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# Regenerative Drugs for Parkinson's Disease

## Summary

- No drug yet has convincing data to prove that it has neuroprotective properties in PD.
- Many agents show promise in the laboratory and are undergoing Phase 2 evaluation of clinical efficacy.
- Repositioning of agents already licensed for use in man avoids major safety and tolerability concerns.
- The existence of a wide range of agents, with diverse mechanisms all related to our latest understanding of PD neurodegeneration, provides hope that one or more of these may translate to a clinically useful therapy.

While neuro-“regeneration” is conceptually distinct from neuro-protection, from the perspective of therapeutic development in Parkinson's disease, progress indicating any effect in slowing, stopping or reversing neurodegeneration would be warmly welcomed. Any mechanism through which an agent may protect against neuronal degeneration, might similarly allow endogenous repair processes to resume, therefore there is no attempt to distinguish between these concepts here.

There have been several major disappointments in this field in recent years. Creatine, Coenzyme Q10 and Cogane all showed promise as potential disease modifying agents in PD but all failed when formally evaluated in large phase 2 trials. Our enthusiasm for the next generation of candidates must thus be tempered by these disappointments and necessitates closer scrutiny of the evidence supporting potential efficacy before the major financial investment is made to embark on further very expensive, large scale trials. The agents that are currently at various stages in the “PD regenerative pipeline” include;

## Isradipine

Some large epidemiological studies have suggested a slightly lower risk of PD among individuals treated with brain penetrating dihydropyridine calcium antagonists such as isradipine.<sup>1</sup> However similar benefits are associated with the non-brain penetrating amlodipine, and this association has been questioned as simply reflecting that patients prescribed these drugs are exposed to a specific pattern of health care, a behaviour which has greater relevance for PD risk than the exposure to the agent itself.<sup>2</sup> However credence is given from laboratory work showing that nigrostriatal cells have calcium dependent pace-making activity which is highly energy demanding that can be blocked by this class of drugs.<sup>3</sup> Furthermore, in mouse models of PD, isradipine protects against dopaminergic cell

death from either the MPTP or 6-hydroxy dopamine mitochondrial toxins.<sup>4</sup> There are, as yet, no data regarding the efficacy of this drug in transgenic animals or animals exposed to alpha synuclein preformed fibrils, currently considered to represent closer models of the neurodegenerative process of PD.<sup>5</sup>

Thus far, the clinical trial data in patients with PD shows that the 10mg dose of the drug is well enough tolerated with respect to blood pressure lowering, although the evidence of beneficial effects (~1 point advantage in the total Unified Parkinson's disease rating scale (UPDRS) score after one year) is modest and did not reach statistical significance.<sup>6</sup> Whether this effect size is of clinical importance is debatable, however these data have already been considered sufficiently strong to secure \$23m funding from NIH to take this agent to a phase 3 trial.

## Inosine

Epidemiological studies also suggest that higher levels of plasma uric acid are associated with a slower rate of progression of PD.<sup>7,8</sup> Again, while intriguing, this does not confirm that this association is in any way causal; perhaps individuals with higher CNS dopamine levels gain greater (dopamine-mediated) pleasure from uric acid rich foods/wines. Nevertheless, there are also some supportive data from the study of in-vivo animal models of PD that uric acid may have neuroprotective properties.<sup>9</sup> Uric acid itself is rapidly metabolised in the gut however oral administration of inosine, the precursor to uric acid, can successfully increase plasma and CSF uric acid levels.<sup>10</sup>

In a pilot clinical trial, patients with low levels of serum urate at baseline were recruited and randomised to receive low or medium doses of inosine or placebo for two years.<sup>11</sup> Most participants continued with their allocated drug for six months, however the number of participants had fallen by 50% at one year and only a small minority were still exposed to inosine/placebo beyond one year, although there appeared to be only a small risk of causing gout or kidney stones. Overall, the difference in the rate of worsening based on change in total UPDRS score per year indicated only a very slight advantage (~1 point) in the higher dose inosine treated group only, and careful consideration must be taken to decide whether this magnitude of signal of effect justifies the major further investment currently being sought.

