

Disease modifying therapies III: novel targets

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Highlights

- Greater insights into the mechanistic pathophysiology of neurodegeneration in PD has clarified multiple potential novel targets for intervention
- Utilizing gut microbial protein products to guide alterations to the gut microbiome in PD patients may be a future approach for disease modification
- Targeting inflammatory pathways at the systemic and central nervous system levels guided by objective measures such as microglial activation may increase success in modifying disease progression
- Suboptimal central nervous system penetration may explain why current trials with c-Abl inhibitors have been unsuccessful and suggests exploration of more brain-penetrant agents in this class of agents
- The promising clinical findings seen in GLP-1 receptor agonist trials have been supported by coherent dopaminergic imaging and insulin resistance molecular pathway changes
- The increased utility of biomarkers to stratify or refine patient selection, measure target engagement and monitor disease progression are potentially improving our approaches to disease modifying clinical trials

Introduction

Treatments that modify the progression of Parkinson's disease (PD) remain a central focus of current basic science and clinical research. Recent advancements in understanding PD pathophysiology have revealed a wide range of additional molecular therapeutic targets that may potentially be influenced with consequences for PD progression. From the outset, this raises questions whether such targets can be used to identify PD subtypes as well as also potentially serve as biomarkers for target engagement and for monitoring disease progression.

A broad range of individual pathways have previously been targeted for disease modification although no agent yet has unequivocal evidence of disease modifying properties in PD. Several aspects likely explain these disappointing outcomes including inadequate preclinical models of human disease, inadequate accounting of patient heterogeneity and therefore patient selection and a lack of utility of disease biomarkers to reliably measure the therapeutic engagement of the target.(Vijiaratnam et al., 2021b) The exact timing, duration, and dose for appropriate use of disease-modifying therapies further adds to the complex deliberations required when selecting patients.(Lang and Espay, 2018) Classification of patients into clinical subtypes that reflect pathophysiological differences and using biological markers which reflect stages of underlying disease have begun to offer prospects for potential individualization of treatment to achieve and demonstrate disease modification.(Van Rooden et al., 2010):(Marras and Lang, 2013) This shift away from traditional clinical markers as outcome measures is particularly critical at earlier disease stages where objective measures such as structural imaging(Mitchell et al., 2019):(Lambert et al., 2013), CSF protein measurement(Mollenhauer et al., 2019) and functional imaging of alpha synuclein pathology (if and when this becomes available)(Uzuegbunam et al., 2020) may provide more reliable confirmation of successful target engagement.

In this review, we explore emerging disease modification approaches that engage a number of novel targets and pathways which are thought to influence the pathogenesis of PD. Immune approaches directly targeting alpha synuclein will be covered in a separate paper in this issue (REFERENCE TO BE ADDED), as will approaches targeting GBA and LRRK2 (REFERENCE TO BE ADDED). A particular interest for consideration has been the proposition that the pathogenesis of PD begins outside the brain before reaching it via enteric neural projections(Braak et al., 2003) while specific factors such as gut microbiota

composition, activation of the immune system, the integrity of the neuronal lysosomal system, and the development of insulin resistance may also trigger or influence the severity of the neurodegenerative process.(Valdinocci et al., 2017)(Reish and Standaert, 2015)(Kotagal et al., 2013) We explore some of these specific aspects and outline therapeutic endeavours that have aimed to exploit their potential role in modifying the progression of PD. (Ongoing strategies are highlighted in table 1)

Novel therapeutic targets

Gut microbiome

The gastrointestinal (GI) tract represents a critical interface between an individual and their environment housing a complex community of microbiota.(Thursby and Juge, 2017) These organisms provide numerous benefits to the host including nutrient absorption(Rinninella et al., 2019), regulation of immunity(Gensollen et al., 2016) and protection against pathogens.(Baümler and Sperandio, 2016) The composition of microbiota tends to remain remarkably stable throughout an individual's life despite small fluctuations induced by environmental and physiological factors.(Karl et al., 2018)(Nagpal et al., 2018)

Alterations in gut microbiota composition and function leading to dysbiosis has been linked to the pathogenesis of several conditions including PD.(Scheperjans et al., 2015) Our understanding of the precise mechanism of how this occurs is growing. (Haikal et al., 2019)(Scheperjans et al., 2018) (Lubomski et al., 2020)(Holmqvist et al., 2014) The aggregation of pathological α -synuclein in some individuals begins in enteric nerve cells and is hypothesized to subsequently be transported to the CNS via the dorsal motor nucleus of the vagus (Braak et al., 2003)(Hawkes et al., 2007)based on evidence from non-human primate experimental models(Arotcarena et al., 2020) and epidemiological evidence suggesting a reduced risk of PD development in patients who undergo truncal vagotomy. (Cersosimo and Benarroch, 2012)(Kim et al., 2019) Further evidence of initial accumulation of α -synuclein in the appendix and a decreased risk of PD in patients who have undergone an appendectomy (Killinger et al., 2018) also supports this, though this finding will need further clarification considering conflicting evidence for appendectomies not increasing the risk of PD also exists. (Marras et al., 2016; Palacios et al., 2018; Svensson et al., 2016) This process of peripheral accumulation is potentially triggered by exposure to bacteria which produce bacterial amyloid proteins(Chen et al., 2016) with animal studies suggesting that microbiota are involved in motor impairments by virtue of gut-brain signalling by microbial

molecules modulating synuclein aggregation, microglia activation, and neuroinflammation.(Sampson et al., 2016)(Svensson et al., 2015)(Liu et al., 2017) The finding of an increased risk of PD in patients with inflammatory bowel disease(Villumsen et al., 2019) and the common finding of similar gastrointestinal symptoms in prodromal PD also provides support for an interaction between inflammation of the gut and neurodegeneration in the brain.(Perez-Pardo et al., 2017)

