

## Online Meeting on Parkinson's Disease (OMPD-2020)

### Virtual Meeting Abstracts

#### Challenge to Target Moonlighting Proteins Hallmarking Parkinsonism

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##### Abstract

With the aging of society, neurological disorders such as Parkinson's diseases (PD) and Multiple System Atrophy (MSA) cause serious socio-economic problem for the society. Currently no appropriate therapy for the healing of the synucleinopathy. Alpha-Synuclein (SYN), a hallmark and these diseases and Tubulin Polymerization Promoting Protein (TPPP/p25), discovered and denoted by our research group, are expressed in neurons and oligodendrocytes in normal brain, respectively; however, they are co-enriched and co-localized in both cell types leading to development of in the case of PD and MSA. These neomorphic moonlighting proteins displaying both physiological and pathological functions with chameleon characteristics, thus neither of them is ideal target for pharmaceutical intervention. Due to the recognition that the soluble homo- and hetero-oligomers of SYN and TPPP/p25 are fatal species in the development of parkinsonism, we evolved a new innovative strategy for the identification of specific drug target. The interfaces of the pathological SYN-TPPP/p25 complex were identified and validated, the targeting of which prevents/destroys of pathological complex without affecting physiological functions of the partner proteins. The innovative strategy established could lead to the development of specific peptidomimetic foldamer-like drugs for the therapy of synucleinopathies.

#### Pre-Dopa DBS: Calling for a Change in Therapeutic Paradigm

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##### Abstract

Levo-dopa is the gold-standard treatment for Parkinson's disease (PD), however, long exposure carries motor and non-motor complications [1]. Deep brain stimulation is generally reserved for patients who become refractory to L-dopa treatment and present with L-dopa induced complications and performed later in the disease. We present five patients, between 50 and 67 years who underwent DBS prior to be treated with L-Dopa therapy. The decision to perform early DBS was not driven by L-Dopa induced motor complications, but by relevant QoL impairment and reluctance to initiate L-Dopa treatment. The target chosen was the STN and all the procedures was uneventful. Follow-up range was between 3 and 10 years. All the patients showed improvement in UPDRS score, in non-motor symptoms and in QoL score. Moreover, all the patients reduced the intake of dopamine agonists and five patients are currently free from L-Dopa medications. No adverse events have been reported. Early DBS is still a matter of debate: surgical procedure is considered too risky to be anticipated in the course of Parkinson's Disease, however, if performed in specialized centers, it is considered a safe procedure [2]. We guess, with these cases, if a change of treatment algorithm could be made, anticipating DBS and therefore delaying L-Dopa induced motor complications. Early application of DBS instead of L-Dopa treatment could have a pathophysiological basis and a neuroprotection role in modulating natural course of Parkinson's Disease.

## Neuroprotective Effect of Bergamot Juice in an *In-vitro* Model of Parkinson's Disease

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### Abstract

Much evidence suggests that both oxidative stress and apoptosis play a key role in the pathogenesis of Parkinson's disease (PD). The present study aims to evaluate the protective effect of bergamot juice (BJ) against 6-hydroxydopamine (6-OHDA)- or H<sub>2</sub>O<sub>2</sub>-induced cell death. Treatment of differentiated SH-SY5Y human neuroblastoma cells with 6-OHDA or H<sub>2</sub>O<sub>2</sub> resulted in cell death that was significantly reduced by the pre-treatment with BJ. The protective effects of BJ seem to correlate with the reduction of intracellular reactive oxygen species and nitric oxide generation caused by 6-OHDA or H<sub>2</sub>O<sub>2</sub>. BJ also attenuated mitochondrial dysfunction, caspase-3 activation, imbalance of pro- and anti-apoptotic proteins, MAPKs activation and reduced NF- $\kappa$ B nuclear translocation evoked by neurotoxic agents. Additionally, BJ exhibited excellent antioxidant capability in cell-free assays. Collectively, our results suggest that BJ exerts neuroprotective effect through the interplay with specific cell targets and its antioxidant activity, making it worthy of consideration for the management of neurodegenerative diseases.

