



# UCL

# **Dementia and neurodegeneration**

## **A window of opportunity**

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**UCL SCHOOL OF LIFE AND MEDICAL SCIENCES**  
Creating knowledge, achieving impact

# PREFACE

**UCL has the expertise to have a significant impact on the treatment of dementia and other neurodegenerative diseases – and the commitment to make it happen.**

UCL's School of Life and Medical Sciences is one of the largest centres of biomedical and health research in Europe, if not the world. Its speciality areas span all levels from the smallest biomolecules to global populations.

Similarly, in dementia and neurodegeneration, the School can lay claim to world-leading expertise across the full spectrum of research, from studies of the genetic causes of disease and their molecular modes of action through to evidence-based psychosocial treatments for patients and carers.

We have identified dementia and neurodegeneration as a strategy priority for the Faculty of Brain Sciences for 2013–18. In part this reflects a desire to build on our undoubted strengths in this area. But it is also a recognition that dementia and neurodegeneration are a national and international priority. As populations age, dementia is inevitably going to become more common. It is distressing for patients and for those around them, and imposes an immense cost on health systems. Currently, there is very little we can do to tackle the root causes of disease.

Yet there are reasons to be optimistic. Mechanisms of disease are being elucidated, opening up new opportunities for therapeutic intervention. And the realisation that neurodegeneration is a long-term process, an accumulation of damage over many years, is opening up a window of opportunity. There is the real prospect that new disease-modifying treatments will be able to slow or even halt this accumulation, postponing the onset of symptoms and extending the duration of healthy life.

Central to this new vision is the Leonard Wolfson Experimental Neurology Centre, a site at which early proof-of-concept studies in people can be carried out – overcoming one of the most important roadblocks in the development of new therapeutics. With the associated progress in imaging and biomarker development providing new tools for rapid assessment of therapeutic agents, the Centre will play a critical role in bringing much-needed medicines to patients.

An important source of new therapeutics will be UCL research itself, progressed through our groundbreaking partnership with the Eisai pharmaceutical company. By creating interdisciplinary teams combining academic and industry expertise, we will accelerate the development of new agents to the point at which they can be tested in people at the Leonard Wolfson Centre.

Our extensive health research platform already contributes to clinical trials, and has the potential to be involved in later large-scale trials of promising therapeutics. It also plays a vital role in improving the quality of life of today's patients and carers as research continues on the next generation of medicines.

This document provides an insight into some of the work on dementia and neurodegeneration being carried out in the Faculty of Brain Sciences, in collaboration with other Faculties within the School, other UCL Schools, national and international academic collaborators, and our industrial partners. Over the next five years – and beyond – we aim to bring the unique strengths of UCL to bear on these profoundly important health problems. I am convinced our collective efforts will make a very real difference to the lives of patients and their families in the years to come.



**Professor Alan Thompson**

Dean, UCL Faculty of Brain Sciences.

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# CHALLENGES AND OPPORTUNITIES

Neurodegeneration research at UCL spans all areas from the molecular and cellular to the social. World-class researchers are developing ways to improve the lives of patients and carers, as well as generating new insights into disease and laying the foundation for the development and testing of new treatments for these common and devastating conditions.

Dementia is one of the greatest and growing challenges to health systems worldwide. In the UK, the annual cost of dementia care is £23bn, a figure projected to treble over the next 30 years. Within a decade, dementia is likely to affect more than a million people.

For individual patients, the outlook is scarcely less gloomy. Existing drugs provide only minor benefits for a subset of patients, and none tackle underlying causes of disease. An army of carers face the daily challenge of looking after people with dementia, often at great cost to their own mental health.

## **New opportunities**

Nevertheless, there are now exciting signs that progress is being made. The mechanisms of disease are gradually being unravelled, and promising new targets are being identified. Genetic studies are revealing key disease processes, which are being explored further in

cellular and animal models. Such models provide an ideal platform for the development and testing of agents to interfere with disease processes.

Perhaps most significant has been the growing belief that interventions need to be targeted as early as possible in disease, and perhaps even preventively. UCL researchers have played a major role – particularly through brain imaging – in demonstrating that damage to the brain is occurring well before clinical symptoms first appear. By intervening early, it may be possible to delay or even prevent the onset of symptoms.

Furthermore, brain imaging and biochemical markers of disease are providing valuable new tools for clinical trials. Because of the sensitivity of these methods, changes in the brain can be tracked in relatively small numbers of patients over manageable time periods, greatly enhancing the opportunities for clinical trials of disease-modifying agents.

These principles underpin activities at the new Leonard Wolfson Experimental Neurology Centre at UCL, funded through a £20m grant from the Leonard Wolfson Foundation. The Centre will provide facilities in which clinical disease can be studied further and, importantly, emerging new treatments can be tested for the first time in people – a key stage in the development of new therapies.

Equally important will be the development of new agents to test. A significant source will be the therapy development partnership established between UCL and the Eisai pharmaceutical company. Industry expertise will help to develop promising lines of research at UCL to the stage at which clinical trials can begin.

## **Health and population research**

These exciting developments in translational research offer the prospect of much-

needed new treatments. In the meantime, there is still an urgent need to support patients and carers.

UCL researchers have played important roles in documenting the surprisingly high incidence of undiagnosed dementia in emergency admissions to hospital, as well as their very poor experience in hospital and markedly worse survival. The findings are having practical impact, underpinning a training programme across UCL-associated hospitals to ensure sites are better prepared to care for people with dementia.

UCL research has also raised the important issue of carer stress. A strategy to improve carers' coping strategy has been shown in a clinical trial to reduce the toll of caring on mental health. In addition, strong evidence has been generated that cognitive stimulation therapy can have significant benefits to patients. The programme is widely used in the UK and many other countries.



Within a decade, dementia is likely to affect a million people.

## UNDERSTANDING DEMENTIA AND NEURODEGENERATION: THE KEY CHALLENGES

**The hallmark of neurodegenerative disease is the death of nerve cells. A key challenge is to understand how and why cells die.**

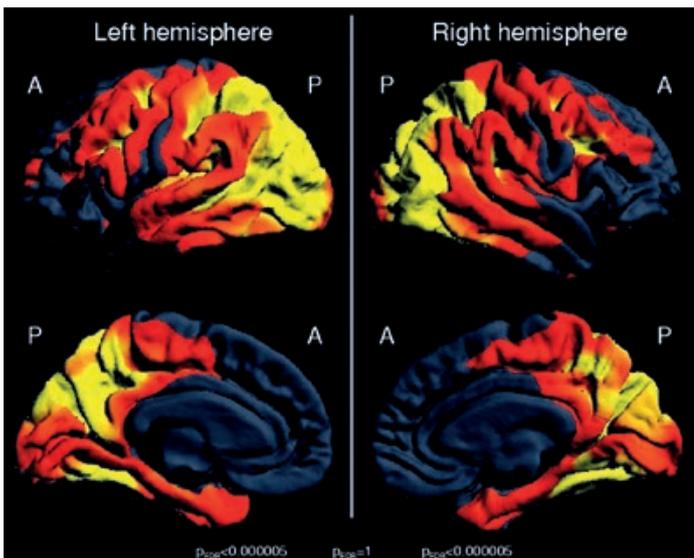
The causes of neurodegeneration are poorly understood. Much insight has come from studies of rare families affected by neurodegenerative disease, which have revealed key genes and biochemical processes involved in Alzheimer's disease, Parkinson's disease and other conditions. These same processes are central to disease in the general population.

A common feature of neurodegenerative disease is the build up of abnormal protein aggregates – including  $\beta$ -amyloid and tau in Alzheimer's disease,  $\alpha$ -synuclein in Parkinson's disease, and prion protein in Creutzfeldt–Jakob disease. Exactly how these aggregates contribute to disease is unclear, and the subject of intense research.

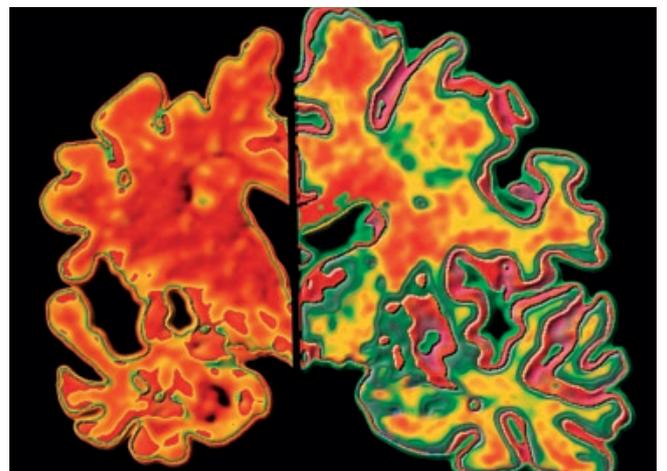
Many cellular and physiological processes are disrupted in neurodegeneration. There is, for example, growing interest in the contribution of immune responses to disease progression. Mitochondrial function and disposal of defective mitochondria have been implicated in Parkinson's disease, as has the cell's protein recycling systems.

Given this complexity, it is conceivable that multiple abnormalities will be important in the development of disease. It will be important to tackle the conditions from many directions, and treatment may also ultimately require multiple lines of attack.

A further challenge is to relate cellular changes to the networks in which neurons operate. For example, loss of synaptic connections as cells deteriorate may be critical to the onset of symptoms. The final link in the chain of understanding is to relate cellular changes to alterations in the activity of specific neural networks, and ultimately to the symptoms experienced by patients.



New imaging methods provide a detailed view of brain degeneration.



As well as patient groups, population cohorts are also making increasing contributions to dementia research. UCL is playing a leading role in several ageing cohorts, work on which will provide valuable new insight into the nature of disease progression and factors that may accelerate disease (or be protective) in the general population.

### Cause for optimism

Dementia is undoubtedly one of the greatest health and social changes facing the UK and the rest of the world. Yet there are reasons to be optimistic. UCL is ideally placed to exploit these opportunities, having established a portfolio of research in dementia and neurodegeneration of unmatched strength and

breadth. Our goal is to exploit this unique resource to drive forward the development of interventions and diagnostics that prevent disease, mitigate its effects or improve the quality of life of those who develop dementia or other neurodegenerative diseases.

# FUNDAMENTAL RESEARCH: FROM MOLECULES TO NEURAL CIRCUITRY

The development of new therapies will depend on a better understanding of the molecular and cellular basis of disease – and, in particular, which changes are most relevant to clinical symptoms.

Neurodegenerative diseases have turned out to be hugely complex. Although many changes have been identified in molecular and cellular processes, it is unclear exactly which have most bearing on the symptoms of disease and premature mortality. The question is of critical importance, as therapy development needs to be focused on the most disease-central pathways.

For Alzheimer's disease, most attention has focused on the  $\beta$ -amyloid pathway. UCL researchers have been instrumental in developing the 'beta-amyloid cascade' theory of disease, which suggests that the pivotal process in disease is the accumulation of  $\beta$ -amyloid deposits.

Even so, exactly how  $\beta$ -amyloid accumulation leads to cell death remains unclear. As well as direct toxicity, recent work has implicated inflammatory responses in the brain, suggesting that overactive immune responses could also contribute to neuronal death.

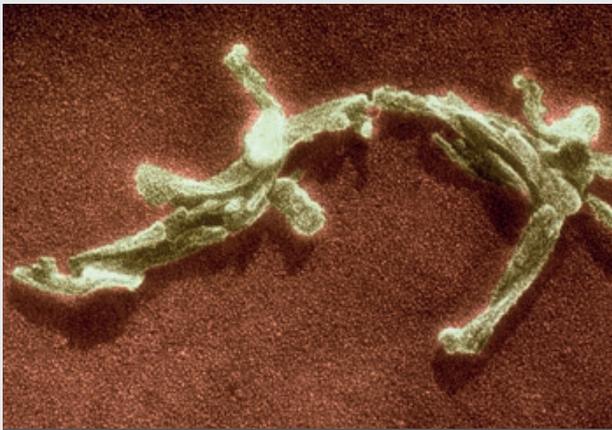
On the other hand, cell death may not be the critical event in disease. Potentially, an earlier stage – loss of synaptic connections – may be instrumental in disease, leading to a breakdown in neural circuitry.

For Parkinson's disease, research is again providing pieces of a jigsaw that are beginning to slot together. Genetic studies have implicated abnormalities

in mitochondrial function in neurodegeneration, and a growing sense that cellular recycling mechanisms – of mitochondria or abnormal protein – may also be central to disease processes.

UCL researchers are using a variety of methods to understand the processes involved in these and other forms of neurodegeneration. Such work is also highlighting connections between different conditions, implying that some underlying cellular and molecular processes may be shared between diseases.

As these pathways are unpicked, more possible targets for pharmacological intervention are being revealed.



Prion protein aggregates.

### CRACKING THE PRION ENIGMA

As well as paving the way to new therapeutics, a better understanding of prion infections has implications for other neurodegenerative diseases.

Prions, infectious protein particles, cause a range of degenerative brain diseases, including Creutzfeldt–Jakob disease. In common with other neurodegenerative conditions, prion infections are characterised by the build up of abnormal protein aggregates. Understanding how such aggregates contribute to disease is a challenge across neurodegeneration. The work of **Professor John Collinge** and colleagues on the mechanisms of prion toxicity may therefore hold important lessons beyond prion disease.

The infectious agent in prion diseases is a misfolded version of a cellular protein. This misfolded form, known as PrP<sup>Sc</sup>, catalyses the conversion of the normal cellular protein, PrP<sup>C</sup>, into more copies of itself, which accumulate into protein aggregates. However, although this ultimately kills the cell, it is far from certain that the aggregates themselves are actually most damaging to the cell – a phenomenon common across neurodegenerative conditions.

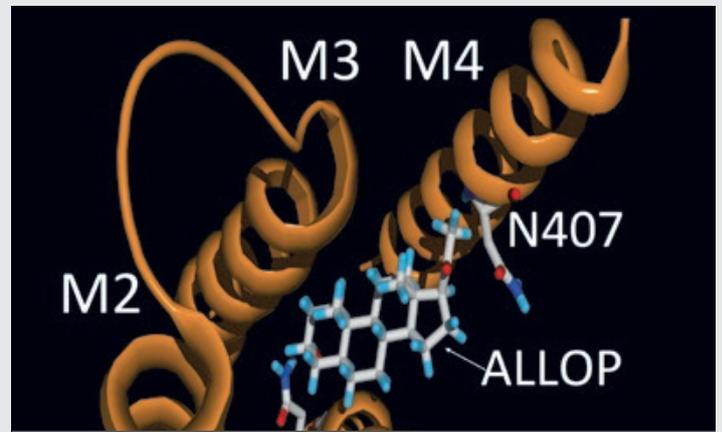
Several key features of prion infection require explanation. For example, prion infections show long incubation periods – decades in humans – but when clinical decline begins, it is extremely rapid, with death occurring within months. There is also no obvious link between levels of PrP<sup>Sc</sup> build up and symptoms, and PrP<sup>Sc</sup> is not toxic to cells unless they also express PrP<sup>C</sup>.

These and other findings led Professor Collinge to propose a model in which infectivity and toxicity are dissociated. PrP<sup>Sc</sup> is the agent responsible for transmission, but some other state – perhaps an intermediate in the transition from PrP<sup>C</sup> to PrP<sup>Sc</sup> – is the neurotoxic agent. Studies of experimental infections in mice provided good evidence in support of this idea.

The model implies that PrP<sup>Sc</sup> is not itself toxic but causes harm through its effects on PrP<sup>C</sup>. Hence, maintaining PrP<sup>C</sup> in its native state should prevent PrP<sup>Sc</sup> from exerting its harmful effects. This is the basis of therapeutic interventions being developed by Professor Collinge's laboratory (see page 14). More generally, the results add to a growing body of evidence that the characteristic large-scale aggregates seen in neurodegenerative conditions may not necessarily be the critical toxic entities.

**Collinge J, Clarke AR.** A general model of prion strains and their pathogenicity. *Science*. 2007;318(5852):930–6.

**Sandberg MK et al.** Prion propagation and toxicity in vivo occur in two distinct mechanistic phases. *Nature*. 2011;470(7335):540–2.



GABA receptor  $\alpha$ -subunit showing neurosteroid-binding site.

### THE BENEFITS OF INHIBITION

The inhibitory neurotransmitter GABA could provide a way to protect neurons from untimely death.

Many abnormalities in neurotransmitter signalling have been identified in Alzheimer's disease, but it remains unclear exactly which contribute to the condition's complex constellation of cognitive and behavioural abnormalities. With a special interest in GABA (gamma-aminobutyric acid) signalling, **Professor Trevor Smart's** group is examining how changes to inhibitory signalling through GABA receptors could be involved in disease.

GABA is the brain's main inhibitory neurotransmitter, helping to keep neural excitation in check. But it also has a valuable neuroprotective role: excitatory amino acids such as glutamate are toxic at high levels, and loss of GABA signalling can leave neurons vulnerable to overexcitation and cell death.

GABA signalling is mediated by two classes of GABA receptor, GABA<sub>A</sub> and GABA<sub>B</sub>, both of which may play some role in neurodegeneration. Professor Smart's work aims to establish links between the molecular and cellular processes underlying GABA signalling and cognition, to understand normal biological function and how it goes wrong in disease.

GABA<sub>A</sub> receptors are the targets of neurosteroids, and there is some evidence that neurosteroid levels are abnormally low in Alzheimer's disease. Furthermore, boosting neurosteroid levels ameliorates the symptoms of a severe childhood form of neurodegeneration, Niemann–Pick disease. To identify key mechanisms, Professor Smart is generating transgenic mice lacking neurosteroid-binding sites in the  $\alpha 1$ ,  $\alpha 2$  and  $\alpha 4$  subunits of the GABA<sub>A</sub> receptor, to see what impact reduced neurosteroid signalling has on neuronal function and survival, and on the animals' cognitive abilities.