The role of altered gut microbiota in the progression of PD remains unclear as it is hard to disentangle what may be cause from consequence as it remains uncertain if biological factors that are altered in PD results in gut microbiome changes or if the contrary occurs. In any case, a pathological imbalance in the microbial community in PD patients seems to be a persistent finding.(Wallen et al., 2020)(Nishiwaki et al., 2020)(Zhang et al., 2020) Bacteria produce small molecules that can have variable impact on host health.(Obrenovich, 2018) Gut microbiota are associated with microglial maturation(Erny et al., 2015) and peripheral immune system responses while also directly being involved in α -synuclein aggregation.(Sampson et al., 2016) Furthermore, there may be a bidirectional relationship in that proinflammatory cytokine environment present in PD also seems to increase intestinal permeability thus further inducing a pathogenic state and alpha-synuclein aggregation/accumulation in both the central and enteric nervous systems.(Devos et al., 2013)(Forsyth et al., 2011)

It is not yet clear which are the precise microbiota of most relevance to PD pathogenesis. Bacteria from the *Lachnospiraceae* family are reduced in PD and tend to be involved in gut mucosal layer formation and production of short chain fatty acids (SCFAs)(Li et al., 2019)(Venegas et al., 2019) which are key mediators of GI function(Soret et al., 2010)(Grider and Piland, 2007) while also modulating inflammation.(Canani et al., 2011)(Koh et al., 2016) Alterations in production of these bioactive molecules is associated with altered gastrointestinal function and more severe PD phenotypes though potential mechanisms for causation requires further exploration. (Cirstea et al., 2020; Tan et al., 2021a) Conversely, an increase in certain species such as bacteria from the *Akkermansia* genus in PD may have negative consequences by increasing GI permeability and exposing neural cells to toxins.(Nishiwaki et al., 2020)

Targeting the Gut–Brain Axis for disease modification

Several studies have explored the use of antibiotics at low concentrations to either inhibit or eliminate microorganisms while also altering CNS pathways.(Bortolanza et al., 2018):(Pradhan et al., 2016) Though not specifically explored for gut microbiome modification, Minocycline has been the most extensively studied antibacterial agent to date in view of its promising anti-inflammatory and neuroprotective properties in animal studies.(Du et al., 2001):(Wu et al., 2002):(Jiang et al., 2014) A phase 2 trial did not however show benefits and a subsequent long-term study found that premature discontinuation was highest with minocycline despite no significant differences in adverse events or subsequent need for symptomatic therapy being noted between groups studied. (Kieburz et al., 2008):(Ravina et al., 2006)

Dietary supplementation approaches such as Omega-3 Fatty Acids and Vitamins have also been explored although formal clinical trials are lacking.(Lorente-picón and Laguna, 2021) More holistic dietary plans like the Mediterranean diet may confer beneficial impacts on the brain and lower the incidence and progression of PD via promoting SCFA production and anti-inflammatory actions while maintaining a healthy microbiota profile. (Statovci et al., 2017):(Maraki et al., 2019):(Yin et al., 2021) Whether manipulation of the diet can lead to significant neuroprotection remains unclear and the conduct of randomized controlled dietary trials poses additional challenges.

Probiotics comprise live microorganisms and have been proposed to confer health benefits to the host(Hill et al., 2014) by modulating gut microbiota and preventing dysbiosis. Encouraging evidence from GI and psychiatric disorders(Derwa et al., 2017):(Wallace and Milev, 2017) has led to this approach being considered in PD(Gazerani, 2019) though current evidence exploring the potential for neuroprotection is still limited to preclinical (Goya et al., 2020):(Srivastav et al., 2019):(Hsieh et al., 2020) and in vitro studies of human samples(Magistrelli et al., 2019) though promising findings for GI symptom management has been noted in clinical studies.(Liao et al., 2020):(Sun et al., 2021):(Barichella et al., 2016):(Tan et al., 2021b)

Prebiotics are non-digestible food ingredients such as dietary fibres that potentially provide benefits to the host by selectively stimulating the growth of beneficial microorganisms.(Pandey et al., 2015):(Hutkins et al., 2016) The lower levels of SCFA producing bacteria in PD has been considered a target for potential correction with prebiotics.

