BTB S3 Episode 7 Dr. Joan Wither Transcript

BTB
Welcome to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host Christian Coté on the podcast today, we're so pleased to be talking with Dr. John Wither, award winning senior scientist at UHN's Krembil Research Institute. Dr. Whizzer is a pioneer in the field of systemic autoimmune rheumatic diseases, or sards such as lupus and Sjogren syndrome. Dr. Wither has been dubbed the biomarker hunter in her research quest to pinpoint the indicators of when someone has sards to help more rapidly and accurately diagnose and treat patients who suffer these diseases. Dr. Joan Wither welcome to Behind the Breakthrough.

DR. JOAN WITHER
Thanks for having me.

BTB
Okay. Systemic autoimmune rheumatic diseases. And from this point on, if you're okay, I'm going to call them. We're going to use the term sards. First, just tell me if I have this right. Our body's immune system is equipped with antibodies and they help us fight off disease and infection. And for some, still unknown reason, in the case of sards, our immune system gets triggered and those antibodies attack our bodies. Is that right?

DR. JOAN WITHER
That's correct. In the sards conditions, people make antibodies against their own cells and their own proteins. And most of these conditions are characterized by antibodies against things that are found in the nucleus of normal cells like DNA and RNA and things like that.

BTB
So what's the scale of sards in Canada? Can you tell us, like the range of the severity of this disease?

DR. JOAN WITHER
About 0.5 percent of Canadians will develop a sard, and the symptoms can vary from relatively mild, with a skin rash and some joint pain to quite severe disease with inflammation of the brain, in the heart, in the kidney. In the case of Sjogren's disease it can cause dry eyes, dry mouth, and these things can be really quite troublesome for patients.

BTB
And is there a typical profile of who gets sards?

DR. JOAN WITHER
Yeah. So they're much more common in women than men. For example, lupus is present about 10 times more frequently in women than in men. Lupus often develops in young women during the period of childbearing age. Same with Sjogrens it is much more common in women than men, although it tends to develop a little bit later in life.

BTB
So once someone has sards, how does this affect your say, your lifestyle and lifespan?

DR. JOAN WITHER
So lupus can shorten your lifespan? It has very high what's called morbidity associated with it, meaning that the quality of life is quite markedly affected. One of the problems with lupus is that it's a relapsing and remitting disease. So patients often don't know from day to day or year, the year how long they'll remain inactive and they could really flare at any time. In the case of Sjogren's disease, often by the time people have significant symptoms, for example, it doesn't sound like such a big problem to have dry eyes. But in fact, when you really have severely dry eyes, they're itchy, they're burning, they're gritty, they're sticky, and there's actually a film over the eyes. So you can't really see. And if you think of when you talk, Sjogrens causes an absence of saliva, and that saliva helps you to talk. So it's difficult to talk with Sjogren syndrome. And also, saliva plays an important role in helping your teeth. So people have very prevalent tooth decay. So although it doesn't sound like that severe condition, it really is associated with quite a large impact on the quality of life of the patients.

BTB
Okay, so what do we have on offer in terms of a cure or treatments for sards?

DR. JOAN WITHER
So we don't have a cure for any of these conditions. In terms of treatment, in the case of lupus, the treatment is prednisone or corticosteroids and immunosuppressive agents because we don't know the specific cause of the condition. We act to sort of globally suppress the immune system to sort of impair the autoantibody production. In the case of Sjogren’s syndrome, the problem is that often by the time that people have symptoms, those symptoms are irreversible because there's been irreversible damage to the gland. And so that makes the treatment of Sjogren somewhat difficult. And really, there's a move to try and diagnose Sjogren's patients earlier and earlier at a time where we might be able to treat and reverse the course of the disease.

BTB
And this is then perfect timing because this is where your research comes in, you're trying to break through many of the challenges to understanding, sards. Let's start with

the big question. And that's why does research tell us about why the body's immune system gets triggered and turns on itself?

