Researchers identify a potential new therapeutic target in Parkinson's disease

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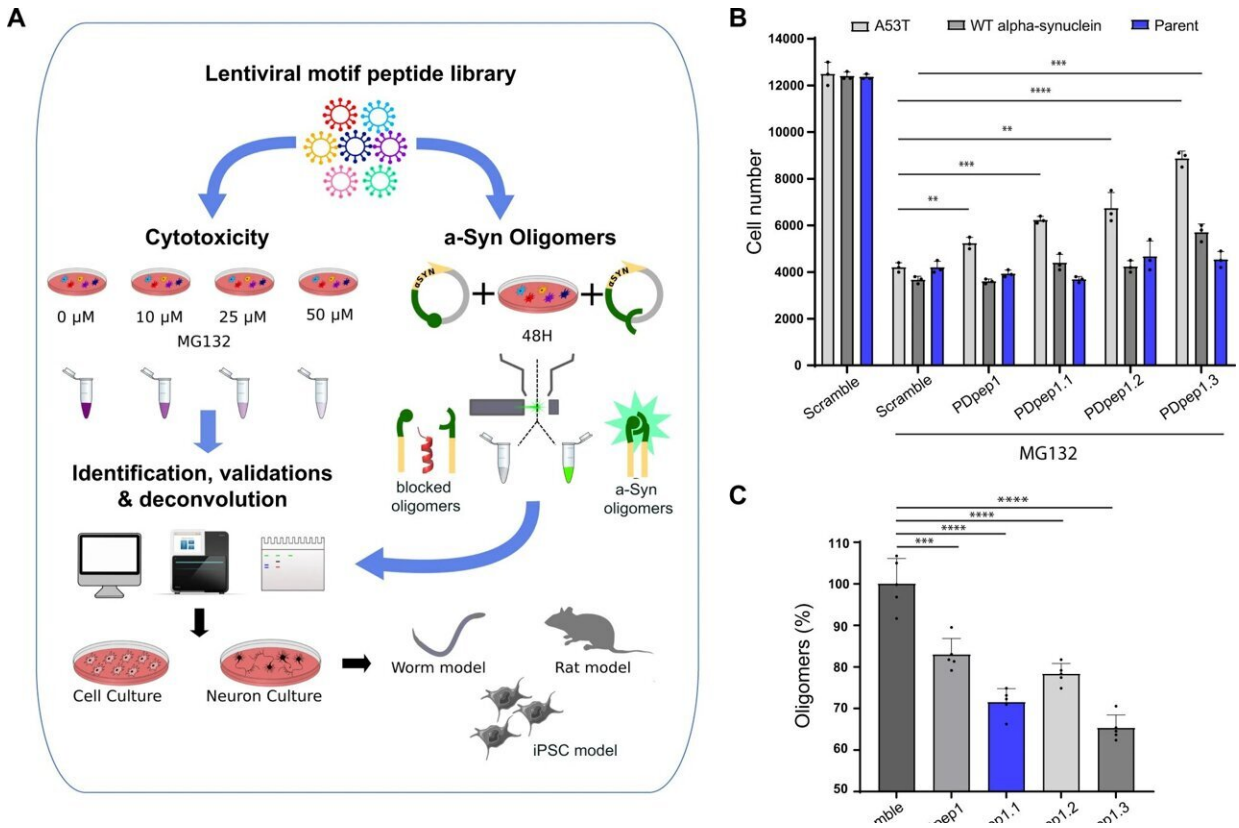

Proteomic screens and in vitro validation of hits. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-37464-2

In a study published in *Nature Communications*, a team led by Krembil Brain Institute at UHN Senior Scientists, Drs. Lorraine Kalia and Suneil

Kalia, and University of Toronto (U of T) Professor, Dr. Philip M. Kim, has identified a protein-protein interaction that contributes to Parkinson's disease.

In the disease, a protein called α-synuclein (a-syn) accumulates in the brain and leads to cell death. Much research is currently focused on clearing a-syn with antibodies or using small molecules to prevent a-syn from aggregating. In this study, the researchers took an alternate approach by looking for protein-protein interactions that may be promoting the accumulation of a-syn in Parkinson's disease.