Studies exploring this are currently confined to the pre-clinical setting.(Zhou et al., 2011):(Cantu-Jungles et al., 2019):(Dong et al., 2020) Combining probiotics and prebiotics synergistically, as “symbiotics” is of potential merit as prebiotic components can potentially selectively favour the growth of probiotic microorganisms with potential superior downstream beneficial effects to the host’s health in comparison to using an individual item. (Markowiak and Ślizewska, 2017) Exploring this approach, healthy controls suffering from constipation were given yogurt containing *Bifidobacterium animalis* and fructo-oligosaccharide prebiotics with improvements in GI symptoms. (De Paula et al., 2008) In PD, a randomised trial follow-up treatment with fermented milk containing strains of probiotics and prebiotic fibre after initial treatment with antibiotics improved constipation in comparison to placebo.(Barichella et al., 2016)

Faecal microbiota transplantation (FMT) from healthy donors has shown success in the management of GI disease.(Paramsothy et al., 2017) The link between PD pathophysiology and gut dysbiosis has led to this approach also being explored as a potential intervention against the neurodegenerative process. FMT studies in mice suggest that when healthy mice are transplanted with faeces from MPTP-intoxicated mice they develop motor impairments and striatal dopamine deficiency while the contrary also holds true.(Sun et al., 2018) This seems to occur by virtue of reduced microglial and inflammatory pathway activation in both the colon and striatum.(Sampson et al., 2016):(Sun et al., 2018) Furthermore, FMT from PD patients into mice overexpressing alpha-synuclein appears to result in a worsening of their motor phenotype.(Sampson et al., 2016) Human studies are currently confined to small studies utilizing FMT from healthy donors either via colonoscopy or a naso-jejunal tube with more significant short term motor and non-motor benefits being noted with the former though mild GI side effects appear to be common with both approaches.(Huang et al., 2019):(Xue et al., 2020) A randomized, placebo-controlled double-blind study utilizing a naso-jejunal approach with either healthy donor or own patient stool is currently underway (NCT03808389). Apart from regular clinical assessments after the procedure, stool samples will also be taken regularly for microbiome analysis over a period of 1 year. This approach will be useful in informing on salient factors for success such as the appropriate microbiota composition.

Microbes can be engineered to act like living therapeutic factories in the human body to treat disorders, as “live biotherapeutic products” (LBPs).(Ainsworth, 2020) This could be useful as

modified organisms potentially have additional benefits beyond producing specific useful molecules such as SCFAs by directly modulating aberrant pathways themselves (Ahmed et al., 2019) while also being more amenable to targeted delivery (Ozdemir et al., 2018) and responsive to salient environmental input such as inflammation. (Charbonneau et al., 2020); (Pedrolli et al., 2019) This approach showed promise in a recent study exploring a strain of *Lactococcus lactis* which was engineered to produce Glucagon-like peptide-1 (GLP-1), a molecule with prior evidence of neuroprotective effects in MPTP treated mice with the engineered LBP reducing neuroinflammation and motor disability. (Fang et al., 2020)

Taken together, the composition of gut microbiota may play an important role in the development and progression of PD. Further clarification is required regarding the precise mechanisms by which organisms' impact on PD pathophysiology and the timing and appropriate composition of organism that would be necessary to alter aberrant mechanisms. Specific biomarkers such as SCFA levels may help guide the precise approach that should be adopted in different individuals at different stages of the disease.

Inflammation

The immune system plays an important role in driving neurodegeneration in PD. Genetic and epidemiological data support this premise. PD is associated with polymorphisms in the human leucocyte antigen (HLA) regions which encode proteins involved in antigen recognition and presentation (Ferreira and Romero-Ramos, 2018); (Nalls et al., 2014) while Genome Wide Association Studies in PD have implicated genes modulating adaptive immunity. (Gagliano et al., 2016); (Holmans et al., 2013) Evidence from epidemiological studies suggesting that non-steroidal anti-inflammatory drug and immunosuppressive therapy intake reduces the risk of developing PD (Samii et al., 2009); (Gao et al., 2011); (Racette et al., 2018). Furthermore, PD patients exhibiting faster motor progression and a higher likelihood of developing cognitive impairment seem to have a proinflammatory serum cytokine profile at baseline. (Williams-Gray et al., 2016)

At the cellular level, inflammation in PD has been recognised for a number of years (McGeer et al., 1988) though its contribution to neurodegeneration has only more recently been appreciated (Ransohoff, 2016). Infiltration of brain parenchyma with T lymphocytes and deposition of immunoglobulin in proximity to Lewy pathology in areas of neurodegeneration have been noted in post-mortem studies. (McGeer et al., 1988); (McGeer et al.,

2003)(Brochard et al., 2009) More recently, profiling of cytokines in blood and cerebrospinal fluid (CSF)(Mollenhauer et al., 2017)(Williams-Gray et al., 2016) as well as radiotracer binding in positron emission tomography studies reflective of microglial activation have provided further evidence supporting a causal link between neuroinflammation and disease progression.(Gerhard et al., 2006)(Koshimori et al., 2015) Human foetal transplant studies seem to suggest early microglial cell infiltration predates Lewy pathology(Warren Olanow et al., 2019) though overexpression of α -synuclein in animals seems to be necessary in inducing an inflammatory response prior to cell loss suggesting an initiator role for α -synuclein and a downstream facilitatory role for inflammation.(Chu et al., 2012)(Sirabella et al., 2018) The inflammatory environment results in neuronal damage as a result of oxidative stress mediated by activation of inflammasomes which are components of the innate immune system that propagate inflammatory responses.(Kannarkat et al., 2013) Dopaminergic neurons are particularly susceptible to this inflammasome activation via microglia, while blood brain barrier dysfunction in response to neurodegeneration further permeates lymphocytic infiltration.(Anderson et al., 2018)

The NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome plays a prominent role in inflammation in PD.(Gordon et al., 2018) NLRP3 binds to microglia triggering pro-caspase 1 aggregation, and therefore release of proinflammatory cytokines, interleukin-1 β (IL-1 β), and IL-18, which mediate pyroptosis, a type of inflammatory programmed cell death.(Latz et al., 2013) This activation occurs early in PD and induces microgliosis.(Gordon et al., 2018) Aggregated human α -synuclein introduction in a primary mesencephalic neuron-glia culture system also seems to induce microglial activation and a proinflammatory profile in the peripheral circulation(Zhang et al., 2005)while this upregulated peripheral immunity is postulated to selectively upregulate cytokines in the nigrostriatal system. (Williams-Gray et al., 2016)(Dursun et al., 2015)

Inflammatory therapeutic targets

Immune manipulation in animal models seems to alter susceptibility to and severity of dopaminergic and/or synuclein related pathology. Firstly, knocking out CD4⁺ lymphocytes and administration of regulatory T cells (T-reg cells) (Brochard et al., 2009)(Reynolds et al., 2010) attenuates dopaminergic cell death in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse models of PD. Furthermore, knocking out major histocompatibility class II in

mice overexpressing alpha-synuclein seems to prevent microglial activation and neurodegeneration.(Harm et al., 2013)

In mouse models of PD, the immunosuppressant ciclosporin (a calcineurin inhibitor) improved motor and cognitive deficits though this has not been explored further in human studies.(Tamburrino et al., 2015) Although animal models have suggested that other immunomodulatory agents such as minocycline and pioglitazone have efficacy against neurodegeneration, phase II trials have been disappointingly negative.(Kiebertz et al., 2008):(Ravina et al., 2006):(Simuni et al., 2015)

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) inhibitor simvastatin appeared to provide dopaminergic and motor behaviour benefits in rodents primarily through immune suppression.(Yan et al., 2014):(Selley, 2005) A recent phase II study did not however demonstrate disease modifying effects in people with PD (C. Carroll, K. Stevens, B. Jones, S. Campbell et al., 2020) (NCT02787590). The promising finding of a less severe deterioration in F-dopa uptake in a recent randomised controlled trial of Lovastatin over 48 weeks however maintains the interest in this class of agents and more prolonged follow-up studies will be required to explore the potential differential effectiveness of agents within this class.(Lin et al., 2021)

Sargramostim, a human recombinant granulocyte–macrophage colony-stimulating factor (GM-CSF) is a promising agent in the early stages of development. This factor seems to have anti-inflammatory properties by improving regulatory T cell function.(Mosley et al., 2012) A phase 1 study in PD patients suggested that sargramostim results in motor improvements and improvements in magnetoencephalography-recorded cortical motor activity as well as regulatory T cell activity after 6-8 weeks of treatment. (Gendelman et al., 2017) Concerns regarding dose-dependent adverse events led to the setup of a further phase 1b study exploring this agent at a lower dose with more prolonged monitoring, in which similar benefits in UPDRS scores and immune markers were noted after 1 year.(Olson et al., 2021) These promising findings will need to be clarified in larger blinded clinical trials though clarity on which PD sub-population would be most amenable to this form of immune modulation potentially guided by T-reg cell activity may be informative.

The agent AZD3241 is an inhibitor of myeloperoxidase (MPO) an enzyme involved in microglial activated inflammation in PD. (Gerhard et al., 2006)(Gellhaar et al., 2017) Early phase studies suggest suppression in microglial activation after 8 weeks of treatment with reductions noted in ligand binding to the microglia marker 18 kDa translocator protein (TSPO) across all examined brain regions with an acceptable safety profile though evidence for dopaminergic neuronal protection and the clinical implications of this reduced activity remain unclear. Further studies will be needed to confirm whether the ligand 11C-PBR28 used in this study is mechanistically related to the pathophysiology of Parkinson's disease as this is currently unclear.(Posener et al., 2014)(Jucaite et al., 2015) Imaging guidance with this radioligand to TPSO to determine which patients might be most likely to benefit from suppression of microglial activation and to thus confirm target engagement in clinical trials would be potentially extremely useful although the associated expense of repeated PET imaging in large numbers of patients that will be required to demonstrate disease modification, is a major issue.

Azathioprine, an immunosuppressant widely used for management of immune-related conditions is a purine analogue that inhibits nucleic acid synthesis with broad effects on reducing lymphocytic proliferation and attenuating immune responses.(Lennard, 1992) Its established efficacy in neurological conditions(Casetta et al., 2007) , ease of administration and well established protocols for toxicity monitoring make it a potential consideration in PD. A 'proof of concept' study has recently opened for recruitment in early PD with the goal of exploring progression over 12 months of treatment and 6 months after drug withdrawal. (Greenland et al., 2020) The trial design has enriched recruitment for patients anticipated to have more rapid disease progression based on their age, and cognitive profile which should allow detection of meaningful effects over a shorter follow up time period. The exploration of blood, CSF and neuroimaging parameters of immune activation as well as the application of inclusion criteria using validated modelling factors that predict rapid disease progression(Velseboer et al., 2016) are of particular interest.

