

# PROGRESS

The research magazine of Parkinson's UK | Spring 2019

## POSTURE AND PARKINSON'S

We ask the expert

## TRIALS TO TREATMENTS

Targeting  
alpha-synuclein

## 50 years of discovery

How far have  
we come?



## GNDF CLINICAL TRIAL

What are the results?

**PARKINSON'S<sup>UK</sup>**  
**CHANGE ATTITUDES.**  
**FIND A CURE.**  
**JOIN US.**

## WELCOME

I'm delighted to introduce this issue of *Progress* magazine, in which we mark 50 years of the charity supporting research to understand Parkinson's and develop new and better treatments.

But reflecting on what's been achieved brings mixed feelings.

The past five decades have seen extraordinary scientific progress, and we're proud to have played an important part in many of these breakthroughs (see page 6). However, the main treatment available to people living with Parkinson's remains dopamine-based medication, which helps to manage some of the symptoms but cannot stop the condition's underlying progression.

We know this isn't good enough, and that we need to do more to convert this pioneering science into transformational treatments.

That's why we've doubled our annual spend on research over the past five years, going from £5million to £10million.

And why we launched the Parkinson's Virtual Biotech in 2017 – to capitalise on the new opportunities emerging from all this scientific progress, to rapidly and systematically develop new treatments.

You can read about the encouraging progress we're making on page 22, and our ambitious plans to expand the programme, including a new clinical trial, in 2019.

I'm now in my 14th year as Chief Executive at Parkinson's UK, and I've never felt more confident that real breakthroughs are within our grasp.

All this is only possible with the drive of people living with the condition. We now have over 5,000 people signed up to our Research Support Network. Thank you to everyone who has joined – by participating in research, working with researchers, volunteering or spreading the word, your contribution is crucial.

I hope reading about the steps we're taking forward will inspire even more of you to get involved and help drive us closer to a cure. ■



**Steve Ford**  
Chief Executive  
of Parkinson's UK





## ON THE COVER

With the explosion in our scientific understanding of Parkinson's over the last 50 years, how close are we to solving it?

■ 6  
50 years  
of discovery

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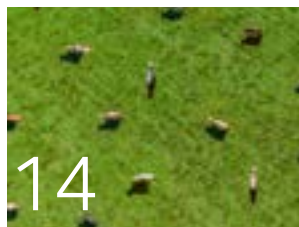
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# NEWS

## ROUNDUP

### Scientists use gene editing to create 'tougher' stem cells

Researchers at the University of Edinburgh have used cutting-edge, gene-editing techniques to create stem cells resistant to developing Parkinson's.

Major progress has already been made into stem cell therapies, but research has suggested that new, healthy brain cells transplanted into the Parkinson's brain may gradually develop the condition themselves.

Researchers believe that this is due to a protein called alpha-synuclein invading healthy cells and triggering the formation of sticky clumps called Lewy bodies.

The team used gene-editing techniques to snip out the alpha-synuclein gene from the stem

cells. These stem cells were then transformed into brain cells that produce dopamine – the type of cell lost in Parkinson's.

When treated with a chemical agent known to induce Lewy bodies, only those cells that had been gene-edited did not form the toxic clumps.

Professor David Dexter, our Deputy Director of Research, says: "This pioneering work has the potential to deliver long-term, life-changing treatments for people with Parkinson's.

"This should mean that the Parkinson's stem cell transplantation trials stand a significantly better chance of providing long-term benefits for people who are suitable for this kind of treatment." ■

## New research into levodopa's influence on Parkinson's progression

A recent clinical trial has produced further evidence that there is no benefit of delaying levodopa therapy.

Research published in the *New England Journal of Medicine* suggests levodopa doesn't influence the progression of Parkinson's.

As part of a controlled trial carried out at the University of Amsterdam, 417 people with early Parkinson's were split into 2 groups:

- Half of the participants received levodopa in combination with carbidopa for 80 weeks.
- Half of the participants received a placebo for 40 weeks and then levodopa in combination with carbidopa for 40 weeks.

The researchers measured Parkinson's symptoms using the Unified Parkinson's Disease Rating Scale at various points in the trial to assess the progression of the condition.

At the end of the 80-week trial there was no significant difference between symptoms and side effects between the two groups.

Dr Katherine Fletcher, our Research Communications Officer, says: "Levodopa is an important tool for managing Parkinson's symptoms. But there are outstanding research questions about how levodopa impacts the progression of Parkinson's and when people should start the treatment.

"This new research suggests that levodopa does not alter the progression of the condition within the tested timescale." ■

## GDNF trial complete and results are in

G lial cell line-derived neurotrophic factor (GDNF) is a special protein that is naturally produced inside the brain and supports the survival of many types of brain cells – including the cells lost in Parkinson's. To investigate the effects of GDNF, 41 people with Parkinson's took part in a groundbreaking clinical trial in Bristol.

Initial analysis suggested that the treatment is safe but there was no clear difference between those who received GDNF and those who received the placebo after 9 months. A full analysis of all the data has now been completed and gives us a much more comprehensive picture of the effects of GDNF.

You can read the full story on page 18. ■

### READ OUR BLOG

Find out the latest research news, and go behind the headlines, by visiting our research blog at [parkinsons.org.uk/blog](https://parkinsons.org.uk/blog) ■



# FIFTY YEARS OF DISCOVERY

How close are  
we to solving  
Parkinson's?

The last 50 years have seen an explosion in our scientific understanding of Parkinson's. We look back at how treatments have evolved and at some of the major lightbulb moments, as well as ahead to the exciting new wave of therapies emerging from these discoveries.



## Problems of the past

### The dopamine delusion

In the 1960s, scientists knew Parkinson's was caused by a loss of dopamine-producing cells, resulting in a marked decrease in dopamine levels in the brain, but little else.

So, treatments that could replace dopamine seemed the obvious solution.

The first truly effective drug, levodopa, was first tested in people with Parkinson's in 1961 and remains the main treatment for the condition to this day.

Once in the brain, levodopa is converted to dopamine – boosting the supply for cells struggling to make their own, which helps to improve symptoms.

But, as the condition progresses and more brain cells are affected, it becomes more and more difficult to deliver the right amount of dopamine at the right time to keep symptoms under control.

Too much, and side effects such as dyskinesia can occur. Too little, and symptoms take hold.



New and different drug treatments were developed in an attempt to address these issues. In the 1970s, the first dopamine agonists emerged. They work by mimicking the action of dopamine. These were followed in the late 80s and 90s by a wave of drugs, such as the combination treatment, levodopa/carbidopa, and selegiline, both of which aim to prolong the action of dopamine in the brain.

In the 1990s, a pioneering surgical approach – deep brain stimulation (DBS) – offered another important option. DBS works by inserting very fine wires carefully into the brain to electrically stimulate particular brain cells involved in controlling movement to adjust their activity. While DBS can provide better, longer-lasting control of symptoms – especially of movement problems – like all medications currently available it cannot stop the progression of Parkinson's.

Targeting dopamine alone was not the answer to solving Parkinson's. To develop new treatment approaches that could slow, stop or reverse the condition we first needed to understand what goes wrong inside the brain.

Scientists across the world have made extraordinary progress in unravelling how and why these precious cells become damaged – offering exciting opportunities to save them.

### Misfiring mitochondria

In the summer of 1982, hospitals in San Francisco were confronted with a mystery. Young men and women were brought in who had suddenly and inexplicably lost the ability to move and speak, appearing frozen.

Doctors were mystified but neurologist Dr Bill Langston recognised the symptoms of advanced Parkinson's and gave them levodopa, which restored their ability to move and talk. But what had caused these individuals to develop advanced symptoms of Parkinson's overnight?

The answer was curious – they had all used synthetic heroin from the same batch, which had been unintentionally contaminated with a manmade chemical called MPTP.

MPTP itself is not toxic but once it reaches the brain it is converted into MPP<sup>+</sup> and is sucked up by dopamine-producing brain cells. There, it attacks the mitochondria – the tiny batteries that power our cells. With its energy supply cut off, the brain cell can no longer function.

### But do problems with mitochondria occur in 'real' Parkinson's?

A few years later, UK scientists examining postmortem brain tissue uncovered problems with mitochondria throughout the damaged and dying brain cells of those with Parkinson's.

Not only are mitochondria in affected cells less efficient at making energy – there are also problems with how these batteries are recycled and replaced.

Mitochondria are busy zipping around cells to deliver energy where it's needed – no mean feat in large and complex brain cells.

This demanding lifestyle means that, just like regular batteries, mitochondria wear out. And, when they do, they need to be recycled and replaced with healthy mitochondria.

But in Parkinson's this recycling process doesn't work properly and worn-out mitochondria end up sticking around in cells for too long.

