Research consortium offers new hope for Parkinson’s disease

DANNY BUCKLAND

Until recently, research progress in the field of Parkinson’s disease has been slow compared with other therapeutic areas. However, a new consortium of pharmaceutical companies, academic researchers and charities – the Critical Path for Parkinson’s Consortium – is helping to accelerate the development of new treatments to slow disease progression.

Parkinson’s disease often seems locked in history. A condition with no cure, limited therapies and research progress that appears steam-driven compared with the sleek, highly funded solutions for other diseases.

While cancer is illuminated by a fierce spotlight of potent research, funding and direct action, Parkinson’s has struggled to make significant advances for its 127,000 population in the UK, which is expected to increase by 28 per cent to 162,000 by 2020 as the baby boomer generation ages, according to the charity Parkinson’s UK.¹

The condition itself – first characterised by English welfare campaigner and doctor James Parkinson in 1817 with the paper “An essay on the shaking palsy” – is an enduring fear for the public and a frustration for physicians.²

The drug of choice, levodopa – or L-dopa – was first unwrapped around 50 years ago but remains the gold standard of treatment. Many clinicians want more than the rating scale to diagnose Parkinson’s disease – which can take years to confirm – and desperately need more firepower than the bag of symptom management drugs currently available.

There is spirited resistance for controlling the tremors, compromised movement and other effects of Parkinson’s disease, but the graph of decline for patients can be a depressing ski-slope profile. Clinicians have also been hobbled by the lack of biomarkers to aid comprehensive and early diagnoses and the reluctance of pharmaceutical companies to pledge multimillion-pound development budgets for a condition that is not fully understood, for which crucial data is fragmented and that has a heritage of costly late-stage clinical trial failures.

The easiest explanation for the cause of Parkinson’s disease is a combination of genetic and environmental factors. But it is a complex and not fully mapped condition with many aspects at play such as mitochondrial dysfunction and premature cell death.

²

DaTSCAN showing functional dopaminergic neurones in a normal subject (top) and a patient with unilateral Parkinson’s disease
The US actor Michael J Fox, who was diagnosed with the condition aged 31 years at the height of his fame in 1991 and who then set up a global research foundation, sums it up: “Genetics loads the gun and the environment pulls the trigger.”

The personal payload is devastating with symptoms stretching way beyond movement issues to pain, anxiety, depression, sleep disturbance, bladder problems, sexual dysfunction and loss of independence.

But the neurodegenerative condition, caused principally by a deficiency of the central neurotransmitter dopamine and evidenced by tremor and motor function difficulties, is now emerging from the shadows.

**New research consortium**

A cure remains distant but efforts to find ways of slowing progression have been energised by recent genetic discoveries and the formation of a consortium of researchers, academics, administrators and pharmaceutical companies to pool knowledge, resources and, critically, the tactical nous to navigate regulatory frameworks to construct effective clinical trials.

The charity Parkinson’s UK has invested over £1 million into the consortium – known as the Critical Path for Parkinson’s Consortium (CPP) – that draws together a powerful range of scientific, medical and complementary talent to bring James Parkinson’s discovery up to date, as the 200th anniversary of his landmark monograph approaches.

A year of careful planning brought the consortium to official life in March 2016 with its reins in the firm grip of the Critical Path Institute (C-Path) in Tucson, Arizona – an independent, nonprofit-making body founded in 2005, which is skilled in utilising global expertise and collaboration to accelerate disease understanding and, ultimately, drug development. It is a system that has already had success in kidney disease, Alzheimer’s disease and tuberculosis.

The route will be via smarter, improved clinical trials that are more likely to succeed, as Parkinson’s UK states: “We, and many others in the research community, believe the problem may not be that the drugs don’t work but that we’re testing them the wrong way.”

The problems of simply diagnosing Parkinson’s disease are highlighted by the revelation that 10 to 20 per cent of patients on some early-stage clinical trials did not even have the condition; their presence skewing the results, according to Parkinson’s UK. Eliminating these patients from trials is a first step to a sharper understanding of how the disease progresses.

