Issue five
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Alzheimer's Society
Leading the fight against dementia

Careandcure

The Alzheimer's Society research magazine

Teaching an old drug new tricks

Testing existing drugs for use against dementia. Page 6

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What's in this issue of Careandcure

It is more than a decade since the last new drug for dementia was approved for use. Drug development is a long, slow and expensive process that is fraught with failure. Although researchers have learned a lot from past drug trial failures, progress has not kept pace with the urgent need for a way to tackle dementia.

'Repurposing' existing drugs offers a way to bypass some of the difficulties faced when developing a drug from scratch. As the feature on page 6 explains, drugs for conditions ranging from asthma to erectile dysfunction are being investigated as potential treatments for dementia. This approach is an important part of our Drug Discovery Programme as it could help to get new drugs to people with dementia within five to 10 years.

In the meantime, it is important to ensure that we are getting the best out of the drugs that we have to hand. As described on page 9, a trial of the common dementia drug donepezil (also known as Aricept) has shown that it could help people in the advanced stages of Alzheimer's disease.

Prevention is better than cure, so the saying goes; the response to a recent study of brain training (see page 3) suggests that many people agree. We received the highest ever number of views on our website on the day the results were announced and over 16,000 people registered to take part in a second phase of the study.

Ian Le Guillou
Editor
Careandcure

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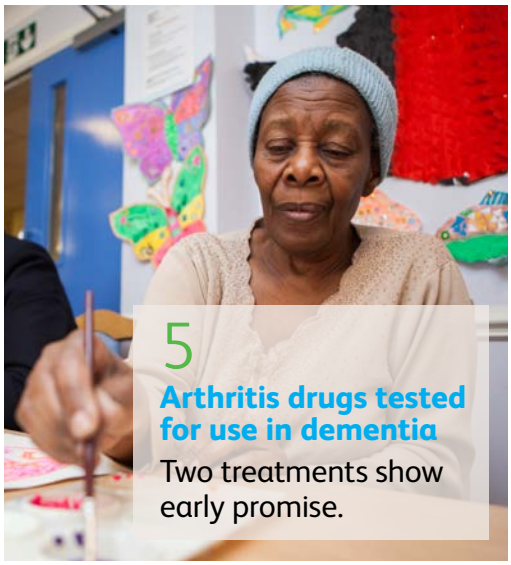

