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● **PERSPECTIVES**

Sigma-1 receptor: a potential new target for Parkinson's disease?

Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by typical motor signs and symptoms that are due to dopamine (DA) depletion in the basal ganglia. The treatment of PD is symptomatic, and aims at replacing the lost DA input using either L-DOPA or DA agonists. The causes of PD are unknown in approximately 90% of the cases, whereas about 10% of the cases are familial and imputable to mutations in a handful of genes (the gene mutations with the strongest association with PD are shown in **Table 1**; for a detailed review see (Poulopoulos et al., 2012)). The genetic forms of PD have spurred an intense research on molecular pathways of neurodegeneration that converge on proteostatic deficits, mitochondrial dysfunction and oxidative stress.

Pharmacological treatments able to interfere with the progressive neurodegenerative process of PD are the most critical unmet need. Unfortunately, all disease-modifying treatments tested so far have failed, either because they did not meet their primary endpoints or because a positive outcome could not be attributed to a neuroprotective effect (Olanow et al., 2008). It is therefore essential to find new targets for disease-modifying interventions. The Sigma-1 receptor (Sig-1R) is a chaperone protein that has been attracting increasing attention for its multiple functions and its implication in several diseases. It is located at the mitochondrion-associated endoplasmic reticulum membrane, where it regulates calcium signaling between the two organelles (Hayashi and Su, 2007). Sig-1R is ubiquitously expressed and can mobilize endogenous defense mechanisms to promote cell survival. Under conditions of cellular stress (or upon pharmacological stimulation with so-called Sig-1R agonists), this protein can redistribute widely within the cell in order to support various functions, such as the regulation of lipid transport, modulation of synaptic signaling, stimulation of axonal outgrowth and dendritic spine arborization (Maurice and Su, 2009). During the last years, several studies reported neuroprotective properties of Sig-1R agonists in animal models of Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and stroke. These effects have been attributed to an attenuation of excitotoxicity and apoptosis by multiple mechanisms, such as up-regulation of protective genes, reduced microglial activation, reduced generation of reactive oxygen species (ROS) and nitric oxide (NO) (see **Figure 1**).

Since mitochondrial dysfunction and nitrosative stress are critical mediators of nigrostriatal dopamine damage, and neuroinflammation is known to contribute to neurodegeneration in parkinsonian disorders (Tansey and Goldberg, 2010), we directed our attention towards Sig-1R as a potential new target for disease-modifying therapy in PD. Using mice with intrastriatal 6-hydroxydopamine (6-OHDA) lesions as a model of PD, we reported that chronic treatment with the Sig-1R agonist PRE-084 produces gradual improvement of parkinsonian-like motor deficits. This behavioral recovery was paralleled by a pattern of cellular and biochemical responses suggesting that stimulation of Sig-1R by PRE-084 had activated endogenous defense and plasticity mechanisms. Indeed, animals treated with PRE-084 showed reduced neuroinflammation, increased density of dopaminergic fibers in the most denervated striatal regions and increased striatal and nigral levels of neurotrophic factors (*i.e.*, brain-derived neurotrophic factor, BDNF, and glial-derived neurotrophic factor, GDNF) and monoamines (dopamine, DA, and serotonin, 5-HT) (Francardo et al., 2014). These effects were obtained when the treatment was started in the first acute phase of the neurodegenerative process, but not when started with a delay of one week. These data suggest that a pharmacological stimulation of Sig-1R could be useful to slow down the progression of PD only when started in the early stages of the disease.

Our preclinical results revealed several interesting features of this treatment. First of all, the data obtained from our study show that the stimulation of Sig-1R does not have only a pro-dopaminergic effect, but potentiate also the serotonergic system, likely *via* the upregulation of BDNF levels (Mattson et al., 2004). Since PD is not only a motor disorder exclusively restricted to DA neurons, but involves all monoaminergic systems in the brain (Halliday et al., 1990), the ability of Sig-1R to act on different monoaminergic pathways suggests a potential effect of its ligands on both motor and non-motor PD symptoms.

We also showed that Sig-1R is expressed in both neurons and astrocytes. Several studies pointed the role of astrocytes as potential modulators of dopaminergic neurodegeneration in PD (Rappold and Tieu, 2010). Indeed, astrocytes have been described to play a dual role. They can confer neuroprotection by releasing neurotrophic factors and metabolic substrates for the survival of the neurons. On the other hand, astrocytes may also release pro-inflammatory cytokines and chemokines detrimental to the neurons. This has been seen to occur in animal models of neurodegenerative diseases (*i.e.*, ALS). A treatment able to have plasticity-boosting effects acting not only directly on neurons but also on their supporting cells (*i.e.*, the glial component) would be then a therapy with an additional value.

