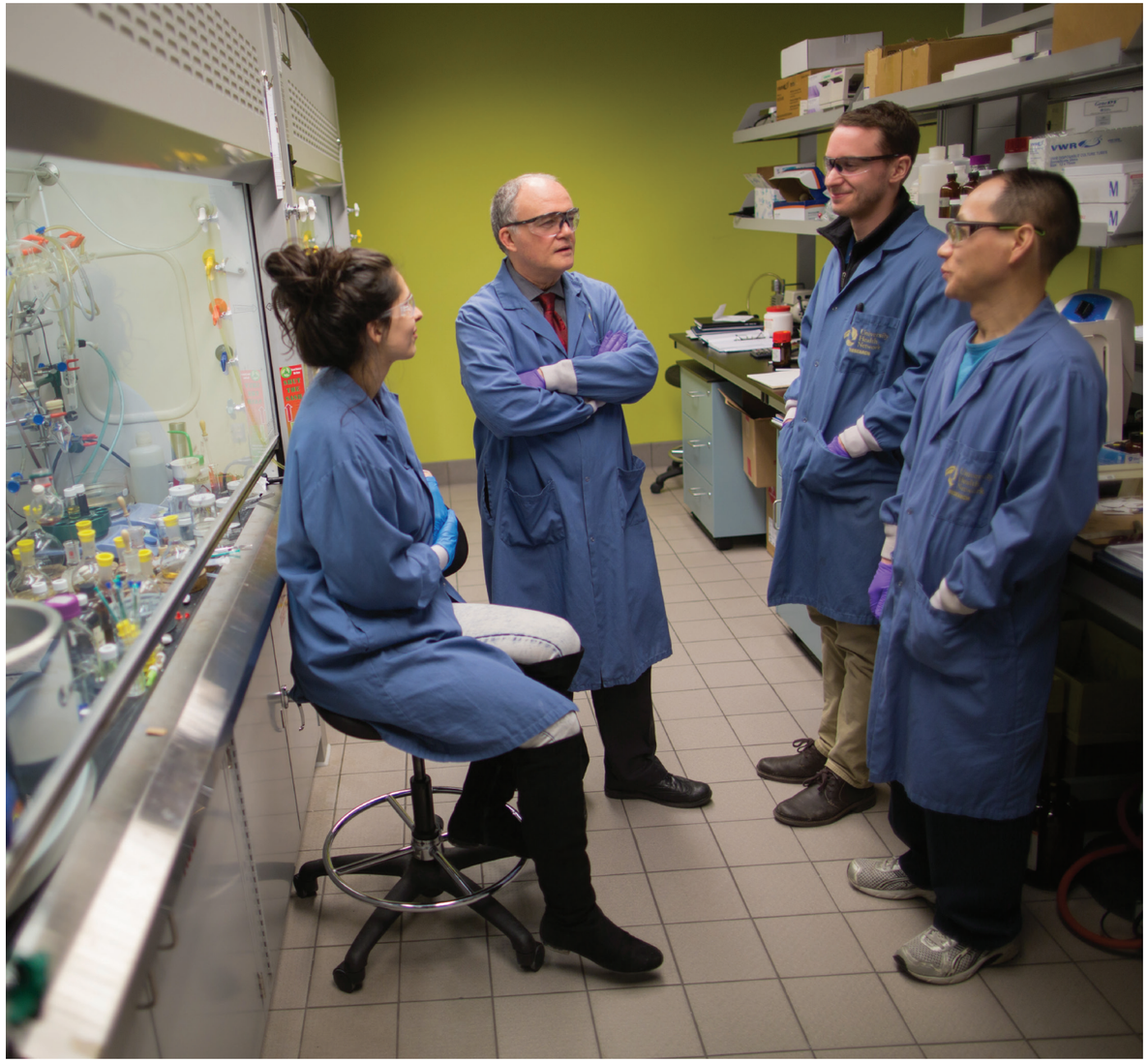

A relentless research quest to end Alzheimer's disease

The pioneering work of Dr. Donald Weaver and his team on a groundbreaking drug offers hope to Canadians

Shelley White

Dr. Donald Weaver's goal in life is to never have to give bad news to an Alzheimer's patient and their family again.