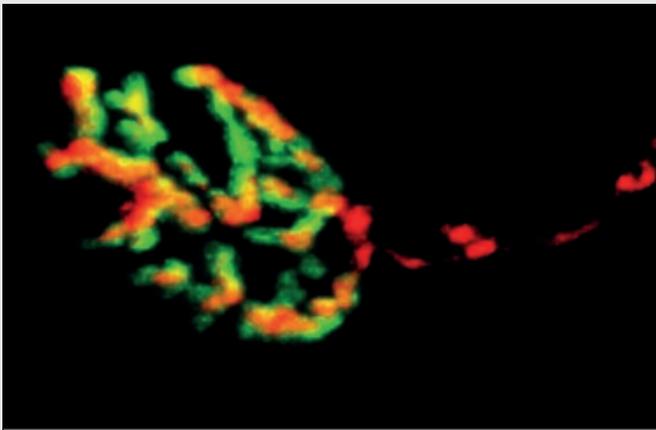
Recently, Professor Smart and colleagues have looked in more detail at GABA and excitotoxicity. Prolonged signalling through excitatory NMDA receptors – a possible downstream effect of  $\beta$ -amyloid accumulation – was found to lead to reduced numbers of cell surface GABA<sub>B</sub> receptors, whereas brief exposure to glutamate increased cell surface GABA<sub>B</sub> receptors, suggesting receptor numbers are determined by a highly dynamic mechanism. These changes were dependent on phosphorylation of a critical site within one subunit of the receptor, which altered intracellular trafficking. Rather than being recycled to the cell surface after internalisation, receptors underwent degradation in lysosomes.

Again using mouse models, Professor Smart aims to understand more about these mechanisms and how they affect neuron survival, neural circuitry and ultimately cognitive symptoms. More generally, as GABA receptors are well-established targets for pharmaceutical interventions, these studies raise the prospect of therapies that interfere with GABA receptors to maintain GABA inhibitory signalling and prevent neurodegeneration.

**Hosie AM et al.** Endogenous neurosteroids regulate GABA<sub>A</sub> receptors through two discrete transmembrane sites. *Nature*. 2006;444(7118):486–9.

**Terunuma M et al.** Prolonged activation of NMDA receptors promotes dephosphorylation and alters postendocytic sorting of GABA<sub>B</sub> receptors. *Proc Natl Acad Sci USA*. 2010;107(31):13918–23.

**Hannan S, Wilkins ME, Smart TG.** Sushi domains confer distinct trafficking profiles on GABA<sub>B</sub> receptors. *Proc Natl Acad Sci USA*. 2012;109(30): 12171–6.



Tracking axonal transport.

## A MOVING STORY

**Might impaired transport of material along axons be a critical factor in neurodegeneration?**

The great length of many neurons poses a considerable challenge to communication between the cell body and nerve terminals. Intracellular transport systems are thus critical to neuron biology. And, as **Dr Gipi Schiavo** and colleagues have discovered, abnormalities in such systems can spell the end of the cell.

Dr Schiavo has had a long-standing interest in both pathogens and neuronal transport. In fact the two are connected, as several pathogens and pathogen products have hijacked the uptake and transport systems of neurons to enter cells and gain a free ride to the cell body. One such protein is tetanus toxin, and by adapting this protein Dr Schiavo has been able to develop probes to explore the mechanisms of neuronal transport.

Using mass spectrometry, he was able to show that transport from the nerve terminal to the cell body – axonal retrograde transport – is dependent on a surprisingly complex organelle containing many hundreds of proteins. At its heart is a molecular motor protein, dynein.

In 2003, work with Professor Elizabeth Fisher identified mutations in dynein in the 'Legs at odd angles' (Loa) mouse mutant, which shows late-onset neuromuscular degeneration. The mutant form of dynein was less able to support rapid retrograde transport in motor neurons. Since other genetic causes of neurodegeneration also affect retrograde transport, the results suggested that abnormal axonal transport could be important in a range of pathological conditions affecting the nervous system.

Indeed, work with Professor Linda Greensmith on another form of motor neuron disease, amyotrophic lateral sclerosis (ALS), provided further support for this idea. Using a newly developed assay, Dr Schiavo was able to visualise vesicle transport in living mice engineered to express a human ALS-causing gene. Significantly, defects in axonal retrograde transport were seen long before physical symptoms were apparent – implying that disruption of transport was an early and perhaps causal event in disease.

In 2013, Dr Schiavo moved from the CRUK London Research Institute to UCL, to forge closer links with Professor Fisher and Professor Greensmith, as well as with UCL's human geneticists and clinicians. Notably, components of neuronal transport systems identified in cellular studies have turned out to be involved in clinical conditions, and further analysis may reveal candidate causes of other unexplained cases. Furthermore, transport abnormalities have also been seen in other neurodegenerative conditions, including Alzheimer's and Huntington's disease, so the process may be of even wider significance.

**Hafezparast M et al.** Mutations in dynein link motor neuron degeneration to defects in retrograde transport. *Science*. 2003;300(5620):808–12.

**Bilsland LG et al.** Deficits in axonal transport precede ALS symptoms in vivo. *Proc Natl Acad Sci USA*. 2010;107(47):20523–8.



Dr Andrey Abramov.

## THE TWO SIDES OF DOPAMINE

**Under different circumstances, dopamine may be either a harbinger of death or a guardian angel.**

One of the puzzles of Parkinson's disease is why such a specific set of neurons, dopaminergic cells of the substantia nigra, are affected. The research of **Dr Andrey Abramov** and colleagues suggests that dopamine itself may be the culprit. Yet, in other circumstances, dopamine may actually protect neurons from premature death.

Familial forms of Parkinson's disease have provided important clues to the cellular mechanisms of disease. In PINK1 deficiency, for example, Dr Abramov's work has highlighted important defects in mitochondrial calcium storage, as well as damaging levels of charged free radicals. Together, these changes render mitochondria unstable and vulnerable to premature death.

Given the specific loss of dopaminergic cells, it has been suggested that dopamine itself may contribute to cell death in the substantia nigra. Working with cells from PINK1 knockout mice, Dr Abramov and colleagues recently found that this is indeed the case.

It turns out that, as well as its classic action on dopamine receptors, dopamine also has receptor-independent effects on cells. In particular, it generates additional calcium signals, while its enzymatic breakdown stimulates a burst of free radical production. These triggers appear to be the final straw that pushes already vulnerable mitochondria over the edge, leading to the death of the cell.

Significantly, these results argue that manipulation of calcium signalling or targeting of the free radical system (to reduce free radical production or to increase levels of mitochondrial antioxidants) could be fruitful therapeutic strategies. Although antioxidant therapy has not yet shown convincing results, this may be because it has not been used early enough to have any beneficial effect.

While dopamine may be the guilty party in Parkinson's disease, paradoxically it may also be a cellular life-saver. After oxygen deprivation, a build up of extracellular glutamate can be lethal to neurons. However, through its action on calcium signalling, Dr Abramov and colleagues have shown that dopamine can block the neurotoxic effects of glutamate. Indeed, he suggests, dopamine may have an important role as a 'safety catch' that prevents glutamate from damaging cells during normal glutamate neurotransmission.

**Vaarmann A, Gandhi S, Abramov AY.** Dopamine induces  $Ca^{2+}$  signaling in astrocytes through reactive oxygen species generated by monoamine oxidase. *J Biol Chem*. 2010;285(32):25018–23.

**Gandhi S et al.** Dopamine induced neurodegeneration in a PINK1 model of Parkinson's disease. *PLoS One*. 2012;7(5):e37564.

**Vaarmann A et al.** Dopamine protects neurons against glutamate-induced excitotoxicity. *Cell Death Dis*. 2013;4:e455.

# HUNTINGTON'S DISEASE: FROM MOLECULES TO BRAIN TRAINING

Professor Sarah Tabrizi is leading a highly varied programme of research in Huntington's, ranging from genetic and cellular studies to advanced brain imaging and innovative interventions. And by maintaining regular contact with patients, she ensures this research is rooted in the realities of disease.



Huntington's disease may be less common than Alzheimer's disease but it strikes early and is impossible to treat. "It's a truly dreadful disease," says Professor Tabrizi, who manages both a major multidisciplinary research programme and one of the UK's leading clinical centres for Huntington's disease. "Huntington's affects people who are around 40, have often nursed a parent with the disease, and whose children are then also at risk."

To support such families, Professor Tabrizi is committed to marrying clinical practice and research, despite the challenges. For a start, clinical practice reveals what really matters to patients and shapes the direction of laboratory research, while research generates advances that make a difference to patients' lives.

But, she adds, patient contact has other benefits: "Seeing patients in clinic always reminds me about why we do what we do, and when things get tough and experiments don't work

– which is common – or research is proving tough, looking after patients helps me get a perspective."

"When I see patients in clinic and witness the devastation that diseases like Huntington's disease cause to families, I don't need any more motivation. It's genuinely humbling."

Professor Tabrizi's research is notably diverse, spanning cellular and neurological themes. The groundbreaking TRACK-HD initiative, for example, has revealed changes in brain structure and other markers years before symptoms are apparent, paving the way for clinical trials in early and even presymptomatic patients (see page 20). Follow-up work, through the Track-On project, is aiming to identify even more sensitive markers for the latter group.

Track-On is also exploring 'neural compensation', whereby patients recruit other brain areas to carry out tasks and maintain performance as brain tissue begins to be lost. An exciting spin-off from this work is the possibility of using

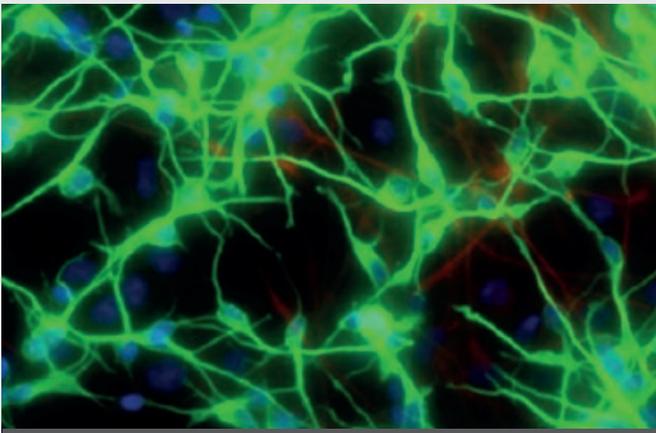
'neurofeedback' techniques as a clinical intervention, to boost compensation. While undergoing functional MRI, patients are encouraged to mentally envisage movement-related activity, and receive real-time visual feedback on activity in motor areas of the brain. With training, patients can learn to enhance this activity, even without visual feedback. Early results show promise that neurofeedback can induce neural compensation with positive effects on behaviour.

Track-On is also focusing on the extremes of the patient sample – the 'fast progressors' and 'slow progressors' – to identify genetic factors that may accelerate or protect against disease. One of the most powerful modifiers is the immune system, and cellular studies in Professor Tabrizi's laboratory have identified key mechanisms underlying the persistent activation of the immune system in Huntington's disease (see page 8). This may lead to new treatments that target the peripheral symptoms of the disease

– such as muscle wasting and weight loss – as well as neurodegeneration, says Professor Tabrizi. "Targeting peripheral pathogenesis like muscle wasting or immune dysregulation may be a more tractable therapeutic in the short term while we work on the very challenging task of modulating the brain."

For the latter, Professor Tabrizi is excited by the potential of gene silencing technologies, which can selectively knockdown levels of mutant huntingtin protein in cells. Approval is being sought for human trials to be undertaken at the Leonard Wolfson Centre, where Professor Tabrizi is a principal investigator.

Along with other charity- and industry-sponsored work, she is optimistic that true disease-modifying treatments are a realistic prospect: "We have therapies that have enormous effects in mice. But treating mice is not our aim – our aim is translating that to humans, and that's where we are now."



Human neural stem cells.

## HUNTINGTON'S DISEASE: THE IMMUNE CONNECTION

**Immune cells as well as brain cells are affected in Huntington's disease – and the two may be closely connected.**

The brain is the main focus of Huntington's disease, but the mutant protein that causes it is present in every cell of the body. Indeed, abnormalities have been identified outside the brain, particularly in the immune system. **Professor Sarah Tabrizi** and colleagues have identified a key mechanism by which the Huntington's mutation leads to overactive innate immune responses, a finding that could have consequences for the brain as well as peripheral tissues.

Huntington's disease is caused by the expansion of a three-nucleotide repeat in the gene for huntingtin, a protein of poorly understood function. The mutation leads to a protein with a run of additional glutamine residues. As well as effects on the brain, mutant huntingtin is known to have a wider impact, causing muscle wasting and weight loss, despite increased calorie intake, and neuroendocrine changes.

Indeed, in 2008, Professor Tabrizi showed that Huntington's disease is associated with elevated levels of a particular cytokine, IL-6, associated with activation of the innate immune response – the first-line, non-specific strand of the immune system. Human macrophages were hyperresponsive, as were both macrophages and microglia (the brain's immune cells) from Huntington's disease model mice. This hyperresponsiveness reflected huntingtin's effect within cells, rather than a response to external signals.

Recently, Professor Tabrizi's group has extended these findings significantly. Immune cells from Huntington's disease patients were found to be releasing high levels of a range of cytokines involved in innate immune responses. These responses were due at least in part to the action of mutant huntingtin on the well-characterised NF- $\kappa$ B intracellular signalling pathway.

Furthermore, using a novel gene-silencing technique – huntingtin-targeting small interfering RNA encased in polysaccharide shells that are readily taken up by phagocytic cells – the group was able to lower huntingtin levels and normalise cytokine production.

Persistently high cytokine levels could underlie a range of health problems in Huntington's disease, such as weight loss and depression. RNA-based methods targeting huntingtin in immune cells could be a viable strategy for ameliorating these effects. Moreover, as evidence is accumulating that immune responses influence disease progression in the brain, the findings also identify the NF- $\kappa$ B pathway as a possible target for interventions that have an impact on neurodegeneration.

**Björkqvist M et al.** A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. *J Exp Med.* 2008;205(8):1869–77.

**Träger U et al.** HTT-lowering reverses Huntington's disease immune dysfunction caused by NF $\kappa$ B-pathway dysregulation [submitted].



Professor Eleanor Maguire.

## MAKING MEMORIES

**A better understanding of the mechanisms of memory may reveal more about the nature of dementia.**

One of many challenges in Alzheimer's disease is to understand the connection between pathological changes and clinical symptoms. Brain imaging reveals the gross impact of neuronal death, yet how these changes relate to symptoms will depend on a better understanding of normal brain function. One of the earliest brain regions affected is the hippocampus, and **Professor Eleanor Maguire** is generating fascinating insight into how this structure is involved in memory formation and retrieval.

The hippocampus has a well-established role in memory formation. A notable illustration has been Professor Maguire's studies on London's taxi drivers, whose hippocampus grows as they learn 'the knowledge' – the names and locations of thousands of London streets and landmarks.

Of the different types of memory, the hippocampus plays a particular role in self-centred or 'episodic' memory. Much of her work has been on patients with amnesia who have suffered focal damage to the hippocampus. One striking finding is that such damage not only affects memories of the past. People with amnesia also struggle to generate coherent visions of the future – suggesting that recalling the past, imagining the future and spatial navigation may be underpinned by a common hippocampal-dependent mechanism.

A further line of research has been the use of high-resolution functional imaging to 'decode' neural signals from the brain. The ambitious goal is to use such recordings to identify traces of specific memories in the hippocampus and its associated cortical areas. Decoding has achieved remarkable success in identifying which virtual room a participant was in, and in identifying neural patterns associated with specific memories of people's life events.

Her recent studies have begun to explore the connections between the hippocampus and cortical areas, and the roles they play in encoding memories of recent or distant events. Again using high-resolution fMRI, Professor Maguire was able to detect signals associated with recent and distant memories, in both the cortex and the hippocampus – arguing that the hippocampus has an important role in accessing distant memories as well as storing new ones.

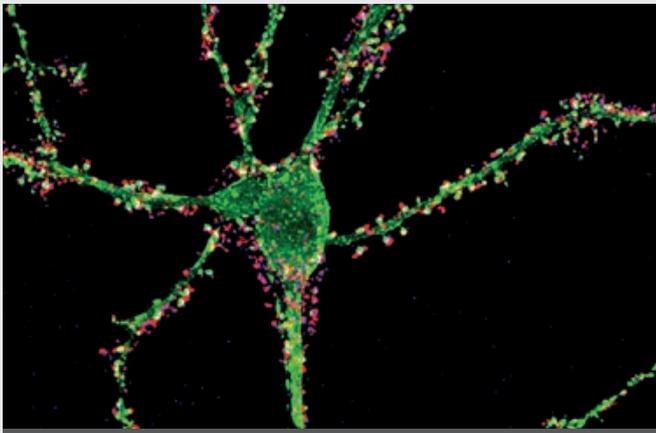
More generally, these new techniques promise to provide a much richer view of memory formation, storage and retrieval, and how and why memories decay across brain structures. Such knowledge will ultimately shed light on how brain tissue loss affects memory and other cognitive abilities in dementia.

**Woollett K, Maguire EA.** Acquiring "the Knowledge" of London's layout drives structural brain changes. *Curr Biol.* 2011;21(24):2109–14.

**Hassabis D, Kumaran D, Vann SD, Maguire EA.** Patients with hippocampal amnesia cannot imagine new experiences. *Proc Natl Acad Sci USA.* 2007;104(5):1726–31.

**Chadwick MJ, Hassabis D, Weiskopf N, Maguire EA.** Decoding individual episodic memory traces in the human hippocampus. *Curr Biol.* 2010;20(6):544–7.

**Bonnici HM et al.** Detecting representations of recent and remote autobiographical memories in vmPFC and hippocampus. *J Neurosci.* 2012;32(47):16982–91.



Dendrites on cultured neurons.

## SURVIVE AND PROSPER

Could a better understanding of cell survival signals be a route to new therapies for Alzheimer's disease?

The 20 or so proteins of the Wnt family have been implicated in many aspects of embryonic development. Recently, though, **Professor Patricia Salinas** has found that they also regulate the strength of synaptic connections. And her most recent work suggests that Wnt signalling could be playing a significant role in Alzheimer's disease.

The idea that Wnt signalling might be important in Alzheimer's disease is actually an old one. Through its action on a critical kinase, GSK3 $\beta$ , Wnt signalling could potentially influence the build up of phosphorylated tau, one of the hallmarks of the disease. The evidence was not strong, however, until genomic studies identified variants at a gene encoding a Wnt co-receptor as risk factors for Alzheimer's disease.

Struck by this finding, Professor Salinas turned her attention to a secreted protein, known as Dickkopf or DKK1, which also binds to the co-receptor, competing with and antagonising the effects of Wnt proteins. Indeed, adding DKK1 to mature cultured neurons had a dramatic effect, reducing synapse numbers by 30 per cent – strongly suggesting that Wnt factors are important for maintaining synapses in mature neurons.