DR. JOAN WITHER
I mean, what we know is that most sards are a partially genetically determined that certain people have an increased likelihood of developing sard based on their genetic background. One of the reasons we know that is that sards tend to run in families so that if you have a family member with a sard, you're much more likely to have a sard yourself and other individuals. Having said that, it's not entirely genetic. For example, if you have two identical twins, the likelihood if one develops lupus of another, developing lupus may only be in the range of 30 to 70 percent, so it's not 100 percent. So we think there's a role of the environment. Having said that, we're not entirely sure what aspect of the environment is acting as a potential trigger

BTB
And what makes it so elusive to understand what I'm guessing is really necessary and basic to be able to make headway with these diseases?

DR. JOAN WITHER
I think part of the problem is that these are what's called complex genetic diseases, and many genes act with each other to promote these diseases. Each of these genes are seen in otherwise healthy individuals and are compatible with relatively normal immune function. But when you have the right combination of genes, they act together with each other to promote the development of disease. And then the other thing is, these diseases tend to be very heterogeneous. So, so they vary a lot from patient to patient. So there's this concept that the patient a can get to the same disease like lupus with multiple different sort of combinations of genes. And b, once they have lupus, the disease can be very variable. One person can just have joint pain and a skin rash. Yet another person can have really severe devastating disease that affects multiple systems that's extremely hard to treat. We don't really understand what promotes that heterogeneity.

BTB
So, Joan, when it comes to the challenge of diagnosis, I understand one of your research breakthroughs is for lupus. You've pioneered a method of finding and identifying those antibodies that attack the body using a simple blood test. So how does that work?

DR. JOAN WITHER
So the problem is that the classic test for these systemic autoimmune rheumatic diseases is the antinuclear antibody test. Which is a test that measures antibodies that are directed against components of the nucleus. And the problem is that 20 percent of healthy women actually have these antibodies at relatively high levels. And of those, only five percent will go on to develop a systemic autoimmune rheumatic disease. The

issue is that these antibodies also are present very early on in people who will progress eventually to a systemic autoimmune disease. So, for example, it's known that the antibodies are present in lupus patients nine years before they develop actual clinical symptoms of lupus and in the case of Sjogren syndrome eighteen years before they develop an actual diagnosis of Sjogren's. So the question is, how do you discriminate? Those people who are ultimately going to go on to develop disease from the vast majority of women who will not go on? We've been focusing on this because a, we would like to identify people who are at increased risk. And then if we understand the immune events that lead to development of sard, we'd like to be in a position perhaps to intervene earlier in these patients to prevent permanent damage. And we recently published that a specific antibody called antero 52 antibody is associated with an increased risk of progressing to sard over the next two years.

BTB
So does this blood test help then eliminate the scare of a false positive for the 20 percent of women you were talking about?

DR. JOAN WITHER
I mean, that's ultimately what we would like to do. So we do know that these ro 52 people are at increased risk. Unfortunately, we're not in a position to say, look, if you have antero 52 antibodies, your risk is 100 percent. And conversely, we're not in a position yet to say that if you don't have antero 52 antibodies, you're not going to progress. But we certainly know that is associated with an increased risk of progression and we've been trying to mix those, that measurement of that antibody with other measurements that we think also are associated with an increased risk. And so we've combined that test with other tests and that we do have a set of tests that if you're positive for these three tests, your likelihood of progressing over the next two years is basically 100 percent. So we do have some markers that indicate people who are at increased risk. At present, these are research markers, but ultimately we'd like to do what's called validate these markers in another subset of patients. And if we can validate them, develop into a test that would indicate people who are at increased risk of what I would call imminent progression, progression during the next two years.

BTB
So I guess this is still investigational. But what I'm guessing then the end result would be is when you get one of those ana tests or the anti nuclear test, that this blood test could then give you more certainty or precision with whether this is a positive diagnosis or not.

DR. JOAN WITHER
Yes, whether somebody is going to progress…

BTB
Right.

DR. JOAN WITHER
And then we would know that we would have to follow them more closely and intervene earlier, whereas people that don't have any of these blood work markers you know, are less likely, certainly much less likely to progress over the next two years. So we know that we can just follow them on less regular basis.

BTB
Got it. You've also come up with an additional tool for diagnosis of lupus based on a simple urine analysis, which eliminates the need for more invasive method of biopsy. Talk to us about this discovery?

