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Review Article

Targeting kinases in Parkinson's disease: A mechanism shared by LRRK2, neurotrophins, exenatide, urate, nilotinib and lithium

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ABSTRACT

Several kinases have been implicated in the pathogenesis of Parkinson's disease (PD), most notably leucine-rich repeat kinase 2 (LRRK2), as *LRRK2* mutations are the most common genetic cause of a late-onset parkinsonism that is clinically indistinguishable from sporadic PD. More recently, several other kinases have emerged as promising disease-modifying targets in PD based on both preclinical studies and clinical reports on exenatide, the urate precursor inosine, nilotinib and lithium use in PD patients. These kinases include protein kinase B (Akt), glycogen synthase kinases-3β and -3α (GSK-3β and GSK-3α), c-Abelson kinase (c-Abl) and cyclin-dependent kinase 5 (cdk5). Activities of each of these kinases are involved either directly or indirectly in phosphorylating tau or increasing α-synuclein levels, intracellular proteins whose toxic oligomeric forms are strongly implicated in the pathogenesis of PD. GSK-3β, GSK-3α and cdk5 are the principle kinases involved in phosphorylating tau at sites critical for the formation of tau oligomers. Exenatide analogues, urate, nilotinib and lithium have been shown to affect one or more of the above kinases, actions that can decrease the formation and increase the clearance of intraneuronal phosphorylated tau and α-synuclein. Here we review the current preclinical and clinical evidence supporting kinase-targeting agents as potential disease-modifying therapies for PD patients enriched with these therapeutic targets and incorporate LRRK2 physiology into this novel model.

1. Introduction

Parkinson's disease (PD) is the second most common and fastest growing neurodegenerative disorder with a worldwide prevalence that is predicted to more than double over the next 25 years [1]. Identification of viable druggable targets that mediate neuroprotection is critical to the search and discovery of disease-modifying treatments for PD, which are treatments that can delay the onset of PD and/or slow PD progression, and many such targets have been proposed [2]. However, cell culture and animal models from which these targets have been identified may not accurately reflect the disease process in humans with PD and, therefore, may result in futile efforts to engage inappropriate targets [3,4]. Although much progress has been made in the development of animal models that appear to more closely reflect PD [5,6], it remains to be determined if such models will bear fruit in identifying clinically meaningful disease-modifying therapies.

Considering this caveat, results from genetic and observational studies and early stage clinical trials that are supportive of disease-modifying actions of an agent may be more informative. Although such data have their own inherent biases, their distinct advantage is that they are derived from PD patients. Recently, such clinical data have identified several FDA-approved or repurposed drugs as potential disease-modifying therapies for PD. These therapies include the diabetes medication exenatide [7]; the urate precursor inosine [8–10]; the cancer medication nilotinib [11]; and the bipolar disorder medication lithium [12–17]. Three of these therapies (exenatide, inosine and nilotinib) are currently being investigated in PD clinical trials [7,18–20] and all 4 have demonstrated neuroprotective actions in preclinical models, which are detailed below. Although these compounds differ extensively in their chemical structures, interestingly, they all share common mechanisms of action. Specifically, each affects one or more kinases that have been implicated in neurodegenerative disease, in general, and PD, in particular. The fact that these diverse therapies all share common targets suggests that one or more of these kinases may be a valid druggable target(s) for disease-modification in PD. Here we review both the preclinical and clinical evidence supporting the

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repurposing of these therapeutics for treating PD and offer a unifying model for how these diverse compounds may mitigate PD neuropathology and clinical progression by affecting one or more kinases. We also incorporate into this model current knowledge regarding leucine-rich repeat kinase 2 (LRRK2) physiology.

It should be noted that clinical PD may actually represent several disease subtypes each with its own relevant therapeutic targets [21]. Therefore, potential PD modifying therapies, including the kinase-targeting therapies reviewed here, may only be effective in PD patients enriched with such therapeutic targets.

2. LRRK2

The kinase that has been most implicated in the pathogenesis of PD is LRRK2. *LRRK2* mutations (*pathLRRK2*) are the most common genetic cause of a late-onset parkinsonism clinically indistinguishable from sporadic PD. [22,23] As a result, there has been much interest in identifying pathLRRK2 physiology as a means to identify potential PD therapeutic targets.

LRRK2 is a large multidomain protein expressed most highly in immune cells, kidney and lung that appears to be involved with a diverse array of cellular processes including microtubule binding, vesicular trafficking, autophagy and mitophagy [24,25]. PathLRRK2 display increased kinase activity compared to wild-type LRRK2 (wtLRRK2) the amplitude of which correlates with the clinical penetrance of each particular *pathLRRK2* [25]. Importantly, even in sporadic PD, LRRK2 kinase is activated in post-mortem substantia nigra (SN) neurons suggesting that LRRK2 kinase inhibition may be a relevant therapy for both *pathLRRK2* and sporadic PD. [26]

On the other hand, evidence from cellular and rodent models indicates that the magnitude of intracellular pathLRRK2 protein levels may contribute more than its kinase activity to neuronal toxicity and death [27,28]. Furthermore, several but not all studies [29], have demonstrated that use of LRRK2 kinase inhibitors promotes LRRK2 protein degradation, introducing a potential confound in the mechanistic interpretation of LRRK2 kinase inhibitor-mediated neuroprotection [27,30–33]. Clinically, individuals with *LRRK2* variants that have decreased kinase activity, so called loss of function variants, have about a 50% reduction in LRRK2 protein levels in peripheral immune cells [34]. Also, in sporadic PD patients, who appear to have increased SN LRRK2 kinase activity [26], LRRK2 protein levels are increased in immune cells compared to healthy controls [35]. These data support LRRK2 kinase activity to be positively linked to its intracellular protein levels, which may explain the similar lung and kidney pathological changes seen in *LRRK2* knock-out and *LRRK2* kinase-dead transgenics as well as LRRK2 kinase inhibitor-treated animals [31,32,36–38]. Thus, although LRRK2 kinase inhibition may prove to be an effective disease-modifying strategy for PD, other pathLRRK2 physiology that would be influenced by its protein levels should be considered as such downstream targets may illuminate effective and, perhaps, safer therapies than LRRK2 kinase inhibitors for PD-modification.

PathLRRK2 PD can have diverse clinical pathology, including α-synuclein and/or tau SN protein aggregates, with > 80% of autopsy-examined cases having typical Lewy Bodies [39–41]. Although the pathological hallmark of sporadic PD is intraneuronal SN Lewy Bodies composed primarily of aggregated α-synuclein, genome-wide association studies (GWAS) consistently show polymorphisms not only in the α-synuclein gene (SNCA) but also in the tau gene (MAPT) to be strongly associated with PD, suggesting that both of these proteins are involved in the pathophysiology of PD. [42–44] In addition to α-synuclein, Lewy Bodies also contain tau aggregates [45,46]. Both phosphorylated-tau (p-tau) and α-synuclein are elevated in post-mortem PD striata [47] as well as in central nervous system-derived plasma exosomes from PD patients, which correlate with PD disease severity [48,49]. These findings, in addition to the known synergistic relationship between α-synuclein and tau and their prion-like actions to promote progressive neuronal demise in preclinical models [50–55], support α-synuclein and tau as potential key contributors to *pathLRRK2* and sporadic PD pathophysiology.

A proposed pathLRRK2 mechanism distinct from its kinase actions is its ability to act as a scaffolding protein bringing other functional protein partners into close proximity thereby greatly increasing their interactions [56–58]. Because this scaffolding action of LRRK2 is a function of its protein structure and not its kinase action, higher LRRK2 protein levels would be expected to lead to greater functional protein partner interactions. Three functional protein partners shown to interact with LRRK2 are tau and two different kinases: glycogen synthase kinase-3 beta (GSK-3β) and cyclin-dependent kinase 5 (cdk5) [57,58]. Importantly, these interactions have been shown to greatly increase the formation of pathogenic p-tau.

Tau normally exists as an unphosphorylated monomer and functions to stabilize microtubules. Several lines of evidence indicate that soluble tau oligomers are the most toxic form to neurons [59]. Inhibition of tau microtubule binding is the first step necessary to increase tau's cytosolic concentration allowing tau oligomerization. Phosphorylation of tau at Thr231 (pThr231) and Ser262 (pSer262), in particular, has been shown to inhibit tau microtubule binding to the greatest extent and, therefore, are predicted to be key events in subsequent tau oligomer formation [59,60]. Indeed, both α-synuclein and pSer262 tau are significantly elevated in post-mortem PD striata [47]. Furthermore, tau oligomers as well as α-synuclein oligomers can seed their own monomers as well as each other's monomers towards an oligomeric conformation, which can then spread from cell to cell in a prion-like fashion [50,52,53,61–64]. These prion-like and synergistic actions of α-synuclein and tau oligomers may, therefore, represent primary processes responsible for the progressive neuronal death and clinical deterioration in PD as well as other synucleinopathies and tauopathies [50]. Thus, inhibiting the formation and/or stimulating the clearance of intraneuronal α-synuclein and tau oligomers represent promising disease-modifying strategies for sporadic and *pathLRRK2* PD. As one pre-clinical example, in the A53T α-synuclein overexpressing mouse model of PD, selectively depleting oligomeric tau via a single injection of tau-specific antibodies led to decreases in cognitive and motor deficits as well as decreases in both tau oligomers and the most toxic form of α-synuclein oligomers [54].

