

Computer simulations developed by Andreas Vitalis, a graduate student in the lab of biophysicist Rohit V. Pappu, PhD (below), may have revealed a major source of harm to nerve cells. This image shows the beginning of a link between two polyglutamine molecules that contain multiple copies of the amino acid glutamine. Such links could spontaneously allow polyglutamine to form larger molecules known as disordered oligomers. Pappu's lab has been a leader in research to understand the structure of oligomers and why they may be harmful.

Tracing molecular missteps

Rohit V. Pappu, PhD *Associate Professor of Biomedical Engineering*
Hope Center Program on Protein Folding and Neurodegeneration

Part of the work of biophysicist Rohit V. Pappu, PhD, concentrates on how proteins clump together.

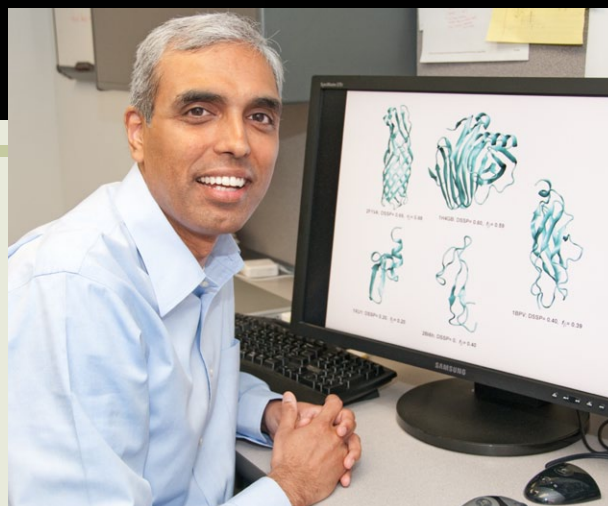
This research is relevant to Huntington's disease — which affects balance, speech and muscle strength, and typically causes death within 20 years — as well as eight other inherited neurodegenerative diseases. All are technically termed polyglutamine expansion disorders, and that means that the affected person produces a protein with an abnormal stretch containing many units of the amino acid glutamine.

In research that answered a long-standing question about why proteins rich in polyglutamine should aggregate, Pappu and coworkers showed that despite the purported "water-loving" nature of glutamine, polyglutamine molecules behave like readily aggregating "greasy" molecules. These findings were

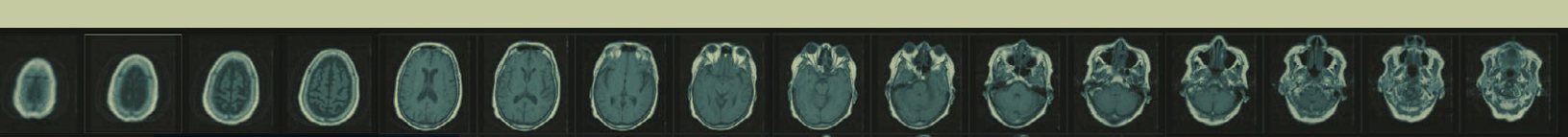
made using novel fluorescence measurements coupled with polymer theory and computer simulations.

Further work showed that this aggregation depends on the length of the polyglutamine stretch. "We showed that the inability of individual polyglutamine molecules to fold into well-defined three dimensional structures promotes aggregation," Pappu says. "By aggregating, the polyglutamine molecules interact to achieve structures that individual polyglutamine molecules cannot achieve on their own."

Pappu is also part of a project led by Jin-Moo Lee, MD, PhD, associate professor of neurology, and Carl Frieden, PhD, professor of biochemistry and molecular biophysics. The study showed that cells take up small



amounts of amyloid beta (Aβeta) — peptides that make up extracellular plaques in brains of people with Alzheimer's disease. Using neuroblastoma cells — malignant but easy-to-work-with cells representative of neurons — the researchers administered Aβeta to cells in small, physiologically relevant amounts. They found that the cells took up Aβeta and packed it into lysosomes, specialized acidic pouches within cells that digest unwanted proteins. However, the acidic conditions and confined space within lysosomes provide conditions that are conducive to Aβeta aggregation, whereby "nature's protection appears to end up becoming a problem."



“In 2004, Hope Happens approached us about working together,” Goldberg recalls. “It was good timing for both groups. We had a plan in place, and it was just what they were looking for. Neurological science was advancing so rapidly that it was time to begin thinking hard about moving quickly to treatments.”

Organizing the science

To that end, the Hope Center set out to explore neurological diseases’ common mechanisms and effects on brain cells at the level of genes and molecules. Two basic research themes developed. The first, the Hope Center Program on Protein Misfolding and Neurodegeneration, is based on the idea that in neurodegenerative diseases, proteins somehow fold incorrectly after they are formed and then create problems as they aggregate. The program will be one of five Interdisciplinary Research Centers (IRCs) formed under BioMed 21, the university’s translational research initiative. Led by Holtzman and Alison Goate, PhD, the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry, the IRC involves 25 researchers whose teams will occupy five laboratories in the new BJC Institute for Health building — the hub for BioMed 21 — when the School of Medicine and Barnes-Jewish Hospital open its doors in January 2010.

Among numerous researchers who have made notable discoveries is Timothy M. Miller, MD, PhD, assistant professor of neurology and director of the Hope Center’s Christopher Hobler Laboratory. Miller’s innovative therapy for ALS that targets the mechanism of protein misfolding has advanced to human trials.

The second major research thrust at the Hope Center is the Program in Axon Injury and Repair. Investigators are seeking to understand how neuronal axons degenerate — with the new realization that when an axon is damaged, the fiber itself triggers a new pathway of active degeneration that could be interrupted with an entirely new kind of treatment. Jeffrey D. Milbrandt, MD, PhD, the David Clayson Professor of Neurology, found that a particular molecule arrests the process and then described the pathway; therapies have since been licensed for clinical development. And in April 2009 — in another example among many — Aaron DiAntonio, MD, PhD, associate professor of developmental biology, discovered a complementary second pathway leading to axon degeneration, suggesting treatments with powerful potential.

“We’re getting so close to truly understanding neurodegenerative disorders and are making headway with new therapies,” says Holtzman, who credits the Hope Center’s infrastructure for its success in both research and funding. He chairs a steering committee of senior scientists (Goate, Goldberg, Milbrandt and Eugene M. Johnson Jr., PhD, professor of neurology and of molecular biology and pharmacology) to evaluate progress, with oversight from the Hope Center’s executive committee. Matthew J. Stowe, JD, administrative director, coordinates the overall team effort.

Eliminating barriers

Still another way the Hope Center ensures progress is by knocking down conventional barriers, creating smoother, faster pathways to translation. In addition to putting the right minds together to solve complicated problems — such as matching basic scientists with clinicians — administrators have provided core facilities for animal models, amyloid-beta microdialysis, neuroimaging and transgenic and viral vectors. New facilities, equipment and instrumentation — most recently, the medical school’s first atomic force microscope — are added, funding permitting, in response to investigators’ needs. And a new collaboration with the Office of Technology Management recently has been implemented to help scientists disclose and patent inventions and to ready their ideas for biotechnology or drug company licensing.

“In one sense, it’s good that our researchers are distributed across the campuses,” says Goldberg. “They can work near their home departments without changing affiliations and neighbors. The only downside is that while we gather regularly, we don’t interact every day. Bumping into people in a hallway can be at the heart of science. Finding new ways to bring scientists together — now, there is a challenge!”

A Danforth Foundation challenge strengthens the Hope Center’s promise for developing better treatments: Please see page 26.

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