Why are researchers interested in gut bacteria?
Hello and welcome to this issue of Progress magazine. I’m delighted to be introducing this issue because in 2020 we’re celebrating 10 years of the Parkinson’s UK Research Support Network – a community of almost 6,000 people who are passionate and active supporters of Parkinson’s research. It’s a community of which I’m proud to be a member.

My wife, Laurel, was diagnosed with Parkinson’s in 2014 at the age of 57. Over the first few months, we went through all the natural emotions of grief and anger. But eventually, the realisation dawned on us that the best way to deal with this unwelcome visitor was to become informed and fight it. We spent ages learning about the condition on the internet, and this gradually encouraged us to find out more about research activities. I became a lay research grant reviewer for Parkinson’s UK and Laurel signed up for various research studies – Discovery, PD-Stat, OxQuip, to name but a few. I joined in the studies as a “healthy control” where I could. We attended several research conferences and started to recognise that to win this battle we must all get involved – so it was a natural next step for us to join the Research Support Network.

Becoming part of the Network provided access to a huge variety of information and opened up opportunities for us to become more engaged – meeting like-minded people affected by Parkinson’s, as well as charity research staff and scientists. This helped us to understand more about the research taking place and the part we could play.

About three years ago, I saw an advert and applied to join the Development Team – a steering group made up of volunteers and staff who help shape and guide the Research Support Network, making sure it meets its members’ needs. As part of my role, I was asked to join the charity’s Research Strategy Board. All of this has been a great privilege, providing the opportunity to meet people from very different backgrounds who are passionate and share a common purpose to find a cure for Parkinson’s.

In October 2019, I was elected as a trustee for Parkinson’s UK. There are exciting challenges ahead as we start a new 5-year strategy, and as a trustee, working at the heart of the charity, I hope to bring my passion and skills to help shape its future. My hope is that we can transform Parkinson’s together by getting it better understood, providing high-quality and more consistent support, and achieving breakthroughs in research.

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I really hope you enjoy this issue of Progress. If you feel inspired, there are so many ways to get involved in research and the first step is joining the Research Support Network. Who knows where it will take you?

Peter Miller
In this news section, we’re highlighting results from three studies using drugs that are already available for other conditions – a strategy called drug repurposing.

The idea is that by finding approved drugs with hidden potential, they can be moved rapidly into clinical trials with the aim of making new drugs available more quickly, easily and cheaply.

I believe we may eventually find that repurposing is most valuable in providing better symptomatic treatments to address major unmet needs – such as improving balance, hallucinations or dyskinesia. I hope we’ll see success in this area and better treatments delivered to people living with Parkinson’s in the next few years.

When it comes to drug repurposing, there are hopeful signs but we’ve also had disappointments – including a phase three trial of isradipine (a blood pressure medication) which failed recently. That’s why I believe it’s vital that we also continue to invest in developing new treatments based on our growing understanding of the condition.

In this news section, we’re highlighting results from three studies using drugs that are already available for other conditions – a strategy called drug repurposing.

Phase three trial of exenatide starting soon
Following encouraging signs in recent phase two studies, a large UK-wide trial of the diabetes drug exenatide will investigate whether this therapy can slow the course of Parkinson’s.

Exenatide works by targeting a receptor in the pancreas called GLP-1 which triggers insulin release. Crucially, these receptors are also present inside the brain and research suggests they play a role in a variety of processes that may be beneficial or protective for the brain cells affected in Parkinson’s.

The upcoming study will involve 200 participants with mild to moderate Parkinson’s in London, Plymouth, Oxford, Manchester and Edinburgh. Participants will be randomly assigned to inject either the study drug (exenatide) or an identical but inactive version (a placebo) once a week for two years.

The aim is to understand if this treatment can slow the progression of Parkinson’s rather than just improving movement symptoms – something no other drug can do.

There are currently many Parkinson’s research studies underway in the UK that need participants – including clinical trials testing potential new therapies. Discover opportunities on pages 30-33 or visit parkinsons.org.uk/takepartresearch to find a study near you.

Results of phase two nilotinib study announced
Results from the US-based phase two clinical trial of nilotinib, a drug that is already approved for treating leukaemia, show that, while safe and tolerable, the drug’s beneficial effects for treating Parkinson’s are not clear cut.

The NILO-PD phase two trial recruited 75 participants with moderate to advanced Parkinson’s. Participants were randomly assigned to receive nilotinib or a placebo daily over 12 months.

The results of the study are complex. Although there were some positive signs, there were no significant differences in the motor and non-motor outcomes between the nilotinib groups and the placebo group.

Claire Bale, Head of Research Communications and Engagement at Parkinson’s UK, said:

“While these results are encouraging, the study was not set up to look at whether boosting GCase levels resulted in any improvement in symptoms or see whether it had any impact on the progression of Parkinson’s.

“Demonstrating that ambroxol can have a beneficial effect would be the aim of larger and longer studies. At this time we would not advise those with the condition to take ambroxol.”

Ambroxol is an approved drug that is used to ease coughing by clearing away mucus in the lungs. Lab experiments have shown it may have potential for treating Parkinson’s by boosting a protein called GCase.

The results from a study of 17 people with Parkinson who took ambroxol daily for six months indicate that ambroxol entered the brain and boosted GCase. And, importantly, no serious safety problems or side effects were reported related to the drug.

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Most would agree that the ultimate aim of medical research should be to find a cure and to improve life for people with conditions like Parkinson’s.

This means that a vital part of developing better treatments, clinical management strategies and care is understanding and being able to measure “quality of life”.

This is a major challenge. There is no single agreed definition of quality of life. It is deeply personal, influenced by many factors and can change suddenly – a new career, friendship or hobby can quickly and dramatically affect it.