Because initial tau oligomer formation is most dependent on its phosphorylation at Thr231 and Ser262 and post-mortem PD striatum has significantly elevated levels of pSer262 and pSer396/404 tau [47,59,60], a logical PD disease-modifying strategy would be to target the primary kinases involved with phosphorylating tau at these sites. GSK-3α, GSK-3β and cdk5 represent such kinases. GSK-3β phosphorylates tau at Thr231 and Ser396/404 highlighting the potential importance of this kinase in regards to tau oligomer formation and post-mortem PD pathology [57,58,65,66]. Cdk5 and, to a lesser extent, GSK-3α play important roles in the formation of pThr231 tau by priming tau through Ser235 phosphorylation, which then robustly increases tau Thr231 phosphorylation by GSK-3β [67,68]. However, GSK-3α, not GSK-3β or cdk5, phosphorylates tau at Ser262 [67]. As previously mentioned, LRRK2 can function as a scaffolding protein increasing the interactions among tau, GSK-3β and cdk5 greatly increasing the formation of p-tau [57,58,69]. Furthermore, pathLRRK2 leads to greater p-tau formation than wtLRRK2 through this scaffolding mechanism. The most common clinical *pathLRRK2* mutation, *G2019S*, approximately doubles GSK-3β-induced tau phosphorylation compared to *wt-LRRK2* [57]. This pathLRRK2-mediated increase in p-tau was shown to be independent of its kinase action because both kinase-dead LRRK2 and LRRK2 inhibitor-treated cells had the same magnitude of p-tau formation in this model [57]. Finally, α-synuclein can also function as a scaffolding protein, akin to pathLRRK2, enhancing the association between GSK-3β and tau and can also directly stimulate GSK-3β resulting in greatly increased p-tau formation (Fig. 1) [66,70]. Thus, therapies shown to inhibit the kinase actions of GSK-3α, GSK-3β and/or cdk5 can

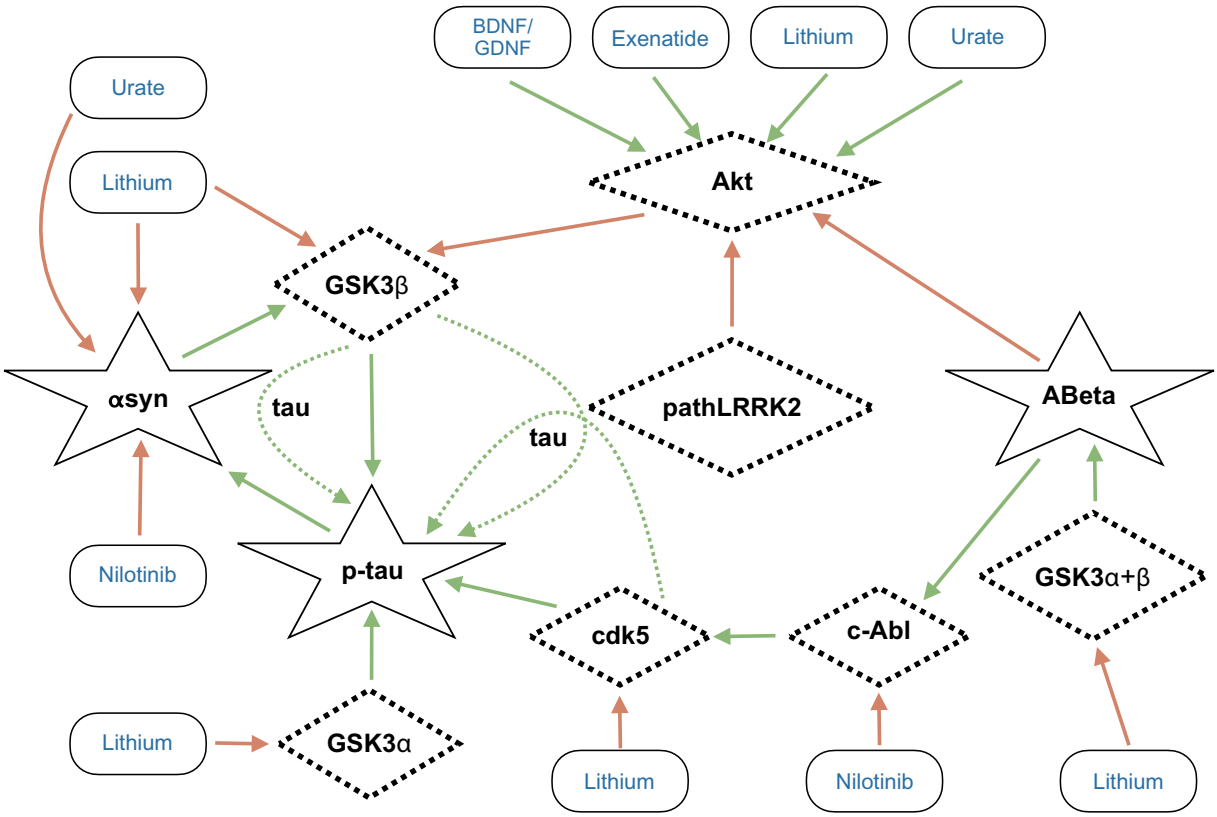

Fig. 1. Interactions among kinases, toxic protein moieties and kinase-targeting potential PD therapeutics.
Toxic proteins and kinase therapeutic targets are depicted as stars and diamonds, respectively. BDNF/GDNF: brain-derived neurotrophic factor/glial cell line-derived neurotrophic factor, Akt: protein kinase B, GSK-3α + β: glycogen synthase kinase-3 alpha and beta, pathLRRK2: pathogenic leucine-rich repeat kinase 2, c-Abl: c-Abelson kinase, cdk5: cyclin-dependent kinase 5, p-tau: phosphorylated tau, α-syn: alpha synuclein, ABeta: Beta amyloid. Green/red arrows depict actions that increase/decrease kinase activity or protein levels. Dashed green lines signify pathLRRK2 and α-syn functioning as scaffolding proteins enhancing the associations of GSK-3β and cdk5 with tau resulting in increased p-tau formation.

not only decrease the formation of tau oligomers but also α-synuclein oligomers by disrupting the viscous cycle between these toxic proteins. Such therapeutic actions would represent promising approaches for both sporadic and *pathLRRK2* PD.

The pathLRRK2 physiology that has received the most attention is its increased kinase-dependent phosphorylation of Rab10 [25,71]. Rab10 belongs to a family of GTPases known to play a critical role in intracellular vesicular trafficking [72]. However, it is currently not known whether pathLRRK2-mediated Rab10 phosphorylation leads to increased p-tau or α-synuclein formation. Another proposed LRRK2 kinase substrate is protein kinase B (Akt) [73]. Akt is an upstream regulator of GSK-3β (Fig. 1) as well as many other substrates including the mammalian target of rapamycin (mTOR), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), cAMP response element-binding protein (CREB) and Bcl-2 all of which are involved with neuronal survival and have been implicated in PD pathophysiology [74–77]. In general, increased Akt kinase activity causes downstream events that promote neuronal survival, such as inhibition of GSK-3β (Fig. 1).

Maximum activation of Akt is dependent on phosphorylation at its Ser473 and Thr308 sites [74]. Post-mortem PD substantia nigra (SN) displays reduced levels of pSer473 and pThr308 Akt compared to healthy controls [78,79]. Of note, the *pathLRRK2* mutations *G2019S*, *I2020T* and *R1441C* also lead to significantly decreased pSer473 Akt levels compared to *wtLRRK2* [73], which would result in deactivation of Akt, activation of GSK-3β and downstream effects impairing neuronal survival. Furthermore, induced pluripotent stem cell (iPSC)-derived neurons from PD patients with the *I2020T pathLRRK2* mutation showed increased p-tau levels and approximately 50% reductions in both pSer473 and pThr308 Akt levels and a 70% reduction in Akt kinase activity compared to healthy control patient iPSC-derived neurons [80]. Because decreased Akt activity would be expected to increase GSK-3β activity and p-tau formation (Fig. 1), tau phosphorylation was assessed in these *I2020T pathLRRK2* iPSC-derived neurons in response to a GSK-3β inhibitor. Interestingly, tau phosphorylation was inhibited to a greater extent following exposure to a GSK-3β inhibitor than to a specific LRRK2 kinase inhibitor indicating that pathLRRK2-mediated tau phosphorylation in this model is more a function of increased GSK-3β kinase activity than increased pathLRRK2 kinase activity [80]. Indeed, post-mortem brain from two *I2020T pathLRRK2* patients showed increased p-tau levels as well as increased GSK-3β kinase activity [80]. Furthermore, levels of activated GSK-3β are increased in post-mortem striata from sporadic PD patients [47,66]. These data indicate that decreased Akt and/or increased GSK-3β activity may contribute to both *pathLRRK2* and sporadic PD pathophysiology.

More recently, several studies have shown the GSK-3β substrate β-catenin to be significantly less active in *pathLRRK2 G2019S*, *R1441G* and *Y1699C* transfected fibroblasts and significantly more active in fibroblasts transfected with the PD protective *LRRK2* mutation, *R1398H* [81], compared to *wtLRRK2* [82,83]. These pathLRRK2 effects were due to direct binding of β-catenin to pathLRRK2 thereby inhibiting the activity of this protein [82]. β-catenin is a transcriptional cofactor that, when concentrated in the nucleus, upregulates the expression of canonical Wnt (Wingless/Int) target genes many of which regulate neuronal survival, axonal outgrowth and synaptic integrity [83–85]. Thus, pathLRRK2-mediated reduction in β-catenin-mediated activity would be expected to impair neuronal survival. Reduced β-catenin-mediated activity has also been implicated in the pathophysiology of common PD

genetic risks, most notably mutations in the glucocerebrosidase gene (*GBA*), which represents the most common genetic risk for PD. [86–89] IPS cells with neuronopathic *GBA* mutations (*pathGBA*) show impaired canonical Wnt/β-catenin signaling, increased levels of activated GSK-3β and impaired ability to differentiate into dopaminergic cells, which are all reversed by either application of a canonical Wnt/β-catenin activator or introduction of functional recombinant glucocerebrosidase [89]. Finally, polymorphisms in the GSK-3β gene leading to increased GSK-3β enzyme activity are associated with an increased rate of sporadic PD. [90] GSK-3β phosphorylates β-catenin leading to its further ubiquitination and eventual proteasomal degradation [91,92], while use of GSK-3β inhibitors decreases β-catenin phosphorylation and increases β-catenin-mediated transcription activity [93].

One transcription factor upregulated by β-catenin is nuclear receptor related 1 (Nurr1), which regulates the expression of genes essential for dopamine cell differentiation, maintenance and survival [94,95]. Nurr1 expression in human SN decreases with increasing age, the major risk factor for PD, and is highly positively correlated with expression of tyrosine hydroxylase, the rate-limiting step in dopamine production [96]. Nurr1 and α-synuclein negatively affect the expression of each other and restoration of Nurr1 expression ameliorates α-synuclein-mediated dopamine cell toxicity [97–99]. Nurr1 levels are reduced by about 65% in PD SN compared to healthy controls [100] and several Nurr1 gene mutations have been identified as genetic risks for both familial and sporadic PD. [94,97,101,102] Thus, therapies that can increase Nurr1 expression, such as GSK-3β inhibitors, could lead to decreased α-synuclein expression and enhanced survival of SN dopamine neurons.