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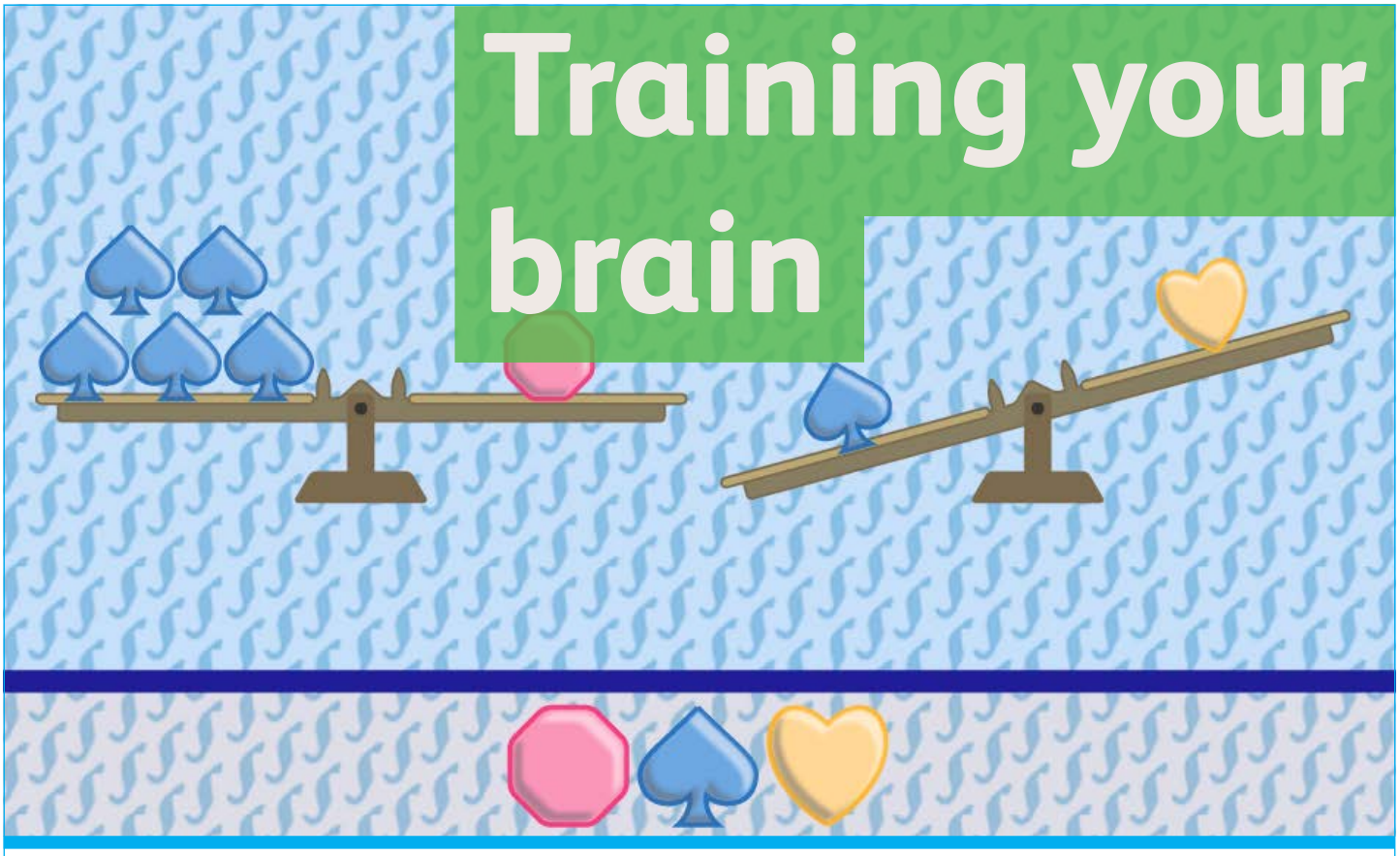
Training your brain



A new study has found that regular use of a brain training game can improve reasoning and help with day-to-day activities.

It has often been observed that people who regularly undertake mentally challenging tasks, such as crosswords or Sudoku puzzles, seem to have a lower risk of developing dementia. However, there is a lack of evidence to show whether specially designed 'brain training' packages can reduce dementia risk.

Alzheimer's Society has funded the largest trial to date to investigate whether a bespoke computer-based brain training package can improve cognitive abilities. The study, by researchers at King's College London, recruited almost 7,000 participants over the age of 50 through a unique partnership with the BBC. The participants played computer-based brain training games designed to challenge their reasoning, attention and memory skills over a period of up to six months.

The study found that people aged 50 or over who played the brain training games showed improvements in their reasoning – for example working out which weight on a see-saw was heaviest – when compared to a control group. People over 60 also reported getting on better with their daily activities after playing the games.

'Online brain training is rapidly growing into a multi-million pound industry and studies like this are vital to help us understand what these games can and cannot do,' says Dr Doug Brown, Director of Research and Development at Alzheimer's Society. 'While this study wasn't long enough to test whether the brain training package can prevent cognitive decline or dementia, we're excited to see that it can have a positive impact on how well people perform essential everyday tasks.'

> **'Online brain training is rapidly growing into a multi-million pound industry and studies like this are vital to help us understand what these games can and cannot do.'**
>
> Dr Brown

The researchers are using the Alzheimer's Society funding to continue to investigate brain training. In this phase of the study, volunteers will also provide genetic information via a mouth swab to help researchers understand whether genetic differences play a part in how well people respond to the brain training.

If you are aged 50 or over and do not have dementia, you can sign up to the brain training trial as part of the PROTECT study at www.protectstudy.org.uk

Try a demonstration of a game used in the study at alzheimers.org.uk/braintraining

New resource for people with learning disabilities

A new research-based booklet that aims to help people with learning disabilities to understand dementia has been published.

