



Valerie Berthelie, PhD

Leading the World in Amyloid Research

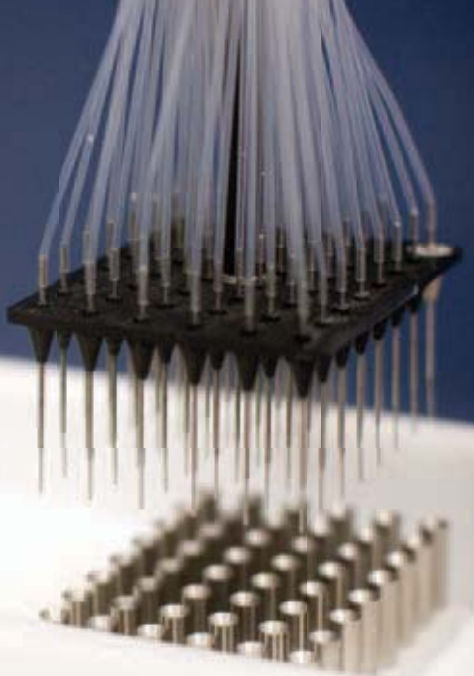
Understanding the cause and composition of a disease-producing substance known as amyloid is the quest of scientists across the globe. Identifying how amyloid forms and affects the living human body has become a mission of the University of Tennessee Medical Center scientists who find themselves revealing new discoveries to the world.

Several issues of *Frontiers* have introduced readers to conditions related to amyloid, protein-rich masses that play a role in serious or life-threatening diseases such as rheumatoid arthritis, type 2 diabetes, multiple myeloma, Alzheimer's, Huntington's, Parkinson's, and other degenerative diseases. Amyloid, a mix of proteins, sugars, and other molecules, occurs when proteins in the body misfold and form insoluble, often toxic and well-structured fibrils. The resulting disease, amyloidosis, can progress rapidly, causing complications that invariably lead to tissue disruption and organ failure.

The University of Tennessee Medical Center and UT Graduate School of Medicine faculty and researchers have been studying amyloid for decades, sharing information with fellow researchers throughout the world. Supported by grants from the National Institutes of Health and others, the teams work daily to unveil ways to diagnose, prevent, or eliminate amyloid from the body.

Valerie M. Berthelie, PhD, is studying Huntington's disease, a hereditary disorder in which nerve cells in the brain degenerate. She and her team are the only researchers in the nation currently using neutrons to determine the structure of the mutant huntingtin protein that is responsible for the disease.

Researchers in the Conformational Diseases and Therapeutics Research Laboratory at the University of Tennessee Graduate School of Medicine are the only ones in the U.S. to use neutrons to study the structure of the mutant huntingtin protein that causes Huntington's Disease. Several members of the team are (back) Christopher Stanley, PhD; (L to R) Monique LeMieux, PhD graduate student; Penney Koeppen, MS; and Valerie Berthelie, PhD, Assistant Professor, Director. Not pictured are team members Erica Rowe, PhD, and Tatiana Perevozchikova, PhD graduate student.



Berthelie hopes to identify compounds that can stabilize stages of protein folding and amyloid formation, determine their toxicity, and ultimately render them harmless. Additionally, these compounds may be able to change the toxic structure of amyloid, which could allow healthy cells to destroy it.

Her research is greatly aided by the campus's proximity to Oak Ridge National Laboratory (ORNL), home to neutron-scattering instruments that are available at only a few locations worldwide.

"Once our proposal is accepted by ORNL, our team is typically assigned three consecutive days once every six months," says Berthelie. "The worldwide demand from scientists for the neutron lab is high. Our team must be well prepared when our turn to use the facility arrives. We take our materials with us, and we work nearly around the clock, taking short rest breaks in the wee hours of the morning."

Research outcomes are recorded and later analyzed back at the UT Graduate School of Medicine labs, where Berthelie and her team continue their quest to understand the formation of the mutant huntingtin protein and the resulting debilitating disease.



Breaking New Ground: Imaging Amyloid Sugars

Recently, the National Institutes of Health awarded UT Graduate School of Medicine researcher and professor Jonathan S. Wall, PhD, a \$2 million, four-year grant to study new ways of capturing pictures of amyloid disease in patients. Discovering how to track the disease and get accurate images of amyloid as it insidiously invades the body's organs can lead to more rapid and effective methods of diagnosis as well as new treatments.

To date, most research around the globe has centered on targeting and imaging the protein fibrils present in amyloid. Wall's team of researchers is breaking new research ground by concentrating its efforts on the sugars that are present in an amyloid mass. "No one else in the world is looking into imaging the unique amyloid-associated sugars as a diagnostic tool," says Wall. "It's an understudied area that will be very important to diagnosing, monitoring, treating, and perhaps preventing death caused by amyloid."

He provides a layperson's explanation: "Sugars are present in all healthy tissues and help cells interact with each other and their surroundings as well as provide a scaffold for the whole tissue. There's an unusually large amount of these sugars found in all amyloid masses. If we can identify molecules that specifically target the sugars, we'll be able to use radioactive isotopes to image amyloid-related diseases, which will allow us to better diagnose and monitor patients. In the near future we can also deliver payloads that can destroy this material, perhaps using the body's own immune system."

Wall and his team are already discovering better ways to image amyloid deposits and tag them for destruction. In only three months, the team has taken the research to the next level, employing small molecules rather than larger proteins to carry

the radioactive tracers to amyloid. "Using these small molecules as transporters of the radioactive molecules is groundbreaking for research into amyloid and Alzheimer's disease," explains Wall. "The molecules can be easily made into a vehicle to carry a radioactive tracer to any area of the body, including the brain with its blood-brain barrier that usually restricts larger molecules."

