Disease-modifying approaches for Parkinson disease

While a cure might be far off, concerted efforts targeting disease modification are ramping up

We need to find a cure for a disease for which we do not know the cause, have no diagnostic test, and strongly suspect is multifactorial, leading to significant heterogeneity. Two hundred years after its initial description, this is precisely where we find ourselves with Parkinson disease. By the time a patient is first diagnosed, there has been significant cell death and, as such, it seems likely that at best any disease-modifying therapy will arrest or, more likely, only slow continued cell death. While data from the recent phase 2 study repurposing the diabetes treatment exenatide offer hope, the field has previously been disappointed by a catalogue of trials that have failed to translate into clinical practice. While clearly too brief, it is hoped that this article will provide the reader with some appreciation of this rapidly expanding topic.

The challenge of Parkinson disease

While our understanding of Parkinson disease has been growing inexorably, this has only served to reveal its ever increasing complexity. We have discovered a variety of clues regarding the underlying neuropathology of this disease, including the identification of epidemiological factors that increase or reduce risk (smoking, pesticides, caffeine exposure), genetic causes (α-synuclein, heterozygous glucocerebrosidase [GBA] mutations) and pre-clinical biomarkers (rapid eye movement sleep behaviour disorder, anosmia, constipation). We are also becoming increasingly aware about the role of specific cellular and more widespread processes implicated in Parkinson disease. For example, neuronal death may be driven intracellularly by a combination of oxidative stress, disrupted calcium homeostasis, mitochondrial dysfunction, and failing protein degradation operating via the proteasome and autophagy-lysosomal pathways.

In addition, at a level beyond the individual neurons, there has been a proposal that Parkinson disease represents a prion-like disease. Ingestion or inhalation of an agent that could cause a reconfiguration of wild type α-synuclein may lead to a cascade where there is misfolding of the protein into a non-degradable form that leads to cell death. The concept of transfection from cell to cell, perhaps by an exocytic mechanism, has been confirmed in a number of animal models. However, while one recent study has shown that α-synuclein derived from the post mortem brains of patients with multiple system atrophy could induce an α-synuclein prion in genetically susceptible mice, results are mixed when using Parkinson disease tissue. A prominent role of neuroinflammation in Parkinson disease has also been proposed, supported by evidence from pathology, neuroimaging and spinal fluid analysis. Whether neuroinflammation represents the primary pathology in Parkinson disease or is a secondary phenomenon is not clear. However, recent work has flagged a possible autoimmune aetiology in Parkinson disease, with researchers reporting that fragments of α-synuclein protein can trigger T cells and potentially drive helper and cytotoxic T cell responses.

How the currently identified intracellular and systemic pathophysiological mechanisms underlying Parkinson disease interact is not understood. Thus, while it is exciting to think that targeting any one of these processes may yield clinical success, further consideration of this complex neurobiological interplay is likely to be required.

Targeting treatments

Epidemiological observations showing a lower prevalence of Parkinson disease among smokers and caffeine drinkers has led to ongoing trials assessing nicotine (ClinicalTrials.gov identifier: NCT01560754) and caffeine (NCT01738178). While the data regarding disease modification from these trials have not yet been reported, both approaches have recently returned null results in relation to symptomatic benefits in Parkinson disease.

One other recently reported significant epidemiological observation highlighted that people who had been prescribed β-agonist medications for asthma (eg, salbutamol) had lower rates of Parkinson disease, whereas increased rates of Parkinson disease were seen in patients taking a β-blocker for hypertension (eg, propranolol). This observation was coupled with the finding that β-agonist drugs are capable of reducing expression of the α-synuclein gene in neuroblastoma cells, an observation that will probably trigger future disease-modifying trials.

The possible role of α-synuclein aggregation and propagation in the pathogenesis of Parkinson disease has led to a number of clinical trials targeting two related approaches, namely active and passive immunisation. In active immunisation, efforts are made to generate an immune response by injecting the subject with small immunogenic peptides that mimic α-synuclein and trigger the production of antibodies. Passive immunisation approaches are harnessing synthesised monoclonal antibodies to reduce α-synuclein levels. Much of this work to date has focused on safety and tolerability, but it appears that the pharmaceutical industry is keen to invest in these approaches.