In summary, *pathLRRK2* may cause PD, in part, by influencing the actions of other kinases including Akt, GSK-3β and cdk-5, which are also relevant therapeutic targets for sporadic PD. With this landscape in mind (Fig. 1), it becomes apparent that several currently available therapies including exenatide, inosine, nilotinib and lithium share common kinase therapeutic targets that may provide disease-modifying effects in sporadic PD or, perhaps, a subtype of sporadic PD enriched with these therapeutic targets [103]. Table 1 summarizes the clinical data supporting each of these therapies' potential disease-modifying effects.

3. BDNF/GDNF

There has been much interest in the use of brain-derived and glial cell line-derived neurotrophic factors (BDNF and GDNF) as disease-modifying therapies in PD due to their neuroprotective actions observed in PD animal models [109]. However, negative results from several neurotrophin PD clinical trials has tempered enthusiasm for this approach [110,111]. BDNF and GDNF act through their plasma membrane receptors (TrkB and Ret, respectively), which results in activation of major signaling pathways including Akt (Fig. 1) [112]. More recently, α-synuclein has been shown to interfere with neurotrophin activity at their receptors, which may help explain the negative results from previous neurotrophin PD trials. For example, α-synuclein can block BDNF-mediated effects by binding to the kinase domain of the TrkB receptor and by down-regulating its expression [113]. Also, α-synuclein can block GDNF-mediated effects by decreasing the expression of transcription factor Nurr1 leading to decreased expression of the GDNF receptor, Ret. [98] Thus, therapies that could decrease intracellular α-synuclein may enable neurotrophin-mediated neuroprotection to be realized in PD by stabilizing TrkB and Ret receptor expression. Further work needs to be performed with α-synuclein targeted therapies to explore this theory.xs

4. Exenatide

Exenatide is a glucagon-like peptide 1 (GLP-1) receptor agonist FDA-approved for treating diabetes mellitus (DM). GLP-1 is an endogenous hormone secreted by the small intestine in response to food intake and, via stimulation of its receptor, mediates glucose homeostasis. GLP-1 is quickly metabolized after secretion and, therefore, would not be a viable exogenous treatment for DM [114]. Long-acting GLP-1 analogues, such as exenatide, were developed after the discovery of the first such analogue, exendin-4, isolated from the saliva of the Gila monster lizard [115]. Although mainly expressed in the pancreas, GLP-1 receptors are also widely expressed in the brain [116]. GLP-1 analogues have demonstrated several neuroprotective actions including reduction in inflammation and enhanced neurotrophic and neurogenic actions [75]. Treatment with GLP-1 analogues diminish SN cell loss and motor deficits and preserve striatal dopamine in MPTP-treated mice [117]. GLP-1 analogue treatment was shown to prevent neuronal toxicity and p-tau formation both in cell culture and a rodent model of DM through activation of Akt and inhibition of GSK-3β (Fig. 1) [118,119]. Interestingly, GSK-3α and GSK-3β were originally identified for their roles in insulin receptor signaling [120,121].

Due to these preclinical neuroprotective actions, a proof-of-concept, single-blind study was performed to compare the progression of symptoms among 45 PD patients randomly assigned to exenatide treatment or no exenatide treatment for 12 months followed by a 2-month washout period [104]. Results showed a significant 2.7 point improvement and 2.2 point worsening in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores in the exenatide and no exenatide groups, respectively, after 12 months. In addition, a significant intergroup difference persisted after the 2-month washout. A follow-up assessment 12 months after subjects discontinued exenatide showed persistence of significant intergroup differences in change in MDS-UPDRS scores as well as change in cognition in favor of exenatide treatment [105].

These promising results led to a double-blind, randomized controlled trial (RCT) examining the effects of exenatide on PD progression [7]. In this study, 62 PD subjects with a mean disease duration of 6.4 years were randomized to exenatide or placebo for 48 weeks followed by a 12-week washout period. The primary outcome was the MDS-UPDRS part 3 motor subscale in the practically defined off-medication state at Week 60. Results showed a significant 3.5-point relative advantage for the exenatide group for the primary outcome. However, on closer examination of the data, maximum improvement in motor scores was achieved by week 12 in the exenatide group, remained fairly

Table 1
Clinical evidence supporting potential disease-modifying effects of exenatide, urate/inosine, nilotinib and lithium.

	Clinical trial data			Observational data
	Double-blind	Single-blind	Open-label	
Exenatide	x[7]	x[104, 105]		
Urate/inosine	*In progress*[19]			x[8, 10, 106]
Nilotinib	*In progress*[18, 20]		x[11]	
Lithium	x[12, 16]			x[13–15, 17, 107, 108]

constant out to week 48 and worsened greatly after the 12-week washout period, suggesting that exenatide mostly provided symptomatic and not disease-modifying benefits. In addition, there were no significant intergroup differences in cognition, mood, activities of daily living or quality of life outcomes. Therefore, despite the supportive preclinical data and promising proof-of-concept clinical trial, the more rigorously designed RCT could not support a strong disease-modifying effect of exenatide in PD; although, it also could not rule it out. Newer generation GLP-1 analogues also show neuroprotective effects in PD animal models and may soon enter PD clinical trials [122]. Nevertheless, the prolonged and inconclusive saga of repurposing exenatide for treating PD exemplifies the urgent need for disease progression biomarkers to be used in such clinical trials in order to more objectively assess a therapy's disease-modifying actions [123]. One such trial examining exenatide's effects on a promising disease progression biomarker in PD, SN free water assessed from diffusion sequence magnetic resonance imaging, is currently in progress [124–126].

5. Urate

Urate, the anionic form of uric acid, is an end product of purine metabolism and serves as an endogenous anti-oxidant accounting for about 60% of the plasma anti-oxidant capacity [127,128]. Because increased oxidative stress is believed to play a central role in PD pathogenesis and post-mortem PD SN has relatively low urate levels [129–131], several studies have explored the association between plasma urate levels and risk of PD. Retrospective studies have shown reduced serum urate levels in PD compared to healthy controls and in more advanced PD compared to early PD. [132] When examining urate levels by PD sub-type, those with tremor dominant PD had higher serum urate levels and striatal dopamine transporter (DAT) binding, an in vivo assessment of nigrostriatal terminal integrity, compared to those with a postural instability/gait disorder phenotype [106]. This is interesting as the tremor dominant PD subtype is known to have a slower disease progression. In addition, individuals that longitudinally maintained a tremor dominant phenotype also had higher urate levels and DAT binding compared to those that converted to the postural instability and gait disorder phenotype [133]. These data all suggest that urate may influence PD progression.

The role of urate in the rate of PD progression has also been retrospectively evaluated in two PD clinical trials: the Parkinson Research Examination of CEP-1347 (PRECEPT) study and the Deprenyl and Tocopherol Antioxidative Therapy in Parkinsonism (DATATOP) study. In the PRECEPT study, when individuals were divided into 5 groups based on baseline urate levels, those in the highest quintile for baseline urate levels were 50% less likely to reach the primary endpoint of need for dopaminergic therapy compared to those in the lowest baseline quintile. In addition, those with higher urate levels had higher striatal DAT binding [10]. In the DATATOP study, analysis of urate levels in serum and CSF also revealed that higher baseline urate levels were associated with slower rates of clinical decline in PD. [8]

In addition to functioning as a potent antioxidant, urate can also ameliorate neurotoxin-induced behavioral deficits and SN cell loss by interfering with neurotoxin-induced Akt inhibition and GSK-3β activation (Fig. 1) [134]. Finally, urate can induce autophagy, the primary process for clearing intraneuronal aggregated α-synuclein, via inhibition of the mammalian target of rapamycin (mTOR) [135]. There is known impairment in autophagy and lysosomal function in PD that contribute to α-synuclein aggregation [136,137]. Thus, urate may not only directly reduce oxidative stress and reduce the formation of p-tau through Akt activation, but may also enhance the clearance of α-synuclein by inducing autophagy (Fig. 1). These mechanisms of action in addition to the PRECEPT and DATATOP clinical data support urate as a potential disease-modifying therapy for PD.

An alternative treatment to the direct administration of urate to individuals with PD is administration of its precursor, inosine. Due to elevated urate levels being associated with increased risk of gout, coronary artery disease, kidney disease, hypertension and stroke [138], the safety of inosine treatment was first explored in the Safety of Urate Elevation in PD (SURE-PD) study. SURE-PD was a RCT that evaluated the safety, tolerability and efficacy of urate elevation with inosine treatment for 24 months [9]. Among 75 early PD subjects not requiring dopaminergic therapy, inosine was found to be generally safe and well tolerated and led to significant urate elevations in both the serum and CSF. Secondary analysis demonstrated non-futility of inosine based on the change in total UPDRS score, but the study was not sufficiently powered to assess the efficacy of inosine compared to placebo. There was also a dose dependent increase in anti-oxidant capacity in serum at 6 months in inosine treated participants compared to placebo but no difference in CSF [139]. Based on the SURE-PD study results, the SURE-PD3 RCT was initiated to assess inosine's ability to slow PD progression over 24 months among 270 early PD subjects [19].

6. Nilotinib

Nilotinib is FDA approved for treating chronic myeloid leukemia (CML). Nilotinib functions as a break point cluster-Abelson (c-Abl) tyrosine kinase inhibitor leading to strong autophagy induction and death of rapidly dividing tumor cells [140]. Administration of low-dose nilotinib penetrates the blood-brain barrier and has been shown to reduce inflammation [141], inhibit brain c-Abl and enhance autophagic clearance of intraneuronal α-synuclein in A53T transgenic mice and lentiviral gene transfer models of PD. [142] c-Abl may also be a therapeutic target to mitigate prion-mediated neurotoxicity [143,144]. Clearance of α-synuclein by nilotinib was associated with reduced SN cell loss and improved motor performance in these studies. Activated c-Abl can phosphorylate α-synuclein and both are increased in post-mortem PD striatum [145,146]. Activated c-Abl can also phosphorylate and inhibit the protein parkin leading to loss of its ubiquitin ligase activity and cytoprotective actions [145]. *Parkin* mutations are known to result in a recessively inherited form of clinical PD likely through a loss of parkin function [147,148]. Therefore, decreased parkin function may also contribute to the pathophysiology of sporadic PD. Use of a c-Abl inhibitor was shown to normalize parkin function and preserve striatal dopamine levels in MPTP-treated mice [145]. Finally, beta amyloid (ABeta), which aggregates into extracellular plaques in Alzheimer's disease, has been shown to activate c-Abl leading to activation of cdk5 and increased p-tau formation all of which were prevented with use of a c-Abl inhibitor (Fig. 1) [149].

