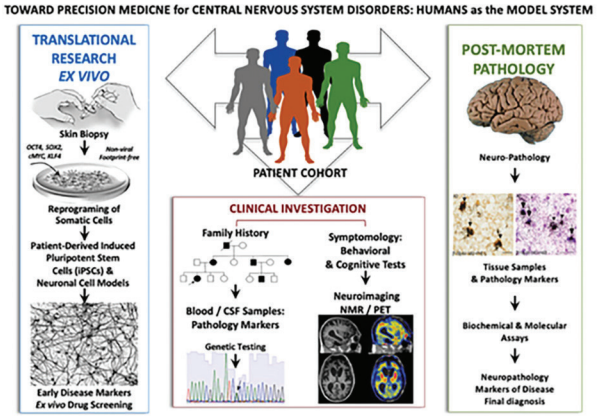

Figure 1. Toward precision medicine for CNS disorders. Humanized CNS drug discovery based around genetically accurate and pathophysiologically relevant cell types generated from the directed differentiation of induced pluripotent stem cells (iPSCs) and integration of neuropathology and clinical investigation using genetics and neuroimaging.

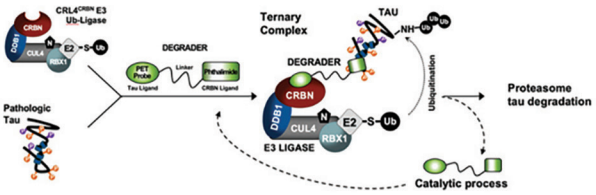

Figure 2. Strategy for Tau Targeted Protein Degradation. Degrader compounds are heterobifunctional molecules composed of a phthalimide derivative, which is recognized by CRBN in the CRL4 E3 ubiquitin ligase complex, and a moiety that recognizes human Tau (endogenous) in neuronal cells. The degrader recruits Tau into proximity of the CRBN-CRL4 E3 ubiquitin ligase complex for ubiquitination and subsequent irreversible degradation by the proteasome, allowing it to have catalytic-like activity and participate in multiple rounds of targeted degradation.

Precision Medicine for Dementia: Patient-Derived Stem Cell Models & Targeted Protein Degradation

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Dr. Haggarty's overall research interest is to gain a fundamental understanding of the molecular and cellular mechanisms of neuroplasticity that enable the nervous system to sense, adapt, and respond to a variety of internal and external stimuli. His long-term goal is to translate this knowledge into the discovery of novel targeted therapeutics for the treatment and prevention of neuropsychiatric disorders.

Alzheimer's disease and related dementias are one of the leading causes of death worldwide. Current treatments are symptomatic in nature and neither prevent cognitive decline nor neuronal loss. Consequently, the burden to grow, with a cost estimate of over $1 trillion in the US alone by 2050. This burden provides a strong impetus for the discovery of effective disease-modifying and preventative treatments that target the core pathological features of Alzheimer's disease including the accumulation of aberrant protein aggregates and neurofibrillary tangles composed of microtubule-associated protein Tau. In support of Tau as a driver of disease pathogenesis, mutations in the MAPT gene encoding Tau are known to be sufficient to cause forms of frontotemporal dementia, and common genetic variation in the MAPT locus is associated with elevated risk for a range of tauopathies. However, as an intrinsically disordered, highly abundant, and predominantly intracellular protein, efforts to use immunotherapies and conventional small molecules to target Tau have encountered challenges.

Using a 'humanized' early-stage CNS drug discovery platform built around genetically accurate, patient-derived stem cell models generated via cellular reprogramming technology, our team has generated tauopathy patient-derived stem cell models (Figure 1). In collaboration with partners,), using this platform we have developed a novel pharmacological strategy for targeted degradation of Tau that exploits conformational changes of pathological, misfolded forms of Tau. This targeted protein degradation (TPD) strategy relies on a bifunctional molecule that simultaneously binds the target protein of interest and recruits an E3 ubiquitin ligase leading to proteasomal degradation (Figure 2). On-going studies seek to further leverage the principle of proximity and apply the power of TPD to other causal drivers of proteinopathies and CNS disorders. Translational efforts focused on advancing optimized 2nd generation Tau degraders are now being led by Proximity Therapeutics, with seed support from Mission Biocapital and the Mass General Brigham Innovation Fund.