## Intra-putaminal Glial cell derived neurotrophic factor (GDNF)

In 2003, an open label trial of intra-putaminal GDNF infusion in PD patients reported positive clinical and radiological outcomes, however a subsequent double blind trial could not replicate these beneficial effects.<sup>12,13</sup> Prolonged

Agent	Putative mechanism of action	Already licensed for use in humans?	Neuroprotective in vivo models?	Stage of human trial development
Isradipine	Calcium channel antagonism	Yes	Protects against MPTP and 6-OH dopamine toxicity in mice	Published phase 2 data. Due to start Phase III
Inosine	Anti-oxidant	Yes	Protects against 6-OH dopamine in rats	Published phase 2 data. Applying for funding for Phase 3.
Intra-putaminal GDNF	Neurotrophic factor	No	Protects against MPTP toxicity in non human primates	Phase 2 trial in progress
GM1 ganglioside	Neurotrophic factor	No	Protects against MPTP toxicity in non human primates	Published delayed start Phase 2 data
Deferiprone	Anti-oxidant	Yes	Protects against MPTP in mice	Published delayed start Phase 2 data.
Exenatide	GLP1 agonist	Yes	Protects against MPTP, 6-OH, LPS dopamine in mice	Published open label data. Due to start double blind phase 2.
Pioglitazone	Anti-inflammatory	Yes	Protects against MPTP toxicity in non human primates	Double blind phase 2 in progress
Alpha synuclein vaccination	Reduction of alpha synuclein levels	No	Reduces neurodegeneration in alpha synuclein transgenic mice	Safety studies in set up
Ambroxol	Increases GCase transcription & increases lysosomal biogenesis	Yes	In vitro data from human fibroblasts only.	Pharmacokinetic studies in set up.

debate followed regarding differences in the methods used to administer the GDNF in the double blind trial that may have explained this discrepancy. However further concerns emerged regarding the significance of a) anti-GDNF antibodies and b) cerebellar toxicity, observed in some laboratory animals treated with prolonged GDNF infusion.<sup>14</sup> Enthusiasm has been further dampened by the subsequent lack of beneficial effect of Cogane, an orally active GDNF inducer, and neurturin – a GDNF analogue delivered via gene therapy vector.<sup>15,16</sup>

Nevertheless, inspired by the original results and long term follow up of patients in the open label trial, the team in Bristol, UK are recruiting further patients to a further double blind trial to revisit and clarify the potential of intra-putaminal administration of GDNF

#### **GM1 ganglioside**

GM1 ganglioside is an important component of neuronal membrane signalling and has been shown to have neuroprotective effects in the toxin based animal models of PD.<sup>17,18</sup> In a double blind delayed start designed trial, early use of GM1 (administered as iv loading injection followed by twice daily subcutaneous injection) had clear acute symptomatic effects (~5 point improvement on the motor subsection of the UPDRS).<sup>19</sup> Individuals allocated to receive GM1 after a 24 week delay also had comparable symptomatic improvement but did not catch up with the benefits seen in the early start group during the two year exposure period. After cessation of the drug, all patients slowly deteriorated but again those individuals treated earlier had a modest advantage at all subsequent time points over the next two years. There is therefore ongoing interest in the potential of GM1 as both a symptomatic as well as a potential neuroprotective drug in PD.

#### **Deferiprone**

Excessive levels of iron have been identified in the substantia nigra of PD patients correlating with disease severity.<sup>20</sup> Deferiprone is a licensed treatment for iron chelation, known to cross the blood brain barrier.<sup>21</sup> In a further delayed start design trial, deferiprone reduced levels of iron in the SN seen using T2\* MRI, associated with a two point improvement in the UPDRS motor subscore.<sup>22</sup> This effect size is clinically important although these data cannot yet be interpreted as neuroprotection given that it remains possible that there is some interaction between iron chelation and dopaminergic treatment. A further pilot trial is ongoing. (Clinical trials.gov NCT01539837).

#### **Exenatide**

Exenatide is an agonist for the Glucagon-like peptide 1 receptor (GLP-1), the stimulation of which leads to an increase in insulin release and proliferation of pancreatic beta islet cells.<sup>23</sup> It is licensed for the treatment of type 2 diabetes mellitus. In vitro studies have suggested additional neurotrophic actions and in vivo studies have shown neuroprotective effects on dopaminergic cells in the toxin based animal models of PD.<sup>24,25,26,27</sup> Exenatide has also been shown to have beneficial effects on noradrenergic and serotonergic systems with positive behavioural effects in animals indicating potential relevance for non-motor symptoms of PD such as memory and mood disturbance.<sup>28,29</sup>

In a small open label trial, administration of exenatide by twice daily subcutaneous injection for 12 months was accompanied by a five point advantage on the motor subsection of the UPDRS together with a similar improvement in cognitive performance.<sup>30,31</sup> These advantages persisted 12 months after cessation of exenatide, however given the open label trial design, these results must be inter-

preted with caution unless/until they are replicated in a double blind trial.