Based on the above preclinical data, a pilot open-label, proof-of-concept study was conducted to evaluate the safety and tolerability of nilotinib in patients with advanced PD, PD with dementia (PDD), or dementia with Lewy bodies (DLB) [11]. Additional exploratory outcomes included measures of motor and cognitive functions and cerebrospinal fluid (CSF) biomarkers.

Twelve subjects with PDD or DLB were randomized to nilotinib 150 mg ($n = 5$) or 300 mg ($n = 7$) for 24 weeks followed by a 12-week washout period. Both motor and cognitive outcomes suggested a possible beneficial effect of the drug. There was an average improvement of 3.4 and 3.6 points in the 150 mg and 300 mg treatment arms, respectively, in the UPDRS-III (motor) scores at week 24 compared to baseline, which were no longer apparent after the 12-week washout period. The mini-mental state examination score improved incrementally during the treatment period by an average of 3.85 and 3.5 points in the two treatment groups, respectively, at week 24, returning to baseline at week 36. Although these clinical results are encouraging, they should be regarded as preliminary due to the large placebo effects that can occur in PD. CSF dopamine metabolite levels were significantly increased at weeks 8 and 24 from baseline and some subjects experienced increased psychotic symptoms and dyskinesias, side effects consistent with increased CNS dopamine levels. In addition, CSF tau was reduced in both treatment arms while ABeta-40 was only reduced in the 300 mg

nilotinib arm. These biomarker findings suggest that nilotinib may have symptomatic and, perhaps, disease-modifying effects in PD. The collective observations from this small, proof-of-concept study has prompted two larger randomized, double-blind, placebo-controlled trials of nilotinib in PD. [18,20]

7. Lithium

Lithium was FDA-approved in 1970 for treating bipolar disorder, although its mechanism of action has never been clearly understood for this indication. In addition to its symptomatic benefits for bipolar disorder, lithium also has several neuroprotective actions including decreasing the aggregation and phosphorylation of α-synuclein and tau; enhancing autophagy and reducing oxidative stress, inflammation, microglia activation and apoptosis [66,150–154]. Lithium has also demonstrated neuroprotective actions in several animal models of PD including neurotoxin and transgenic models [155–157]. Lithium's ability to inhibit GSK-3β, GSK-3α and cdk5 and activate Akt have been implicated in most of lithium's neuroprotective actions (Fig. 1).

Lithium inhibits GSK-3β at physiologic concentrations by increasing its phosphorylation at Ser9, which results in reduced p-tau formation [158–160]. Some studies have shown lithium-mediated GSK-3β Ser9 phosphorylation to be dependent on its ability to stimulate Akt activity (Fig. 1) [161,162]. Clinically, lithium treatment in patients with bipolar disorder is associated with an 8-fold increase in pSer9 GSK-3β levels in peripheral blood mononuclear cells compared to healthy controls [163]. A prospective trial among 27 bipolar disorder patients also showed lithium treatment to significantly increase platelet pSer9 GSK-3β levels and for this increase to positively correlate with clinical improvement [164].

Besides GSK-3β, the other major kinase that phosphorylates tau is cyclin-dependent kinase 5 (cdk5) which, as previously noted, has been implicated in pathLRRK2 physiology [58]. One study showed single nucleotide polymorphisms in GSK-3β and cdk5 to have a synergistic interaction leading to a doubling in sporadic PD risk [165]. Lithium can prevent cdk5 activation by inhibiting calcium-mediated activation of calpain-1 and cleavage of p35 to p25 (Fig. 1) [166–168].

Perhaps due to its ability to inhibit GSK-3β and cdk5, the clinical use of lithium was shown to reduce CSF p-tau levels. A randomized controlled trial (RCT) among 45 patients with amnestic mild cognitive impairment (aMCI) examined the effects of 1-year of low-dose lithium therapy (about ½ the dosages used for bipolar disorder) on cognition and CSF biomarkers. This RCT showed low-dose lithium therapy to provide significant improvements to cognition and to significantly reduce CSF p-tau levels compared to placebo [12]. Lithium treatment also led to a 45% reduced rate of conversion from aMCI to Alzheimer's disease; however, this failed to reach statistical significance perhaps due to the very small sample size. Interestingly, subgroup analyses showed that among the lithium-treated subjects, significant reductions in CSF p-tau occurred only in those who did not progress from aMCI to Alzheimer's disease, suggesting that CSF p-tau may be a therapeutic biomarker of disease-modifying effects in aMCI. Several epidemiologic studies have also associated lithium use with a reduced risk of Alzheimer's disease [13–15,17,107].

In addition to reducing p-tau levels, GSK-3β inhibition by lithium also leads to increased β-catenin levels and increased expression of Nurr1 protein, which has been shown to enhance dopaminergic cell viability and reduce the expression of α-synuclein [85,93]. As noted above, reduced β-catenin-mediated activity has been implicated in sporadic PD as well as pathLRRK2 and pathGBA physiology [82,83,86,100]. Therefore, lithium therapy could potentially provide disease-modifying effects in PD through inhibition of GSK-3β resulting in decreased p-tau formation, enhanced β-catenin signaling, increased Nurr1 expression and reduced α-synuclein expression.

Multiple studies have shown low CSF ABeta levels, which reflect high brain ABeta deposition, to consistently predict more rapid cognitive decline in PD. [169] Considering that dementia is a common long-term sequela of PD and is highly disabling [170], interfering with ABeta-mediated physiology could potentially help preserve cognition longitudinally in PD. ABeta can inhibit Akt and stimulate c-Abelson kinase (c-Abl), actions known to increased p-tau formation via activation of GSK-3β and cdk5, respectively [149,171]. Besides lithium's ability to inhibit ABeta's downstream effects via inhibition of GSK-3β and cdk5, lithium can also decrease ABeta formation through inhibition of GSK-3β and GSK-3α (Fig. 1) [172–174]. Lithium-mediated inhibition of GSK-3α can also decrease tau phosphorylation at Ser262, which is one of two key phosphorylation sites leading to tau dissociation from microtubules and eventual formation of toxic tau oligomers, as reviewed above [67]. Reducing p-tau formation may also slow cognitive decline in PD. [175]

As previously noted, the autophagy-lysosomal pathway is a key route for degradation of intracellular aggregate-prone proteins such as α-synuclein and p-tau [137]. Autophagy can be regulated through the mTOR pathway [176]. Lithium can enhance autophagy and directly reduce α-synuclein levels through mTOR-independent pathways via inhibition of inositol monophosphate and elevation of heat shock protein-70 expression [154,177,178]. Because SN α-synuclein accumulation leads to impaired autophagy and lysosomal function [179], which then impairs α-synuclein clearance, therapies that can stimulate the autophagy-lysosomal pathway- such as lithium, urate and nilotinib (Fig. 1)- may break this vicious cycle of α-synuclein accumulation and associated neuronal demise [137].

Although epidemiology and clinical trial data support possible disease-modifying effects of lithium for aMCI and Alzheimer's disease [12–15,17,107], no such data currently exist for PD. On the other hand, multiple epidemiologic studies have consistently shown cigarette smokers to have a > 50% reduced risk of Parkinson's disease (PD) with large prospective cohort studies showing a mean 77% reduced risk [180–182]. These consistent epidemiologic findings suggest that tobacco may contain one or more neuroprotective elements that can markedly reduce the incidence of PD. [183–185] In 1980, high levels of lithium were reported in tobacco from India: levels about 20-fold higher than any plant or animal food tested [186]. We recently reported that tobacco from popular western cigarette brands has as high or higher lithium levels than Indian tobacco and estimated that a pack-per-day smoker may absorb about 169–338 μg of lithium/day [108]. For comparison, a daily oral lithium dose of 300 μg for 15 months was shown to significantly slow cognitive decline in a RCT among 110 patients with early Alzheimer's disease [16]. These combined data raise the possibility that daily microdose lithium might not only slow neurodegeneration in Alzheimer's disease, but that a similar biological neuroprotective mechanism of microdose lithium might underlie the reduced risk of PD in smokers.

It was also proposed that the current lack of epidemiologic data associating lithium use in bipolar disorder patients with a reduced incidence of PD may be due to the common occurrence of lithium-induced hand tremors being misdiagnosed as PD when dosed for mood stabilization (about 800–2000 mg/day) [108,187]. Because lithium-induced hand tremors are dose related, such tremors would not be expected to occur from daily exposure to 169–338 μg of lithium in pack-per-day cigarette smokers and, therefore, not obfuscate its potential ability to reduce incident PD in this population.

These clinical findings in addition to the breadth of preclinical evidence supporting lithium's ability to inhibit key kinases implicated in pathLRRK2, pathGBA and sporadic PD pathophysiology support future clinical investigation of lithium's potential disease-modifying effects in PD. In addition, adjunct lithium therapy may have symptomatic benefits in PD and appears to be well tolerated when used in low doses in PD patients with motor fluctuations [188–190].

8. Conclusion

Genetic risks and causes of PD as well as PD brain pathology point strongly towards oligomeric α-synuclein and tau as primary mediators of the progressive neuronal demise in PD. The therapies reviewed here (exenatide, inosine, nilotinib and lithium) can all decrease the formation and/or increase the clearance of these toxic intraneuronal protein species in pre-clinical models. More importantly, use of all four therapies has been associated with improved clinical outcomes in PD. It remains to be determined whether one or more of these therapies has true disease-modifying effects in PD patients enriched with these therapeutic targets. However, the realization that all share common kinase targets increases the chance that one or more are valid targets, which may guide the development of current and future disease-modifying therapies for PD. For example, PD clinical trials may be more informative by assessing Akt, GSK-3β, GSK-3α and cdk-5 kinase activities in subjects' peripheral blood mononuclear cells to not only confirm target engagement but also to identify PD patients most likely to benefit from kinase-targeting therapies.

