Speaker         Dennis J. Selkoe, MD, The Vincent and Stella Coates Professor of Neurologic Diseases, Harvard Medical School  
Time            4pm, Departmental Tea immediately following.  
Date            Friday, 6 February 2009  
Place           Singleton Auditorium, 46-3002  
Title           Presenilin, APP and the Genesis of Alzheimer's Disease.  
Host            Sue Corkin

Abstract:  
Research focused on the pathogenesis of human disease has often provided novel insights into fundamental mechanisms of cell biology. The study of Alzheimer's disease (AD) provides a salient example: the discovery of intramembrane proteolysis as a widespread protein processing and signaling mechanism arose in part from the identification of presenilin as an unusual aspartyl protease that cleaves APP within the membrane to release the amyloid β-protein (Aβ). The contemporaneous discovery that Notch receptors are cleaved by presenilin/γ-secretase in an indistinguishable manner suggests how AD arose in the human population: a conserved proteolytic mechanism required for life in all metazoans can also generate a small hydrophobic peptide (Aβ) that accumulates with age in the limbic and association cortices of all primates and can progressively impair synaptic function. A key step towards proving the identity of a causative agent in human disease is to isolate the suspected agent from affected tissues of patients and recapitulate the disease phenotype by administering it to an experimental animal (Koch's postulate). Whereas many studies have examined synthetic and cell-derived Aβ oligomers, the neural effects of Aβ assemblies obtained directly from AD patients have not been established. We recently isolated soluble Aβ oligomers (principally dimers) and insoluble amyloid plaque cores from the cerebral cortex of patients with typical AD but not from patients with non-AD dementias. The soluble oligomers dose-dependently inhibited long-term potentiation (LTP), enhanced long-term synaptic depression (LTD) and reduced dendritic spine density in normal rodent hippocampus. Further, the human oligomers potently disrupted the memory of a learned behavior in normal adult rats. These effects were specifically attributable to soluble, low-n Aβ oligomers at low nanomolar concentrations in the absence of amyloid fibrils; Aβ monomers were inactive. Mechanistically, activation of metabotropic glutamate receptors was required for the LTD effect and of NMDA receptors for the spine loss. Therapeutically, immunodepleting oligomers from the AD brain isolates reversed all effects, and co-administering antibodies to the N- (but not C-) terminus of Aβ prevented both the LTP and LTD deficits. Insoluble amyloid plaque cores from AD cortex did not impair LTP unless they were first solubilized to release Aβ dimers, suggesting that plaque cores are themselves largely inactive but sequester Aβ dimers that are potentially synaptotoxic. We conclude that Aβ oligomers extracted directly from AD brains potently impair synapse structure and function in hippocampus and that soluble dimers are the minimal synaptotoxic species. These findings fulfill a key criterion for establishing disease causation in AD.