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## Role of FKBP's in Parkinson's Disease

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### 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease among the elderly. While sporadic PD constitutes 99% of the cases, the remaining 1% is of genetic origin. The neuropathological hallmarks of PD are progressive degeneration of dopaminergic (DA) neurons and presence of Lewy neurites and Lewy bodies (LBs) - intracytoplasmic proteinaceous inclusions that contain  $\alpha$ -synuclein (SYN), synphilin-1, components of the ubiquitin proteasomal pathway and parkin (Dawson, 2006). The loss of DA neurons in substantia nigra pars compacta (SNpc) results in decreased signalling in the striatum thereby giving rise to motor defects like resting tremor, bradykinesia, rigidity and posture instability. Besides DA neuronal loss, microglial activation and increased astroglial and lymphocyte infiltration also occur in PD. A role for inflammation in PD has been inferred from the identification of human leukocyte antigen (HLA)-DR positive reactive microglia in the brains of PD patients (McGeer *et al.*, 1988). Additionally, levels of pro-inflammatory cytokines like IL-6, IL-1 $\beta$ , TNF $\alpha$  have been found to be elevated in the blood and cerebrospinal fluid (CSF) of PD patients (Nagatsu & Sawada, 2005; Dawson, 2006). Although these inflammatory components might serve as useful biomarkers, the aetiology of striatal DA degeneration still remains enigmatic.

In the last decade, identification of mutations in several distinct genes (*LRRK2*, *parkin*, *PINK1*, *DJ-1*,  *$\alpha$ -synuclein*, *MAPT*, *UCHL1* etc) linked to different forms of familial Parkinsonism has imparted a new direction to understanding PD pathogenesis (Tong & Shen, 2009). The question as to how seemingly divergent genes cause PD still remains unanswered, as there is no common molecular pathway involving these gene products. While parkin,  $\alpha$ -synuclein (SYN) and ubiquitin C-terminal hydrolase L1 (UCHL1) are functionally associated with the cellular ubiquitin proteasomal system (UPS), DJ-1 and PINK1 protect against oxidative stress and mitochondrial dysfunction. More recently, microarray analysis of SNpc from parkinsonian brain (Mandel *et al.*, 2005) has shown that 68 genes related to protein degradation, signal transduction, dopaminergic transmission, iron transport and glycolysis are downregulated. Prominent among these are the protein chaperone HSC-70, subunits of the UPS and SKP1A, a member of the E3 ubiquitin ligase complex. Therefore, it is most likely that impairment in energy metabolism and/or alterations in UPS are the underlying mechanisms for PD pathogenesis (Eriksen *et al.*, 2005; Mandel *et al.*, 2005).

Current PD treatment regimes can be divided into three categories: symptomatic, protective and restorative. Only symptomatic treatment via the administration of L-dopa and other

drugs affecting neurological transmission have shown efficacy. However, side effects like dyskinesia, motor fluctuations and neurological complications limit their long-term use (Gold & Nutt, 2002). The neuroimmunophilins ligands (NILs) are a promising new class of drugs for treatment of PD as well as other neurodegenerative diseases. NILs are derived from the immunosuppressant, FK506 (tacrolimus) and exert their activity not via any cellular mechanism involving the immune system but by binding to a group of proteins termed FK506 binding proteins (FKBPs). When compared to the immune system, FKBP expression levels are highly enriched (10-50 fold greater) in both the central and peripheral nervous system. In this chapter, we review our current understanding of the role of FKFBPs in the nervous system with an emphasis on the protein partners that interface with FKFBPs inside cells. For brevity, we limit our discussions to FKFBPs that are enriched in the nervous systems and may have important role in Parkinson's disease pathogenesis. We also highlight the mode of action of the NILs with the hope that knowledge of such interaction will enable rationale design of new drugs with improved efficacy for treatment of Parkinson's disease as well as other neurodegenerative disorders.

## 2. Role of FKFBPs in the nervous system

FKFBPs together with cyclophilins (CyPs) comprise a family of phylogenetically conserved immunophilins that have peptidyl prolyl isomerase activity (PPIase; EC 5.2.1.8), producing the *cis-trans* isomerization of X-Pro peptide bond, an essential but rate-limiting step in the protein folding process (Barik, 2006). Initial isolation and purification of immunophilins were based on their differential affinity towards the principal immunosuppressant drugs - rapamycin, FK506 and cyclosporin A (CsA). While CyPs bind to only CsA, FKFBPs have affinities for both FK506 and rapamycin. Immunosuppressive activity mediated by these drugs is brought about by their binding to the cognate immunophilins. The FK506/FKBP or CsA/CyP binary complexes bind to the Ca<sup>2+</sup>/calmodulin dependent protein serine/threonine phosphatase, calcineurin (CaN) and inhibit its phosphatase activity. The resulting FKBP-FK506-CaN ternary complex cannot dephosphorylate the key transcription factor, nuclear factor of activated T-cells (NF-AT). Inactive NF-AT remains in the cytoplasm thereby preventing interleukin-2 (IL-2) secretion (**Figure 1**). Consequently, both T-cell activation and proliferation is inhibited. On the other hand, FKBP-rapamycin complex exerts immunosuppression by inhibiting the serine/threonine kinase activity of mammalian target of rapamycin (mTOR) (Sharma *et al.*, 1994).

The role of FKFBPs in the nervous system was initiated by observations that the brain is abundantly enriched in CyPs and FKFBPs (Maki *et al.*, 1990; Steiner *et al.*, 1992; Dawson *et al.*, 1994). The importance of immunophilins in the nervous system was firmly established from studies showing that FK506 potently (as low as 0.1 nM) increases neurite outgrowth in both PC-12 (Lyons *et al.*, 1994) and SH-SY5Y cell culture models as well as in primary cultures of chick dorsal root ganglion and hippocampal neurons (Hamilton and Steiner, 1998). Efforts to explain this neurotrophic effect focussed on the calcineurin-dependent pathway involving the CaN substrate, GAP-43 (growth-associated protein-43). GAP-43 selectively localizes to developing neurons and its phosphorylation is known to enhance its neurite extension activity (Meiri *et al.*, 1991). Though initially tenable, the hypothesis was challenged when it was shown that both CsA (Gold, 1997) and non-immunosuppressive (hence non-calcineurin binding) derivatives of FK506 exhibit neurotrophic effect with similar potencies as that of FK506. Therefore, it is most likely that nerve growth proceeds via a calcineurin-independent pathway.