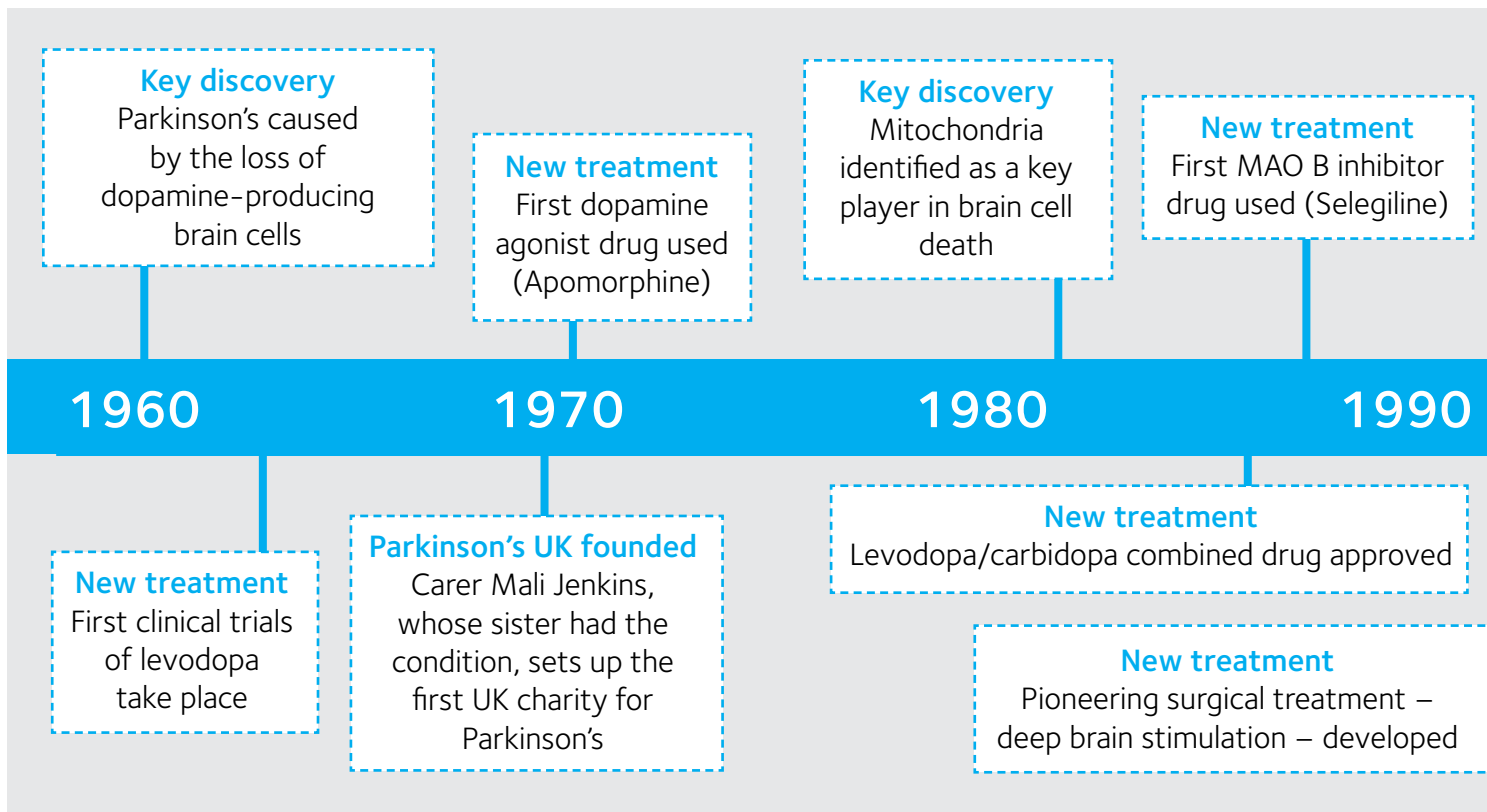
Old mitochondria are less efficient at producing energy and also produce noxious chemicals called free radicals that contribute to oxidative stress – a destructive state that can lead to cell death.

These landmark discoveries suggest that mitochondria lie at the heart of brain cell death in Parkinson's and researchers across the world are continuing to investigate their role.

### A problem protein

Lewy bodies – the spherical clumps found inside brain cells that are the trademark feature of Parkinson's – were first discovered by Dr Friedrich Lewy, a German-born neurologist, back in 1912.

## FEATURE



### What is alpha-synuclein and how is it involved in Parkinson's?

The alpha-synuclein protein is found in cells throughout the body and is found at particularly high levels inside brain cells. Exactly what it does inside cells is still a bit of a mystery, but it's believed to play a role in releasing neurotransmitters (like dopamine) from cells.

In its normal, healthy form, individual alpha-synuclein molecules float about harmlessly within the cell. But for some reason in Parkinson's, alpha-synuclein changes shape and starts to clump together forming sticky bundles called Lewy bodies.

However, it wasn't until over 80 years later that scientists really started to unravel the mysteries of their role in the condition. In 1997, researchers in Cambridge identified alpha-synuclein as the major protein that makes up Lewy bodies.

Abnormal, sticky forms of alpha-synuclein can cause problems with a range of important activities inside the cell, including recycling proteins, mitochondrial health and activity, and the release of dopamine.

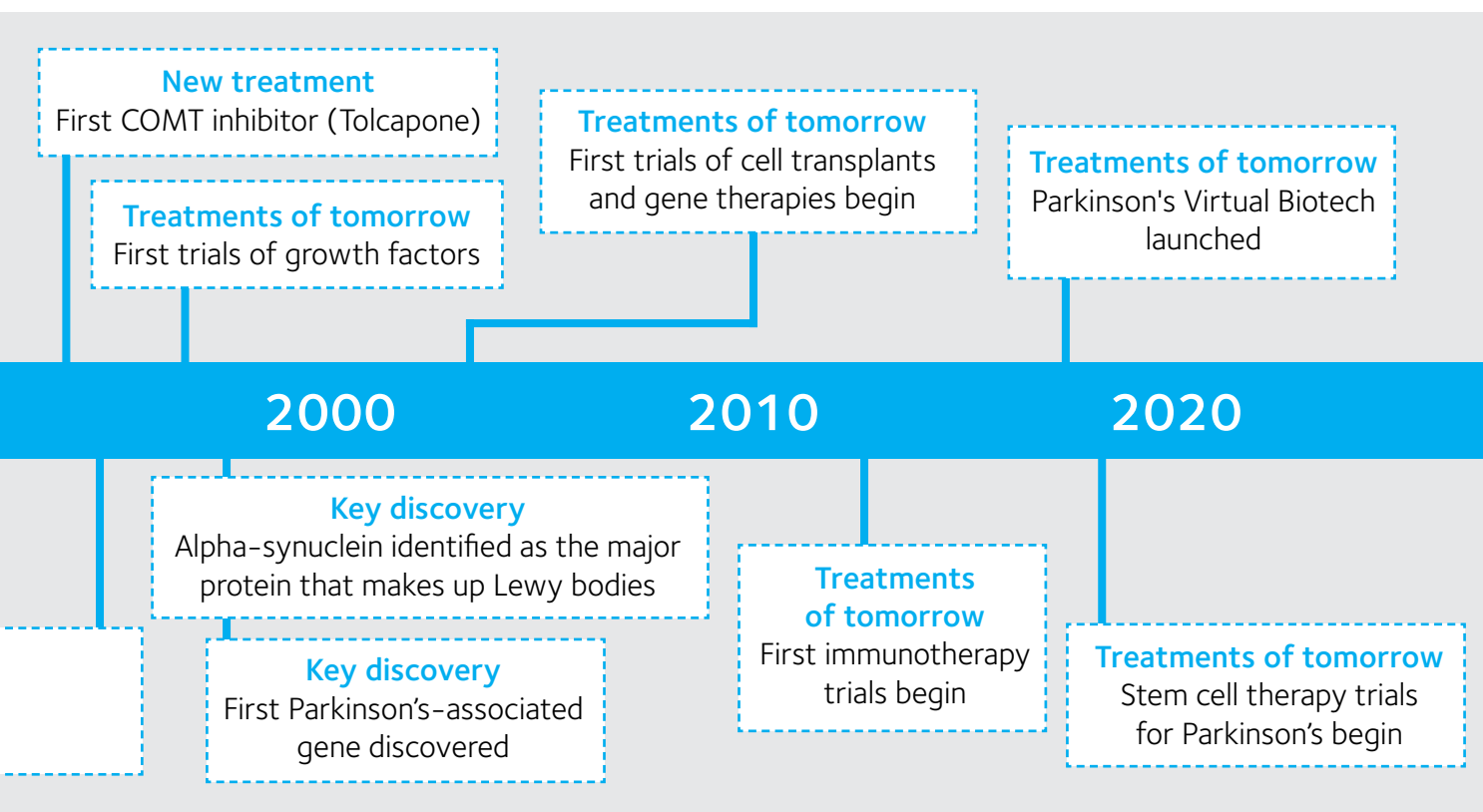
Experiments have also shown that alpha-synuclein can puncture and escape from damaged brain cells and enter neighbouring cells. Once there, it may then set in motion the chain of events that leads to cell death.

This domino effect is now widely believed to be responsible for the spread of Parkinson's throughout the brain and the progression of the condition itself. Emerging studies even suggest that the march of alpha-synuclein could begin far outside the brain – in the gut.

Sticky bundles of alpha-synuclein, like those found inside brain cells, can be present in the system of nerves that control the gastrointestinal tract and appendix. There is even evidence that people who have their appendix removed, or have a procedure to cut the vagus nerve (the highway between the gut and the brain), may be less likely to get Parkinson's.

As a result, alpha-synuclein is widely considered to be an





important target for treatments that may one day slow or even prevent Parkinson's.

### The genetic jigsaw

Our understanding of Parkinson's changed forever in 1997. Researchers studied an Italian family where many members were affected by the condition. They discovered a mutation in the gene that provides the instructions for making the alpha-synuclein protein. The finding that Parkinson's could be caused by a single genetic misprint was just the start of a whole new scientific frontier.

Further discoveries quickly followed, with researchers identifying changes in other genes including PINK1, Parkin and LRRK2 that could also cause rare inherited forms of the condition.

They also provided more evidence that genetics plays a role in the condition. Major advances in genetic sequencing and computer technology meant researchers were no longer restricted to studying the genetics of rare inherited forms of Parkinson's in isolated families.

Suddenly, huge collaborative studies involving DNA from thousands of people – called genome wide association studies – were not only possible, but affordable. They allowed scientists to investigate the whole genome and look for differences between people with and without the condition.

