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CRYAB INHIBITION AS A NEW METHOD OF TREATING DISEASES OF AGING

TECHNOLOGY DESCRIPTION

The Alpha-crystallin B chain (also referred to as CRYAB) is a protein in the small heat shock protein family and is evolutionarily conserved across mammals. Increase and aggregation of the CRYAB protein in multiple human tissues and its association with multiple diseases such as cancer and neurodegenerative diseases, like Alzheimer's and Parkinson's disease, has been widely described, including by Buck's own Melov Lab which studied CRYAB expression and aggregation in human muscle tissues, making it an attractive investigational target.

Recently, Buck investigators in the Melov Lab identified a cholesterol metabolite known as 25-hydroxycholesterol (or 25-HC) that is seen to inhibit CRYAB and reverse its aggregation by acting as a senolytic in multiple cell types. Supporting data has been collected *in vitro* in mouse and human tissues and *in vivo* in mice. This discovery opens the avenue to develop new senolytics for treating a wide range of diseases associated with aging.

APPLICATIONS

- Development of 25-HC or derivatives as a clinical candidate for treating vascular disease, Alzheimer's disease and related dementias, amyloid or other cause-mediated mild cognitive impairment (MCI), brain or spinal cord injury (including, but not limited to stroke), Huntington's disease, and Parkinson's disease.
- Development of 25-HC or derivatives as a clinical candidate for treatment of senescence-associated diseases
- Foundational platform for disease treatment through leveraging CRYAB as a target and 25-HC's ability to inhibit it via senolysis

PUBLICATIONS

Senolysis induced by 25-hydroxycholesterol targets CRYAB in multiple cell types, Limbad et al., *iScience*, Feb 2, 2022

Single nuclei profiling identifies cell specific markers of skeletal muscle aging, frailty, and senescence, Perez et al., *Aging*, Dec 13, 2022

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