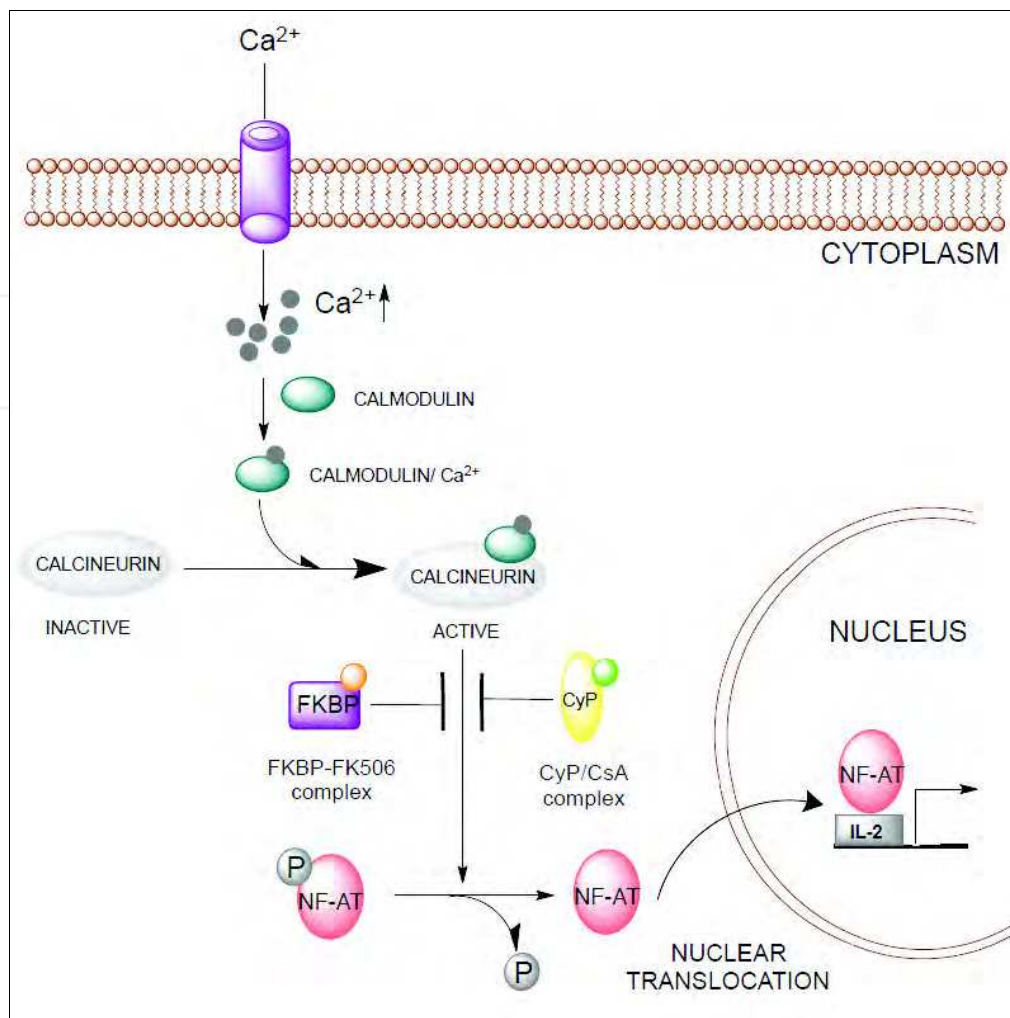


Fig. 1. Immunosuppressive effect of neuroimmunophilin ligands: T-cell receptor activation leads to a rapid increase in intracellular calcium levels with concomitant activation of the  $\text{Ca}^{2+}$ /calmodulin-dependent phosphatase, calcineurin (CaN). Active CaN dephosphorylates the transcription factor NF-AT, allowing its nuclear translocation and thereby upregulating IL-2 expression. Addition of FK506 or CsA results in formation of FKBP-FK506-CaN/CyP-CsA-CaN ternary complexes that inhibits CaN-dependent NF-AT dephosphorylation, as a result T-cell activation and IL-2 secretion does not occur.

When FK506-treated brain lysates were probed for proteins with increased phosphorylation levels, one of the identified targets was neuronal nitric oxide synthase (nNOS). In the brain, nNOS catalyzes the formation of nitric oxide (NO) from arginine and its catalytic activity is inhibited by phosphorylation. Following cerebral vascular occlusion, there is a massive increase in the excitatory neurotransmitter glutamate. Elevated glutamate levels, acting through the N-methyl-D-aspartate (NMDA) receptor, activates nNOS resulting in increased NO formation and neurotoxicity (**Figure 2**). Toxicity may involve NO itself or its combination with superoxide free radical ( $\text{O}_2^-$ ) to form peroxy-nitrite that decomposes to hydroxide ( $\text{OH}^-$ ) and  $\text{NO}_2$  ( $\text{NO}_2^-$ ) free radicals with subsequent cellular damage by oxidation of nucleic acids, proteins and membrane lipids (Snyder, 1992). By enhancing phospho nNOS levels, FKBP inhibits NO formation and thereby attenuate glutamate toxicity following vascular stroke (Snyder *et al.*, 1998). Contrary to nerve regeneration, FKBP-

mediated neuroprotection proceeds via calcineurin inhibition as anti-stroke effects were also seen with CsA.

