University of Alberta researchers work to address deadly misfolded proteins

KEITH GEREIN

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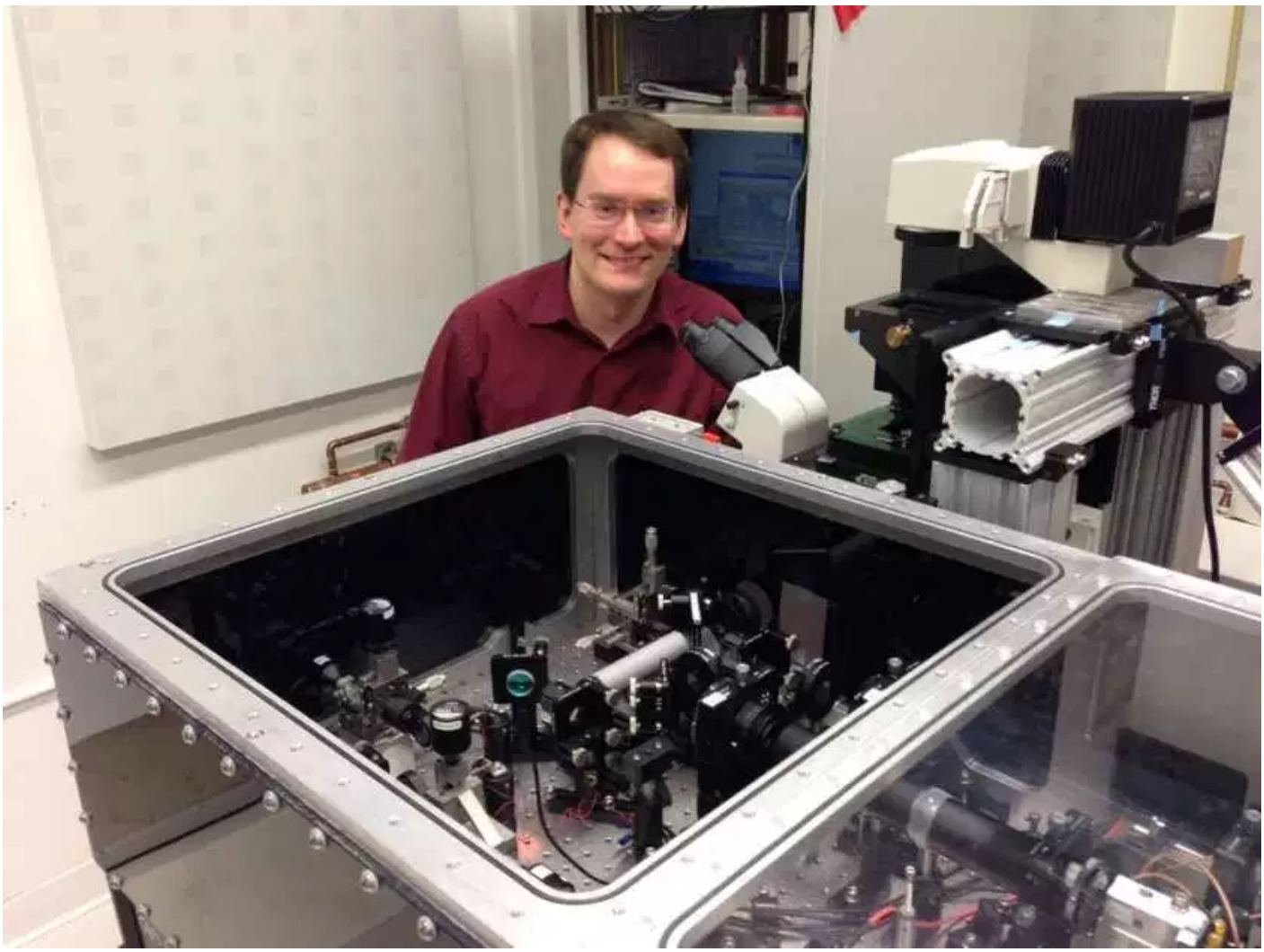

Michael Woodside, University of Alberta professor *SUPPLIED*

A new University of Alberta-led study is helping scientists to better understand the workings of potential treatments for deadly prion illnesses such as mad cow and Creutzfeld-Jakob disease.

"The idea is to give us clues to the mechanism of action that we should be targeting when we develop drugs," said Michael Woodside, a U of A physics researcher who also works within the National Institute for Nanotechnology.

"We don't have any good therapeutics for prion diseases. The problem is that if you don't know what a (drug compound) is doing in the first place, it's hard to know what characteristics you should keep and what you should throw away as you try and improve it."

Prion diseases are driven by rogue proteins that interact with normal proteins and cause them to contort into toxic, misfolded shapes. Over time, the misshapen structures build up and cause significant brain damage.

Bovine spongiform encephalopathy (mad cow) and chronic wasting disease in deer and elk are the most commonly known forms of prion disease. Creutzfeld-Jakob is a rare human variant, however; more common illnesses including Alzheimer's, ALS and Parkinson's have also been linked to misshapen proteins.

Though the development of drugs has proven difficult, scientists have taken some initial steps by finding a variety of chemical compounds that seem to interact with proteins and help prevent them from misfolding.

Woodside and his team decided to take one of these compounds — a chemical discovered in Britain about six years ago — and analyze it at the molecular level to see how it affects a protein.

To do so, the team used a set of custom-built "laser tweezers" housed in a quiet, temperature-controlled wing of the nanotechnology institute. The tool is sensitive enough to measure extremely tiny forces and changes in distance, which allows scientists to pull apart a protein, watch it reform and then determine if the protein has changed shape.

"We grab onto its ends and ask, has the length of that protein changed? We can measure changes on the order of just a few atoms," Woodside said.

"They are really cool instruments. They basically use the very tiny pressure that photons in a laser beam apply to generate force."

For their experiments, the scientists added the compound to an isolated protein, and then used the tweezers to pull it apart to see what happened.

Not surprisingly, they confirmed the compound does indeed bind to the correct structure of the protein and stabilizes it — making it harder to pull apart. This effect had been reported in previous research.

However, Woodside's team then noted two other behaviors showing the compound's effects to be more complex than originally thought.

In addition to making the protein more stable energetically, the compound also makes it more rigid mechanically.

"The analogy I like to use is that it acted like a staple between the two ends of the protein. So this makes it even harder to pull the structure apart," Woodside said.

As well, the team discovered the compound has an ability to block the interactions between proteins that induce them to misfold into incorrect structures.

"It was basically acting to slow down the folding and give the protein a bit of room and time to find the right structure," Woodside said.

He said this last effect is very similar to a natural process in the body, which contains "chaperone" molecules that ward off proteins with incorrect structures from affecting other proteins. Unfortunately, these chaperones can sometimes become overwhelmed, which allows the disease to spread.

The next step, Woodside said, is to test if this same chaperone effect of the compound is happening in some of the other compounds scientists are exploring. Eventually, the work could help researchers to design a drug effective at battling misfolding diseases.

The study is published in the June 27 edition of Nature Communications, an open-access interdisciplinary journal.

kgerein@postmedia.com (mailto:kgerein@epostmedia.com)

twitter.com/keithgerein (http://twitter.com/keithgerein)

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