But in its simplest form, quality of life is the standard of health, comfort and happiness of an individual or group. And it is affected by physical, psychological and social factors.

How does living with Parkinson’s affect quality of life?

Unsurprisingly, research suggests that people with Parkinson’s have a reduced quality of life compared to people without the condition of the same age.

It also suggests quality of life deteriorates as the condition progresses.

A study which compared people with Parkinson’s to people in the general population found that the main areas responsible for poorer quality of life were related to mobility and physical abilities. The greatest difference was seen in the area of self-care, which involves activities such as washing oneself or getting dressed. Here, people with Parkinson’s reported problems up to 10 times more frequently than people without the condition. Other aspects that seem to have a major impact are depression, disability and problems with thinking and memory.

Parkinson’s also affects carers. A recent study highlighted that areas of life including relationships, mental health and self-care are all affected. Carers are five times more likely to develop health problems than the age-matched population.

One of the greatest impacts on quality of life is if their loved one experiences falls. Research shows this can increase anxiety, and restrict normal activities and contact with friends and neighbours.

Here, Linda Brown, who cares for her husband who has Parkinson’s, shares her story:

“Having a loved one diagnosed with Parkinson’s affects the quality of life of families, friends and carers in many ways, both physically and mentally.

“In my case, my husband had to give up work and we had to sell our house as he was too young to take his pension. I had to increase my working hours and he developed severe depression while I ended up with stress and anxiety. I was in a very unhappy and bleak place.

“Seven years on, I can honestly say Parkinson’s now has enriched our lives in many ways.

“I am a more positive person. I appreciate life more and we do as much as we are able. We travel, we both volunteer for Parkinson’s UK and get lots of satisfaction from that. I have met and made friends with so many lovely people, I have joined a choir – and that is so uplifting – and I go swimming and to Pilates, which is relaxing.

“I feel it’s important if you are caring for someone that you are able to do things just for you. It helps you look at the positive side and that in turn makes you a more effective carer when you can be dealing with frustrating and difficult situations.”
**How do we measure quality of life?**

In research, quality of life is almost always measured using tick box questionnaires where people rate their own health, wellbeing and ability to do activities.

In Parkinson’s studies, quality of life is usually measured using the Parkinson’s Disease Questionnaire 39 (or PDQ-39) – a 39-question tick box questionnaire – developed through research funded by Parkinson’s UK and first published in 1995. It is the major tool used in clinical trials worldwide to capture quality of life and patient benefit.

The questions were developed based on in-depth interviews with people with Parkinson’s to understand the main aspects of quality of life. She shares her thoughts on the importance of perspective:

“The current ‘gold standard’ questionnaire, the PDQ-39, measures health-related quality of life. It is based on the assumption that the worse our symptoms, the worse our quality of life. Just completing it can be quite a depressing experience, as you’re answering questions about how much the condition is limiting your life.

“They say that Parkinson’s is an unwanted visitor that turns up and won’t go away. But the visitor brings gifts – including, for me, going to the World Parkinson Congress in Kyoto in 2019, meeting and working with extraordinary people, doing more fun exercise than I have done in my life – Dance for Parkinson’s, Latin dancing, Taiko drumming, Tai Chi (with weapons!).

“Health-related questionnaires will always be relevant and necessary, but they are only one part of a rich and complex picture. We’re looking at quality of life from the other side of the coin, de-coupling it from health. Asking people what they can do rather than what they can’t, asking about moments of sharing laughter and joy, of learning new things. And giving space for people to report abilities and emotions that have gotten better – which, after all, is the aim of the new treatments being developed.”

**What can improve quality of life?**

So, if we can measure quality of life in research, what are the things that can make a major difference?

We asked attendees (both in person and online) of our 2019 Research Support Network conference: “What is the single most important thing you do to maintain or improve your quality of life?”

72 people responded and, perhaps unsurprisingly, the most frequent response was exercise in one form or another. However, other important aspects included things like staying positive, continuing to work, seeing friends and family, and humour.

**What does research say?**

**Nurses**

A number of research studies have highlighted the importance of Parkinson’s specialist nurses – a role pioneered in the UK – in providing joined-up, personalised care for people with the condition.

Back in 2002, research part-funded by Parkinson’s UK first demonstrated the impact of Parkinson’s nurse specialists. The two-year randomised controlled trial showed that nurse specialists had little effect on the clinical condition of patients, but they did improve their sense of wellbeing, with no increase in healthcare costs.

A recent study conducted in Germany showed that people who received integrated care from a team including a neurologist, movement disorder specialist and Parkinson’s nurse had better quality of life than those who received standard care.

The researchers particularly highlighted the importance of the specialist nurse. They ensured a faster response to queries, helped people cope with the condition and social concerns, supervised therapy plans, and generally acted as the lynchpin to integrated care.

**Exercise**

In recent years, there has been an explosion in research into the benefits of exercise for people with Parkinson’s and other brain conditions. We now believe that exercise is a vital part of maintaining health and quality of life and should be considered as essential as medication.

A recent study looked at the results of over a hundred studies conducted across a range of conditions including Alzheimer’s, multiple sclerosis and Parkinson’s.

They found that exercise has a medium-sized beneficial effect on quality of life and a large beneficial effect on depressive symptoms. Interestingly, the researchers found that the more time people spend on exercise per week, the larger the reduction in depressive symptoms. Crucially, they also identified a small but significant beneficial effect on cognition (thinking and memory) – another vital factor that influences quality of life for people with Parkinson’s and their loved ones.
Driving forward research to improve life

Research is changing. The expertise of people living with health conditions is increasingly being recognised as crucial to the development of new therapies, management strategies and care.

Who better to drive forward research to improve life than the people living with the condition?

