

# Care and cure

The Alzheimer's Society research magazine

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**Dr Tim Shakespeare**  
Magazine Editor

## Welcome to Care and cure magazine

This July, researchers from around the world are gathering in London for the Alzheimer's Association International Conference. This brings thousands of scientists together to share their results, learn from each other and develop their ideas to move everyone's research forwards.

This collaborative spirit is an essential part of successful research. It helps researchers to develop large, ambitious projects that they couldn't attempt alone and provides access to ideas and facilities. The strength of collaboration in our research programme shines through in this issue of Care and cure.

We highlight how Alzheimer's Society has united against vascular dementia with the Stroke Association and British Heart Foundation to fund pioneering research by teams across England and Scotland. We profile the work of Dr Raffaele Ferrari, who is using data collected in 20 countries to investigate the genetics of frontotemporal dementia. We also reveal the five new centres that will work together to form the UK Dementia Research Institute, along with its headquarters in London.

By joining forces, researchers can be more ambitious and answer questions that couldn't be addressed by any one person or team. But this isn't only about researchers. Your involvement is vital, whether you support our research programme, share your insights through the Research Network or volunteer to take part in a study. It's time for us all to unite against dementia.

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## About us

Since 1990, Alzheimer's Society has funded £40 million of cutting-edge dementia research. We aim to increase investment in our research programme to at least £150 million over the next decade. This money funds important research that helps to improve the quality of life of people with dementia by investigating prevention, improving practice in care and pursuing a cure.

[alzheimers.org.uk/research](https://alzheimers.org.uk/research)

# A new job for old drugs

Two existing drugs can block cell death in mice.

Building on an earlier breakthrough, Professor Giovanna Mallucci and her team at the University of Cambridge have identified two drugs that can block the death of brain cells in mice with a neurodegenerative disease.

The drugs target a natural defence mechanism in cells called the unfolded protein response. This response is activated when 'misfolded' proteins build up in several diseases where brain cells degenerate, including Alzheimer's.

Professor Mallucci said, 'We screened through over 1,000 different compounds in the lab to find ones that could block the unfolded protein response and found two promising drug candidates.'

The drugs, an antidepressant called trazodone and a compound found in liquorice called dibenzoylmethane, were tested in mice that had prion-related diseases.

Prions are toxic misfolded proteins that cause Creutzfeldt-Jakob disease. They provide a useful model to study neurodegeneration. The study showed that the drugs protected brain cells from dying.

The researchers also tested the drugs on mice with frontotemporal dementia. They were particularly looking at how drugs affected the protein tau, which forms harmful clumps in several forms of dementia, including Alzheimer's disease. They found that the drugs were also able to prevent the death of brain cells and improve memory abilities in these mice.

Dr Doug Brown, Director of Research and Development at Alzheimer's Society, said, 'We're excited by the potential of these findings. They show that a treatment approach originally discovered while researching prion disease might also work to prevent the death of brain cells in some forms of dementia.'



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**'We screened through over 1,000 different compounds in the lab to find ones that could block the unfolded protein response.'**  
**Professor Mallucci**

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The next steps are for these drugs to be tested in animals that have Alzheimer's disease and to begin testing the antidepressant – already a licensed drug – in people in the earlier stages of Alzheimer's.

'A clinical trial is now possible, to test whether the protective effects of the drug we see on brain cells in mice with neurodegeneration also apply to people in the early stages of Alzheimer's disease or other dementias,' says Professor Mallucci.

Despite trazodone being an existing medication, Professor Mallucci advised against jumping to conclusions until further research is completed. Its benefits need to be weighed carefully against potential side effects before it can be approved for people with early stages of dementia.

The findings were published in the journal *Brain*, and the research was funded by the Medical Research Council, Alzheimer's Society and Alzheimer Drug Discovery Foundation.



# Diabetes link discovered

Brain changes reveal a mechanism that could link diabetes and dementia.