Jenny's diary is the result of a study by Dr Karen Watchman at the University of the West of Scotland. Her findings showed that some people with learning disabilities may struggle to understand what dementia is or the changes that are happening to them or their loved one.

Jenny's diary, which was funded by Alzheimer's Society, also makes use of previous research by Dr Irene Tuffrey-Wijne at St George's, University of London, about the best way to discuss bad news with people with learning disabilities.

This booklet is especially important as people with learning disabilities, particularly Down's syndrome, may be at higher risk of developing dementia at an early age. It features postcards with different everyday scenarios to highlight the impact of dementia and suggested strategies for support.

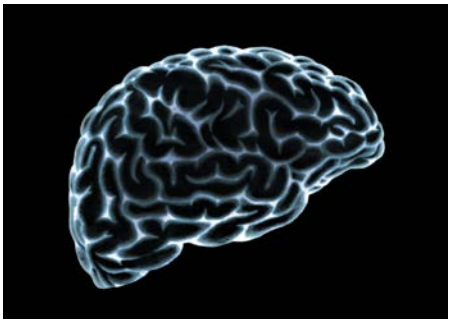
For more information and to download a copy of Jenny's diary, please go to www.uws.ac.uk/jennysdiary

Brain implants for memory loss in development

Researchers are working to develop a prosthetic brain implant that could have the potential to help treat people with memory loss.

The device is being designed by DARPA (the US Defence Advanced Research Projects Agency) to help soldiers with memory loss, but could also benefit people with dementia.

Dementia often causes damage to the hippocampus, a part of the brain that is responsible for processing memories before they are passed to other areas of the brain for long-term storage. In theory, this implant would work by allowing the signals to bypass the damaged hippocampus and be processed artificially into a signal that can be committed to memory.



Using electrical recordings from the brains of nine people, the researchers have developed a computer model of how the human hippocampus forms memories.

The next steps will be to design an implant device that can send electrical signals into the human brain and test it in people who have a damaged hippocampus.

Arthritis drugs tested for use in dementia

Two drugs that fight arthritis are being studied for their potential as treatments for Alzheimer's disease.

Etanercept and salsalate have been used for a number of years to treat arthritis, but new research studies have looked at whether they could be repurposed for dementia.

It is hoped that etanercept could reduce inflammation in the body to counter the inflammation seen in Alzheimer's disease. It was shown to have few side-effects in a trial of people with mild-to-moderate Alzheimer's disease but there was little sign of benefit for memory or daily activities. Forty-one people took part in the study, receiving etanercept or a placebo by injections under the skin once a week for 24 weeks.

A new trial co-funded by Alzheimer's Society is now testing whether etanercept has any benefit for people with mild cognitive impairment (memory problems beyond those associated with normal ageing), who have a higher risk of developing dementia. The trial will take place over a year, making a clear result more likely.

> 'What we need now is confirmation of whether it works for people with dementia.'
> Dr Brown

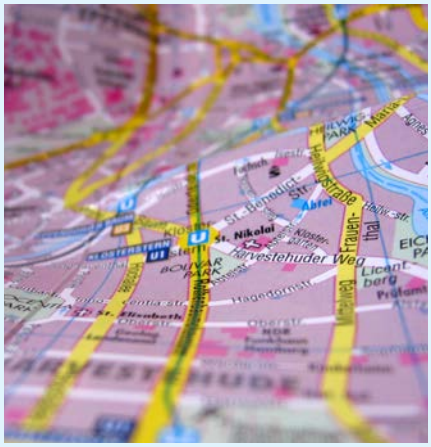
Salsalate, which is from the same class of drugs as aspirin, is in the earlier stages of testing. New research in mice has shown that the drug reduces levels of tau protein, which can be toxic when it accumulates, causing damage to brain cells in Alzheimer's disease and frontotemporal dementia. The mice already had signs of tau accumulation, yet the drug was able to reverse the decline in memory ability.

'As this drug is already prescribed to people with arthritis we know a lot about how it works and its side-effects,' says Dr Doug Brown, Director of Research and Development at Alzheimer's Society. 'What we need now is confirmation of whether it works for people with dementia.'