At Parkinson’s UK, people affected are identifying the problems that research needs to solve and working with researchers to develop the solutions.

Sidestepping falls
A phase three clinical trial is about to get underway to test whether rivastigmine – a type of drug usually used for dementia – can help to prevent falls in people with Parkinson’s. Results from an earlier study funded by Parkinson’s UK showed it may reduce falls in people with Parkinson’s by 45%, compared to a placebo or “dummy” treatment. Importantly, the research team, led by Emily Henderson, are involving people with Parkinson’s in the design, running and dissemination of this new larger trial. You can find out about taking part in this study on pages 30-33.

Road-testing mindfulness
Parkinson’s UK-funded research explored the potential of mindfulness – a technique that helps individuals pay more attention to the present moment, including thoughts and feelings. The technique has been shown to help ease feelings of stress and anxiety. The research team worked with people affected by Parkinson’s to adapt an existing mindfulness course to ensure that the course was specific to the needs and challenges associated with the condition. Full results are due to be published soon.

Embracing technology
The rise of technology has led to an explosion in research to develop and test technological approaches to improve life for people living with Parkinson’s. One of the many projects in this area is called SCAMPI, which stands for Self-Care Advice, Monitoring, Planning and Intervention. The aim is to create a toolkit that will help people with dementia and Parkinson’s live independently at home, with the best quality of life possible. The team is working closely with people with dementia and/or Parkinson’s, as well as their informal carers, to shape, develop and test the technology to make it user-friendly and practical.

Get involved
There are many ways to get involved in driving forward research to improve life for both people with Parkinson’s and their loved ones. From participating in studies and surveys to help us understand how the condition affects everyday life, to working in partnership with researchers to develop better ways to measure what matters – everyone can play a part.

Join the Research Support Network and get involved at parkinsons.org.uk/rsn
Everyone can play a role in the search for a cure for Parkinson’s. The more people who get involved, the faster we’ll get there. That’s why Parkinson’s UK has a Research Support Network.

A central objective of Parkinson’s UK is to communicate, collaborate and involve people affected by Parkinson’s in everything we do. That promise includes research. Our mission to find a cure and better treatments has to mean putting people affected by Parkinson’s at the centre of our research.

That’s why the Parkinson’s UK Research Support Network was born nearly 10 years ago. Designed and created in partnership with a passionate group of people affected by the condition, its aim is: to bring together people who are driven to help find a cure and better treatments for Parkinson’s.

And have we brought people together? We started out with a couple of hundred members with a clear vision of what we could achieve together. Today, the Research Support Network has 6,000 members. So we must be doing something right! The Network is growing and succeeding because what started as simple aspirations have been transformed into a focused programme that supports people to get involved in research in three main ways.

**Get connected to Parkinson’s research and the scientists carrying it out**

All too often, research can feel distant and inaccessible. People may not know what’s happening near them and how they can contribute. The Research Support Network connects people to information, scientists and opportunities to support research locally.

Members get all the latest Parkinson’s news and opportunities to get involved delivered straight to their inbox by email.

A vibrant programme of events, lectures and talks up and down the UK, and streamed online, is giving more people than ever the chance to hear first-hand from researchers about their work.

What’s more, a growing movement of volunteers is working to bring research to people at a local level. Research Champions are spreading the word and supporting others to get involved in Parkinson’s UK groups. Meanwhile, Research Interest Groups have sprung up around the country, run by volunteers and researchers to raise the profile of, and engagement in, research regionally.

Marc van Grieken, Chair of the Dundee Research Interest Group, says:

“I believe that as people living with Parkinson’s we must do everything we can to influence and support the research being done to develop better treatments in the short term and ultimately a cure.

“Our Group connects Parkinson’s researchers at the University of Dundee with people living with the condition. We work together with some fantastic researchers to share information about their work with the community, and to bring the opinions of people with the condition to their research.

“The relationship we’ve developed with the researchers is absolutely invaluable and goes beyond science. It is inspiring and gives us hope. When I signed up to do the Great Scottish Run in Glasgow, eight researchers from the university joined to support me in raising funds and awareness. The more we’re able to work together and break down any remaining barriers between research and people with Parkinson’s, the faster we’ll find the solutions we need.”

**Take part in clinical trials and studies**

Although many people affected by Parkinson’s are keen to take part in research, many studies still struggle to find the participants they need. Recruitment issues slow down research and can even mean that studies fail altogether.

It’s a problem the Research Support Network is working to solve. A dedicated team made up of volunteers, researchers and staff is driving forward work to raise awareness of the importance of participation. They are developing tools and resources to make taking part in Parkinson’s research relevant and accessible to everyone.

One of the major barriers they identified to people taking part was simply being able to find opportunities in their area. So in 2017, Parkinson’s UK launched the Take Part Hub – a simple, searchable list of UK studies. The hub is designed to be as user-friendly as possible. All people need to do is enter their postcode or town to start browsing research opportunities near them.

The Take Part Hub has been a huge step forward. In our most recent survey, almost half of the Research Support Network told us they had taken part in research. But not everyone with Parkinson’s is online. So we’re now working to raise awareness with healthcare professionals, encouraging them to use the hub to highlight opportunities to their patients.

**We’ve shared more than 250 opportunities to take part in research since 2015**
Dr Penny Foulds, University of Lancaster and MAC Clinical Research, says:

“We recently worked with Parkinson’s UK to help find participants for a phase one clinical trial that is being carried out in hospitals across Europe. The study is testing an experimental new drug, which aims to reduce the activity of a key protein called LRRK2 that is hyperactive in Parkinson’s. The drug has the potential to slow the progression of the condition.

“Phase one studies can be challenging to find participants for because they often require a major commitment. In our case, participants need to stay in hospital for several days at the beginning and end of the study to allow us to closely monitor their response to the drug.

