognitive control, Professor Nilli Lavie is keen to see it have practical impact.

Professor Nilli Lavie’s research interests lie in the areas of attention and perception, particularly how the brain processes information from multiple sources, in conditions of overload. What captures attention and how can the brain focus in the face of irrelevant distraction? Her work has addressed the long-standing issue of whether the brain can multitask and has essentially unlimited capacity, or has limited resources and must prioritise. Professor Lavie has developed a theory to resolve this paradox, and is exploring opportunities to apply her theory in a range of settings in which processing of large amounts of information is critical.

Professor Lavie’s theory contends that selectivity is a function of how much data the brain has to deal with – information load. At low information loads, the brain is not selective – it does not need to be. But at high information loads, a selective process automatically kicks in to focus attention. In such conditions, the brain ceases to respond to some features of the environment, and people may experience ‘inattentive blindness’. In these cases, it is important to consider what information will be missed, how to alert people so that they can still detect critical information, and how to capture their attention so that important messages get noticed.

The work has numerous potential practical applications. In many sectors, it is important to find out how people respond to large amounts of information, and find ways to improve their perception to minimise inattentive blindness and avoid its potentially disastrous ramifications. Driver or pilot inattention, for example, is a common cause of crashes.

The ways in which information can be designed to capture attention, and so be detected even in situations of brain overload, feed into areas such as interface design and neuromarketing. Brain training programmes that enhance information-processing capacity could also prove valuable in many sectors, from complex defence operations to competitive sports.

Professor Lavie has established a collaboration with Toyota to investigate some of these questions. She is also working with UCL’s Space Medicine Laboratory, to understand how the brain responds in pressurised situations with high information loads – obviously crucial to the success of space expeditions. More recently, she has teamed up with the Ministry of Defence’s Defence Science and Technology Laboratory to establish new tests for processing capacity as well as new methods of brain training.

As a scientist who likes to explore the practical implications of her work, as well as a self-confessed gadget fan, Professor Lavie has been delighted to collaborate with world-leading engineering firms in the automotive and aerospace industries. But the whole experience has been enriching, she suggests, providing a wealth of opportunities to expand her and her collaborators’ horizons.

PAST, PRESENT AND FUTURE

Through the Abcodia UCL spinout company, biological samples collected for an ovarian cancer screening trial may lead to tests for other common cancers.

In the UKCTOCS trial, launched in 2001 at UCL by Professor Ian Jacobs and coordinated by Professor Usha Menon, some 200,000 women have provided blood samples to help validate a screening test for ovarian cancer. Recognising that these samples may have additional medical value, the UKCTOCS team arranged for any residual samples to be frozen and stored. Now, the UCL spinout company Abcodia, led by Dr Julie Barnes and initially funded by UCLB, is using this biobank resource to develop a successful business based on the development and testing of cancer biomarkers.

As part of the UKCTOCS trial, 200,000 post-menopausal women aged 50 and above provided an initial blood sample in 2001 and 50,000 women have provided samples yearly ever since, the total sample collection now exceeding five million. More than 27,000 women have gone on to develop a wide range of cancers. Crucially, because the samples were collected before diagnosis, they potentially hold clues to changes occurring before disease became established.

Through Abcodia, companies can gain access to UKCTOCS samples in order to develop new early-detection biomarkers or to validate existing assays. Abcodia also works with academic groups looking to develop tests, offering additional advice on commercialisation.

In 2013, the company also acquired rights to the screening test used in the UKCTOCS trial, known as ROCA (Risk of Ovarian Cancer Algorithm), which was developed by Professor Jacobs and biostatistician Professor Steve Skates. Abcodia has licensed the IP relating to ROCA and will be making the test available commercially.

Abcodia is also examining whether existing clinical biomarkers can be incorporated into ROCA-like algorithms. One example is the CA19-9 test for pancreatic cancer, which is not currently recommended for diagnostic use. An analysis of changes in CA19-9, however, alongside other biological information, may enable a diagnostically useful tool to be developed.

The company has also established a partnership with Cancer Research UK (CRUK) to stimulate the development of new screening methods. CRUK is providing funding so that companies or academic groups can apply novel technologies to UKCTOCS samples to identify new diagnostic biomarkers. Abcodia and CRUK’s technology transfer arm, Cancer Research Technology, will work jointly to commercialise any promising biomarkers.

The initiative has relied on the consent provided by the UKCTOCS participants, which allows for academic and commercial research on data and samples. The company maintains close contact with the UCL UKCTOCS team, which remains guardians of the study, to agree use of samples and to manage IP arising from commercial and academic studies. Ultimately, this close liaison will ensure not only that new patient benefits emerge from research on the samples but also that UCL gains a financial return.
POWER OF THE PEOPLE

‘Genomic epidemiology’ offers an innovative new way to improve the efficiency of drug development, says Professor Aroon Hingorani.