DKK1 levels are also increased in Alzheimer's disease patients and some animal models of Alzheimer's disease. Potentially, then, DKK1-driven loss of synapses, rather than cell death per se, could be contributing to the cognitive decline seen in patients.

To explore further, Professor Salinas examined the effect of  $\beta$ -amyloid on DKK1 levels in brain slice cultures. Sure enough,  $\beta$ -amyloid triggered an increase in DKK1 levels, leading to loss of synapses. Most excitingly, though, antibodies against DKK1 blocked the toxic effect of  $\beta$ -amyloid on synapses.

Professor Salinas has recently extended this work, developing mice in which DKK1 can be selectively switched on in localised regions of the brain in adulthood. In these animals, elevated DKK1 in the hippocampus mimicked the effects of  $\beta$ -amyloid, reducing the number of synaptic connections. And, although there was no sign of significant cell death, the animal's cognitive abilities were markedly impaired.

The results therefore suggest that the impact of Wnt signalling and DKK1 on synapse numbers could be playing an important role in Alzheimer's disease. Furthermore, they argue that targeting DKK1 and Wnt signalling, to maintain synaptic integrity, could be a therapeutic strategy to slow or prevent the loss of cognitive abilities.

**Ciani L et al.** Wnt7a signaling promotes dendritic spine growth and synaptic strength through Ca<sup>2+</sup>/Calmodulin-dependent protein kinase II. *Proc Natl Acad Sci USA*. 2011;108(26):10732–7.

**Purro SA, Dickins EM, Salinas PC.** The secreted Wnt antagonist Dickkopf-1 is required for amyloid  $\beta$ -mediated synaptic loss. *J Neurosci*. 2012;32(10):3492–8.



Professor Anthony Schapira.

## A CYCLE OF DEATH

A rare metabolic disease is providing important clues to the mechanisms of Parkinson's disease.

People who inherit two copies of an abnormal glucocerebrosidase gene (*GBA*) develop Gaucher's disease, suffering multiple symptoms due to the build up of toxic lipid molecules in their tissues. They are also at significantly increased risk of Parkinson's disease – and **Professor Anthony Schapira's** recent studies have revealed how the conditions are connected.

The *GBA* gene codes for a lysosomal enzyme that digests certain lipid molecules; in the complete absence of the enzyme, these lipid molecules build up to toxic levels. However, although carriers with one abnormal gene are spared Gaucher's disease, they are still 20–30 times more likely to develop Parkinson's disease than the general population. Indeed, *GBA* is the most common gene implicated in Parkinson's disease.

By examining post-mortem tissue, Professor Schapira and colleagues found that levels of glucocerebrosidase activity in Parkinson's disease patients with *GBA* mutations were lower than those in normal brains, most markedly in the substantia nigra, the structure affected in Parkinson's disease.

Furthermore, enzyme activity was also lower in the brains of sporadic Parkinson's patients, even though they have two normal *GBA* genes. The likely explanation is that  $\alpha$ -synuclein, the characteristic misfolded protein found in Parkinson's disease, disrupts the function of glucocerebrosidase.

These striking findings argue for a two-way interaction between glucocerebrosidase and  $\alpha$ -synuclein. When glucocerebrosidase levels are abnormally low, lysosomal function is compromised and disposal of  $\alpha$ -synuclein is disrupted; when glucocerebrosidase levels are normal, build up of  $\alpha$ -synuclein inhibits enzyme function. Hence there is potential for a vicious cycle, driven either by loss of glucocerebrosidase function or  $\alpha$ -synuclein accumulation.

*In vitro* studies on glucocerebrosidase suggest a further possible link to Parkinson's disease processes. Inhibition of the enzyme leads to abnormal mitochondrial function and an increase in free radical levels – factors previously implicated in cell death in Parkinson's disease.

The results suggest that targeting glucocerebrosidase could be an effective strategy for patients with *GBA* mutations. Indeed, in mouse models Professor Schapira is investigating the potential of 'chaperone'-like drugs to promote the folding and intracellular trafficking of abnormal glucocerebrosidase, as a way of boosting enzyme activity.

**Gegg ME et al.** Glucocerebrosidase deficiency in substantia nigra of Parkinson disease brains. *Ann Neurol*. 2012;72(3):455–63.

**Cleeter MW et al.** Glucocerebrosidase inhibition causes mitochondrial dysfunction and free radical damage. *Neurochem Int*. 2013;62(1):1–7.

**Schapira AH, Gegg ME.** Glucocerebrosidase in the pathogenesis and treatment of Parkinson disease. *Proc Natl Acad Sci USA*. 2013;110(9):3214–5.

# TRANSLATIONAL RESEARCH: GENETIC INSIGHTS, DISEASE MODELS AND INTERVENTION DEVELOPMENT

Cellular and animal models are providing platforms for understanding disease processes and testing of new diagnostics and treatments.



Genetic approaches have identified key processes involved in neurodegeneration – an area in which UCL has a long track record. Studies of families have identified rare single-gene causes of Alzheimer's disease, Parkinson's disease and other conditions. Genome-wide screens have revealed genetic variants affecting the risk of disease. Although most have only small impact, they highlight pathways likely to be involved in disease.

Increasingly, direct sequencing is likely to identify variants that are too rare to be picked up by genome-wide analyses and, although having a significant effect on disease risk, do not generate obvious patterns of inheritance. A prime example is *TREM2*, the identification

of which has stimulated great interest in the role of inflammation and the brain's immune cells, microglia, in Alzheimer's disease.

Genetics therefore provides a route into disease processes. Follow-up functional studies can then begin to reveal how they exert their effects.

Animal models of disease have the advantage that they provide information on abnormal function in the context of whole-animal physiology (although good animal models of Alzheimer's disease and Parkinson's disease have been difficult to generate).

Cellular studies are an important complement to animal studies. As well as cultured cells from patients, induced pluripotent stem

(iPS) cells derived from patients are increasingly being used to gain insight into disease processes. Patient skin cells are collected, reprogrammed into a pluripotent state and then differentiated into the specific cell types affected in neurodegenerative disease.

In collaboration with other UK centres, UCL researchers are developing a suite of iPS cell lines with differing genetic abnormalities for use in research. As well as tools in elucidating disease processes, cellular and animal models will be valuable in the development of new therapies.

Promising therapies are being explored in Alzheimer's disease and prion disease, with agents

developed to prevent the accumulation of toxic protein assemblies. An existing drug, exenatide, has shown promise in a Parkinson's disease trial.

The landmark agreement signed with the Eisai pharmaceutical company will also promote research into new therapeutics targeting neurodegenerative disease processes.



Genetic approaches are revealing the causes of neurodegeneration.

## AN INFLAMMATORY FINDING

Work on two Turkish families with dementia led to the discovery of one of the most important genetic risk factors yet identified in Alzheimer's disease.

Sequencing of coding regions of the genome has become a cost-effective way to identify the genes underlying inherited diseases, including familial dementias. For **Dr Rita Guerreiro** in **Professor John Hardy's** lab, an analysis of Turkish families affected by early-onset frontotemporal dementia led to the identification of a risk factor with the second biggest impact on disease after apolipoprotein E (ApoE) and sparked a flurry of interest in the role of inflammation in Alzheimer's disease.

Through sequencing, Professor Hardy and colleagues discovered that three family members with dementia had mutations in a gene known as *TREM2*. Notably, *TREM2* was known to be involved in regulating the activity of microglia, the brain's immune cells.

With evidence growing of an inflammatory component to Alzheimer's disease, Dr Guerreiro then carried out a routine check on sequence data from sporadic Alzheimer's disease cases. To her surprise, she discovered *TREM2* variants in a significant number of patients. Systematic genotyping of more than 1000 patients revealed *TREM2* variants in 22 cases but just five controls. *TREM2* variants increase the risk of developing Alzheimer's disease around threefold, about as much as the well-recognised ApoE4 risk factor (though *TREM2* variants are much less common).

Perhaps most exciting is the insight the discovery provides into the mechanisms of disease. There has been growing interest in inflammation in Alzheimer's disease, particularly as genome-wide sweeps for genetic risk factors have implicated several genes involved in immune responses.

Signalling through *TREM2* is thought to dampen down microglia. Full mutations may leave it unable to prevent runaway inflammatory responses, leading to rapid neurodegeneration and early-onset dementia in people inheriting two copies of the faulty gene. The Alzheimer's-linked variants may mean that microglia are more active than is ideal, and respond too aggressively to  $\beta$ -amyloid, increasing the risk of Alzheimer's disease.

*TREM2* is certainly the strongest hint yet that neuroinflammation is an important feature of Alzheimer's disease – and a potential route to new therapies, perhaps by boosting *TREM2* levels or more generally by targeting other aspects of the inflammatory response.

**Guerreiro R et al.** *TREM2* variants in Alzheimer's disease. *N Engl J Med.* 2013;368(2):117–27.



Dr Helene Plun-Favreau.

## CELLS UNDER STRESS

Cellular studies have implicated both defective disposal of mitochondria and abnormal mitochondrial function in Parkinson's disease and other neurodegenerative conditions.

As with all neurodegenerative diseases, the underlying mechanisms of Parkinson's disease remain poorly understood. Genes causing inherited forms of the disease provide a point of access to disease processes, and by collaborating with human geneticists, **Dr Helene Plun-Favreau** is dissecting the function of these genes and their role in disease.

The power of this approach was illustrated by the discovery that two common causes of inherited Parkinson's disease, *PINK1* and *parkin*, both affected mitochondria, placing this organelle at the heart of studies into mechanisms of disease. *PINK1* and *parkin* physically interact with each other, and appear to be involved in the controlled disposal of defective mitochondria (mitophagy). Defects in either lead to the persistence of defective mitochondria, which ultimately lead to death of the cell.

More recently, Dr Plun-Favreau and colleagues have discovered that another Parkinson's disease gene, *Fbxo7*, is implicated in the *PINK1*–*parkin* pathway, further emphasising the importance of the defective removal of damaged mitochondria in Parkinson's disease.

As well as abnormal mitochondrial recycling, loss of mitochondrial function may also play a role in Parkinson's disease, and other forms of neurodegeneration, as well illustrated by Dr Plun-Favreau and colleagues' work on valosin-containing protein (VCP). Mutations in VCP lead to a range of conditions, including muscle degeneration, frontotemporal dementia and amyotrophic lateral sclerosis. Notably, while the amount of oxygen consumed by mitochondria in the cells of patients with VCP mutations was dramatically increased, ATP production was abnormally low – even though the two processes are usually tightly coupled.

Because of this uncoupling, cells struggle to produce enough ATP to cope with energy-intensive cellular processes. They are thus highly vulnerable to further stresses, which can trigger processes leading to cell death.

Cellular studies are therefore shedding important light on the biochemical pathways and cellular processes that are disturbed when particular proteins are absent or abnormal. Looking forward, Dr Plun-Favreau will be aiming to generate pluripotent stem cells from patients and differentiate them in culture – providing opportunities to study disease processes within critical cell types.

**Burchell VS et al.** The Parkinson's disease genes *Fbxo7* and *Parkin* interact to mediate mitophagy. *Nat Neurosci.* 2013;16(9):1257–65.

**Plun-Favreau H et al.** The mitochondrial protease *HtrA2* is regulated by Parkinson's disease-associated kinase *PINK1*. *Nat Cell Biol.* 2007;9(11):1243–52.

**Bartolome F et al.** Pathogenic VCP Mutations Induce Mitochondrial Uncoupling and Reduced ATP Levels. *Neuron.* 2013;78(1):57–64.



Elizabeth Fisher (centre) with Frances Wiseman and Xun Choong.

## IN SEARCH OF THE PERFECT MODEL

Increasingly sophisticated approaches are being used to generate mouse models of neurodegenerative disease.

For all neurodegenerative diseases, understanding mechanisms of disease remains an important challenge. While cellular studies have their place, there is also much to be gained from work on mouse models of disease. Although none is perfect, collectively they provide key insight into disease processes. As **Professor Elizabeth Fisher's** work illustrates, new technologies and insight from other studies are helping to shape a new generation of mouse models more closely mimicking human disease.

With long-term collaborator Dr Victor Tybulewicz at the MRC National Institute for Medical Research, Professor Fisher has been responsible for one of the most remarkable feats of mouse engineering – a mouse model of Down syndrome, Tc1, containing a near-complete version of human chromosome 21. Notably, people with Down syndrome are at high risk of developing Alzheimer's disease at a relatively early age, and show the characteristic Alzheimer's brain pathology of  $\beta$ -amyloid plaques and hyperphosphorylated tau tangles. Hence, alongside insight into the cognitive and other abnormalities associated with Down syndrome, Tc1 mice may also shed light on the origins of Alzheimer's disease.

Having developed the model, Professor Fisher and Dr Tybulewicz also collaborate with other groups investigating its biology. Work with Professor Tim Bliss, for example, identified distinctive memory impairments in the mice. Recently, work with UCL's Dr Frances Wiseman revealed key features of tau phosphorylation in the ageing mouse brain.

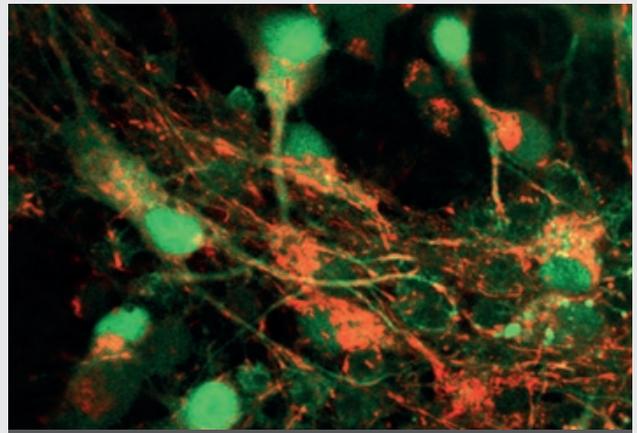
The Tc1 mouse is trisomic for 200 genes, but some human chromosome 21 genes are missing. Notably, this includes the *APP* gene, which codes for a precursor of  $\beta$ -amyloid protein. This can be an advantage – for example, it provides an opportunity to study tau in the absence of abnormal *APP* – but also has drawbacks. A recent detailed genetic analysis, carried out in collaboration with the Wellcome Trust Sanger Institute, provided a clearer view of the genetic make up of the human chromosome, including other unsuspected genetic rearrangements. As part of the LonDownS Consortium (see page 22), Professor Fisher and Dr Tybulewicz aim to develop an improved 'mark 2' mouse.

As well as Tc1, Professor Fisher has also generated models of other neurodegenerative conditions, including amyotrophic lateral sclerosis, which has a lifetime risk of up to one in 250. Her goal is to generate strains that include the precise genetic abnormality found in inherited forms of disease, to ensure models are as similar as possible to the human condition.

**O'Doherty A et al.** An aneuploid mouse strain carrying human chromosome 21 with Down syndrome phenotypes. *Science*. 2005;309(5743):2033–7.

**Morice E et al.** Preservation of long-term memory and synaptic plasticity despite short-term impairments in the Tc1 mouse model of Down syndrome. *Learn Mem*. 2008;15(7):492–500.

**Sheppard O et al.** Altered regulation of tau phosphorylation in a mouse model of Down syndrome aging. *Neurobiol Aging*. 2012;33(4):828.e31–44.



Monitoring of mitochondria (red) and  $Ca^{2+}$  (green) in neurons.

## THE DEVIL IN THE DETAIL

Biology and biophysics are being combined to clarify the role of  $\alpha$ -synuclein in Parkinson's disease.

The build up of  $\alpha$ -synuclein is a hallmark of Parkinson's disease, but it is not absolutely clear how its detrimental effects are mediated. By teaming up with researchers in Cambridge specialising in single-molecule studies of protein aggregation, **Dr Sonia Gandhi** in **Dr Andrey Abramov's** laboratory aims to shed new light on this key question.

Professor David Klenerman, Professor Chris Dobson and colleagues in Cambridge have developed innovative biophysical tools for tracking the aggregation of proteins, including  $\alpha$ -synuclein. Fluorescent tags that are sensitive to the state of aggregation are attached to the protein. By monitoring changing fluorescent signals in highly dilute solutions, the group can follow the aggregation of  $\alpha$ -synuclein into oligomers and then fibrils – as well as the reverse process, fibril disassembly – at essentially single-molecule level.

Recently, **Professor Nick Wood** and the Cambridge team showed that this process has profound biological consequences. The biophysical experiments confirmed that  $\alpha$ -synuclein aggregates into oligomers, of varying sizes. Before aggregating into fibrils, however, oligomers underwent a structural change into a protease-resistant form. Notably, when applied to cells, protease-resistant oligomers generated far more damaging reactive oxygen species, suggesting they are the most toxic form of  $\alpha$ -synuclein.

Recently awarded a four-year fellowship from the Wellcome Trust, Dr Gandhi will be following up these striking findings, splitting her time between UCL and Cambridge. She will be investigating the effects of the different aggregates of  $\alpha$ -synuclein on a range of cell types from patients with familial forms of Parkinson's disease and people with genetic variants increasing the risk of disease. The key readouts will be their effects on mitochondrial function and calcium signalling – processes implicated in the death of neurons.

A further strand of research will make use of 'nanobodies' – labelling reagents based on the unusual antibodies produced by members of the camel family. These are small and specific enough to visualise the location of different forms of  $\alpha$ -synuclein within the cell.

The work has important therapeutic implications. If the protease-resistant form of  $\alpha$ -synuclein is the most toxic, aggregation into fibrils may actually be a mechanism to sequester them and limit cell damage. Preventing conversion of  $\alpha$ -synuclein into a toxic conformation could be a good therapeutic strategy – but promoting disaggregation of fibrils could be counterproductive, leading to the release of more toxic oligomers. Resolving this process with molecular precision should yield important insights for therapy.

**Cremades N et al.** Direct observation of the interconversion of normal and toxic forms of  $\alpha$ -synuclein. *Cell*. 2012;149(5):1048–59.

# THE GENE MACHINE

Professor John Hardy identified the first gene causing inherited Alzheimer's disease and led the team that identified *TREM2* as a major risk factor. Genetics has provided great insight into disease mechanisms but, he suggests, all the most critical genes may now have been found.



As a new postdoc in Newcastle in the 1980s, Professor John Hardy attended a talk from his lab head. "He said 'there are two things we know about Alzheimer's disease: it's not genetic and it doesn't involve inflammation.'" As Professor Hardy's work has revealed, he was wrong on both counts.