Research has shown that diabetes can increase the risk of developing Alzheimer's disease and vascular dementia, but we don't fully understand how and why these conditions are linked. A new study from the University of Bath has found a relationship between high glucose levels and Alzheimer's, which helps to explain this link.

The study used human brain tissue that had been donated through Brains for Dementia Research, and was published in the journal *Scientific Reports*. Researchers compared brain tissue from 30 people with and without Alzheimer's disease. They tested whether proteins had been altered by a process called glycation, which is caused by high blood sugar.

The team found that a particular enzyme was glycated in the brains of people with Alzheimer's disease, and that this stopped the enzyme from working properly. This enzyme, called macrophage migration inhibitory factor, has previously been implicated in the inflammatory response that occurs in Alzheimer's.

Dr Clare Walton, Research Communications Manager at Alzheimer's Society, said, 'With diabetes on the rise, a better understanding of how it affects brain cells can help us to find ways to help people with diabetes manage their risk of dementia.'

Alzheimer's Society is funding a clinical trial to see whether a diabetes drug called liraglutide can be used as a treatment for Alzheimer's disease. This involves carrying out brain scans to see if the drug prevents damage to the brain and will assess whether the drug prevents memory loss.

**Learn more about the trial of liraglutide that we're funding at [alzheimers.org.uk/drugdiscovery](https://www.alzheimers.org.uk/drugdiscovery)**

# Dementia and autoimmune disease

A study published in the *Journal of Epidemiology and Community Health* suggests that people admitted to hospital with an autoimmune disease are 20 per cent more likely to be admitted with dementia later on.

The researchers, based at the University of Oxford, looked at the data of more than 1.8 million people admitted to hospital with autoimmune disease from 1998 to 2012.

Of the 25 autoimmune diseases investigated – including coeliac disease, multiple sclerosis, rheumatoid arthritis and ulcerative colitis – 18 were associated with dementia in this way.

Although the type of dementia was not always documented, in cases where it was known, the risk was stronger for vascular dementia than for Alzheimer's.

Dr Clare Walton at the Society said, 'The causes of dementia are complex and we are increasingly learning about links between dementia and other health conditions.'

'This research reinforces earlier evidence that shows the immune system plays an important role in developing dementia, which opens up new avenues to find effective treatments.'

'Alzheimer's Society is funding a study to test whether a rheumatoid arthritis treatment can also work for people with early stage Alzheimer's disease.'



**In the lab.** Dr Rob Williams, Dr Omar Kassar and Professor Jean van den Elsen led the research at the University of Bath.



## Diet drinks and dementia

Unclear association between artificially-sweetened beverages and dementia.

People who drink at least one artificially-sweetened beverage every day may have an increased risk of developing a stroke or dementia compared to those who drink them less than once a week, according to research carried out in Massachusetts.

The researchers reviewed what people were drinking at three different points in time over seven years. People reported their eating and drinking habits by completing questionnaires.

The researchers kept in touch with the same people for the next 10 years to see who developed a stroke or dementia. There was a link between developing dementia and drinking artificially-sweetened beverages, but not with drinking ones that had been sweetened with sugar.

Dr James Pickett, Head of Research at Alzheimer's Society, said, 'This research does not show that artificially-sweetened drinks cause dementia. But it does highlight a worrying association that requires further investigation.'

'Research into dietary factors is very complex and there are a number of issues that need clarifying – for example, why drinks sweetened with sugar were not associated with an increased risk in this study – and teasing out links between all types of sugary drinks, diabetes and dementia.'

'What we do know is that the things we eat and drink can have an effect on our brain health. Evidence shows that along with eating a healthy diet, including watching what you drink, the best way to reduce your risk of dementia is to take plenty of exercise and to not smoke.'

