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Short Communication

Academic-Industry R/D Partnership Platform

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Exploring Prolyl-Lecuyl-glycinamide (PLG) and PLG Peptidomimetic: PAOPA [3(R)- [(2(S)pyrrolidinylcarbonyl)amino]-2-oxo-1 pyrrolidineacetamide] as a novel Dopamine receptor:D-2/D-4 Allosteric Modulator in Brain Disorders.

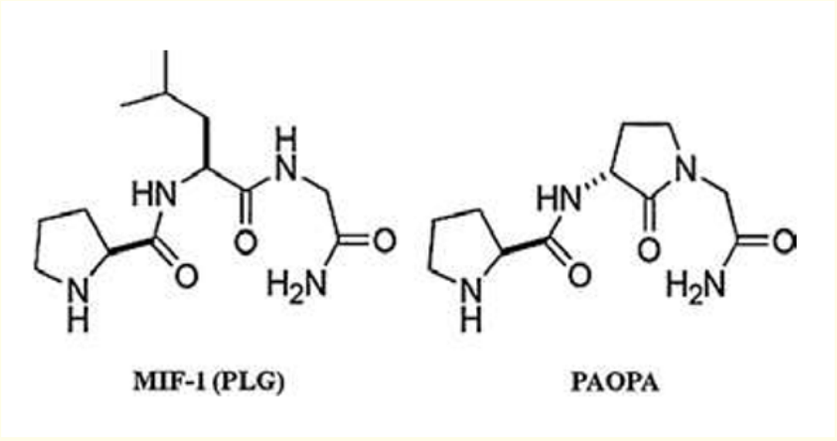

Figure : *Chemical Structure of a) MIF-1 characterized as PLG b) PLG Peptidomimetic: PAOPA 3(R)-[(2(S)pyrrolidinylcarbonyl)amino]-2- oxo-1-pyrrolidineacetamide.*

Key players in the academia/industry R/D collaborative network:

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CNS targets of PLG and PAOPA: Bridging the laboratory-clinical gap

In the l970s.Kastin and Schally, New Orleans LA in the l970s successfully isolated and identified the hypothalamic factor inhibiting the release of alpha-melanocyte releasing hormone (MIF-1) as the tripeptide. L-Prolyl-L-leucyl-glycinamide (PLG) (1,2) and shown that PLG was split from the posterior pituitary hormone, oxytocin. Barbeau et al Montreal Neurological Institute, Montreal PQ Canada initiated a series of clinical studies of PLG in patients diagnosed as Parkinson's Disease (PD). In a RCT design, PLG at the 200 mg iv bolus, was found to significantly potentiate the beneficial effects of L-DOPA in motor performance and cognitive functioning.

Subchronic intravenous infusion of PLG at daily dosage of 400 mg for 9 consecutive days, resulted in substantial improvements in dexterity, tremor, rigidity and overall motor performance. Ehrensing., *et al*. in an open label study of psychiatric institutionalized psychotic patients maintained on antipsychotic drugs found transient but significant decrease in the oral-facial-torso dyskinesia (tardive dyskinesia). Positive effect on mood was found with subcutaneous dosage of PLG at 10 mg for five day. In the total of 14 clinical studies (1972-94) PLG was highly tolerated with no serious adverse events.

The UMN-MUMC group led by R Johnson and R Mishra has taken a systematic Structure-activity relationship (SAR) approach based on the original finding of Mishra on PLG in modulating the sensitivity and affinity of dopamine receptors in the brain. More than 50 conformationally constrained analogues of PLG with Type II beta- turn have been synthesized in Johnson's laboratory: compound # 47 with gamma-lactam was found to be 1000 times more potent than PLG in the G- protein-mediated dopamine receptor assay. PLG analogues were also found to be metabolically stable in resisting degradation of plasma peptidases.

