Breakthrough Prize for Life Science

Jeffery Kelly, Ph.D.

Pioneering biochemist **Jeffery Kelly, Ph.D.**, has been awarded a $3 million *Breakthrough Prize* for demonstrating that nervous system and heart diseases can be caused by protein clumping-associated toxicity, and for inventing a medication to slow progression of such diseases.

The 2022 *Breakthrough Prizes* in Fundamental Physics, Life Sciences and Mathematics are recognized as one of the world's most prestigious science prizes. Kelly's award, one of three life science prizes announced Thursday, recognizes transformative advances in the understanding of neurological disease.

"It is a tremendous honor to receive the *Breakthrough Prize* and to be included in the terrific company of this year's other recipients and those of years past," says Kelly, the Lita Annenberg Hazen Professor of Chemistry at **Scripps Research**, a Professor of Molecular Medicine, and a Scripps Research Trustee.

Scripps Research President and CEO **Peter Schultz, Ph.D.**, notes that Kelly has been a leader in the field of protein misfolding and aggregation, helping illuminate its role in neurodegenerative disease progression.

"His breakthrough was in translating our knowledge of protein folding diseases to a human therapeutic through rational, structure-based drug design to prevent protein aggregation," Schultz says. "The impact of this work on patients with transthyretin cardiomyopathy has been transformational."

In its announcement, the **Breakthrough Prize Foundation** noted that Kelly's work impacts scientific understanding of Alzheimer's and beyond. A hallmark of the brains of people with Alzheimer's is the presence of abnormal beta-amyloid plaques.

Proteins are built from genetic instructions within the cell. As they are built, they fold into origami-like shapes that are key to their function. Mistakes in folding, or ability to maintain a fold, can create misshapen clumps inside or outside cells. This process contributes to degenerative diseases, as with alpha-synuclein in Parkinson's and beta-amyloid in Alzheimer's.

Kelly has spent much of his career asking whether neurodegenerative disease could be stopped by preventing the clumping of a normal protein into amyloid plaques. These toxic substances can wreak havoc beyond the brain. Kelly notes that around 40 diseases have been named after the amyloid structure, including a rare inherited or sporadic condition called transthyretin amyloidosis. It leads to progressive damage to the eyes, heart, and peripheral, autonomic and central nervous systems.

Through painstaking work, Kelly designed molecules that stabilize proteins in their correct shapes, much like a stick jammed into the spokes of a wheel can stop it from turning. In this way, Kelly and colleagues created a first-in-class treatment for transthyretin amyloidosis, including cardiomyopathy, a stiffening and thickening of heart muscle. They also raised hope for treating other protein clumping diseases.

His drug tafamidis, sold under the brand names Vyndaqel® and Vyndamax®, was initially approved in more than 40 countries for treatment of polyneuropathy. The U.S. Food and Drug Administration and additional regulators recently approved tafamidis for treatment of the heart condition transthyretin amyloid cardiomyopathy.

"Through the fashioning of small molecule drugs that can stabilize proteins against abnormal protein aggregation, I think we learned two really important things," Kelly says. "One is the process of protein aggregation really does drive neurodegeneration. The second is that treating these patients early is absolutely critical."

To that end, Kelly is now teaming with other experts at Scripps Research on a strategy to aid early diagnosis and improve the body's ability to clear toxic protein clumps.

"There are 40ish proteins that have the propensity to aggregate and lead to either peripheral and/or central nervous system degeneration," Kelly says. "It has taken us 25 years to develop a drug to slow one of these, so everything we do in the lab is now focused on developing drugs that have the potential to treat multiple amyloid diseases."

The Breakthrough Prize was founded by the innovators behind Facebook and Google. Each prize is $3 million and presented in the fields of Life Sciences (three per year), Fundamental Physics (one per year) and Mathematics (one per year). The Breakthrough Prizes were founded by Sergey Brin, Priscilla Chan and Mark Zuckerberg, Yuri and Julia Milner, and Anne Wojcicki. Information on the *Breakthrough Prize* is available at breakthroughprize.org.

Kelly earned his Ph.D. in organic chemistry at the University of North Carolina and went on to Rockefeller University for postdoctoral work. He joined Scripps Research in 1997, and served as dean of the Skaggs Graduate School of Chemical and Biological Sciences from 2000 to 2008.

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