Treatments targeting the NLRP3 inflammasome pathway has been of recent interest and largely comprise agents which target IL-1. The recombinant IL-1 receptor antagonist Anakinra, neutralizing IL-1 β antibody Canakinumab and the soluble IL-1 receptor Riloncept are all credible candidates for exploration in PD with demonstrated efficacy profiles in other immunological disorders sharing this mechanism.(Dinarello and van der Meer, 2013) The

sulfonylurea glyburide also appears to inhibit the NLRP3 inflammasome by virtue of reducing IL-1 β production(Lamkanfi et al., 2009) . The small molecule inhibitor MCC950 shares a similar structure to sulfonylureas and appears promising in NLRP3 inflammasome inhibition. This treatment appears to prevent dopaminergic cell loss and disrupt a-synuclein propagation while also inhibiting cross reaction between a-synuclein and microglia. (Gordon et al., 2018)(Franklin et al., 2014) A phase 1 trial exploring an agent with this mode of action, Inzomelid (NCT04015076) recently completed recruitment. Results of safety and tolerability as well as biomarker outcome measures of NLRP3 inhibition in blood will be of particular interest.

MicroRNAs (miRNA) are involved in post-transcriptional regulation of gene expression and may also play a role in NLRP3 inflammasome-mediated neuroinflammation. Transfection of miR-7 or miR-153 in vitro reduces NLRP3 protein levels, while downregulating microglial activation and rescue from neurodegeneration.(Zhou et al., 2016)(Fragkouli and Doxakis, 2014) The downregulation of other pro-inflammatory molecules such as miR-155 reduces microgliosis and neurodegeneration and have also shown promise in animal studies(Thome et al., 2016) though the lack of brain regional specificity of this class of agents may limit future prospects.(Leggio et al., 2017)

Neurotrophic factors

Neurotrophic factors are a family of growth factor secreted proteins involved in the promotion of development, functioning and survival of neurons. The loss of neurotrophins predisposes to neurodegeneration and neuroinflammation(Ferreira et al., 2018) while their administration reduces these effects.(Elkouzi et al., 2019) The glial-cell derived neurotrophic factor (GDNF) family is a group of related proteins which promote neurite outgrowth, synapse formation, and midbrain dopamine release thus making them an attractive target for slowing PD degeneration.(Ibáñez and Andressoo, 2017) This is thought to occur by GDNF binding to multiple receptors though neuroprotection specifically seems to be dependent upon the tyrosine kinase receptor Ret.(Drinkut et al., 2016)

Prevention of neurodegeneration with GDNF injections seems to vary between mouse models studied(Hoffer and Harvey, 2011) though chronic infusion in normal Rhesus monkeys results in retrograde transport to nigral dopamine cell bodies.(Ai et al., 2003) Clinical trials have however, been disappointing to date.(Gill et al., 2003)(Lang et al., 2006)(Slevin et al.,

2007)(A. Whone et al., 2019a)(A. L. Whone et al., 2019b) Despite being well tolerated, and F-dopa imaging changes suggesting encouraging responses to continuous putaminal GDNF infusion, the primary end point of improvements in UPDRS scores has not been met in any double blinded trial. Potential explanations relate to the timing of the intervention and/or whether the GDNF “ret” receptor is downregulated in the presence of alpha synuclein pathology.(Decressac et al., 2011)

A separate phase I trial of GDNF gene delivery with the adeno associated virus 2 (AAV2) using intraoperative MRI to target vector to the putamen, while monitoring convection-enhanced delivery with a surrogate tracer (NCT01621581) reported improvements in ¹⁸F-DOPA PET signal though still with limited putaminal coverage despite the novel techniques adopted suggesting the need for further optimization of delivery methods.(Heiss et al., 2019) A separate phase 1 trial is currently underway (NCT04167540) with the aims of recruiting patients with earlier disease while achieving more optimal tissue coverage by using a novel neurosurgical approach.(Bankiewicz et al., 2016) A homologue of GDNF, neurturin (NRTN) has also been explored as a potential therapy.(Kotzbauer et al., 1996) Results of recombinant NRTN injections in animal models of PD have been mixed(Gasmi et al., 2007)(Herzog et al., 2007) and while (AAV2- neurturin/CERE-120) showed promising UPDRS score improvements in a phase I study(Marks et al., 2008), similar to GDNF infusion trials, no clinical improvements were noted in a subsequent phase II study.(Marks et al., 2010) Improvements in secondary outcomes in a sub-group of treated patients at delayed assessments however emphasize the possible need for more prolonged follow-up in these studies. Furthermore, findings from post mortem studies of patients with PD and those treated with this modality suggest the importance of targeting patients earlier, with less severe nigrostriatal degeneration while also improving surgical delivery techniques to enhance volumes of infusate.(Bartus et al., 2015)(Kordower et al., 2013) Despite mitigating some of these aspects, the most recent clinical trial failed to meet primary outcome improvements in UPDRS 3 scores after 24 months(Warren Olanow et al., 2015) though a subsequent post mortem study on 1 patient enrolled in the trial suggested ongoing robust expression of NTRN but limited tissue coverage despite improvements in delivery technique.(Chu et al., 2020)

