Gliacor Therapeutics is developing a novel class of compounds that prevent neuroinflammatory injury based upon technology derived from research at Colorado State University in partnership with the Texas A&M University Health Sciences Center. Neuroinflammation is now understood to play a critical role in the progression of Parkinson’s disease (PD). Unfortunately, current therapies do not address this problem, being focused on ameliorating the symptoms of dopamine loss rather than on targeting the underlying causes of injury to dopaminergic neurons. Thus, there remains no ‘disease modifying’ therapeutic agent that has been approved for the treatment of PD. Gliacor’s approach targets the molecular signaling pathways regulating expression of neuroinflammatory genes in glial cells in order to prevent further loss of dopamine producing neurons. The principal scientists at Gliacor include the lead PI at Colorado State University, Dr. Ronald Tjalkens, Associate Professor of Neuroscience and Neurotoxicology, whose research focuses on neuroinflammation and the role of glial cells in neurodegenerative disease. The research team also includes Dr. Stephen Safe, a medicinal chemist and pharmacologist and Distinguished University Professor at Texas A&M University Health Sciences Center. Dr. Safe developed the composition of matter for the C-DIM compounds and has extensively characterized their specificity and mechanism of action. A third key member of the research team at Gliacor is Dr. Dorothy Colagiovanni, an industry expert in toxicology and safety pharmacology and adjunct professor at the University of Colorado Denver Anschutz Medical Campus. The interdisciplinary team leading research and development efforts at Gliacor is working closely with the technology licensing offices at Colorado State University and Texas A&M University to establish preclinical development strategies for these compounds.

Opportunity Overview

Loss of dopamine-producing neurons in Parkinson’s disease (PD) is accompanied by inflammatory activation of surrounding microglia and astrocytes, termed glial cells. This inflammatory state in glial cells results in the production of neurotoxic substances that further damage neurons, leading to a vicious cycle of inflammatory damage that ultimately contributes to the progression of the disease. Levodopa (L-dopa) and its derivatives have been the standard of care for PD patients for decades but they are only symptomatic treatments and don’t slow progression of the disease, so that patients become refractory to these treatments as neuron loss becomes more severe. Better treatments are desperately needed as our population ages and the number of people diagnosed with PD increases. We are proposing a novel, oral therapy that has the potential to slow the progression of PD in order to maintain quality of life in patients. The studies supported by the Michael J. Fox Foundation expand on our existing work with a unique series of small molecule agents termed para-substituted diindoylmethane (C-DIM) compounds, that block the molecular signals that activate neuroinflammation and dramatically slow the disease process in animal models, thereby offering possibility of a disease-modifying therapeutic agent for PD. The C-DIM compounds under investigation are based upon phytochemical structures found naturally in cruciferous vegetables and a library of structural variants has been synthesized by Dr. Safe to optimize their anti-neuroinflammatory efficacy. These compounds also display a high level of safety in initial animal studies and excellent distribution to the brain following oral delivery. In parallel, we are also characterizing the molecular mechanisms underlying the capacity of C-DIM compounds to provide neuroprotection, while at the same time, potentially providing symptomatic benefit. The ability of a small molecule agent to provide both neuroprotective and symptomatic benefits would be truly unique and set these compounds apart from existing PD therapies.
The objective of this project was to test the efficacy and mechanism of action of a novel series of phytochemical-based compounds (para-substituted diindolylmethanes, C-DIM’s) with high anti-inflammatory activity that have been structurally modified to selectively interact with signaling pathways regulating neuroinflammatory genes in glial cells. By interacting with nuclear receptor target proteins, C-DIM compounds effectively suppress expression of inflammatory genes that are regulated by the signaling factor, NF-κB, which is often described as a master regulator inflammatory gene expression. In a series of studies, it was shown that specific C-DIM analogs have transcriptional activity through several different NR4A family nuclear receptors including Nurr1 (Inamoto et al., 2008) and Nur77 (Chintharlapalli et al., 2005). In addition to transcriptional activity, these receptors possess striking anti-inflammatory capacity to prevent the induction of NF-κB-regulated genes through a process now termed ‘transrepression’, similar to that described for the glucocorticoid receptor and liver X receptor, as well as for Nurr1. In previously published studies, we also reported that one C-DIM analog (C-DIM4), blocked NF-κB-dependent expression of inflammatory genes in astrocytes and protected co-cultured neurons from astrocyte-mediated apoptosis following treatment with MPTP and inflammatory cytokines (Carbone et al., 2009). Therefore, employing the transrepressive activity of C-DIM compounds to interdict NF-κB-dependent inflammatory signaling in glial cells represents a very novel therapeutic approach with the potential indication as a frontline neuroprotective agent to slow disease progression in PD patients.