“Initially we were quite concerned that we might not be able to find the 12 participants we needed within the required timeframe. If that had happened, we might have had to cancel the study at our hospital and lose the opportunity to be involved in developing this cutting-edge new therapy.

“We reached out to Parkinson’s UK who were able to share information about the study with the community. As a result, we actually ended up recruiting all the participants we needed well before our deadline, which was absolutely fantastic.

“Our success in recruiting to this study means we’ll be an attractive partner for future Parkinson’s trials of new treatments. We need to make the UK a great place to do these groundbreaking studies otherwise people with the condition will miss out.”

Have your say on what research is needed and how it is done

People with Parkinson’s and their loved ones are the experts on living with the condition. Through the Research Support Network, your voices are heard in research both at Parkinson’s UK and beyond.

Since the 1980s, people living with Parkinson’s have been involved in deciding on the research that the charity funds. Our volunteer lay grant reviewers assess every application for funding and their scores and comments are given equal weight to those of the scientific reviewers.

In 2014, we partnered with the James Lind Alliance to carry out a Priority Setting Partnership with people affected by Parkinson’s, their families and health care professionals. The result was a list of urgent priorities for improving everyday life that has resulted in research into areas of unmet need, including mental health, balance problems and continence issues.

More recently, the Research Support Network has been enabling researchers to work with people affected by Parkinson’s to develop, inform and shape their work. This has now developed into a world-leading Patient and Public Involvement programme. The programme has over 100 trained volunteers using their insights and experiences to make research more relevant, focused and practical for people with Parkinson’s.

We’re leading people-powered research – including bringing companies together with people affected by Parkinson’s to find better treatments and a cure. Alongside the Parkinson’s Foundation, a charity in the United States, we’re enabling people living with Parkinson’s to work with the global pharmaceutical company UCB, helping to guide and shape their research and development in Parkinson’s.

Kate Trenam, UCB’s Patient Advocacy Group Lead for the UK, says:

“Our collaboration with Parkinson’s UK and engagement with people affected by Parkinson’s is invaluable. Our scientists work hard in finding innovative treatments, and by working with people who live with and understand Parkinson’s, we’re able to develop medicines that may really make a difference to their lives.”

What next?

Huge progress has been made in the last decade to inspire more people than ever to get involved in the search for better treatments and a cure for Parkinson’s. But to accelerate progress we need to continue to do more and expand our reach further.

The Research Support Network Development Team, made up of volunteers and staff, helps provide thoughtful leadership on opportunities and priorities and has been helping to shape the Network from the start. But what the Network can achieve in the coming years will be down to your energy and enthusiasm as members. Together, we will find better treatments and a cure – faster. Join the Network and help us get there.

“As co-chair of the Research Support Network Development Team, I personally believe that the next decade will herald a breakthrough in Parkinson’s research. The RSN epitomises the true sense of working together for the good of the Parkinson’s community.”

Carroll Siu
Brain cells need a lot of energy to function, and cell batteries – called mitochondria – play a crucial role in providing this. But just like regular batteries, mitochondria can become worn out or damaged and stop working properly. Our first two projects are investigating different ways to help cells manage these malfunctioning mitochondria.

Here, we highlight some of our newest research projects – including studies on targeting cell batteries, boosting waste disposal, and the impact of physiotherapy.

Enhancing mitochondria to protect brain cells

Who? Dr Nicoleta Moisoi
Where? De Montfort University
What? £49,224 over two years
Stage? Scientific discovery in the lab

Nicoleta and her team have recently found that a protein called CLPP plays a role in the repair and regeneration of the cell batteries. This project will investigate if a class of drugs derived from natural compounds can boost CLPP levels and see what effect this has on brain cells.

“Our data shows that a class of drugs derived from natural compounds are able to activate mitochondrial CLPP in human cells, improving mitochondrial function and regulation. Positive results in this study will provide important proof-of-concept data to advance CLPP as a therapeutic target for Parkinson's.”

Dr Nicoleta Moisoi
Removing damaged mitochondria to halt Parkinson’s progression

Who? Professor Sylvie Urbé
Where? University of Liverpool
What? £225,159 over three years
Stage? Scientific discovery in the lab

The buildup of malfunctioning mitochondria is thought to play a critical role in the loss of healthy brain cells in Parkinson’s. This project aims to understand more about the disposal of damaged mitochondria. This research could pave the way for designing new therapies that could halt the progression of Parkinson’s.

“If we are successful in this endeavour, we will work together with academic and industrial partners to design drugs to help clear damaged mitochondria. Ultimately, the work we propose will identify new approaches to improve the health and survival of the brain cells affected in Parkinson’s.”

Professor Sylvie Urbé

Is physiotherapy effective in early stages of Parkinson’s?

Who? Dr Rob Skelly
Where? University Hospitals of Derby and Burton NHS Foundation Trust
What? £95,202 over three years
Stage? Clinical trial

We know exercise and physical activity is beneficial for people with Parkinson’s. Physiotherapists play a role in advising which exercises may be suitable, and encouraging people to keep active. This research project will explore the views and experiences of people with Parkinson’s who have undertaken physiotherapy.

The team will also assess if people may benefit from undertaking physiotherapy at an earlier stage in their condition – before movement problems have been identified. The aim of this research is to gather evidence on the best ways to treat Parkinson’s and, ultimately, to improve care for those living with the condition.

“While there is evidence that exercise in early Parkinson’s is beneficial, there is little evidence that patients without movement problems benefit from physiotherapy. We expect early physiotherapy will help people with Parkinson’s to maintain independence.”