#### **Pioglitazone**

Pioglitazone is a licensed treatment for type 2 diabetes mellitus, and acts to improve insulin resistance via an action on the peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) receptor. In the laboratory it has been shown that this agent reduces the expression of pro inflammatory cytokines by reactive microglia.<sup>32</sup> In the non-human primate MPTP model of PD, pioglitazone was found to reduce the loss of dopaminergic neurons and preserve motor function.<sup>33</sup>

As a result of these observations, a phase 2 trial of pioglitazone in 216 patients with PD is underway but as yet there are no efficacy data in humans with PD. However, despite the robust laboratory data supporting study of pioglitazone in tandem with intriguing mechanistic links between pioglitazone, mitochondrial function and PD, a potential association between pioglitazone and a small increased risk of bladder cancer has recently been discovered; in a meta-analysis it was calculated that this amounted to approximately five cases of bladder cancer for every 100,000 person years of pioglitazone treatment.<sup>34</sup> Careful scrutiny of clinical trial data regarding any benefit on PD progression will be required before any conclusion can be drawn in evaluating the acceptability of this level of risk.

#### **Alpha synuclein vaccination**

Given that we know that excessive levels of (even normal) alpha synuclein are sufficient to cause PD, the concept of using vaccination has arisen, to try and lower these levels.<sup>35</sup> The major problem has been identifying whether and how a peripherally administered antibody can access the central nervous system and target a predominantly intracellular



protein, and have sufficient selectivity for alpha synuclein and no other synucleins. In a transgenic mouse over-expressing human alpha synuclein, such an antibody has been shown to successfully lower alpha synuclein aggregation in neuronal cell bodies even after peripheral administration.<sup>36,37</sup> This has led to the initiation of two safety trials in small numbers of either healthy individuals (Clinicaltrials.gov/NCT02095171) or patients with early PD (Clinicaltrials.gov/NCT01885494). Similar attempts are underway to try and lower beta amyloid levels as a treatment for Alzheimer's disease.

### GCCase stimulation

The GBA gene encodes the enzyme glucosylceramidase (GCCase), and homozygous or compound heterozygous mutations in this gene are the cause of Gaucher's disease. Carrying a single GBA mutation has been shown to be the commonest genetic risk factor for PD.<sup>38</sup> There is a reduction in the activity of GCCase in brain tissue from PD and DLB patients (with or without GBA mutations).<sup>39</sup> This enzyme is thus a potentially very important target for the treatment of PD. Ambroxol hydrochloride is a small molecule that protects GCCase from thermal denaturation and boosts the function of GCCase through upregulation of the transcription factor TFEB.<sup>40</sup> It is licensed for use in humans and is present in many cough syrups as it also has a role as a mucolytic. It can cross the blood brain barrier.<sup>41</sup> Laboratory data therefore lend strong support to taking this agent into phase I clinical trial in PD patients.

### Interpretation

There can be some enthusiasm for the agents that currently represent the major focus as neuroprotective / neuroregenerative agents in PD. However, as yet none have emerged with robust double blind data to demonstrate a major neuroprotective effect in patients with PD.

Ongoing work to develop more useful animal models of PD neurodegeneration, and to develop a reliable biomarker that can be used to judge effects in humans with PD will be enormously helpful. Furthermore, while it is hoped that the identification of a disease modifying agent in PD will be of use in individuals with established disease, other initiatives are underway to try and identify "at-risk" populations who might be more responsive to treatments that require a relatively intact cellular architecture.

These issues and further work to understand PD pathogenesis remain of vital importance, but from a pragmatic perspective there is an urgency to efficiently confirm or exclude beneficial effects of those agents with the strongest supportive data without undue delay. To this end, there are considerable efforts to streamline and "de-risk" this process through the linked clinical trials initiative.<sup>42</sup> The challenges are great but with the breadth and depth of the efforts being made to overcome these challenges, it is reasonable to be optimistic. ♦

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