

New methods to identify Alzheimer's drug candidates with anti-aging properties

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Researchers Pamela Maher and Dave Schubert report new methods to identify Alzheimer's drug candidates that have anti-aging properties. Credit: Salk Institute

Old age is the greatest risk factor for many diseases, including

Alzheimer's disease (AD) and cancer. Geroprotectors are a recently identified class of anti-aging compounds. New Salk research has now identified a unique subclass of these compounds, dubbed geroneuroprotectors (GNPs), which are AD drug candidates and slow the aging process in mice.

"The argument for geroprotectors is that if one can extend the lifespan of model organisms, such as mice, and translate this effect to humans, then you should be able to slow down the appearance of many diseases that are associated with aging, such as Alzheimer's, Parkinson's, cancer and overall frailty," says first author Dave Schubert, Salk professor and head of Salk's Cellular Neurobiology Laboratory

The study, which appeared in the journal *Trends in Pharmacological Sciences*, on November 13, 2018, was conducted in collaboration with Salk Senior Staff Scientist Pamela Maher, whose lab is in the Cellular Neurobiology department and who is the study's senior author.

The team started with two chemicals found in plants that have demonstrated medicinal properties: fisetin, a natural product derived from fruits and vegetables, and curcumin, from the curry spice turmeric. From these, the team synthesized three AD [drug](#) candidates based upon their ability to protect neurons from multiple toxicities associated with the aging brain. The lab showed that these three synthetic candidates (known as CMS121, CAD31 and J147), as well as fisetin and curcumin, reduced the molecular markers of aging, as well as dementia, and extended the median lifespan of mice or flies.

Importantly, the group demonstrated that the molecular pathways engaged by these AD drug candidates are the same as two other well-researched synthetic compounds that are known to extend the lifespan of many animals. For this reason, and based on the results of their previous studies, the team says fisetin, curcumin and the three AD drug

candidates all meet the definition of being geroneuroprotectors.

The group is now focusing on getting two GNPs into [human clinical trials](#). The fisetin derivative, CMS121, is currently in the animal toxicology studies required for FDA approval to start clinical trials. The curcumin derivative, J147, is under FDA review for allowance to start clinical trials for AD early next year. The group plans to incorporate biochemical markers for aging into the [clinical trials](#) to assay for potential geroprotective effects.

"Since we found that the natural products curcumin and fisetin are also GNPs and commercially available as supplements, they could provide some therapeutic benefits right now," says Maher.

Other studies in the lab are determining whether these compounds have effects on organs outside of the brain. "If these drugs have benefits for other body systems, such as maintaining kidney function and overall muscle health, they could be used in additional ways to treat or prevent the diseases of aging," Schubert says.

The investigators say that the discovery of these AD drug candidates validates the drug discovery model they have developed as a plausible method for identifying additional GNP compounds that will help promote healthy aging. This could greatly accelerate the pipeline for drugs to treat the diseases of aging for which there are currently no cures.

More information: David Schubert et al, Geroneuroprotectors: Effective Geroprotectors for the Brain, *Trends in Pharmacological Sciences* (2018). [DOI: 10.1016/j.tips.2018.09.008](https://doi.org/10.1016/j.tips.2018.09.008)

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