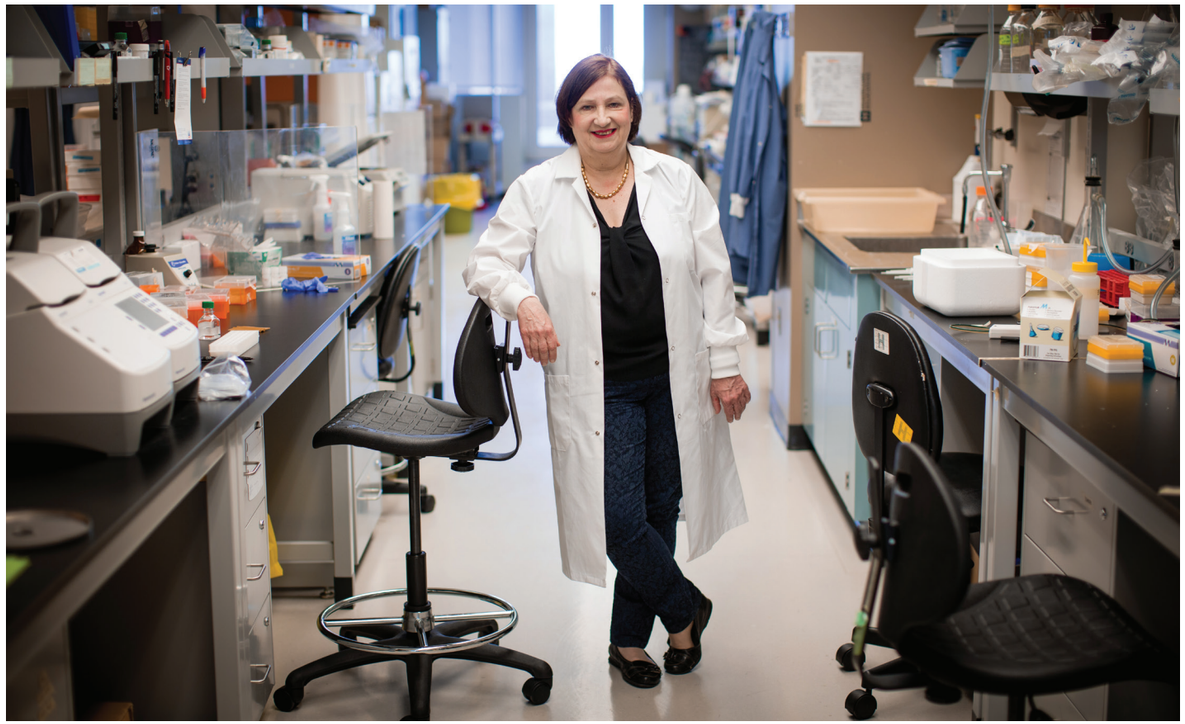

# Hunting for biomarkers

## Dr. Joan Wither's quest to unlock the mysteries of autoimmune disease

*David Israelson*

Finding the clues to diseases such as lupus and kidney disease is one of the most complicated research puzzles for modern medicine. But Dr. Joan Wither and her research team intend to meet that challenge head-on.

It can be a mouthful simply to explain the groundbreaking research that Dr. Wither, a senior scientist at the Krembil Research Institute and a rheumatologist in the Arthritis Program at Toronto Western Hospital, is conducting.

Her research program focuses on identifying the genetic and immune system abnormalities that lead to systemic autoimmune rheumatic diseases (SARD), including systemic lupus erythematosus (SLE), Sjögren's syndrome and scleroderma.

Dr. Wither is hunting for biomarkers for these diseases, which are related.

A biomarker is exactly what it sounds like – a measurable substance in a person, or any organism, that indicates some sort of change such as an infection or a disease.

Her SARD research has four goals, the first of which is to identify biomarkers for the early identification of patients at risk of developing SARD. Dr. Wither is also looking to evaluate therapies for prevention and to map and understand the immune mechanisms that lead to "flares"in autoimmune diseases and their progression, so there can be better diagnosis and treatment for every patient's disease. Finally, she says, it's important to develop diagnostic tests using biomarkers to monitor how SARD progresses and anticipate when it leads to more severe problems, such as renal (kidney) disease.

Dr. Wither is looking at people with antinuclear antibodies, antibodies that bind to the nucleus of cells.

We all have antibodies in our blood, preventing us from getting sick or minimizing illness. Sometimes antibodies develop that work against our own bodies to trigger an autoimmune reaction that can damage our organs, such as the antinuclear antibodies that are found in SARD. The amount and pattern of these antibodies can be tested through an antinuclear antibody (ANA) test.

Some people have abnormal levels of these antibodies. "We focus on the patients who have positive ANA tests," Dr. Wither explains. The project, one of several in which Dr. Wither is involved, is just starting to produce results that can be analyzed for future treatment programs. Dr. Wither has co-written a paper on her work that has been recently published and other papers are being prepared for publication soon that will share her findings with her peers around the world.

