

Novel Compounds with Neuroprotective & Anti-Inflammatory Properties

INVENTION: Salk investigators have developed synthetic derivatives of the naturally occurring flavonoid fisetin that is commonly found in fruits and vegetables. These derivatives retain the neuroprotective and anti-inflammatory properties of the parent molecule but display a lower EC₅₀, and have improved medicinal chemical properties more consistent with those of known CNS drugs.

APPLICATIONS:

- Treating and/or preventing age-related neurological diseases
- Treating diabetic complications
- Amelioration of ischemic damage

ADVANTAGES:

- Improved bioavailability and pharmacological properties compared to parent molecule
- Enhanced neuroprotection
- Enhanced anti-inflammatory activity

STAGE OF DEVELOPMENT:

- Extensive in vitro and chemical modeling data
- Preclinical in vivo data, including ADME (absorption, distribution, metabolism, excretion)

BACKGROUND: Fisetin is a naturally occurring flavonoid commonly found in fruits and vegetables. Studies at the Salk Institute have found that fisetin is able to modulate key pathways involved in neurodegeneration. Although fisetin is effective in Alzheimer's disease as well as other animal models of neurological disorders, its relatively high EC₅₀ in cell-based assays (2-5 μ M) as well as its low lipophilicity (cLogP:1.24), high tPSA, and high number of hydrogen bond donors (n=5) suggest that there is room for improvement if fisetin is to be used therapeutically for CNS disorders. Using structure-activity relationship-driven iterative chemistry, the investigators synthesized more than 160 derivatives of fisetin based on several different chemical scaffolds. They used a multi-tiered approach to screening that allowed them to identify fisetin derivatives with significantly enhanced neuroprotective activity in an in vitro neuroprotection assay while at the same time maintaining other key properties, including anti-inflammatory activity. At least twenty of these derivatives have improved pharmacological properties similar to that of most FDA-approved CNS drugs.

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PATENT STATUS:

U.S. Patents 8,466,195 and 7,987,647.

U.S. patent applications US-2015-0186328-A1 and US-2016-0206609 A1

PUBLICATIONS: Currais, et al., 2014. Modulation of p25 and inflammatory pathways by fisetin maintains cognitive function in Alzheimer's disease transgenic mice. *Aging Cell*, 13:379-390.

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