

Early-stage drug candidate diminishes deficits in Parkinson's disease

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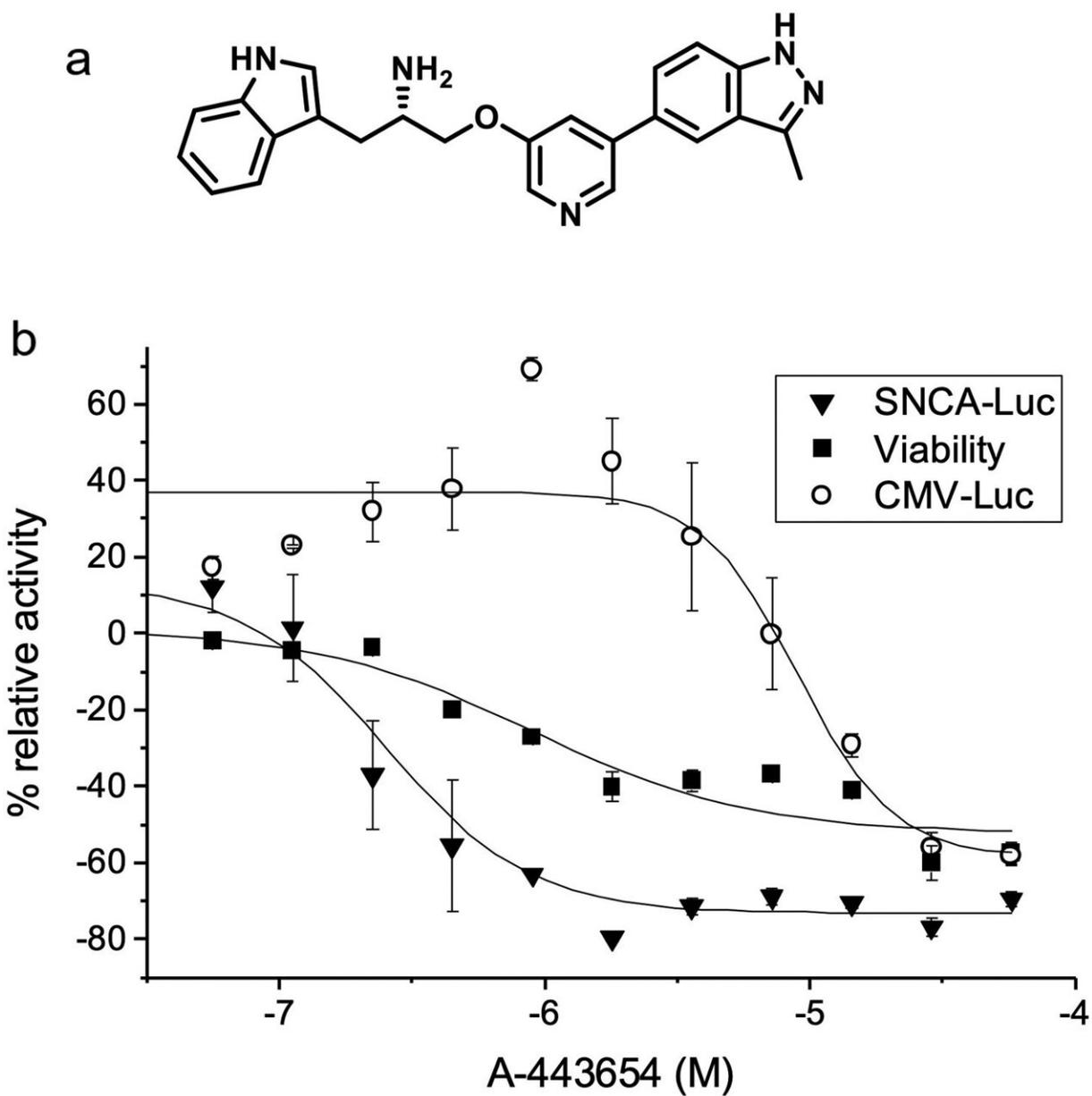


Figure 1. Activity of A-443654 in qHTS assays. (a) Molecular structure of A-443654. (b) Relative luciferase activity in SNCA-Luc (IC₅₀=251 nM, triangles), CMV-luc (open circles) and viability (squares) of SNCA-luc cells measured after 24 hrs of treatment with A-443654 at the indicated doses. Credit: DOI: 10.1016/j.jbc.2021.101191

University of Utah Health scientists have identified a molecule that slows cells' production of alpha-synuclein, a protein that forms toxic aggregates in the brains of people with Parkinson's disease. Its discovery points toward a new strategy for treating the disease and potentially stopping its progression.

