Targeting 'undruggable' proteins promises new approach for treating neurodegenerative diseases

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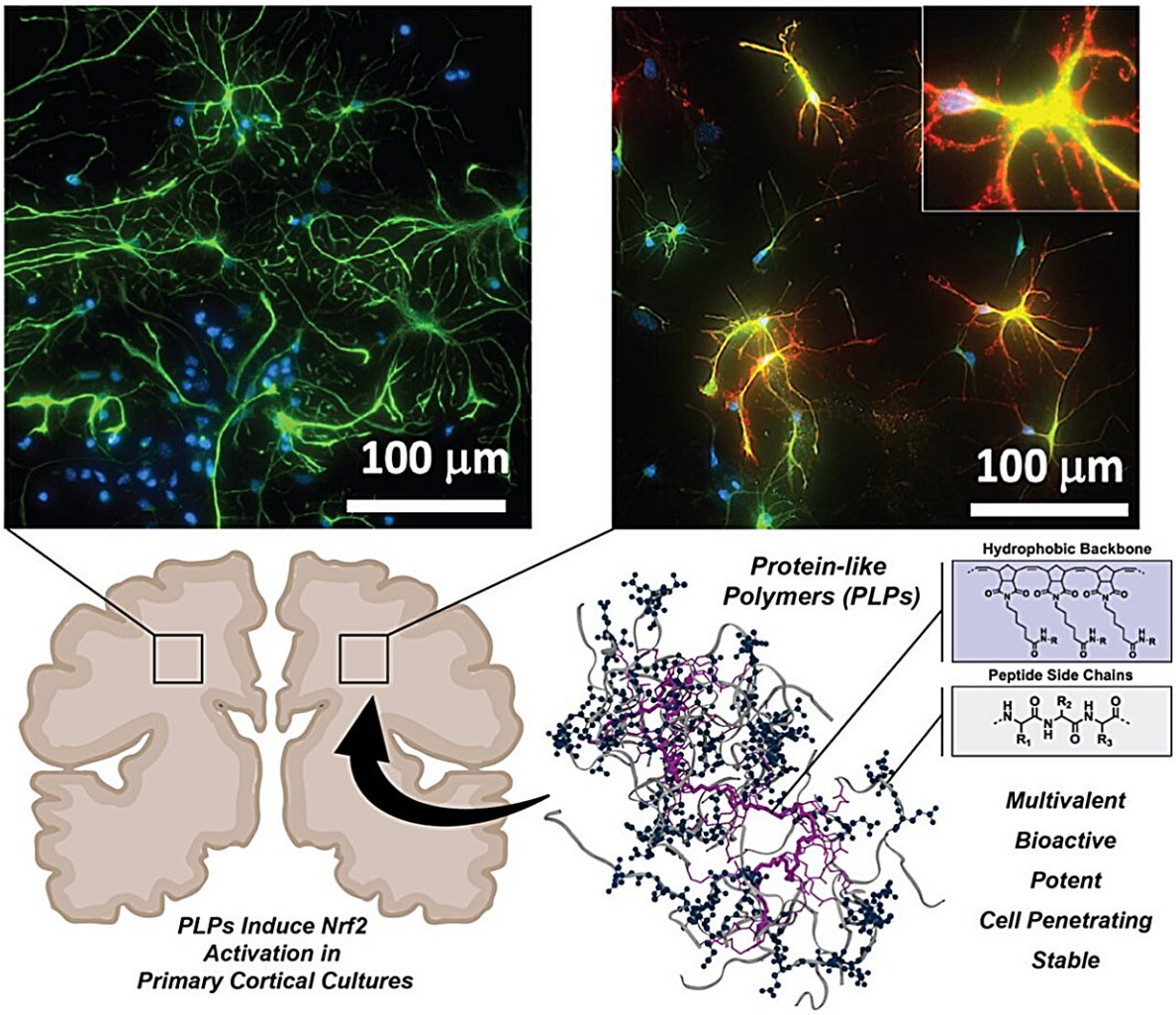

Proteins are nature's polymers, governing biological processes at every level. A new study presents artificial proteins made using modern, precision polymers to

intervene and alter natural processes towards a new way of developing therapeutics. Credit: Northwestern University/University of Wisconsin

Researchers led by Northwestern University and the University of Wisconsin-Madison have introduced a pioneering approach aimed at combating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic lateral sclerosis (ALS).

In a new study, researchers discovered a new way to enhance the body's antioxidant response, which is crucial for cellular protection against the oxidative stress implicated in many neurodegenerative diseases.

The study published today in the journal *Advanced Materials*.