## Two Novel Small Molecules to Prevent Alpha-Synuclein Aggregation

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### Abstract

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide. The loss of dopaminergic neurons in the substantia nigra pars compacta induces a significant decrease in dopamine levels, provoking the characteristic motor symptoms of PD such as bradykinesia, rigidity or resting tremor, among others. Affected tissues present intracellular inclusions named Lewy's bodies and neurites, whose main component are amyloid aggregates of  $\alpha$ -synuclein ( $\alpha$ -Syn). PD belongs to a group of disorders called synucleinopathies, which include Multiple System Atrophy and Dementia with Lewy Bodies. These disorders share a common neuropathological feature, the presence of  $\alpha$ -Syn deposits, but differ in the cellular and anatomical compartment in which these inclusions accumulate.

$\alpha$ -Syn is an intrinsically disordered protein involved in presynaptic vesicle trafficking, which can aggregate and form amyloid fibrils. *In vivo*,  $\alpha$ -Syn aggregates exert a toxic effect and can be transmitted from cell to cell in a prion-like manner, seeding native  $\alpha$ -synuclein aggregation in healthy neighboring neurons. Preventing the aggregation of  $\alpha$ -Syn has been envisioned as the best strategy for a future treatment of these disorders and numerous molecules have been described to block or revert this process. SynuClean-D and ZPD-2 are two small molecules identified by high-throughput screening methodologies that inhibit the aggregation of  $\alpha$ -Syn *in vitro* by targeting different aggregated species, with effects at substoichiometric levels, and the aggregation of H50Q and A30P variants. The administration of SynuClean-D and ZPD-2 to different *Caenorhabditis elegans* models of PD reduced the accumulation of  $\alpha$ -Syn aggregates, which was translated into phenotypic improvement and neuroprotection.

## Immunogenetics in Parkinson's Disease Antigen Presentation Capacity Regulates Microglial Activation, Alpha-Synuclein Pathology and Dopaminergic Neurodegeneration *In-vivo*

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### Abstract

Neuropathologically, PD is characterized by a progressive intraneuronal accumulation of  $\alpha$ -synuclein ( $\alpha$ syn) in Lewy bodies and Lewy neurites, degeneration of dopaminergic neurons in the substantia nigra pars compacta and neuroinflammation.

The neuroinflammation observed in PD brains includes activation of microglia, up-regulation of major histocompatibility

class II (MHCII) molecules, expression of inflammatory mediators and infiltration of T-lymphocytes. These conditions allow activated microglia expressing MHCII to present antigens to CD4-positive (CD4+) T-lymphocytes, and the presence of circulating  $\alpha$ syn-reactive CD4+ T-lymphocytes has recently been reported from PD patients. These findings suggest that antigen presentation has a functional role in PD. Interestingly, several genetic studies have reported risk variants for PD in the human leukocyte antigen (HLA) region encoding MHCII molecules. The importance of immunogenetics in PD is supported by the fact that several genes associated to idiopathic or familial PD have roles in inflammatory reactions.

To study the impact of immunogenetics on antigen presentation, microglial activation and  $\alpha$ syn-induced PD-like pathology, we have studied rats with allelic differences in the MHCII transactivator (*Mhc2ta*) gene. When exposing the nigrostriatal system to human  $\alpha$ syn, our results show that reduced *Mhc2ta* levels lead to lower MHCII expression, enhanced microglial activation, and a more pro-inflammatory immune profile. In addition, the lower *Mhc2ta* levels are also associated with increased propagation and aggregation of  $\alpha$ syn, increased dopaminergic neurodegeneration and enhanced motor impairment. These findings strongly support a key role for MHCII and antigen presentation capacity in PD etiology and motivates further studies on immunogenetic mechanisms in PD.

## Analysis and Treatment of Parkinson's Diseases *via* Quantum Chinese Medicine

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### Abstract

Parkinson's disease was investigated via two high tech invention from Quantum Chinese Medicine. The first high tech invention is: High resolution body surface infrared image device, which was used to take high resolution infrared pictures. The pictures were analyzed by the meridian theory of Chinese medicine. In the two cases we found that the frontal, left and right brain were inflamed but not the back brain. The digestive system of small intestine, stomach, and large intestine were inflamed. The immune system as indicated by the heart meridian acupoint HT 1 under the armpit was inflamed. The inflammation was reduced by daily drinking of one to three bottles of Xenwater R. One bottle of Xenwater (60 ml) contained more than 3 million solid water particles. Solid water particles contain only water molecules, which are aligned and emitted strong electric field. The solid water particles helped to repair blocked meridians, and enhanced qi and blood to flow freely. With sufficient nutrients from blood, cells and organs recovered. Symptoms of Parkinson's diseases were improved.

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