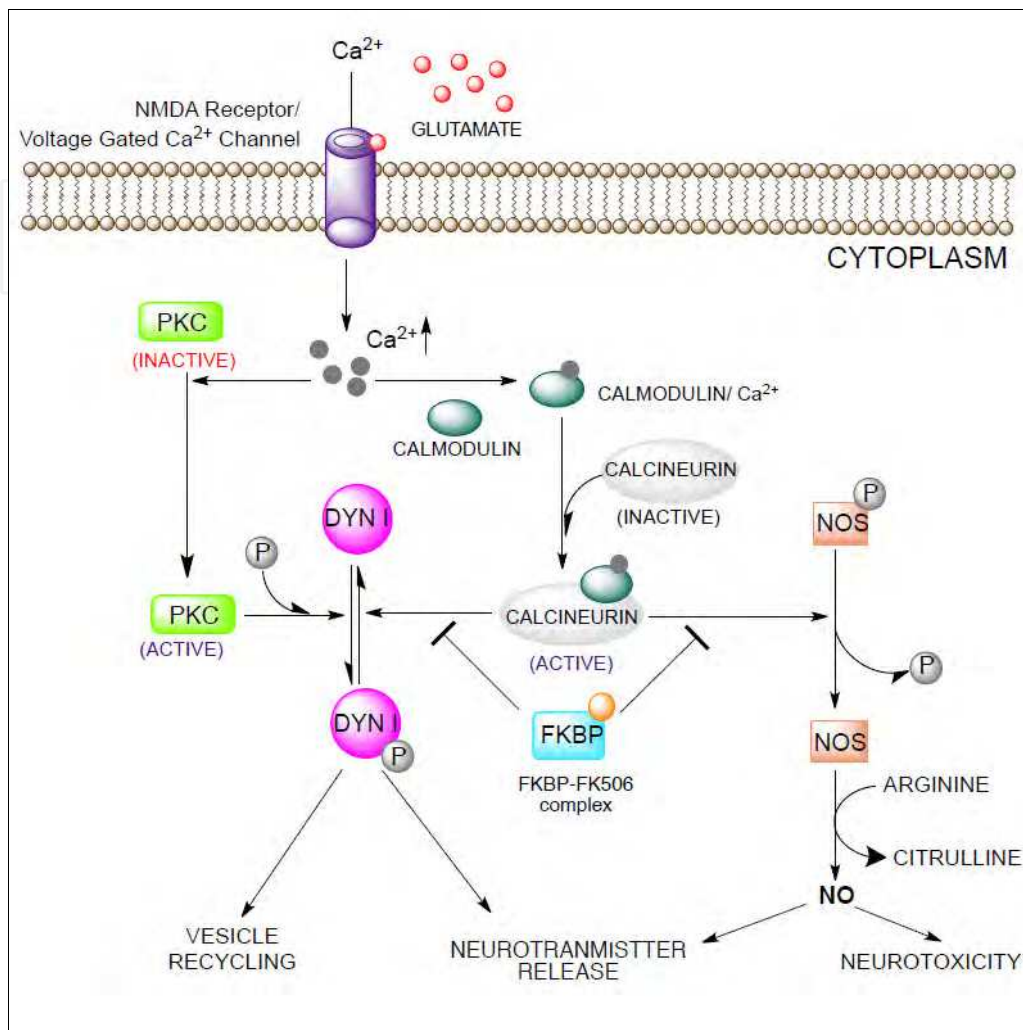


Fig. 2. N1Ls regulate neurotoxicity and neurotransmitter release: Glutamate-mediated influx of calcium through the NMDA receptor activates calcineurin (CaN) that in turn dephosphorylates nNOS and increases its catalytic activity. nNOS activation leads to increased NO formation and subsequent neurotoxicity and neurotransmitter release. FK506/CsA can counteract this neuronal toxicity by inhibiting CaN-dependent nNOS activation. Influx of Ca<sup>2+</sup> also activates PKC and CaN that have opposing effect on phosphorylation state of the GTPase, dynamin I. While PKC-mediated phosphorylation of dynamin I increases its GTPase activity and leads to increased neurotransmitter release, CaN dephosphorylates and inactivates dynamin I. By inhibiting CaN, FK506 and CsA enhances phospho-dynamin I levels and subsequent depolarization-evoked neurotransmitter release.

FK506 has contradictory roles in neurotransmitter release - it inhibits NMDA induced neurotransmitter release while augmenting depolarization-induced release. Since neurotransmitter release proceeds via calcineurin-dependent pathway, this discrepancy in FK506 response can be attributed to the involvement of distinct calcineurin substrates, nNOS and dynamin I (**Figure 2**). FK506 reduces glutamate release from NMDA-stimulated



striatal synaptosomes as well as acetylcholine and dopamine release from PC12 cells that have been differentiated by NGF (Steiner *et al.*, 1996). Similar reductions seen with the nNOS inhibitor, nitro-L-arginine, indicates that NO regulates neurotransmitter release in PC12 and synaptosomes. In presence of FK506 and CsA, inhibition of calcineurin and subsequent reduction of nNOS activity results in decreased NO levels and therefore reduced neurotransmitter release.

In contrast, FK506 fails to inhibit potassium depolarization-evoked neurotransmitter release. Both CsA and L-683590 (FK506 analog that inhibits calcineurin), augment glutamate release from synaptosomes that have been treated with the K<sup>+</sup>-channel blocker, 4-aminopyridine. In this case, the *bona fide* calcineurin substrate, dynamin I and not nNOS is involved (Nichols *et al.*, 1994). Dynamin I, a GTPase that regulates vesicular recycling, is active in its phosphorylated form; enhanced GTPase activity results in greater synaptic vesicular trafficking and increased rate of neurotransmitter release. CsA and FK506 mediated inhibition of calcineurin enhances dynamin I phosphorylation and hence its activity.