Over the 30 years he's been a neurologist and Alzheimer's disease (AD) researcher, Dr. Weaver has grown accustomed to informing patients and their families about AD's grim prognosis.

"Last week I met yet another family that I really felt badly for," says Dr. Weaver, sitting in his office at the Krembil Research Institute in Toronto, where he's director.

"This family brought in a loved one who is 53 years old, well-advanced in AD. They had seen their general practitioner, who told them, 'Go see a neurologist, now.' So the family comes in, and they ask, 'Do you have a pill that's going to make this all better?' And you have to say, 'No, I don't.' I tell them what they have and I tell them what the prognosis is. And the room is filled with tears," says Dr. Weaver.

"I've been doing this for decades, and I'm tired of doing it. Someone needs to come up with a drug," he says.

Alzheimer's is a disease that strikes fear into people's hearts, largely because its progression cannot be stopped. No matter when someone is diagnosed, there is no escaping the fact that a patient's memory loss and cognitive decline will continue until the patient passes away.

Currently, there are no disease-modifying drugs for Alzheimer's available, and yet it's one of the fastest-growing diseases. There are more than 550,000 Canadians living with AD or other forms of dementia today, and it's estimated that in 15 years, that number will jump to more than 900,000.

But what if there were a drug that could stop AD in its tracks and prevent the disease from progressing?

It's a prospect that could be a reality in only a few years, thanks to the pioneering work of Dr. Weaver and his team at Krembil. They are working on a groundbreaking, disease-modifying Alzheimer's drug that could profoundly affect the lives of hundreds of thousands of Canadians and millions worldwide. Finding that drug is Dr. Weaver's mission in life.

"When we hire new people, I say, 'We only have one goal: getting a drug that works for Alzheimer's,'" says Dr. Weaver. "It's not producing a pretty paper in a journal. To me, that's just a stepping stone. Our goal is the drug. Our goal is helping people."

UNLOCKING THE SECRETS OF MISSHAPEN PROTEINS

Dr. Weaver and his team began their research by analyzing the abnormal proteins implicated in Alzheimer's disease – beta-amyloid and tau. The shape of a protein is controlled by a process called "folding," but in patients with AD, these folds are misshapen.

"Proteins are dynamic. Proteins move. They flex," explains Dr. Weaver, who as a medicinal chemist and a neurologist has a unique skill set. "And for reasons that are unclear, they twist into a particular shape, and that's the 'bad-news' shape. When proteins get into that shape, an aggregation or 'clumping' process starts."

This clumping creates the signature plaques and tangles found in the brains of AD patients. Although scientists aren't absolutely sure what causes the cell death and tissue loss that leads to progressive cognitive decline, these misshapen aggregates are the prime suspects.

Dr. Weaver notes that everyone may have some beta-amyloid or tau, but "as long as it's sitting there and it's by itself, you're good," he says. "But for some people, there are just a lot of them. They clump."

Why the misshapen proteins aggregate in one person and not another is one of the mysteries of the disease, he adds.

"There are certain risk factors – family history, repetitive head trauma – but on average, it's just bad luck."

The first major breakthrough in Dr. Weaver's lab came when the team was able to identify a shape found in both beta-amyloid and tau proteins that predisposes them to misfold, which they called the Common Conformational Motif. This particular shape appears to trigger the "cascade" of clumping proteins found in AD.

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>
> – Dr. Donald Weaver

Having studied and modelled the folds that predicate the clumping process, the team began work on the next step: finding a drug that would impede the clumping process.

Dr. Weaver's lab is split in half – an academic half and a commercial half. The commercial half is called Treventis, and this is where the drug is being developed.

The key to developing a disease-modifying drug is to find a drug-like chemical that binds to the misshapen protein when in its singular or "monomeric" form, preventing clumping from happening in the first place.

To illustrate, Dr. Weaver gives the example of building a log cabin:

"When you stack logs, you have a log and then you put on the next layer and the next layer. But if I put a bump on the log, the next one doesn't sit correctly, and I can't stack it," he says. "I always tell people we're trying to invent a molecule that's a bump on a log. We're trying to come up with a molecule that's a bump on beta-amyloid and tau."

