CurePSP Research
CURRENT PROJECTS
Gene Replacement Therapy for Tauopathies

Dr. Rachel Baily
Center for Alzheimer’s and Neurodegenerative Diseases, UT Southwestern Medical Center, Dallas, TX

The abnormal misfolding and aggregation of proteins are common pathologic features of most neurodegenerative diseases, including tauopathies. Toxic gain or loss of normal protein function is often an underlying mechanism of neuronal death in the brain. This project will test a gene therapy approach for tauopathies such as PSP. The goal is to achieve silencing of the toxic protein in combination with the restoration of normal protein function. To achieve that, Dr. Baily aims to deliver a gene that produces a tau protein that doesn’t aggregate. If successful, this could establish a new avenue for a therapy approach relevant to PSP, CBD, and a number of protein-linked neurodegenerative diseases such as Alzheimer’s Disease and Frontotemporal Dementia.

Aminopeptidase Enhancers as Novel PSP Pharmacotherapies

Dr. Daniel H. Geschwind
Department of Neurology, University of Southern California, Los Angeles, CA

Tau reduction may be one of the most promising therapeutic approaches for treating tauopathies—a group of neurodegenerative diseases characterized by pathological tau protein accumulation. Here, Dr. Geschwind and his team will target tau reduction via an entirely novel mechanism that was discovered and characterized over the last decade: enhancing the activity of a neuroprotective enzyme called puromycin sensitive aminopeptidase (NPEPPS). Based on preliminary observations, enhancing NPEPPS activity is effective in reducing tau levels. The team conducted a high-throughput screen to identify drugs that increase cellular NPEPPS activity. They successfully identified two types of promising molecules that can reduce pathological tau without toxicity in stem cell-derived neurons from patients, a human “disease-in-a-dish” model used to predict clinical outcomes of drugs. Dr. Geschwind’s team showed that early treatment of one of these compounds suppresses pathological tau in a mouse model of tauopathy. They are now characterizing their top compounds in a mouse model of tauopathies—a key preclinical step before seeking FDA approval to test these new approaches in humans.

Investigation of ULK1-Based Autophagy Activators as Therapeutics for Tauopathies

Dr. Maria Catarina Lima da Silva
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

A characteristic of PSP, CBD, and other Tauopathies, is the weakening of the cellular machinery responsible for the removal of protein aggregates. These mechanisms are part of the autophagy pathway. Using a drug screen focused on autophagy enhancement and tau clearance in PSP patient-derived neurons, the team has identified an alternative regulator of autophagy, the serine/threonine-kinase ULK1. Two small-molecule activators of ULK1 were found to promote autophagy in human neurons. This activation was shown to reduce tau burden and neuronal toxicity. The proposed studies will characterize the mechanism of action of ULK1 activators that lead to tau clearance in neuronal models of disease. Another objective of the study is to focus on the synthesis and testing of new drug-like molecules with improved properties for neurological diseases therapeutics. The strength of this approach relies on pharmacological strategies for drug discovery utilizing patient-specific neurons cultured in a dish, to identify potential drugs with relevance across different forms of tauopathy.

Identification of Microglia Phenotypes Associated with Tau Pathology in PSP and CBD

Dr. Marta Olah
Department of Neurology, Columbia University, New York, NY

Microglia, the resident immune cells of the brain, have been implicated in tau aggregation and spread as well as in neuronal cell death. Microglia involvement in neurodegenerative processes has been long documented based on their morphological activation, but the exact nature of specific microglia involvement in brain diseases is not yet known in humans. This project will identify microglia molecular markers associated with the aggregation and spread of pathological tau protein in PSP and CBD donors. Using a recently published pipeline for single-cell gene expression profiling of live microglia extracted from fresh autopsy brain samples the team will establish a molecular atlas of microglia in different brain regions affected by tau pathology in PSP and CBD. Dr. Olah work will determine the similarities and differences in microglia between PSP and CBD. Overall, this study will lay the foundation for potential therapeutic interventions that inhibit disease progression.
CURRENTLY FUNDED RESEARCH GRANTS

Connecting GWAS Signal in Tau Locus to Effector Variant in Tauopathies
Dr. Rueben Das
Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

Investigating PSP and CBD Tau Strain Biology to Support Novel Diagnostic Development
Dr. Amanda L. Woerman
University of Massachusetts, Amherst, MA

Small Molecule Regulation of a Protein Quality Control E3 to Treat PSP
Dr. Kenneth Matthew Scaglione
Molecular Genetics and Microbiology, Duke University, Durham, NC

Bifunctional Intrabodies to Lower Tau
Dr. David C. Butler
Neural Stem Cell Institute, Regenerative Research Foundation, Rensselaer, NY

Low-Dose Efavirenz as a Disease-Modifying Intervention for Primary Tauopathies
Dr. Rik van der Kant
Functional Genomics Department, Vrije Universiteit Amsterdam, Amsterdam, Holland

The Influence of TRIM11 on Tau, Aggregation, Release and Propagation
Dr. Jonathan Mark Cooper
Institute of Neurology, Dept of Clinical and Movement Neurosciences, University College, London, UK

Biomarkers in Brain-Derived Blood Exosomes for Improved PSP Diagnosis
Gal Bitan, PhD
University of Southern California, Los Angeles, CA

Uncovering Unique Tau Profiles That Distinguish PSP From Other Tauopathies
Dr. Todd L. Cohen
The University of North Carolina at Chapel Hill, NC

Dissecting Neuronal Dysfunction Under 3R:4R Tau Isoform Imbalance
Maria-Elena Avale, PhD
Institute for Research in Genetic Engineering and Molecular Biology, Buenos Aires, Argentina

Eloise H. Troxel Memorial Brain Bank
Dr. Dennis Dickson
Mayo Clinic, Jacksonville, FL

Structural Basis for Tau Strain Conformation in CBD and PSP
Dr. Lukasz Joachimiak
Center for Alzheimer’s and Neurodegenerative Diseases, UT Southwestern Medical Center, Dallas, TX

Do distinct 4R-tau seeding strains cause disease heterogeneity in PSP and CBD?
Dr. Rohan de Silva
UCL Queen Square Institute of Neurology, London, UK
Using Single-Cell Transcriptomics in 3D Organoids to Understand Changes in Cell Subpopulations and Gene Expression Associated with Tauopathy-Causing MAPT Mutations

Dr. Sally Temple
Neural Stem Cell Institute, Rensselaer, NY

Dr. Alison Goate
Icahn School of Medicine at Mount Sinai, New York, NY

Researchers can now generate 3D neuronal cell cultures (organoids) using skin stem cells from patients suffering with neurological diseases and from healthy individuals. These human-derived disease models offer new avenues to study tauopathies. This study, in collaboration with the Rainwater Charitable Foundation and its Tau Consortium Stem Cell Research Group, will further establish the most comprehensive collection of organoids carrying tau mutations and will provide insights at the single-cell level on the effect of these mutations on neuronal biology.