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References

[1] E.R. Dorsey, B.R. Bloem, The Parkinson pandemic-a call to action, JAMA Neurol. 75 (1) (2017) 9–10.
[2] T.M. Dawson, V.L. Dawson, Molecular pathways of neurodegeneration in Parkinson's disease, Science 302 (2003) 819–822.
[3] C.W. Olanow, J.H. Kordower, Modeling Parkinson's disease, Ann. Neurol. 66 (2009) 432–436.
[4] C.W. Olanow, K. Kieburtz, R. Katz, Clinical approaches to the development of a neuroprotective therapy for PD, Exp. Neurol. 298 (2017) 246–251.
[5] Y. Li, W. Liu, T.F. Oo, et al., Mutant LRRK2(R1441G) BAC transgenic mice recapitulate cardinal features of Parkinson's disease, Nat. Neurosci. 12 (2009) 826–828.
[6] J.R. Cannon, V. Tapias, H.M. Na, A.S. Honick, R.E. Drolet, J.T. Greenamyre, A highly reproducible rotenone model of Parkinson's disease, Neurobiol. Dis. 34 (2009) 279–290.
[7] D. Athauda, K. Maclagan, S.S. Skene, et al., Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial, Lancet 390 (2017) 1664–1675.
[8] A. Ascherio, P.A. LeWitt, K. Xu, et al., Urate as a predictor of the rate of clinical decline in Parkinson disease, Arch. Neurol. 66 (2009) 1460–1468.
[9] Parkinson Study Group S-PDI, M.A. Schwarzschild, A. Ascherio, et al., Inosine to increase serum and cerebrospinal fluid urate in Parkinson disease: a randomized clinical trial, JAMA Neurol. 71 (2014) 141–150.
[10] M.A. Schwarzschild, S.R. Schwid, K. Marek, et al., Serum urate as a predictor of clinical and radiographic progression in Parkinson disease, Arch. Neurol. 65 (2008) 716–723.
[11] F. Pagan, M. Hebron, E.H. Valadez, et al., Nilotinib effects in Parkinson's disease and dementia with Lewy bodies, J. Park. Dis. 6 (2016) 503–517.
[12] O.V. Forlenza, B.S. Diniz, M. Radanovic, F.S. Santos, L.L. Talib, W.F. Gattaz, Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial, Br. J. Psychiatry 198 (2011) 351–356.
[13] L.V. Kessing, J.L. Forman, P.K. Andersen, Does lithium protect against dementia? Bipolar Disord. 12 (2010) 87–94.
[14] L.V. Kessing, T.A. Gerds, N.N. Knudsen, et al., Association of Lithium in drinking water with the incidence of dementia, JAMA Psychiatry 74 (2017) 1005–1010.
[15] L.V. Kessing, L. Sondergard, J.L. Forman, P.K. Andersen, Lithium treatment and risk of dementia, Arch. Gen. Psychiatry 65 (2008) 1331–1335.
[16] M.A. Nunes, T.A. Viel, H.S. Buck, Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease, Curr. Alzheimer Res. 10 (2013) 104–107.
[17] P.V. Nunes, O.V. Forlenza, W.F. Gattaz, Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder, Br. J. Psychiatry 190 (2007) 359–360.
[18] F. Pagan, Impact of Nilotinib on Safety, Tolerability, Pharmacokinetics and Biomarkers in Parkinson's Disease (PD Nilotinib), Available at: https://clinicaltrials.gov/ct2/show/NCT02954978?term=NCT02954978&rank=1, (2016) , Accessed date: 1 March 2019.
[19] M. Schwarzschild, Study of Urate Elevation in Parkinson's Disease, Phase 3 (SURE-PD3), Available at https://clinicaltrials.gov/ct2/show/NCT02642393, (2019) , Accessed date: 13 December 2018.
[20] T. Simuni, Nilo-PD, Available at https://clinicaltrials.gov/ct2/show/NCT03205488?term=NILO-PD&rank=1, (2017) , Accessed date: 10 December 2018.
[21] A.E. Lang, A.J. Espay, Disease modification in Parkinson's disease: current approaches, challenges, and future considerations, Mov. Disord. 33 (2018) 660–677.
[22] Z.K. Wszolek, B. Pfeiffer, J.R. Fulgham, et al., Western Nebraska family (family D) with autosomal dominant parkinsonism, Neurology 45 (1995) 502–505.
[23] K. Haugarvoll, R. Rademakers, J.M. Kachergus, et al., Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease, Neurology 70 (2008) 1456–1460.
[24] D.A. Roosen, M.R. Cookson, LRRK2 at the interface of autophagosomes, endosomes and lysosomes, Mol. Neurodegener. 11 (2016) 73.
[25] A.B. West, Achieving neuroprotection with LRRK2 kinase inhibitors in Parkinson disease, Exp. Neurol. 298 (2017) 236–245.
[26] R. Di Maio, E.K. Hoffman, E.M. Rocha, et al., LRRK2 activation in idiopathic Parkinson's disease, Sci. Transl. Med. 10 (2018).
[27] G. Skibinski, K. Nakamura, M.R. Cookson, S. Finkbeiner, Mutant LRRK2 toxicity in neurons depends on LRRK2 levels and synuclein but not kinase activity or inclusion bodies, J. Neurosci. 34 (2014) 418–433.
[28] X. Lin, L. Parisiadou, X.L. Gu, et al., Leucine-rich repeat kinase 2 regulates the progression of neuropathology induced by Parkinson's-disease-related mutant alpha-synuclein, Neuron 64 (2009) 807–827.
[29] K. Kelly, S. Wang, R. Boddu, et al., The G2019S mutation in LRRK2 imparts resiliency to kinase inhibition, Exp. Neurol. 309 (2018) 1–13.
[30] E. Lobbestael, L. Civiero, T. De Wit, J.M. Taymans, E. Greggio, V. Baekelandt, Pharmacological LRRK2 kinase inhibition induces LRRK2 protein destabilization and proteasomal degradation, Sci. Rep. 6 (2016) 33897.
[31] R.N. Fuji, M. Flagella, M. Baca, et al., Effect of selective LRRK2 kinase inhibition on nonhuman primate lung, Sci. Transl. Med. 7 (2015) 273ra15.
[32] M.C. Herzig, C. Kolly, E. Persohn, et al., LRRK2 protein levels are determined by kinase function and are crucial for kidney and lung homeostasis in mice, Hum. Mol. Genet. 20 (2011) 4209–4223.
[33] J. Zhao, T.P. Molitor, J.W. Langston, R.J. Nichols, LRRK2 dephosphorylation increases its ubiquitination, Biochem. J. 469 (2015) 107–120.
[34] C. Blauwendraat, X. Reed, D.A. Kia, et al., Frequency of loss of function variants in LRRK2 in Parkinson disease, JAMA Neurol. 75 (2018) 1416–1422.
[35] D.A. Cook, G.T. Kannarkat, A.F. Cintron, et al., LRRK2 levels in immune cells are increased in Parkinson's disease, NPJ Parkinsons Dis. 3 (2017) 11.
[36] M.J. Fell, C. Mirescu, K. Basu, et al., MLi-2, a potent, selective, and centrally active compound for exploring the therapeutic potential and safety of LRRK2 kinase inhibition, J. Pharmacol. Exp. Ther. 355 (2015) 397–409.
[37] M.A. Baptista, K.D. Dave, M.A. Frasier, et al., Loss of leucine-rich repeat kinase 2 (LRRK2) in rats leads to progressive abnormal phenotypes in peripheral organs, PLoS One 8 (2013) e80705.
[38] P. Miklavc, K. Ehinger, K.E. Thompson, N. Hobi, D.R. Shimshek, M. Frick, Surfactant secretion in LRRK2 knock-out rats: changes in lamellar body morphology and rate of exocytosis, PLoS One 9 (2014) e84926.
[39] A. Zimprich, S. Biskup, P. Leitner, et al., Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology, Neuron 44 (2004) 601–607.
[40] A. Rajput, D.W. Dickson, C.A. Robinson, et al., Parkinsonism, Lrrk2 G2019S, and tau neuropathology, Neurology 67 (2006) 1506–1508.
[41] O.A. Ross, M. Toft, A.J. Whittle, et al., Lrrk2 and Lewy body disease, Ann. Neurol. 59 (2006) 388–393.
[42] W. Satake, Y. Nakabayashi, I. Mizuta, et al., Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease, Nat. Genet. 41 (2009) 1303–1307.
[43] J. Simon-Sanchez, C. Schulte, J.M. Bras, et al., Genome-wide association study reveals genetic risk underlying Parkinson's disease, Nat. Genet. 41 (2009) 1308–1312.
[44] T.L. Edwards, W.K. Scott, C. Almonte, et al., Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease, Ann. Hum. Genet. 74 (2010) 97–109.
[45] T. Ishizawa, P. Mattila, P. Davies, D. Wang, D.W. Dickson, Colocalization of tau and alpha-synuclein epitopes in Lewy bodies, J. Neuropathol. Exp. Neurol. 62 (2003) 389–397.
[46] K. Arima, S. Hirai, N. Sunohara, et al., Cellular co-localization of phosphorylated tau- and NACP/alpha-synuclein-epitopes in lewy bodies in sporadic Parkinson's disease and in dementia with Lewy bodies, Brain Res. 843 (1999) 53–61.
[47] J. Wills, J. Jones, T. Haggerty, V. Duka, J.N. Joyce, A. Sidhu, Elevated tauopathy and alpha-synuclein pathology in postmortem Parkinson's disease brains with and without dementia, Exp. Neurol. 225 (2010) 210–218.
[48] M. Shi, A. Kovac, A. Korff, et al., CNS tau efflux via exosomes is likely increased in Parkinson's disease but not in Alzheimer's disease, Alzheimer's & Dementia : J. Alzheimer's Assoc. 12 (2016) 1125–1131.
[49] M. Shi, C. Liu, T.J. Cook, et al., Plasma exosomal alpha-synuclein is likely CNS-derived and increased in Parkinson's disease, Acta Neuropathol. 128 (2014) 639–650.
[50] M. Jucker, L.C. Walker, Self-propagation of pathogenic protein aggregates in neurodegenerative diseases, Nature 501 (2013) 45–51.
[51] S. Moussaud, D.R. Jones, E.L. Moussaud-Lamodiere, M. Delenclos, O.A. Ross, P.J. McLean, Alpha-synuclein and tau: teammates in neurodegeneration? Mol. Neurodegener. 9 (2014).
[52] B.I. Giasson, M.S. Forman, M. Higuchi, et al., Initiation and synergistic fibrillization of tau and alpha-synuclein, Science 300 (2003) 636–640.
[53] D.L. Castillo-Carranza, M.J. Guerrero-Munoz, U. Sengupta, J.E. Gerson, R. Kayed, Alpha-synuclein oligomers induce a unique toxic tau strain, Biol. Psychiatry 84 (2018) 499–508.

