Project Title:

Targeting GDNF-GFR Signaling in Neurodegeneration: Exploring Therapeutic Pathways in Dopaminergic Neuron Health

Summary of Proposal:

Neurotrophic factors, such as the Glial cell line-derived neurotrophic factor (GDNF), are vital signaling molecules that promote the growth and survival of neurons, particularly dopaminergic (DA-ergic) neurons, which are crucial for motor control and cognitive functions. GDNF, through its receptor GFR, plays a pivotal role in maintaining neuronal health and preventing neurodegeneration, a key factor in conditions like Parkinson's and Alzheimer's diseases. Disruptions in GDNF signaling can lead to abnormal brain development and neurodegeneration, affecting millions of people globally.

Our research focuses on understanding how GDNF-GFR signaling influences the DA-ergic system and neurodegeneration, particularly during critical periods of brain and gonadal development. By exploring these mechanisms, we aim to identify new therapeutic targets that can mitigate neurodegenerative diseases, potentially improving the quality of life for those affected. Given the increasing prevalence of neurodegenerative disorders, this research has significant societal implications. It not only aims to advance scientific understanding of brain function and development but also strives to develop strategies that could lead to regeneration effective treatments and reducing debilitating conditions.

Utilizing mammalian models known for their remarkable brain plasticity and resistance to neurodegenerative conditions study promises to provide insights at multiple biological levels. These findings could pave the way for novel therapeutic approaches, ultimately contributing to the fight against neurodegenerative diseases and enhancing health and longevity.

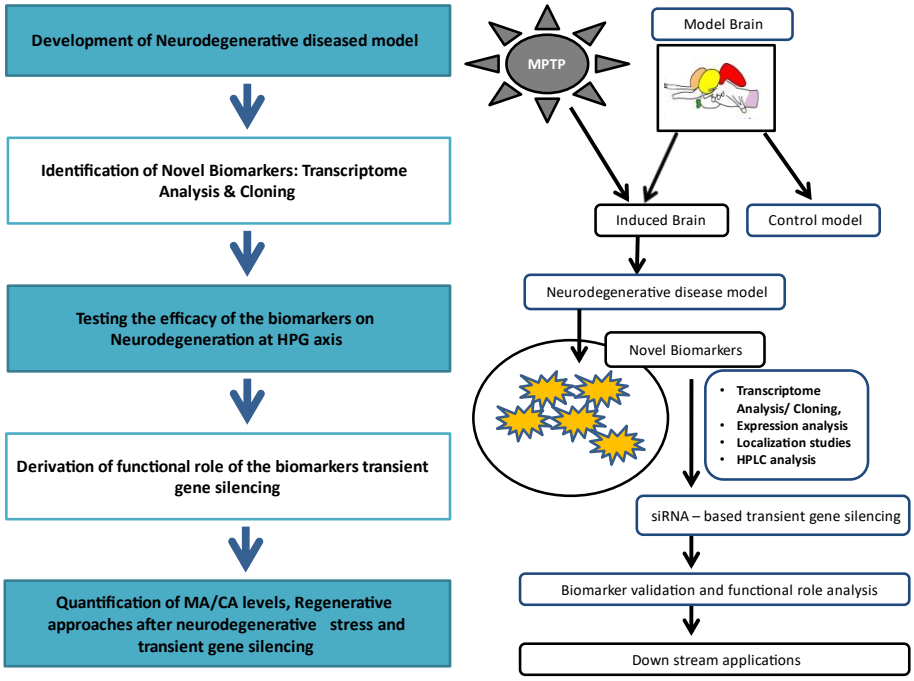
Objectives Formulated

Objective 1: Develop an MPTP-induced neurodegenerative model to study DA-ergic neuron loss and analyze key biomarkers via RNA-Seq to identify key biomarkers, pathways, and molecular mechanisms involved in DA-ergic function.