These groundbreaking studies identified a host of genetic changes that are more common, but do not cause the condition

directly. This means that the people who have them are only slightly more likely to develop Parkinson's than those who don't – often by 1-2% at the most.

The most exciting aspect of all these genetic discoveries is that they are steadily revealing a detailed and coherent picture of what causes the condition. Our genes provide the instruction manual for building and running our bodies. So, each new gene we identify adds a new piece to the puzzle and, gratifyingly, the pieces are beginning to slot neatly together. Many of the genes linked to Parkinson's so far are involved in – yep, you guessed it – mitochondria and protein recycling. Others have been linked to processes such as immunity and inflammation. All open up brand new avenues of research.



### Treatments of tomorrow

Thanks to this explosion in our understanding of the biological changes involved in Parkinson's, a whole host of new, experimental therapies are on the way. Some have already started being tested in people with the condition in early-stage clinical trials.

#### GROWTH FACTORS

Growth factors are naturally occurring molecules that support the development, growth and survival of our brains. Their extraordinary properties make them an exciting prospect for developing new treatments that could help repair damaged brain cells.

The first clinical trials of growth factor treatment in people with Parkinson's were carried out in the mid 1990s. Getting these large, complex molecules to the right part of the brain is a challenge. However, advances in technology and surgical techniques mean we could be close to solving these issues. Read more about our groundbreaking growth factor trial on page 18.

#### GENE THERAPIES

Gene therapies work by using genes as a treatment. The idea is to provide the genetic instructions cells need to change their fate. This could be by replacing a faulty gene with a functional one or by providing

the instructions the cell needs to make certain protective factors.

A number of different types of gene therapy are being explored for Parkinson's. Initial trials in the early 2000s showed promise and this continues to be an active area of development.

#### IMMUNOTHERAPIES

Immunotherapies take inspiration from our own immune system to create treatments. Scientists have created manmade antibodies in the lab that can recognise and remove sticky alpha-synuclein.

By targeting the rogue protein believed to be responsible for the spread of problems through the brain, they aim to stop the progression. Initial trials of the first immunotherapies started in 2012. You can read more about current clinical trials in this area on p26.

#### STEM CELLS

Stem cells offer what seems the simplest and most obvious solution. That's because they can be used to grow new, healthy brain cells that could be transplanted into the brain to replace the cells lost and damaged in Parkinson's. Initial transplantation trials, with foetal tissue, took place in the 1990s and produced mixed results. The first trials using stem cells have

got under way in the last couple of years.

#### PERSONALISED MEDICINE

Personalised medicine asks – rather than treating everyone with the same therapy, can we choose the right treatments for the right people to give ourselves a better chance of success?

Some of the most advanced examples for Parkinson's have been inspired by recent discoveries in genetics. New drugs called LRRK2 inhibitors have been developed to calm the overactivity of the LRRK2 protein. And these innovative new drugs will be tested in people with Parkinson's who carry a genetic misprint in the LRRK2 gene.

Finally, while huge strides forwards are being made in developing innovative new therapies for Parkinson's, we believe there are still many exciting opportunities that have yet to be explored.

That's why we launched the Parkinson's Virtual Biotech in 2017 – to seek out new and untapped ideas that could lead to transformational new treatments. We already have three exciting projects under way and aim to launch our first clinical trials through this exciting initiative in 2019. Read more on page 22. ■

# United in research

Research isn't driven just by scientists – people with and without Parkinson's can take part and help shape the future of research. Whether you're a friend, family member or carer, we are all united in driving research towards better treatments and a cure.

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**F**irst of all, let's meet Anne (pictured opposite) who cared for her mother who had Parkinson's and is working alongside researchers to shape their studies and priorities.

**Q** What was your motivation for getting involved with research?

I cared for my mother who had Parkinson's. I knew very little about Parkinson's when she was first diagnosed but soon realised its complexities.

By the time she died, I had a head full of information and experience – and I wanted to do something to make a difference to others. So, a few weeks after she died I joined the Research Support Network. Volunteering has been a way for me to give back to the charity that gave me so much support and information.

**Q** As someone without Parkinson's what can you offer?

As a bereaved carer I have knowledge of Parkinson's from diagnosis to the later stages. You can't learn that in any other way than by first-hand experience. Since my mother died, this is a way to fill the big hole of time, energy and emotion to make a difference for people still living with Parkinson's. I am not constrained by my physical health and can get involved without needing to consider my carer's role.

**Q** What research activities are you involved with?

I have been involved in reviewing grants, and have taken part in a variety of studies as a control – a person without the condition who may otherwise share similar features such as age and gender who can be used as a comparison.



I also got involved with the Patient and Public Involvement initiatives at Parkinson's UK. This volunteer opportunity, available through the Research Support Network, allows me to help shape research. And I have loved being in touch with researchers and talking with them to support their work.

We are not expected to know everything about Parkinson's – but to reflect and comment on projects based on our personal experience. Sometimes, what we know is unknown by the researchers. They have the scientific knowledge but not the practical, personal experience of life with Parkinson's.

**Q** Did you have any concerns about volunteering?

I was unsure what I would be able to offer. But I quickly realised that my input was valued for the insight into life with Parkinson's. Over the years, reading the documents and reviewing them has become much easier. I can choose what, when and how much I do.

There are currently 145,000 people in the UK living with Parkinson's, and by 2040 that number is predicted to double.

Research like the PREDICT PD study at University College Hospital is providing crucial insights into early risk factors.

And by studying those without the condition, it can also help us understand who within the general population might be more likely to develop Parkinson's.

The more we know about what the early stages of Parkinson's are, the closer we're getting to finding better treatments and a cure.

George, pictured below, talks to us about taking part in PREDICT PD.



**Q How did you hear about this study and why did you take part?**

I heard about PREDICT PD through my brother who has Parkinson's. I was simply motivated to contribute in the hope that people with Parkinson's will eventually benefit. When I think about the symptoms suffered by people like my brother, and the trivial inconvenience of participating in this study, I've no doubt that it's worthwhile to become involved.

**Q Did you have any concerns about taking part?**

There was nothing to worry about. Signing up to the study and the initial tasks were simple, fairly quick and non-invasive.

**Q What did it involve?**

Initially I did scratch-and-sniff and keyboard co-ordination exercises. A couple of years later, I gave consent to be visited and interviewed – which led to being invited to have a brain scan at University College Hospital.

While there, I was also asked whether some blood samples could be taken. This whole exercise took up about half a day and was no more concerning than a visit to the nurse for a flu jab.

Another couple of years on, and I agreed to wear a pair of electronic data loggers on my wrists for five days to track my arm movements. All relevant data for the study.

**Q Have you taken part in any other opportunities or will you in the future?**

I am not involved in any other research studies, but I'd always be happy to do so in the future.

### Spread the word

This study now needs 10,000 people without Parkinson's between the ages of 60–80 to do an online survey. Find out more at [predictpd.com](https://predictpd.com) ■



**We have a large Research Support Network, made up of a variety of people including those supporting a friend or a partner with Parkinson's.**

**Anyone can sign up to receive research updates and opportunities via email – and hear about research events happening across the country.**

**Let's hear from Steve, pictured right with his wife Nicola, who is an active member of our network and Co-chair of the Yorkshire Research Interest Group.**

**Q What involvement do you have with research?**

As well as being a Research Support Network member, I am an active member of a local research interest group where we meet and discuss Parkinson's research. I also take part in research studies. I will do anything, as long as it is not too invasive. I have been a control for various studies – from cognitive tests to more clinical tests looking at the electrical activity of my brain.

**Q What was your motivation to get involved?**

My partner has Parkinson's and we both have a scientific background – microbiology to be specific. I felt I could contribute both as a person with a scientific background and as a layperson.

**Q What has been your highlight this year in terms of an event/lecture/moment?**

My highlight is when researchers come to our local research interest group and deliver talks and updates and answer questions.

**Q Did you have any concerns with getting involved?**

I personally had no concerns about getting involved. But I understand that there are people who will do anything to contribute to research and others that just want to be kept updated. I respect all of these opinions.



**Q What have you gained from being involved?**

I am aware about, and up to date on, Parkinson's research and have learnt a lot about other people's feelings towards research. Research can be frustrating because of the long timescales involved in drug development, but by being connected with research I get to see the progress being made.

**Find out more**

Find out about the latest opportunities to get involved in research by joining the Research Support Network at [parkinsons.org.uk/rsn](https://parkinsons.org.uk/rsn) ■





# NEW

Find out more about our newest research projects, including understanding how genetics can influence progression and how a probiotic, originally developed for cows, could help manage symptoms.

# RESEARCH





## ① Understanding and predicting Parkinson's progression

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**Who?** Professor Huw Morris

**Where?** University College London

**What?** £99,169 over three years

Huw's team is interested in finding out how people's genetic makeup may influence the progression of Parkinson's. They will combine clinical and genetic data from several large research studies to create the largest dataset of Parkinson's progression to date. They also aim to predict Parkinson's progression on an individual level.

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"Predicting the progression will help us to test new medication in smaller, more uniform groups of people with Parkinson's who are likely to benefit from treatment. We hope this will be a step towards delivering personalised treatments."

**Professor Huw Morris**

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## ② Studying early brain changes in Parkinson's

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**Who?** Professor Nicola Pavese

**Where?** Newcastle University

**What?** £36,049 over two years

Using brain scans, we are now able to observe changes in the brain that happen in Parkinson's. However, by the time of diagnosis, many people will have had symptoms for at least several months, so we still don't know what changes happen in the earliest stages of the condition. This research is studying people with rapid eye movement (REM) sleep behaviour disorder – who are at high risk of developing Parkinson's – to identify areas of the brain that may be affected early on.