FK506 and its derivatives have also shown neuroprotective activity in neuropathy models mimicking stroke and dementia. For example, FK506-mediated calcineurin inhibition protects against ischemic brain injury (Sharkey & Butcher, 1994), desensitizes NMDA receptors (Tong *et al.*, 1995), prevents long-term depression (LTD) in rat hippocampus (Hodgkiss & Kelly, 1995) and modulates long-term potentiation (LTP) in rat visual cortex (Funauchi *et al.*, 1994). Stabilization of mitochondrial function was suggested to account for the anti-ischemic activities of FK506. FK506 does not target the mitochondrial potential transition pore (MTP) but prevents deterioration in mitochondrial respiration while maintaining cellular ATP levels and Ca<sup>2+</sup> homeostasis. Furthermore, the role of FKBP<sub>s</sub> in the central nervous system has been extensively probed using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) induced lesions of dopaminergic neurons. Both agents cause massive degeneration of nigrostriatal DA neurons thereby making MPTP and 6-OHDA treatment experimental paradigms for Parkinson's disease (Gerlach *et al.*, 1991). Treatment with GPI-1046, a FK506 analog was able to substantially recover the MPTP-damaged DA neurons as evidenced by increased tyrosine hydroxylase staining while rats lesioned with 6-OHDA showed morphological and functional recovery with increased striatal catecholamine levels and reduced amphetamine-induced rotations (Steiner *et al.*, 1997).

How might immunophilin ligands exert their neurotrophic and neuroprotective actions? The data suggests that PPIase activity of FKBP<sub>s</sub> maybe involved but no conclusive evidence has been provided so far. Several studies have tried to identify the FKBP(s) involved and elucidate the mechanism-of-action. This has proved particularly difficult as (1) most of the FKBP family members bind FK506 or its derivatives, albeit with varying degrees of affinity; (2) activities of both FKBP<sub>s</sub> and the protein phosphatase, calcineurin are inhibited by FK506 and its analogues and (3) FKBP<sub>s</sub> perform multifarious roles in protein folding, translocation and regulation as well as have a wide range of tissue/organelle distribution. Initial studies implicated a role for FKBP12 as elevated mRNA and protein levels were observed in 6-OHDA model of PD (Nilsson *et al.*, 2007). Moreover, higher levels of FKBP12 have also been reported in brains of PD patients (Avramut & Achim, 2002). Therefore, a possible link between FKBP<sub>s</sub> and PD might stem from the increase in expression or redistribution of chaperone proteins in stress conditions. In addition to FKBP12, the human brain is enriched in FKBP38, FKBP51, FKBP52 and FKBP65 (Charters *et al.*, 1994; Coss *et al.*, 1998; Chambraud *et al.*, 2010; Jinwal

*et al.*, 2010). Collectively, these immunophilins enriched in the nervous system are termed neuroimmunophilins. In the following sections, we will discuss the role of only those neuroimmunophilins that may be important for PD pathogenesis.

### 3. Molecular interacting partners of neuroimmunophilins

The neuroprotective and neurotrophic functions observed with NILs together with studies showing that chaperone proteins like HSP70 can suppresses  $\alpha$ -synuclein ( $\alpha$ -SYN) mediated loss of dopaminergic neurons in *Drosophila* model of PD (Auluck *et al.*, 2002; Muchowski, 2002), posits that FKBP's may have important role(s) in preventing PD-associated neurodegeneration. FKBP's, together with other chaperones may convert the toxic conformations of misfolded proteins to non-toxic form that is tolerated by cells. Alternatively, they may prevent the formation of toxic pre-fibrillar intermediates, or accelerate their conversion to nontoxic, amorphous aggregates that can be degraded by the cellular proteolytic machinery.

#### 3.1 FKBP's interact with $\alpha$ -synuclein both *in vitro* and *in vivo*

$\alpha$ -SYN is a small (140 amino acid) intrinsically disordered protein predominantly localized to the presynaptic terminals.  $\alpha$ -SYN regulates the functions of several other proteins - synphilin-1, parkin, tyrosine hydroxylase, dopamine transporter and phospholipase D, via stoichiometric protein-protein and protein-lipid interactions (Goedert, 2001; Ischiropoulos, 2003). In PD,  $\alpha$ -SYN aggregates into characteristic fibrillar  $\beta$ -pleated structures in Lewy bodies. Besides LBs,  $\alpha$ -SYN also forms intermediate-state oligomers that when released from the neurons activate microglia leading to an increased production of ROS and proinflammatory cytokines (Glass *et al.*, 2010). Activated microglia further amplifies this inflammatory response in a positive feedback loop. In  $\alpha$ -SYN, the ability of the central hydrophobic NAC (non A $\beta$ -component of amyloid plaques in Alzheimer's disease) domain to aggregate is normally counteracted by the highly charged hydrophilic C-terminal domain. Interestingly, all 5 proline residues (Pro<sup>108</sup>, Pro<sup>117</sup>, Pro<sup>120</sup>, Pro<sup>128</sup>, Pro<sup>138</sup>) of  $\alpha$ -SYN are located at the C-terminal of the protein. Changes to the C-terminal domain through deletion, point mutations or via posttranslational modifications such as phosphorylation (Kragh *et al.*, 2009) expose the NAC domain leading to hydrophobic interaction driven aggregation. For example, the E3-ubiquitin ligase, parkin can protect against  $\alpha$ -SYN-induced toxicity by altering the phosphorylation levels of  $\alpha$ -SYN (Figure 3). By simultaneously reducing PLK2 levels and activating PP2A, parkin decreases Ser<sup>87</sup> and Ser<sup>129</sup> phosphorylation thereby decreasing aggregation of phosphorylated  $\alpha$ -SYN in LBs (Khandelwal *et al.*, 2010). The role of FKBP's in synucleinopathy has been probed both *in vitro* (Gerard *et al.*, 2006) and *in vivo* (Gerard *et al.*, 2010). *In vitro*, fluorescence correlation spectroscopy (FCS) measurements showed that addition of FKBP12 accelerates  $\alpha$ -SYN aggregation into fibrillar structures that mimic aggregates formed in LBs. FKBP12 significantly alters the rate for both the nucleation and fibril formation stages (Gerard *et al.*, 2008). Since FKBP's catalyze the cis-trans isomerization of X-Pro peptide bond, the importance of C-terminal proline residues of  $\alpha$ -SYN was also investigated. Changing one or more proline residues to alanine increased the aggregation kinetics of mutant  $\alpha$ -SYN (Meuvis *et al.*, 2010). Additionally, FKBP12 did not interact with a proline deficient  $\alpha$ -SYN mutant and this mutant was also found to be more structured.