Professor Hardy holds the distinction of being the world's most highly cited Alzheimer's disease researcher. His work, and that of other human geneticists, has arguably provided the greatest insight into neurodegeneration, with genetic discoveries revealing biochemical pathways central to disease.

The genetic approach began in earnest in the mid-1980s, when Professor Hardy and Professor Martin Rossor first began collecting families. At that time, mapping disease genes was a laborious process, but Professor Hardy and colleagues eventually nailed down the first Alzheimer's disease gene, *APP*. The gene codes for a precursor of  $\beta$ -amyloid and was strong evidence for the 'beta-amyloid cascade theory' – that beta-amyloid accumulation was a cause not a consequence of disease.

Inherited Alzheimer's disease is rare, however, and in sporadic cases no single gene triggers disease. Over the past decade, genome-wide association studies (GWAS) have identified dozens of genetic risk factors for Alzheimer's and other neurodegenerative diseases, thanks to the efforts of large international collaborations. Professor Hardy has contributed to Alzheimer's disease GWAS and led studies of frontotemporal dementia (FTD) and Parkinson's disease (with Professor Nick Wood).

While family studies reveal rare genes of large effect, GWAS identify common variants of small effect. Both approaches may be nearing the limits of their usefulness, Professor Hardy suggests: "I think we've discovered all the Mendelian genes for Alzheimer's disease." And for Alzheimer's disease at least, the genome may soon be mined out of common variants. It is the middle ground where the action now lies, with genes that have a big impact on disease risk but are not common enough to be picked up in GWAS and not severe enough to be obviously familial.

This is precisely the territory of *TREM2*, which increases the risk of Alzheimer's

disease fivefold (see page 11). *TREM2* also places microglia and the immune system in the spotlight. "From our perspective it's a nice finding because it gives a mechanisms straight away," says Professor Hardy, "but also it's the first high risk gene to be found since APOE in 1995."

The root to further disease genes, he believes, will be through genome sequencing: "The way you find them is by brute force sequencing in cases and controls. That's what we've started to do in Alzheimer's disease, with some success."

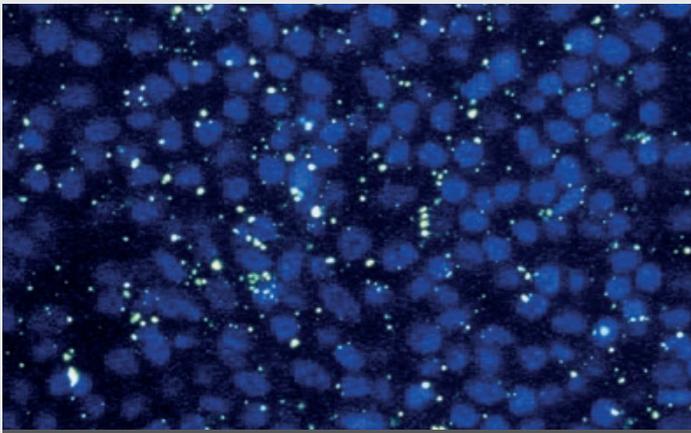
As more genetic causes of dementia are discovered, it is proving possible to screen patients with unexplained dementia. Professor Hardy's colleague Dr Allan Pittman is developing new sequencing tools to screen all known dementia-causing mutations, as a service to UCL clinicians. More generally, though, it is the insight into disease processes that has been most helpful, with functional follow up in cells and animal models.

Professor Hardy also worked on the curious *C9ORF72* gene, mutations in which can cause either a form of motor neuron disease or FTD. Professor Hardy made the

intriguing discovery that all cases could be traced back to a single origin, centred on Scandinavia: "I thought it was a Viking founder. The mutation is incredibly common in Finland and Sweden. It explains about 30 per cent of motor neuron disease in Finland."

Recent discoveries have also shed interesting new light on genetic contributions to disease. It has generally been thought that carriers of recessive disease-causing genes suffer no ill-effects, but with *TREM2* and the *GBA* gene (see page 9), carriers are at significantly increased risk of an entirely different disease (Alzheimer's disease and Parkinson's disease, respectively).

Professor Hardy is also, in his words, 'grandfathering' genetic components of other UCL projects, which are looking for genetic modifiers influencing age of onset or severity of symptoms. These include the LonDownS consortium (see page 22) and the 1946 Birth Cohort (see page 28), as well as studies of early-onset Alzheimer's disease and Huntington's disease. While the major genes may all have been tracked down, genetics has not entirely run its course in dementia just yet.



Detecting neuronal death in the retina.

## AN EYE ON ALZHEIMER'S

Imaging the retina may provide a novel way to diagnose Alzheimer's disease and other neurodegenerative conditions.

Thanks to the neural connections between them, the eye can provide a window into the brain of living organisms. A new imaging technique developed by ophthalmologist **Professor Francesca Cordeiro** is exploiting this opportunity to detect early signs of neuronal death in the retina – an approach that may lead to simple new diagnostic tests for Alzheimer's disease and other neurodegenerative conditions.

Professor Cordeiro's original interests lay in glaucoma, increased fluid pressure in the eye that can lead to blindness due to the death of retinal ganglion cells (RGCs). Diagnosis of glaucoma is not straightforward and disease progression is difficult to track, relying on monitoring of changes in vision.

Death of RGCs followed an orderly pathway of programmed cell death, or apoptosis, and leads to the appearance of characteristic lipids on the surface of cells. Professor Cordeiro developed a fluorescently labelled version of a protein known to bind these lipids, annexin A5, and showed that the technique – called DARC (detection of apoptosing retinal cells) – could sensitively detect RGCs undergoing apoptosis using standard ophthalmological equipment.

With translational funding from the Wellcome Trust, Professor Cordeiro has been preparing for first-in-human glaucoma trials. However, Professor Cordeiro also realised that DARC could find application in neurodegenerative conditions, where loss of RGCs is also seen. Studies in a range of animal models of Alzheimer's disease (and Parkinson's disease) have shown that there is a good correlation between the eye damage detected by DARC and levels of brain pathology.

Symptom-based diagnosis of dementia is challenging. Brain imaging and biochemical biomarker analysis are also not entirely accurate, and not well suited to routine clinical use. A simple eye-based diagnostic test could therefore have a significant impact on clinical practice.

Phase I trials with DARC will use intravenous injection to deliver labelling agents. In the longer term, Professor Cordeiro is pinning her hopes on an innovative eye drop delivery system which could easily be delivered by a technician. If phase I studies go according to plan, she hopes to move to phase II studies for both glaucoma and Alzheimer's disease, and has begun discussions with Dr Jonathan Schott in UCL's Dementia Research Centre to explore the practicalities of studies in Alzheimer's patients.

**Cordeiro MF et al.** Real-time imaging of single nerve cell apoptosis in retinal neurodegeneration. *Proc Natl Acad Sci USA*. 2004;101(36):13352–6.

**Normando EM, Turner LA, Cordeiro MF.** The potential of annexin-labelling for the diagnosis and follow-up of glaucoma. *Cell Tissue Res*. 2013;353(2):279–85.

**Guo L, Duggan J, Cordeiro MF.** Alzheimer's disease and retinal neurodegeneration. *Curr Alzheimer Res*. 2010;7(1):3–14.



A molecular model of prion protein.

## THE SHAPE OF THINGS TO COME

Targeting cellular prion protein may be a way to prevent pathogenic prions from harming the cell.

**Professor John Collinge** has carried out groundbreaking work on the mechanisms of action of infectious prion protein (see page 5). This work has suggested that the toxic prion entity may not be the infectious form itself but a species arising during the conversion of the cellular prion protein (PrP<sup>C</sup>) to its infectious form (PrP<sup>Sc</sup>). This suggested a novel therapeutic strategy – protecting PrP<sup>C</sup> so it cannot be converted into PrP<sup>Sc</sup>.

Other work suggested this approach was feasible. The function of PrP<sup>C</sup> remains unclear, but it does not appear to be essential – mice lacking PrP<sup>C</sup> show no obvious abnormalities. Perhaps most excitingly, Professor Collinge showed that when PrP<sup>C</sup> gene expression was turned off in infected adult mice, disease processes were halted and the mice actually showed signs of recovery.

Professor Collinge and colleagues have been pursuing a two-pronged approach, exploring the potential of both monoclonal antibodies and small molecules to protect PrP<sup>C</sup>. Many antibodies against prion protein block prion propagation in cellular and animal models. Professor Collinge has shown that the potency of such antibodies is dependent on their binding to PrP<sup>C</sup>, acting as 'molecular chaperones' to maintain their native conformation.

With MRC funding, Professor Collinge has shown that monoclonal antibodies are highly effective at halting prion propagation in animal models. These antibodies have been 'humanised' for use in people, and discussions have begun with regulatory authorities about the possible format of clinical trials with Creutzfeldt–Jakob disease patients.

In collaboration with GSK, Professor Collinge has also been developing small molecule inhibitors with chaperone-like properties. Past work has provided proof of principle, with a cationic tetrapyrrole molecule being shown to have potent anti-prion activity by binding to and stabilising PrP<sup>C</sup>. Screens of chemical libraries have revealed other promising hits.

Such agents may yet have further value. Recent work has suggested that prion protein may be a route through which  $\beta$ -amyloid exerts its harmful effects in Alzheimer's disease. As well as confirming this effect using brain-derived  $\beta$ -amyloid, Professor Collinge has shown that PrP<sup>C</sup> antibodies can block interactions with  $\beta$ -amyloid and reduce its neurotoxic effects. If the prion therapies do prove safe and effective, they might therefore also have application in Alzheimer's disease.

**Mallucci GR et al.** Targeting cellular prion protein reverses early cognitive deficits and neurophysiological dysfunction in prion-infected mice. *Neuron*. 2007;53(3):325–35.

**Antonyuk SV et al.** Crystal structure of human prion protein bound to a therapeutic antibody. *Proc Natl Acad Sci USA*. 2009;106(8):2554–8.

**Nicoll AJ et al.** Pharmacological chaperone for the structured domain of human prion protein. *Proc Natl Acad Sci USA*. 2010;107(41):17610–5.

**Freir DB et al.** Interaction between prion protein and toxic amyloid  $\beta$  assemblies can be therapeutically targeted at multiple sites. *Nat Commun*. 2011;2:336.



Exenatide may be a novel treatment for Parkinson's disease.

## ACCELERATING DRUG TESTING

**A drug used to treat diabetes has shown promising effects in an innovative Parkinson's disease trial.**

In recent years, evidence has been accumulating that the hormone glucagon-like peptide-1 might be a good target for Parkinson's disease. Furthermore, a drug targeting GLP-1, exenatide, a derivative of a compound found in the saliva of the Gila monster, has already been licensed to treat type 2 diabetes. Keen to test its effects in Parkinson's disease, **Dr Thomas Foltynie** worked with the drug's manufacturer and the Cure Parkinson's Trust to organise an innovative proof of concept trial, with positive results.

With safety data already available from earlier studies, a randomised controlled trial could in theory have been organised to test exenatide's efficacy in Parkinson's disease. However, such trials are expensive and there is inevitably a high risk of failure. Exenatide's makers were reluctant to commit to this step without gathering further evidence of its likely impact on disease.

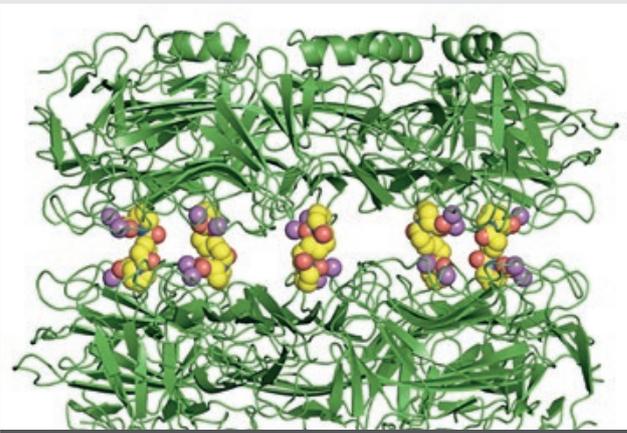
Dr Foltynie and the Cure Parkinson's Trust, however, were keen to move things along faster. A major challenge to a large trial would have been the need to develop a placebo version of the pen-like device used to inject exenatide. Dr Foltynie therefore suggested running a single-blind randomised controlled – so patients would know whether or not they were taking the drug but assessors would not. The main drawback of this trial design is that any positive impact might simply reflect a placebo effect.

The trial of 45 patients lasted a year, and generated highly encouraging results. Not only did exenatide prevent the decline in motor and cognitive symptoms seen in control patients but performance actually improved, suggesting exenatide is not just neuroprotective but also has additional positive effects.

While placebo effects cannot be excluded with certainty, there are reasons to believe they were not a key factor. For example, improvement was gradual and sustained while a placebo effect would typically be more immediate and then decline.

Most importantly, quickly and at relatively low cost the trial has generated data suggesting that further studies of exenatide are warranted. Its manufacturers and the Michael J Fox Foundation are now supporting a larger placebo-controlled trial which Dr Foltynie will be leading. More generally, the trial illustrates how 'mini-trials' may act as cost-effective stepping stones in the development of promising therapeutics, enabling more agents to be tested in patients and reducing the risk of expensive failure at phase III.

**Aviles-Olmos I et al.** Exenatide and the treatment of patients with Parkinson's disease. *J Clin Invest.* 2013;123(6):2730–6.



Cross-linking of serum amyloid P component by CPHPC (centre).

## ZAPSAP – TARGETED PROTEIN DEPLETION IN ALZHEIMER'S DISEASE

**A unique mechanism of drug action may be applicable to Alzheimer's disease, with work towards a clinical trial in progress.**

**Professor Sir Mark Pepys FRS** has worked on amyloid for 40 years with a major focus on the normal blood protein, serum amyloid P component (SAP), which is always concentrated in amyloid deposits.

Amyloid is an abnormal, insoluble, fibrous protein material which can accumulate in body tissues, damaging their structure and function and causing fatal disease. Amyloidosis, the disease caused by amyloid deposits, is rare, affecting about 6,000 people in the UK. Alzheimer's disease is very much more common; patients' brains always contain a particular type of amyloid, A $\beta$ , but it is not known whether these A $\beta$  amyloid deposits cause dementia. Nevertheless, A $\beta$  amyloid is always loaded with SAP, which binds avidly to A $\beta$  amyloid fibres.

Sir Mark has shown that SAP contributes to the formation and persistence of amyloid and developed a drug, known by the initials of its chemical name, CPHPC, which uniquely removes all SAP from the blood. CPHPC treatment and SAP depletion have no adverse effects.

SAP depletion alone does not cure amyloidosis. Sir Mark therefore introduced a novel use of antibodies to target amyloid, which is only possible when patients have been treated with CPHPC. This invention has now been developed in collaboration with GlaxoSmithKline and the first clinical trial in amyloidosis patients is currently in progress.

Meanwhile Sir Mark and his colleagues have lately confirmed and extended earlier research showing that, unrelated to amyloid, SAP itself is damaging to brain nerve cells. All Alzheimer's disease patients have abnormally increased amounts of SAP in their brains. Removal of SAP from the brain is therefore a valid and very attractive new approach to treatment and possibly prevention of Alzheimer's disease.

In a preliminary small scale, 3 month, clinical study, Professor Martin Rossor demonstrated that CPHPC removed all SAP from the cerebrospinal fluid that bathes the brain – zapsap! The drug was well tolerated but the study was too short to show clinical benefit.

Work is now in progress, funded by the NIHR UCL/UCLH BRC, in preparation for a one year, double blind, placebo controlled, clinical trial of CPHPC in Alzheimer's disease. Sir Mark and Professor Rossor, with GlaxoSmithKline's participation, have been invited by the MRC to apply for funding of this trial, with a decision expected early in 2014.

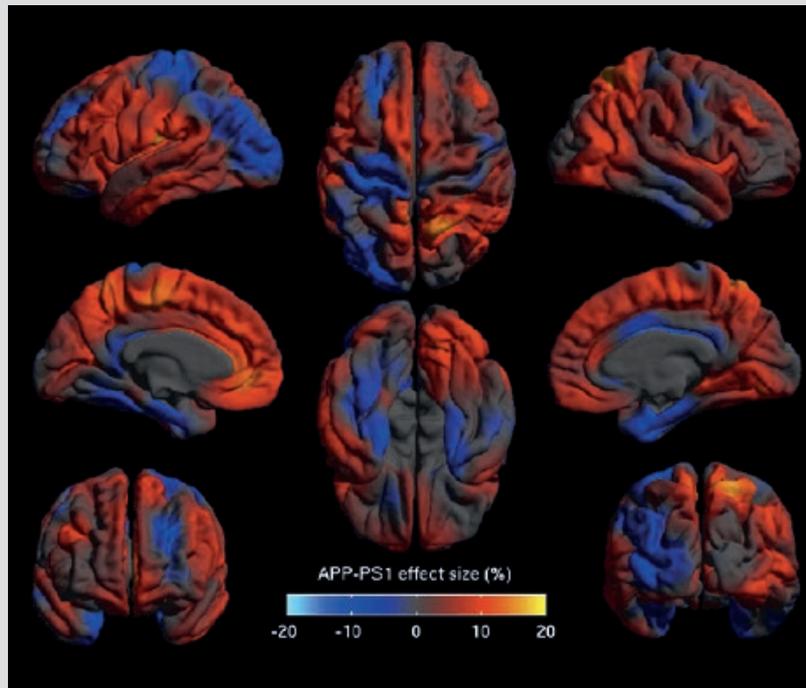
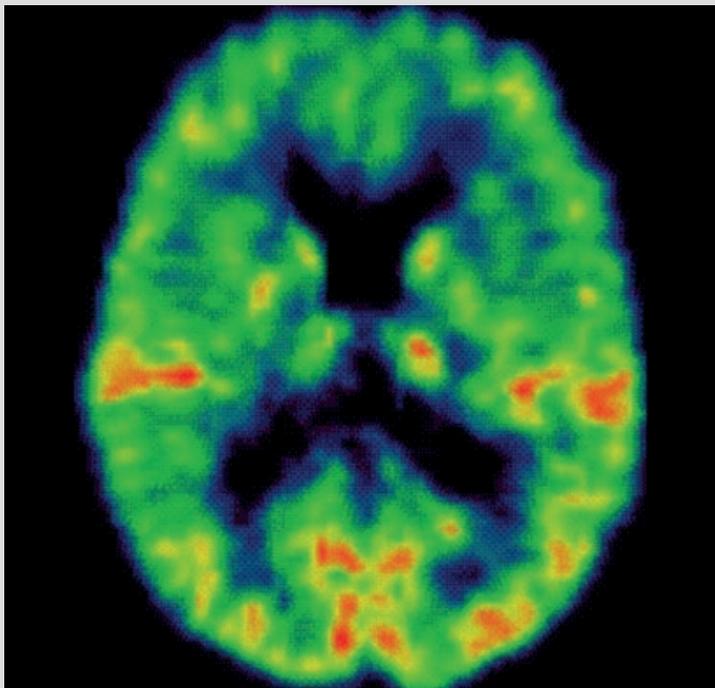
**Pepys MB et al.** Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature.* 2002;417(6886):254–9.