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"We believe that, through applying new imaging techniques, we have an exciting opportunity to identify markers to help early diagnosis of Parkinson's and identify targets for new treatments. Early brain changes could predict the likelihood of someone developing Parkinson's, the subtype and rate of progression. This could lead to better decisions regarding treatment and management strategies."

**Professor Nicola Pavese**

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### ③ Reducing anxiety in Parkinson's

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**Who?** Professor Richard Brown

**Where?** King's College London

**What?** £44,196 over one and a half years

Anxiety is a common symptom in Parkinson's and can have a severe impact on quality of life. When a person is anxious, they see the world in a more negative and threatening way, even when there is no danger. Richard and his team hope to explore the reason behind anxiety in Parkinson's. They also plan to test a technique to reduce anxiety using simple online exercises.

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"I believe that worry and anxiety can be the main reasons why people with Parkinson's start to restrict their activity. Reducing anxiety would allow people to continue with aspects of their life important for their mental and physical health. We will be recruiting anyone with Parkinson's who would like to take part – both worriers and non-worriers."

**Professor Richard Brown**

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### ④ Using nicotine or nicotine-like drugs to help restore memory and movement in Parkinson's

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**Who?** Dr Mohammed Shoaib

**Where?** Newcastle University

**What?** £240,589 over three years

Memory and thinking problems are a common symptom in Parkinson's. Previous work has shown that nicotine binds cells in the region of the brain responsible for memory and co-ordination of movement and may be able to improve symptoms in Parkinson's.

In this project, the team will investigate new compounds that have these positive, nicotine-like effects on brain cells, but without the side effects such as addiction. The nicotine-like compounds will be tested in the lab to see whether they reduce memory loss and movement disorders.

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"We know the activity of nerve cells controlling memory and movement is reduced in Parkinson's, and nicotine plays a protective role. I hope that this research using compounds based on nicotine could lead to new therapies, which will help people with Parkinson's who experience memory problems and dyskinesia."

**Dr Mohammed Shoaib**

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You can donate directly to this research project by giving to our Research Appeal. Find out more at [parkinsons.org.uk/nicotine](https://parkinsons.org.uk/nicotine)







Research like this only happens because of the participants. To find research projects in your area, visit [parkinsons.org.uk/takeparthub](https://parkinsons.org.uk/takeparthub)

## 5 A clinical trial of the probiotic Symprove

**Who?** Professor K Ray Chaudhuri

**Where?** King's College London

**What?** £38,563 over two years

Researchers have recently discovered that abnormal clumps of protein seen in Parkinson's, called Lewy bodies, can be found in the gut and may be able to spread from there to the brain.

Exactly how and why the clumps start to form is still much of a mystery, but some of the latest research highlights the importance of a healthy gut. So, rebuilding a healthy community of bacteria in the gut – in theory – may help to protect against Parkinson's and combat symptoms.

Symprove is an oral, drinkable probiotic that claims to be able to deliver live bacteria to the lower gut. The development of the treatment has a rather interesting back story. Back in 1986, Barry Smith was working in the farmyard. As an ex-military nurse, he was concerned about what might be in the food he was giving his cattle, and how antibiotics might be wiping out good bacteria and affecting their health. His solution was to develop clean food of germinated grain that he laced with live bacteria to help support a balanced, healthy gut in his livestock.

Today, the solution has been refined greatly since those early days. Symprove is now a unique, multi-strain, liquid probiotic that aims to get beneficial bacteria through the acidic stomach intact, so they can reach and thrive in the gut – and help improve gut health.

The research team has some evidence that Symprove may be able to reduce motor and non-motor symptoms in people with Parkinson's. Now they want to test its potential in a placebo-controlled trial. ■

“In our experience at the Parkinson's Centre at King's College Hospital, some people with Parkinson's have shown a considerable improvement in motor and non-motor aspects after taking Symprove for extended periods. The rationale behind this observation may rest with Symprove-induced improvement in gut microbiota. However, there are no studies that have addressed a possible beneficial effect of Symprove in a controlled study.

“Our project will be a world first – a UK-led, randomised, double-blind, placebo-controlled study comparing 60 people with Parkinson's with gastrointestinal dysfunction with either oral Symprove or a placebo for three months. We believe that the proposed intervention, if effective, has the potential to have a significant impact on the health and wellbeing of people with Parkinson's.”

**Professor K Ray Chaudhuri**





# The GDNF trial

Between 2012 and 2017, a pioneering clinical trials programme investigated whether delivering an experimental treatment called GDNF directly to the brain could slow, stop or reverse Parkinson's. The results are complex but offer hope that it may be possible to restore the cells damaged in Parkinson's.



## A brief history of GDNF

**G**DNF (or glial cell line-derived neurotrophic factor) is a special protein naturally produced inside the brain that supports the survival of many types of brain cells – including those cells lost in Parkinson's.

Lab studies have suggested that when GDNF is given to brain cells, it has the ability to encourage these cells to grow again and may be able to stop the progression of Parkinson's. This is something no current treatment can do. But, because GDNF is a large protein, it cannot reach the brain if taken as a pill or injected into a vein. This means it needs to be delivered directly to the brain using a surgical approach.

Previous attempts to get GDNF into the brain to treat Parkinson's included trials in the early 2000s in which participants had tubes, or catheters, implanted into their brains. This enabled GDNF to be slowly but constantly infused from a reservoir pump in participants' stomachs.

However, at the end of these trials, the GDNF treatment did not show any benefit over placebo treatment. One reason for this may have been the slow rate of the infusions, which allowed the GDNF to reach cells within only a few millimetres of the catheter tip. This would have meant the majority of the target brain area – a walnut-sized region called the putamen – would have been left untreated.

## The recent trial

To address this challenge, neurosurgeon Professor Steven Gill, in collaboration with engineering company Renishaw, designed a sophisticated new delivery system. Instead of a slow, constant flow of GDNF, the new system used a process called convection enhanced delivery (CED) to allow a full month's drug dose to be delivered in around two hours. The idea being that delivering GDNF at higher pressure would help it penetrate the brain tissue better.

Armed with this new purpose-built delivery system, at last the clinical trials were ready to commence.

The new studies were led by Dr Alan Whone and his team at North Bristol NHS Trust, and split into three distinct stages:

### STAGE 1

- Six participants were involved in an initial safety and feasibility study to ensure the surgery, device and drug were safe and acceptable to patients.

### STAGE 2

- 35 participants were recruited to the main study – with half receiving monthly infusions of GDNF and half receiving a placebo for nine months. Neither the participants or researchers knew who was receiving the active drug.

### STAGE 3

- Once participants had completed the first nine months, they were offered the opportunity to continue for a further nine months – where they knew they would receive GDNF.

## The results

The study was successfully completed in February 2017 and the full findings were published in February 2019.

### GDNF not significantly better than placebo

Early results from the first nine-month, double-blind phase of the trial, published in July 2017, were ultimately disappointing. Initial analysis suggested that the treatment is safe. But, while those who received GDNF improved more than the placebo group over the nine months, the difference between the two groups was too small to be conclusive.

However, the initial results only scratched the surface of the huge amount of information collected throughout the study, which has generated over 20,000 sheets of data.

And, despite the disappointment of this central result, when you look a little deeper there are some compelling signs that GDNF may have exciting beneficial effects.

### SOME OF THE AMAZING PARTICIPANTS

Darren  
Calder



Vicki  
Dillon



Andy  
Rollin



Jeff  
Tottle



### Brain scans reveal positive effects on damaged brain cells

All participants had specialised brain scans (called PET scans) before starting the trial and after nine months. Participants had an injection of a radioactive version of dopamine (18F-dopa) so that the PET scanner could then track the movement of dopamine through their brains.

After nine months, there was no change in the scans of those who received a placebo. However, the group who received GDNF showed an improvement of 100% in the targeted part of the putamen, and between 20-50% improvement in the rest of this brain area.

This finding shows that the device successfully delivered the drug to the target brain area and that GDNF was having a biological effect on cells.

This offers real hope that it may be possible to reawaken and restore damaged brain cells in

Parkinson's. But, to prove that GDNF is an effective treatment, these improvements in brain scans need to be reflected in measurable benefits for those living with the condition.

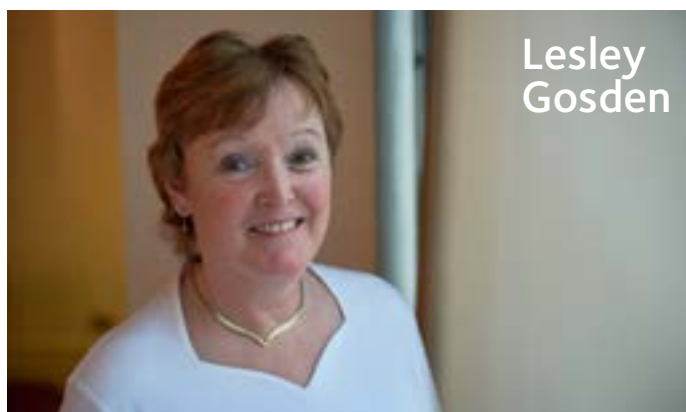
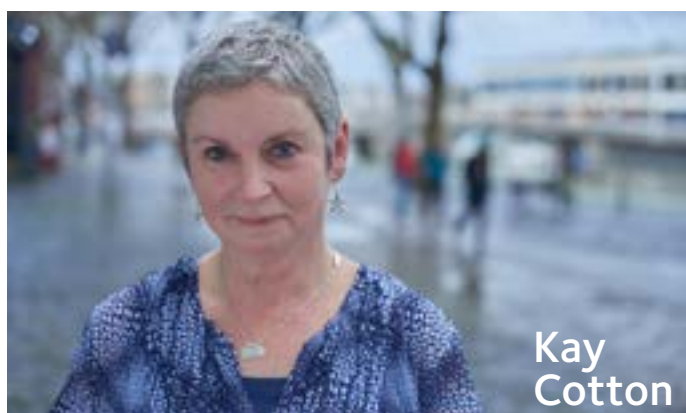
### Positive trends in favour of GDNF across almost all assessments

Those who received GDNF showed greater improvements than the placebo group in almost all clinical assessments throughout the initial nine-month, double-blind period.

