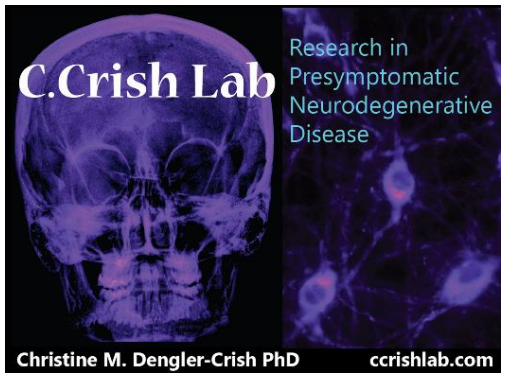

The data presented in **SFN 2019 poster #564.03** directly aligns with work currently being conducted by Integrated Pharmaceutical Medicine Graduate Program doctoral student **Katie Bretland** in the Christine Crish Lab at the Northeast Ohio Medical University (NEOMED).

Katie recently received the Alan & Janice Woll Graduate Assistant Fellowship in Neurodegenerative Disease. This fellowship was made possible by a philanthropic donation to the Neurodegenerative Disease and Aging Research Group at NEOMED to conduct research on the therapeutic effectiveness of the exercise hormone irisin in Alzheimer's disease. Currently, she is working on the following project:

Irisin as a potential neuroprotectant against tauopathy in Alzheimer's and other dementias.

Summary

The recently (2012) identified hormone irisin has been shown to protect against Alzheimer's (AD) related brain pathology. Irisin (also known as FNDC5) is released from muscles, adipose tissue, and brain cells (including neurons and neuroglia) during endurance exercise. In the adult brain, irisin can powerfully elicit BDNF expression in the hippocampus, stimulating neurogenesis. Clinical studies have found AD patients to be deficient in both serum and cerebrospinal fluid levels of irisin compared to age-matched healthy controls. Importantly, deficient irisin is also a feature of major metabolic risk factors of late-onset sporadic AD, which include type II diabetes, hyperlipidemia, and cardiovascular disease. Likewise, exciting preliminary studies show that treatment with exogenous irisin improves insulin resistance, reduces inflammation, and restores metabolic function in these disorders. Critical to our work, there is evidence that irisin may reduce both a) toxic amyloid beta cleavage and b) neuroinflammation in amyloid-dominant experimental models of AD. However, what remains unknown is whether irisin is protective against tauopathy—the other major neuropathological hallmark of AD and other forms of dementia.

Irisin is known to be a systemic mediator of inflammation and enhancer of cellular metabolic function. Studies in cell preparations show that irisin binds directly to APP proteins to prevent toxic amyloid beta cleavage; other work in amyloid-dominant APP/PS1 mice indicates that irisin may also exert its protective effects by reducing neuroinflammation. Of interest to our research, other labs are beginning to find early evidence of **tauopathy** associated with metabolic conditions such as insulin resistance, making tau an interesting target to investigate the effects of metabolic enhancers such as irisin. Tauopathy has always been associated with neuroinflammation in other neurodegenerative diseases, and while its production has been attributed to amyloid beta-driven mechanisms in AD, evidence also suggests that tau hyperphosphorylation (ptau) can arise independently from this toxic peptide. Currently, it is unknown whether irisin can reduce tauopathy or associated neuroinflammation via an amyloid-independent mechanism.

We plan to investigate the broader role of irisin on neuropathology in AD and frontotemporal dementia by determining the impact of irisin treatment on hippocampal ptau expression in a tauopathy-selective neurodegenerative mouse model (htau mice) and determining mechanisms by which this hormone may reduce neuroinflammation.

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