Objective 2: Identify novel brain biomarkers using siRNA gene silencing (RNA interference) in vivo and in vitro. Analyze expression changes (qRT-PCR) after neurodegenerative stress. and assess expression changes after neurodegenerative stress.

Objective 3: Analyze GDNF-GFRα and biomarkers through IHC and HPLC-ECD; test therapeutic efficacy in a neurodegenerative model. Test the efficacy of therapeutic biomarkers and regeneration approaches in a neurodegenerative disease model (Pister Rat) compared to controls.

Illustration:



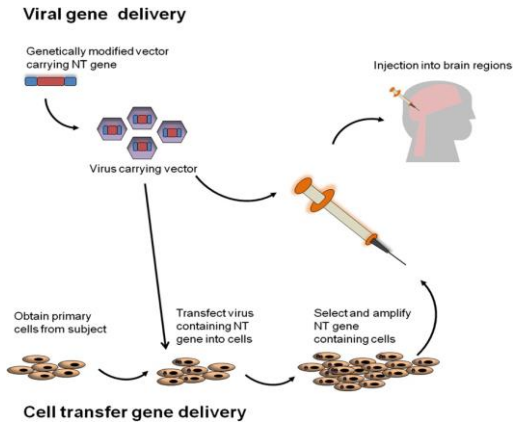
Outcomes and Impact: The core focus of my research has been to unravel the intricate molecular mechanisms underlying brain signaling, with a particular emphasis on the role of Glial Cell Line-Derived Neurotrophic Factor (GDNF) and its receptors (GFRα-1,4), as well as Transforming Growth Factor (TGF) and other key transcription factors. My work aims to decode how these signaling molecules contribute to the establishment and regulation of gene expression patterns that are essential for both neuronal and gonadal development and functions. GDNF, a potent neurotrophic factor, is critical for the survival and maintenance of dopaminergic neurons, which are vital for proper motor and cognitive functions. By investigating the interactions between GDNF and its receptors, this research will shed light on how these signaling pathways influence the differentiation, survival, and regeneration of neurons, which has profound implications for neurodegenerative diseases.

Furthermore, this research will extend to the role of TGF and other transcription factors in modulating these pathways, offering insights into their involvement in neurogenesis and gonadal function. Understanding these pathways is crucial for identifying how disruptions can lead to developmental disorders or diseases.

In short, this research holds significant potential for advancing clinical applications, particularly in developing therapies targeting the DA-ergic system and enhancing neuroprotection against neurodegeneration. The anticipated outcomes will contribute to the broader scientific understanding of neuroscience, specifically in the mechanisms of neurodegeneration and the critical role of neurotrophic factors in maintaining brain health. Ultimately, these insights could have far-reaching implications for improving human health and combating neurological diseases.

Possible Directions for Future Research

The molecular mechanisms involved in neurodegenerative disorders are essential. This research could uncover how these processes influence overall human health, potentially leading to new insights into disease prevention and treatment.



Combinational Therapy with Steroids, Neurotrophins, and Small Molecules Investigate the efficacy of combination therapies that incorporate steroids, neurotrophic factors, and small molecules. This approach could enhance neuroprotection and improve outcomes in the treatment of neurodegenerative diseases.

Translational Neurodegeneration: Focus on translating basic neuroscience research into clinical applications. By refining therapeutic strategies for neurodegenerative diseases, this research could bridge the gap between laboratory discoveries and patient care. Advancements in Neurotrophic Factor Therapy for Neurodegenerative Disorders: Continue to assess the latest advancements in the use of neurotrophic factors as treatment options for neurodegenerative diseases. This research could lead to more effective therapies that slow or halt disease progression.

Efficacy Testing of Biomarkers in Chemically Induced Disease Models: Develop and utilize hybrid disease models to rigorously test the efficacy of specific biomarkers and associated factors. This approach could validate the therapeutic potential of these biomarkers, paving the way for new treatment modalities.

Applicant Signature:

Mamta Sajwan Khatri