These assessments included measuring movement symptoms, non-movement symptoms, ability to perform everyday activities, and how well regular Parkinson's medications were working.

The difference between the two groups was not big enough to be conclusive in any of these individual assessments. However, the fact that the GDNF group seemed to be doing better than the placebo group across the board is encouraging.





### **Substantial improvements in symptoms at 18 months**

After the initial nine months on either GDNF or a placebo, all 41 participants chose to continue on to the second 'open-label' phase of the study. In this phase, everyone received a further nine months on GDNF. By the end of this second nine-month period, both groups showed moderate -to-large improvements in their symptoms and ability to perform everyday activities, compared with their scores at the start of the studies.

The scale of these improvements is encouraging. But, because participants knew they were receiving GDNF in the second nine months, the results need to be treated with caution in case these improvements are due to the placebo effect.

### **What happens next?**

The major improvements seen in the brain scans, coupled with the benefits in symptoms after 18 months, offer hope. They suggest it may be possible to reawaken and restore the brain cells gradually

destroyed in the condition. But, while these results show promise that GDNF may have protective or even restorative effects, they are far from conclusive.

Taking GDNF forwards means planning a further clinical trial that definitively addresses the challenges and questions raised by the previous studies. There are lots of factors to consider – from what dose to use and how best to measure the effects of GDNF to assembling the right team to deliver it successfully. Finding the right route forward isn't guaranteed as we need a plan that works scientifically and ethically and is financially feasible, not least for any future trial participants.

### **FIND OUT MORE**

We hope there will be more news to share about further studies soon. Keep up to date with all the latest news and developments by joining our Research Support Network at [parkinsons.org.uk/rsn](https://parkinsons.org.uk/rsn) ■



# PIONEERING DRUG DISCOVERY

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Launched in March 2017, the Parkinson's Virtual Biotech is the drug development arm of Parkinson's UK. Its mission is to fast-track the most promising discoveries to rapidly develop promising treatments with the potential to transform life for people with the condition.

### How does it work?

Our Virtual Biotech works just like a regular biotech company to create and test new treatments. It's virtual because we do not have our own labs, equipment or an army of scientific staff. Instead, we collaborate with universities and companies who do have these facilities and resources.

This means we can use the latest technology, expertise and scientific knowledge but our virtual approach is very cost-effective and flexible.

And, unlike a commercial biotech, success for us is not about making a profit but delivering new and better treatments for people affected by Parkinson's within years rather than decades.

### **Project 1: Developing drugs to target oxidative stress**

Parkinson's UK investment to date:  
**£2million**

Oxidative stress is a toxic process believed to play a central role in the death of brain cells in Parkinson's. In March 2017, Parkinson's UK and the University of Sheffield formed the spin-out company Keapstone Therapeutics to develop new drugs that can protect these cells against oxidative stress.

The project capitalises on pioneering research led by Dr Richard Mead at the University of Sheffield involving a protein called Nrf2. Nrf2 is a key player in our cells' natural defences against oxidative stress. The problem is that another protein called KEAP1 can stick to Nrf2 and interfere with it doing its job.

The project has made progress in creating new molecules that can block KEAP1, leaving the Nrf2 protein free to defend the nerve cells against oxidative stress. The team is now conducting crucial further testing and development of these molecules.

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"Keapstone was the very first company we helped launch as part of the Parkinson's Virtual Biotech programme – to accelerate promising research and bring forward better treatments or a cure for Parkinson's.

"We are very pleased with Keapstone's progress so far and are hopeful these molecules could be the key in creating treatments that could slow or even stop the progression of Parkinson's."

**Arthur Roach, Director of Research at Parkinson's UK**

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### **Project 2: Developing a new drug to treat dyskinesia**

Parkinson's UK investment to date:  
**£780,000**

Levodopa, which is used to treat Parkinson's, can have severe side effects. One of the most debilitating side effects is dyskinesia – involuntary jerky or twitchy movements that affect various parts of the body. A new treatment to stop this distressing and debilitating side effect would be transformational for people living with Parkinson's.

Launched at the start of 2018, this project is a nine-month collaboration with US company Neurolix – developing a promising drug (NLX-112) to combat dyskinesia. This project is at a much later developmental stage than the Keystone project, as the drug has already been tested in people in phase II clinical trials as a potential pain treatment. Although NLX-112 was not effective for pain, lab studies have demonstrated its potential for treating dyskinesia.

Our investment has funded the vital final stages of research required before NLX-112 can move forward into clinical trials. This work is now complete and Neurolix has received approval to go ahead with clinical trials in people with Parkinson's who experience dyskinesia. We hope these will start before the end of 2019.

“It's incredibly exhausting – to be constantly writhing around – and it can be very violent. Just last year, I ripped a muscle in my shoulder because of a particularly violent jerk of my arm. It was so painful and took a very long time to heal. Being able to take something that could give me back control of my body would be amazing – a game-changer.”  
**Matt, who experiences dyskinesia**

### **Project 3: Creating new drugs to improve symptoms and slow Parkinson's**

Parkinson's UK investment to date:  
**£2.5million**

Our third Virtual Biotech project was announced in March 2018.

We're collaborating with one of the UK's leading contract research companies, Selcia, to create new molecules that can increase the activity of a selection of genes.

Dialling up the activity of these genes has the potential to increase dopamine production and boost the production of protective proteins to slow or halt the progressive damage and loss of precious brain cells.

This means that, if we're successful, it could lead to a unique treatment that not only improves symptoms but can also slow, stop or even reverse the underlying condition.

“Although this project only got started just over a year ago, we've already produced new drug-like molecules that can turn on the target genes and are able to get into the brain. This can be a stumbling block for many new drugs. We have recently invested a further £1.48million to take these exciting molecules forwards and closer to benefitting people with Parkinson's.”

**Richard Morphy, Drug Discovery Manager, Parkinson's UK**



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## What to look out for in 2019

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We're keen to continue to grow and expand the Parkinson's Virtual Biotech. And we've set ourselves the ambitious target of raising and investing a further £5million to drive forwards even more treatments in 2019.

### More projects, including our first clinical trial

Ultimately, to deliver effective new treatments we need to create a broad portfolio of projects. That will give us the best chance of success, especially if we address the condition and symptoms from a range of angles.

In 2019, we'll continue to search out and support more projects, including new and experimental therapies ready to be tested

in clinical trials, to take a step closer to helping people with the condition.

For example, we are in the final stages of planning for our fourth project and our first clinical trial of a promising new therapy for Parkinson's. We hope to launch the study and begin recruiting for participants in summer 2019 – so watch this space!

### Using artificial intelligence to identify potential new treatments

In 2018, we joined forces with The Cure Parkinson's Trust to win a prestigious new partnership with leading British artificial intelligence company BenevolentAI.

This year, we'll be working together to use artificial intelligence (AI) to unlock the masses of existing research data to identify currently available medicines that could be repurposed to address Parkinson's.

It could also lead us to uncover fresh opportunities for developing new treatments.

Any promising new opportunities uncovered through this pioneering approach will be rapidly taken forward for further development and testing through the Parkinson's Virtual Biotech. ■





# Trials to treatments: targeting alpha- synuclein

Today, there are numerous clinical trials targeting alpha-synuclein that aim to protect brain cells and slow down Parkinson's. We take a look at how they work and where the research is currently at.

Despite decades of research, we still have an incomplete understanding of a mysterious protein that plays an important role in Parkinson's – called alpha-synuclein. When it's working properly, it is believed to play a role in helping brain cells to send messages, but it may be involved in several other activities too. However, when it's not working properly, it can cause problems inside these cells.

### When folding goes wrong

Proteins carry out all the jobs that happen inside our cells. There are lots of different types of proteins with many different roles – such as enzymes that build and break down other molecules or hormones that help to send messages.

To function properly, proteins have to be the correct shape and this depends on them folding properly. You could think of this like a paper aeroplane – when the paper is folded in a specific way it forms the correct shape needed to fly.

Misfolded proteins can clog up cells, stopping them from working, so it is important that cells remove them and prevent this waste building up. But in conditions like Alzheimer's and Parkinson's we know that misfolded proteins become a big problem for brain cells.

In Parkinson's, the main protein that misfolds is alpha-synuclein. When the protein misfolds, sticky clumps called Lewy bodies start to form. The misfolded alpha-synuclein causes a secondary problem by triggering more of the protein to misfold. This adds to the build-up

of waste inside cells, increasing its toxic effect and eventually leading to the loss of brain cells.

### Stopping the spread of alpha-synuclein

Research has suggested that alpha-synuclein may be important in the spread of problems from cell to cell inside the brain.

But the brain isn't the only place where the spread of toxic alpha-synuclein may be happening. Recent research has found misfolded alpha-synuclein in the gut and appendix of those in the early stages of Parkinson's.

This finding has led some researchers to believe that Parkinson's may, at least for some, start in the gut and travel to the brain. So targeting this protein could slow down Parkinson's and may even be able to stop the clumps of alpha-synuclein from getting to the brain.

Research teams worldwide are working to develop new treatments – including vaccines and drug therapies – that could halt the spread of alpha-synuclein or stop it from forming clumps and clogging up cells.