News in brief

Researchers have found traces of amyloid protein, a hallmark of Alzheimer's disease, in the brains of some people who received growth hormone injections in the 1970s. The study was based on samples from people who died of Creutzfeldt-Jakob disease after receiving contaminated injections. The researchers suggested that the amyloid might also have been transferred through the injections.

Resting for 10 minutes after learning a new route can help people to remember directions based on landmarks. It can also help people to understand where landmarks are in relation to each other and take shortcuts. The technique, known as minimal interference, could be developed further to help people with memory problems.



A six-week course of the asthma drug montelukast (Singulair) improves memory and learning in rats, according to a new study. The drug seems to work by reducing inflammation and encouraging new brain cells to grow. The drug had no effect in younger animals, but it improved performance in older rats.

Teaching an old drug new tricks

Istvan Takacs

Developing a new drug can take 10 to 15 years and cost up to a billion pounds. Even after that, there is still no guarantee that the drug will work and be approved for use. One promising approach to make this process cheaper and faster is to test existing drugs to see if they have the potential to treat an entirely different disease.

In 1988, Nobel Prize winner James Black said, 'The most fruitful basis for the discovery of a new drug is to start with an old drug.' Despite huge technological advances since then, his words remain relevant today. In recent years, researchers have not only drawn inspiration from old drugs, but are increasingly taking them wholesale and testing them against other diseases.

In 2012, an Alzheimer's Society research review highlighted five existing drugs that might be suitable for testing against dementia. This was the start of the Society's Drug Discovery Programme, which has focused on 'repurposing' drugs for dementia. Since the review was published all five of the drugs listed have been tested or are currently in trials.

The advantage of studying existing drugs is that we already understand how they behave in the body and what the side-effects are. Often they may also be cheaper to buy. This is a promising approach that is also being used for other conditions such as multiple sclerosis and breast cancer.

Improving blood flow

One drug that is currently being tested is tadalafil, a treatment for erectile dysfunction. Dr Atticus Hainsworth and his team at St George's Hospital are investigating whether tadalafil might also help people with vascular dementia. There are currently no treatments for vascular dementia, which is caused when the blood supply to the brain is impaired. It is the second most common cause of dementia in the UK, affecting 150,000 people.

The study is testing whether tadalafil improves the blood supply to deep regions of the brain in people with small vessel disease – the main cause of vascular dementia in older people. 'These are people who do not have dementia, although they will be at risk of developing it later, by virtue of having already had some vascular disease in their brain, so people who have had small strokes. From the MRI scan we can see that there is a certain amount of damage already, so they've got the pathological process, that's how we know we've

got the right people,' says Dr Jeremy Isaacs, Consultant Neurologist and Principal Investigator of the study.

'The reason the brain cells get damaged in vascular disease is to do with changes in blood supply – small blood vessels become more rigid and narrow,' adds Dr Hainsworth, who is a Senior Lecturer in Cerebrovascular Disease. 'If we could open up these blood vessels and get more blood through them, that could help.'

One step at a time

The tadalafil study is at the 'proof of concept' stage, which aims to show that the drug does have a biologically relevant effect in people. 'We're particularly interested in what it does in the arteries in the brain,' says Dr Hainsworth. 'The next step is to ask does it have some effect on brain function itself. Two years from now, we may be back asking for funding to do the bigger trial – the real efficacy trial that would tell us about improved cognition.'

Often the idea to test existing drugs comes after research into the fundamental biology of the disease reveals a new potential target for treatment. If there's already a drug available that has been designed to treat that target, then it could cut out much of the process for developing a new drug and testing its safety.

This was the case for the tadalafil study, which came about when earlier research conducted by Dr Hainsworth and colleagues found that the target for tadalafil (an enzyme called PDE5) is present in brain arteries. This led to the idea that vasodilator drugs, which increase blood flow, might be beneficial to people who have small vessel disease.

Repurposing revival

Repurposing drugs is nothing new; in fact tadalafil is closely related to one of the most famous repurposed drugs – Viagra. That was originally developed to treat high blood pressure but researchers noted that it had an unexpected, and highly profitable, side-effect.