[54] J.E. Gerson, K.M. Farmer, N. Henson, et al., Tau oligomers mediate alpha-synuclein toxicity and can be targeted by immunotherapy, Mol. Neurodegener. 13 (2018) 13.
[55] V.M. Lee, B.I. Giasson, J.Q. Trojanowski, More than just two peas in a pod: common amyloidogenic properties of tau and alpha-synuclein in neurodegenerative diseases, Trends Neurosci. 27 (2004) 129–134.
[56] R. Wallings, C. Manzoni, R. Bandopadhyay, Cellular processes associated with LRRK2 function and dysfunction, FEBS J. 282 (2015) 2806–2826.
[57] F. Kawakami, N. Shimada, E. Ohta, et al., Leucine-rich repeat kinase 2 regulates tau phosphorylation through direct activation of glycogen synthase kinase-3beta, FEBS J. 281 (2014) 3–13.
[58] M.R. Shanley, D. Hawley, S. Leung, et al., LRRK2 facilitates tau phosphorylation through strong interaction with tau and cdk5, Biochemistry 54 (2015) 5198–5208.
[59] C.A. Lasagna-Reeves, D.L. Castillo-Carranza, U. Sengupta, et al., Identification of oligomers at early stages of tau aggregation in Alzheimer's disease, FASEB J. 26 (2012) 1946–1959.
[60] A. Sengupta, J. Kabat, M. Novak, Q. Wu, I. Grundke-Iqbal, K. Iqbal, Phosphorylation of tau at both Thr 231 and Ser 262 is required for maximal inhibition of its binding to microtubules, Arch. Biochem. Biophys. 357 (1998) 299–309.
[61] S.J. Lee, P. Desplats, C. Sigurdson, I. Tsigelny, E. Masliah, Cell-to-cell transmission of non-prion protein aggregates, Nat. Rev. Neurol. 6 (2010) 702–706.
[62] P.J. Khandelwal, S.B. Dumanis, A.M. Herman, G.W. Rebeck, C.E. Moussa, Wild type and P301L mutant tau promote neuro-inflammation and alpha-Synuclein accumulation in lentiviral gene delivery models, Mol. Cell. Neurosci. 49 (2012) 44–53.
[63] A.P. Kozikowski, I.N. Gaisina, P.A. Petukhov, et al., Highly potent and specific GSK-3beta inhibitors that block tau phosphorylation and decrease alpha-synuclein protein expression in a cellular model of Parkinson's disease, ChemMedChem 1 (2006) 256–266.
[64] C.A. Lasagna-Reeves, D.L. Castillo-Carranza, M.J. Guerrero-Muoz, G.R. Jackson, R. Kayed, Preparation and characterization of neurotoxic tau oligomers, Biochemistry 49 (2010) 10039–10041.
[65] S.D. Yang, J.S. Song, J.S. Yu, S.G. Shiah, Protein kinase FA/GSK-3 phosphorylates tau on Ser235-pro and Ser404-pro that are abnormally phosphorylated in Alzheimer's disease brain, J. Neurochem. 61 (1993) 1742–1747.
[66] T. Duka, V. Duka, J.N. Joyce, A. Sidhu, Alpha-Synuclein contributes to GSK-3beta-catalyzed tau phosphorylation in Parkinson's disease models, FASEB J. 23 (2009) 2820–2830.
[67] A. Sengupta, M. Novak, I. Grundke-Iqbal, K. Iqbal, Regulation of phosphorylation of tau by cyclin-dependent kinase 5 and glycogen synthase kinase-3 at substrate level, FEBS Lett. 580 (2006) 5925–5933.
[68] J.H. Cho, G.V. Johnson, Primed phosphorylation of tau at Thr231 by glycogen synthase kinase 3beta (GSK3beta) plays a critical role in regulating tau's ability to bind and stabilize microtubules, J. Neurochem. 88 (2004) 349–358.
[69] C.H. Lin, P.I. Tsai, R.M. Wu, C.T. Chien, LRRK2 G2019S mutation induces dendrite degeneration through mislocalization and phosphorylation of tau by recruiting autoactivated GSK3ss, J. Neurosci. 30 (2010) 13138–13149.
[70] F. Kawakami, M. Suzuki, N. Shimada, et al., Stimulatory effect of alpha-synuclein on the tau-phosphorylation by GSK-3beta, FEBS J. 278 (2011) 4895–4904.
[71] M. Steger, F. Tonelli, G. Ito, et al., Phosphoproteomics reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases, Elife 5 (2016).
[72] W. Zou, S. Yadav, L. DeVault, Y. Nung Jan, D.R. Sherwood, RAB-10-dependent membrane transport is required for dendrite arborization, PLoS Genet. 11 (2015) e1005484.
[73] E. Ohta, F. Kawakami, M. Kubo, F. Obata, LRRK2 directly phosphorylates Akt1 as a possible physiological substrate: impairment of the kinase activity by Parkinson's disease-associated mutations, FEBS Lett. 585 (2011) 2165–2170.
[74] B.D. Manning, A. Toker, AKT/PKB signaling: navigating the network, Cell 169 (2017) 381–405.
[75] D. Athauda, T. Foltynie, The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action, Drug Discov. Today 21 (2016) 802–818.
[76] S.R. Kim, X. Chen, T.F. Oo, et al., Dopaminergic pathway reconstruction by Akt/Rheb-induced axon regeneration, Ann. Neurol. 70 (2011) 110–120.
[77] V. Ries, C. Henchcliffe, T. Kareva, et al., Oncoprotein Akt/PKB induces trophic effects in murine models of Parkinson's disease, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 18757–18762.
[78] S. Timmons, M.F. Coakley, A.M. Moloney, C ON. Akt signal transduction dysfunction in Parkinson's disease, Neurosci. Lett. 467 (2009) 30–35.
[79] C. Malagelada, Z.H. Jin, L.A. Greene, RTP801 is induced in Parkinson's disease and mediates neuron death by inhibiting Akt phosphorylation/activation, J. Neurosci. 28 (2008) 14363–14371.
[80] E. Ohta, T. Nihira, A. Uchino, et al., I2020T mutant LRRK2 iPSC-derived neurons in the Sagamihara family exhibit increased tau phosphorylation through the AKT/GSK-3beta signaling pathway, Hum. Mol. Genet. 24 (2015) 4879–4900.
[81] M.G. Heckman, A. Elbaz, A.I. Soto-Ortolaza, et al., Protective effect of LRRK2 p.R1398H on risk of Parkinson's disease is independent of MAPT and SNCA variants, Neurobiol. Aging 35 (2014) (266 e5-14).
[82] D.C. Berwick, B. Javaheri, A. Wetzel, et al., Pathogenic LRRK2 variants are gain-of-function mutations that enhance LRRK2-mediated repression of beta-catenin signaling, Mol. Neurodegener. 12 (2017) 9.
[83] J. Nixon-Abell, D.C. Berwick, S. Granno, V.A. Spain, C. Blackstone, K. Harvey, Protective LRRK2 R1398H variant enhances GTPase and Wnt signaling activity, Front. Mol. Neurosci. 9 (2016) 18.
[84] S.A. Purro, S. Galli, P.C. Salinas, Dysfunction of Wnt signaling and synaptic disassembly in neurodegenerative diseases, J. Mol. Cell Biol. 6 (2014) 75–80.
[85] B.T. MacDonald, K. Tamai, X. He, Wnt/beta-catenin signaling: components, mechanisms, and diseases, Dev. Cell 17 (2009) 9–26.
[86] D.C. Berwick, K. Harvey, The importance of Wnt signalling for neurodegeneration in Parkinson's disease, Biochem. Soc. Trans. 40 (2012) 1123–1128.
[87] S. Gollamudi, A. Johri, N.Y. Calingasan, L. Yang, O. Elemento, M.F. Beal, Concordant signaling pathways produced by pesticide exposure in mice correspond to pathways identified in human Parkinson's disease, PLoS One 7 (2012) e36191.
[88] I. Zancan, S. Bellesso, R. Costa, et al., Glucocerebrosidase deficiency in zebrafish affects primary bone ossification through increased oxidative stress and reduced Wnt/beta-catenin signaling, Hum. Mol. Genet. 24 (2015) 1280–1294.
[89] O. Awad, L.M. Panicker, R.M. Deranieh, et al., Altered differentiation potential of Gaucher's disease iPSC neuronal progenitors due to Wnt/beta-catenin down-regulation, Stem Cell. Rep. 9 (2017) 1853–1867.
[90] J.B. Kwok, M. Hallupp, C.T. Loy, et al., GSK3B polymorphisms alter transcription and splicing in Parkinson's disease, Ann. Neurol. 58 (2005) 829–839.
[91] R. van Amerongen, R. Nusse, Towards an integrated view of Wnt signaling in development, Development 136 (2009) 3205–3214.
[92] E.M. Verheyen, C.J. Gottardi, Regulation of Wnt/beta-catenin signaling by protein kinases, Dev. Dyn. 239 (2010) 34–44.
[93] L. Zhang, L. Cen, S. Qu, et al., Enhancing Beta-catenin activity via GSK3beta inhibition protects PC12 cells against rotenone toxicity through Nurr1 induction, PLoS One 11 (2016) e0152931.
[94] M. Decressac, N. Volakakis, A. Bjorklund, T. Perlmann, NURR1 in Parkinson disease–from pathogenesis to therapeutic potential, Nat. Rev. Neurol. 9 (2013) 629–636.
[95] W. Le, O.M. Conneely, L. Zou, et al., Selective agenesis of mesencephalic dopaminergic neurons in Nurr1-deficient mice, Exp. Neurol. 159 (1999) 451–458.
[96] Y. Chu, K. Kompoliti, E.J. Cochran, E.J. Mufson, J.H. Kordower, Age-related decreases in Nurr1 immunoreactivity in the human substantia nigra, J. Comp. Neurol. 450 (2002) 203–214.
[97] Y.X. Yang, D.S. Latchman, Nurr1 transcriptionally regulates the expression of alpha-synuclein, Neuroreport 19 (2008) 867–871.
[98] M. Decressac, B. Kadkhodaei, B. Mattsson, A. Laguna, T. Perlmann, A. Bjorklund, Alpha-Synuclein-induced down-regulation of Nurr1 disrupts GDNF signaling in nigral dopamine neurons, Sci. Transl. Med. 4 (2012) 163ra56.
[99] X. Lin, L. Parisiadou, C. Sgobio, et al., Conditional expression of Parkinson's disease-related mutant alpha-synuclein in the midbrain dopaminergic neurons causes progressive neurodegeneration and degradation of transcription factor nuclear receptor related 1, J. Neurosci. 32 (2012) 9248–9264.
[100] Y. Chu, W. Le, K. Kompoliti, J. Jankovic, E.J. Mufson, J.H. Kordower, Nurr1 in Parkinson's disease and related disorders, J. Comp. Neurol. 494 (2006) 495–514.
[101] J. Dong, S. Li, J.L. Mo, H.B. Cai, W.D. Le, Nurr1-based therapies for Parkinson's disease, CNS Neurosci. Ther. 22 (2016) 351–359.
[102] K. Zheng, B. Heydari, D.K. Simon, A common NURR1 polymorphism associated with Parkinson disease and diffuse Lewy body disease, Arch. Neurol. 60 (2003) 722–725.
[103] A.J. Espay, J.A. Vizcarra, L. Marsili, et al., Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases, Neurology 92 (2019) 329–337.
[104] I. Aviles-Olmos, J. Dickson, Z. Kefalopoulou, et al., Exenatide and the treatment of patients with Parkinson's disease, J. Clin. Invest. 123 (2013) 2730–2736.
[105] I. Aviles-Olmos, J. Dickson, Z. Kefalopoulou, et al., Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease, J. Park. Dis. 4 (2014) 337–344.
[106] P. Lolekha, P. Wongwan, K. Kulkantrakorn, Association between serum uric acid and motor subtypes of Parkinson's disease, J. Clin. Neurosci. 22 (2015) 1264–1267.
[107] T. Gerhard, D.P. Devanand, C. Huang, S. Crystal, M. Olfson, Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study, Br. J. Psychiatry 207 (2015) 46–51.
[108] T. Guttuso Jr., E. Russak, M.T. De Blanco, M. Ramanathan, Could high lithium levels in tobacco contribute to reduced risk of Parkinson's disease in smokers? J. Neurol. Sci. 397 (2019) 179–180.
[109] D.M. Gash, Z. Zhang, A. Ovadia, et al., Functional recovery in parkinsonian monkeys treated with GDNF, Nature 380 (1996) 252–255.
[110] W.J. Marks Jr., R.T. Bartus, J. Siffert, et al., Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial, Lancet Neurol. 9 (2010) 1164–1172.
[111] A.E. Lang, S. Gill, N.K. Patel, et al., Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease, Ann. Neurol. 59 (2006) 459–466.
[112] A. Yoshii, M. Constantine-Paton, Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease, Dev. Neurobiol. 70 (2010) 304–322.
[113] S.S. Kang, Z. Zhang, X. Liu, et al., TrkB neurotrophic activities are blocked by alpha-synuclein, triggering dopaminergic cell death in Parkinson's disease, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 10773–10778.
[114] T.J. Kieffer, C.H. McIntosh, R.A. Pederson, Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV, Endocrinology 136 (1995) 3585–3596.
[115] D.G. Parkes, K.F. Mace, M.E. Trautmann, Discovery and development of exenatide: the first antidiabetic agent to leverage the multiple benefits of the incretin hormone, GLP-1, Expert Opin. Drug Discovery 8 (2013) 219–244.
[116] E. Alvarez, M.D. Martinez, I. Roncero, et al., The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human