MUMC/UMN have conducted a series of crucial translational studies to characterize the molecular footprints of PLG peptiomimetic PAOPA. A study using the neuroblastoma SH-SY5Y cells stably transfected with respective cDNAs revealed that PLG and PAOPA increased the population and affinity of the high-affinity form of the D2L receptor and, furthermore, attenuated guanosine 5'- (beta, gamma-imido)-triphosphate-induced inhibition of high-affinity agonist binding sites for the DA D2L receptor. It is evident that PLG requires the D2L receptor/G protein complex to increase agonist binding. The results of our study suggest that PLG and PAOPA modulate DA D2S, D2L, and D4 receptors in an allosteric manner and that the coupling of D2 receptors to the G protein is essential for this modulation to occur. These considerations lead to the characterization of PLG and PAOPA as allosteric modulator of DA receptor via interacting with the G-protein system. PLG and PAOPA belong to the emerging class of allosteric modulator of Dopamine Receptor-G-protein-coupled receptors (DA-GPCR) targeting primarily G-protein receptor Kinase (GRK) regulating DA-GPCR The UMN group has further provided evidence for successful identifying the crucial stereochemical elements for shifting PLG peptidomimetics from positive to negative DA modulators. Steric bulk would be introduced by inserting the methyl groups on the β- methylene carbon of the thiazolidine ring into the topological space that the β-methylene carbon is believed to occupy in the negative allosteric modulators of the dopamine D2 receptor. On the other hand, un-methylated PLG peptidomimetics will function as positive modulators. These considerations lead us to conclude that PAOPA most likely behaves as a PAM and NAM (Positive allosteric modulator) and NAM (Negative allosteric modulator)-DA receptor depending on the brain specificity, the intra- and extra-cellular milieu and the functional sensitivity of the DA receptor complex. The unique dual role of PAOPA as PAM and NAM explains why PAOPA is active in both Parkinson disease (PD) tardive dyskinesia (TD) and schizophrenia.

Therapeutic indications: Despite the eclipse of PLG to the unwelcome status of an "orphan drug", MUMC-UMN have published an enriched series of translational studies of PLG and PAOPA generously funded by NIH, Canadian Institute of Health Research CIHR, Ontario Mental Health Foundation (OMHF), and more recently, Lawson health Research Institute London ON (seed grant program) [see Appendix

II]. Positive findings are reported on the beneficial effects of PAOPA in 1) models of schizophrenia [amphetamine sensitization model, phencyclidine induced psychosis, MK-801 NMDA antagonist-induced psychosis]; 2) models of Parkinson Disease [MPTP PD model, 6-hydroxydopamine lesion model, rotenone model of psychosis]; 3) models of tardive dyskinesia (TD): rodent VCM model, antipsychotic-induced DA supersensitivity. It is noteworthy that the phenotype of schizophrenia overlaps to a limited extent with autism spectrum disorder (ASD). In view of the finding of PLG on DA-driven GRK2/GRK5 inflammation signaling, we suggest that PLG and PAOPA may also be active in Alzheimer dementia and Parkinson dementia. Taken together, we propose the following therapeutic indications:

1. Parkinson disease (PD), PD-psychosis, PD-dementia (PDD, LBD: Lewy body dementia).
2. Schizophrenia targeting positive, negative and cognitive symptoms and tardive dyskinesia.
3. Mood spectrum disorder: Major depressive disorder and bipolar depression.
4. Autism spectrum disorder.
5. ADME and first in human study.

Crucial milestones for fast-tracking PAOPA to clinical forefront of CNS pipeline drugs

a) **PD/PDpsychosis/PDD**: The phenotype of autosomal dominant G2019S mutation accounting for 85% of PD cases associated with the LRRK2 gene exhibiting both LRRK_2 GTPase and Kinase domains resembles sporadic PD. We plan to complete the crucial study to validate the hypothesis that PAOPA targets LRRK2-GTPAase in the LRRK-2 mutant model of PD. We have carried out a LRRK-2 mutant young rat study. Our results showed that, expression patterns of Conserved Dopamine Neurotrophic Factor (CDNF) in the hippocampus differed significantly between LRRK-2 mutant and wild type. In the pre-motor stage, no marked motor abnormalities was observed in both Control and young LRRK-2 mutant rodents groups. Our study provides for the first time preliminary evidence of the Non-motor prodromal phenotype of PD. Since LRRK-2 kinase can influence LRRK- GTPase, resetting LRRK2-GTP ase can be a therapeutic target within the GRK/GPCR machinery. Mishra et al first demonstrated that PLG inhibits GTPase in the striatum. We will evaluate whether PAOPA treatment *in vivo* will prevent LRRK-2 kinase overexpression and will restore the changes in expression of CDNF and LRRK-2 GTPase and LRRK-2 kinase and Alpha-Synclein in the striatum, the hippocampus and prefrontal cortex. We expect PAOPA will exert similar actions. The endpoints are motor symptoms, DA (+) neuron count and apoptosis index. We will expand our study to examine whether in another cohort: the aged LRRK-2 mutant, motor and cognitive abnormalities emerge resembling LBD.