Drug development is a long complex process with a high risk of failure. Late-stage failure in particular can mean the loss of huge sums of money. One way to lower this risk, argues Professor Aroon Hingorani, is to take advantage of the natural genetic variation in human populations to shed light on disease mechanisms and validate potential targets.

Professor Hingorani and his colleague Dr Juan Casas Romero are advocates of an approach known as ‘Mendelian randomisation’. Population studies can identify associations between biomarkers and disease, but such associations could be a secondary effect independent of disease or a consequence rather than cause of disease (‘reverse causation’). Mendelian randomisation addresses this issue. It relies on the fact that genetic variants affecting levels of a particular biomarker are distributed at random through a population, and do not change.

So, if high levels of a particular biomarker are truly contributing to disease, genetic variants affecting this biomarker should also be associated with disease.

To test the idea, Professor Hingorani, Dr Casas Romero and colleagues have examined a range of cardiovascular conditions in which biomarkers have been identified as potential risk factors. Using a range of patient and healthy population cohorts, they have then looked to see whether genetic variants affecting these risk factors are associated with disease.

In a striking proof of principle, they found that two metabolites argued to be important in heart disease – C-reactive protein and fibrinogen – were actually unlikely to be causally involved in disease. Increased levels were likely to be a consequence of other disease processes.

Furthermore, the approach may also suggest new uses for existing drugs. High levels of interleukin-6 (IL-6) are associated with increased risk of heart disease, suggesting that the IL-6 signalling pathway could be an important therapeutic target. Notably, an antibody targeting the IL-6 receptor, used to treat rheumatoid arthritis, reduces inflammation and has potential application in heart disease. By confirming that disease risk was influenced by natural genetic variants affecting IL-6 receptor levels, Professor Hingorani and colleagues were able to validate the pathway as a target and provide evidence in support of trials in heart disease.

Although so far applied mainly in heart disease, the approach is suitable for other complex conditions where biomarkers have been identified, says Professor Hingorani. Such studies have the advantage that they are examining the biology of disease in human subjects rather than animal models. They can also be carried out in early stages of drug development, informing decision-making before expensive clinical trials are run. His group is looking to establish collaborations with industrial partners to apply the approach to improve the efficiency of drug development.

THE TROUBLE WITH MEN

Dr Sarah Hawkes sees influencing policy as a critical aspect of public health research.

Dr Sarah Hawkes focuses on the links between research evidence and policy processes. Based in UCL’s Institute for Global Health, she has a particular interest in sexual health. While sexual health covers a wide range of areas, from HIV to gender-based violence, Dr Hawkes has a particular focus on men – not just their attitudes and behaviour towards women but also their concepts of masculinity and behaviour towards each other.

Having spent the last 20 years living or working in south Asia, Dr Hawkes has an in-depth knowledge of the region. And having gained extensive knowledge of sexual health and gender issues, and established close ties with bodies such as the WHO and UN agencies, she is often called upon to advise local organisations, governments and multilateral agencies on ways to influence policy and practice.

Research generates a body of knowledge to support evidence-based policy making. Although health officials could draw on this published evidence, Dr Hawkes suggests they have neither the time nor possibly the expertise to evaluate research information. They require information more specifically tailored to their needs.

This is where consultants such as Dr Hawkes can play a critical role, using their expertise to analyse and interpret information, and to advise on possible courses of action. This kind of work, she suggests, is an important way of bridging the gap between the wealth of evidence generated by academic studies and its use in practice. One challenge is to recognise that advice needs to be pragmatic and reflect political realities: policy typically evolves in small steps rather than through revolution.

Dr Hawkes is a committed supporter of using knowledge gained through research. Publication of research findings, she suggests, should be a starting point not an end in itself. The next step should be to see evidence used in ways that deliver benefits. As research funders may not see that as their responsibility, consultancy can be the critical link to achieving an impact on global and national policy and practice.

A good example is her work on mother-to-child transmission of syphilis. Although largely eliminated in many countries, with UN funding Dr Hawkes was able to show that it was still affecting some 1.3 million pregnancies a year worldwide and resulting in hundreds of thousands of lost pregnancies. This information has been used by the WHO to call for national programmes to roll out syphilis testing for every pregnant woman. Achieving change is hugely satisfying, she says, but not trivial – the rollout programmes are the culmination of at least a decade’s work.