The most active of these compounds identified from screening studies were tested using the subacute MPTP/probenecid model in transgenic NF-κB reporter mice in order to examine both protection against loss of dopamine neurons as well as efficacy in preventing glial-specific activation of neuroinflammatory gene expression. These studies were designed to fulfill two critical criteria: 1) the drugs were delivered orally once daily and 2) drug administration was not begun until after seven days of dosing with MPTP and probenecid, whereupon no further loss of dopaminergic neurons was observed by day 14. These studies demonstrated that the C-DIM compounds investigated were extremely effective at suppressing both neuroinflammatory activation of glia and loss of dopaminergic neurons in the substantia nigra pars compacta, even after onset of dopaminergic neuron loss. We also conducted pharmacokinetic studies of the compounds employed in the efficacy model that demonstrated oral bioavailability of 30-40%, excellent brain penetration following oral delivery, and sustained plasma levels consistent with therapeutically relevant rates of elimination. These findings demonstrate that suppressing neuroinflammatory signaling pathways in glial cells with orally delivered C-DIM compounds effectively prevented progressive loss of dopaminergic neurons in the substantia nigra. The results suggest they may be promising clinical leads for halting disease progression and thereby preserve quality of life in patients diagnosed with PD.

Results and Potential Next Steps

We conducted in vivo efficacy and pharmacokinetic (PK) studies with several top leads from a unique series of substituted diindolylmethane (C-DIM) compounds that display highly selective activity towards NR4A receptors (including NR4A1/Nur77 and NR4A2/Nurr1), as well as the ability to potently suppress neuroinflammatory activation of NF-κB in microglia and astrocytes. Results from pharmacokinetic studies indicated that three of these compounds had excellent oral bioavailability and clearance values and also reached peak concentrations in brain exceeding 1000 ng/ml (for C-DIM12, a Nurr1 activator). Based upon these favorable PK parameters, we used the subacute MPTP/probenecid (MPTPp) model in NF-κB-EGP reporter mice and found that three of these C-DIM compounds, particularly C-DIM12, were very effective at preventing loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), even when delivered one week after lesioning with MPTPp. Orally delivered C-DIM compounds also suppressed activation of NF-κB in glia and reduced protein nitrination in TH-positive neurons in the SNpc, indicating a high degree of protection from neuroinflammatory injury. Notably, C-DIM5, an activator of NR4A1/Nur77, had similar effective to C-DIM12 (a Nurr1 activator) at preventing loss of TH-positive neurons in the SNpc. Because these compounds are highly selective in which NR4A family member they activate, these data suggest that a distinct mechanism is responsible for the observed anti-neuroinflammatory effects in glia. Next steps in this research program will examine in greater detail the specificity and receptor-dependence of C-DIM-mediated blockade of NF-κB-regulated inflammatory genes in glial cells, structure-activity relationships underlying efficacy of the pharmacophore and early off-target and preclinical safety screening.

Intellectual Property Status

The composition of matter for C-DIM compounds is protected by awarded US and international patents and an additional use patent has been filed with the USPTO for neurological/neurodegenerative indications by Colorado State University. An arrangement to sublicense the composition of matter for the use in neurological/neurodegenerative disease was completed between CSU and Texas A&M University and an option for Gliacor to exclusively license this technology is also in place.

Tjalkens, Page 2

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