Even some of the currently available treatments for Alzheimer's disease are repurposed drugs. Memantine was originally developed in 1968 to treat flu and galantamine was discovered in the 1950s and has been used in anaesthesia and the treatment of nerve pain.

The repurposing of drugs is going through a renaissance as researchers investigating a number of diseases try to make the most of what is already available. An annual conference dedicated to drug repurposing is now in its fifth year, drawing in experts from around the world to share their ideas. Earlier this year a multiple sclerosis trial began testing drugs originally developed for heart disease, depression and motor neurone disease.

'Brain cell damage in vascular disease is to do with changes in blood supply. If we could open up the blood vessels and get more blood through them, that could help.'

Dr Hainsworth

Similarly, a wide range of drugs is being investigated in dementia research. There are currently trials testing available drugs for arthritis, diabetes, blood pressure and even an antibiotic. These drugs would not be able to treat the root cause of the dementia. Instead it is hoped that they might be able to treat some of the many changes that happen in the brain, such as inflammation, blood flow or insulin resistance. This could help to reduce the stress on brain cells and hopefully slow the progression of dementia or even delay its onset, if caught early enough.

Although it is still early days for tadalafil, Dr Hainsworth can see its potential. 'For me, a success would be a drug on the shelves - in the clinic, that we could give to patients. Either when they've got a diagnosis but more likely in a prevention strategy if you find you have risk factors. If you could say to someone in their sixties, "I'm afraid you're going to have to take this pill every morning and it will cut your risk of dementia," I think they'd probably do it.'

Making connections

Alzheimer's Society Drug Discovery Fellow Dr Caroline Woffindale is in the first year of a three-year funded project in the Translational Neuroscience and Dementia Research Group led by Professor Simon Lovestone at the University of Oxford.

As a student, I became increasingly interested in how the brain is able to store and retrieve the complex information of our memories. As I learned more about the devastating consequences that occur when anything goes wrong with these processes, such as dementia, I decided that I wanted to do all that I could to help.

With the number of people with dementia predicted to grow, and unfortunately having now witnessed relatives begin to go through this experience, my desire to understand the causes of Alzheimer's disease and to help to find a cure for this distressing condition has grown even stronger.

Despite a growing understanding of the causes of Alzheimer's disease and many attempts to find a disease-modifying drug, as yet there are no drugs available that can prevent or cure the disease.

Two key proteins, amyloid and tau, have been shown to be important in the development of Alzheimer's disease. However, we still don't know if or how these two proteins may interact to cause the damage to brain cells responsible for Alzheimer's disease.

Work within our lab previously revealed a potential link between the toxic effects of both amyloid and tau via another protein called DKK1.

This work, supported by Alzheimer's Society funding, showed that the lab-based treatment of brain cells with either amyloid or DKK1 proteins led to the activation of several genes, which appeared to reduce the toxic effects of amyloid and tau proteins.

By providing a potential link between two established proteins associated with Alzheimer's disease, these genes may represent new targets for drugs.

My fellowship is focusing on identifying drugs that target this specific pattern of gene activation and might therefore be useful in the treatment of Alzheimer's disease. To do this, I am using an online resource called the Connectivity Map, which can be used to link genes, drugs and diseases.

The Connectivity Map is a database of gene activation data collected from human cells that have been treated with a large number of different drugs. Using the genes identified by our previous work, it allows us to identify existing drugs that may be able to reverse the pattern of gene activation seen in Alzheimer's disease.

Using this approach, I have identified a number of drugs, many of which are already approved for the treatment of other diseases, which appear to influence our genes of interest.

I am now testing these potential drugs in rat brain cells which mimic Alzheimer's disease to determine whether or not they are able to have an effect on the disease.

As the Connectivity Map generates information based on existing drugs, some of which are already approved for the treatment of disease, this may speed up the development process for any promising drugs.

> **'The Connectivity Map allows us to identify existing drugs that may be able to reverse the gene activation seen in Alzheimer's disease.'**
>
> Dr Woffindale

We are very grateful to Alzheimer's Society for all its support, which allows our work to continue. It is an exciting time to be involved in Alzheimer's disease research, with the next big breakthrough hopefully just around the corner!