### Trials of vaccines against alpha-synuclein

One way alpha-synuclein can be targeted is by developing 'passive' vaccines that contain an antibody designed specifically to stick to clumps of alpha-synuclein. The hope is this will prevent the clumps from spreading and having toxic effects on brain cells.

A number of biotech companies are currently working on developing antibody vaccines – the BII054, Prasinezumab and MEDI1341 vaccines are currently progressing through early phase I and II clinical trials.

In addition to these passive vaccines, there is also a trial of an 'active' vaccine for Parkinson's being carried out by Austria-based biotech Affris. Active vaccinations trigger our own immune system and, as such, could have longer-lasting effects.

A phase I clinical trial of the AFFITOPE PD01A vaccine has been completed. Results suggested the vaccine was safe and caused the immune system to make its own antibodies targeting alpha-synuclein. Now plans are in place for a larger phase II clinical trial.

### **Trials of potential drugs targeting alpha-synuclein**

As well as vaccines, researchers have been developing new drugs that may stop alpha-synuclein having toxic effects on brain cells. Drugs like phenylbutyrate-triglyceride (PBT) and NPT 200-11 have shown potential to remove toxic alpha-synuclein from the brain and stop the formation of clumps.

Other drugs that were originally designed for alternative purposes – known as repurposed medications – are also being investigated for their anti-alpha-synuclein potential. Nilotinib (a cancer drug) and ambroxal (cough medicine) are currently going through phase II trials for Parkinson's.

### **Targeting alpha-synuclein outside the brain**

In their efforts to tackle alpha-synuclein, researchers are also looking at other areas of the body where this protein may be causing problems. The US biotech company Enterin has developed ENT-01 to target the removal of alpha-synuclein from the gut. They hope this will help constipation, disturbed sleep and even hallucinations.

### **Learnings from Alzheimer's**

Targeting alpha-synuclein offers a promising way to stop the toxic effects of this protein in Parkinson's. But, before we see these treatments being made available, more trials will need to be done to see the long-term safety and impact on symptoms and progression.

And when it comes to targeting troublesome proteins the story doesn't end there. While most research has focused on alpha-synuclein, there are other proteins involved in Parkinson's that need to fold properly to protect brain cells. This is also the case in Alzheimer's.

One drug treatment – LMTX – is currently being studied for its potential for Alzheimer's. While results from clinical trials in Alzheimer's were mixed, in 2018 researchers discovered the active component of LMTX had potentially positive implications for Parkinson's. It was shown in the lab to reduce clumps of alpha-synuclein, leading to improved movement and decreased anxiety traits in mice.

This will need to be tested in people and there have yet to be reports of a clinical trial. However, we already know a lot about the safety of this drug from the Alzheimer's trial, which could speed up future trials.

### **Towards new treatments for Parkinson's**

It is too early to tell if any of these treatments really can slow Parkinson's, or improve symptoms. But, as alpha-synuclein clumps can be found inside the brains of every person with the condition, targeting this protein has real potential for helping millions of people worldwide.

Clinical trials are expected to continue in this area and, while they are ongoing, the next generation of treatments is already being produced. Researchers in labs around the world continue to develop new ideas about ways to target this problematic protein. And – one thing is for sure – with every passing day we move closer to a therapy that can stop the spread of Parkinson's. ■





# POSTURE AND PARKINSON'S: ASK THE EXPERT

Many people experience changes in their posture during the course of Parkinson's. For some, changes may be subtle – such as developing a slight stoop – but for others they become pronounced, forcing them into extremely painful positions. Even subtle changes in posture can cause discomfort, make it harder to walk and affect balance. For those who develop more severe postural problems, the impact on everyday life can be profound. It can cause breathing difficulties, pain that most commonly affects the arms, legs, joints and back, falls, and severe difficulties with walking and mobility.

## ASK THE EXPERT

**P**rofessor Bettina Debu is from the Institute of Neuroscience at the University of Grenoble Alpes. She is trained in both neuroscience and physical education, with her research interests focused on postural and movement control. Bettina is a leading expert in posture and gait in Parkinson's. We're delighted she's sharing her knowledge about postural changes in Parkinson's, highlighting which questions still need to be answered.

### **Q** What postural problems can affect people with Parkinson's?

It's very common for people with Parkinson's to experience changes in posture that may not be visible at first but will affect balance as the condition progresses.

We're unaware of it but we are constantly making tiny, unconscious adjustments to our posture to keep ourselves balanced and our centre of gravity in the right place.

This control of our posture significantly depends upon the brainstem – a part of the brain that can be affected in the later stages of Parkinson's.

When the brainstem is no longer able to do this automatically, people have to start to control their posture and balance consciously. So often people with Parkinson's may find they actually need to concentrate on these things.

People with Parkinson's can also experience more serious postural problems that cause visible physical deformities.

The two most common issues are:

- 1. Camptocormia** – also known as 'bent spine syndrome', which is when people become very severely bent forward.
- 2. Pisa syndrome** – named after the famous leaning tower, in which people lean over to one side.

With both, the problems are present when upright and are eased or can even completely disappear when lying down. It's not clear exactly how common these are in Parkinson's but the impact on quality of life can be profound. These postural deformities can be extremely painful and can interfere with simple daily activities. Those with camptocormia are so bent over that it is difficult for them to look ahead when they're walking, and the effort in doing so is very tiring. People with these severe postural changes can also often feel very isolated and stigmatised.

### **Q** Why do some people develop severe postural problems?

The reasons why some people experience severe postural



problems in Parkinson's are very poorly understood. People who have a history of back problems or injuries do seem to be at higher risk but, other than that, it is very difficult to predict.

In some cases, taking certain medications – including antipsychotics or anti-Parkinson's medications – or surgical treatments such as deep brain stimulation can trigger the sudden appearance, or worsening, of postural problems. In these cases, simply adjusting medication, or the level of stimulation being delivered, is often enough to reverse or ease the problems.

However, for most people the development of postural problems is gradual and there is no clear, single cause. Research suggests that there may be a number of complex and connected factors involved.

### Living with posture problems

Jenny is 72 and has been living with Parkinson's for 10 years.

JENNY:

I have always had very rounded shoulders, which I think may have been caused by my being left-handed as it meant that I had real problems writing at school and had to adopt odd positions. My neck and shoulders do get very painful, which I think is partly due to my poor posture.

The thing that I find most helpful is exercise. I used to practise Pilates and it has helped my posture and core strength enormously. Unfortunately, I've had to give it up since I got my apomorphine pump because it became too difficult to do all the Pilates movements without worrying about disturbing the pump and tubes. But I still make sure I exercise regularly.

These may involve:

#### 1. Changes in muscle tone

Some muscles may become overactive, other muscles may become weakened, or a combination of both. If these changes cause the muscles supporting the spine and trunk to become imbalanced, it may lead to the emergence of severe postural changes.

Interestingly, although you would probably expect people to lean towards the side of the body that is more severely affected by their Parkinson's symptoms, this is not always the case. Studies that have looked at Pisa syndrome have found that there is no clear pattern in which way people with Parkinson's lean.

#### 2. Changes in 'proprioception'

Proprioception is the sense through which we perceive the position and movement of our bodies. Body schema perception enables us to orient and adjust our vertical position based on sensory information.

Some studies suggest that Parkinson's may interfere with how the brain processes the messages it receives from muscles and joints about the position of the body. This may result in people no longer feeling that they are leaning or bending, as well as leading to changes in muscle tone.

Other researchers have suggested Pisa syndrome may be caused by a shift in the visual perception of verticality, meaning patients can no longer tell when an object is vertical.

They would then align their body to the shifted visual vertical and feel they are standing upright. Indeed, in Pisa syndrome people quite often don't realise they are leaning over, and it's actually their partner who first notices the problem.

However, studies we've conducted suggest that these changes in the perception of what is vertical may actually be the brain adapting to people's

new position, rather than causing it.

We simply do not know enough about the root causes of postural problems. With both muscular changes and brain changes, it's very difficult to know whether they are causing the problems, or are actually an effect of, or reaction to, the original cause.

Either way, it's likely there are a number of factors involved and that these may be different from person to person.

#### Q How are postural problems treated?

Treating postural problems is complex but there are ways to both alleviate the pain that many people experience and to try and correct the postural problems.

##### 1. Drug treatments

There is a range of drug treatments available:

- Adjusting Parkinson's medication may be helpful if

the postural problems worsen when drugs start wearing off.

- Injections of muscle relaxants (such as Botox) can be used to ease tense muscles to improve posture.
- Injections of anaesthetic drugs into the muscles can provide effective pain relief.

### 2. Surgery

There is now also a growing body of evidence that deep brain stimulation (DBS) may be beneficial. A recent study which looked at cases in Germany found that DBS was effective in 60% of camptocormia cases, and other studies have suggested it may also be beneficial for Pisa syndrome.

These findings offer additional evidence that changes in the brain may play a crucial role in causing postural changes. But it appears that surgical approaches need to be used early – within two years of the onset of severe postural changes – to have these benefits.

### 3. Exercise

Exercise and physical therapy are very important avenues for improving postural problems and should be undertaken as early as possible. Ideally, people with Parkinson's should start exercising (or continue if they are already active) from diagnosis onwards to delay or even prevent the onset of postural problems.

Although studies have tended to be small and short term, they do suggest that 2–3 hours of weekly exercise can significantly improve posture and pain.

It also seems that, as well as doing exercises to improve general fitness, activities that really focus on balance, posture and proprioception may be particularly helpful for people with postural problems. These include dance, tai chi and Pilates. Many of these activities can be adapted so that people can do them when they are seated or even lying down.