A number of other novel formulations of GDNF have shown promise in the pre-clinical setting. AGT-190, a recombinant GDNF plus human insulin receptor targeting chimeric monoclonal antibody IgG-fusion protein was developed with the goal of facilitating GDNF

transport across the blood-brain-barrier when intravenously administered. This agent increased striatal tyrosine hydroxylase activity and improved limb function in 6-hydroxydopamine (6-OHDA) lesioned mice (Fu et al., 2010) while proving to be well tolerated in Rhesus monkeys. (Pardridge and Boado, 2009) BT-13 is a further novel GDNF mimetic that seems to reverse cell death and improve pain sensitivity in animal studies when administered peripherally though further pre-clinical molecular adjustments to improve brain penetration are ongoing. (Mahato et al., 2020) (Sidorova et al., 2017)

Cerebral dopamine neurotrophic factor (CDNF) is a protein with structural and functional properties distinct from other neurotrophic factors and is involved in the regulation of inflammation and apoptosis. This protein also specifically targets injured tissues thus making it of interest in improving nigrostriatal cellular dysfunction. (Lindahl et al., 2017) CDNF was found to be neuroprotective in midbrain dopaminergic neurons in a rat model. (Lindholm et al., 2007) Several phase I/II studies evaluating the value of direct putaminal infusion of this agent have now been completed with a press release confirming safety and tolerability by PD patients and encouraging PET imaging data (“Herantis Pharma Plc Announces Topline Results of Phase 1-2 CDNF Trial,” n.d.) though clinical results are not yet in the public domain (NCT03775538, NCT03295786) while a long-term follow-up study is currently still active (NCT04228653).

Platelet-derived growth factors (PDGFs) exist in several isoforms. The PDGF-BB dimer has been demonstrated to have restorative effects in the dopaminergic system in pre-clinical PD studies. (Zachrisson et al., 2011) (Pietza et al., 1996) Intravenously administered recombinant human PDGF-BB was recently explored in a phase 1/2a study. Safety outcomes were met and efficacy benefits confined to DAT binding improvements. (Paul et al., 2015) Future studies will need to establish if clinical end points can be met over a more prolonged follow-up period and if repeated doses of treatment is necessary to achieve this. Other neurotrophins such as brain-derived neurotrophic factor and vascular endothelial growth factor have not yet passed the preclinical stage. (Tsukahara et al., 1995) (Yasuhara et al., 2004)

The potential of trophic factors as disease modifying agents in PD hangs in the balance following the most recent failed results of GDNF trials. Nevertheless, there remains enthusiasm for this approach and there may be a subpopulation of patients who may benefit from GDNF or other neurotrophic factors, and further exploration of this type of approach is

likely despite the mixed findings to date. Challenges do however need to be overcome and include determining whether some or all individuals express the receptor for GDNF, the determination of the appropriate delivery method as well as the potential relative merits of the different individual factors or a combination of neurotrophic factors.

c-ABL

The tyrosine-protein kinase abelson (c-ABL) is involved in a variety of physiological functions including autophagy and as a mediator of oxidative stress.(Hantschel and Superti-Furga, 2004) c-Abl is activated in PD with higher levels noted in human post-mortem brains and toxin animal model studies. This leads to inhibition of parkin through tyrosine phosphorylation, and therefore loss of α -synuclein recycling(Brahmachari et al., 2017) with resultant neural degeneration from accumulation of toxic substrates which correlates with disease progression.(Karuppagounder et al., 2014) Deletion of c-abl appears to reduce α -synuclein aggregation, pathology, and behavioural deficits thus making inhibitors of c-abl a potential therapeutic prospect.(Brahmachari et al., 2016)

Nilotinib is a c-abl inhibitor used for the treatment of chronic myeloid leukaemia. Evidence from an MPTP animal model PD study also suggests that nilotinib can protect dopaminergic neurons.(Karuppagounder et al., 2014) An initial pilot study showed good safety and tolerability.(Pagan et al., 2016) A recent phase 2, randomized, double-blind, placebo-controlled trial of 75 patients examined target engagement with either 150mg or 300mg per day of nilotinib. This study found mean nilotinib concentrations in the CSF of 0.94nM and 1.6nM for the 2 doses respectively in comparison to the reported cellular half-maximal inhibitory concentration of 20nM for the inhibition of c-abl by nilotinib.(Weisberg et al., 2006) The authors did report changes in dopamine metabolites in the CSF although these findings were confounded by the increased use of levodopa in the cohort while a reduction in α -synuclein oligomers was only noted with the lower 150 mg dose.(Pagan et al., 2020) A further concern in the study was a noted worsening in functional and cognitive assessments among participants using the 300mg dose. The Nilo-PD study also investigated the use of nilotinib at the same 2 doses in patients with moderate to advanced stages of PD. The study again demonstrated poor CSF penetration by nilotinib and a lack of clinical improvement after 6 months.(Simuni et al., 2021) Taken together, these studies provide little justification for further exploration of this drug in PD. Alternatives in this class of agents with better CNS penetration potential may, however, still offer hope for PD disease modification. Promising

findings were noted with Radotinib in preclinical studies (Lee et al., 2018) with recruitment into a phase 1 study imminent (NCT04691661). SCC-138 (K-0706), an alternative c-Abl inhibitor has shown promise in achieving desirable CSF concentrations and good safety and tolerability in an early phase study. (Goldfine et al., 2019) A Phase 2 randomized, double-blind, placebo-controlled study (PROSEEK; NCT03655236) is currently underway in early, treatment naive PD patients. The utility of biomarkers such as Dat SPECT imaging and skin biopsies as outcome measures in addition to other measures of target engagement is of interest and may improve interpretability.