Having a positive ANA test doesn't necessarily mean that these patients have an autoimmune disease. "The majority of people with a positive ANA test will not develop a SARD and some patients can have a positive test for many years before they develop symptoms of those diseases," Dr. Wither says.

"The concept behind my research is to see if there is some way we can tell early on who is going to evolve into what condition. If we knew with certainty who is going to evolve, we could maybe intervene and try to prevent the condition from developing."

Understanding this would be an important breakthrough for people who live with a wide range of autoimmune diseases.

"For example, in SLE patients when they first present the symptoms, there can be many organs involved. They can end up in intensive care, and it's difficult to get the disease under control. Sometimes these patients end up with significant damage to their kidneys or other organs.

Other patients have scleroderma, a disease that causes patients' skin and other tissues to tighten. "Again, there can be serious damage during the first three years," Dr. Wither says.

Another autoimmune disease that Dr. Wither is investigating, called Sjögren's syndrome, affects more than 400,000 Canadians. It inflames the salivary and tear glands, causing dry eyes and mouth, and inflammation of the blood vessels, lungs and joints. Sjögren's can also cause deterioration in vision and dental health.

"Once a patient presents with those symptoms, it's very hard to treat," Dr. Wither says.

What Dr. Wither is trying to achieve through her work at Krembil is to identify an early warning system – to find biomarkers within cells to identify patients at risk of developing one of the SARD group of diseases.

It's complicated by the fact that many patients who are tested have positive ANA readings – abnormal levels of antibodies – yet will never get one of the SARDs.

"There are lots of healthy women who have positive ANAs [abnormal levels]. We're looking for the critical checkpoints that 'convert' somebody who has an ANA, but has no symptoms [of an autoimmune disease], to one who has symptoms. Can we block that?" Dr. Wither says.

Dr. Wither, whose research at Krembil includes a clinical program, says diagnosis of SARD patients can be difficult, because many patients start out showing symptoms of an autoimmune disease without enough evidence to make a firm diagnosis.

"We see people who have a positive ANA test and have no symptoms of SARD, and we see people who have one or two symptoms of SARD. We look at a patient's immune profile," she says, which includes looking at a patient's DNA and their genetic profile.

"We're trying to define what's different about the immune system when a patient progresses to having a disease, compared with what happens to those who don't progress," Dr. Wither explains.

"It's a long-term research program. We see patients on a regular basis. We're looking to see if they have progressive changes that we can't pick up with our usual tests."

The clinic typically follows patients for at least three years, which is often the time during which symptoms of an autoimmune disease will appear. But Dr. Wither doesn't rule out continuing to follow patients for much longer, to determine what might be revealed over time.

She is highly sympathetic to the uncertain situation that patients – more often than not women for some types of autoimmune diseases – find themselves in.

"It's very tough to have a positive ANA test, and maybe to have symptoms consistent with a SARD, but not knowing, 'Am I going to get one of these conditions or not?' I try to reassure patients that there's only a 5 to 10 per cent chance," Dr. Wither says.

"It would be helpful if we could have a better test that could determine if a patient with a positive ANA test is going to get a disease or not. Then we could reassure a lot of people." ■





### Exploring the link between lupus and kidney disease

Lupus is known as the disease with a thousand faces. There are many types, and the severity, symptoms and frequency of flare-ups can vary.

Women of childbearing age (15 to 45 years old) are most affected, and in Canada, the estimates of the number of lupus patients vary widely, ranging from 15,000 to 50,000.

What is known about lupus is that about 70 per cent of lupus patients develop kidney disease. "Of those, probably 10 to 15 per cent [of patients] will have significant renal involvement – ultimately leading to renal failure and requiring dialysis or a transplant," says Dr. Joan Wither.

"The problem with kidney disease is that once it appears, it's easy to diagnose, but we actually don't have any really good [bio] markers that tell us whether the kidney disease is responding to therapy. We only detect kidney disease by the damage that occurs," Dr. Wither says.

She is conducting research to change this.

The research, published in *Arthritis Research & Therapy* last year, is incredibly complicated in its science, but deceptively simple in its premise. Dr. Wither and her team are looking for biomarkers for kidney disease, using urine samples.

"We became interested a number of years ago, so we gathered a large cohort of patients who had flare-ups of kidney disease," she explains.

"They were treated and followed over time, so we knew exactly what was going on in their kidneys, and at the same time we obtained urine samples. The kidney produces the urine and [that] tells us whatever is going on in the kidney," says Dr. Wither.

"We also obtained urine from patients with recent kidney biopsies and samples from lupus patients who had flare-ups that did not involve their kidneys. Finally, we obtained samples from people who had kidney disease and had already been treated, and it had settled down.

"We found seven [bio]markers that could give us insight into the kidneys' involvement in lupus and may replace the need for repeat biopsies in the future," she says.

This research is important because it may also enable doctors to predict a flare-up before the damage occurs and adjust their therapy to get the best response to treatment.

*– David Israelson*