Dr Rob Skelly

Boosting waste disposal in the brain to protect cells from damage

Who? Dr Ian Harrison
Where? University College London
What? £245,909 over three years
Stage? Scientific discovery in the lab

The gradual buildup of toxic proteins is thought to play a major role in damaging brain cells in both Parkinson’s and Alzheimer’s. The glymphatic system – a recently discovered brain-wide pathway – works to remove waste products from the brain. Previous research has shown that sleep, exercise and low levels of alcohol may help the glymphatic system to clear out toxic proteins in the cerebrospinal fluid of mice.

This new project, co-funded with Alzheimer’s Research UK, will build upon these promising findings. It will investigate whether boosting the glymphatic system with drug-like molecules can help the brain rid itself of toxic proteins, and whether this could protect it from damage.

“We know that the glymphatic system can help clear away some of the proteins that build up in other conditions – such as beta-amyloid in Alzheimer’s. But we don’t yet know whether alpha-synuclein can be cleared by this same system.

“Some initial experiments suggest that it can. So, in this project, we will investigate whether we can harness the glymphatic system to reduce the buildup of alpha-synuclein in Parkinson’s.”

Dr Ian Harrison
While Parkinson’s is fundamentally a condition that affects the brain, it has become increasingly clear that the gut plays a major role.

Researchers are not exactly sure what causes Parkinson’s or why dopamine-producing brain cells are lost over time. Evidence suggests that Parkinson’s tends to develop gradually — changes in the body may occur years before someone receives a diagnosis. One part of the body these changes may occur in is the gut.

There are a few clues as to what might be causing the death of these vital brain cells. One clue is that toxic proteins are clogging up brain cells, causing problems in Parkinson’s. These toxic proteins have also been shown to be present in the gut, leading to the theory that Parkinson’s may originate there.

What do we mean by ‘toxic proteins’?

Proteins carry out most of the jobs that happen inside our cells. There are many different types of proteins, with many different roles. 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 (diagram 1).

Misfolded proteins can clog up cells, stopping them from working. 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. Researchers believe that this protein might be responsible for the spread of the condition.

**COULD PARKINSON’S START IN THE GUT?**

**Brief summary**

- A toxic protein that contributes to the loss of brain cells in Parkinson’s may originate in the gut and travel to the brain.
- Gut bacteria differ in people with and without Parkinson’s, and may play a role in the development and progression of the condition.
- Researchers are looking at various methods to boost gut health. Identifying which bacteria are involved in contributing to Parkinson’s will help accelerate the search for better treatments and a cure.
Additional evidence of the involvement of the gut in Parkinson’s comes from a procedure for treating ulcers. Vagotomy was common in the 1970s and 80s, and involved cutting the information flow between the gut and the brain by severing the vagus nerve. Research has since shown this procedure has been linked to a reduced risk of Parkinson’s. This suggests it may have inadvertently stopped alpha-synuclein clumps making the journey from the gut to the brain, and ultimately causing the loss of brain cells.

These findings have caused researchers to rethink where Parkinson’s actually starts. It could mean, for some, the condition may start in the gut or elsewhere in the body, and travel up the vagus nerve towards areas of the brain affected in Parkinson’s.

Diagram 1: Paper aeroplane analogy
Proteins such as alpha-synuclein have to have the correct shape to function properly – just like a paper aeroplane. If the paper isn’t folded properly the paper aeroplane won’t fly, and results in a pile of discarded paper. You could think of the scrunched-up paper as clumps of misfolded alpha-synuclein, the protein that causes problems in brain cells.

Does Parkinson’s start in the gut?

The brain isn’t the only place where the spread of toxic alpha-synuclein may be happening. Recent research has also found misfolded alpha-synuclein in the gut of those in the early stages of the condition. This finding has led some researchers to believe that Parkinson’s may, for some, start in the gut and travel to the brain.

There is evidence that alpha-synuclein might be travelling via the vagus nerve, which connects the gut to the brain (diagram 2). Studies have found clumps of alpha-synuclein in the vagus nerve, further supporting the idea that the clumps may not originate in the brain.

Researchers don’t fully understand how alpha-synuclein spreads, or what causes these toxic clumps of protein to form in the first place. Understanding this may help shine a light on how we could stop the spread of the condition or, if it does start in the gut, how we could stop it reaching the brain at all.

Gut bacteria and Parkinson’s

There is more than one way that the gut could be linked to Parkinson’s. As well as misfolded alpha-synuclein clumps, there is evidence that gut bacteria play a role in the development of the condition.

Up to a trillion microbes live in our gut. Many are beneficial “good bacteria” – helping us digest food, make vitamins and fight bad bacteria and infection. Our gut bacteria interact with the rest of the body by releasing chemicals. The vagus nerve is able to send information from the gut to our brain (diagram 2) where it influences our unconscious or otherwise involuntary behaviours.

The makeup of gut bacteria will vary from person to person and can change over time. As well as these individual differences, there is evidence that gut bacteria may change in different health conditions and this may be the case in Parkinson’s. Recent research has shown that gut bacteria in individuals with Parkinson’s differs from that of people without Parkinson’s. Scientists now believe that harmful gut bacteria may produce chemicals that are important in the development of the condition. In fact, bacteria from the gut of people with Parkinson’s have been shown to make motor symptoms in mice worse.

However, there have been various research studies that have looked to identify which gut bacteria are altered in Parkinson’s and the results so far have been variable. There is work to be done to get a better picture of what bacteria are increasing or decreasing in the condition, and at what stage of the condition this happens in different people. This is essential if we are to fully understand the role of gut bacteria in Parkinson’s.

Targeting the gut

With increasing understanding that the gut is linked to Parkinson’s, researchers around the world are working to find ways to turn knowledge about the gut into new treatments.