**Bodin K et al.** Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. *Nature.* 2010;468(7320):93–7.

**Kolstoe SE et al.** Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component. *Proc Natl Acad Sci USA.* 2009;106(18):7619–23.

# LEONARD WOLFSON EXPERIMENTAL NEUROLOGY CENTRE

The Leonard Wolfson Experimental Neurology Centre will play a pivotal role in testing the idea that early intervention is critical to the success of treatments for neurodegeneration.



A strong theme running across multiple neurodegenerative conditions is that disease is an extended process. Damage to cells accumulates over many years, even if symptoms are not immediately apparent. Moreover, there is also evidence that diseases accelerate over time, either through spreading of pathology or because of positive feedback processes. Hence, there are compelling arguments in favour of early intervention, to halt or at least slow the damage that ultimately leads to clinical symptoms – ideally interventions would be applied when the minimum of brain cells have been irreversibly lost.

This principle is the cornerstone of the new Leonard Wolfson Experimental Neurology Centre, funded through a £20m award from the

Leonard Wolfson Foundation. Situated within the National Hospital for Neurology and Neurosurgery in Queen Square, it is providing facilities in which new experimental therapies for neurodegenerative disease can be tested in people.

The opening of the Centre heralds a new era in therapeutic R&D in neurodegenerative disease. Advances in understanding of disease mechanisms are revealing new targets for drug development. A variety of different types of therapy are under development. These range from small-chemical molecules, such as the 'palindromic' drug developed by Professor Sir Mark Pepys (page 15), to the antibody-based therapies being tested in the Dominantly Inherited Alzheimer's Network) DIAN trial (page 22). Other innovative technologies are in the pipeline, including

RNA-based gene silencing approaches in Huntington's disease, to be led by Professor Sarah Tabrizi.

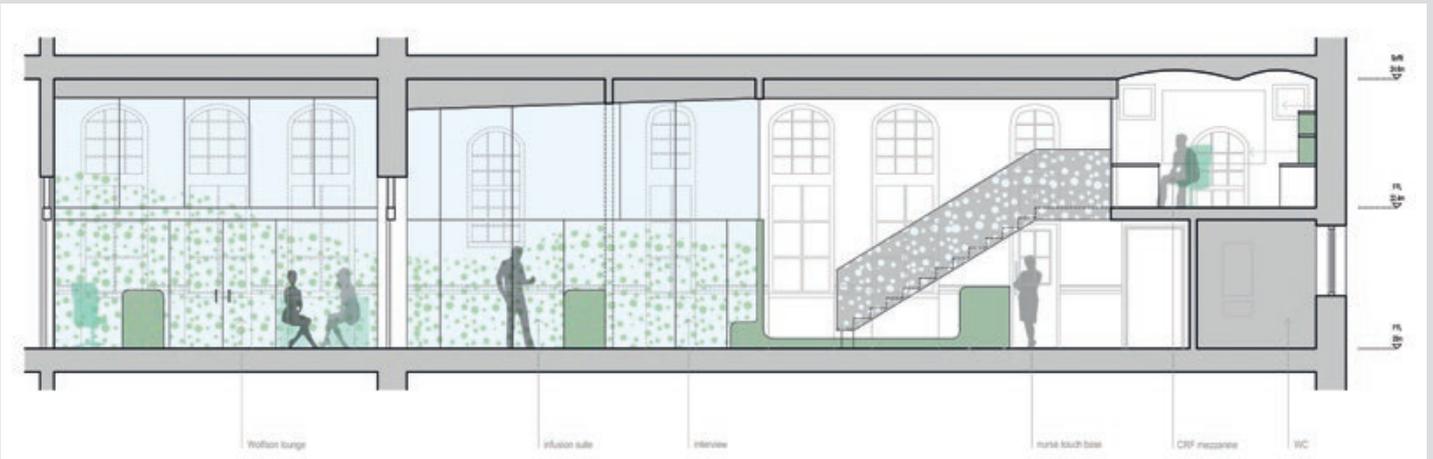
A further important factor is the increasingly close interaction with industry, whose expertise will be essential if effective drugs are to reach patients. UCL's pioneering partnership with Eisai Pharmaceuticals (see Box) is an important step towards this goal.

Other advances have laid the foundations for this new venture. Of paramount importance has been the development of 'biomarkers' to assess the impact of treatment. Brain imaging and biochemical biomarkers in cerebrospinal fluid now provide sensitive ways to assess disease progression and the impact of interventions, potentially enabling proof-of-concept studies and trials to be carried out on much smaller

numbers of patients – and, crucially, in advance of the appearance of symptoms.

A further important theme at the Leonard Wolfson Centre is training. Successful translation of new therapeutics and diagnostics will call for close integration of expertise in fundamental neuroscience, neurology and engineering. With sponsorship from Eisai, the Centre has launched a clinical fellowship and four-year PhD programme to provide an interdisciplinary grounding to both basic scientists and clinicians; a similar scheme exists for engineers.

After a first year spent of formal tuition and laboratory rotations providing first-hand experience of a range of techniques, students undertake a three-year PhD project with one of UCL's world-leading neuroscientists, including the eight principal investigators



associated with the Centre (see Box). Students also have the opportunity to gain industry experience through a placement with Eisai.

As well as trials of therapeutics, the Centre will also have an important role in studies generating more information about disease processes. For example, it will provide the facilities for studies on members of ageing population cohorts (page 27).

The Leonard Wolfson Centre will play a nationally important role in a critical phase in treatment development – the first-in-human studies of new therapeutics. It will help to overcome a key bottleneck in the drug development process, and accelerate the development of agents across a wide range of devastating conditions for which few if any disease-modifying treatments are currently available.

## AN INNOVATION PARTNERSHIP

**The pioneering partnership between UCL and Eisai will bring together complementary expertise in academia and industry to drive forward the development of novel therapeutics for neurodegenerative diseases.**

UCL and Eisai have had a long history of collaboration but the agreement signed in December 2012 to establish a Therapeutic Innovation Group takes this to another level. By working together, the partnership aims to accelerate the development of new agents, with the Leonard Wolfson Centre an important facility in which the most promising can be first tested in proof of concept studies in patients.

The initiative reflects both UCL's strong commitment to working in partnership with industry and Eisai's embracing of open innovation principles. 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.

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 translational researchers redeployed to alternative projects if a project is terminated. Work began on the first project in 2013, with Professor Michael Duchon leading a project looking at mitochondrial dysfunction in neurodegenerative disease.

## CENTRE PRINCIPAL INVESTIGATORS

**Professor John Collinge  
Professor Nick Fox  
Professor John Hardy  
Professor Martin Rossor  
Professor Anthony Schapira  
Professor Sarah Tabrizi  
Professor Alan Thompson  
Professor Nick Wood**

# PATIENT-ORIENTED RESEARCH: UNDERSTANDING, AND PREVENTING, BRAIN ATROPHY

Research on patients has provided a clearer view of disease progression, offering the possibility of therapeutic trials early in disease – or even before disease develops.

UCL's Dementia Research Centre has pioneered the use of brain imaging, notably magnetic resonance imaging (MRI), to characterise the changes in brain structure in people with all kinds of dementia, particularly Alzheimer's disease. Importantly, by working with families affected by inherited forms of the condition, researchers have been able to document significant changes to the brain well in advance of any symptoms appearing.

These findings have led to the idea that overt Alzheimer's disease is a late stage in a process of neurodegeneration that begins years or even decades earlier. They have provided strong support for the notion that treatments for Alzheimer's disease should

be given as earlier as possible, to prevent or delay the neuronal death that ultimately leads to loss of cognitive function.

Furthermore, they have had a further important benefit. Advances in the sensitivity of brain imaging and image processing enable even small changes in brain volume to be detected over a period of a year or so. Brain imaging can therefore be used as a 'biomarker' to track disease progression. As well as being far more sensitive than cognitive tests, imaging can also be used at early stages before symptoms are apparent.

In addition, detection of characteristic molecules in cerebrospinal fluid is providing additional biochemical biomarkers

for tracking the progression of Alzheimer's disease.

As well as Alzheimer's disease, imaging has provided key insight into the development of brain degeneration in Huntington's disease. The landmark TRACK-HD study, led from UCL, has provided clear evidence of early brain atrophy years in advance of clinical symptoms.

Most excitingly, these biomarkers are opening the doors to new clinical trials of therapeutics. The new Leonard Wolfson Centre for Experimental Neurology provides an exceptional platform for such studies. It will host trials of agents targeting  $\beta$ -amyloid, as well as planned tests of innovative gene silencing therapy for Huntington's disease. Further

therapeutics will emerge from the drug development partnership established with Eisai.

Finally, work continues to characterise Alzheimer's disease and other dementias, in particular to identify genetic or other factors that accelerate or protect against disease.



MRI has revealed much about the processes of neurodegeneration.

## INSIDE THE BRAIN

The ability to study the structure of the brain in living people has yielded new insights disease, and provided a crucial platform for clinical trials.

Although post-mortem analysis long ago revealed the brain abnormalities associated with Alzheimer's disease, only with the imaging techniques of CT and, in particular, MRI have changes in living brain tissue been visualised. **Professor Nick Fox** has pioneered studies to characterise brain pathology in dementia, and in individuals in advance of disease. His work has not only established that brain changes occur well in advance of clinical disease, but has also provided a platform for reliably assessing the impact of interventions in clinical trials.

In the mid-1990s, Professor Fox and Professor Martin Rossor realised that advances in MRI were providing opportunities to characterise the brains of dementia patients, and to distinguish pathological effects from those seen in normal ageing. Furthermore, they recognised that families with inherited forms of the disease, although rare, provided unique opportunities to study the onset of disease. Because dementia was far more likely to develop in this group than in the general population, and at earlier ages, it was practical to study them intensively in advance of disease onset.

Over the next 20 years, Professor Fox and colleagues conducted multiple studies to track brain atrophy in Alzheimer's disease and other dementias. One of the most profound conclusions was that loss of brain tissue was occurring before cognitive symptoms are apparent. This influential discovery has driven a radical reappraisal of Alzheimer's disease, to encompass both a 'pre-dementia' phase, with minor cognitive deterioration, and a 'pre-clinical phase' – potentially decades long – when the pathology of Alzheimer's is accumulating in advance of symptoms of cognitive decline.

Furthermore, this idea has emphasised the need to treat Alzheimer's disease as early as possible. By the time serious symptoms are apparent, the brain may already be beyond repair. This emphasis on early intervention is a central principle of the new Leonard Wolfson Experimental Neurology Centre.

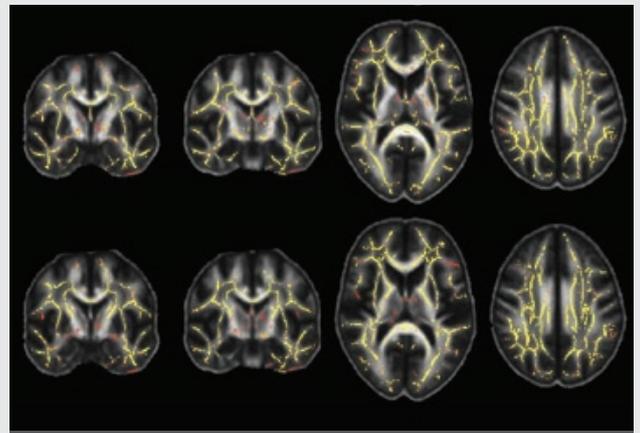
Significantly, thanks to the exquisite sensitivity with which brain imaging can track changes in brain structure, clinical trials are now feasible on relatively small numbers of patients. Nevertheless, Professor Fox is continuing to characterise patterns of tissue loss and other changes, such as the build up of  $\beta$ -amyloid using PET imaging, for example in groups showing early onset of disease. This deep understanding will reveal more about the biology of disease, but will also be a critical way to stratify patients in trials.

**Rossor MN et al.** Incomplete penetrance of familial Alzheimer's disease in a pedigree with a novel presenilin-1 gene mutation. *Lancet*. 1996;347(9014):1560.

**Fox NC, Schill RI, Crum WR, Rossor MN.** Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology*. 1999;52(8):1687–9.

**Fox NC et al.** Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. *Lancet*. 2001;358(9277):201–5.

**Ryan NS et al.** Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease. *Brain*. 2013;136(Pt 5):1399–414



Tracking white matter changes in pre-symptomatic patients.

## ENGINEERING A BETTER SCAN

Large-scale imaging studies of neurodegeneration rely on engineering expertise.

For patient and clinician, symptoms are the critical feature of a neurodegenerative disease. Yet, although standard cognitive tests exist, they are not a particularly sensitive way of assessing neurodegeneration. This presents challenges to clinical trials, which would need to assess thousands of patients in order to detect an effect reliably. These numbers can be reduced by an order of magnitude through use of brain imaging, thanks to input from engineers such as **Professor Seb Ourselin**.

Although based in the Faculty of Engineering, Professor Ourselin spends much of his time at the Dementia Research Centre. Over the past decade, he has worked with several members of the Centre to refine methods of MRI scanning and to gather an ever more detailed picture of brain anatomy and function in Alzheimer's disease and other dementias.

The work is technically challenging. Brain imaging is attempting to characterise changes in brain volume of just 1–2 per cent per year. But being able to achieve such sensitivity and accuracy means that trials can be carried out on just a few hundred patients. As the need grows for more trials of therapeutic agents on targeted patient groups, such methodologies will be essential to ensure that clinical trials do not become a bottleneck in the development pathway. Furthermore, unlike cognitive tests, measures of brain loss can be used in trials on pre-symptomatic patients.

To date, Professor Ourselin's work has focused on total brain volume or areas such as the hippocampus, a site of early neurodegeneration. His group develops image-analysis algorithms to extract information from scan data. A major challenge is to ensure that the results gathered from multiple international sites are compatible, with shared protocols for imaging and for data analysis. For effective translation, imaging technologies must also be integrated into the clinical environment.

There is also growing interest in the use of PET imaging, which can reveal  $\beta$ -amyloid build up but does not yet have the spatial sensitivity of MRI. Professor Ourselin also plans to make more use of methods such as diffusion imaging, which characterises white matter microstructure, and functional MRI. Such studies will provide complementary information to that obtained by structural MRI, and bring imaging closer to the biological function of neural circuitry. Ultimately, the range of methods will provide a more detailed characterisation of patients, and may allow correlations to be drawn between patient traits and response to therapies.

**Leung KK et al.** Robust atrophy rate measurement in Alzheimer's disease using multi-site serial MRI: tissue-specific intensity normalization and parameter selection. *Neuroimage*. 2010;50(2):516–23.

**Keihaninejad S et al.** The importance of group-wise registration in tract based spatial statistics study of neurodegeneration: a simulation study in Alzheimer's disease. *PLoS One*. 2012;7(11):e45996.

**Ryan NS et al.** Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease. *Brain*. 2013;136(Pt 5):1399–414.



Professor Henrik Zetterberg.

## MARKERS FOR LIFE

**Cerebrospinal fluid biomarkers can track Alzheimer's disease progression – but also provide clues to disease mechanisms.**

Tracking neurodegeneration, particularly before symptoms appear, is a key challenge in dementia research. Alongside brain imaging, there is growing interest in measurement of biochemical markers in cerebrospinal fluid – which, suggests new UCL recruit **Professor Henrik Zetterberg**, may also provide insight into the cellular changes occurring in the brain.

It is now clear that the origins of Alzheimer's disease go back decades, as neurons accumulate abnormal proteins and die, even before symptoms appear. Measurement of key proteins in cerebrospinal fluid provides a window into these critical changes.

Of great interest, levels of a truncated form of  $\beta$ -amyloid ( $A\beta_{42}$ ) fall markedly in people destined to develop Alzheimer's disease. Other characteristic changes include an increase in levels of both total tau protein and phosphorylated tau. These markers have recently been incorporated into diagnostic criteria for Alzheimer's disease and the mild cognitive impairment that precedes it.

Furthermore, they may also provide insight into disease mechanisms, as they reflect different aspects of disease. The drop in  $A\beta_{42}$  probably reflects the sequestration of  $\beta$ -amyloid into plaques, total tau assays neuronal death, which leads to the release of intracellular tau, while phospho-tau levels track the formation of fibrillary tangles. Notably, the decline in  $A\beta_{42}$  precedes changes in tau, arguing that it represents an earlier stage in the disease process.

As well as diagnosis, cerebrospinal fluid biomarkers also provide a complementary tool to brain imaging for tracking disease progression. Since changes are apparent years before symptoms appear, they can be used in trials of therapies targeting early, pre-symptomatic phases of disease. Moreover, certain molecular biomarkers will be highly relevant to particular therapeutic strategies –  $A\beta_{42}$ , for example, for therapies targeting  $\beta$ -amyloid.

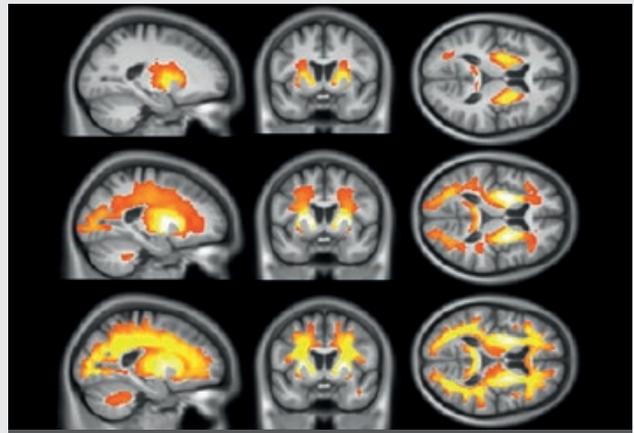
Professor Zetterberg has taken up a position at UCL while maintaining his group in Gothenburg, Sweden – a centre with renowned expertise in biomarker research. As well as these well-characterised biomarkers, he will also be studying the potential of other metabolites – first example, of markers of inflammation or loss of synapses – which may reflect important disease processes. He will also be undertaking proteomic studies to identify new components of cerebrospinal fluid of potential relevance to neurodegeneration.