Lysosomal Dysfunction

The autophagy–lysosome system facilitates the degradation of proteins and malfunctioning or senescent cellular organelles. (Yu et al., 2018) Loss of function variations in genes encoding proteins involved in lysosomal function (e.g. *GBA1*, *LRRK2*, *VPS35*, *ATP13A2*, etc) can lead to their dysfunction (Futerman and Van Meer, 2004) and commonly occur as either single damaging alleles or (in up to 20% of cases) multiple damaging variants in combination. (Chang et al., 2017) (Robak et al., 2017) The coexistence of genetic variants involved in lysosomal vesicular trafficking in PD that have previously been noted in other conditions such as *NPC1* in Niemann-Pick type C (NPC) disease (Kluenemann et al., 2013) and α -N-acetylglucosaminidase (*NAGLU*) in Sanfilippo syndrome (Winder-Rhodes et al., 2012) further supports the contribution of lysosomal dysfunction in the pathogenesis and progression of PD. These variants appear to compound cellular dysfunction via a variety of downstream pathways ultimately leading to dysfunction. (Klein and Mazzulli, 2018) Lysosomal dysfunction then results in accumulation of α -synuclein by virtue of its reduced degradation. (Cuervo, 2004) This potentially drives further pathological aggregation of alpha synuclein by selective polymerization of the protein due to hydrophobic residues that specifically render the protein susceptible (Giasson et al., 2001) while other accumulating metabolites such as glucosylceramide further interact and induce aggregation. (Mazzulli et al., 2011) Toxic aggregates of alpha synuclein then negatively impact on lysosomal function in a bidirectional pathogenic loop. (Mazzulli et al., 2011)

Therapies encompassing a range of approaches targeting lysosomal pathways to improve α -synuclein degradation have been considered including enzyme replacement, substrate reduction, inhibition of pathways causing cell death and stimulation of pathways which compensate for loss of lysosomal proteins. Of the PD-associated genes identified thus far,

GBA1 and *LRRK2* and their downstream proteins have been best explored as targets and are covered in detail in an accompanying review (REFERENCE TO BE INSERTED).

Alternative lysosomal targets that are in earlier stages of evaluation include therapies used for treating NPC that lower cholesterol levels. These agents have shown promise in reducing accumulation of α -synuclein in a PD mouse model (Bar-On et al., 2006) and have potential for future clinical trial exploration in PD patients. Transcription factor EB (TFEB), a regulator of the autophagy-lysosomal pathway has also been gaining interest. Overexpression of TFEB in rat models rescues midbrain DA neurons (Decressac et al., 2013) and reduces protein aggregation in ageing neural stem cells and fibroblasts.(Leeman et al., 2018)(Johmura et al., 2021) Furthermore, inhibition of mammalian target of rapamycin (mTOR), a negative regulator of autophagy induces nuclear translocation of TFEB (Martina et al., 2012) while intracerebral infusion and oral intake of rapamycin, an mTOR inhibitor reduces α -synuclein accumulation in transgenic mice (Crews et al., 2010) and improves their motor performance.(Bai et al., 2015) Human studies with rapamycin are challenging in view of potential detrimental long-term side effects. (Blagosklonny, 2019) Trehalose is an alternate activator of autophagy that bypasses mTOR and inhibits the glucose transporter solute carrier 2A. (DeBosch et al., 2016) This agent is orally administered and has been shown to enhance the clearance of α -synuclein in a number of animal studies (Lan et al., 2012)(Rodríguez-Navarro et al., 2010)(Sarkar et al., 2007) while also improving motor deficits.(He et al., 2016)

Autophagy is also partly regulated by chaperones such as heat shock cognate protein 70 (Hsc70). Hsc70 targets and transports cytoplasmic proteins into lysosomes for degradation through association with the lysosome associated membrane protein 2A (LAMP2A). Wild-type α -synuclein is partly degraded via this pathway whereas mutant α -synuclein interferes with it.(Cuervo, 2004) Overexpression of LAMP2A upregulates autophagy, decreases α -synuclein accumulation and protects against α -synuclein toxicity (Xilouri et al., 2013) thus potentially making it a potentially interesting therapeutic avenue. Geniposide, a bioactive glycoside is one such example which has been shown to indirectly increase LAMP2A expression with resultant reductions in α -synuclein levels in an animal study. (Su et al., 2016)

