Buck Institute Technology Summary

Increased Lifespan and Healthy Aging with Anti-Aggregation Compounds

Buck Institute Case No. BI-383

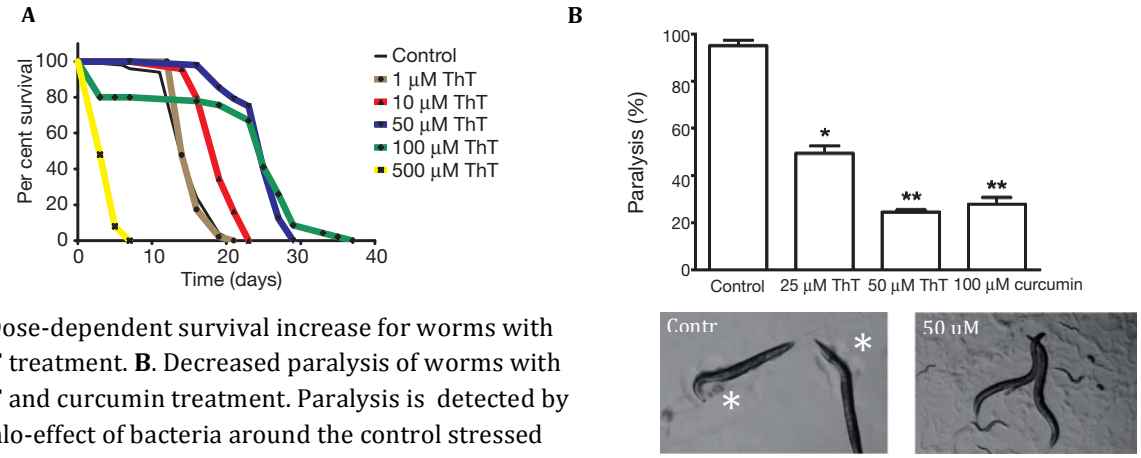
Background

During aging there is a disruption to normal protein processing, leading to the deposit of insoluble misfolded proteins, or aggregates. In particular, protein aggregates are a hallmark of common neurodegenerative diseases, for example α-synuclein aggregation in Parkinson's Disease and β-amyloid aggregation in Alzheimer's Disease. For decades, compounds have been used to image these aggregates in postmortem brain tissue and more recently in patients, using modern imaging systems. These aggregate imaging dyes have also been found to prevent the formation of aggregates in cell culture. Scientists at the Buck Institute hypothesized that these compounds may prevent aggregation *in vivo* and therefore have a therapeutic effect in addition to their current diagnostic use.

The Technology

Dr. Silvestre Alavez in the Lithgow Lab used a selective screen directed to analyze a group of small molecules, traditionally employed in histopathology to stain amyloids in tissues, in the nematode worm *C. elegans*. This screen revealed that indeed some of these compounds not only bind protein fibrils but slow aggregation and increase lifespan in *C. Elegans*. Promising compounds included the turmeric component curcumin, the antibiotic rifampicin and other compositions. One compound, Thioflavin T ("ThT"), was confirmed to have superior results. ThT was found to extend the lifespan of worms by up to 60%, as well as slowing the physiological aging process, in particular improving frailty by decreasing motor dysfunction (see graphs). These results are reproducible, occur in a dose-dependent manner and were published in the prestigious journal, *Nature*, in 2011.

ThT has been used for over 50 years as an imaging agent to understand the aggregation of soluble amyloid proteins into beta-sheet fibrils and has been explored as an *in vivo* diagnostic for imaging β-amyloid plaques. This is the first time that ThT and related compounds have been identified as potential therapeutics to reduce aggregation and improve healthy aging.



A. Dose-dependent survival increase for worms with ThT treatment. **B**. Decreased paralysis of worms with ThT and curcumin treatment. Paralysis is detected by a halo-effect of bacteria around the control stressed worms unable to feed (asterisks) compared to the treated stressed worms with decreased frailty.

The Lithgow lab has shown that this novel mechanism of action likely occurs through ramping up of the endogenous stress-response and protein degradation pathways. While this finding was made in nematode worms, preliminary results in collaboration with researchers at the Barshop Institute suggest that HBX, a ThT structurally related compound that crosses the blood brain barrier, improves the prognosis in a mouse model of neurodegenerative disease. In addition, the Andersen lab at the Buck Institute has shown that HBX effectively suppresses neuronal inflammation associated with neurological disease. These findings indicate a key role for the maintenance of protein homeostasis during aging.

Opportunity

Research conducted in the Lithgow Lab at the Buck Institute represents the first example of amyloid-binding dyes for use in extending lifespan and reducing age-related frailty. Furthermore, these studies suggest a novel and critical role for protein aggregation in controlling physiological aging. ThT and related compounds have potential as therapeutic agents, improving healthspan by controlling protein aggregation in chronic human disease.

Work continues at the Buck regarding this new approach to diseases with aggregation. The Buck seeks developmental partners who can collaborate and further develop these agents to treat the myriad diseases caused or exacerbated by aggregation.

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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