She is also pleased to see young researchers equally eager to have an impact on policy and practice. Her advice is to ensure they have a sound basis on which to begin attempts to influence policy. Recommendations are likely to carry greater weight when backed up by a credible academic reputation.
of Health. The Institute is now engaged in a wide variety of national and international work on the impact of inequalities on health and how they can be addressed.

As well contributing to consultation exercises, researchers can also use their expertise as formal consultants, synthesising evidence for governments, international bodies or other clients. With support from UCL Consultants, Dr Sarah Hawkes, for example, has drawn upon her extensive knowledge of sexual health to advise a wide range of national and international clients (see page 42).

UCL has also joined forces with the University of Oxford to establish the Centre for the Advancement of Sustainable Medical Innovation (CASMI). CASMI aims to harness the unmatched interdisciplinary expertise at its host institutions to develop new models of innovation within the health service, with the ultimate aim of accelerating the development and implementation of new therapies and devices within the UK health system. It is addressing a wide range of issues, from open innovation to the translation of stem cell technologies.

UCL public health researchers have also worked directly with large companies on workforce health. Professor Elizabeth Murray has collaborated with BT on a project addressing staff alcohol consumption, while Professor Andrew Steptoe and colleagues have worked with Google and Roche on staff well-being programmes.

Acting as a consultant can enable UCL staff to draw upon their in-depth knowledge in unusual areas. Professor David Balding’s knowledge of statistics and genetics, for example, is in high demand by the legal profession (see right). Other individuals have advised Kew Gardens on the use of micro-organisms as biological agents in pest control and the United Arab Emirates on cloning of their national bird, the endangered Houbara bustard.

IN THE DOCK

A mathematician by background, Professor David Balding has carved out a niche as an expert in the legal use of DNA evidence.

In his day job, Professor David Balding uses his statistical skills and genetic knowledge in studies of genetic contributions to disease, or in ethnographic studies of human genetic diversity. Much of his time, however, is now spent advising courts on the interpretation of DNA evidence.

Professor Balding became involved in forensic applications in the 1990s when a friend alerted him to the difficulties the Metropolitan Police Forensic Science Laboratory were experiencing with the interpretation of DNA evidence, particularly dealing with the influence of population structure. Professor Balding realised he had the expertise to help, and gradually found himself called on as an expert witness.

DNA evidence has been particularly contentious since the introduction of ‘low copy number’ methods to analyse vanishingly small amounts of material. The technology was heavily criticised by the judge in the trial of Sean Hoey for involvement in the Omagh bombing. Following a review by Brian Caddy, the technique remains in use in the UK and increasingly in other countries.

The key challenges, says Professor Balding, relate to the interpretation of phenomena such as ‘drop outs’ or ‘drop ins’, unexpected omissions or additional peaks that lead to imperfect matches. ‘Masking’ may also be an issue, whereby low-level DNA alleles from a contributor of interest are not visible because they are hidden by DNA from a victim, or by artefacts that can arise under highly sensitive profiling protocols. The point is not to ignore such evidence, he suggests, but to analyse it correctly and to be aware of what it means.

Initially, his work was mainly advising defendants, where he was dismayed at the standard of evidence being put forward by prosecutions. Despite his protestations, nothing seemed to change – prompting him to write a paper describing how evidence should be handled and to develop software tools to support the interpretation of DNA evidence.

Now he works closely with a company, Cellmark, which refers complicated cases to him. With heavy demands on his time, he hopes to train Cellmark staff in use of his software so he does not need to be directly involved.

Recently, using data in the public domain, he reanalysed evidence presented at the high-profile trial in Italy of Amanda Knox and Raffaele Sollecito, charged with the murder of Meredith Kercher. The pair were first convicted then freed, following a challenge to the DNA evidence. Professor Balding’s analysis suggested that it was highly unlikely that Knox had been at the scene of the crime. After his paper was published, he was contacted by both sides in the prosecution appeal.

Professor Balding’s work is arranged through UCL Consultants, and generates a steady stream of income and interesting work – plus the satisfaction of contributing to better presentation of evidence. The downside, he adds, is a lot of time spent hanging around in courts.
UCL has established a strategy and infrastructure to support and promote enterprise among students and staff.

**THE ABC OF UCL ENTERPRISE**

UCL Enterprise provides an institutional framework for developing and implementing UCL-wide enterprise strategy and coordinating commercially oriented activities. Led by the Vice-Provost for Enterprise, it includes three key units:

- UCL Advances
- UCL Business
- UCL Consultants

As well as these pan-UCL structures, within the UCL School of Life and Medical Sciences, the Translational Research Office plays a lead role in coordinating partnerships with the pharmaceutical industry and supporting researchers undertaking translational research.