## News in brief

### No link with Marmite

Although a number of headlines proposed that Marmite could help prevent dementia, researchers didn't propose a link. Eating Marmite was found to affect brain activity when young people were given a visual task. The story arose because a chemical messenger called GABA was implicated, and GABA is also altered in dementia. However, it's not reasonable to draw any conclusions about dementia from this study.

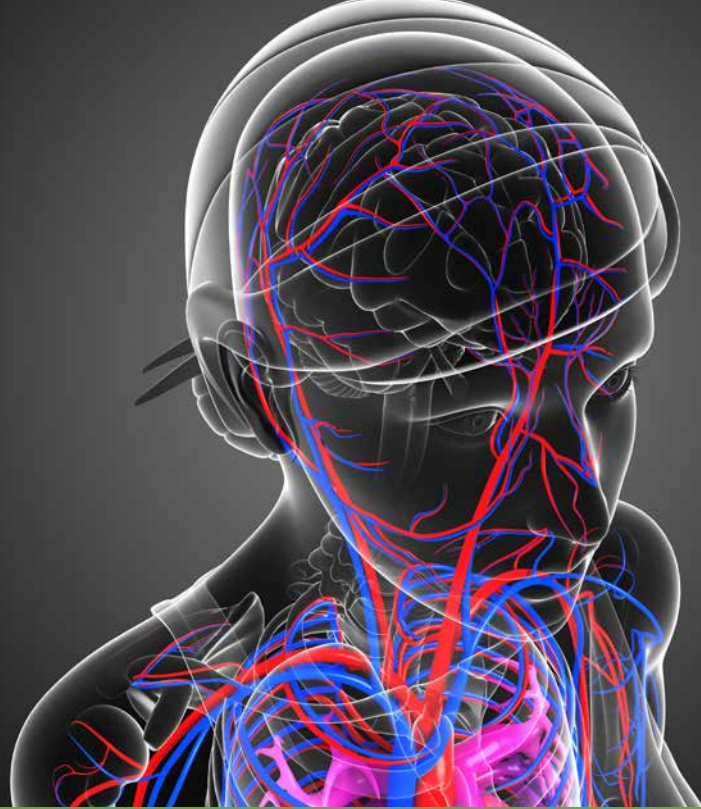
### Benefits of exercise

Aerobic and resistance exercise can improve thinking skills, according to a study that reviewed previous research on trials of supervised exercise programmes. Taking up moderate or vigorous exercise improved people's performance on tests of thinking skills, but the study didn't look at whether this reduced their likelihood of developing dementia.



### Losing connections

Toxic clumps of a protein called amyloid are key hallmarks of Alzheimer's disease, but it is unclear precisely how amyloid affects brain cells. New research in mice has discovered that amyloid clumps can 'switch on' a protein called Ephexin5 that is normally switched off, and that this could contribute towards the loss of important connections between brain cells.



## Hearts and minds

A funding boost for vascular dementia research promises to advance our understanding of this common but under-researched condition.

We all know the importance of a healthy blood supply and nowhere is that more important than in the brain. Over two litres of blood flows around the adult brain every three minutes, delivering essential nutrients and oxygen to cells and transporting waste away. This relentless supply keeps the brain in a delicate balance. If it's cut off, as happens in a stroke, the impact can have long-lasting and life-threatening effects.

Vascular dementia is a progressive decline in thinking skills due to changes in the brain's blood supply. It affects around 150,000 people in the UK and one of the biggest risk factors for vascular dementia is stroke. However, there are a number of different types of vascular dementia and not all of them involve strokes.

Despite the fact that it is the second most common type of dementia, there are still fundamental gaps in

our understanding of why people develop vascular dementia and how it should be treated.

Stroke and vascular dementia have often been studied separately, but a more joined up approach is needed in order to understand how they relate to each other. Alzheimer's Society has joined with the Stroke Association and British Heart Foundation to change this. Together, we have awarded a total of £2.2 million to three projects that will fill critical gaps in our knowledge.