As well as disease groups, Professor Zetterberg will also be studying members of the 1946 Birth Cohort (see page 28). Such studies will reveal the 'natural history' of biomarker change, and allow comparisons between those who develop Alzheimer's disease and those who do not.

**Rosén C, Zetterberg H.** Cerebrospinal fluid biomarkers for pathological processes in Alzheimer's disease. *Curr Opin Psychiatry*. 2013;26(3):276-82.

**Hölttä M et al.** Peptidome analysis of cerebrospinal fluid by LC-MALDI MS. *PLoS One*. 2012;7(8):e42555.

**Buchhave P et al.** Cerebrospinal fluid levels of  $\beta$ -amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch Gen Psychiatry*. 2012;69(1):98-106.



Tracking white matter atrophy in Huntington's disease.

## TRACKING HUNTINGTON'S DISEASE

**A landmark long-term study of Huntington's disease has identified brain and other changes years before symptoms appear.**

If treatment of neurodegenerative disease is to begin early – possibly, even before symptoms appear – methods will be needed to track disease progression over time. In the short term, such tools will be required to assess the impact of new therapeutics in clinical trials. For Huntington's disease, **Professor Sarah Tabrizi** has led a groundbreaking international collaboration, TRACK-HD, that has identified a suite of suitable markers, for patients early in disease and even those yet to experience symptoms.

Huntington's disease provides a rare opportunity to study neurodegeneration preclinically. Because it is caused by a single faulty gene, and everyone with the gene will get the disease, affected individuals can be identified using genetic tests and then followed over time.

The TRACK-HD study has been following some 300 Huntington's disease gene carriers in four North American and European countries. As well as tests of motor and coordination skills, and assessments of mood and other neuropsychiatric indicators, TRACK-HD has undertaken detailed imaging of the brain's white and grey matter.

Recently published third year results have provided a wealth of valuable information. Perhaps most striking was the identification of several signs of neurodegeneration years before individuals are likely to experience symptoms. These included loss of grey matter in particular regions of the brain, as well as changes in simple behavioural tests such as finger tapping regularity.

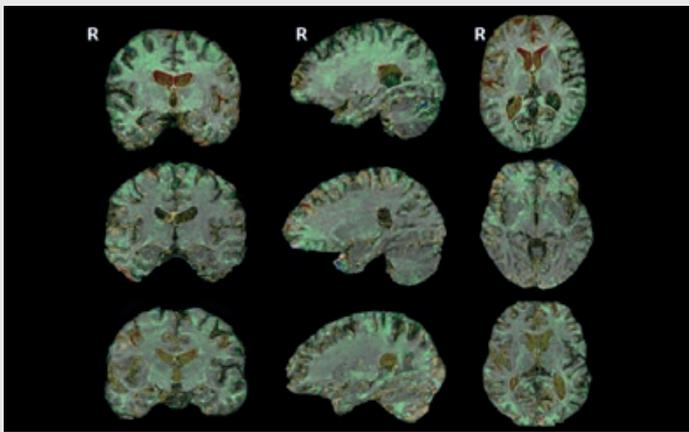
Furthermore, some baseline measures – primarily low grey matter volumes in certain areas of the brain – were predictive of later clinical decline, providing markers of those most vulnerable to the disease. The trial had further benefits, providing new insights into the patterns and dynamics of neural circuitry breakdown as disease progresses, and the data are being used to look for genetic modifiers of the speed of disease progression.

Crucially, the changes identified will provide biomarkers for clinical trials in presymptomatic gene carriers. In addition, the baseline markers of susceptibility will enable patients to be stratified according to their underlying vulnerability. With new agents for Huntington's disease close to human use, TRACK-HD's findings will ensure that they can be tested in patients yet to experience symptoms, when they are likely to be most beneficial.

**Tabrizi SJ et al.** Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol*. 2013;12(7):637-49.

**Tabrizi SJ et al.** Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol*. 2012;11(1):42-53.

**Tabrizi SJ et al.** Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol*. 2011;10(1):31-42.



Areas of contraction (green) and expansion (red) in FTD brains.

## A WORLD WITHOUT MEANING

Can specific symptoms of dementia be linked to abnormal neural networks, and perhaps even to underlying molecular causes?

A major challenge in dementia research is to establish connections between symptoms and changes in the brain. Ideally, it would be valuable to drill down still further to relate these abnormalities to underlying molecular mechanisms, as these will be the target of pharmacological interventions. **Dr Jason Warren** is attempting to develop a better understanding of this 'chain of causation', using complex sound, taste and smell processing as model systems.

A major focus of Dr Warren's research is frontotemporal dementia (FTD). FTD strikes relatively early in life, generally from the late 40s onwards, and is characterised by a variety of symptoms including behavioural changes, speech difficulties, and loss of the meanings of words and objects (semantic dementia). As its name suggests, FTD is associated with loss of tissue in the frontal lobes.

Notably, specific genetic causes are relatively common in FTD, offering hope that it may be possible to track the chain of events from molecular defect through cellular and neural network abnormalities to symptoms. Unfortunately, although some links can be made, there appears to be no simple correlation between a gene defect and clinical symptoms. Indeed, mutations in the newly discovered *C9ORF72* gene can cause either FTD or a form of motor neuron disease.

The behavioural changes seen in FTD reflect the loss of particular cognitive abilities. Dr Warren is using brain imaging and other techniques to pin down more precisely which aspects of cognition are affected and the neural basis of these changes, and to link these where possible to molecular defects.

For example, patients often appear unemotional, reflecting an effect on emotion-processing brain pathways. Unusual eating habits, such as strange food combinations, hint at defects in flavour or taste processing. Simple tools such as flavoured jellybeans, including combinations with either congruent or clashing flavour combinations, are helping to reveal which aspects of flavour processing are disrupted. This work has shown that these behavioural processes have specific neuroanatomical associations.

Similarly, extensive work on complex sound processing, including speech and music, has generated important insights into the nature of deficits (as well as shedding light on music processing in the brain). Music may be a useful model for understanding how the brain interprets ambiguous social signals, and how this goes so catastrophically wrong in FTD. Ultimately, by connecting the dots from molecular abnormality to network disturbance to manifest symptom, this intensive multilevel characterisation may make it possible to identify the most appropriate interventions for particular classes of patient.

**Omar R, Mahoney CJ, Buckley AH, Warren JD.** Flavour identification in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry*. 2013;84(1):88–93.

**Goll JC et al.** Nonverbal sound processing in semantic dementia: a functional MRI study. *Neuroimage*. 2012;61(1):170–80.

**Rohrer JD et al.** Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain*. 2011;134(Pt 9):2565–81.



Dr Jonathan Schott.

## ENIGMA OF THE VARIATION

Why does the time-course of Alzheimer's disease vary so greatly?

Sporadic Alzheimer's disease can differ markedly in its age of onset. Although typically a disease of later life, it can strike while people are in their sixties or even earlier. **Dr Jonathan Schott** aims to identify factors influencing age of onset, which calls for an integration of multiple ways of assessing disease.

Alzheimer's symptoms are difficult to quantify sensitively and, moreover, may not easily distinguish Alzheimer's disease from other conditions, particularly early in disease. Researchers have therefore adopted a range of other techniques to probe the underlying biological changes occurring during Alzheimer's disease, and to gauge disease progression.

Different forms of brain imaging, particularly MRI, can reveal characteristic changes in brain structure – importantly, even before symptoms are apparent. Similarly, PET imaging of  $\beta$ -amyloid can now reveal the tell-tale signs of amyloid plaque formation in the brains of living people. Biochemical markers, particularly in cerebrospinal fluid, can also provide an early warning sign of cellular damage.

Combining these measures with detailed clinical assessments and cognitive tests provides a means of characterising patients, and tracking changes over time. Key challenges are to understand precisely which markers of disease are most relevant to cognitive decline, to aid diagnosis and risk prediction, to gain a better understanding of the course of disease, and for monitoring changes during clinical trials.

Working with Professor Nick Fox and others, Dr Schott has been involved in several studies characterising changes in the brain, and the influence of factors such as genetic variants implicated in risk of disease. His latest research is extending this characterisation to two contrasting populations.

The first is a large group of individuals with young-onset Alzheimer's disease. The key challenge is to understand why this group has turned out to be vulnerable to dementia decades before the disease becomes common.

By contrast, Dr Schott's second group is, in effect, an entirely random population sample – of people all born in the same week in March 1946. Members of the MRC National Survey of Health and Development 1946 Birth Cohort (see page 28) are reaching the age at which dementia is starting to become apparent. Dr Schott, Professor Fox, Professor Richards and others are beginning a detailed assessment of some study members to try to identify those at risk of Alzheimer's and those who will be spared. Comparisons between these groups may reveal factors that influence if and when individuals will develop the disease.

**Schott JM et al.** Neuropsychological correlates of whole brain atrophy in Alzheimer's disease. *Neuropsychologia*. 2008;46(6):1732–7.

**Schott JM et al.** Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid  $A\beta$ 1-42. *Ann Neurol*. 2010;68(6):825–34.

**Andrews KA et al.** Atrophy rates in asymptomatic amyloidosis: implications for Alzheimer prevention trials. *PLoS One*. 2013;8(3):e58816.



Dr Andre Strydom, who is leading the LonDownS Consortium.

## DECIPHERING THE DOWN DEMENTIA LINK

**A major new programme is examining why people with Down syndrome are often protected against dementia despite showing neuropathology of Alzheimer's disease.**

Down syndrome, the most common chromosomal abnormality, is caused by an additional copy of chromosome 21. As well as a range of cognitive and health issues, people with Down syndrome are prone to develop Alzheimer's disease, and at relative early ages. LonDownS, a new multicentre collaboration being led by UCL's **Dr Andre Strydom**, aims to get to the root of this susceptibility – knowledge that could benefit both people with Down syndrome and others with dementia.

Funded through a £2.5m Strategic Award from the Wellcome Trust, the LonDownS Consortium brings together clinical assessment, human genetics, mouse modelling, cellular studies and cognitive profiling. The main aim is to understand how the additional copy of chromosome 21 affects cells, circuitry and cognition, and ultimately leads to Alzheimer's disease.

Genetic work will be led by Professor John Hardy. Chromosome 21 includes the *APP* gene, which Professor Hardy identified as a major risk factor for Alzheimer's disease. The additional copy of *APP*, which codes for a precursor of the  $\beta$ -amyloid protein that builds up in Alzheimer's disease, is likely to be key to disease, but additional factors on chromosome 21 (or elsewhere in the genome) could explain why not all people with Down syndrome are affected by dementia (even when they have high levels of  $\beta$ -amyloid in their brains). The main focus will be on 'extremes' – those with very early onset and those showing relatively little change in old age.

Professor Elizabeth Fisher and Dr Victor Tybulewicz will investigate biological processes in their mouse model of Down syndrome (see page 12). This work will be complemented by the cellular studies of Professor Dean Nizetic at Queen Mary, University of London. He will be generating induced pluripotent stem cells from people with Down syndrome and differentiating them into neural cells, to investigate pathological process in key cell types.

Finally, Professor Annette Karmiloff-Smith of Birkbeck University of London will be undertaking cognitive profiling of infants with Down syndrome, using similar tests used by Dr Strydom in young adults before the onset of dementia. The aim will be to see if the risk factors identified in older patients with dementia correlate with any traits seen in infants and young people – which would provide a way to identify early in life those at risk of dementia in adulthood.

The unusual background to Down syndrome provides a unique set of circumstances in which to study the mechanisms underlying Alzheimer's disease. As the disease is essentially the same as that seen in the general population, the findings will be of benefit not just to those with Down syndrome but also patients more widely.



Professor Martin Rossor.

## TRIALS AND TRIBULATIONS

**Families with inherited forms of Alzheimer's disease have made huge contributions to dementia research. Now they may finally be gaining the rewards.**

With Professor Nick Fox, **Professor Martin Rossor** has pioneered the involvement of families affected by inherited Alzheimer's disease in research. Ironically, though, clinical trials of interventions have typically excluded such individuals. With the emphasis shifting to early treatment, however, such families will now be participating in an exciting new wave of trials.

For more than 20 years, Professor Rossor has worked with families affected by inherited forms of dementia, helping to track down the genes affected and mapping changes in the brain as disease progresses. Such work has provided enormous insight into both the molecular mechanisms of disease and the natural history of disease progression.

Professor Rossor has also been involved in key international trials testing new interventions. Among the most exciting was a trial of antibody therapy targeted at  $\beta$ -amyloid. Unfortunately, although the trial showed positive effects on brain  $\beta$ -amyloid levels and cerebrospinal fluid biomarkers, the therapies had little impact on cognitive performance.

However, the results do not necessarily imply that the therapeutic strategy is wrong. It has been argued that the trial's patients, all of whom had well-established Alzheimer's disease, had already incurred too much tissue damage for the therapy to be effective. Given what is now known about the trajectory of  $\beta$ -amyloid build-up, and the appearance of symptoms, a window of opportunity exists in presymptomatic or early-stage individuals to block or delay  $\beta$ -amyloid-induced damage.

This idea is now being tested in the international DIAN (Dominantly Inherited Alzheimer Network) trial, the UK arm of which is being led by Professor Rossor. The 13 DIAN centres in the USA, Europe and Australia, led from Washington University School of Medicine, St Louis, have previously collaborated to establish joint systems for tracking brain atrophy and assessing biomarkers. The latest trial will enroll 240 members of affected families and will initially compare three existing immunotherapies, using their impact on biomarkers to identify which would be best to take forward into trials assessing effects on cognition.

The UK arm will be one of several studies making use of facilities in the new Leonard Wolfson Experimental Neurology Centre. Professor Rossor has also been involved in other trials of novel therapies, including the innovative therapy developed by Professor Sir Mark Pepys (see page 15).

**Bateman RJ et al.** Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med.* 2012;367(9):795–804.

**Rinne JO et al.** 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol.* 2010;9(4):363–72.

**Kolstoe SE et al.** Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component. *Proc Natl Acad Sci USA.* 2009;106(18):7619–23.

# A FAMILY AFFAIR

Professor Nick Fox has worked for many years with families affected by inherited Alzheimer's disease. Through the Leonard Wolfson Centre, they will now finally be able to take part in trials of new therapeutics.



The Leonard Wolfson Experimental Neurology Centre will play a critical role in testing promising new therapeutics for Alzheimer's disease and other neurodegenerative disorders. Professor Nick Fox has played a significant role in developing plans for the Centre, and the vision behind it draws heavily on the idea that interventions need to be given early. Furthermore, clinical trials will depend upon the advances in imaging developed by Professor Fox and colleagues.

Yet this progress, Professor Fox is at pains to point out, has relied on the contributions made by affected families. "We've been following families where Alzheimer's disease occurred early and frequently, even before the first genes were found. Gradually those families have yielded really important genetic discoveries. That has been a remarkable stimulus to research."

As well as providing clues to disease mechanisms, genetic discoveries have allowed the development of transgenic disease models. These have formed the test bed of new therapies

targeting specific disease processes, such as  $\beta$ -amyloid accumulation. Yet, despite Professor Fox's best efforts, for a variety of reasons trials have routinely excluded families. "Which is bizarre, because they're the ones closest to the transgenic models and they're the ones where therapy is most likely to work."

Now, however, through initiatives such as the Dominantly Inherited Alzheimer's Network (DIAN) trial (see page 22), families are finally being enrolled: "I'm really pleased that, after 20 years, the first trials have been approved."

The DIAN trial marks a profound shift in strategy: "The revolutionary step is that this will include people who are not affected, who are presymptomatic." Clinical trials of antibody-based therapies have been disappointing but, points out Professor Fox, they were carried out in patients with advanced disease: "A lot of us feel it may have been too little too late."

He draws an analogy with multiple sclerosis: "The lesson from MS is that a lot of the therapies that have

been revolutionary, that have been truly disease-modifying, those therapies initially failed in more severe disease." Benefits came only when they were used early in disease. "With familial Alzheimer's disease we know with certainty somebody will be affected, so we can go really quite early."

As well as establishing the Leonard Wolfson Centre, Professor Fox is also involved in initiatives to characterise further the 'natural history' of Alzheimer's disease, which shows considerable variation in age of onset and speed of decline. In part this will come from studies of young-onset Alzheimer's disease, where symptoms are manifest while people are in their 50s or 60s.

"There must be something that means that disease comes on 20–30 years earlier," says Professor Fox. "How do these people differ, what is it about them, is it something about their genetic make-up or is it something that imaging or biomarkers will give us a clue to?"

A further exciting initiative is work with the 1946 Birth Cohort (see page 28), where some 500 people

will undergo scanning and biomarker assessment. "That will allow us to have imaging, biomarker, clinical assessments including markers of presymptomatic Alzheimer's disease and subclinical vascular damage in a truly representative cohort who've been followed since birth, which is unique."

This work will also draw on the facilities of the Leonard Wolfson Centre, which will provide a platform for much future work. For Professor Fox there is a pleasing symmetry that the first beneficiaries may be those whose participation in research made it all possible. "It's the coming together of work that people like Martin Rossor and John Hardy did in the 1980s, finding the first families, finding the first genes, all coming full circle with the facility and the first trials."

# POPULATION AND HEALTH RESEARCH: ESSENTIAL SUPPORT FOR PATIENTS AND CARERS

The School's research has identified psychosocial therapies that benefit dementia patients and their carers.



Dementia imposes a huge burden on patients, their carers and health systems. The number of people with dementia is projected to rise to a million by 2025. One in three people over 65 are likely to have dementia at the time of their death.