**UCL ADVANCES**

UCL Advances is the centre for entrepreneurship at UCL. It offers training, networking and business support for staff and students, not just to establish new enterprises but also to promote a culture of entrepreneurship and encourage entrepreneurial thinking. For students, entrepreneurial skills such as leadership, innovative thinking, creativity, and a can-do mentality are of value in a range of commercial environments.

UCL Advances offers a range of training, networking and mentoring opportunities for students and staff, including workshops, an Enterprise Bootcamp and short courses in areas such as small business management. UCL Advances already engages with 300 small companies and supports 50 companies, and has plans to expand this to 125 by 2016.

Students can also gain workplace experience through paid internships. In addition, they have the chance to gain consultancy experience. Groups of students receive in-depth briefing on business and consultancy, before undertaking consultancy projects with local start-ups.

For students who are keen to develop a business idea, funding in the form of loans is available through the Bright Idea scheme, while UCL Advances can also help budding entrepreneurs identify other potential sources of financial support. Space is also available in an incubator, The Hatcher, providing a base from which students can develop a new business.

[www.ucl.ac.uk/advances](http://www.ucl.ac.uk/advances)

**UCL BUSINESS**

UCL Business (UCLB) is the technology transfer company of UCL, with a mission ‘to help support and commercialise UCL research for the benefit of humankind in its widest sense’. It offers a support service to UCL researchers, offering practical advice on protection of intellectual property and other key aspects of commercialisation.

UCLB’s business managers work closely with institutes and departments within the School to identify business opportunities and to protect intellectual property interests. UCLB works with UCL researchers to identify the most appropriate routes of commercialisation, for example by negotiating licensing agreements or establishing start-up companies.

UCLB also provides a range of funding to support the commercialisation of research, including Proof of Concept funds and a range of schemes run with external partners. It provided nearly £1m Proof of Concept funding in 2012/13. It also invested £2.3m in spinout companies during the year.

Many UCL start-up companies have gone on to achieve considerable commercial success. Stanmore Implants Worldwide, for example, has established itself as a world leader in advanced prosthetics, medical imaging company IXICO recently achieved listing on the Alternative Investment Market, while Spirogen was the subject of a US$200m acquisition by AstraZeneca.

UCLB also supports the development of new social enterprises – using new knowledge for socially desirable ends. Examples include the Tiny Tastes evidence-based resource developed by Dr Lucy Cook to encourage healthy eating in young children and the Trim Tots’ programme, developed by Professor Atul Singhal and Julie Lanigan, which is designed to promote healthy lifestyles in pre-school children from disadvantaged backgrounds. UCLB has also worked with UnLtd and STORM Skills Training on a guide to social enterprise development for university researchers.

[www.uclb.com](http://www.uclb.com)
**UCL CONSULTANTS**

UCL Consultants manages the relationship between UCL-based consultants and external clients. UCL academics are in considerable demand, and are able to undertake up to 40 days' consultancy a year. Many researchers within the UCL School of Life and Medical Sciences act as consultants to pharmaceutical or biotech companies, but also often undertake policy-related work or act as expert advisers in legal cases.

UCL Consultants raises awareness of consultancy opportunities, and works with UCL academics on the negotiation and management of consultancy agreements. It organises workshops to prepare academics looking to maximise the benefits of presenting their academic research to business audiences.

[www.ucl.ac.uk/consultants](http://www.ucl.ac.uk/consultants)

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**TRANSLATIONAL RESEARCH OFFICE**

The Translational Research Office (TRO) has three core functions. One is to support researchers in the School by raising awareness of translational research opportunities, supporting the development of funding applications, and managing translational projects that are awarded funding.

Its Translational Project Managers all have experience of research in the pharmaceutical and biotech sector, so are well placed to offer advice and practical support, and to take a lead role in the management of projects (many of which are featured in this publication).

The TRO runs two funding schemes for translational research. It is responsible for MRC Confidence in Concept funding, which provides support for early stages of translation, to explore the potential of new ideas and pave the way to larger applications. UCL was awarded £700,000 by the MRC in each of the first two rounds of the Confidence in Concept initiative. Grants of up to £100,000 are awarded competitively, with some seven to eight awarded in each round.

The Therapeutic Innovation Fund, also run competitively, provides up to £60,000 for early translational projects. Some 16 projects have been awarded funding, and have laid the foundations for successful bids for external funding of more than £2.2m from government, charity and industry sources.