One idea is to replace good bacteria lost in Parkinson’s through faecal microbiota transplantation. This involves collecting bacteria that live in the gut of a healthy donor from a stool sample, and transplanting them via a tube directly into the gut of the recipient.

The first clinical trial of this procedure is underway at the University of Ghent in Belgium. The team will investigate if faecal transplantation can improve the symptoms of 40 people with Parkinson’s. However, questions remain on how to determine who is considered a “healthy” donor as gut bacteria differs from person to person.

Research into diet and probiotics

Transplantation isn’t the only way to change the bacteria living in our guts. Research has shown certain diets, including high fibre diets, have been linked to potential gut related benefits. Benefits include the promotion of potentially beneficial bacteria by a Mediterranean diet, or the inhibition of pathogenic bacteria such as E.coli in vegetarians.
On top of this, there is ongoing research to evaluate the links between different diets and Parkinson’s. Researchers are also interested in the idea of boosting “good” bacteria with drinkable probiotics. This idea has been around for a while. Unfortunately, the bacteria in many commercial probiotics are unlikely to reach the lower gut, where they are needed, as most types of bacteria are wiped out by the acidic environment in the stomach.

But an oral, water-based probiotic called Symprove claims to be able to deliver live bacteria to the lower gut.

Results from previous placebo-controlled clinical trials have suggested Symprove may have beneficial properties for irritable bowel syndrome, constipation in Parkinson’s and diverticular disease – a condition that causes abdominal pain. And now research funded by Parkinson’s UK is underway to test if it could improve motor and non-motor symptoms of Parkinson’s.

Another less well-known concept is the idea of using probiotics to improve gut health. Unlike probiotics, prebiotics do not contain live bacteria, but consist of ingredients that could promote the growth of “good” bacteria. Research done in the lab, looking at a prebiotic called sodium butyrate, found that it could pinpoint those that are harmful and develop a treatment that could target the damaging bacteria – while leaving the beneficial ones unharmed. Or, we could even develop treatments that help the best bacteria flourish.

It sounds simple, and understanding the effects of different bacteria could form the basis of new treatments. But when you consider there are hundreds of different species in the gut, it becomes a little harder to figure out which bacteria are good, bad or somewhere in the middle.

Fortunately, researchers like Dr. Maria Doitsidou and her team at the University of Edinburgh are on the case. The group’s research focus is to identify interventions that prevent damage to the brain cells affected by Parkinson’s. And now, funded by Parkinson’s UK, they are systematically studying the various types of bacteria to identify those that play an important role in the progression of the condition.

The team is using a microscopic and transparent type of C. elegans worm (picture 3) to study the effects of individual types of bacteria on the build up of alpha-synuclein protein. These worms happily eat bacteria, so the researchers simply feed a different type of bacteria to each group of worms. The worms have been engineered so that the alpha-synuclein glows green under the microscope.

From the hundreds of bacteria that may play a role, the team hopes to identify the key ones that they can then look at in more detail. They will then try to discover the mechanisms by which these bacteria have either protective or damaging properties – knowledge which could lead to new treatments.

We asked Dr Maria Doitsidou to tell us why she thinks this research is important, and to give us an update on the team’s progress.

Why is a treatment that targets the gut instead of the brain attractive?

“First, because the gut may be the origin of the problem. Thus, finding ways to stop alpha-synuclein buildup in the gastrointestinal tract may be an important approach for targeting the root cause of the problem.

“Second, the brain and the gut are much more closely linked than one might think. The bacteria that live in the gastrointestinal tract have multiple ways to communicate with the brain and affect its function. This makes our gut microbiome a very attractive target.

“Another advantage is that targeting the gut is much easier. It is very difficult to deliver drugs to the brain in effective doses. But it is very easy to deliver live bacteria to the intestine. For example, to deliver a beneficial type of bacteria to the gut one would simply have to ingest a capsule of ‘good’ bacteria. A very exciting prospect, not only for Parkinson’s but also for other brain conditions, is that in the future we may be able to change the bacteria in the gut and let the microbes do the work for us.”

What has your research found so far?

“Our most exciting finding is the discovery that the probiotic bacterium Bacillus subtilis protects against aggregation of alpha-synuclein in our worm model of Parkinson’s. We found that when we feed these probiotic bacteria to the worms, they not only slow the accumulation of alpha-synuclein, but also help to clear some of the already formed protein clumps.”

What are the next steps?

“Our next steps are to progress to studies with mouse models of Parkinson’s and, to fast-track human clinical trials to confirm the ability of Bacillus subtilis to inhibit the formation of alpha-synuclein aggregates.

“Understanding which bacteria in the human gut microbiome may improve or worsen aspects of Parkinson’s means that we can try and boost certain ‘good’ bacteria to fight Parkinson’s progression, perhaps using probiotic supplements. Conversely, we could try to eliminate the ‘bad’ bacteria in a targeted way, to slow the condition.”

It’s early days as scientists are only just starting to learn about how the gut may be linked to conditions like Parkinson’s, but this project will give us invaluable insight and potentially lead to new treatments. And while there will still be many questions to answer, the hope is that research projects like this – that aim to better understand the gut – will be key to treating many health conditions.
RESEARCH RESULTS

At Parkinson’s UK, we back the best and brightest minds to unlock the ideas that will lead to new treatments and, one day, a cure.

Here are some of the latest findings from Parkinson’s UK funded research projects.

Molecule offers hope for halting Parkinson’s

Researchers at the University of Helsinki, led by Professor Mart Saarma and Dr. Yulia Sidorova, have published their findings that a small molecule called BT13 can boost dopamine levels in the brains of mice. The results make it an attractive candidate to develop as a potential treatment to slow or stop Parkinson’s.

