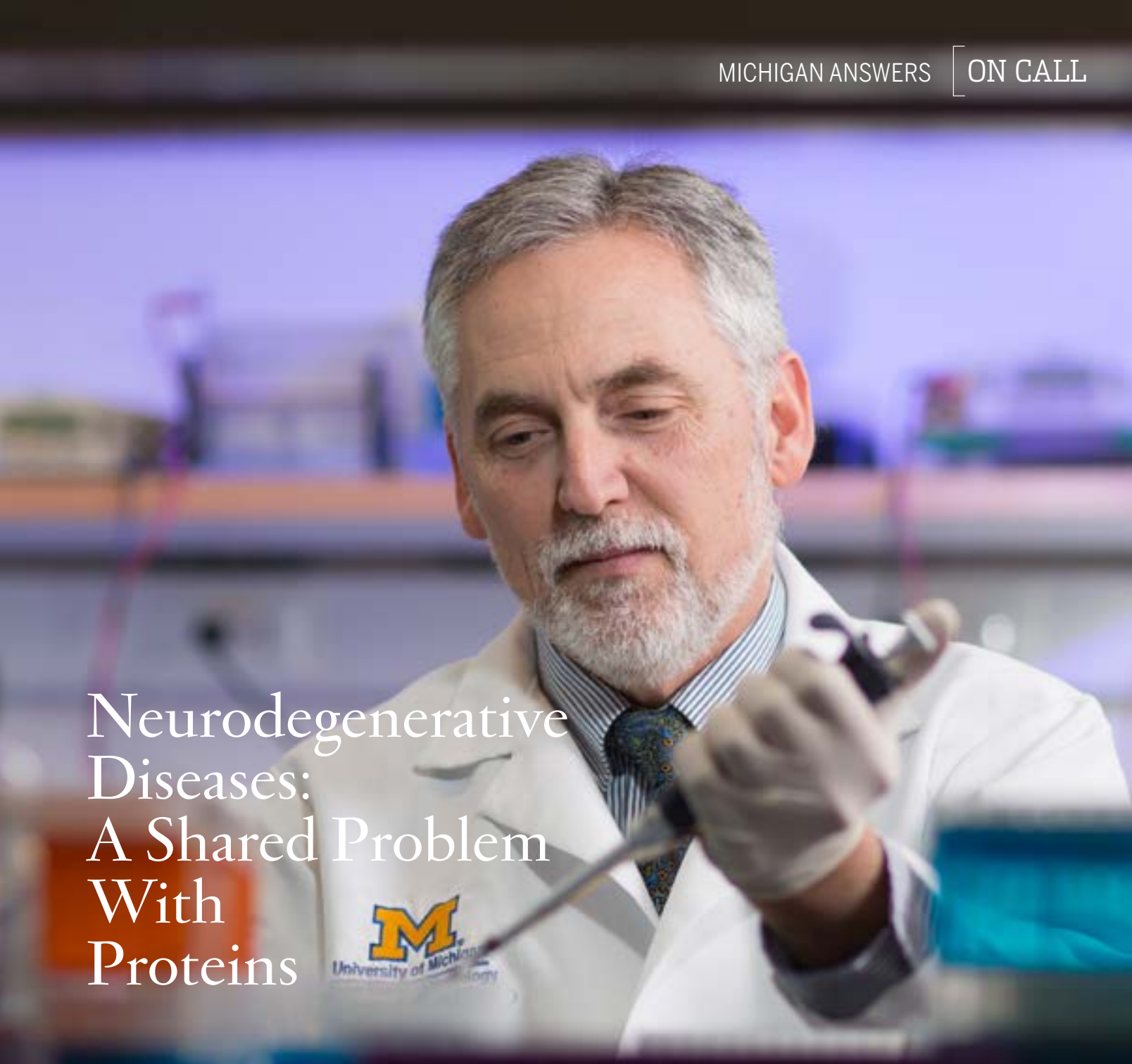

Neurodegenerative Diseases: A Shared Problem With Proteins

U-M researchers are broadening the search for more effective treatments and cures of neurodegenerative diseases. Central to that search is the U-M Protein Folding Diseases Initiative and its more than 50 investigators. Proteins fold properly into three-dimensional structures to function correctly. Yet in many diseases, proteins become abnormally shaped and clump together. Henry L. Paulson, M.D., Ph.D., the Lucile Groff Professor of Neurology for Alzheimer's Disease and Related Disorders, spoke with the magazine about the iniative. Also the director of the Michigan Alzheimer's Disease Center and an A. Alfred Taubman Medical Research Institute Scholar, Paulson partnered with Andrew P. Lieberman, M.D., Ph.D., the Abrams Collegiate Professor of Pathology, to lead the effort. →

SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

Q: Why is it important for researchers working on protein malfunctions across the Medical School to collaborate?