DR. JOAN WITHER
Yeah, so, one of the major manifestations of systemic lupus erythematosus is kidney disease. So about 70 percent of lupus patients will develop kidney disease. And again, this can have a relapsing and remitting course. And of those 70 percent, about 15 percent can go into renal failure. We were interested in whether we could develop a test that was better than existing tests at a, making the diagnosis and be, monitoring people over time in terms of their response to therapy. So one of the problems with kidney disease in lupus is that it can cause changes in the urine, and those changes can be very persistent. So when you treat people with lupus nephritis, it's very hard to tell whether they're responding to therapy or not. If they're not responding to therapy, then there's ongoing inflammation. And every time you have one of these episodes, more and more damage occurs to the point where the kidneys function is irretrievable.

So in order to see whether we could get a better measure of inflammation in the kidney, we looked at the urine and we measured inflammatory markers in the urine. We measured a whole bunch of these and we found that a certain subset of inflammatory markers were associated with inflammation in the kidney. And to some extent, certain inflammatory markers told you the kind of inflammation that you had in the kidney. Ultimately, we'd like to use this to develop a clinical test that allows us to monitor the response to therapy. And also, there is some indication from our initial study that perhaps we might be able to use some of these urinary biomarkers to replace the need for a kidney biopsy because some of them are associated with a more severe type of inflammation in the kidney.

BTB
And do you have a sense, Joan, where you might be translating this into say, I know it's investigational at this point, but am trialing it?

DR. JOAN WITHER
So we've been working on this for a number of years. I mean, initially we defined the biomarkers that were associated with inflammation in the kidney, and then we did a subsequent study where we looked at which ones were most responsive to change with

treatment. And that sort of honed down the set of biomarkers that we were interested in. And we just completed a prospective study of completely unselected patients to see how good these biomarkers were at distinguishing people with active kidney disease from all the rest of the lupus patients. And I think we're almost at the point where we might be able to, trial these on a limited basis as potential biomarkers to be used clinically.

BTB
You mentioned flare ups, and I understand one of the hallmarks of sards is these symptoms ebb and flow, and these flare ups can arise with no warning. Talk to us about the research you're doing to help on that front?

DR. JOAN WITHER
So there are a couple of things we've done is, we've done a study that we recently published on trying to determine, are there some biomarkers that we can use as an indicator of who is going to have severe disease and who is not going to have severe disease? So one of the biomarkers that we were interested in is something called the interferon signature. And basically, interferon is a blood chemical that's found at high levels in lupus patients, and the levels of these interferons can vary from patient to patient. And so what we did was look to see whether these interferons had any predictive value in terms of how severe your disease would be.

And so we used the interference signature to measure how high these levels of interferons were. And what we found was that people who had very high interferon signatures had a much worse disease course over the subsequent five years. So they had more flares, they required more treatment with more immunosuppressive agents, and they were harder to shut down with a treatment with corticosteroids. So that indicates to us that interferon, a plays an important role in setting the severity of the disease and b, that it could be used as a potential biomarker to define people that might need more aggressive treatment than those who do not.

The other studies that we've focused on in terms of flare are trying to define what are the mechanisms and or what are the triggers with maybe a bit of a focus on the environment to flares because at present flares or rather unpredictable. So basically what happens is the lupus patient flares they get treated with prednisone, possibly or a change in their drug agent. Many of these immunosuppressive agents have side effects. Certainly, prednisone has side effects, and as a result, these are tapered and then they have another flare, and each flare, at least theoretically, can cause more and more damage. So we've been trying to understand what are the immune mechanisms that lead to flare so that we can maybe target them a little more specifically rather than using non-specific immunosuppression.

So to do that, we've been following patients through periods of episodes when they have an acute flare that has just started and studying their immune function at that point and then studying them over time as they respond to therapy. And so we looked at a number

of people with acute flares, and we compared them to people who didn't have flares, who had had prolonged disease quiescence to try to define the immune abnormalities that promote flares. And there's this concept overall in the literature that maybe you get two flares with multiple different mechanisms that different patients have different mechanisms of flare. And as a result, treating lupus is very complex because you don't know precisely what mechanism is causing the flare in what patient.