Using a neuronal model of synucleinopathy in which  $\alpha$ -SYN aggregation and cell death was induced by oxidative stress, Gerard and coworkers have shown that both FK506 and knockdown of FKBP12/FKBP52 can counter the effects of oxidative stress. Likewise, it was shown that overexpression of FKBP12 and -52 enhances  $\alpha$ -SYN aggregation. FKBP52 was less potent than FKBP12 in inducing fibrillar aggregation. *In vivo*, FKBP12 was shown to colocalize with  $\alpha$ -SYN in the brain of A30P- $\alpha$ -SYN transgenic mice model. Furthermore, FK506 administration reduced both the  $\alpha$ -SYN aggregation in cells as well as increased survival of  $\alpha$ -SYN overexpressing neurons in the striatum. Collectively, these studies validate FKBP as a novel target for PD.

Besides  $\alpha$ -SYN, other interacting partners of FKBP12 identified from 6-OHDA treated rat model of PD include 1-cys peroxyredoxin, HSP70, 14-3-3 zeta, M2-type pyruvate kinase (PKM2), annexin A2 and  $\alpha$ -enolase (ENO1) (Nilsson *et al.*, 2007). It has been known that levels of PKM2, 14-3-3 zeta and ENO1 are altered during neurodegenerative diseases like PD and Alzheimer's (Poon *et al.*, 2006).

Given that FKBP are chaperone proteins having important roles in protein folding, it is counterintuitive to note that the interaction between FKBP(s) and  $\alpha$ -SYN results in  $\alpha$ -SYN aggregation. It is likely that  $\alpha$ -SYN inclusions may not result simply from precipitated misfolded protein but rather from an active process meant to sequester soluble misfolded proteins from the cellular milieu (Kopito, 2000). Accordingly, inclusion body formation might serve as a cellular defense mechanism aimed at removing toxic insoluble proteins.

### 3.2 FKBP52 interacts with RET51 in a phosphorylation-dependent manner

RET51, a tyrosine kinase (TK) receptor, has important roles in the development and maintenance of the nervous system. Recently, FKBP52 was found to be novel interacting partner for RET51 in a split ubiquitin two-hybrid screen (Fusco *et al.*, 2010). Neurotrophins like NGF and glial-cell line derived neurotrophic factor (GDNF) promote the phosphorylation driven formation of RET51/FKBP52 complex; phosphorylation occurs on Tyr<sup>905</sup> within the TK domain of RET51 and is a pre-requisite for complex formation. Association of RET51 with FKBP52 does not depend on HSP90 or other chaperones. The involvement of RET51 in PD comes from the genetic analysis of an early onset-PD patient heterozygous for mutations on both *RET51* and *FKBP52* genes (Fusco *et al.*, 2010). Mutations on both proteins disrupt formation of RET51/FKBP52 complex and its downstream signaling pathway. The detail of this signaling mechanism remains to be elucidated.

### 3.3 FKBP38 promotes trafficking of membrane channels

FKBP38 is distributed to both the mitochondria (Shirane & Nakayama, 2003) and endoplasmic reticulum (Wang *et al.*, 2005). Only the C-terminal tail is membrane anchored while the bulk of the protein is exposed to the cytosol. The unique topology of FKBP38 allows it to juxtapose between cytosolic and ER chaperone proteins. FKBP38 functions as a co-chaperone to HSC70/HSP90 complex to mediate proper folding and trafficking of membrane proteins like the multidomain cAMP-regulated chloride channel, CFTR (Wang *et al.*, 2006) and the voltage-dependent K<sup>+</sup> channel, HERG (Walker *et al.*, 2007). The immature form of HERG localizes to the endoplasmic reticulum whereas the fully glycosylated mature protein is present in the Golgi or the cell surface. While siRNA mediated knockdown of FKBP38 reduced HERG maturation, overexpression of FKBP38 was able to rescue the HERG F805C trafficking mutant. FKBP38 is involved in the late stages of HERG folding and ER



export, as majority of FKBP38 has been found to associate with immature HERG. It is likely that natively folded HERG is released from its final chaperone complex while still attached with FKBP38. The bound FKBP38 could further mediate the attachment of HERG with the motor protein kinesin for transport to the plasma membrane. HERG mutations have been associated with the Long QT syndrome, a cardiac disorder characterized by long QT intervals. PD patients have an increased susceptibility to cardiac arrest as is evident from a prolongation of the QT interval (Hurst *et al.*, 2003). Therefore, it is likely that FKBP38-mediated HERG trafficking plays an important role in PD pathogenesis.

### 3.4 FKBP mediated regulation of Tau function and its effect on microtubule dynamics

Tau, a member of the microtubule-associated protein family (MAP), binds and stabilizes microtubules (MTs) and is therefore intrinsically linked with MT dynamics. Six isoforms of tau are present in humans, the longest one having four MT-binding repeat motifs. Normal biological functions of tau are dependent on its phosphorylation state. Involvement of tau in PD pathogenesis comes from the observations that (1) it accumulates in LBs together with  $\alpha$ -SYN (Ishizawa *et al.*, 2003); (2) analysis of synapse-enriched fractions from PD brains show an increased phosphorylation for both tau and  $\alpha$ -SYN (Muntane *et al.*, 2008) and (3) tau and synuclein synergistically promote *in vitro* fibrillization of each other (Giasson *et al.*, 2003).  $\alpha$ -SYN mediates tau phosphorylation at Ser<sup>262/356</sup> by activating protein kinase A (PKA) (Jensen *et al.*, 1999) while in MPTP models of PD,  $\alpha$ -SYN recruits GSK $\beta$ 3 kinase to phosphorylate tau at Ser<sup>396/404</sup> (Duka *et al.*, 2009). Hyperphosphorylation of tau results in MT destabilization by interfering with its binding.