A: We think of protein misfolding and accumulation as being a common problem in degenerative brain diseases such as Alzheimer's, Parkinson's and Huntington's, but problems in the handling of proteins contribute to well over 100 disorders, including diabetes, heart disease and cancer.

Q: What will the initiative accomplish, and how will Alzheimer's disease benefit?

A: We have created four research hubs that bring together U-M scientists with different backgrounds and perspectives to address common problems in these diseases. Our goal is to reduce the barriers to discovery across departments. Many of the conditions these faculty study are untreatable and fatal, and we need new insights to come up with new or better therapies. Alzheimer's and related brain diseases may be the largest group of diseases studied in this initiative, but the medical problem is much bigger than brain diseases alone.

Q: The Protein Folding Diseases Initiative was one of the first projects funded by the Medical School's Fast Forward Initiative. What impact did that support have?

A: The initiative only exists because of Fast Forward. Fast Forward has provided the resources and the infrastructure to make it go and the funding that allows us to test new ideas. We are tremendously grateful that we have been given this opportunity.

Q: How significant are Michigan's contributions to the field?

A: The Protein Folding Diseases Initiative is the first of its kind in the country. We are in a privileged position. When outside investigators reviewed our proposal for the initiative, they were wowed by the strengths at the University of Michigan. We are fortunate to have investigators in many different departments who are at the top of their fields looking at protein misfolding, protein aggregation and routes to therapy. I have been at the University of Michigan now for six years, and it still amazes me what a tremendous place it is.

Q: What advances are we seeing in Alzheimer's disease research across the board?

A: In past decades, a lot of excitement centered on the small protein known as beta-amyloid, which accumulates in plaques outside of brain cells. We now recognize that many other proteins and pathways contribute to Alzheimer's in all phases. While the attention has not turned away from beta-amyloid, we are also now looking carefully at other targets, including a protein called tau, which accumulates in tangles inside brain cells in Alzheimer's.

Another exciting development is that brain imaging has led to new, easily measured biomarkers of the disease. Having the ability to see what the future might hold is extremely powerful when we think about preventive therapies. And we now know that specific genes and genetically regulated pathways are affected in people who have Alzheimer's. We don't have therapies yet from these new clues, but there is a lot of excitement because we are moving in that direction. At the U-M, we are also interested in making new connections between Alzheimer's disease and vascular changes, diabetes, metabolic changes and inflammation.

Q: Tell us about those connections.