The repurposing of existing medications or the use of dietary supplements offers an obvious appeal in terms of safety, cost and time to market. It should also be highlighted that these agents must possess a sound scientific rationale for their evaluation in this space. For example, coenzyme Q10 acts in the mitochondrial

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electron transport chain and is a free radical scavenger, suggesting a broad role as an anti-oxidant that might support mitochondrial function. Likewise, when creatine is converted to phosphocreatine, it can act as a short term energy source. However, neither coenzyme Q10 or creatine delivered positive outcomes when trialled for disease modification in Parkinson disease.\(^9,10\)

Inosine is a precursor of urate, which in addition to having anti-oxidant properties, can also elevate serum urate — a potentially useful effect, given the observation that patients with higher serum urate levels tend to have more slowly progressive Parkinson disease. While a previous study has shown the safety of inosine, the results of a phase 3 trial are still pending (NCT02642393). Many additional existing medications have been highlighted for repurposing, including the calcium channel blockers (eg, isradipine; NCT02168842), with a view to regulating calcium homeostasis, and deferiprone (NCT02728843, NCT01539837), an iron chelating agent targeting the known excessive deposition of this metal in the substantia nigra of patients with Parkinson disease.

The repurposing of drugs used to treat diabetes has shown mixed results. A phase 2 trial failed to confirm disease slowing using pioglitazone — a peroxisome proliferator-activated receptor-\(\gamma\) agonist with combined actions on mitochondrial energy regulation and neuroinflammation, where it inactivates microglia by reducing inflammatory cytokine release.\(^11\) However, the recent positive outcome from the phase 2 trial of the glucagon-like peptide-1 agonist exenatide\(^1\) has prompted calls for a larger multicentre validation. This requirement underscores, given the potentially symptomatic rather than neuroprotective benefits that may have underpinned the primary outcome measure in light of the relationship between Parkinson disease and diabetes.\(^12\) The actions of glucagon-like peptide-1 agonists are not well understood, but in addition to their peripheral action of increasing insulin release, it appears that in neurons they operate via a number of complex cascades that, among other things, affect autophagy, enhance anti-oxidant pathways, inhibit pro-inflammatory pathways and enhance neuronal plasticity.\(^13\)

Insights from the genetic causes of Parkinson disease are also likely to inform future disease-modifying studies. For example, \(\text{GBA}\) mutations represent the most common genetic risk factor identified for Parkinson disease. Much work has already been done developing enzyme replacement and substrate reduction therapies for patients with Gaucher disease who have homozygous \(\text{GBA}\) mutations.\(^14\) The role of cell-based therapies (eg, induced pluripotent stem cells), gene delivery systems, photobiomodulation, fasting diets and modulation of the gut microbiome are all being extensively investigated as approaches for slowing disease progression.

### Barriers to success

One of the major problems is whether a single treatment will work in any individual patient or indeed whether one treatment will work across every patient. It would appear that in any single patient, there are multiple pathophysiological processes concurrently at play. It is not known whether the relationships between these processes are compensatory or causative or, indeed, whether they act in parallel or have cross-talk. As such, it is possible that treating one aspect of the pathology (eg, removing \(\alpha\)-synuclein or reducing neuroinflammation) may serve to drive the disease rather than slow it. Moreover, just stabilising one process (eg, calcium homeostasis, mitochondrial dysfunction) may be insufficient, and it is possible that we might disregard useful treatments that had good target engagement simply because we needed to act across all of the disrupted pathways.

Across the population of Parkinson disease, it is possible (some might argue, likely) that there will be clear differences in the disease process itself, with some patients having a genetic driver and others having an environmental or toxic cause. This degree of heterogeneity is slowly being addressed by our understanding of the need for precision medicine in Parkinson disease.\(^15\)

Finally, there are also concerns about who is being recruited into disease-modifying trials and how we came to decide on the neuroprotective agent being trialled. The absence of a diagnostic test for Parkinson disease and the greater difficulty in making the clinical diagnosis, especially in the earlier stages of the disease, where most of our future trials will be focused, could potentially hinder our efforts. Furthermore, the current selection of our putative neuroprotective agents is often drawn from a screening panel of drugs being used in animal, cell or toxic lesion models of the disease; but after all, these are just models and may not accurately reflect what is actually going on in patients.

### Conclusions

It is true to say that there has never been a more exciting time in the pursuit of an effective treatment to slow, stop or reverse Parkinson disease, and disease-modifying trials are rapidly spreading around the world. However, despite the shifting balance from hype to hope, we must accept the fact that we may never have a cure for Parkinson disease, and we should continue to focus on delivering the very best of care to patients with whatever we can muster from our armoury.

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