### Rates, risks and routes

The largest of these projects is a national study to understand memory and thinking problems after stroke. Rates, Risks and Routes to Reduction of Vascular Dementia (R4-VaD) involves a team of experienced clinical researchers from hospitals in Cambridge, Edinburgh, Glasgow, Leicester, London, Manchester, Nottingham and Oxford. They will recruit 2,000 people who have had a stroke or ministroke and use a wide range of tests to find out why some develop cognitive impairment or dementia while others do not.

Studies so far have found a wide variation in the number of people who develop dementia after a stroke, and the reasons for this are not completely clear. It could be due to differences in the type or severity of stroke, pre-existing damage to small blood vessels in the brain, or differences in risk factors such as age and smoking. In the R4-VaD study, people will be given brain scans and tests of thinking and memory, in addition to genetic analysis and tests of vascular function and inflammation.

Professor Joanna Wardlaw, who leads the R4-VaD team, says, 'Comparing those who do and don't develop memory and thinking problems will help us determine how to predict vascular dementia, what causes it and how we can prevent it.'

'We will test memory and thinking skills at regular intervals for up to two years after people have had a stroke, along with information on tiredness, mood and ability to cope with daily life.'

Factors that may cause development of memory and thinking problems could relate to clinical disorders such as high blood pressure, lifestyle factors like smoking, or pre-existing changes in the brain (measured using brain scans).

Professor Wardlaw says, 'In the long run, the results will improve how we look for, and look after, thinking and memory problems due to brain vessel disease.'



They will help clinical teams give the best care, assist policy makers in planning services and help researchers run studies to find successful treatments.'

This study will advance our understanding of what causes vascular dementia, but also lay the groundwork for future efforts to prevent the condition.

'In this project we are developing an infrastructure and strong national foundation that means future studies will be easier and cheaper to undertake, as well as being quicker, because suitable individuals will have been identified already,' says Professor Wardlaw.

## Underlying changes

Two further projects will investigate changes in brain cells that lead to vascular dementia. A project led by Professor Karen Horsburgh in Edinburgh will focus on a particular type of change to the vascular system of the brain.

About a quarter of strokes are caused by a failure of small blood vessels in the brain to regulate blood flow properly. Called cerebral small vessel disease, it is the most common disease process underlying vascular dementia.

Professor Horsburgh's team have previously contributed to research showing that a mutation in a gene called collagen 4 can increase a person's

chances of stroke. In this project, the researchers want to understand how this gene affects the relationship between the brain and its blood supply.

They will use stem cells from humans along with animals that have been given the genetic mutation to find out what happens at the molecular level. By finding the mechanism that causes the blood supply to be impaired, the researchers hope to identify how drugs could intervene to prevent damage.

Another project looking for insights that could lead to new treatments, but taking a different angle, is led by Dr Roxana Carare at the University of Southampton. This will consider whether a failure of the blood's waste removal function could play an important role in vascular dementia. Dr Carare will investigate how the brain's waste clearance is affected by small vessel disease, and how this could contribute to brain cell damage.

## Joint effort

Together, these grants represent a joint effort from three charities and three teams of researchers to answer fundamental questions about vascular dementia. If successful, these projects will move us closer to finding new treatments for people with vascular dementia, and help to identify who is most likely to benefit from them. This substantial investment has the potential to bring vascular dementia research out of the shadows.

## Living with vascular dementia

Danny Brown has vascular dementia and lives in Antrim, Northern Ireland. He says, 'I can remember things from 20 years ago, but I have difficulty with my short-term memory. I use prompts to remind me to do things like turn off the oven. I don't remember names and who people are.'

Danny first noticed problems with his memory around 10 years ago, and had a stroke in 2009. After a series of scans and assessments, Danny was diagnosed with vascular dementia in 2014.

Danny says ways to improve diagnosis could be helpful but it's a difficult task. 'It would take the best brains in the world to put something in place so that if someone's losing memory they could within a few months have the right diagnosis.'