Maximising benefit

Although there are many promising drugs in development, it is important to make the most of the dementia drugs that are already available. The DOMINO-AD trial has shown that one drug currently in use could be helpful for people in the later stages of Alzheimer's disease.

When new drugs are being tested in people they progress through different stages of clinical trials. Phase one focuses on the safety of the drug, which is often tested in a few healthy young people. If that is successful, it progresses to phase two where the drug is tested for biological effects in a few dozen patients. The final stage, phase three, is the definitive trial to test the drug in hundreds of patients to see if it has an effect on the disease.

New drugs have to overcome all these hurdles before they can be approved and prescribed by doctors. However a lesser-known stage, phase four, examines the effectiveness of the drug once it is already being widely prescribed. This phase can help to identify any additional side-effects or groups of people who might benefit from receiving the drug.

Acetylcholinesterase inhibitors, the most popular class of dementia drugs which includes donepezil (Aricept), are only recommended for people with mild-to-moderate Alzheimer's disease. The DOMINO-AD trial was set up in 2008 to find out whether these drugs could benefit people in the later stages of the condition. It studied the effects of withdrawing or continuing donepezil treatment in nearly 300 people with moderate-to-severe Alzheimer's disease.

The trial, which was funded by the Medical Research Council and Alzheimer's Society, found that people who continued taking donepezil showed a third less decline in their memory, compared to those who were given a placebo. It also

had benefits for people's functional abilities such as dressing or eating.

'Even when patients had progressed to the moderate or severe stages of their dementia, continuing with donepezil treatment provided modest benefits in cognitive function and in how well people could perform their daily activities,' says Robert Howard, Professor of Old Age Psychiatry at University College London, who led the trial.

These results, published in 2012, were contrary to the perceptions of many doctors at the time. A year later, two-thirds of old age psychiatrists surveyed felt that the future practice of prescribing donepezil and similar drugs would be altered based on the trial's results.

> **'We are all impatient for the advent of true disease-modifying drugs.'**
>
> Prof Howard

'With no new treatments for Alzheimer's disease in over a decade, it is absolutely crucial that we make the most of the drugs we have available,' says Dr Doug Brown, Director of Research and Development at Alzheimer's Society.

A follow-up of the people who took part in the study, published in October 2015, found that continuing to take donepezil also reduced their chances of moving to a nursing home. This benefit did not last beyond the end of the trial when the participants were able to choose their medication with their doctor.

Professor Howard says, 'Our new results show that these benefits translate into a delay in becoming dependent on residential care, a point that many of us dread. We are all impatient for the advent of true disease-modifying drugs that can slow or halt the Alzheimer process, but donepezil is available right now and at modest cost.'

Serious gaps in dementia research

A comprehensive review of the dementia research workforce has revealed serious gaps in capacity and recommends measures to attract and retain researchers.

The Alzheimer's Society report finds that too few researchers are choosing a career in dementia, with five times more people choosing to work on cancer. Retention is also poor, with 70 per cent of those who complete a PhD on dementia leaving the field within four years.

There is also a critical lack of people from care and clinical professions focusing on dementia research. Less than 2 per cent of the top 200 most prolific UK dementia researchers specialise in social care and social work, even though people with dementia are among the biggest users of adult social care.

The report highlights the many barriers faced by academics, clinicians and care professionals pursuing a research career in this area, including:

- the lack of a secure career path for researchers, which is an issue in many biological and health fields but amplified in dementia due to the relative scarcity of funding
- too few mid-level positions that would enable postdoctoral researchers to move into their first independent research post
- a lack of junior-level posts and PhD studentships for allied health and social care professionals, such as physiotherapists and social workers, to gain experience in dementia research
- a lingering view that there is not much that can be done for people with dementia and that dementia research has faced many setbacks to date.

Dr Jose Bras, an Alzheimer's Society Research Fellow, says, 'There isn't a system in place that allows researchers like me to move from individual fellowships to academic positions. Although this is not a new problem, it creates insecure career paths that are likely to be driving away some of the bright researchers that the field should do its best to hold on to.'