The CPP follows on the heels of last year’s launch of the UK Parkinson’s Excellence Network, which unites health professionals, caregivers, experts and patients to transform services by sharing information and education.

C-Path has attracted some big players, with AbbVie, AstraZeneca, Biogen, Eli Lilly and Company, Merck Sharp and Dohme, Pfizer and UCB signing up to the CPP. The consortium involves a major commitment, both financially and spiritually, from pharma companies, who have to leave their competitive swords at the door to build an alliance dedicated to conquering Parkinson’s disease.

The collaborative approach is enhanced by the UK Parkinson’s Disease Consortium (UKPDC), which assembles a potent force of clinical, chemical, scientific, technology and associated experts to unpick every aspect of Parkinson’s. Supported by the Medical Research Council and the Wellcome Trust, its work ranges the length and breadth of the disease pathway, examining genetic nooks and crannies and mapping the causes and variants so that disease-modifying treatments can be targeted early and development of new treatments has not kept pace,” says Dr Arthur Roach, director of research at Parkinson’s UK. “New treatments are desperately needed to deal with the devastating effects of this progressive condition.”

He explains that the UK, with its impressive track record of neurological research and highly trained medical staff, is well placed in what it can offer patients, but existing therapies only go so far. “They work well in the early stages and for certain symptoms, but there are other symptoms for which we and no one else has any effective treatment. Nor do we, or anyone else, have anything to slow progression, which is critical in these degenerative neurological conditions. So, compared to other places, the UK is doing well, but the disease itself is still winning.”

Dr Roach adds: “Slowness is a big factor. Look at all these types of disorder – Alzheimer’s, Huntingdon’s, amyotrophic lateral sclerosis (ALS) – for each, there is a struggle to come up with treatments that slow the progression of the disease. It is partly because they come on very slowly and often the underlying pathology is very advanced before the patient is aware they have the condition and it is too late to go back.”

**We, and many others in the research community, believe the problem may not be that the drugs don’t work but that we’re testing them the wrong way.**

*Parkinson’s UK*
“It is very difficult compared to other areas, which has meant, in turn, that investment from other players, such as pharma companies, has sometimes waxed and waned. There have been times that companies have invested in promising science that didn’t turn into important new treatments and they then scaled back their investment. But the science we and others have been investing in at universities has led to new avenues and insights into what is causing the condition as well as ideas about treatment, so the challenge is to turn those ideas into treatments.”

The obstacles are not just in the laboratories, he concedes. Governments, regulators, pharma and charities all have to readjust their practices to smooth the pathway from bench to bedside. The promise is out there, with genetic studies pointing towards key proteins as well as technology offering innovative routes to identify and monitor Parkinson’s. Pfizer launched a project with computing giant IBM in April to use off-the-shelf sensors and mobile monitoring devices to provide round-the-clock data on patients that could be shared with doctors and researchers and analysed to spot links that could influence medication dosage and frequency.

The job of decoding Parkinson’s, which has at least five subtypes, is the fascinating intellectual test, but de-linking the regulatory framework, although more prosaic, is fundamental. “The CPP is not necessarily just about providing scientific horse power, it is focusing on the regulatory aspects that were inefficient. You could have 10 companies in a row involved in confidential meetings with regulators, asking similar questions and often getting similar answers, but with all that information remaining private and disconnected,” explains Dr Roach.

“Trials in early Parkinson’s are in the area of promise, but right now companies and regulators are uncertain how to do trials in that area. Badly designed trials will often end up with disappointing results that contaminate the whole field. People then think: ‘this is too difficult, everything is failing, let’s go away and do something else’.

“This new approach will show a path that makes sense and is carefully thought out. There is always a risk, but there is now a more acceptable risk to invest in developing a drug for Parkinson’s, so we expect to see more companies stepping forward. Greater understanding and clear regulatory guidance will encourage investment.

“What has inspired me is hearing from colleagues in the Alzheimer’s field who experienced the failure of some trials, but have now adopted a C-Path style for all new trials, using its decisions, tools and guidance to make sure drugs don’t fail for technical reasons. If we follow that path, we could have streamlined trials that should lead to the faster and cheaper development of products,” Dr Roach concludes.