Secondly, the TRO has established a central medicinal chemistry facility, based in the UCL School of Pharmacy. Its industry-experienced medicinal chemists provide drug discovery advice and practical support to an increasing portfolio of drug discovery projects drawn from across UCL.

Finally, the TRO is also involved in establishing and maintaining relationships with Industry, negotiating agreements that play to the strengths of both parties and accelerate the development of new therapeutic agents and medical technologies.

[www.ucl.ac.uk/translational-research/](http://www.ucl.ac.uk/translational-research/)
UCL School of Life and Medical Sciences

Partners

UCL School of Life and Medical Sciences works closely with a range of local, national and international partners. Of particular significance are its close links to local NHS bodies, collectively forming UCL Partners, one of just five UK Academic Health Science Centres. These links underpin UCL’s NIHR Biomedical Research Centres at UCLH, the UCL Institute of Child Health (with Great Ormond Street Hospital) and the UCL Institute of Ophthalmology (with Moorfields Eye Hospital).

The School has also developed ties with nearby academic centres, including the London School of Hygiene and Tropical Medicine and Birkbeck College. As well as many joint research initiatives, the institutions also liaise at a strategic level.

With the MRC, Wellcome Trust and Cancer Research UK, UCL is also a founding partner of the Francis Crick Institute, led by Professor Sir Paul Nurse, which is due to open in 2015.

UCL also establishes wider partnerships in the UK, for example with Imperial College to set up the London Centre for Nanotechnology, and with Imperial, King’s College London, the MRC and GlaxoSmithKline on the ‘Imanova’ clinical imaging initiative.

As well as numerous international research collaborations, UCL has developed a strategic alliance with Yale University, the Yale–UCL Collaborative, to promote cross-fertilisation and joint ventures across education, research and application.
Support: Resource centres and platforms

The scale of UCL’s research enables it to provide a range of technical infrastructure platforms to support research. These include outstanding facilities and technical expertise in molecular and cellular imaging, as well as pre-clinical and clinical imaging, and several sites specialising in high-throughput sequencing and genome analysis.

Other core platform technologies cover small-chemical libraries, proteomics, biological services, and transgenics, and informatics. UCL researchers are also involved in numerous biobanking initiatives and cohort studies, providing access to extensive collections of materials and data.

UCL also provides capital infrastructure funding to enable labs to develop their equipment base.

For clinical research, a Clinical Research Support Centre provides access to essential support for work on people and patients, including liaison with the UCLH/UCL NIHR Biomedical Research Centre, UCL Clinical Trials Unit and UCLH/UCL Clinical Research Facility.

The Translational Research Office works to promote the translation of research into therapies, techniques and products with therapeutic value.

www.ucl.ac.uk/platforms/
www.ucl.ac.uk/slms/research_support_centre

Research income

‘Live’ grants as at 1 September 2011

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Figures refer to research within the UCL School of Life and Medical Sciences. NIHR: National Institute for Health Research; MRC: Medical Research Council; NIH: National Institutes of Health.

UCL Research Strategy

The UCL Research Strategy calls for a transformation of the understanding of the role of our comprehensive research-intensive university in the 21st century.

In addition to highlighting the need to nurture and celebrate individual curiosity-driven research, the strategy sets out for UCL an innovative cross-disciplinary research agenda – designed to deliver immediate, medium- and long-term benefits to humanity.

UCL will marshal the breadth of its expert perspectives, in order to address issues in their full complexity and contribute to the resolution of the world’s major problems. Its key aims are to:

- continue to foster **leadership grounded in excellence** in discipline-based research
- expand the distinctive **cross-disciplinarity** of our research, collaboration and partnerships
- increase the **impact** of our global university’s research, locally, regionally, nationally and internationally.
Sponsors of research

We are grateful to all the individuals and organisations who support research in the UCL School of Life and Medical Sciences.

About UCL

UCL is one of the world's top universities. Based in the heart of London it is a modern, outward-looking institution. At its establishment in 1826 UCL was radical and responsive to the needs of society, and this ethos – that excellence should go hand-in-hand with enriching society – continues today.

UCL's excellence extends across all academic disciplines; from one of Europe's largest and most productive hubs for biomedical science interacting with several leading London hospitals, to world-renowned centres for architecture (UCL Bartlett) and fine art (UCL Slade School).

UCL is in practice a university in its own right, although constitutionally a college within the federal University of London. With an annual turnover exceeding £800 million, it is financially and managerially independent of the University of London.

UCL's staff and former students have included 21 Nobel prizewinners. It is a truly international community: more than one-third of our student body – around 25,000 strong – come from nearly 140 countries and nearly one-third of staff are from outside the UK.

www.ucl.ac.uk

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