Recent studies have shown that both FKBP51 (Jinwal *et al.*, 2010) and FKBP52 (Chambraud *et al.*, 2007; Chambraud *et al.*, 2010) can interact with tau. FKBP52 preferentially binds to hyperphosphorylated tau and colocalizes with tau at the growth cones in both cortical neurons and PC12 cells. Interestingly, FKBP52 could inhibit tau-mediated tubulin polymerization *in vitro*. This is consistent with the observation that overexpression of FKBP52 impairs neurite outgrowth in cultured neurons (Chambraud *et al.*, 2010). Interaction of FKBP52 with tau was mapped to the C-terminal TPR domain of FKBP52 (Chambraud *et al.*, 2007). Currently it is not known if the neuroprotection mediated by “anti-tau” activity of FKBP52 is linked to proteasomal degradation of hyperphosphorylated tau via enhanced trafficking or by increased aggregation of toxic tau into fibrillary tangles.

FKBP51, a member of the HSP90 chaperone complex, directly associates with tau and its overexpression significantly increases the levels of phospho- and total tau in cells. Contrary to FKBP52, FKBP51 enhances the tau-mediated MT polymerization and the PPIase activity of FKBP51 is crucial for its function in tau processing. The data by Dickey and coworkers suggest a model whereby binding of FKBP51-HSP90 complex to phosphorylated tau triggers its dephosphorylation and recycling to the microtubules thereby facilitating MT polymerization and stabilization (Jinwal *et al.*, 2010). HSP90-FKBP51 binding also shields tau from CHIP (carboxy terminus of the HSC70-interacting protein) mediated ubiquitination and subsequent proteasomal degradation (Figure 3).

### 3.5 FKBP38 anchors Bcl-2 to the mitochondria and regulates apoptosis

The C-terminal tail of the noncanonical FKBP, FKBP38, localizes the protein to the ER and mitochondrial membrane where it interacts with the anti-apoptotic proteins, Bcl-2 and Bcl-x<sub>L</sub> and regulates their functions. FKBP38 is critical for the mitochondrial localization of Bcl-2 and Bcl-x<sub>L</sub>, expression of mitochondrial targeting defective FKBP38 mutants and RNAi mediated