hypothalamus and brainstem, J. Neurochem. 92 (2005) 798–806.
[117] Y. Li, T. Perry, M.S. Kindy, et al., GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 1285–1290.
[118] S. Chen, F.M. An, L. Yin, et al., Glucagon-like peptide-1 protects hippocampal neurons against advanced glycation end product-induced tau hyperphosphorylation, Neuroscience 256 (2014) 137–146.
[119] W. Xu, Y. Yang, G. Yuan, W. Zhu, D. Ma, S. Hu, Exendin-4, a glucagon-like peptide-1 receptor agonist, reduces Alzheimer disease-associated tau hyperphosphorylation in the hippocampus of rats with type 2 diabetes, J. Invest. Med.: Off. Publ. Am. Fed. Clin. Res. 63 (2015) 267–272.
[120] N. Embi, D.B. Rylatt, P. Cohen, Glycogen synthase kinase-3 from rabbit skeletal muscle. Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase, Eur. J. Biochem. 107 (1980) 519–527.
[121] D.A. Cross, D.R. Alessi, P. Cohen, M. Andjelkovich, B.A. Hemmings, Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B, Nature 378 (1995) 785–789.
[122] W. Liu, J. Jalewa, M. Sharma, G. Li, L. Li, C. Holscher, Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease, Neuroscience 303 (2015) 42–50.
[123] C.W. Olanow, K. Kieburtz, Defining disease-modifying therapies for PD—a road map for moving forward, Mov. Disord. 25 (2010) 1774–1779.
[124] D. Vaillancourt, Effects of Exenatide on Motor Function and the Brain, (2019) Available at https://clinicaltrials.gov/ct2/show/NCT03456687?term=NCT03456687&rank=1 , Accessed date: 15 December 2018.
[125] R.G. Burciu, E. Ofori, D.B. Archer, et al., Progression marker of Parkinson's disease: a 4-year multisite imaging study, Brain 140 (2017) 2183–2192.
[126] T. Guttuso Jr., N. Bergsland, J. Hagemeier, D.G. Lichter, O. Pasternak, R. Zivadinov, Substantia Nigra free water increases longitudinally in Parkinson disease, AJNR Am. J. Neuroradiol. 39 (2018) 479–484.
[127] G.F. Crotty, A. Ascherio, M.A. Schwarzschild, Targeting urate to reduce oxidative stress in Parkinson disease, Exp. Neurol. 298 (2017) 210–224.
[128] K.J. Yeum, R.M. Russell, N.I. Krinsky, G. Aldini, Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma, Arch. Biochem. Biophys. 430 (2004) 97–103.
[129] J. Blesa, I. Trigo-Damas, A. Quiroga-Varela, V.R. Jackson-Lewis, Oxidative stress and Parkinson's disease, Front. Neuroanat. 9 (2015) 91.
[130] J. Xu, S.Y. Kao, F.J. Lee, W. Song, L.W. Jin, B.A. Yankner, Dopamine-dependent neurotoxicity of alpha-synuclein: a mechanism for selective neurodegeneration in Parkinson disease, Nat. Med. 8 (2002) 600–606.
[131] W.H. Church, V.L. Ward, Uric acid is reduced in the substantia nigra in Parkinson's disease: effect on dopamine oxidation, Brain Res. Bull. 33 (1994) 419–425.
[132] E. Vieru, A. Koksal, B. Mutluay, A.C. Dirican, Y. Altunkaynak, S. Baybas, The relation of serum uric acid levels with L-Dopa treatment and progression in patients with Parkinson's disease, Neurol. Sci. 37 (2016) 743–747.
[133] I. Huertas, S. Jesus, J.A. Lojo, et al., Lower levels of uric acid and striatal dopamine in non-tremor dominant Parkinson's disease subtype, PLoS One 12 (2017) e0174644.
[134] L. Gong, Q.L. Zhang, N. Zhang, et al., Neuroprotection by urate on 6-OHDA-lesioned rat model of Parkinson's disease: linking to Akt/GSK3beta signaling pathway, J. Neurochem. 123 (2012) 876–885.
[135] Y.L. Sheng, X. Chen, X.O. Hou, et al., Urate promotes SNCA/alpha-synuclein clearance via regulating mTOR-dependent macroautophagy, Exp. Neurol. 297 (2017) 138–147.
[136] T. Moors, S. Paciotti, D. Chiasserini, et al., Lysosomal dysfunction and alpha-synuclein aggregation in Parkinson's disease: diagnostic links, Mov. Disord. 31 (2016) 791–801.
[137] M. Xilouri, O.R. Brekk, L. Stefanis, Autophagy and alpha-synuclein: relevance to Parkinson's disease and related synucleopathies, Mov. Disord. 31 (2016) 178–192.
[138] M. Jin, F. Yang, I. Yang, et al., Uric acid, hyperuricemia and vascular diseases, Front. Biosci. (Landmark Ed) 17 (2012) 656–669.
[139] S. Bhattacharyya, R. Bakshi, R. Logan, A. Ascherio, E.A. Macklin, M.A. Schwarzschild, Oral inosine persistently elevates plasma antioxidant capacity in Parkinson's disease, Mov. Disord. 31 (2016) 417–421.
[140] P. Salomoni, B. Calabretta, Targeted therapies and autophagy: new insights from chronic myeloid leukemia, Autophagy 5 (2009) 1050–1051.
[141] M.L. Hebron, I. Lonskaya, P. Olopade, S.T. Selby, F. Pagan, C.E. Moussa, Tyrosine kinase inhibition regulates early systemic immune changes and modulates the neuroimmune response in alpha-synucleinopathy, J. Clin. Cell Immunol. 5 (2014) 259.
[142] M.L. Hebron, I. Lonskaya, C.E. Moussa, Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of alpha-synuclein in Parkinson's disease models, Hum. Mol. Genet. 22 (2013) 3315–3328.
[143] B. Pan, L. Yang, J. Wang, et al., C-Abl tyrosine kinase mediates neurotoxic prion peptide-induced neuronal apoptosis via regulating mitochondrial homeostasis, Mol. Neurobiol. 49 (2014) 1102–1116.
[144] Y. Pan, L. Sun, J. Wang, et al., STI571 protects neuronal cells from neurotoxic prion protein fragment-induced apoptosis, Neuropharmacology 93 (2015) 191–198.
[145] S.Z. Imam, Q. Zhou, A. Yamamoto, et al., Novel regulation of parkin function through c-Abl-mediated tyrosine phosphorylation: implications for Parkinson's disease, J. Neurosci. 31 (2011) 157–163.
[146] A.L. Mahul-Mellier, B. Fauvet, A. Gysbers, et al., c-Abl phosphorylates alpha-synuclein and regulates its degradation: implication for alpha-synuclein clearance and contribution to the pathogenesis of Parkinson's disease, Hum. Mol. Genet. 23 (2014) 2858–2879.
[147] H. Shimura, N. Hattori, S. Kubo, et al., Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase, Nat. Genet. 25 (2000) 302–305.
[148] N. Matsuda, T. Kitami, T. Suzuki, Y. Mizuno, N. Hattori, K. Tanaka, Diverse effects of pathogenic mutations of parkin that catalyze multiple monoubiquitylation in vitro, J. Biol. Chem. 281 (2006) 3204–3209.
[149] G.I. Cancino, K. Perez de Arce, P.U. Castro, E.M. Toledo, R. von Bernhardi, A.R. Alvarez, c-Abl tyrosine kinase modulates tau pathology and Cdk5 phosphorylation in AD transgenic mice, Neurobiol. Aging 32 (2011) 1249–1261.
[150] O.V. Forlenza, V.J. De-Paula, B.S. Diniz, Neuroprotective effects of lithium: implications for the treatment of Alzheimer's disease and related neurodegenerative disorders, ACS Chem. Neurosci. 5 (2014) 443–450.
[151] C.A. Lazzara, Y.H. Kim, Potential application of lithium in Parkinson's and other neurodegenerative diseases, Front. Neurosci. 9 (2015) 403.
[152] Y.H. Yuan, W.F. Yan, J.D. Sun, J.Y. Huang, Z. Mu, N.H. Chen, The molecular mechanism of rotenone-induced alpha-synuclein aggregation: emphasizing the role of the calcium/GSK3beta pathway, Toxicol. Lett. 233 (2015) 163–171.
[153] Y. Motoi, K. Shimada, K. Ishiguro, N. Hattori, Lithium and autophagy, ACS Chem. Neurosci. 5 (2014) 434–442.
[154] S. Sarkar, R.A. Floto, Z. Berger, et al., Lithium induces autophagy by inhibiting inositol monophosphatase, J. Cell Biol. 170 (2005) 1101–1111.
[155] Y.H. Kim, A. Rane, S. Lussier, J.K. Andersen, Lithium protects against oxidative stress-mediated cell death in alpha-synuclein-overexpressing in vitro and in vivo models of Parkinson's disease, J. Neurosci. Res. 89 (2011) 1666–1675.
[156] C.A. Lieu, C.M. Dewey, S.J. Chinta, et al., Lithium prevents parkinsonian behavioral and striatal phenotypes in an aged parkin mutant transgenic mouse model, Brain Res. 1591 (2014) 111–117.
[157] M.B. Youdim, Z. Arraf, Prevention of MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) dopaminergic neurotoxicity in mice by chronic lithium: involvements of Bcl-2 and Bax, Neuropharmacology 46 (2004) 1130–1140.
[158] L. Freland, J.M. Beaulieu, Inhibition of GSK3 by lithium, from single molecules to signaling networks, Front. Mol. Neurosci. 5 (2012) 14.
[159] P. De Sarno, X. Li, R.S. Jope, Regulation of Akt and glycogen synthase kinase-3 beta phosphorylation by sodium valproate and lithium, Neuropharmacology 43 (2002) 1158–1164.
[160] W. Noble, E. Planel, C. Zehr, et al., Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 6990–6995.
[161] J.M. Beaulieu, T.D. Sotnikova, W.D. Yao, et al., Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 5099–5104.
[162] J.Q. Pan, M.C. Lewis, J.K. Ketterman, et al., AKT kinase activity is required for lithium to modulate mood-related behaviors in mice, Neuropsychopharmacology 36 (2011) 1397–1411.
[163] X. Li, A.B. Friedman, W. Zhu, et al., Lithium regulates glycogen synthase kinase-3beta in human peripheral blood mononuclear cells: implication in the treatment of bipolar disorder, Biol. Psychiatry 61 (2007) 216–222.
[164] R.T. de Sousa, M.V. Zanetti, L.L. Talib, et al., Lithium increases platelet serine-9 phosphorylated GSK-3beta levels in drug-free bipolar disorder during depressive episodes, J. Psychiatr. Res. 62 (2015) 78–83.
[165] G. Das, A.K. Misra, S.K. Das, K. Ray, J. Ray, Role of tau kinases (CDK5R1 and GSK3B) in Parkinson's disease: a study from India, Neurobiol. Aging 33 (2012) (1485 e9-15).
[166] N. Crespo-Biel, A. Camins, M. Pallas, A.M. Canudas, Evidence of calpain/cdk5 pathway inhibition by lithium in 3-nitropropionic acid toxicity in vivo and in vitro, Neuropharmacology 56 (2009) 422–428.
[167] C.A. Lazzara, R.R. Riley, A. Rane, J.K. Andersen, Y.H. Kim, The combination of lithium and l-Dopa/Carbidopa reduces MPTP-induced abnormal involuntary movements (AIMs) via calpain-1 inhibition in a mouse model: relevance for Parkinsons disease therapy, Brain Res. 1622 (2015) 127–136.
[168] E.G. Jorda, E. Verdaguer, A.M. Canudas, et al., Implication of cyclin-dependent kinase 5 in the neuroprotective properties of lithium, Neuroscience 134 (2005) 1001–1011.
[169] D. Aarsland, B. Creese, M. Politis, et al., Cognitive decline in Parkinson disease, Nat. Rev. Neurol. 13 (2017) 217–231.
[170] D. Aarsland, K. Andersen, J.P. Larsen, A. Lolk, P. Kragh-Sorensen, Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study, Arch. Neurol. 60 (2003) 387–392.
[171] A. Takashima, GSK-3 is essential in the pathogenesis of Alzheimer's disease, J. Alzheimers Dis. 9 (2006) 309–317.
[172] Y. Su, J. Ryder, B. Li, et al., Lithium, a common drug for bipolar disorder treatment, regulates amyloid-beta precursor protein processing, Biochemistry 43 (2004) 6899–6908.
[173] C.J. Phiel, C.A. Wilson, V.M. Lee, P.S. Klein, GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides, Nature 423 (2003) 435–439.
[174] X. Sun, S. Sato, O. Murayama, et al., Lithium inhibits amyloid secretion in COS7 cells transfected with amyloid precursor protein C100, Neurosci. Lett. 321 (2002) 61–64.
[175] S. Hall, Y. Surova, A. Ohrfelt, et al., Longitudinal measurements of cerebrospinal fluid biomarkers in Parkinson's disease, Mov. Disord. 31 (2016) 898–905.
[176] J.O. Lipton, M. Sahin, The neurology of mTOR, Neuron 84 (2014) 275–291.
[177] M. Ren, V.V. Senatorov, R.W. Chen, D.M. Chuang, Postinsult treatment with lithium reduces brain damage and facilitates neurological recovery in a rat ischemia/reperfusion model, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 6210–6215.
[178] Y. Chu, J.H. Kordower, Age-associated increases of alpha-synuclein in monkeys and humans are associated with nigrostriatal dopamine depletion: is this the target for Parkinson's disease? Neurobiol. Dis. 25 (2007) 134–149.