However, the most important thing is that people continue to

## Living with posture problems

**Paul is from Huddersfield, and is married to Silvia, who also has Parkinson's. They have four children aged between 8 and 14.**

**PAUL:**

I was diagnosed around four years ago and, although I only realised it later, changes in my posture were one of the first signs of the condition. Now, when I look at photos from before my diagnosis, I can clearly see the changes but I was totally unaware of them at the time. My main problem is leaning forwards when I'm walking and it is getting more pronounced. I am conscious of it so I do my best to correct it. I am waiting to see a physio and hope they'll be able to give me some tips and exercises that I can do to improve my posture.

I'd say that my posture is the thing about my condition that bothers me most regularly. I don't like looking like a stooped old man and I think it affects my ability to do simple things like get up from the sofa. I went to my children's school recently and had to sit in a really low seat when I was speaking to one of the teachers. I really struggled to stand up afterwards, which was embarrassing and frustrating.





exercise regularly to get the most out of it. That means it's vital people try out different types of exercise and find something they really enjoy and can stick to. Physiotherapy can also be really helpful for providing more one-to-one tailored exercises that specifically target areas the individual can focus on.

#### 4. Other approaches

There is also research under way that looks at whether changing the proprioceptive feedback that the brain receives from the muscles and joints can ease postural problems.

One of the simplest examples is when people with camptocormia wear higher heels, or even just stand with their heels on a thick

book for a while, it can help them to stand up straighter. Unfortunately, it seems this simple trick only provides temporary relief – if people wear raised heels all the time, it seems to wear off so it's not a long-term solution. However, we do know that some people use this technique when they know they want to be able to be more upright and find it helpful.

#### **Q** What's next for postural research?

As with so many things, the key to improving and even reversing postural problems is early recognition and management. However, diagnosing these problems early isn't happening and one of the major reasons is

we do not have an international consensus on diagnostic criteria.

Developing a shared, agreed understanding of when and how to diagnose and quantify these issues is the most urgent priority for improving management, care and outcomes for people with Parkinson's.

Alongside this, we also need more research on postural problems and how they develop and change over time, so that we can finally pin down the root causes of these issues.

And finally, of course, we need better, larger studies to develop and assess the effectiveness of treatments and management strategies. ■

# RESEARCH RESULTS

## Stopping the build-up of alpha-synuclein

**A**lpha-synuclein is one of the main proteins found inside Lewy bodies – the sticky clumps of proteins that appear inside the brain cells of everyone with Parkinson's. Finding ways to reduce the levels of this potentially toxic protein could be the key to finding new treatments and stopping the loss of precious brain cells.

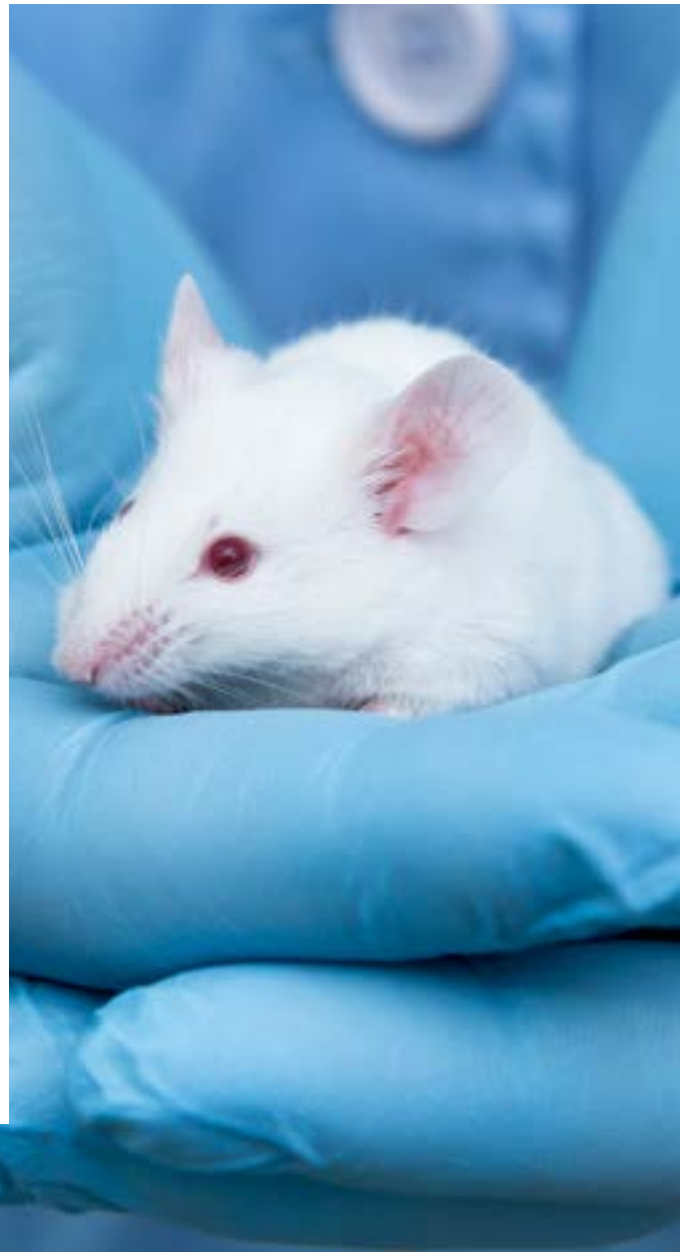
Researchers at University College London (UCL), led by Professor Anthony Schapira, have discovered that a drug known to improve the function of a protein called GCase may also be able to reduce the amount of alpha-synuclein in brain cells.

Mutations in the GBA1 gene, which makes GCase, are the greatest known genetic risk factor for developing Parkinson's. The activity of GCase is reduced in people with Parkinson's, both with and without GBA1 mutations – suggesting it plays a key role in the condition.

Using both nerve cells grown in a dish and mice with GBA1 mutations, the UCL team discovered that loss of GCase affects the removal of alpha-synuclein. They also found that a cough medicine drug called ambroxol could boost GCase activity, which in turn reduced alpha-synuclein levels in the mouse brain cells.

"If ambroxol can be shown to increase GCase activity in the brains of people with Parkinson's, like it does in mice brains, the drug could be a possible treatment. A small clinical trial is under way to investigate whether ambroxol can get into the brains of humans and affect GCase activity."

**Professor Anthony Schapira**





## Stem cell therapies: targeting non-motor symptoms

Cell transplants have the potential to reverse the damage that occurs inside the brain in Parkinson's. The first stem cell transplant trials in people with Parkinson's are now under way. However, there are still many questions around how this therapy works and if it can also help address the many non-motor symptoms of the condition.

The team in Cardiff, led by Dr Mariah Lelos, is transplanting new dopamine-producing cells into the brains of rats with Parkinson's-like symptoms to see if they can improve movement symptoms and non-motor symptoms. Non-motor symptoms include problems with thinking, memory, anxiety, and smell.

The research project will continue until 2020. But one surprising finding so far is that transplanting dopamine-producing cells may cause dyskinesia – a side effect that can be experienced by those taking Parkinson's medication. The team has identified that inflammation in the brain is the likely cause of this side effect.

“My research aims to understand how this stem cell therapy works and to optimise the therapy to target a wider range of symptoms.

“I am also seeking to eliminate any potential side effects, and develop methods to control the transplanted cells using drugs and to avoid the need for strong immune-suppressant drugs.

“There is still considerable work to be undertaken to ensure people with Parkinson's get the most comprehensive, optimised therapy possible, bringing the maximum benefit with the fewest side effects.

“This could be life changing if people with Parkinson's could have a treatment that allows them to stop taking dopamine-based drugs and to experience long-term improvements in motor and non-motor symptoms.”

**Dr Mariah Lelos**



### Understanding PINK1 in Parkinson's

We know that the PINK1 protein plays an important role in protecting brain cells against stress. Researchers believe drugs that switch the protein back on could protect cells in Parkinson's. But one of the challenges in developing these treatments comes from the fact that we cannot measure the activity of PINK1.

Inherited changes in the PINK1 gene – that stop the PINK1 protein from working properly – were first linked to the condition by Parkinson's UK researchers in 2004. They are now known to be one of the most common causes of early-onset Parkinson's.

In this project, Dr Miratul Muqit's team built on a recent discovery – that the PINK1 protein interacts with one or more of a group of proteins called Rabs. By figuring out which Rabs are regulated by PINK1, they have been able to learn more about the role of PINK1 in Parkinson's and have found a way to measure its activity.

This finding could provide a new biomarker for a genetic form of Parkinson's and allow researchers to develop new treatments that target Rab.

“We have now developed a new antibody for a Rab protein that will be an important tool to measure PINK1 activity in Parkinson's. We have also discovered an interplay between PINK1 and LRRK2 – another gene involved in Parkinson's. This suggests that treatments directed at activating PINK1 may also benefit people with mutations in LRRK2.”

**Dr Miratul Muqit**

### Developing better brain scans for Parkinson's

There is currently no definitive diagnostic test for Parkinson's and receiving a diagnosis often takes some time. Research suggests that magnetic resonance imaging (MRI) – a type of brain scan – may help doctors to make the diagnosis quicker and more confidently. And MRI could help researchers to test new treatments that aim to slow Parkinson's.

A team in Nottingham, led by Professor Dorothee Auer, looked for changes that happen in the brain during the early stages of Parkinson's to investigate if brain scans could be used as a reliable way to detect the condition. By scanning the brains of 125 people who took part in the study, they discovered two changes, or biomarkers, that could be used to diagnose Parkinson's. As well as improving diagnosis, it's hoped that these findings could also speed up developing new treatments for Parkinson's.

“An image similar in shape to a swallow's tail can be seen on MRI scans in the healthy brain. We have confirmed that the loss of the tail is a telltale sign of Parkinson's. A second promising MRI biomarker assesses the pigmentation of the dopamine-producing cells in the brainstem – the loss of which is another sign of Parkinson's.