The team found that BT13 was able to activate a specific type of protein to promote the survival of dopamine-producing brain cells in the lab. BT13 was also able to boost dopamine levels in a specific region of the mouse brain that is affected in Parkinson’s.

BT13 targets the same family of proteins as GDNF. The advantages of BT13 is that it’s able to cross the blood-brain barrier and therefore could be administered as a treatment in a less invasive way.

What is GDNF?

GDNF is a naturally occurring protective protein, which featured in a 2019 BBC documentary as an experimental treatment for Parkinson’s.

The GDNF protein has been shown to protect and repair dopamine-producing cells in the lab. Clinical trials to date have been complex and rely on invasive brain surgery, because it is a large molecule that cannot cross the blood-brain barrier.

Progress in gene therapy treatment for Parkinson’s

Gene therapies are treatments that contain genetic information to change how cells behave. There are currently a number of gene therapies in clinical trials for Parkinson’s.

Now researchers, funded by Parkinson’s UK, have published positive results for enhancing a gene therapy treatment that directly targets the production of the alpha-synuclein protein.

While normal alpha-synuclein is thought to help brain cells communicate, one or more toxic forms of this protein are linked to Parkinson’s. Recent research also suggests that the protein is responsible for the spread of Parkinson’s from cell to cell. As such, there’s a lot of interest in targeting alpha-synuclein as a treatment for Parkinson’s.

You can read more about alpha-synuclein in the feature on page 20.
How do gene therapies work?
The idea is that the gene therapy provides the genetic instructions that cells need – this could be by replacing a faulty gene with a functional one, or providing instructions for switching off the production of misbehaving proteins like alpha-synuclein.

However, getting the lab-made DNA inside nerve cells is tricky. Right now, the most effective way of putting DNA into a cell is to “hijack” a virus, but there are alternative ways to package up the genetic instructions.

The team, led by Dr Lydia Alvarez, have been working on how to package the anti-alpha-synuclein gene therapy to help it get into the brain and make it work for longer. Their research could make gene therapy more suitable for treating long-term neurodegenerative conditions like Parkinson’s. The team found that by making the gene therapy instructions into minicircles – microscopic circular pieces of DNA with no unnecessary packaging – they were able to reduce the loss of brain cells and improve symptoms in a mouse model of Parkinson’s.

“Gene therapy is extremely promising as a potential treatment to slow or stop the development of Parkinson’s. There’s been important progress in gene therapy for neurodegenerative diseases in the last few years and the results are promising.” Dr Lydia Alvarez

Results from the largest ever study of pain in Parkinson’s

More than half of all people with Parkinson’s experience chronic pain. Despite this, there’s not been much research on pain in Parkinson’s.

For the past six years, researchers at Manchester’s Salford Royal Foundation Trust have been investigating why some people with Parkinson’s experience chronic pain.

The study, led by Dr Monty Silverdale, is helping us understand why pain occurs in Parkinson’s and has shown that there’s no relationship between pain and mobility factors. These findings highlight that pain is a specific symptom of Parkinson’s, rather than being a consequence of reduced mobility, stiffness or poor posture.

The team have also been looking at whether chronic pain in Parkinson’s may be caused by subtle genetic variations. They found that a change in a protein that responds to cannabinoids may influence whether or not people with the condition develop pain. This has sparked the team’s interest in the potential of using cannabinoids to treat pain in Parkinson’s.

“Gene therapy is extremely promising as a potential treatment to slow or stop the development of Parkinson’s. There’s been important progress in gene therapy for neurodegenerative diseases in the last few years and the results are promising.” Dr Lydia Alvarez

What are cannabinoids?
Cannabinoids are the naturally occurring chemicals that are found in the cannabis plant, with Cannabidiol (CBD) being one of these substances. Parkinson’s UK has recently funded a £1.2m clinical trial through the Parkinson’s Virtual Biotech, to investigate if CBD may be beneficial for treating Parkinson’s psychosis.

“Gene therapy is extremely promising as a potential treatment to slow or stop the development of Parkinson’s. There’s been important progress in gene therapy for neurodegenerative diseases in the last few years and the results are promising.” Dr Lydia Alvarez

What is cell recycling?
Cells (including brain cells) recycle old and damaged proteins to help them remain healthy and functional. It is also thought that cell recycling is a way that cells can get rid of toxic proteins, such as alpha-synuclein, that can build up and cause problems in Parkinson’s.

It has been shown that this recycling system may not be functioning properly in the condition. There is a cell recycling enhancer, nilotinib, in clinical trials for Parkinson’s.
This project has been shaped by people affected by Parkinson’s, including Russ Bradford, Co-Founder and Volunteer at Parkinson’s Concierge Ltd, who reflects on his experience.

“There are so many examples of my own Parkinson’s nurse going above and beyond the call of duty. They are truly awesome. It is imperative that their role is protected, understood, and challenged.”

Who do the researchers need?
People with and without Parkinson’s
400 people affected by Parkinson’s. This can be people with Parkinson’s, or family and friends interested in sharing their thoughts.

What does it involve?
At home
Completing a one-off online survey which should take no more than 45 minutes. You may be approached at a later date about a face-to-face interview if you express an interest when asked during the research.

Interested?
For more information and to access the survey, visit the Take Part Hub at parkinsons.org.uk/impactofnurses

Improving care and support for people with Parkinson’s and their carers
It’s essential to better understand how Parkinson’s impacts lives in order for people to receive the best quality of care and support.

“People with Parkinson’s and their families often say how important their Parkinson’s nurse is to them. Healthcare workers also talk about the importance of Parkinson’s nurses.

“This is a two-year research study to help us understand: the different types of specialist nurses working with people with Parkinson’s; the best ways for Parkinson’s nurses to be trained and work; and the strengths and weaknesses of the different types of Parkinson’s nurses and their impact.” Dr Annette Hand
Researchers are looking to find out more about the events that can suddenly increase care needs for people with long-term conditions.