In the UK, the cost of dementia to the economy is £26.3 billion, yet less than £74 million was spent by government and charities on research in 2013. Despite this, the review finds that the UK ranks second in the world for the amount of dementia research it produces, punching well above its weight.

'Dementia research is going from strength to strength in the UK but this report highlights that there are still too few people choosing it as a career, especially those from clinical and care professions. We must build the reputation of dementia research to show that it is one of the most cutting-edge areas of research that is poised to make significant advances in the next decade,' says Dr Doug Brown, Director of Research and Development at Alzheimer's Society.

'By attracting and retaining more of the very best researchers in dementia, we will be able to significantly speed up progress towards innovative care and that all-important cure. Alzheimer's Society is leading the way to address this challenge. We have recently invested over £6.5 million to support 75 individuals to develop their careers in dementia research and intend to do much more in the years to come.'

For more information and to download a copy of the report, please go to alzheimers.org.uk/researchreport2015

Student bursaries for career development

Alzheimer's Society bursaries have enabled four dementia research PhD students in Northern Ireland to take part in an international training programme on ageing, organised by the Centre for Ageing Research and Development in Ireland.

The research interests of the bursary recipients reflects the diverse range of dementia research, from the importance of design and architecture in creating dementia-friendly environments to investigating better ways to diagnose Alzheimer's disease.

Bridgeen McCloskey is researching the use of end-of-life medication for people with dementia. 'Research has shown that people with dementia approaching the end of life often receive suboptimal end-of-life care and as a result have been referred to as the "disadvantaged dying",' she explains. 'The optimal use of medications in end-of-life patients, especially in those dying from conditions other than cancer, remains mostly unexplored.'

Nicola Quinn, pictured below, is investigating whether there is any association between the progression of Alzheimer's disease and the state of the retina, which is at the back of the eye. She says, 'Since the retina is an extension of the brain, invaluable information could be found that could help to diagnose Alzheimer's disease before pathology is found in the brain, giving patients a better prognosis and thus a better quality of life.'

Another bursary recipient, Pamela Topping, pictured above, is investigating design and colour in the building of dementia-friendly environments. 'My journey in dementia research started with my first job as a nurse. My passion was working with people who had a diagnosis of dementia. However, when a back injury forced me to leave my job I returned to education and graduated as a designer,' she explains.

'It was at this time I realised how little progress had been made within the discipline of design that would directly empower and support the person with dementia in the built environment. I became involved in dementia design research as my nursing skills gave me a greater understanding of what living with dementia meant and the empathy and compassion is translated into my design thinking.'

Attending the international training programme gave the PhD students the opportunity to understand more about dementia as a whole. Nicola says, 'It was great to hear about all the different approaches people are taking in their journey of researching dementia. It has given me thorough background knowledge of dementia and also gave me research ideas I can implement in my own work.'

For Bridgeen, a talk given by a person living with dementia was particularly interesting. She says, 'Hearing this person's experience gave me a greater understanding of the problems people with dementia face and how important research in this area is to improve the lives of those living and dying with dementia.'

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About us

Alzheimer's Society is the leading support and research charity for people with dementia, their families and carers.

Since 1990, Alzheimer's Society has funded over £35 million of cutting-edge dementia research. We aim to increase our investment in our research programme to around £10 million a year by 2017 and £100 million over the next decade.

This money funds important research that will help us to improve the quality of life of people with dementia, by tackling questions related to the causes of dementia, investigating good practice in care and treatment, and pursuing a cure.

Research Network

One distinctive feature of our ground-breaking research programme is the integral involvement of people with dementia and carers.

As part of our Research Network, volunteers with direct experience of living with dementia inform our research priorities.

If you have been a carer for someone with dementia or you have dementia and are interested in joining the Research Network, please contact Anna Grinbergs-Saull, Research Engagement Officer, for an application form or apply online at **alzheimers.org.uk/researchnetwork**

Alzheimer's Society maintains editorial independence over the content of this magazine.

Sunrise Senior Living is generously sponsoring the Research Network.

For more information please visit **www.sunrise-care.co.uk**

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