

## **MPP-021 – ‘Selectively Non-Selective’ CNS Drug Candidate as Anticonvulsant, Neuroprotectant, and Analgesic**

MediProPharma, Inc., Salt Lake City, UT, USA

MediProPharma is a virtual pharmaceutical company. We implement the strategy of nonclassical repositioning via identification of drug candidates with established clinical safety and efficacy, but with unknown target(s)/mechanism(s) of action. We elucidate the biological targets and mechanisms of action of clinically validated drug candidates, prepare novel analogs with improved pharmacological profiles, explore novel therapeutic utilities, and develop drug candidates to commercial viability.

We have identified and are developing multifunctional mechanism-based CNS drugs. Our strategy involves development of ‘selectively non-selective’ CNS drugs which concurrently act at several biological targets. Drugs with multiple mechanisms of action are predicted to be (1) more efficacious against a specific disorder than a drug with a single mechanism of action, (2) effective against a broader range of disorders or insults, and (3) may comprise a preventive therapy against development of a disease or disorder.

Our lead compound MPP-021, a clinically validated cognitive enhancer is currently in pre-clinical evaluation for the treatment of neurological and neurodegenerative diseases and disorders. We have identified several CNS targets and mechanisms of action for MPP-021 through initial screening at 227 ion channels, receptors, enzymes and transporters (Brain Panel at Cerep), and at 442 kinases (KINOMEscan™ at Ambit Biosciences), with follow-on studies in the functional assays. The pharmacological mechanisms of action of MPP-021 may involve interaction with quinone reductase 2 (QR2/MT3), DYRK1A and GRK2 kinases, neuronal L-type calcium channels, purinergic (P2Y), serotonin (5-HT2B), kainate, and GABAA receptors.

In collaboration with Anticonvulsant Screening Program (ASP) at the National Institute of Neurological Disorders and Stroke (NINDS), MPP-021 and its novel analogs have been and continue to be evaluated in vivo and in vitro as anticonvulsants, neuroprotectants and analgesics. The in vitro effects of MPP-021 are correlated with clinically-validated and novel kinase-mediated mechanisms of action and supported by in vivo efficacy in animal models of seizures, cognitive impairment, hypoxia, traumatic shock, and acute pain. MPP-021 has favorable pharmacokinetic profile for oral administration by non-GLP evaluation in rat, with a brain-plasma ratio of ~3. MPP-021 did not exhibit hypotensive or other cardiovascular side-effects in rat studies at acute IV single doses of 8- and 15-fold higher than a single dose in humans. Comprehensive pharmacokinetic and cardiovascular safety studies with MPP-021 in dog and evaluation in additional disease-relevant animal models are in progress.

In summary, the therapeutic potential for development of MPP-021 as a novel AED, anticonvulsant or an adjuvant antiepileptic agent is supported by its anticonvulsant and neuroprotective profile, and adjuvant analgesic effects. Importantly, MPP-021 possesses pronounced and clinically-validated cognitive enhancing properties in contrast to marketed AEDs, which include cognitive impairment as one of the most common side effects. Noteworthy, MPP-021 is also being evaluated for the treatment of neurodegenerative diseases such as Down syndrome (DS) and Alzheimer’s disease (AD) via a novel DYRK1A kinase-mediated mechanism of action. With up to 84% of DS patients developing seizures and the high probability of seizures in AD patients, a therapeutic approach to the treatment of neurodegeneration may also comprise a preventive therapy for acquired epilepsy in patients with DS and AD.