Impact of Parkinson’s disease

The aspiration is bold, but the road may be long. Parkinson’s symptoms are easily misdiagnosed and it has emerged that up to 20 per cent of patients enrolled into some failed trials did not have the condition, observes Dr Diane Stephenson, a neuroscientist with 30 years’ experience in academic neuroscience and drug discovery, who co-directs the CPP with Dr Roach.

“The climate has changed and there is a lot more optimism now. We are not at the point where we can say there is a cure on the horizon but, as with so many diseases, the therapeutic advances have

**Figure 1.** Charitable funding for research by health category, neurological diseases, of which Parkinson’s is only a part, receive just 8 per cent of charitable funding for research.
been so great recently that there is hope of improved treatments,” she says.

Wrangling a framework into a constructive shape is the unglamorous side of drug discovery, but the task is never just process-driven, as Dr Stephenson has family experience of Parkinson’s disease. Her brother, Cliff, was diagnosed with early onset Parkinson’s five years ago and the 52-year-old with two young children is struggling.

“I’ve experienced the devastating impact of this disease. It is unbelievably impairing – like for my brother, who is in the prime of his life with two young children. He had symptoms for a long time and it was clear there was something wrong even before he was diagnosed,” she says.

“Getting the diagnosis was very difficult. There are very few movement disorder specialists and the kind of symptoms he has now are not effectively treated with medication. There is no approved drug for cognitive dysfunction. He’s very confused, has problems with daily activity and planning. He was a computer scientist and is now on disability benefits. He never had tremors, but the main problems are so disabling. There is gastrointestinal disturbance, confusion, lack of motivation and apathy. He doesn’t want to admit it, but he is depressed, and he is also dealing with dizziness and the likelihood of falling. It is devastating seeing it in someone you love and you can’t help,” she adds.

The experiences of her brother and the other 6.3 million Parkinson’s patients around the world are not only moving but also provide the statistical markers essential for research. C-Path has already collated the records of 4300 patients in the USA and 3000 from Europe to identify the right subjects for clinical trials.

“Working with different companies is one of the most rewarding aspects of my job,” Dr Stephenson notes. “It is a delicate balance. They are competing with each other and they want a drug that is going to get approved. They are all looking for that home run that will stop disease progression. But this is precompetitive and it is so rewarding to get these groups, who might not love each other, to all work together for the right reasons.”

The FDA and the EMA have representatives in the CPP discussions giving immediate guidance rather than the usual treadmill of companies waiting up to eight months for a 30-minute audience.

“All this data we are bringing together is going to help us find out what the genes and what the environmental triggers are. We may not have a prevention in the next few years, but if people know what to look out for, they can make lifestyle changes,” explains Dr Stephenson.

**Research underway**

UK data from the multidisciplinary Oxford Parkinson’s Disease Centre (OPDC) and the Tracking Parkinson’s study, led by clinical neurologist Dr Donald Grosset of Glasgow University’s Institute of Neurosciences, will be valuable to C-Path’s analytics. The Tracking Parkinson’s observational study has recruited 2247 patients with recently diagnosed or young-onset Parkinson’s and more than 300 of their siblings with the aim of finding biomarkers, and defining and explaining the clinical and genetic variations in Parkinson’s disease.8

The research, carried out at 70 centres across the UK, has been running for 4.5 years and will feed into the C-Path crucible of data. “We have turned a corner because up until now, we have looked at Parkinson’s as one entity while there is now global agreement that we should be at least planning to analyse by subtype if not designing by subtype,” says Dr Grosset. “C-Path could be good at identifying and presenting a subtype so that trials can be finessed for it.

“There is a range of difficulties with new cases of Parkinson’s that come across the threshold. Some are straightforward to diagnose and patients respond well to treatment; with others, the clinical picture is less clear. They might have co-morbidities and drugs that have contributed to that picture and therefore there is a delay in being certain of the diagnosis, which can be frustrating on both sides of the table.