Dementia presents great challenges to health systems. An influential study by UCL researchers, tracking 600 consecutive unplanned admissions to a London hospital, found that 42 per cent of patients had dementia, many of whom had not previously been diagnosed. Patients with dementia were more likely to die during admission and had worse survival after discharge. A follow-up study of a cohort of dementia patients provided more

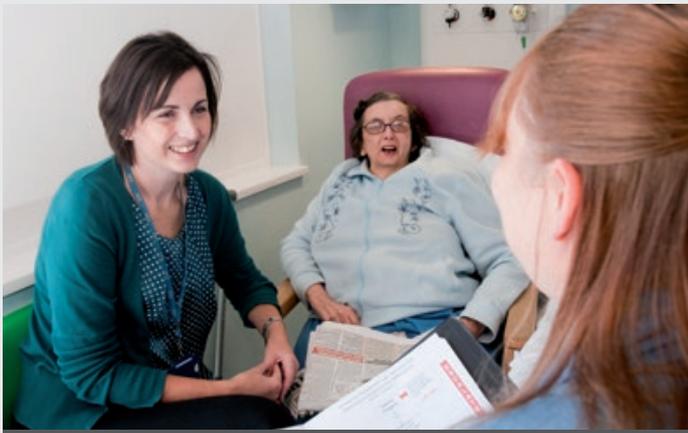
evidence of the problems they face in hospital, work that is underpinning a new training programme for emergency admissions staff across UCL-associated hospitals.

In the absence of truly effective pharmacological treatments, there is a valuable role for psychosocial interventions. UCL researchers have generated compelling evidence of the effectiveness of a cognitive stimulation therapy which is now in widespread use in the UK and many other countries.

In addition, important forms of support are being developed for carers. Caring for someone with dementia can be highly demanding, leading to high levels of stress and depression.

A new coping strategy developed at UCL has been shown in trials both to help those with depression and prevent its development.

Population-based studies are also providing new insight into disease. UCL is responsible for a unique collection of population cohorts, including the 1946 Birth Cohort (the National Survey of Health and Development), the English Longitudinal Study of Ageing and the Whitehall II study. As these cohorts reach the age at which cognitive decline and early signs of dementia are apparent, they are providing rich information on the nature of changes in the general population and factors that may accelerate or protect against disease.



Dr Liz Sampson.

## TOWARDS 'DEMENTIA-FRIENDLY' HOSPITALS

**Shocking statistics on the experience of dementia patients in hospitals are catalysing major changes in practice.**

Hospitals can be intimidating places at the best of times. For patients with dementia, they can be highly distressing. Having documented the enormous difficulties dementia patients experience in hospitals, **Dr Liz Sampson's** research is feeding into a training programme across north London to raise awareness among acute care staff at all levels – from porters to chief executives – of the needs of dementia patients.

The impact of emergency admission to hospital was graphically illustrated in a prospective study of more than 600 acute admissions of people aged over 70. Some 42 per cent were suffering from dementia, though only half had previously been diagnosed. Perhaps most striking, they suffered markedly higher mortality – 24 per cent of patients with cognitive impairment died during admission, five times the proportion of those without impairment.

Their long-term survival was also much worse. Median survival was 2.7 years for those without dementia but just 1.1 years for those with dementia.

Additional studies on a cohort of 230 patients with dementia, followed through their hospital stay, have provided more detail on the difficulties such patients face. Behavioural disturbances are extremely common, but this was strongly associated with undiagnosed pain – patients struggling to communicate that they are in pain often become agitated.

The key issue is that hospital systems are simply not geared to the special needs of dementia patients. To help remedy this, Dr Sampson has developed a training package designed to help acute care staff provide better support for patients with dementia. Working with 'dementia champions' across UCL Partners – which provides services to six million people – Dr Sampson has helped to train more than 1000 members of staff. Having real data to draw upon, she suggests, has a profound impact – one chief executive was visibly shocked to discover that 75 per cent of dementia patients showed some form of aggressive or agitated behaviour during admission.

As well as evaluating the training programme, Dr Sampson is also investigating other ways in which health systems may need to adapt to accommodate dementia patients. The standard way of assessing pain levels, for example, using a series of faces showing varying levels of distress, is impossible for many patients to use, owing to their cognitive impairments. With the numbers of dementia patients certain to rise sharply, there is an urgent need to ensure hospital facilities offer a more suitable service to this highly vulnerable group of patients.

**Sampson EL et al.** Dementia in the acute hospital: prospective cohort study of prevalence and mortality. *Br J Psychiatry*. 2009;195(1):61–6.

**Watkin L, Blanchard MR, Tookman A, Sampson EL.** Prospective cohort study of adverse events in older people admitted to the acute general hospital: risk factors and the impact of dementia. *Int J Geriatr Psychiatry*. 2012;27(1):76–82.

**Sampson EL et al.** Survival of people with dementia after unplanned acute hospital admission: a prospective cohort study. *Int J Geriatr Psychiatry*. 2013;28(10):1015–22.



Professor Martin Orrell.

## STIMULATING SUCCESS

**An enjoyable programme of cognitive stimulation improves both cognitive skills and the quality of life of dementia patients.**

With pharmaceutical approaches yet to deliver substantial benefits to dementia patients, psychosocial interventions may offer an alternative route to protect memory and other cognitive skills. Indeed, a cognitive stimulation programme developed by **Professor Martin Orrell, Dr Aimee Spector** and colleagues has been shown to provide multiple benefits, and has now been widely implemented in the UK and internationally.

Professor Orrell became interested in cognitive stimulation therapy while undertaking a systematic review of mental stimulation approaches in dementia. The evidence suggested that such approaches had a positive impact on cognitive skills and quality of life, and were also cost-effective. What was lacking, however, were large-scale multicentre trials to confirm these promising findings.

Drawing on best practice from these studies, Professor Orrell went on to develop a seven-week cognitive stimulation programme, delivered in groups, with accompanying manual and DVD. Randomised controlled trials confirmed that the programme improved cognition and quality of life at least as well as pharmaceutical interventions. It was positively received by patients and carers, was practical to deliver and cost-effective.

The programme aims to be engaging and enjoyable. It makes extensive use of puzzles to get mental juices flowing, touching upon areas such as money management, current affairs and diet. The programme, *Making a Difference*, now in its second incarnation, has been endorsed by the National Institute for Health and Care Excellence (NICE) and recommended by Alzheimer's Disease International. It is in widespread use across the UK and has been adapted for other cultures, being used in at least 15 other countries.

Professor Orrell is continuing to work on cognitive stimulation therapy. Recent studies have suggested that longer-term use of six months delivers additional benefits, and notably that it acts synergistically with drug treatments for Alzheimer's disease.

As well as additional work on the training needs of programme facilitators, he has also begun a major programme to examine the effectiveness of individual cognitive stimulation therapy – a more flexible approach that carers could use with people with dementia. As group therapy is not suitable for all patients, the individual course could bring the benefits of cognitive stimulation therapy to much larger numbers of people.

**Spector A et al.** Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *Br J Psychiatry*. 2003;183:248–54.

**Knapp M et al.** Cognitive stimulation therapy for people with dementia: cost-effectiveness analysis. *Br J Psychiatry*. 2006;188:574–80.

**Spector A, Gardner C, Orrell M.** The impact of Cognitive Stimulation Therapy groups on people with dementia: views from participants, their carers and group facilitators. *Ageing Ment Health*. 2011;15(8):945–9.



Professor Gill Livingston.

## CARING FOR CARERS

**A simple intervention, delivered by psychology graduates, can improve the quality of life of people caring for dementia patients.**

Two-thirds of people with dementia live at home, so the bulk of the caring burden falls on family members. Without such carers, the economic impact of dementia would be even higher than the current £23bn a year, but this saving has its own health impact: some 40 per cent of family carers suffer from clinical anxiety or depression. To help such individuals, **Professor Gill Livingston** and colleagues have adapted a US programme designed to boost carers' coping skills – and a recent randomised controlled trial confirmed it is both effective and cost-effective.

With Dr Claudia Cooper, Professor Livingston led a programme that uncovered alarmingly high levels of abuse of people with dementia by carers. Most cases reflected the inability of family members to cope with the challenges of caring. The findings led her to consider what could be done to help carers, and by extension the people they were caring for.

People's coping strategies vary. Some approaches may offer short-term relief but store up long-term problems. Encouraging more positive coping strategies may therefore better prepare carers for the challenges they will inevitably face.

In the USA, the 'Coping with Caring' programme, a manual-based group intervention, has been shown to reduce depression in carers. However, the use of groups and need for trained clinical psychologists would make it difficult to implement widely in the UK. Professor Livingston therefore modified the programme so it could be delivered to individuals by graduates (under supervision).

The 'START' programme is based on sound cognitive psychological principles. It helps carers accept that patients will show difficult behaviours, which they will not be able to influence, and encourages them to look for things to enjoy, even small moments like shared cups of tea, and to find ways to do more of them.

A trial of 260 carers found that the START programme significantly reduced anxiety and depression, and improved carers' quality of life. There were also hints of a fall in levels of abuse, something that will be examined further in follow up. Notably, the intervention had both preventive effects and therapeutic benefits for those already depressed. Health economic analyses suggested it is also cost-effective.

This is the first evidence that a cost-effective psychosocial intervention can benefit carers of dementia patients. Professor Livingston is helping to implement the programme locally, and encouraging its take up more widely.

**Cooper C et al.** The determinants of family carers' abusive behaviour to people with dementia: results of the CARDstudy. *J Affect Disord.* 2010;121(1-2):136–42.

**Livingston G et al.** Clinical effectiveness of a manual based coping strategy programme (START, STrAtegies for RelaTives) in promoting the mental health of carers of family members with dementia: pragmatic randomised controlled trial. *BMJ.* 2013;347:f6276.

**Knapp M et al.** Cost effectiveness of a manual based coping strategy programme in promoting the mental health of family carers of people with dementia (the START (STrAtegies for RelaTives) study): a pragmatic randomised controlled trial. *BMJ.* 2013;347:f6342.



Professor Steve Iliffe.

## IN PURSUIT OF TIMELY DIAGNOSIS

**An educational package helps GPs spot early signs of dementia, but has no impact on their clinical behaviour.**

The English National Dementia Strategy, published in 2009, included a focus on timely diagnosis. However, distinguishing between the inevitable decline associated with ageing and early signs of dementia is not straightforward. An educational programme for GPs developed by **Professor Steve Iliffe** and colleagues has been successful at one level, helping GPs make this distinction. Strikingly, though, it has not actually changed what they document about their everyday practice with people with dementia.

Timely diagnosis is important as it relieves uncertainty, allowing patients and carers to plan for the future and be prepared for changes in mood and behaviour. Treatment can also be initiated in a timely fashion.

Nevertheless, there is good evidence that dementia is not well recognised in primary care. In part, this reflects the diagnostic challenge. But there are other more subtle influences at work. Dementia still carries a stigma, and GPs may be reluctant to attach the label to patients. With few effective therapies available, they may feel a diagnosis offers few positives but plenty of negatives.

In an initial study, Professor Iliffe and colleagues compared the effectiveness of three approaches designed to improve timely diagnosis: a CD-ROM, practice-based workshops and decision-support software. While the latter two clearly helped GPs spot dementia better, they had no impact on practice behaviour.

Building on this trial, Professor Iliffe developed the 'EVIDEM' educational package, drawing on both multidisciplinary expert input on dementia diagnosis and adult educational theory, and integrating practice-based workshops and electronic resources. The trial included detailed needs assessment in practices, and materials geared to doctors of varying degrees of experience. Everything was done to ensure that new knowledge could readily be applied during doctors' routine work. This pragmatic, practice-based approach was designed to minimise the barriers to implementation.

However, results from this larger EVIDEM-ED trial, based on 23 primary care practices, mirrored those from the earlier study. Diagnostic skills were enhanced, but there was no increase in diagnoses and management practice with patients remained unchanged. Professor Iliffe is now undertaking qualitative research with practices to try to uncover the factors that prevent them from adhering to clinical guidelines.

**Downs M et al.** Effectiveness of educational interventions in improving detection and management of dementia in primary care: cluster randomised controlled study. *BMJ.* 2006;332(7543):692–6.

**Iliffe S et al.** Evidence-based interventions in dementia: A pragmatic cluster-randomised trial of an educational intervention to promote earlier recognition and response to dementia in primary care (EVIDEM-ED). *Trials.* 2010;11:13.



Dementia may be difficult to diagnose in those who use sign language.

## DEAFNESS AND DEMENTIA

**A new screening tool tailored to deaf people who are sign language users may lead to more timely diagnosis of dementia.**

The early stages of dementia are difficult to distinguish from normal ageing, and it is recognised that dementia is not well diagnosed in primary care. Patients who are deaf are even less likely to receive a timely diagnosis. Through the Deaf with Dementia project, **Professor Bencie Woll** and colleagues are developing tools to enhance detection of dementia among deaf people, so they receive better support and care at this critical phase.

The first signs of dementia are typically memory loss or other cognitive difficulties. Communicating such problems can be difficult for a deaf person, unless a doctor is familiar with sign language (which few are). In particular, lack of interaction may be put down to a difficulty with communication rather than a sign of dementia. Furthermore, standard screening tools are not suitable for people who have been deaf since birth, whose cognitive skills will be different in significant respects from those of hearing people. As a result, diagnosis and early management of dementia in deaf individuals is generally poor.

The Deaf with Dementia project – a partnership between the ESRC Deafness, Cognition and Language Research Centre at UCL (DCAL), the University of Manchester, City University London and the Royal Association for Deaf People – aims to rectify this situation. In particular, DCAL has led the development of culturally and linguistically appropriate tools for diagnosis.

A team of neuropsychologists and linguists, several of whom are themselves deaf, has adapted existing assessments and created new ones to develop a tool that better reflects the differing cognitive abilities and experiences of deaf people. Memory tests, for example, include events of particular resonance to deaf people, such as the death of Diana, Princess of Wales, Patron of the British Deaf Association.

To provide a yardstick against which cognitive deterioration can be assessed, data have been collected from more than 200 healthy older members of the deaf community aged 50–89, attendees at an annual Darby and Joan Club outing to a seaside holiday camp.

In collaboration with DCAL, the National Hospital for Neurology and Neurosurgery has established a special memory clinic for deaf patients that uses the tool in its assessment. More generally, Professor Woll and DCAL are aiming to improve the assessment and management of the estimated 6–8000 sign language users in the UK with a neurological condition.

**Atkinson J, Woll B et al.** The health of deaf people. *Lancet*. 2012;379(9833):2239.



Social contact may protect against cognitive decline.

## A TWO-WAY STREET

**An ageing cohort is providing insight into both the causes and consequences of cognitive decline, with implications for both health and social policy.**

The **English Longitudinal Study of Ageing** has been tracking more than 10,000 people aged 50 or more since 2002. Unusually, it captures data across a wide range of social, economic and health indicators, an interdisciplinary perspective that allows links to be made between health and wellbeing and social circumstances.

Management of the cohort is coordinated by **Professor Andrew Steptoe** at UCL in partnership with the Institute of Fiscal Studies and other academic groups. Unusually, data are released as rapidly as possible to other researchers, to encourage their use in evidence-based policy-making.

Among the data collected are measures of cognitive ability. Given that cognitive decline is a well-recognised staging post on the path to dementia, any factors influencing this decline could have later implications for disease. For example, if disease onset could be delayed by five years, some 30,000 fewer people would die from dementia each year.

One factor that could influence the decline of cognitive skills is social isolation. Recently, Professor Steptoe and colleagues have explored the potential impact of both isolation – an objective measure of people's social networks – and loneliness, a subjective assessment of connectedness (which may not necessarily reflect actual degree of isolation).

Notably, the degree of cognitive decline was more closely related with isolation than loneliness. Such studies suggest possible strategies for intervention, for example by promoting social network development in vulnerable populations.

The cognitive data have also provided an unusual opportunity to explore its impact on real-life financial decision-making. This is of particular interest to policy-makers, for example to guide pension policy. One use of ELSA data has been to examine how cognitive performance and numeracy affect savings behaviour around retirement.

Finally, ELSA has been modelled on the US Health and Retirement Survey, enabling international comparisons to be made. As well as revealing that US seniors cognitively outperform their UK peers (despite typically being less healthy), cross-country comparisons also suggest that cognitive skills in old age are strongly influenced by life course – the elders in industrialised countries are cognitively healthier because of the better living standards they enjoyed when younger.

**Shankar A, Hamer M, McMunn A, Steptoe A.** Social isolation and loneliness: relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. *Psychosom Med*. 2013;75(2):161–70.

**Langa KM et al.** Cognitive health among older adults in the United States and in England. *BMC Geriatr*. 2009;9:23.

**Skirbekk V, Loichinger E, Weber D.** Variation in cognitive functioning as a refined approach to comparing aging across countries. *Proc Natl Acad Sci USA*. 2012;109(3):770–4.



A historic birth cohort is now contributing to dementia research.

## THE CLASS OF 46

The 1946 birth cohort will shed light on the emergence of dementia in the general population.

In 1946 a remarkable experiment began. All infants born during a single week in March were enrolled in a national maternity survey, generating invaluable data on early health and the cost of childbirth. Subsequently, researchers have continued to follow a subset of these infants, who became the 1946 birth cohort and have gone on to provide unique insight into factors affecting health and wellbeing across the life course. And as cohort members reach their later years, they are yet again contributing to our understanding of disease – this time, early signs of dementia.

The 1946 cohort, the world's longest running birth cohort, is coordinated by the MRC Unit for Lifelong Health and Ageing (LHA), led by **Professor Diana Kuh**. From the 5000 or so infants, more than half are still contributing regularly, undergoing periodic health checkups, taking tests of cognition, and contributing medical and lifestyle data.

As participants reach their late 60s, they have become of increasing interest to the field of healthy ageing. Uniquely, the wealth of data collected over their lifetime can reveal factors influencing health and wellbeing in old age.

Furthermore, for dementia researchers, the cohort is a golden opportunity to study an entirely unbiased population sample as they begin to show signs of cognitive impairment. Even if symptoms are not apparent, their brains may still be showing the distinctive changes that precede overt loss of cognitive function.

To gain insight into the changes, 500 cohort members are being invited to participate in a dementia substudy, being led by **Professor Marcus Richards** at the LHA and Dr Jonathan Schott and Professor Nick Fox in UCL's Dementia Research Centre. Participants will undergo combined PET–MRI scanning, to characterise brain structure and levels of  $\beta$ -amyloid. They will also provide biological samples for biomarker assessment and genetic analysis, and undertake various performance tests. After a baseline scan, study members will be scanned again in two to three years' time.

The study is a rare opportunity to collect data from large numbers of healthy individuals and to relate them to the subsequent development of disease. In addition, analysis of historical data will also shed light on multiple other factors, from education to blood pressure, that could conceivably affect the onset of symptoms. This most intensively studied group of individuals therefore look set to benefit medicine all the way from cradle to grave.