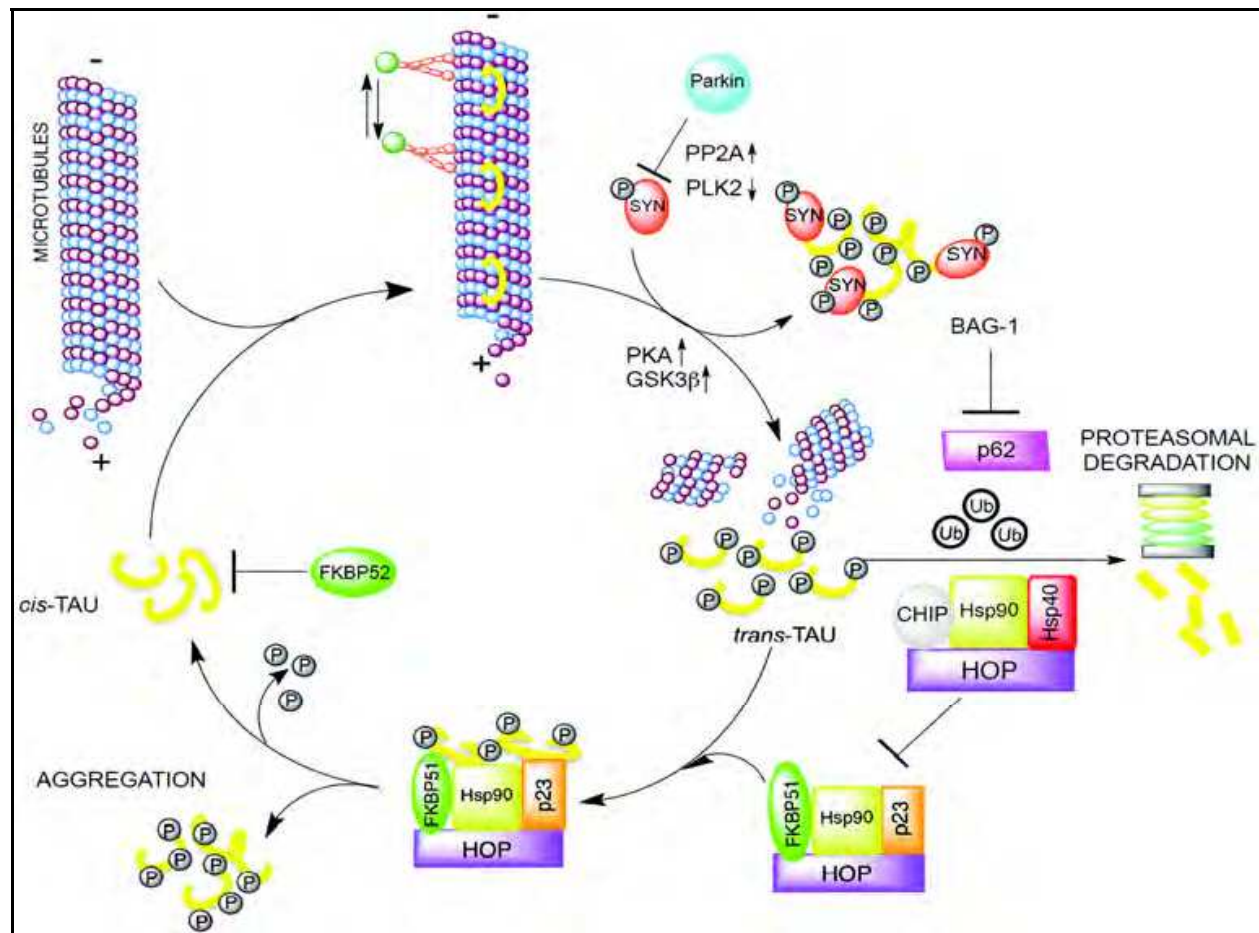


Fig. 3. FKBP regulates microtubule stability by interacting with the microtubule-associated protein, tau. FKBP51 and FKBP52 have opposing effects on microtubule (MT) stability. FKBP52 exhibits "anti-tau" activity; by sequestering tau, it prevents its association with MT thereby destabilizing MTs. Together with the HSP90 complex, FKBP51 binds phosphorylated tau in its *trans*-conformation, isomerizes it to the *cis*-form and recycles it back to the MTs. Alternatively FKBP51 can accelerate aggregation of phospho-tau species. Phospho-tau can also be degraded by the cellular proteasomal system following CHIP-mediated polyubiquitination. Binding of FKBP51 and CHIP to phosphorylated tau is mutually exclusive. By recruiting PKA/GSK3 $\beta$ ,  $\alpha$ -SYN promotes tau-phosphorylation within the MT-binding domain and its subsequent removal from MTs. Activity of  $\alpha$ -SYN is in turn regulated by the E3 ubiquitin ligase, Parkin. By inhibiting PLK2 kinase and enhancing PP2A phosphatase activity, Parkin decreases  $\alpha$ -SYN phosphorylation and interferes with its activity.

knockdown of FKBP38 causes the cellular redistribution of these proteins. Furthermore FKBP38-mediated mitochondrial targeting is responsible for the anti-apoptotic activity of FKBP38 (Shirane & Nakayama, 2003; Kang *et al.*, 2005). Nishimura and colleagues have shown FKBP38 is a *bona fide* substrate for the aspartyl protease, presenilin 1 and 2 (PS1/2) (Wang *et al.*, 2005). Under physiological conditions PS1/2 forms macromolecular heteromeric complexes with FKBP38 and Bcl-2 and sequesters them in the ER/Golgi via a  $\gamma$ -secretase independent mechanism. Thus by inhibiting the FKBP38 mediated mitochondrial targeting of Bcl-2, PS1/2 antagonizes the anti-apoptotic effect of FKBP38.

In neuroblastoma cells, FKBP38 exhibits  $\text{Ca}^{2+}/\text{CaM}$  stimulated PPIase activity and the FKBP38/ $\text{Ca}^{2+}/\text{CaM}$  ternary complex binds Bcl-2. This binding is interrupted by GPI-1046, indicating that the active site of FKBP38 is involved in Bcl-2 interaction. HSP90 in the HSP90/Bcl-2/ $\text{Ca}^{2+}/\text{CaM}$  ternary complex has also been shown to inhibit the Bcl-2-FKBP38 interaction by blocking access to the enzyme active site (Edlich *et al.*, 2007). GPI-1046 and RNAi-mediated depletion of FKBP38 activity was able to promote neuronal cell survival thus indicating that, in neuronal cells, FKBP38 has proapoptotic function. This observation contradicts earlier reports wherein it was shown that FKBP38 has anti-apoptotic effect (Shirane & Nakayama, 2003; Kang *et al.*, 2005). One plausible explanation for this discrepancy could be explained on the basis of the different cell lines, neuronal versus non-neuronal, used in these studies. The potent neuroprotective and neuroregenerative effects of low molecular weight FKBP38 inhibitors in neuroblastoma cells concur well with the proapoptotic role of FKBP38. Furthermore, the ability of the FKBP38 inhibitor - *N*-(*N*',*N*'-dimethylcarboxamidomethyl)-cycloheximide to elicit neural stem proliferation and neuronal differentiation in a rat model of transient cerebral ischemia underscores the importance of FKBP38 in neuronal apoptosis (Edlich *et al.*, 2006).

#### 4. Neuroimmunophilin ligands as therapeutics for PD

Currently available drugs aimed at PD treatment do not have the capacity to inhibit PD progression but can only alleviate symptoms and/or delay neuronal atrophy by altering neurotransmitter metabolism. Neuroimmunophilin ligands are non-immunosuppressive and mediate the beneficial effects by multiple mechanisms that include inhibition of apoptosis, increased neurotrophic signaling and/or reducing oxidative stress by interfering with mitochondrial dysfunction (Tanaka & Ogawa, 2004). Several groups have reported that NILs like FK506, GPI-1046 and V-10367 (Figure 4A) promote striatal dopaminergic innervations in MPTP- or 6-OHDA models of PD (Kitamura *et al.*, 1994; Steiner *et al.*, 1997; Costantini *et al.*, 1998; Guo *et al.*, 2001). Studies have also shown that GPI-1046 protects against the *p*-chloroamphetamine-induced destruction of central serotonergic neurons and