Protein-protein interactions govern virtually all the inner workings of the cell, including breaking down disease-causing proteins. Inhibiting certain interactions has emerged as a promising approach to treat diseases such as stroke and cancer.

"Identifying a particular interaction that contributes to a disease and then finding ways to disrupt it, can be a painstaking and incredibly slow process," explains Dr. Lorraine Kalia, who is also a staff neurologist at UHN and a scientist at U of T's Tanz Centre for Research in Neurodegenerative Diseases, in the Temerty Faculty of Medicine.

"We all started out a bit skeptical that we would have something useful at the end, and so the fact that we do have something that warrants further work is much more than we anticipated," says Dr. Kalia.

According to Dr. Kim, the team took the reverse approach to expedite the discovery of potential therapies: "We developed a platform to screen molecules called peptide motifs—short strings of amino acids that can disrupt protein-protein interactions—for their ability to protect cells from a-syn. Once we identified candidate peptides, we determined which protein-protein interactions they target."

Through this approach, the team identified a peptide that reduced a-syn levels in cells by disrupting the interaction between a-syn and a protein subunit of the cellular machinery called endosomal sorting complex required for transport III (ESCRT-III).

"ESCRT-III is a component of a pathway that cells use to break down proteins, called the endolysosomal pathway," explains Dr. Lorraine Kalia. "We discovered that a-syn interacts with a protein within ESCRT-III—CHMP2B—to inhibit this pathway, thereby preventing its own destruction.

"We were impressed that the platform worked," she adds. "But I think what was more interesting is that, by doing this kind of screening, we were able to find an interaction that was really not previously characterized, and we also found a pathway that's not yet been targeted for therapeutics."

According to Dr. Suneil Kalia, once the group identified this interaction, they confirmed that they could use their peptide to disrupt it, preventing a-syn from evading the cell's natural clearance pathways.

"We tested the peptide in multiple experimental models of Parkinson's disease, and we consistently found that it restored endolysosomal function, promoted a-syn clearance and prevented cell death," he said.

These findings indicate that the a-syn-CHMP2B interaction is a potential therapeutic target for the disease, as well as other conditions that involve a buildup of a-syn, such as dementia with Lewy bodies.

The next steps for this research are to clarify exactly how a-syn and CHMP2B interact to disrupt endolysosomal activity. Ongoing studies are also determining the best approach for delivering potential therapeutics to the brain.

"This research is still in its early stages—more work is definitely needed to translate this peptide into a viable therapeutic," cautions Dr. Lorraine Kalia. "Nonetheless, our findings are very exciting because they suggest a new avenue for developing treatments for Parkinson's disease and other neurodegenerative conditions."

This study also highlights the value of multidisciplinary collaborations in health research.

"We simply could not have conducted this study in a silo," says Dr. Suneil Kalia. "The endolysosomal pathway is underexplored, so it was not an obvious place to look for potential disease-related protein-protein interactions. Dr. Kim's screening platform was critical for pointing us in the right direction."

"It is extraordinary to see this platform—which we initially used to find potential therapeutics for cancer—yielding advances in brain research. The pathways that cells use to stay healthy are fundamentally very similar across tissues, so the insights that we gain about one organ system or disease could have important implications in other contexts," says Dr. Kim.

"This is our first collaboration with Dr. Kim and it has been a productive one with a lot of synergy," says Dr. Lorraine Kalia. "Seeking out technologies that are being used in other fields and applying them to our own field, we hope this will accelerate Parkinson's research."

She adds, "It's really brand new science and brand new targets that haven't been a focus for drug development for Parkinson's. We hope this changes the landscape for treatment of this disease, which is so in need of new therapies."

More information: Satra Nim et al, Disrupting the α-synuclein-

ESCRT interaction with a peptide inhibitor mitigates neurodegeneration in preclinical models of Parkinson's disease, *Nature Communications* (2023). DOI: 10.1038/s41467-023-37464-2