“With the ability to observe the changes over time, our MRI measures will support studies into how lifestyle and other factors can affect Parkinson's. Importantly, our research will also accelerate the development of new treatments by providing novel objective outcome measures for clinical trials.”

**Professor Dorothee Auer**

# JOIN US AT A RESEARCH EVENT

Bringing research closer to you



We offer many opportunities to meet and engage with researchers, and to hear about the latest developments in Parkinson's research. Below are just a few of the events coming up this year.

### Research events in 2019

1. [Research talk](#)  
Redditch and Bromsgrove Branch  
22 May 2019
2. [Research event](#)  
Kendal South Lakes • 12 June 2019
3. [Research talk](#)  
Kensington and Chelsea Support Group  
20 June 2019
4. [East of England research event](#)  
Cambridge • September 2019
5. [South-west England research event](#)  
Plymouth • 30 September 2019
6. [Research Support Network conference and livestream](#)  
Solihull • 16 November 2019
7. [Research lecture and livestream](#)  
London • November 2019
8. [Edinburgh lecture](#)  
Edinburgh • November 2019

For the latest events, please check the research events page on our website at [parkinsons.org.uk/researchevents](https://parkinsons.org.uk/researchevents). Or join our Research Support Network at [parkinsons.org.uk/rsn](https://parkinsons.org.uk/rsn) and we'll email you when events are happening in your area.

### Discover more on YouTube

In addition to our events, Parkinson's UK also has an online video channel where you can learn more about Parkinson's research – with videos filmed in the labs of some of the world's leading researchers. Discover more at [youtube.com/ParkinsonsUK](https://youtube.com/ParkinsonsUK) ■

# THE JOURNEY TO DISCOVERY – ONE BRAIN AT A TIME

The Parkinson's UK Brain Bank is a vital resource in the search for new and better treatments. Katherine Fletcher, Research Communications Officer at Parkinson's UK met with Sue Fordham and Ville Pitkaaho from the Brain Bank to learn more.

**"A**s a relatively new person to Parkinson's UK, I went on my first trip to the Brain Bank – part of Imperial College London at Hammersmith Hospital. This is where people can donate their brains to help Parkinson's research.

Both people with and without Parkinson's can sign up to donate their brains. The precious tissue is supplied to researchers all over the world and is used to help find a cure and improve life for everyone affected by Parkinson's.

I didn't know what to expect from my visit, but I was welcomed by Sue, the Brain Bank's administrator, and Ville, a research nurse. I asked them to explain to me the journey of a brain donated to research.

### Where does the journey begin?

I discovered that brain donation starts with people

seeking information about leaving their brains to Parkinson's research and having discussions with the people around them.

Sue says: "It is crucial that family, friends and GPs are on board to ensure people's wishes to be donors can be upheld in the future.

"If this is something that someone wants to do, the next stage is to fill in the consent forms. Then a Brain Bank donor card is sent out and the donor keeps it with them.

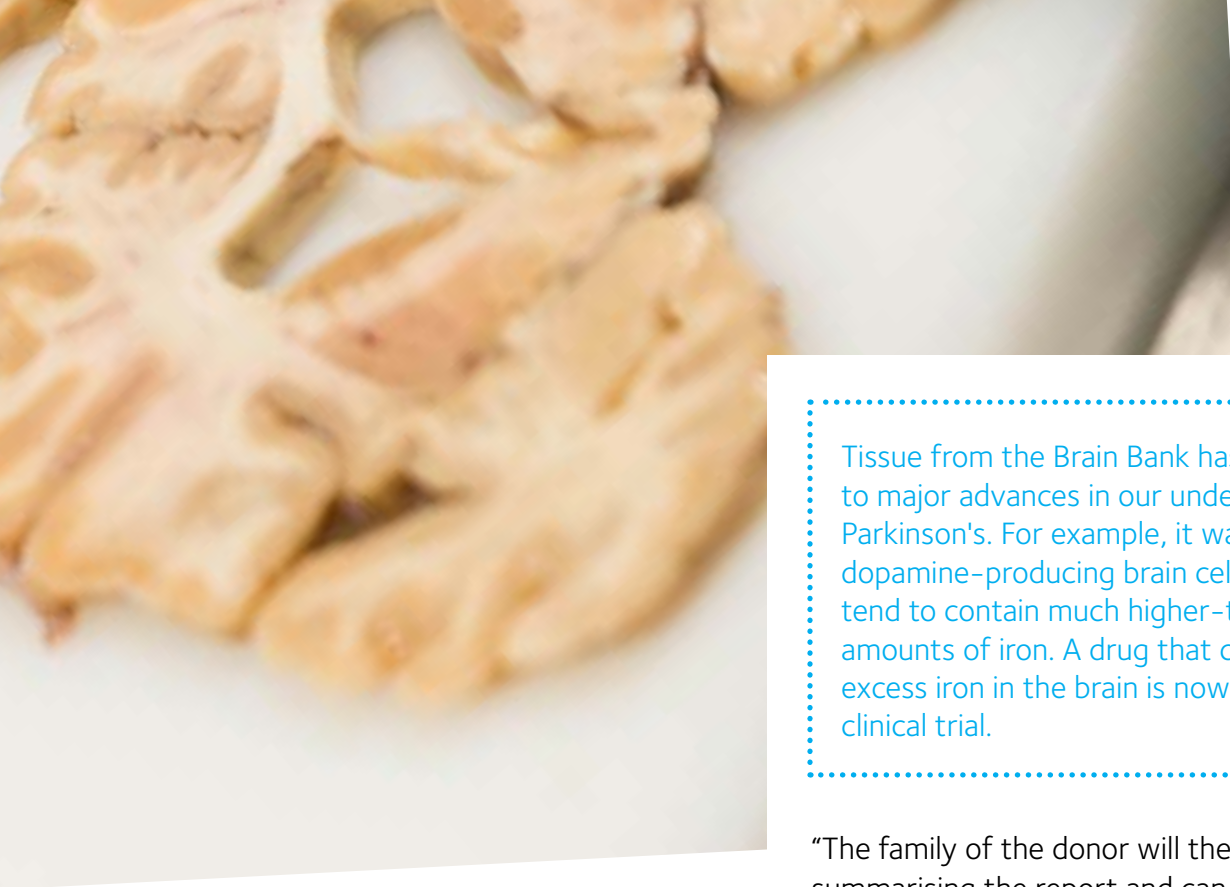
"This decision is not final and people can change their minds. The main reason people change their minds is due to family concerns, so I always encourage anyone to ring me and chat through these decisions."

### What happens when a donor dies?

When a donor passes away, Sue and Ville advise that a close family member or friend should call the emergency number provided as soon as possible.

This process needs to be quick as it is essential that the donor brain reaches the Brain Bank no more than 24-48 hours after death.





Tissue from the Brain Bank has already led to major advances in our understanding of Parkinson's. For example, it was found that dopamine-producing brain cells in Parkinson's tend to contain much higher-than-usual amounts of iron. A drug that can remove excess iron in the brain is now in a Europe-wide clinical trial.

Sue says: "During this tricky time, the Brain Bank team does everything they can to make the donation process as smooth as possible.

"We encourage donors' families to contact us if they have any questions before or after their loved one passes away.

"Please be assured that brain retrieval does not disfigure the donor or delay a funeral. The brain is usually collected from the hospital mortuary by one of our technicians."

### What happens to the brain when it arrives at the Brain Bank?

Ville says: "The brain is checked for its external appearance and then photographed. One brain hemisphere is then suspended in formalin and the other is frozen at  $-85^{\circ}\text{C}$ . These methods allow the brain to be preserved for decades to be used by researchers around the world for investigation.

"Regions of interest of the donated brain are prepared on microscope slides for a neuropathologist to confirm diagnosis and form a detailed report. The report includes information such as the clinical history of the donor, weight of the brain and imaging findings.

"The family of the donor will then receive a letter summarising the report and can ring to discuss this and request the full scientific report if they wish."

### So at this stage the researchers can request brain tissue?

I learnt that researchers fill in a request form expressing their wishes to use brain tissue to aid their research. This request is discussed by a panel of scientists and laypeople to decide if the research is ethically and scientifically worthy of using the tissue from the Brain Bank.

The brain tissue that is given to the researchers is anonymous.

Ville says: "Brain tissue mainly goes to researchers within the UK and Europe but some brain tissue goes all over the world, for instance Australia or Japan."

So one brain can have a far-reaching impact on research that may lead to better treatments and a cure for Parkinson's. ”

### Find out more

Find out more about the Parkinson's UK Brain Bank and how to register at [parkinsons.org.uk/brainbank](https://parkinsons.org.uk/brainbank). Or contact the Brain Bank directly at [brainbank@imperial.ac.uk](mailto:brainbank@imperial.ac.uk) or on 020 7594 9732. ■

Every hour, two people in the UK are told they have Parkinson's – a brain condition that turns lives upside down, leaving a future full of uncertainty.

Parkinson's UK is here to make sure people have whatever they need to take back control – from information to inspiration.

We want everyone to get the best health and social care. So we bring professionals together to drive improvements that enable people to live life to the full.

Ultimately, we want to end Parkinson's. That's why we inspire and support the international research community to develop life-changing treatments, faster. And we won't stop until we find a cure.

**Together we can bring forward the day  
when no one fears Parkinson's.**

Parkinson's UK  
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London SW1V 1EJ

Free confidential helpline **0808 800 0303**  
(Monday to Friday 9am–7pm,  
Saturday 10am–2pm). Interpreting available.  
NGT Relay **18001 0808 800 0303**  
(for textphone users only)

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