A TL1 Team Approach to CNS-Localized Delivery of Glial Cell-Derived Neurotrophic Factor for Treatment of Parkinson’s Disease*

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OBJECTIVES/GOALS: Develop a strategy to restrict GDNF diffusion to an injury site. GDNF-G3 is a human protein that binds to β-galactoside residues of cell surface and matrix glycoproteins. We characterized the binding of G3 fusion proteins to various glycoproteins and primary human myeloid cells. We incubated G3 fusions with CNS tissue ex vivo to measure their binding and depth of penetration via diffusion. We next plan to administer GDNF-G3 via CNS intracranial infusion in a murine PD model and then conduct behavioral PD phenotype testing via rota-rod and pole descent to compare to non-parkinsonian controls. We will further examine the effects of GDNF-G3 on degeneration using immunohistochemical examination of post-mortem brain tissue. RESULTS/ANTICIPATED RESULTS: Based on results from previous clinical trials of GDNF delivery, we anticipate that a successful intervention using GDNF-G3 will result in rescue of midbrain dopaminergic neurons in a murine PD model. In murine CNS tissue, we observed binding to glycans at the tissue surfaces when incubated with G3 fusion proteins ex vivo, suggesting GDNF-G3 will remain localized to the injection site. Next we will administer GDNF-G3 via CNS intracranial infusion in a murine PD model and assess efficacy by behavior and histopathology. GDNF-G3-mediated dopamine neuron rescue are expected to slow or reverse the progression of PD in these animal models. DISCUSSION/SIGNIFICANCE OF IMPACT: PD treatments focus on symptomatic relief. Standard therapies have not been efficacious in rescuing of dopaminergic neurons. GDNF-G3 administered at the site of neurodegeneration would allow for localized delivery while minimizing off-target effects. Successful intervention using GDNF-G3 will result in rescue of midbrain dopaminergic neurons in a murine PD model and then conduct behavioral PD phenotype testing via rota-rod and pole descent to compare to non-parkinsonian controls.

Allopregnanolone Dose Finding for Status Epilepticus Treatment by Pharmacokinetic-Pharmacodynamic Modeling using Quantitative EEG in Dogs

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OBJECTIVES/GOALS: Allopregnanolone (ALLO), a modulator of GABA receptors, may be useful as a treatment for human and canine benzodiazepine-refractory status epilepticus (SE). Our objective was to develop a pharmacokinetic-pharmacodynamic (PKPD) model relating ALLO plasma concentrations to electroencephalographic (EEG) effects in dogs. METHODS/STUDY POPULATION: Four healthy dogs and one dog with epilepsy that had implanted intracranial electrodes were utilized. ALLO doses ranging from 1-6 mg/kg were administered IV over 5 min. EEG data were collected during four IM doses (1-2 mg/kg). Blood samples were collected up to 6 h following dosing. ALLO concentrations were measured using