Nathan Gianneschi, the Jacob & Rosaline Cohn Professor of Chemistry at Northwestern's Weinberg College of Arts and Sciences and member of the International Institute for Nanotechnology, led the work with Jeffrey A. Johnson and Delinda A. Johnson of the University of Wisconsin-Madison School of Pharmacy.

Targeting neurodegenerative diseases

Alzheimer's disease, characterized by the accumulation of beta-amyloid plaques and tau protein tangles; Parkinson's disease, known for its loss of dopaminergic neurons and presence of Lewy bodies; and ALS, involving the degeneration of motor neurons, all share a common thread of oxidative stress contributing to disease pathology.

The study focuses on disrupting the Keap1/Nrf2 protein-protein interaction (PPI), which plays a role in the body's antioxidant response. By preventing the degradation of Nrf2 through selective inhibition of its

interaction with Keap1, the research holds promise for mitigating the cellular damage that underlies these debilitating conditions.

"We established Nrf2 as a principal target for the treatment of neurodegenerative diseases over the past two decades, but this novel approach for activating the pathway holds great promise to develop disease-modifying therapies," Jeffrey Johnson said.

Limitations of current therapeutics

The research team embarked on addressing one of the most challenging aspects of neurodegenerative disease treatment: the precise targeting of PPIs within the cell. Traditional methods, including small molecule inhibitors and peptide-based therapies, have fallen short due to lack of specificity, stability and cellular uptake.

The study introduces an innovative solution: protein-like polymers, or PLPs, are high-density brush macromolecular architectures synthesized via the ring-opening metathesis polymerization (ROMP) of norbornenyl-peptide-based monomers. These globular, proteomimetic structures display bioactive peptide side chains that can penetrate cell membranes, exhibit remarkable stability and resist proteolysis.

This targeted approach to inhibit the Keap1/Nrf2 PPI represents a significant leap forward. By preventing Keap1 from marking Nrf2 for degradation, Nrf2 accumulates in the nucleus, activating the Antioxidant Response Element (ARE) and driving the expression of detoxifying and antioxidant genes. This mechanism effectively enhances the cellular antioxidant response, providing a potent therapeutic strategy against the oxidative stress implicated in many neurodegenerative diseases.

The innovation behind protein-like polymers

PLPs, developed by Gianneschi's team, could represent a significant breakthrough in halting or reversing damage offering hope for improved treatments and outcomes.

Focusing on the challenge of activating processes crucial for the body's antioxidant response, the team's research offers a novel solution. The team provides a robust, selective method enabling enhanced cellular protection and offering a promising therapeutic strategy for a range of diseases including neurodegenerative conditions.

"Through modern polymer chemistry, we can begin to think about mimicking complex proteins," Gianneschi said. "The promise lies in the development of a new modality for the design of therapeutics. This could be a way to address diseases like Alzheimer's and Parkinson's among others where traditional approaches have struggled."

This approach not only represents a significant advance in targeting transcription factors and disordered proteins, but also showcases the PLP technology's versatility and potential to revolutionize the development of therapeutics. The technology's modularity and efficacy in inhibiting the Keap1/Nrf2 interaction underscore its potential for impact as a therapeutic, but also as a tool for studying the biochemistry of these processes.

A collaboration of minds

Highlighting the study's collaborative nature, Gianneschi's team worked closely with experts across disciplines, illustrating the rich potential of combining materials science with cellular biology to tackle complex medical challenges.

"We were contacted by Professor Gianneschi and colleagues proposing to use this novel PLP technology in neurodegenerative diseases due to

our previous work on Nrf2 in models of Alzheimer's disease, Parkinson's disease, ALS and Huntington's disease," Jeffrey Johnson said. "We had never heard of this approach for Nrf2 activation and immediately agreed to initiate this collaborative effort that led to the generation of great data and this publication."

This partnership underscores the importance of interdisciplinary research in developing new therapeutic modalities.

Impact

With the development of this innovative technology, Gianneschi and his colleagues at the International Institute for Nanotechnology and the Johnson Lab at the University of Wisconsin-Madison, are not just advancing the field of medicinal chemistry, they are opening new pathways to combat some of the most challenging and devastating neurodegenerative diseases faced by society today. As this research progresses towards clinical application, it may soon offer new hope to those suffering from diseases of oxidative stress such as Alzheimer's and Parkinson's diseases.

"By controlling materials at the scale of single nanometers, we're opening new possibilities in the fight against diseases that are more prevalent than ever, yet remain untreatable," Gianneschi said. "This study is just the beginning. We're excited about the possibilities as we continue to explore and expand the development of macromolecular drugs, capable of mimicking some of the aspects of proteins using our PLP platform."

More information: Kendal P. Carrow et al, Inhibiting the Keap1/Nrf2 Protein-Protein Interaction with Protein-Like Polymers, *Advanced Materials* (2024). DOI: 10.1002/adma.202311467

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