

Worming our way to new treatments for Alzheimer's disease

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According to a 2012 World Health Organization report, over 35 million people worldwide currently have dementia, a number that is expected to double by 2030 (66 million) and triple by 2050 (115 million).

Alzheimer's disease, the most common form of dementia, has no cure and there are currently only a handful of approved treatments that slow, but do not prevent, the progression of symptoms.

New drug development, no matter the disease, is a slow, expensive, and risky process. Thus, innovative techniques to study and assess the possibilities of already-existing drugs for different diseases can be used to alleviate the traditional burdens of cost and time. Detailed in their new article in *Biological Psychiatry*, researchers from the University of Washington, led by Dr. Brian Kraemer, have developed an exciting new approach to screening potential new treatments for Alzheimer's disease using *C. elegans*, a small transparent worm.

Their focus was on tau, a protein involved in maintaining brain [cell structure](#). In Alzheimer's disease and related disorders, [tau protein](#) becomes abnormally modified and forms [clumps](#) of protein called aggregates. These aggregates are a hallmark of the dying nerve cells in Alzheimer's disease and other related disorders. Diseases with abnormal tau are called tauopathies.

Dr. Kraemer's lab previously developed a worm model for tauopathy by expressing human tau in *C. elegans* nerve cells. This model has [behavioral abnormalities](#), accumulates abnormal tau protein, and exhibits

loss of nerve cells—all of which are general features of Alzheimer's disease.

Using their worm model for this study, they screened a library of 1,120 drugs approved for human use and tested each at three different concentrations to identify compounds that suppress the effects of abnormal tau aggregation.

"We have identified six compounds capable of reliably alleviating tau induced behavioral abnormalities in our *C. elegans* model for tauopathy. In a human cultured cell model for abnormal tau protein, we have also seen that azaperone treatment can decrease the amount of abnormal tau," said Kraemer.

Azaperone, an antipsychotic drug, normally binds to certain dopamine receptors found in [nerve cells](#). They demonstrated that removing those receptors in either *C. elegans* or human cells has the same effect as azaperone treatment, indicating that azaperone and related drugs should alter abnormal tau accumulation. Other antipsychotic drugs also have a similar effect to azaperone.

Tests of these compounds for anti-tau properties are now underway in existing mouse models of Alzheimer's disease.

"This study is an exemplary instance of how a simple *C. elegans* model system may be used to rapidly screen drugs for diseases and evaluate mechanism of action," said Drs. Sangeetha Iyer and Jonathan Pierce-Shimomura, authors of a commentary that accompanies this article.

Dr. John Krystal, Editor of [Biological Psychiatry](#), agrees and added: "Studying the worm, *C. elegans*, has already provided us with fundamental insights into how the brain develops. The new approach described by McCormick and colleagues suggests that this animal model

may be a powerful new approach to studying novel treatments that prevent its decline."

More information: The article is "Dopamine D2 Receptor Antagonism Suppresses Tau Aggregation and Neurotoxicity" by Allyson V. McCormick, Jeanna M. Wheeler, Chris R. Guthrie, Nicole F. Liachko, and Brian C. Kraemer ([doi: 10.1016/j.biopsych.2012.08.027](https://doi.org/10.1016/j.biopsych.2012.08.027)). The commentary is "Worming Our Way to Alzheimer's Disease Drug Discovery" by Sangeetha Iyer and Jonathan T. Pierce-Shimomura ([doi: 10.1016/j.biopsych.2012.12.026](https://doi.org/10.1016/j.biopsych.2012.12.026)). Both appear in *Biological Psychiatry*, Volume 73, Issue 5 (March 1, 2013)

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