New research will benefit those living with dementia.

## IMPROVING EVERYDAY LIFE

Three UCL research teams have been awarded multimillion pound funding for programmes that could make a significant difference to patients' and carers' quality of life.

In 2013, three UCL groups launched major new research programmes designed to generate rapid benefits for dementia patients and their carers.

The MARQUE (Managing Agitation and Raising Quality of Life) programme, led by **Professor Gill Livingston**, is focusing on the distressing and common agitation experienced by patients with moderate to severe dementia. Generally linked to the inability to express an unmet need, agitation has a great impact on quality of life and is highly challenging for carers. An interdisciplinary team is carrying out a trial of an intervention developed to ensure that the culture of care homes minimises agitation, as well as pilot studies of an approach designed to improve quality of life for carers and patients in the last six months of life.

The PRIDE (Promoting Independence in Dementia) study, led by **Professor Martin Orrell**, targets those in early stages of dementia. One aim is to use data from the English Longitudinal Study on Ageing (ELSA) to investigate the social and lifestyle factors associated with cognitive decline and its consequences for individuals' sense of wellbeing. New questions will be added to future rounds of ELSA data collection, to capture additional information about cognitive decline, and people's expectations and experiences. A complementary aim is to develop a social intervention to promote behaviours found to protect against cognitive decline, identified by consultation with people with dementia and their carers and by review of published evidence. The intervention will be evaluated in a multicentre clinical trial.

The 'Seeing what they see' study, led by **Dr Sebastian Crutch**, is addressing an underappreciated aspect of Alzheimer's disease – loss of visual skills. Impaired visual perception can significantly interfere with everyday life, and lead to falls, hallucinations and poor diet. The interdisciplinary project will focus on patients with posterior cortical atrophy, a form of Alzheimer's disease in which vision is particularly affected. By characterising these and other Alzheimer's patients in an artificial domestic environment, developed by UCL's Engineering Department, the project aims to identify practical adaptations and coping strategies that can be then be evaluated in a trial based in patients' homes and care homes.

# DEALING WITH DEMENTIA

Maggie Williams's husband Andy was diagnosed with posterior cortical atrophy (PCA) in 2011. The PCA Support Group run by UCL's Dementia Research Centre has helped them both adjust to the implications of this life-changing diagnosis.



Before his diagnosis, Andy had been enduring tough times. He had been made redundant twice and had recently lost his brother. When he began to experience other problems, particularly with driving, it was initially put down to stress. As is often the case with PCA – a form of dementia that affects the visual areas of the brain – it was problems with vision that proved the key to diagnosis.

"We went and had an eye test done," says Maggie, "and the optician picked up early stage cataracts. We then got referred on to an ophthalmic surgeon. He was very much on the ball, and he picked up that there was something else going on. We had a brain scan and it just went from there."

Andy was formally diagnosed in December 2011, yet in retrospect Maggie believes the signs were present years earlier: "Looking back, we saw the start of symptoms in 2008. As you do, you just think it is something else."

By the time all the tests had been completed, Maggie already had an inkling of what Andy's problem was:

"To get a diagnosis was a relief. We knew then what we were dealing with. As horrible as it is, we knew then what it was."

Since then, the family has been adjusting to the new circumstances. Andy is in the early stages of disease and Maggie is able to leave him on his own, continuing to work part-time. Perhaps the biggest blow to Andy has been the fact that he can no longer drive, as much of his working life had been spent on the road. "That was a shock for him," says Maggie.

With their children returning to live at home, it is, says Maggie, "a busy house", and the family tries to minimise the impact of Andy's diagnosis. "At the time it was awful," says Maggie, "but you just accept it. You live your life around it. You carry on as best you can. Though I have a good sob most days, out of earshot of anyone else!"

What has been a great help, she adds, is the PCA Support Group. Through regular meetings in London, a newsletter and other mechanisms, she has been able to make contact with other families in a similar situation. She and Andy

have been able to find out practical information about the benefit system and other support that is available. Hearing first hand from people who have navigated the system has been invaluable.

The social contacts they have made have also been enormously helpful, though tinged with sadness. "You see people that are further on in the journey, and it's heartbreaking. But you need to be aware of what is ahead."

Through the PCA Support Group, Maggie and Andy met Dr Sebastian Crutch, and volunteered to take part in research being carried out at the DRC. Both have been taking part in studies examining their vision and visual memory, an experience both have enjoyed. "It's lovely, the staff there are very helpful, you meet like-minded people."

For people like Andy, few therapeutic options are available. He has been prescribed Aricept, which may slow the decline of Alzheimer's and other forms of dementia in some patients. "We think it's helping," says Maggie, Andy's memory

score having improved on his last clinical assessment.

She laments the lack of funding for dementia research, which bears little relation to the enormous clinical and economic impact of the condition. And attitudes more generally still need to change, she suggests: "It's still got a stigma attached to it. Alzheimer's disease and dementia in general, it's like cancer was 10–15 years ago. You mention that and people just run away. Which is very sad."

**Information about the PCA Support Group, run in partnership with the National Hospital for Neurology and Neurosurgery and with support from the Myrtle Ellis Fund, can be found at [www.ucl.ac.uk/drc/pcasupport](http://www.ucl.ac.uk/drc/pcasupport). The website includes information for patients and families and for healthcare professionals, and includes short films of patients discussing their experience, including well-known fantasy novelist Terry Pratchett, who was diagnosed with PCA in 2007.**

# FACILITIES AND RESOURCES: A PLATFORM FOR SUCCESS

UCL has the intellectual firepower and infrastructure to make a real difference in dementia research. Our future ambitions are to build on this foundation to further understand the disease, accelerate the development of new treatments, and improve the healthcare delivered to patients.

The UK is a global leader in the dementia field, publishing nine per cent of the world's research in this area in 2008/09, second only to the USA. UCL is the leading UK institution in dementia research, contributing more than 15 per cent of the UK output. Given the breadth and depth of neuroscience research and, in particular, our clinical strengths, we are well positioned to be at the forefront of dementia research and healthcare, and to respond to future research funding opportunities. Our aim is to consolidate our position as the leading UK centre for dementia research and to establish ourselves as an international leader.

## Facilities and resources

UCL includes a range of centres making nationally

and internationally significant contributions to research across the spectrum from basic to health research. Outstanding research and clinical resources are available to support this research.

### Dementia Research Centre:

Based at the National Hospital for Neurology and Neurosurgery in Queen Square, the Centre is one of the UK's leading sites for clinical research into dementia, and the hospital is the lead centre for trialling new drugs to slow the progression of Alzheimer's disease.

**MRC Prion Unit:** The Unit is a national centre of excellence undertaking research in prions and related diseases. Research programmes within the Unit

include studies of molecular structure, genetics, biochemistry, immunology, cell and animal models, and clinical research, including treatment trials.

### Institute of Neurology Department of Molecular Neuroscience:

The Department's research portfolio encompasses the full range of neurodegenerative disorders. It houses the **Queen Square Brain Bank**, which has Europe's largest collection of frozen Parkinson's disease brains as well as extensive collections of rare disorders and of progressive supranuclear palsy and multisystem atrophy. The collection also includes donated brains from prospectively studied people with familial dementias.

The Reta Lila Weston Institute within the Department is a world-renowned centre in the study of movement disorders.

### Institute of Neurology Department of Neurodegeneration:

The Department's research encompasses prion diseases (predominantly within the embedded MRC Prion Unit), Alzheimer's disease and other neurodegenerative disorders including Huntington's disease, frontotemporal dementia and studies of the pathways of cellular senescence. It includes studies of the genetic basis of two disorders that involve neurodegeneration, motor neuron diseases and Down syndrome, using mouse models.

### **Leonard Wolfson Experimental Neurology**

**Centre:** A dedicated, specialist centre for the conduct of first-in-human studies of novel therapies for the treatment of neurodegenerative diseases.

### **Wolfson Biomarker**

**Core:** The Core provides biobanking resources and facilities for biomarker analyses and research. The Core collaborates with Professor Henrik Zetterberg's laboratory in Sweden and with the proteomics and metabolomics unit at the Institute of Child Health.

### **NIHR Queen Square Dementia Biomedical**

**Research Unit:** The unit is one of four NIHR BRUs which undertake translational clinical research in dementia. It focuses on early-onset and familial disease to improve diagnosis and facilitate early-phase trials of novel interventions.

### **UCL/UCLH NIHR Biomedical Research**

**Centre:** The centre has four major programmes, including neurosciences. The neurosciences programme has four strategic objectives, which align well with the Faculty strategy for dementia: (1) aligning human imaging to redefine diseases, improve diagnosis and facilitate the discovery of effective treatments; (2) identifying and studying early-stage disease; (3) data handling and bioinformatics; (4) biomarkers.

### **Queen Square Clinical**

**Trials Unit:** The Unit aims to increase clinical trial activity in neuroscience by supporting and facilitating research and by linking with the UCL Clinical Trials Unit and the Central and East London (CEL) Clinical Research Network.

### **Wolfson Drug Discovery**

**Unit:** Based at the Royal Free Hospital Campus, the Unit has a major programme of drug development for amyloidosis and potentially Alzheimer's disease and other dementias, supported by the MRC, the NIHR via the UCLH/UCL Biomedical Research Centre and GSK.

In addition, UCL manages or has access to a wide range of resources and platforms that support and facilitate dementia research. These include:

### **Clinical and population**

**cohorts:** UCL has access to a large number of unique patient cohorts that can be used for both the understanding of dementia and the testing of new therapeutic strategies. It also plays a key role in several population cohorts, including the MRC National Survey of Health and Development (the 1946 Birth Cohort) and the English Longitudinal Study of Ageing, which are making increasing contributions to cognitive ageing and dementia research.

**DeNDRoN:** UCL is one of two national hosts of the NIHR Dementia and Neurodegenerative Diseases Research Network (DeNDRoN), which aims to facilitate clinical research into dementia and related diseases.

**CHAPTER:** The Centre for Health Service and Academic Partnership in Translational E-Health Research is one of four E-Health Informatics Research Centres funded by the MRC. The aim is to maximise translational impact from discovery through trials to clinical practice, service delivery, patient outcomes and public health.

### **NIHR Bioresource:**

UCL/UCLH leads one of the Biomedical Research Centres involved in the national NIHR Bioresource and is the lead institution for the neurological theme. The Bioresource will enable the recruitment of patients for stratified experimental medicine studies, as well as providing the potential to study the molecular bases of disease, identify the most appropriate biomarkers for diagnosis and drug discovery, and test the mechanism of action and effects of new drugs.

### **Rare Disease Initiative:**

This new UCL initiative will develop a comprehensive rare disease portfolio that connects databases, registries, biobanks and clinical bioinformatics for rare disease research, including neurodegeneration.

### **Sainsbury Wellcome Centre for Neurocircuits:**

The Centre will use state-of-the-art molecular and cellular biology, imaging, electrophysiology and behavioural techniques, supported by computational modelling, to investigate how brain circuits process information to create neural representations and guide behaviour.

### **Francis Crick Institute:**

The partnership with the Francis Crick Institute, an interdisciplinary medical research institute supported by a consortium of six scientific and academic organisations (the MRC, Cancer Research UK, the Wellcome Trust, UCL, Imperial College London and King's College London), will further add to the strength of basic biological research in neuroscience.

### **Neuroscience Domain:**

The Domain provides a mechanism to draw together UCL's world-leading community of neuroscientists working across all the School's Faculties, as well as researchers working in UCL's other two Schools.

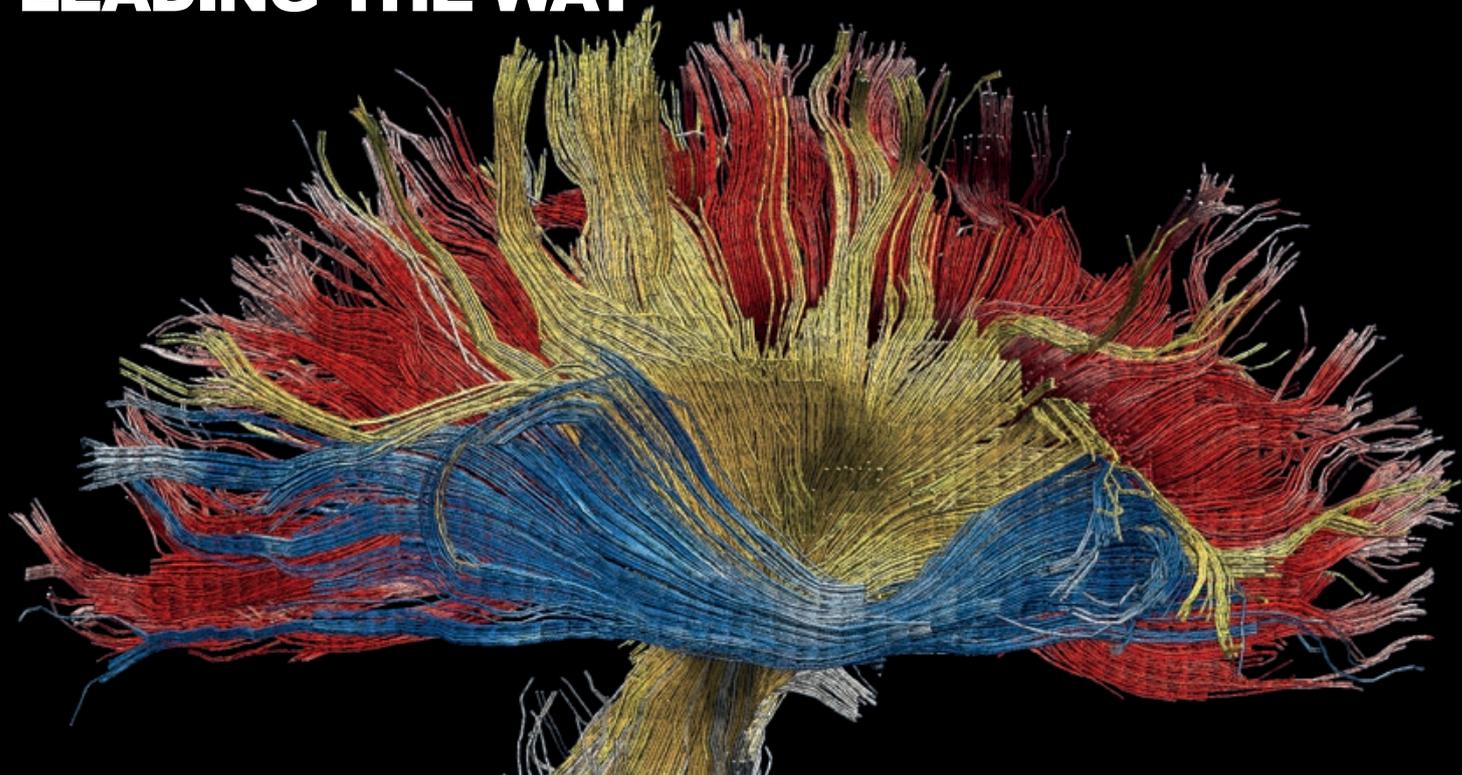
### **Industrial collaboration**

The involvement of the pharmaceutical sector will be essential for the development of new therapeutics. UCL has an outstanding tradition of working with industry, and well-established partnerships with companies such as GSK and others. Of particular significance is the drug discovery and development partnership established with Eisai, which will see researchers from both organisations working together to develop new ways to treat neurological diseases such as Alzheimer's and Parkinson's disease.

### **Training**

Training is an integral component of the Leonard Wolfson Experimental Neurology Centre, which will provide clinical and basic scientists with insight into different diseases areas and experimental techniques in neurodegeneration. More generally, UCL offers unrivalled opportunities for PhD research in all aspects of neuroscience, basic and clinical. This training is provided in the laboratories of researchers who are among the leaders of their fields, using the most modern techniques to address important problems of basic and clinical neuroscience.

# LEADING THE WAY



UCL is one of the world's leading multifaculty interdisciplinary universities, with a breadth and depth of research expertise that, when brought together, will have a major impact on the health issues facing our society. In order to achieve impact in tackling dementia, and to ensure that UCL maintains and builds its position as an internationally leading centre for dementia, the different strands of research from basic through to clinical, combined with cutting-edge technologies, will become integrated into a coherent strategy. We have identified a number of research challenges that will be addressed over the next five years, and beyond, and which will lead to the development of new therapeutics and treatment strategies for dementia. We will further develop our relationships and dialogue with the funding bodies, charities, government departments, and with patient groups, to ensure that UCL both informs on, and responds to, the latest developments in dementia research.

## **Basic:**

- improve our understanding of the molecular mechanisms resulting in dementia
- understand the changes in neural circuitry underpinning dementia

## **Translational:**

- develop better animal models of dementia
- explore the use of stem cells as a therapeutic strategy
- use cellular models of disease to screen for new therapeutics diagnosis, including metabolomic and proteomic approaches

## **Clinical:**

- increase the number of early-phase and phase III trials and accelerate recruitment into trials
- develop presymptomatic markers to improve early diagnosis and that are sensitive to change in first-in-human studies

## **Social:**

- improve our understanding of cognitive health and its changes over the entire life course
- develop and enhance interventions to improve the health and quality of life of patients and their carers

## **Furthermore, we will also:**

- improve communication and interaction between researchers, to achieve better translation between basic and clinical sciences
- expand our programmes to train the next generation of researchers such as the built environment and economics
- increase public engagement and public/patient involvement.

## UCL FACULTY OF BRAIN SCIENCES

The UCL Faculty of Brain Sciences brings together world-leading expertise at the forefront of neurology, ophthalmology, audiology, cognitive neuroscience and mental health sciences.

The Faculty seeks to understand and solve the greatest health and wellbeing problems in the brain sciences, in order to transform society and reduce the global burden of disease.

Research within the Faculty addresses all the major conditions affecting the brain and nervous system. For 2013–18, the Faculty has identified four strategic research priorities:

- Neurodegeneration and neuroprotection
- Mental health
- Sensory systems and therapies
- Cognitive ageing

The Faculty of Brain Sciences is one of the four component faculties of the UCL School of Life and Medical Sciences, arguably the greatest concentration of expertise in biomedical science and population health in Europe. By drawing on the expertise in other Faculties and in other UCL Schools, the Faculty of Brain Sciences can develop genuinely interdisciplinary programmes of research from the level of single molecules to global populations.

### CREDITS

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## **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](http://www.ucl.ac.uk)

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