Dominic M. Walsh, PhD
Associate Professor
Laboratory for Neurodegenerative Research
Center for Neurologic Diseases
Brigham & Women's Hospital
Harvard Institutes of Medicine (R921)
77 Avenue Louis Pasteur
Boston
MA 02115

Email: dwalsh3@partners.org

Lab website: http://brighamandwomens.org/research/labs/walsh/default.aspx

Title: **Coming to grips with brain-derived water-soluble Aβ and its interaction with the Prion protein.**

Alzheimer's disease (AD) represents a personal and societal tragedy that demands an accelerated effort towards effective therapies. Genetic and biomarker data strongly suggest that the amyloid β-protein (Aβ) plays an early and important role in all cases. However, clinical trials of Aβ-targeting agents have proved disappointing and there is lingering concern about the relevance of Aβ to AD causation. Unlike agents in other conditions, there is no robust connection between fibrillar Aβ pathology and disease, that is plaque density and number poorly correlate with the presence and severity of disease. An explanation for this apparent lack of pathological cause and effect is that histologically-invisible soluble forms of Aβ, loosely referred to as "oligomers", are the primary mediators of neurotoxicity. While numerous studies indicate that oligomers formed in vitro have toxic activity, surprisingly little effort has been devoted to analyzing bioactive forms of brain-derived Aβ. We have found that the aqueous phase of AD brain contains four prominent Aβ species: (i) monomer, (ii) SDS-stable dimer, (iii) intermediate molecular weight and (iv) high molecular weight assemblies formed largely from dimers. Our results indicate that assemblies formed from Aβ dimers have potent plasticity and memory disrupting activities that depend on expression of the prion protein (PrP). Exploiting this knowledge about Aβ dimers, their assembly and interaction with PrP might offer novel avenues for the treatment and diagnosis of AD.