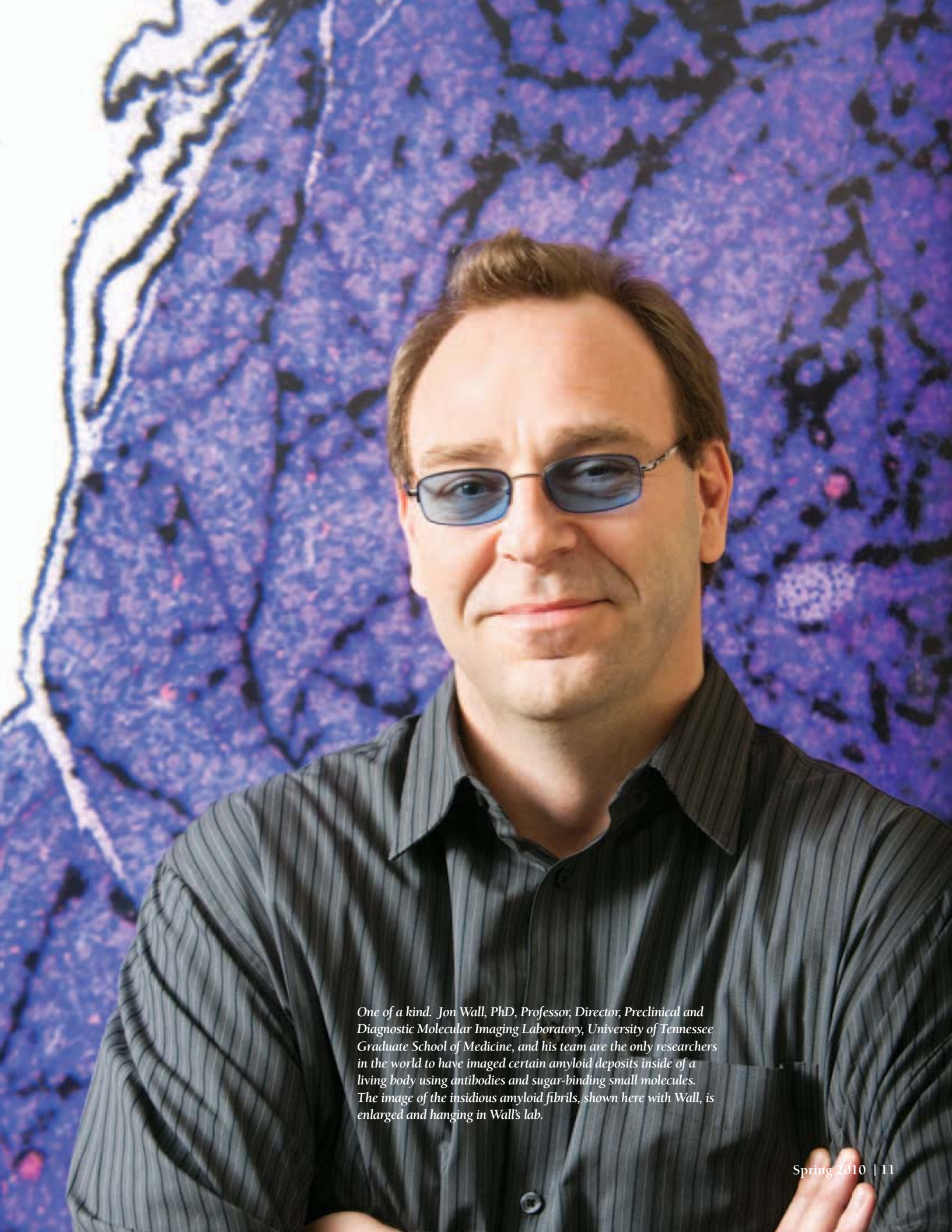
He sees opportunity on the horizon. "If we continue on the path we're on now, we can reach an obtainable dream." His matter-of-fact demeanor belies the excitement brewing under the surface as he describes his vision of establishing the nation's first amyloid imaging and treatment facility at the University of Tennessee Medical Center. "We have the finest imaging equipment available through our partnership with Siemens," he says. "Our faculty includes Dr. Alan Solomon, one of the world's premier amyloid researcher-clinicians, from whom all amyloid research stems. Thanks to his invaluable and ongoing research in this field, we're already making phenomenal discoveries that will have an impact on the diagnosis and treatment of these awful diseases. This dream is within our grasp."

Although the research Wall is conducting is different from Berthelie's, both labs are working together to understand the consequences of the misfolding process. "No one is certain what happens between the time mutant proteins evolve through an intermediate stage when small toxic structures appear and the next stage where large intertwined fibrils can be found," Berthelie points out. "The discovery of what occurs during this process can be a key factor in developing treatments that will eliminate the toxicity or prevent the process altogether."

Lea Anne Law & Amanda F. Johnson

The team of researchers in the Diagnostic and Preclinical Molecular Imaging Laboratory are imaging amyloid and its associated sugars to fight diseases such as rheumatoid arthritis, type 2 diabetes, Alzheimer's, and other diseases. Team members include (L to R) Amy LeBlanc, DVM, Director, Translational Research; Jon Wall, PhD, Professor, Director; Alan Stuckey, BA, CNMT, Research Leader; Tina Richey, MS, Experimental Model Specialist and Steve Kennel, PhD, Associate Professor.





One of a kind. Jon Wall, PhD, Professor, Director, Preclinical and Diagnostic Molecular Imaging Laboratory, University of Tennessee Graduate School of Medicine, and his team are the only researchers in the world to have imaged certain amyloid deposits inside of a living body using antibodies and sugar-binding small molecules. The image of the insidious amyloid fibrils, shown here with Wall, is enlarged and hanging in Wall's lab.