These first encouraging preclinical results suggesting a disease-modifying effect of Sig-1R agonists call for further investigations on the neuroprotective potential of Sig-1R ligands in other animal models of PD. Indeed, among all the rodent models of PD developed in the last decades, there's no one able to replicate all the hallmarks of the human pathology. In the intrastriatal 6-OHDA mouse model, which is the PD model used in our study assessing the neuroprotective/neurorestorative effects of PRE-084, the heterogeneous pattern and biphasic time-course of neurodegeneration closely reproduce the evolution of nigrostriatal dopamine degeneration occurring in the human PD. In addition to the degeneration of the nigrostriatal DA pathway, 6-OHDA injections also cause a marked inflammatory response, inducing the production of reactive oxygen species, quinones and microglial activation in the brain. However, the suitability of the 6-OHDA model to test potential neuroprotective/neurorestorative treatments is often questioned, particularly after the evidence that GDNF effects on the nigrostriatal DA system seem to be abrogated by alpha-synuclein overexpression in DA neurons, feature which is not present in animals sustaining 6-OHDA lesions. When testing a potential disease-modifying treatment is therefore crucial to combine more animal models, in order to observe the effects of a tested compound on a broader spectrum of features of the idiopathic disease. Robust preclinical data are needed in order to push forward the preclinical research towards clinical trials. Future important steps in the preclinical research on Sigma-1 agonists would be for example to test these compounds in transgenic alpha-synuclein overexpressing mice. Indeed, thanks to the capacity of Sig-1R to counteract several aspects of cellular stress caused by protein misfolding, such as the activation of ER-stress apoptotic pathways, ROS generation and dysregulation of calcium, Sig-1R agonists could potentially alleviate mechanisms of alpha-synuclein toxicity (reviewed in (Wales et al., 2013). Moreover, pharmacological treatments promoting endogenous plasticity mechanisms have been shown to improve both behavioral and pathological features in transgenic alpha-synuclein overexpressing mice (Ubhi et al., 2012).

Importantly, several compounds already approved for clinical use have proven to exert agonistic activity at the Sig-1R (Ishikawa

Table 1 Parkinson's disease-causing genes (mendelian inheritance)

Autosomal dominant

Gene	Protein	Chromosomal locus
SNCA	Alpha-synuclein	PARK1
LRRK2	Leucine-rich repeat kinase 2	PARK8

Autosomal recessive

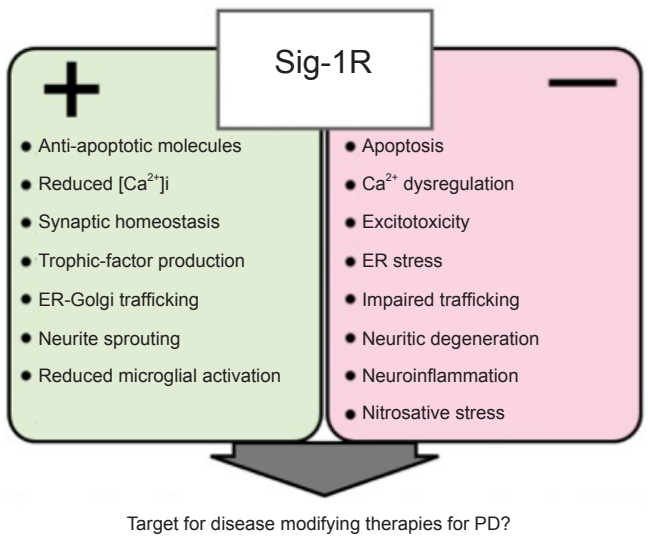| Gene	Protein	Chromosomal locus
Parkin	Parkin	PARK2
PINK1	PTEN-induced putative kinase 1	PARK6
DJ-1	DJ-1	PARK7

Figure 1 Mechanisms of action of Sig-1R.
Mechanisms of cellular defense (+) or cell damage (–) that are regulated by Sig-1R. The cartoon summarizes a vast literature from various *in vitro* and *in vivo* models of disease. Sig-1R: Sigma-1 receptor.

and Hashimoto, 2010). These include, for example, the Sig-1R agonist fluvoxamine, which is already used in the treatment of psychotic major depression, obsessive-compulsive disorders, and anxiety disorders. However, because finding the correct dose window will be essential to clinical success, when using compounds with additional targets and mechanisms of action, it will be important to determine the contribution of the different mechanisms on the final effect. Our first data obtained with PRE-084 provide a useful tool to screen other potential clinical candidates with agonistic activity at the Sig-1R. Indeed, comparing the effects given by several doses of different Sig-1R agonists with the ones shown by the effective dose of PRE-084 will help to find the therapeutic window of the tested compounds.

In the last years several studies also reported anti-amnesic and neuroprotective effects of Sig-1R ligands in animal models of AD (Maurice and Su, 2009). Clinical trials in patients with AD are now ongoing (further informations can be found at www.anavex.com), and the aim for the future is to accelerate the steps from preclinical to clinical trials also on PD patients.

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Poster and oral presentations of this study:

1. Francardo V. (Nov 11-12, 2014) "Pre-clinical trials: new treatment targeting versatile protein in Parkinson's disease" Clinical Trials in CNS (London, United Kingdom).

2. Francardo V, Bez F, Wieloch T, Nissbrandt H, Ruscher K and Cenci MA (June 8-12,2014). Neurorestorative effects of a selective sigma-1 receptor agonist in experimental parkinsonism. Congress of Parkinson's disease and Movement Disorders (MDS), Stockholm (Sweden).

3. Francardo V, Bez F, Wieloch T, Nissbrandt H, Ruscher K and Cenci MA (Nov9-13,2013). "Pharmacological stimulation of sigma-1 receptor has neurorestorative effects in experimental parkinsonism" Society for Neuroscience (SFN), San Diego (California).

4. Francardo V, Bez F, Wieloch T, Nissbrandt H, Ruscher K and Cenci MA (Oct1-4,2013). "Nigrostriatal expression and modulation of sigma-1 receptor in experimental parkinsonism" World Parkinson Congress (WPC), Montreal (Canada).

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