Buck Institute Technology Summary

Novel Caspase Inhibitors as Therapeutics for Huntington's Disease

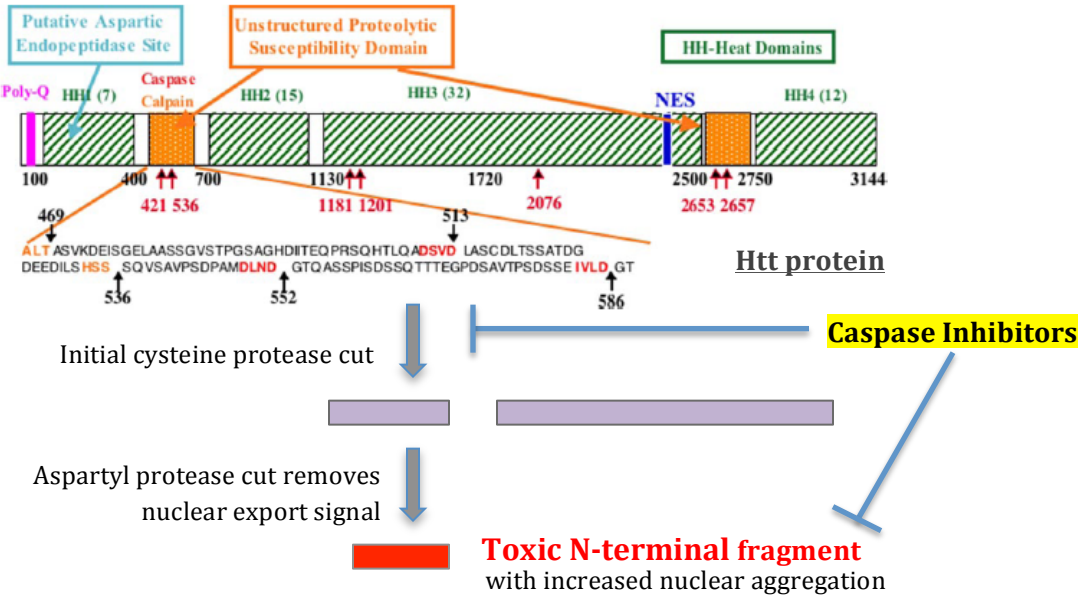
Buck Institute Case No. BI-380

Background

Huntington's disease (HD) is an autosomal-dominant progressive neurodegenerative disorder leading to loss of function and viability of neurons in the striatum and cortex, resulting in severe physical and cognitive decline and early morbidity. HD is primarily a disease of western European descent with a prevalence of approximately 30,000 in the US and Canada and over 400,000 people worldwide. The approximate cost of HD in the US alone is calculated at over 2.5Bn USD per year not to mention the suffering of HD patients and their family members. There is currently no therapeutic intervention for HD. The only approved medication for HD is tetrabenazine, which treats hyperkinetic movements seen with disease progression.

It is believed that cleavage of mutant huntingtin (Htt) into protein fragments may be a critical molecular event triggering selective neuronal loss, known as the "toxic fragment hypothesis" (see figure below). Enzymatic cleavage of mutant Htt by multiple cysteine proteases, in particular caspase-3 and caspase-6, has been shown to correlate with cytotoxicity in HD cell culture and mouse models. Aberrant activity of these caspases is also implicated in other neurological diseases, including Alzheimer's disease and stroke.

"Toxic Fragment Hypothesis" Model of HD



The Technology

Given strong evidence for the "toxic fragment hypothesis" in HD, there has been a determined effort to find caspase inhibitors to delay neuronal death. Most studies have focused on peptidic compounds that have poor bioavailability.

Drs. Lisa Ellerby (Buck Institute) and Jon Ellman (UC Berkeley/Yale University) recently used a substrate library to screen for non-peptidic caspase inhibitors (Chemistry and Biology 17, 1189-1200, 2010). Substrate activity screening (SAS), a fragment-based identification method, yielded multiple novel, low-molecular weight substrates that were optimized and converted from substrates to potent, non-peptidic inhibitors of caspase-3 and -6. These compounds were shown to be easily dosed, had good bioavailability to the brain and did not provoke any acute adverse events. In key HD models, these caspase inhibitors blocked proteolysis of Htt at amino acid 513 (caspase-3 site) and 586 (caspase-6 site) and suppressed neuronal toxicity. They are expected to prove useful in prophylaxis or treatment of HD as well as other chronic diseases.

Opportunity

Huntington's disease is a rare neurodegenerative disease that represents a significant unmet medical need. Additionally, it offers a unique opportunity in understanding and treating other neurodegenerative diseases, particularly those characterized by similar toxic protein accumulation and neuronal toxicity, including Parkinson's and Alzheimer's disease. Patent applications have been filed by the Buck Institute on behalf of the Ellerby and Ellman laboratories, and the compounds are currently being evaluated in additional mouse models for efficacy. The Buck Institute welcomes interested parties to inquire regarding licensure or collaboration of this technology.

The Buck Institute is the only free standing institute dedicated to aging and age-related research in the United States. We actively partner with industry to develop therapeutics, diagnostics or tools that make a difference. For more information on this or another technology or opportunity, please contact:

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