b) **Schizophrenia and ASD:** In Dr. Mishra's laboratory, we have developed siRNA model of ASD by silencing Synapsin II the at-risk gene of ASD which is also involved in schizophrenia. We plan to complete the preclinical treatment trial of dose-finding effect of PAOPA in the siRNA-Synapsin II hybrid model of ASD/schizophrenia. We define the therapeutic endpoint as the change from baseline-to-end of treatment of PAOPA over 12 weeks to examine whether PAOPA restore the DA-synapsin signaling and behavioral abnormalities, and to correlate the behavioral changes with brain-specific changes in Synapsin II signaling, vesicle derived exosomes and the dopamine-mediated inflammasome (NLP3). We will expand previous studies of oxytocin in ASD by evaluating whether PAOPA and PLG induce changes in oxytocin and PLG levels in the plasma and in the brain. Both intranasal and oral formulation of PAOPA will be used in the siRNA-Synapsin II Knockout rodent model. This will address the Go-vs No Go algorithm for PAOPA as potential drug lead in ASD at a competitive edge with ASD pipeline drugs.

c) **Alzheimer Dementia**: i) Effect of PAOPA on p25-TG AD model. To examine the neuroprotective effect of PAOPA in attenuating hyper-phosphorylated Tau in the p25 neuroinflammation rodent model. ii) *In vitro* neuroinflammation AD model to test

whether PAOPA treatment can block the Lipopolysaccharide (LPS)-induced inflammatory response in glial and neuronal cell lines via resetting GPCR-DA/ GRK and Interleukins: Il-2, Il-6 and TNF. We want to examine the dose-response relationship of PAOPA in protecting against the inflammatory responses through the GPCR-DA/GRK-2 and GRK-5*The results of our proposed Milestone I/II will move our drug discovery project closer towards designing IND-enabling clinical studies (Phase I and Phase II).

d) **ADME and First-in-Human (FIH) study**: We will contract with the FDA-approved General Manufacturing Practice MP compatible biotechnology company to finalize the upscale formulation of PAOPA. We have completed PK study in the rodent species. We found that showed that acute and 40-day sub-chronic treatment of PAOPA at dosages: 1 mg/kg, 10 mg/kg and 100 mg/kg administered through the intraperitoneal route were highly tolerated with no neurobehavioral adverse events. No changes in metabolic profile, kidney and liver function tests, blood pressure or body weights were noted. Plasma PAOPA revealed acute iv PAOPA resulted in rapid rise in PAOPA but dropped to 3 ng/ml by 18 hr. We will expand PK study to the aged canine species. Our second objective is to evaluate the interaction of PAOPA with cytochrome P450 enzyme system: CYP. This is vital to ADME assessment of PAOPA prior to human studies, for predicting any potential drug-drug interactions. With the development of highly selective luminogenic substrates for *in vitro* CYP CYP1A1, CYP1A2, CYP2C9, CYP3A4, CYP3A7, CYP4A and CYP4F, we will use standardized bioluminescent assay kits for human recombinant CYP species (from Promega Bioscience USA) to study PAOPA interaction with CYP. Once we have FDA IND clearance, we will design FIH study with adaptive Bayesian design.

Patent landscape: Patent PAOPA belongs exclusively and solely to Dr. Ram Mishra, McMaster University Hamilton ON Canada and Dr. Rodney Johnson University of Minnesota, MN USA. Dr. R Mishra (MUMC) and Dr. R Johnson (UM) are very flexible to negotiate with Pharmaceutical industry regarding Patent co-development. Dr. Simon Chiu University of Western Ontario defines his coordinating role as core R/D team. We are fully aware of the importance of filing with US Patent office for various formulations under development: intranasal, oral, subcutaneous and intravenous route with the US Patent office.

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