## Real-world data

Dr Raffaele Ferrari, an Alzheimer's Society junior fellow in the Department of Molecular Neuroscience at University College London, describes how international collaboration makes his work possible.

I am researching frontotemporal dementia, a less common type of dementia that affects people's behaviour, personality and language skills.

Our understanding of precisely what causes the development of frontotemporal dementia is limited. A better knowledge of genetics could help us understand the processes that take place within and between brain cells, and which lead to brain shrinkage and symptoms.

Therefore, although genetics is the main focus of my research, I collaborate closely with other specialists to discover the impact of these genes in brain cells. This understanding is critical to find potential targets for new drugs.

I have always been intrigued by the thought that a unique combination of chemical reactions forms the basis of all life. I studied molecular biology at the University of Genova in Italy and moved to the US after graduation. There I realised that my interest in biology could become more than a mere exercise of the mind.

I saw clinicians and researchers working together to understand how the smallest imbalance of the body's biological equilibrium could trigger disease.

I began to see that I could direct my work, knowledge and creativity towards understanding the changes in brain cells that underpin disease and finding ways to intervene.

By studying dementia I hope to shed light on some parts of the bigger picture, helping our research community to eventually prevent or cure dementia.

During my PhD I had the opportunity to lead the first international genome-wide association study in frontotemporal dementia. This type of study takes the genetic information of thousands of people with and without the disease, comparing it to find genetic markers that are more common in people who have frontotemporal dementia.

The study identified new genes that increase people's risk of frontotemporal dementia. It also led to the creation of the International Frontotemporal dementia-Genomics Consortium (IFGC), which I currently co-ordinate.

The IFGC includes up to 40 research groups from more than 20 countries in Europe, North America and Australia. Clinicians from these groups send me DNA samples from people who have frontotemporal dementia for analysis here in London.

Since 2008, I have analysed around 3,500 samples. Through my project recently funded by Alzheimer's Society, I will be able to analyse around 2,400 more.

Big numbers are critical for my research and the reason is simple – the more samples I can study, the more accurately I can find alterations in DNA that are linked to frontotemporal dementia. To interpret the genetic data, I work with colleagues to combine information from large databases about the biological effects of the genes.

I am convinced that this multidisciplinary approach – combining knowledge of which genes are involved and how they affect brain cells – will help our scientific community to speed up the development of ways to prevent and treat dementia.



# Agreed terms

An international project has laid out the consensus on how to describe different types of vascular dementia, allowing better communication between research groups.

One of the great strengths of science is that researchers across the world share their findings and learn from each other. In this way, each small addition to shared knowledge brings us closer to the next breakthrough.

For this collaboration to work well, researchers need a common language and an agreed understanding of the topic. With vascular dementia, there have been recent advances in our knowledge of how the brain can be affected and of its symptoms and diagnosis. This has resulted in different groups using different terminology.

The lack of well-established definitions makes it difficult to compare findings and build on each other's work. A consensus is needed to bring shared understanding and make research comparable, regardless of where it takes place.

Alzheimer's Society gave funding to Professor Patrick Kehoe and Dr Olivia Skrobot to lead an international project to agree how vascular dementia should be classified and described. The Vascular Impairment of Cognition Classification Consensus Study involved over 150 scientists and clinicians from 27 countries.

Participants completed questionnaires looking at existing guidelines and suggested improvements. In a number of rounds, they refined guidelines and moved towards a new agreed description.

Through this process, the study clarified what is meant by the terms 'vascular cognitive impairment' and 'vascular dementia', which are sometimes used interchangeably.

According to this new consensus, vascular cognitive impairment is an overall term that encompasses the earliest stages of the condition – mild vascular cognitive impairment – and the moderate and severe stages described as vascular dementia.



