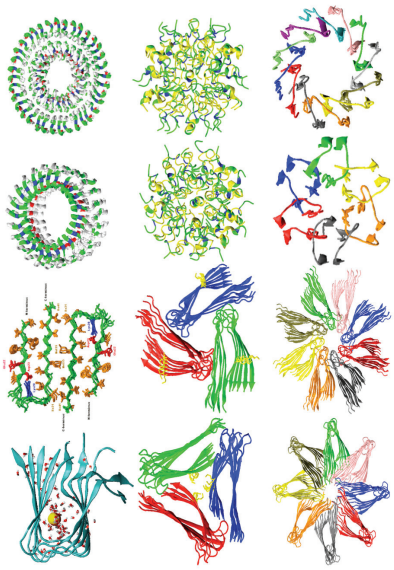


above: Using computer simulations, Jie Zheng can predict and validate several molecular models of Aß oligomers to bettter understand how they are formed and accumulate in Alzheimer's disease.

Simulating misfolded proteins in Alzheimer's

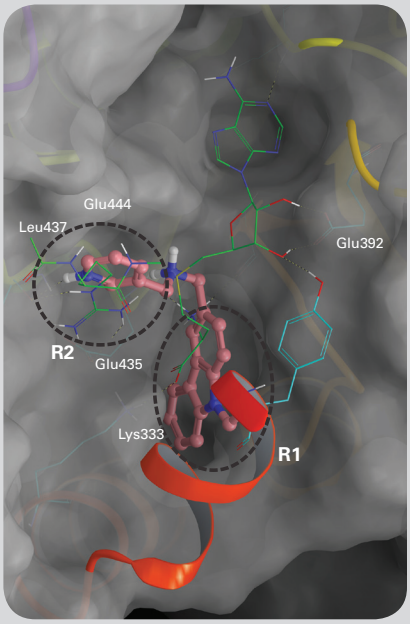
Alzheimer's disease is the most common human neurodegenerative disorder, affecting as many as 5.1 million people in America alone. Alzheimer's leads to progressive and irreversible memory loss, disability and, eventually, death through a complex series of events that take place in the brain over a period of many years.

In the nucleus of nearly every human cell, long strands of DNA are packed tightly together to form chromosomes. To deliver these instructions to various other cellular structures, the chromosomes dispatch very small protein fibers – called oligomers – that fold into three-dimensional shapes. Misfolded proteins – called amyloid fibrils – cannot function properly and tend to accumulate into tangles and clumps of waxy plaque, robbing brain cells of their ability to operate and communicate with each other.

"The exact mechanism of amyloid formation and the origin of its toxicity are not fully understood, primarily due to a lack of sufficient atomic-level structural information from traditional experimental approaches," explained Jie Zheng, Ph.D., an assistant professor of chemical and biomolecular engineering at the University of Akron. "Molecular simulations, in contrast, allow one to study the three-dimensional structure and its kinetic pathway of amyloid oligomers at full atomic resolution."

Zheng's research group is leveraging the computational muscle of the IBM Cluster 1350 system at the Ohio Supercomputer Center to develop a multiscale modeling and simulation platform that aims to establish a direct correlation between the formation of oligomers and their biological activity in cell membranes. ■

Project lead: Jie Zheng, University of Akron
Research title: Exploring kinetics and structures of Alzheimer's amyloid ß-protein formation
Funding source: National Science Foundation



above: Chenglong Li is creating complex molecular dynamics simulations involving the PRMT5 enzyme to help discover a drug that will allow the human body to better suppress invasive brain tumors.

Discovering drugs for cancer therapies

Chenglong Li, Ph.D., an assistant professor in the College of Pharmacy at The Ohio State University, is using computational chemistry to help develop a genetically targeted drug that could surpass current approaches to treating a type of aggressive brain tumor called glioblastoma multiforme (GBM).

The survival outcome of patients diagnosed with a GBM is relatively poor and has improved only marginally over several decades. Combinations of surgery, radiation and chemotherapy remain the most common therapy, yet surgeons often can't completely remove the tumors without causing serious damage, radiation is rarely effective and chemotherapy usually produces serious side effects.

"My group has been conducting molecular dynamics simulations of the PRMT5 enzyme to gain insights on its catalytic mechanisms," said Li. "We then conduct virtual screenings of more than 100,000 pharmaceutical compounds to identify drugs that prevent that enzyme from blocking the body's cancer suppression genes. This novel approach is called epigenetic cancer therapy, where molecular compounds 'reawaken' natural human tumor-fighting genes that stay dormant in many types of cancers."

Kiran Mahasenan, a graduate student on Li's research team, developed molecular models using the IBM Cluster 1350 system at the Ohio Supercomputer Center, which the team also used to screen drug candidates. Once the most promising drug candidates are identified, the data is passed along to Dr. Robert A. Baiocchi, an oncologist at The James Comprehensive Cancer Center, who conducts clinical tests to evaluate the effectiveness, toxicity and dosage of each drug. ■

Project lead: Chenglong Li, The Ohio State University
Research title: Pursuing drugs to 'reawaken' nature's cancer-fighting genes
Funding source: National Institutes of Health, The Ohio State University College of Pharmacy