By identifying a compound that will act as a physical barrier preventing the clumping process, the team could then create a drug that would halt the progression of Alzheimer's.

"If it's given preclinically, so before the person has symptoms, then we would be curative. If it's given after you actually have symptoms, then we are disease-stabilizing," says Dr. Weaver.

"A drug that targets both beta-amyloid and tau, and prevents their misfolding should be disease-modifying at any stage in the disease, right from presymptomatic to full-blown."

THE SEARCH FOR THE ELUSIVE 'BUMP ON A LOG'

Down the hall from Dr. Weaver's office, chemist Dr. Christopher Barden clicks open a file. It's a 3-D model of the "bad-news" shape of a misfolded beta-amyloid protein. The model is an intricate network of matchstick-like molecular bonds in white, red and blue, standing out vividly from the black background. Nestled right in the middle of the protein is a rectangular cluster of grey and red spheres, looking a bit like a spaceship stuck in a spider's web.

That cluster is a model of a new chemical entity, and it's one of the promising compounds that could be the elusive "bump on a log," binding with the protein to stop the progression of AD.

Computer modelling technology has enabled the team to test millions of chemical compounds to see which ones will bind best with beta-amyloid and tau, says Dr. Barden. Doing testing on that scale with real proteins and compounds would be next to impossible.

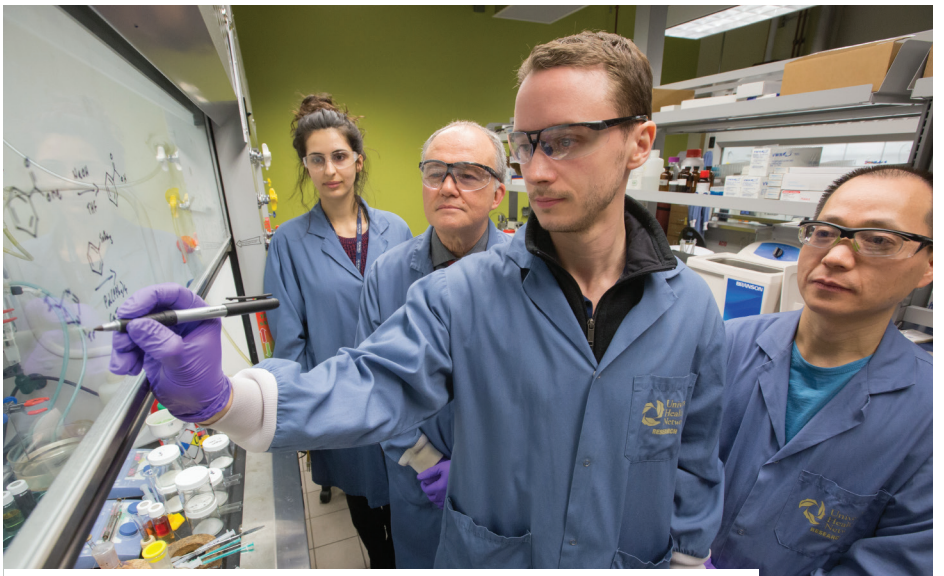
"The problem with diseases like Alzheimer's is that this misfolded protein is by its very nature not going to stay in one place in that particular shape," he says. "It's intrinsically disordered, and so it's hard to get a picture of that. What we've done instead is to create these computer models to stand in for the picture we would otherwise have for drug design."

Since identifying the misshapen proteins, Dr. Weaver says the team has done an "in-silico," or in-computer, screening of 11.8 million compounds to see what would stick.

"We basically threw everything at it, saying, 'We've got to find something that binds to this shape,'" says Dr. Weaver. "We got 130 hits. We looked at them and then once we got one that really bound well, we synthesized analogues of it. We probably did a thousand variants on the first lead."

As the computer model narrowed the options down, the discovery process went from virtual to physical. Promising chemical compositions were created in the lab, so they could be tested in vitro to see if they really would bind to beta-amyloid and tau.

"We have to make the compound and then test the compound. If it doesn't work, it's back to the drawing board," says Dr. Weaver.



Dr. Donald Weaver, second from the left, and his dedicated research team have generated a lot of excitement in the scientific community with their results based on unique computer modelling technology.

