Bradley T. Hyman, M.D., Ph.D.
Massachusetts General Hospital
Charlestown, Massachusetts

Untangling Tangles in Alzheimer’s Disease
Candidate for 2009 Zenith Fellows Award

Tau protein plays a vital role in maintaining the health of nerve cells. Tau is normally modified by a process called phosphorylation, or the attachment of phosphate molecules. During Alzheimer’s disease, however, tau becomes excessively phosphorylated and tends to accumulate into harmful structures called neurofibrillary tangles. Scientists have long believed that these structures are among the key hallmarks of Alzheimer’s. However, recent studies have suggested that tau tangles may actually prove beneficial to brain health by absorbing and neutralizing smaller and more toxic tau clumps. To resolve this contradiction, scientists need to acquire a better understanding of how tau tangles form and how they may or may not harm brain cells.

Bradley T. Hyman, M.D., Ph.D., and colleagues have developed a sophisticated imaging method that can better show the development of neurofibrillary tangles over time. Their method can also image the development of cellular damage that scientists have traditionally associated with tau. The researchers believe their technique can help resolve whether or not tau tangles are detrimental to brain cells.

For this grant, Dr. Hyman’s team will use a compound called phenothiazine methylene blue, which has been shown to break down components of neurofibrillary tangles. The investigators will inject this compound into the brains of mice genetically engineered to produce abnormal tau. They will then use their imaging technique to determine if the drug is able to “disentangle” neurofibrillary tangles in the mice brains, and if the soluble forms of tau released by such disentangling prove harmful or beneficial to nerve cells. The investigators will also test the effectiveness of a protein called carboxy-terminus HSP70 interacting protein (CHIP), which has been shown to inhibit the production of abnormal tau. They hope to determine whether CHIP can prevent certain neuronal damage that is thought to be caused by tau. For both of these experiments, the team will also conduct similar studies on autopsied brain tissue from people who had developed Alzheimer’s. Overall, the results of this work should refine our understanding of how abnormal tau may affect dementia progression.