[179] A.M. Cuervo, L. Stefanis, R. Fredenburg, P.T. Lansbury, D. Sulzer, Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy, Science 305 (2004) 1292–1295.
[180] H.F. Dorn, Tobacco consumption and mortality from cancer and other diseases, Public Health Rep. 74 (1959) 581–593.
[181] B. Ritz, A. Ascherio, H. Checkoway, et al., Pooled analysis of tobacco use and risk of Parkinson disease, Arch. Neurol. 64 (2007) 990–997.
[182] V. Gallo, P. Vineis, M. Cancellieri, et al., Exploring causality of the association between smoking and Parkinson's disease, Int. J. Epidemiol. (2018).
[183] S. Searles Nielsen, L.G. Gallagher, J.I. Lundin, et al., Environmental tobacco smoke and Parkinson's disease, Mov. Disord. 27 (2012) 293–296.
[184] N. Morozova, E.J. O'Reilly, A. Ascherio, Variations in gender ratios support the connection between smoking and Parkinson's disease, Mov. Disord. 23 (2008) 1414–1419.
[185] R. Savica, B.R. Grossardt, J.H. Bower, J.E. Ahlskog, W.A. Rocca, Time trends in the incidence of Parkinson disease, JAMA Neurol. 73 (2016) 981–989.
[186] V.S. Jathar, P.R. Pendharkar, V.K. Pandey, et al., Manic depressive psychosis in India and the possible role of lithium as a natural prophylactic. II—Lithium content of diet and some biological fluids in Indian subjects, J. Postgrad. Med. 26 (1980) 39–44.
[187] C. Marras, N. Herrmann, H.D. Fischer, et al., Lithium use in older adults is associated with increased prescribing of Parkinson medications, Am. J. Geriatr. Psychiatry 24 (2016) 301–309.
[188] C.E. Coffey, D.R. Ross, E.L. Ferren, J.L. Sullivan, C.W. Olanow, Treatment of the "on-off" phenomenon in parkinsonism with lithium carbonate, Ann. Neurol. 12 (1982) 375–379.
[189] C.E. Coffey, D.R. Ross, E.W. Massey, C.W. Olanow, Dyskinesias associated with lithium therapy in parkinsonism, Clin. Neuropharmacol. 7 (1984) 223–229.
[190] T. Guttuso Jr., Low-dose lithium adjunct therapy associated with reduced off-time in Parkinson's disease: a case series, J. Neurol. Sci. 368 (2016) 221–222.