"If something fails, you get knowledge from it."

After 11 million compounds tested in silico and dozens of compounds tested in the lab, Dr. Weaver says they are down to a final 20 to 30 promising compounds.

"We hope to say, 'This is our molecule' and do the preclinical work in 2017 and then be in a human trial by 2018."

The team's innovative research has generated a lot of excitement in the scientific community and beyond. They've been invited to present their findings at the Alzheimer's Association International Conference for two years in a row and garnered media attention worldwide.

Dr. Weaver notes that researchers in other parts of the country (and the world) are also in the race to solve the Alzheimer's riddle, with some taking different approaches. But for Dr. Weaver, that proliferation of ideas can only be a positive.

"There are other people working on other avenues, and so I would like to think that in five to 10 years, someone – maybe not us, but hopefully us – will have a disease-modifying drug out there. And that would be huge."

Dr. Bradly Wouters, executive vice-president, science and research at University Health Network (UHN), says that Dr. Weaver's research is important because Alzheimer's affects such a large percentage of the Canadian population and will continue to grow as the population ages.

"Currently, there are no effective treatments to either stop or reverse its progression," says Dr. Wouters. "Dr. Weaver's research is aimed directly at identifying novel therapies that can stop the progression of Alzheimer's."

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– **Dr. Bradly Wouters,**
Executive Vice-President,
Science and Research, UHN

GETTING THE DRUG FROM LAB TO PATIENT

Dr. Weaver acknowledges that the road to a potentially disease-modifying Alzheimer's drug can be long, and the challenges are many. Financial support is always an issue because testing and trials can cost millions of dollars. Plus, there are numerous safety and efficacy issues to work out.

"Compounds need to be chemically stable and affordable to make," he points out. "There are lots of beautiful molecules out there, but once you swallow them they could be destroyed either by the stomach or the liver and thus can't go from the gums to the brain. So, we have to engineer both safety and efficacy in the molecule. Then you have to worry about your toxicology because this is not something that you're taking for five to 10 days. This is something that you're taking for 10 to 20 years."

Another issue is how often a patient has to take the drug, he points out.

"If you have a memory problem, four times a day is not a good idea," says Dr. Weaver. "And so then we have to engineer into the molecule the capacity for once a day."

Dr. Weaver's interaction with his AD patients means he's constantly reminded of these kinds of real-life challenges. This connection to patients is an important element of his success as a researcher, says Dr. Wouters.

"At UHN, our purpose is to transform the lives of patients and communities through excellence in care, discovery and learning. Dr. Weaver represents an individual who embodies all three elements of this approach. He is a clinician who sees and cares for his patients and understands the devastation of the disease and our limited ability to treat it effectively. This focuses his own research efforts to identify therapeutic approaches that can impact the lives of patients with Alzheimer's and their families."

Dr. Albert Jin is an associate professor of neurology at Queen's University in Kingston, Ont., with a cross-appointment to the Department of Biomedical and Molecular Sciences. He's known Dr. Weaver since he was one of his graduate students in the early 1990s.

"He's someone who can bring together the knowledge and the experience from two very different areas of inquiry," says Dr. Jin. "He's a neurologist and he's also a chemist, and to marry those two fields is very difficult. And he's the only person I know who can do that as successfully as he has."

Dr. Jin agrees that unlike many academic researchers, Dr. Weaver is able to go beyond the thrill of the science and really understand what kind of impact his discoveries could have on the world.

"He has no illusions about how difficult it is to make a difference as a chemist to the world, but the world makes a difference to him," he says. "So what he sees with patients and the sometimes awful things that people go through, that's what drives him."

In addition to his cutting-edge work as a scientist and the care he provides for his patients, Dr. Weaver finds a creative outlet in writing poetry in his spare time.

"A number of years ago I started writing what I call therapeutic poems, and I give them to patients," he says. "And some patients, they really like it."

One of his poems about Alzheimer's disease was published in the July 2016 issue of *Neurology*, the journal of the American Academy of Neurology. The last two lines seem to sum up his goal as a researcher and a doctor:

"To cure AD... the mind, the brain,
With scientific hand humane." ■