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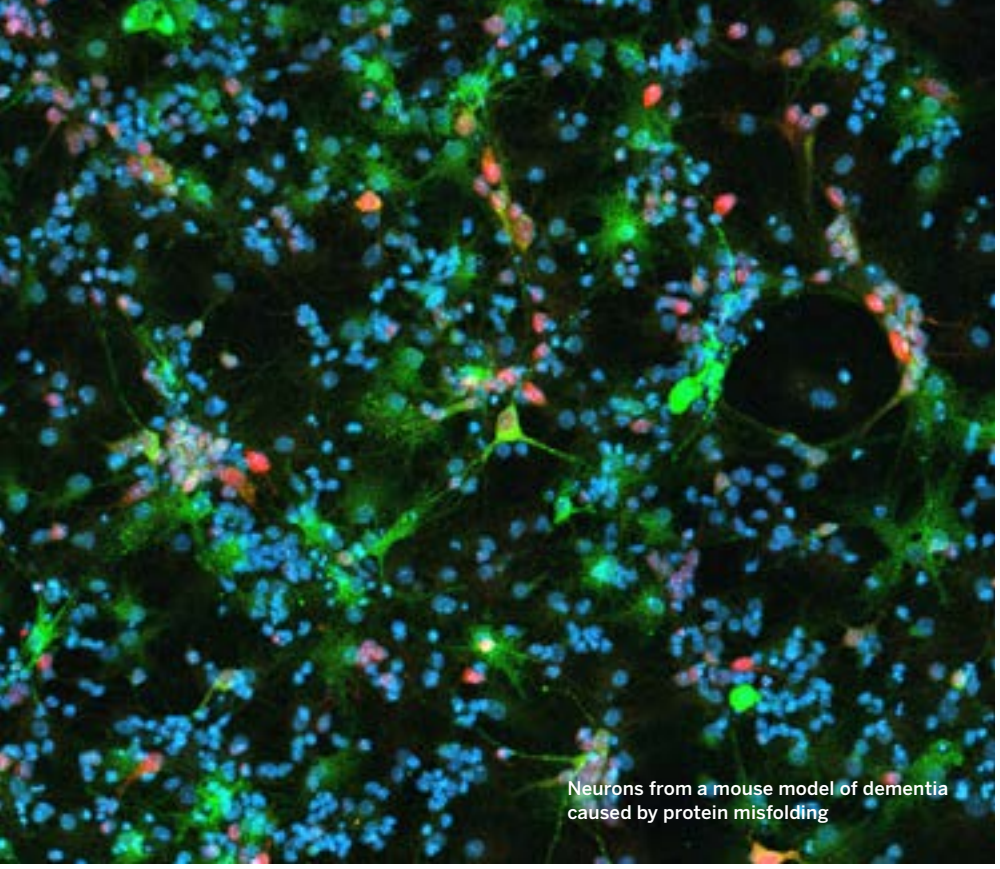

Neurons from a mouse model of dementia caused by protein misfolding

COURTESY OF HENRY PAULSON'S LAB

A: Our brain is subjected to all kinds of insult as we age. One common insult is diabetes, and we believe that diabetes intersects with the age-related disease processes in Alzheimer's, Parkinson's and other diseases of the nervous system. At U-M, we have powerful teams of neurodegenerative disease scientists, and scientists and clinicians who are experts in diabetes and metabolic disorders. Those investigators are now teaming up to address how diabetes affects brain function as we age.

Q: What is happening in the area of prevention?

A: So many important things have been learned about the genes and the biological pathways underlying Alzheimer's in the past 10 years. Now we are moving to that next, important phase — testing preventive therapies. I'm hopeful that in the near future the Alzheimer's field will identify drugs that can modulate the course of disease.

At our center, we have a strong interest in identifying the risks underlying Alzheimer's disease and disclosing those risks to people who have a family history. Scott Roberts, Ph.D., who heads the outreach, recruitment and education core activities in our center, is particularly interested in understanding how people respond to learning information about their risk of disease.

But I would remind everyone — whether they have a family history of Alzheimer's or not — that it's important to exercise, sleep enough, eat right and engage your brain in stimulating activities. These are simple measures to help make sure your brain and body age gracefully. They are probably as important as any medication.

Q: What advances have we made in caring for patients?

A: There is increasing interest in understanding the early phase of the disease, but let's not forget that there are already 5 million Americans who have Alzheimer's, many in the advanced stages of the disease. We do have some medications that provide some symptomatic benefit for people with manifest Alzheimer's disease. But the care of people with memory loss and dementia requires much more than medications. At our center, one area of emphasis is our new wellness initiative, which is helping patients with memory loss and their caregivers cope with the problems they experience.

Q: What wellness programs are in place for patients and families?

A: Several programs on campus seek to promote wellness, including the Geriatrics Center, the Program for Positive Aging, and our own center. For example, the Silver Club programs at the Geriatrics Center allow people who have signs of Alzheimer's and related conditions to come together and discuss topics of interest to them. And our own Wellness Initiative supports the Catching Your Breath program at Matthaei Botanical Gardens, where caregivers can discuss how they are coping with the issues they may face. Caring for people who have Alzheimer's disease comes with its own types of stress and difficulties.

Q: Do we collaborate with other Alzheimer's disease programs?

A: We just submitted a grant proposal that, if funded, will bring into the fold both Wayne State University and Michigan State University, making our center a truly regional center that will benefit residents across Michigan. We also collaborate with eight Alzheimer's disease centers spanning the country. That kind of collaboration is critically important for a disease as common and complex as Alzheimer's. We need to work together if we are serious about tackling this tough disease.

Interview by MargaretAnn Cross