Researchers led by Associate Professor of Neurology Daniel Scoles, Ph.D., reported on the molecule, known as A-443654 in the *Journal of Biological Chemistry*.

More than 10 million people worldwide live with Parkinson's [disease](#), a neurodegenerative disorder that causes problems with movement and balance. These symptoms, which worsen as the disease progresses, are due to the loss of dopamine-producing neurons in the brain. Medications that mimic dopamine or boost the neurotransmitter's levels in the brain can help control symptoms. But existing therapies do not eliminate the disease or stop its progression.

As researchers seek better options for patients, many have their sights set on [alpha-synuclein](#). In healthy brains, alpha-synuclein is thought to help nerve cells communicate. But in patients with Parkinson's disease and certain other neurodegenerative disorders, including Lewy body dementia and multiple system atrophy, alpha-synuclein molecules stick to one another and form abnormal aggregates inside neurons. As the protein coalesces into slender fibrils and larger aggregates, it interferes

with the cells' health and, scientists suspect, eventually kills them.

While the exact cause of neuron death in Parkinson's disease is not known, alpha-synuclein seems to be a significant instigator. "Most cases of Parkinson's disease are characterized by an overabundance of alpha-synuclein," explains Scoles. "The prevailing thought is that if you lower its overall abundance, this would be therapeutic."

Scoles and colleagues hoped to achieve this by finding a way to rein in cells' production of the potentially toxic protein. Duong Huynh, Ph.D., a Research Associate Professor at Department of Neurology in the Department of Neurology, devised a novel way of conducting the search.

Using gene editing tools, he inserted a gene that encodes a light-producing protein from fireflies into lab-grown [human cells](#), positioning it where it would be turned on whenever the alpha-synuclein gene was active. Under the right growing conditions, the human cells glow when the alpha-synuclein gene is on. When that gene becomes less active, the light dims.

Huynh teamed up with Scoles, Stefan Pulst, M.D., Dr. Med, Chair of the Department of Neurology, and researchers at the National Center for Advancing Translational Sciences (NCATS) to put the light-producing cells to work, screening a vast collection of small molecules for their effects on the alpha-synuclein gene.

Millions of assays were performed to evaluate 155,885 different compounds using a high-throughput, robotic setup in an NCATS facility. A-443654 emerged from those analyses as a likely inhibitor of alpha-synuclein production. Postdoctoral researcher Mandi Gandelman, Ph.D., who joined the project after Dr. Huynh's death in 2018, conducted further tests and found that A-443654 not only dialed down activity of the alpha-synuclein gene in human cells—including neurons derived

from the cells of a patient with Parkinson's disease—it also reduced the translation of RNA copies of the gene into alpha-synuclein protein.

Gandelman says there were other signs of the compound's therapeutic potential, as well. When alpha-synuclein aggregates accumulate and grow, they stress the systems that cells use to deal with broken, misshapen, or otherwise unwanted proteins. Gandelman's experiments indicated that A-443654 can alleviate this stress. That's a sign that [cells](#) are no longer overwhelmed by high levels of alpha-synuclein; it may also free up those systems to break down aggregates that have already formed. "We can stop production, but we also need to degrade what's already in aggregate," Gandelman says. "The more aggregated this is, the more toxic it becomes."

Further research is needed to determine whether A-443654 itself can be developed into a potential treatment for Parkinson's disease or other disorders involving alpha-synuclein aggregates. Meanwhile, the team also plans to explore additional molecules that their screen identified as potential inhibitors of alpha-synuclein production.

More information: Mandi Gandelman et al, The AKT modulator A-443654 reduces α -synuclein expression and normalizes ER stress and autophagy, *Journal of Biological Chemistry* (2021). [DOI: 10.1016/j.jbc.2021.101191](#)

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