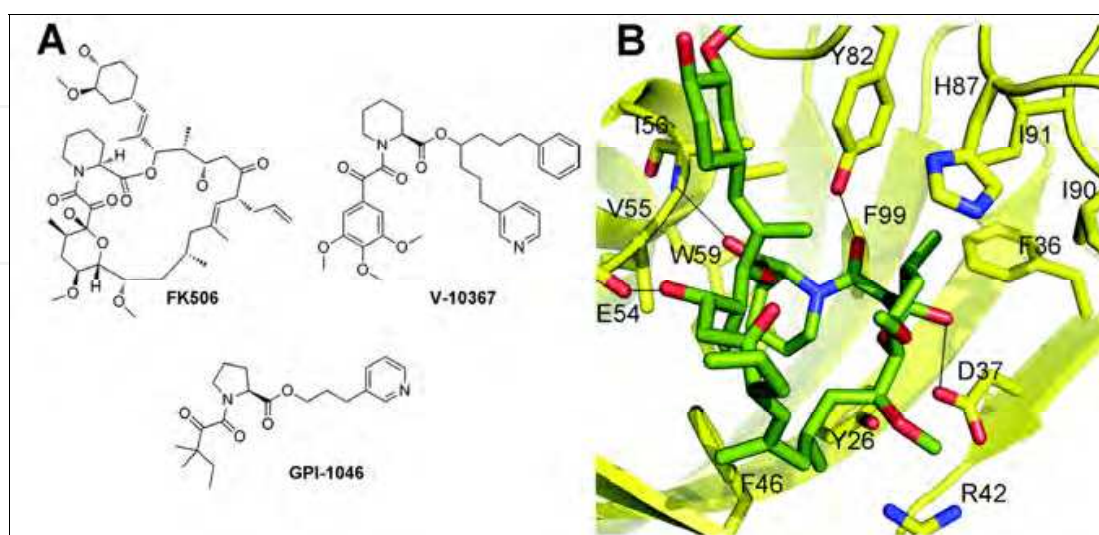


Fig. 4. (A) Structure of the neuroimmunophilin ligand FK506 and its non-immunosuppressive derivatives, GPI-1046 and V-10367. (B) Binding of FK506 (green) into the active site pocket of FKBP12 “(represented by cartoon model).



senescence-related atrophy of medial septal cholinergic neurons (Sauer *et al.*, 1999). Furthermore, rotational behavior and loss of corticostriatal long-term potentiation (LTP) in 6-OHDA treated rats was alleviated by GPI-1046. However, as similar efficacy was obtained with an analog that does not bind FKBP12 (V-13670), the importance of FKBP12 in mediating neurotrophic effects is debatable. Besides FK506 derivatives, CsA has been shown to protect against dopaminergic degeneration, promote regeneration of DA neurons and even suppress microglial cytotoxicity, as activated microglia has been known to generate free radicals (Banati *et al.*, 1993).

The binding mode of FK506 and its non-immunosuppressive counterpart, GPI-1046 has been elucidated (Van Duyne *et al.*, 1993; Sich *et al.*, 2000). Minimal binding motif comprises of the central pipercolic acid ring, the  $\alpha$ -dicarbonyl amide linkage and pyranose ring. In the FK506-FKBP12 crystal structure (Van Duyne *et al.*, 1993), the pipercoline ring sits in the cavity defined by Trp<sup>59</sup> and Tyr<sup>26</sup>, Phe<sup>46</sup>, Val<sup>55</sup>, Ile<sup>56</sup>, Phe<sup>99</sup> side chains, whereas the  $\alpha$ -dicarbonyl amide is hydrogen-bonded to -COOH and -OH group of Asp<sup>37</sup> and Tyr<sup>82</sup>, respectively (**Figure 4B**). The hydrophobic pocket formed by Phe<sup>36</sup>, Asp<sup>37</sup>, Tyr<sup>82</sup>, His<sup>87</sup>, Ile<sup>90</sup> and Ile<sup>91</sup> buries the pyranose ring while the cyclohexyl ester chain is engaged in hydrophobic interactions within a shallow surface groove. SAR studies have shown that the  $\alpha$ -dicarbonyl amide functionality is indispensable for enzyme inhibition as replacement of either one or both carbonyl groups reduces potency. Similarly, pipercolic ring opening drastically increases the inhibition constant of the derivatives. GPI-1046 binds in a manner analogous to that of FK506 with the amide bond in *trans* configuration; the only exception being the replacement of pipercolyl moiety of FK506 by the prolyl ring of GPI-1046. Even though GPI-1046 has fewer favorable protein-ligand interactions, its effect on protein dynamics is essentially same as FK506, that is, stabilize the conformation of solvent exposed residues that are important in protein-protein and protein-ligand interactions.

The therapeutic utility of NILs has been questioned by work from other groups (Harper *et al.*, 1999; Parker *et al.*, 2000; Bocquet *et al.*, 2001) as many of the initial observations could not be replicated in identical systems. For instance, Harper and colleagues observed that GPI-1046 causes only a marginal increase in neurite outgrowth of chick dorsal root ganglia in culture under conditions where a very robust effect of nerve growth factor was seen. GPI-1046 did not restore tyrosine hydroxylase-positive fibers after 6-OHDA administration neither did it protect cultured dopaminergic neurons against MPTP induced toxicity. One possibility for the observed differences could be the levels of dopaminergic dysfunction. GPI-1046 provided neuroprotection in cases when the degradation was mild to moderate; it has no effect in severe cases when DA neuron levels deplete to 20% of that in normal controls. Other parameters like variability in culture conditions, differences in days *in vitro* prior to experimentation, can potentially account for the contrasting observations (Pong and Zaleska, 2003). Furthermore, neuroprotective effects of GPI-1046 could not be replicated in monkey model of MPTP toxicity (Emborg *et al.*, 2001) suggesting species-specific differences with respect to GPI-1046 activity.

## 5. Conclusion

FKBPs have emerged as novel cellular target for treatment of Parkinson's disease and other neurological disorders. The extraordinary unmet need for therapeutic intervention in PD continues to drive the search for potential drug candidates. Non-immunosuppressive NILs with their small size, target specificity, bioavailability and stability provide excellent scaffolds for the development of new drugs. Although our present knowledge of the mode of action of NILs is still fragmentary, there is increasing evidence that the neurotrophic,



neuroprotective and restorative potential of these compounds is mediated by signaling pathways that can have antagonistic or additive effect. For example, multiple pathways may crosstalk via common integral components such as c-Jun (Gold *et al.*, 1999; Winter *et al.*, 2000). So far, the nervous system has been found to be enriched in only five FKBP - FKBP-12, -38, -51, -52 and -65. Much work needs to be done so as to identify unique neuroimmunophilins and their interacting partners, assess their cellular function as well as their response to injury. Furthermore, issues such as reproducibility of pre-clinical data, structure-activity relationship studies, drug evaluation in appropriate animal models, and implementation of proper clinical designs and endpoints needs immediate attention as such information will aid in the development of novel NILs with improved efficacies, target selectivity and potency. FKBP and NILs seem to be a promising area for therapeutic intervention of PD and other neurodegenerative disorders.

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## **Mechanisms in Parkinson's Disease - Models and Treatments**

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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