New drug screening method answers why Alzheimer's drugs fail, suggests new targets

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By analyzing disease mechanisms in human neurons, researchers led by the University of California San Diego developed a new method to screen drugs for treating Alzheimer's disease. Their work sheds light on why Alzheimer's drugs so far have been ineffective at curing or reversing the disease and identifies new targets for drug development.

The findings, reported in a paper published Jan. 27 in *Alzheimer's &*

Dementia: The Journal of the Alzheimer's Association, could help pave the way for radically new therapeutic approaches to treating Alzheimer's.

Drug development for Alzheimer's has long been driven by the hypothesis that amyloid plaques—formed by the buildup of amyloid-beta proteins in the brain—are what kill neurons and cause Alzheimer's. As a result, many research efforts have focused on designing drugs that clear out these plaques.

"But this approach has not led to a cure or improved dementia in patients. Sometimes it has made the disease worse," said senior author Shankar Subramaniam, a professor of bioengineering at the UC San Diego Jacobs School of Engineering.

To understand why, Subramaniam and his collaborators developed a drug screening method that looks at what disease mechanisms, or endotypes, change in patients' neurons as a result of treatment. The most widely studied Alzheimer's endotype is amyloid plaque formation. But there are other endotypes—reported for the first time by Subramaniam and colleagues in a previous study—that also warrant attention. These include de-differentiation of neurons to an earlier "non-neuron" cell state; suppression of neuronal genes; and loss of synaptic connections.

"This is a new test for measuring whether an Alzheimer's drug works," said Subramaniam. "The key here is that we are using the endotypes that we discovered to see how current drugs fail. When drugs interact with human neurons, what endotypes do the drugs fix, and what endotypes do they not fix in the process?"

What's also special about this method is that it screens drugs on actual patient cells. "The power of this is that you can do precision medicine and have a good model system to study Alzheimer's," said Subramaniam.

The method involves taking human induced pluripotent stem cells derived from patients with familial Alzheimer's disease, which is a hereditary form of Alzheimer's, and transforming them into neurons. The researchers treat these neurons with drugs and use next generation sequencing techniques to evaluate what endotypes change before and after treatment. The researchers also perform this drug screen on neurons derived from healthy individuals as a control experiment.

In this study, the researchers screened two experimental Alzheimer's drugs that were designed to reduce or prevent growth of amyloid plaques. One was a drug candidate developed by Eli Lilly, called semagacestat, which had failed late-stage clinical trials. The other was a drug candidate developed by Subramaniam's collaborator and co-author on the study, Steven Wagner, who is a professor of neurosciences at UC San Diego School of Medicine.

The researchers found that the drugs only fix some endotypes, such as the formation of amyloid plaques. The drugs also partly fix the de-differentiation endotype, by triggering "non-neuron" cells to transform back into neurons. However, this transformation is not complete, noted Subramaniam, because the neurons still lack synaptic connections and therefore cannot communicate with each other.

"Now we have a prescription for what endotypes to target during drug screening," said Subramaniam. "What we are seeing is that fixing amyloid plaque formation does not reverse the disease in any way. It turns out that this endotype is way downstream, so it's too late. Once neurons de-differentiate into non-neurons, they lose their synaptic connections, which leads to loss of memory and cognition and as a consequence, dementia."

"I am very excited to use these novel screening strategies for the Alzheimer's drugs that are being developed in my laboratory," added

Wagner. "In my experience in industry and now academia, this is the first effort to use multiple endotypes for overcoming the failures of drugs targeted only at amyloid plaques."

Next, the researchers will evaluate their drug screening method on brain organoids. "We want to take this a step further to screen drugs on more realistic tissues, not just neurons in a dish," said Subramaniam. The team will also work on developing new Alzheimer's drug candidates and screening them with their method.

More information: Andrew B. Caldwell et al, Endotype reversal as a novel strategy for screening drugs targeting familial Alzheimer's disease, *Alzheimer's & Dementia* (2022). DOI: 10.1002/alz.12553

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