ENHANCING PROTEASOMAL ACTIVITY TO FACILITATE THE PROTEOLYTIC DEGRADATION AND CLEARANCE OF MISFOLDED PROTEINS ASSOCIATED WITH NEURODEGENERATIVE DISEASES

S. Jacobsen\textsuperscript{1}, C. Conrad\textsuperscript{1}, B. Tait\textsuperscript{1}, R. Chambers\textsuperscript{1}, M. Foley\textsuperscript{1}, M. Goulet\textsuperscript{1}, E. Nokes\textsuperscript{1}, R. King\textsuperscript{2}, D. Finley\textsuperscript{2}, P. Reinhart\textsuperscript{1}

\textsuperscript{1}Proteostasis Therapeutics, Inc., Suite 402, Cambridge, \textsuperscript{2}Cell Biology, Harvard Medical School, Boston, MA, USA

Introduction: Alzheimer's is a progressive neurological disease associated with the accumulation and deposition of misfolded Abeta and tau peptides in the brain. These peptides are thought to be causative in the etiology of pathogenesis and their accumulation leads to an intracellular environment of oxidative stress, mitochondrial dysfunction, neurotoxicity and neurodegeneration. One of the primary mechanisms of intracellular clearance of these peptides involves degradation of the ubiquitin-peptide conjugates by the proteasome. The proteasome-associated deubquitinating enzyme USP14 inhibits the degradation of ubiquitin-protein conjugates both in vitro and in cellular models. It has recently been demonstrated that small molecule inhibitors of USP 14 enhance proteasome activity and stimulate the degradation of tau in these models.

Aims: To demonstrate that USP14 inhibition leads to the degradation of more pathologically relevant species of hyperphosphorylated/truncated tau both in vitro and in cultured neurons.

Methods: Both soluble and insoluble (hyperphosphorylated/truncated) species of tau extracted from the brains of transgenic mice expressing human tau will be used as substrate for in vitro reconstruction studies. The effects of proteasomal degradation on 'disease-relevant' tau substrate following the treatment with inhibitors of USP14 will be examined both in vitro and in cultured human neurons expressing recombinant tau.

Results: The enhancement of proteasomal-mediated ubiquitin-protein conjugate degradation by this novel approach will be discussed.

Conclusions: The use of small molecules to manipulate proteasomal activity is one of several strategies Proteostasis Therapeutics, Inc. is employing to modulate homeostasis and the proteostatic network to assist cells in correcting the folding, trafficking or degradation of proteins.