Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease found at autopsy that underlies a variety of clinical dementia syndromes, and is the second most common cause of dementia under age 65 [1]. Patients with FTLD-related dementias are underserved in part because the complex relationship between dementias and underlying pathology is not well understood. Much of the complexity lies in the fact that the same pathology can cause different dementia syndromes and, conversely, that a single dementia syndrome can be caused by multiple pathologies. The **goal of this proposal** is to disentangle the complex relationship between dementia syndromes, anatomic atrophy, cell death, and a specific form of FTLD, known as FTLD-tau. In doing so, this work will help identify the putative substrates of neurodegeneration in FTLD-tau.

This study focuses on a robust cohort of postmortem human specimens that show the most common forms of FTLD-tau: Pick’s disease and the frontotemporal lobar tauopathies of the corticobasal and progressive supranuclear palsy types (CBD-PSP). These tauopathies can underlie primary progressive aphasia (PPA), a clinical dementia syndrome characterized by progressive language impairment, and behavioral variant frontotemporal dementia (bvFTD), a clinical dementia syndrome characterized by progressive changes in comportment. **Aim 1** will determine the specific targets and cellular features of a single tauopathy (Pick’s disease) in cases diagnosed antemortem with different dementia syndromes: the semantic and agrammatic variants of PPA (PPA-S and PPA-G, respectively) and bvFTD. These dementia syndromes are each associated with distinct patterns of atrophy and clinical profiles, providing an ideal model to explore the selective vulnerabilities of anatomic regions responsible for cognition or behavior. **Aim 2** will study the converse relationship by investigating multiple pathologies (Pick’s disease and CBD-PSP) in cases diagnosed antemortem with a single dementia syndrome (PPA-G or bvFTD). Histological and unbiased stereological methods will be used to determine relationships between FTLD-tau pathology, not only to detailed clinical profiles and quantitative MRI atrophy patterns, but also to neuronal, glial, and synaptic abnormalities. A **central hypothesis** of this work is that regional distributions of FTLD-tau—and related cellular features—will show concordance with anatomic patterns of atrophy and distinct clinical profiles.

This is one of the first works of its kind that aims to establish clinical, anatomic, and pathologic concordance of high specificity between clinical dementia syndromes and the tauopathies that cause them. PPA and bvFTD, specifically, offer exciting opportunities for exploring the organization and pathologic targets of anatomic networks in neurodegenerative diseases. Outcomes of this multidisciplinary study will clarify the pathologic underpinnings of clinical heterogeneity in dementias, sharpen our understanding of the principles of selective vulnerability, and are highly relevant for the development of tauopathy-specific diagnostic tools and treatments.