Image credit: Dr David Thomas and Dr Magdalena Sokolska, UCL

## Blood vessels made visible

A special kind of brain scan called magnetic resonance angiography shows some of the major blood vessels in the brain.

The researchers settled on four sub-types of vascular dementia:

- Post-stroke dementia is the term used when cognitive decline begins within six months after a stroke.
- Subcortical ischaemic vascular dementia is caused by restriction in blood supply to brain tissue, mainly caused by disease of the small blood vessels.
- Multi-infarct dementia describes cases where multiple large areas of brain tissue are damaged due to changes in the blood supply.
- Mixed dementia is a term used for people who have signs of vascular damage, but also another cause of dementia such as Alzheimer's disease.

These guidelines have now been published in the journal Alzheimer's & Dementia. They will be used widely and will make it easier for different researchers to compare their findings and work together in collaborative ways to advance vascular dementia research.

# Taking part

Martin Keats is taking part in the PREVENT Dementia study, which receives funding from Alzheimer's Society. He tells us about the study and reflects on his experience of having a lumbar puncture for research.

I found out about the PREVENT Dementia study from a colleague while I was working at Imperial College London. She mentioned that they were looking for people aged between 40 and 59, so I thought I'd put myself forward to help out.

I'm not aware that anyone in my family has ever had dementia, but I felt it would be good to get involved. My colleague informed me that the study included regular brain scans and an optional lumbar puncture, and she sent me more detailed information about it by email.

I joined the study in May 2014 after reading information about it and completing the consent forms, including one for the lumbar puncture. The study involves being assessed every two years, so I've had two assessments so far – a baseline in 2014 and a follow up in 2016.

The idea is that we will be assessed for years to come so that the earliest signs of any onset of dementia might be studied using the different types of information collected.

The main session involves going to an assessment clinic for most of a day. It starts with a fasting blood sample and things like weight and blood pressure measurements, followed by breakfast.

The researchers ask questions about any medications you're taking and if you've had any medical problems, and they do a series of health checks.

Then there is a series of computer-based cognitive tests, which I found enjoyable but rather challenging. My childhood memories of doing similar tests at school came flooding back! Later I went to have a brain scan, which lasted about an hour.



## Not so scary after all

At first I was a little wary of the idea of a lumbar puncture, fearing the possibility of back pain or headache, which are common side-effects. I am used to migraine headaches and was not keen on experiencing another, brought on by a medical procedure.

The notes given to me before I joined the study were pretty reassuring and the doctor who performed it let me know that it is a fairly common procedure in the NHS. Actually, the lumbar puncture procedure went like clockwork. I was given a local anaesthetic and from there on, though fully conscious, I felt nothing at all. I was also fortunate not to experience any subsequent headache or back pain.

My advice for anyone considering taking part in research would very much depend on how demanding the study might prove to be. I find being involved in the PREVENT study rather fun and scientifically interesting. It is also reassuring to know that, if any potential health issues arise out of the tests, I would be referred to my GP for advice or treatment.

Visit [alzheimers.org.uk/researchvideos](https://www.alzheimers.org.uk/researchvideos) to watch the videos of Martin and two other volunteers, Gary and Eva, as they take part in dementia research.

# UK Dementia Research Institute centres announced

Plans for the UK's first dedicated Dementia Research Institute are moving forwards with the announcement of the first research topics and five new centres.

The first 27 research programmes at the UK Dementia Research Institute have been announced. Worth a combined investment of £55 million, the programmes will provide answers to some of the most pressing questions in the field of neurodegenerative disease.

Five new centres will be established at the University of Cambridge, Cardiff University, University of Edinburgh, Imperial College London and King's College London.