“DaTSCANs [SPECT scans for imaging dopaminergic activity in the brain] show dopamine deficiency, but there are other disorders that can also give that result, so the wish list has to include diagnostic and monitoring biomarkers to measure changes over time.” Further work is needed on genetic traits, the influence of co-morbidities and the potential risk of increased vascular disease, similar to Alzheimer’s and MS, Dr Grosset adds.

The Tracking Parkinson’s project has a series of add-on studies seeking to understand the chronic pain that patients suffer, screening for subtle changes in proteins found in blood samples to identify biomarkers and developing better brain scans.

CPP member UCB is developing a preclinical drug designed to stabilise the brain protein alpha-synuclein, whose misfolding is associated with Parkinson’s disease, as well as exploring biomarkers to create a landscape where progression-modifying drugs could take over from the current symptom-control drugs.

“The remit is to pool the information we have that looks at progression of the disease to examine markers or combinations of markers that are reliable in showing progression and we can then use these to see if the drugs are effective,” says Duncan McHale, head of global exploratory development at the Brussels-based company.

“We feel strongly that this is about creating a set of knowledge and a framework that all of the companies and community can use to monitor disease progression to see if these drugs work. It will benefit everyone, particularly the patients.”

It may not speed up the drug development process, as clinical trial safety elements are immovable, but it will create a confidence for companies to advance with promising drug targets knowing that the data is anchored in a consistent format, he adds.

One of the first areas to benefit could be the revived interest in the protein glial cell-derived neurotrophic factor (GDNF), a natural brain growth factor, hailed for its ability to encourage survival of dopaminergic neurones. Although trials were halted in 2004, the Cure Parkinson’s Trust, Parkinson’s UK and North Bristol NHS Trust are collaborating on a new £2 million trial.

Studies are also investigating mitochondrial mutations and the brain’s autophagy system, which involves the
breakdown and recycling of cellular components.

The willingness of pharma companies to invest in cutting-edge research is further testimony to the changing climate around Parkinson’s disease. UCB has just struck a deal with a University of Oxford research project that tracks the eye movement of patients at different stages of disease progression. Dr Chrystalina Antoniades, of the Nuffield Department of Clinical Neuroscience, is principal investigator in an assessment study into saccades (fast eye movements) and hand-tapping movements of patients with a view to develop a cheap neurophysiological test to aid accurate diagnosis and monitor disease progression.

The Oxford Parkinson’s Disease Centre (OPDC), established in 2010, is also engaged with a suite of promising research into how dopaminergic neurons control movement and how proteins in the gut could provide the basis of a biomarker for Parkinson’s disease.

Hope on the horizon
Neurological disorders, of which Parkinson’s disease is only a part, receive 8 per cent of charitable funding for research, compared with 37.7 per cent for cancer and 10.4 per cent for cardiovascular conditions, figures from the Association of Medical Research Charities revealed in March (see Figure 1). But that does not deter Dr Antoniades and other investigators: “We are all excited because we recognise we are at a point where we have turned a page and are no longer just considering a hypothesis – the truth is, we are getting there. Talking about a cure is misleading for patients, but new developments to help diagnose Parkinson’s and retard disease progression are very close. To achieve this even to a certain extent would be a huge step.”

References
1. Parkinson’s UK. About Parkinson’s. http://www.parkinsons.org.uk/content/about-parkinsons
5. UCL Institute of Neurology. UK Parkinson’s Disease Consortium. http://www.ucl.ac.uk/ukpdc
8. Parkinson’s UK. Tracking Parkinson’s. http://www.parkinsons.org.uk/content/tracking-parkinsons

Declaration of interests
See http://www.mjauk.org/author/bucklandd/

Danny Buckland is a freelance health journalist

POEMS

Early peanut consumption reduces the risk of later peanut allergy

Clinical question: Does avoiding peanut consumption early in life decrease the likelihood of a later peanut allergy?

Bottom line: Early peanut avoidance increases the likelihood of developing peanut allergy in children at risk for allergy, which is counter-intuitive to many parents (and clinicians). This study adds that after early introduction, a period of peanut avoidance does not increase the risk of allergy. (LOE = 1b)