Iron is a crucial cofactor in oxidation–reduction reactions which regulate cellular function(Ward et al., 2014) though it can be harmful in excess. The injection of iron into rats

results in decreased striatal dopamine and parkinsonism (Ben-Shachar and Youdim, 1991) while iron deposition in the basal ganglia occurs in PD in excess of normal aging and potentially precedes symptom onset.(Ward et al., 2014) Mutations and dysregulation of iron-related proteins result in iron accumulation in dopaminergic neurons. (Castellani et al., 2000) (Jiang et al., 2010)(Jia et al., 2015) This may partly contribute to α -Synuclein oligomerization(Peng et al., 2010) although increased levels of α -Synuclein can further result in increased levels of intracellular iron. Iron deposition can result in defective autophagy further contributing to increased α -synuclein levels in dopaminergic neurons.(Wan et al., 2017)

Iron chelators such as deferoxamine (DFO) appear to induce autophagy in pre-clinical studies.(Wu et al., 2010) (Pullarkat et al., 2014) Iron chelation with deferiprone has been shown to improve iron content on imaging while also mitigating clinical progression in 2 small human studies.(Devos et al., 2014)(Martin-Bastida et al., 2017) Results from a larger placebo-controlled study (FAIRPARK-II) are expected in 2021.

Insulin resistance

Type 2 diabetes mellitus (T2DM) is now firmly established as a risk factor for developing PD(Chohan et al., 2021; De Pablo-Fernandez et al., 2018) while its coexistence with PD also results in more severe axial motor features and the development of earlier cognitive impairment.(Kotagal et al., 2013)(Bosco et al., 2012; Chohan et al., 2021) This link may be at least in part explained by disruptions in physiological insulin signalling (insulin resistance). Insulin resistance can occur as a direct consequence of alpha-synuclein pathology (Gao et al., 2015) and can also contribute to ongoing neurodegenerative processes thus impacting on neuronal survival.(Athauda and Foltynie, 2016) The restoration of these dysfunctional pathways via routes bypassing the insulin receptor have therefore been of therapeutic interest.(Girges et al., 2021)

Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for the treatment of type 2 diabetes. These agents stimulate glucose level-dependent insulin release, and β islet cell proliferation.(Buse et al., 2004) GLP-1 receptors exist in the brain and agonists appear beneficial in PD animal models for a variety of reasons including reducing insulin resistance, inflammation(Yun et al., 2018)(Harkavyi et al., 2008)(Weder et al., 2014) and the

accumulation of α -synuclein (Zhang et al., 2019) while also exhibiting neurotrophic properties.(Perry et al., 2002) These findings are further supported by a recent cohort study of T2DM patients demonstrating that patients treated with GLP-1 agents have a reduced risk of developing PD than people with or without diabetes even after adjustment for potential confounders.(Brauer et al., 2020)

Exenatide is the most widely tested of these agents. In an open label Phase II study, use of this drug was associated with motor and cognitive improvements in comparison to randomised controls (Aviles-Olmos et al., 2013) which persisted for 12 months after drug withdrawal.(Aviles-Olmos et al., 2015) A follow-up double-blind Phase II trial demonstrated similar improvements in motor outcomes after 48 weeks of exposure though the effect, while still significant, was less in magnitude 12 weeks after drug withdrawal, raising the question whether its mechanism of action may partly relate to maintenance or transient restoration of neuronal dopaminergic function.(Athauda et al., 2017) The trial included an assessment of target engagement using extracellular vesicle biomarker analysis which confirmed changes in the insulin signalling pathway in association with exenatide exposure.(Athauda et al., 2019)

A Phase III trial of exenatide is currently actively recruiting (NCT04232969) with results expected in 2024.(Vijjaratnam et al., 2021a) Other trials of GLP-1 agonists are also currently underway. An open label Phase I study of exenatide (NCT03456687) is exploring if exenatide results in changes in free water MRI, while Phase II studies of Liraglutide and Lixisenatide (NCT03439943) are also due to report their findings. A number of other novel long acting GLP-1 agonists are also currently undergoing studies- NLY01 (NCT03672604), Semaglutide (NCT03659682), PT320 (NCT00964262).

3.0 Conclusion and future direction

PD pathophysiology is complex and the mechanisms contributing to neurodegeneration are increasingly recognised to extend beyond α - synuclein aggregation including; dysfunction in lysosomes, contributions from neuroinflammation and the insulin signalling pathway while encompassing abnormalities outside the central nervous system such as the gastrointestinal tract and its ecosystem. These intertwined pathways and the consequent clinical heterogeneity in the pathogenetic mechanisms between PD patients have likely not been adequately factored into current therapeutic endeavours and may be critical moving forward. Advances

in techniques that objectively quantify the extent to which an individual may respond to a specific disease modifying approach based on biomarker assessment of specific abnormalities and subsequent target engagement will be increasingly important.

There are a broad range of neuroprotective agents currently being explored in clinical trials. Considering the heterogeneity of PD and growing evidence of the relevance of different biological pathways, trial designs will need to consider patient stratification issues. Multiple therapies or even combinations of therapies may be required and platform trials enabling testing multiple agents in parallel will improve the efficiency of drug assessment.

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NV prepared the first draft of the manuscript. All authors provided edits and revised the manuscript for intellectual content.

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Data Statement

Not applicable at this stage.