

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

"We found a peptide that's never been described before, an interaction that's never been appreciated before, and a potential new avenue for therapeutics in Parkinson's disease"

TORONTO - In a study published in [Nature Communications](#), a team led by Krembil Brain Institute Senior Scientists, Drs. Lorraine Kalia and Suneil Kalia, and University of Toronto (U of T) Professor, Dr. Philip M. Kim, 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."

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.”

This work was supported by the Canadian Institutes of Health Research, the Michael J. Fox Foundation for Parkinson’s Research, Parkinson’s UK, the Canada Foundation for Innovation, the Ontario Research Fund, the Krembil Research Institute and the UHN Foundation. Dr. Lorraine Kalia is an Associate Professor in the Division of Neurology, Department of Medicine, and in the Department of Laboratory Medicine and Pathobiology, at U of T. Dr. Suneil Kalia is an Associate Professor in the Division of Neurosurgery, Department of Surgery, and the R.R. Tasker Chair in Stereotactic and Functional Neurosurgery at UHN. Dr. Philip Kim is a Professor and Principal Investigator in the Department of Molecular Genetics, Donnelly Centre for Cellular and Biomolecular Research, UofT.

The University of Toronto submitted a patent application covering the composition and use of the peptides and screening methods outlined in this study, with Drs. Satra Nim, Carles Corbi-Verge, Suneil Kalia, Lorraine Kalia and Philip Kim as inventors. Drs. Suneil Kalia, Lorraine Kalia and Philip Kim co-founded Synepark Therapeutics Inc. to commercialize aspects of this research.

About the Krembil Brain Institute

The Krembil Brain Institute at Toronto Western Hospital, part of University Health Network, is home to one of the world’s largest and most comprehensive teams of physicians and scientists uniquely working hand-in-hand to prevent and confront problems of the brain and spine. One

in three Canadians will experience a brain-related condition such as Parkinson's, Alzheimer's or epilepsy in their lifetime. Through state-of-the-art patient care and advanced research, we are working relentlessly to find new treatments and cures. For more information:

<https://www.uhn.ca/krembil>

About University Health Network

University Health Network consists of Toronto General and Toronto Western Hospitals, the Princess Margaret Cancer Centre, Toronto Rehabilitation Institute, and The Michener Institute of Education at UHN. The scope of research and complexity of cases at University Health Network has made it a national and international source for discovery, education and patient care. It has the largest hospital-based research program in Canada, with major research in cardiology, transplantation, neurosciences, oncology, surgical innovation, infectious diseases, genomic medicine and rehabilitation medicine. University Health Network is a research hospital affiliated with the University of Toronto. For more information: <https://www.uhn.ca/>

About the Temerty Faculty of Medicine at the University of Toronto:

The Temerty Faculty of Medicine at the University of Toronto is at the centre one of North America's largest biomedical research, education and clinical care networks. With nine fully affiliated research-intensive hospitals — and dozens of community and clinical care sites — Temerty Medicine offers unparalleled opportunities in Canada's most dynamic city for our more than 9,000 faculty and staff and 7,000 learners at all levels. For more information:

<https://temertymedicine.utoronto.ca/>

MEDIA CONTACTS:

Heather Sherman

Communications Manager, Krembil Brain Institute/UHN

Heather.sherman@uhn.ca

Jim Oldfield

Senior Communications Officer, Temerty Faculty of Medicine/U of T

jim.oldfield@utoronto.ca