“The Neuro LTC study is important because it seeks to identify factors that affect care needs from the perspective of people with Parkinson’s and their carers. It really focuses on what patients and carers think and have personally experienced.

“We’re very grateful to all the participants who have already completed the survey, but we still need more people to take part to help us better understand this vital perspective.”

Dr Sarah Fearn

Who do the researchers need?
People with and without Parkinson’s.
They want to hear from people with Parkinson’s, carers and former carers.

What does it involve?
At home
You will be asked to complete a survey, either online, on paper or over the phone.

Interested?
For more information and to access the survey, visit the Take Part Hub at parkinsons.org.uk/careneeds

Not online? To complete the survey over the phone or to request a paper copy, please call Sandra on 023 8120 6132.

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Take part in trialling a new treatment

A phase three trial investigating a treatment to reduce falls

People with Parkinson’s often have trouble with balance and falls. People living with the condition have told us that this should be a top research priority.

Researchers are currently investigating a treatment to see if it can reduce falls in people with Parkinson’s. The phase three trial is looking for people to take part and is happening at 26 sites across the UK.

“If successful, this treatment will improve the lives of people living with Parkinson’s now. We are working hard to tackle one of the most disabling complications of Parkinson’s.”

Dr Emily Henderson

Who do the researchers need?
People with Parkinson’s
600 participants with Parkinson’s who have experienced a fall in the last year.

What does it involve?
Visiting a hospital and taking medication via a patch
People will be randomly assigned to either receive the real drug via a patch or receive a placebo (dummy) patch. Participants will take the medication for 12 months and record any falls that they experience in diaries.

Interested?
For more information, visit the Take Part Hub at parkinsons.org.uk/reducingfalls

Investigating a new treatment for sudden drops in blood pressure in people with Parkinson’s

Researchers are looking for people to take part in a phase three clinical trial to investigate a new medication for patients experiencing symptoms of orthostatic hypotension. This is when people may feel faint or dizzy when standing up, and can be a symptom of Parkinson’s.

“It’s a very exciting time for Parkinson’s research. Our team of brain and mind experts at Re:Cognition Health are dedicated to helping understand the causes, finding new medications to help treat symptoms and ultimately find a cure for Parkinson’s through final phase clinical trials.

Dr Emer MacSweeney, CEO and Consultant Neuroradiologist at Re:Cognition Health

Who do the researchers need?
People with Parkinson’s
22 people aged 30 years over, who have been diagnosed with Parkinson’s and symptomatic neurogenic orthostatic hypotension.

What does it involve?
Visiting a hospital and taking oral medication
You will initially need to attend one of the study sites for a screening visit. During this time, you will have a number of assessments performed to review your suitability for the trial.

If you are eligible, you will either receive the treatment or the placebo for four weeks, which will involve multiple trips to the study site.

Interested?
To find out where the research is happening and how to get involved, visit the Take Part Hub at parkinsons.org.uk/clinicaltrialdizziness

Where can I go to find out more?
• Call our free, confidential helpline on 0808 800 0303. Our advisers will be able to discuss what you’re interested in and put you through to our Research team.

• Join our Research Support Network. As a member, you will receive regular emails telling you about any research you can take part in. Find out more at parkinsons.org.uk/rsn

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Yes
At Parkinson’s UK, our Research team has a wealth of knowledge about all aspects of Parkinson’s research and we often use this to help answer your questions. Here are a few answers we wanted to share.

**How long before there’s a new drug for Parkinson’s?**

A variety of new drugs are being developed for Parkinson’s and there are many already being tested in clinical trials.

Some are better ways to give existing drug treatments. Apomorphine, a drug currently only available via injection or infusion, is being developed into a strip that dissolves under the tongue. This new form of apomorphine is in the very final stages of clinical trials and could be available in the next couple of years.

Some are drugs that are already in use for other conditions. Several are already entering late-stage clinical trials, including the diabetes drug exenatide which may slow the progression of Parkinson’s, and drugs currently used for dementia which may help to prevent falls. These trials are just getting started but if successful, could lead to better drug treatments in years rather than decades.

Finally, there is an exciting wave of brand new therapies in the earlier stages of development. These include gene therapy approaches, which target key genes linked to Parkinson’s, and vaccines that target the alpha-synuclein protein. Many are already in early-stage clinical trials and we hope to see positive results from these soon.

**Should we all be on terazosin – if not contra-indicated?**

Research is currently ongoing into terazosin, a drug used to treat enlarged prostates, that has been found to have promise for treating Parkinson’s.

The research done so far has been in animal models of Parkinson’s. More research is needed to fully assess the potential benefits and risks of terazosin for treating people with Parkinson’s. Because of this, we would not recommend everyone takes this drug. But we’ll be keeping an eye out for results from clinical trials that are being planned in the US.

You can read more about this on our website: parkinsons.org.uk/newsterazosin

**Do you know of a recommended artificial stimulation method for back muscles to help one’s posture?**

There is currently no recommended stimulation method for posture but this is an active area of research.

Scientists are looking at how spinal cord stimulation could be used to combat problems such as posture and freezing in Parkinson’s.

You can read about research and current therapeutic options in our ask the expert blog post: parkinsons.org.uk/postureblog

And we’ve recently highlighted some of the latest research on spinal cord stimulation on our website: parkinsons.org.uk/newsspinalstimulation

Got a question about research you’d like answered in Progress? Email your question to research@parkinsons.org.uk and make sure to include the word “Progress” in the subject line.
We are Parkinson’s UK. Powered by people. Funded by you. Improving life for everyone affected by Parkinson’s. Together we’ll find a cure.

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