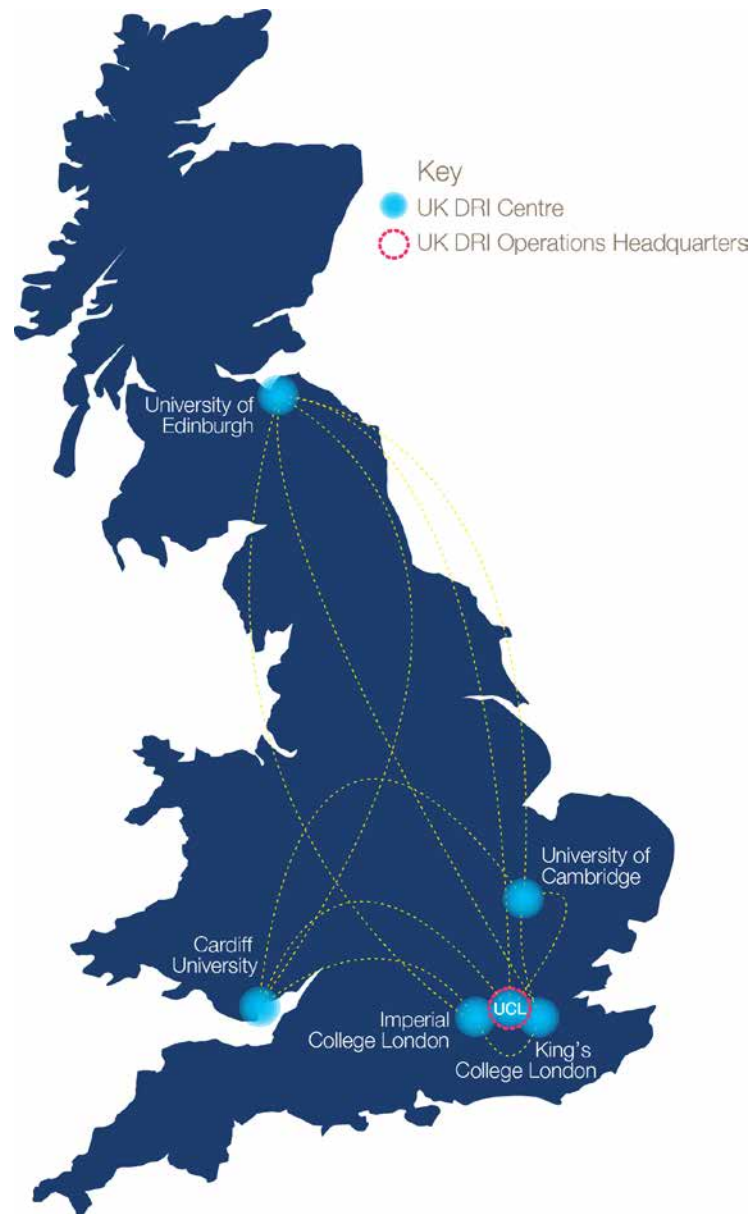
Together with the headquarters at UCL (University College London), they will lay the foundations for an eventual 400-strong community of UK Dementia Research Institute researchers.

Using state-of-the-art research facilities at these leading UK universities, the initial programmes will get to the core of what causes neurodegenerative disease.

Researchers will study how factors such as genetics, metabolism and the immune system contribute to the microscopic changes that cause loss of brain cells.

By advancing our understanding of precisely what goes wrong in the brain, researchers at the institute will identify new ways to intervene that can be developed into new treatments for dementia.

The UK Dementia Research Institute will explore ways to detect dementia and to monitor how the diseases progress over time – information that could be useful for diagnosis and to test whether new treatments are working.



Dr Doug Brown, Director of Research and Development at Alzheimer's Society, said, 'The institute provides a dynamic, collaborative and fresh approach that will transform dementia research and deliver life-changing discoveries for people affected by dementia. It's incredibly exciting to see its first pioneering research programmes take shape across the six centres.'

'Alzheimer's Society has committed £50 million to fund new research at the institute, maximising the impact it will have for people with dementia today and in the future. With the first research programmes now in place, we have the right ingredients for innovative discovery that will rejuvenate the development of dementia treatments.'





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