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).

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