What we found was that some of that, what we would call heterogeneity and how the immune system abnormalities are. That are associated with flares was actually due to the time of sampling in relation to flare. That very early on, in the flare, you often can't see much in the blood because probably the immune systems have all been recruited into the tissues and that with treatment of the flare, these immune cells actually migrate back into the circulation so that at least some of the heterogeneity is due to the fact that these cells are moving in and out of the circulation as immune cells are supposed to do.

You know, when we have a stimulus to our immune system like an infection, the cells move to the source of infection and they respond to the infection. And then after they've cleared the infection, then they move back into the circulation. While this appears to be exactly what's happening in lupus patients. So far, we think that perhaps there is not as much heterogeneity in the immune responses as people thought. I think there is some element of it, but not as much as people thought because of this concept of cells. Moving in in and out of the tissues.

BTB
You know, it strikes me as you talk about these hallmarks of sards, you know, the symptoms can be all over the place. The disease onset can be very gradual like years. There's constantly changing meds, the flare ups of pain. I'm curious, how does all of this affect the patient's mental wellness in enduring these diseases?

DR. JOAN WITHER
I'm going to talk, I guess, more specifically on lupus, because 80 percent of the people with lupus have a relapsing and remitting course and the treatments are, have significant side effects. I think it's somewhat difficult for the patients because there is this element of uncertainty. They don't know exactly when they're going to flare and the treatments have, for example, prednisone, you know, is associated with weight gain and weakness of the muscles and thinning of the skin. And there can be abnormal weight distribution with what's called a moon face with swelling around the face. And because of that, I mean, the treatment is difficult for the patients, and the side effects of the treatments are difficult for the patients, but also the uncertainty with regard to how you're going to do over the future and whether or not you're going to have another flare, I think it's also difficult for the patients.

BTB
In terms of your research, you've been working towards greater clarity when it comes to diagnosis so that treatment can begin sooner. Does this in any way advance your knowledge or progression towards cure?

DR. JOAN WITHER
You know, when we study these people who are preclinical, meaning that they haven't yet developed the disease. And when we study people who have and don't have flares and as they resolve their flares, the focus is on trying to not only identify biomarkers, but to identify the immune abnormalities that are causing the flare or the onset of clinical symptoms. And somebody who previously had no clinical symptoms so that we can actually target the immune system abnormality specifically to prevent flare or to prevent onset of disease. So through these experiments, I think we've learned quite a bit about what distinguishes, for example, symptomatic patients from people who don't have symptoms. And I think we got some surprising findings in that. We found, for example, that people who have anti-nuclear antibodies who are otherwise healthy have quite substantial activation of their immune system as compared to people who don't have anti-nuclear antibodies. And some of the changes that were ascribed to having sard are actually changes that are associated with being a and a positive. And when we first started working on this, almost everything we looked for was the same in sard and same in a and a positive individuals. So we were going, well, where are the differences? And we actually had to search quite a bit and for quite a while before we could find what are the differences that distinguish symptomatic patients from asymptomatic patients?

BTB
You're listening to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host, Christian Coté, and today we're in conversation with Dr. Joan Wither award winning senior scientist at UHN’s Krembil research institute. Dr. Wither’s, pioneering research in the field of systemic autoimmune rheumatic diseases, or sards, is made possible in part thanks to generous donor support. If you'd like to contribute to Dr. Withers groundbreaking medical research, please go to www.uhnfoundation. That's all one word uhnfoundation.ca/ podcast.

Joan, when you were born and raised in Calgary, you excelled in science through high school and after you were drawn to med school. But when you went on to the university of Alberta, I understand you were still a little unsure of your direction because you were a competitive gymnast. You ended up choosing science. But I'm curious the rigor and discipline and precision of gymnastics training. Did that dedication to sport prepare you at all for your career in science?

DR. JOAN WITHER
I think so. I mean, in order to excel in a sport, I mean, you really have to have dedication and you have to work hard, you know, natural talent will only take you so far. Beyond that, it's
really just hanging in there and working hard.

BTB
Hard work. Yeah.

DR. JOAN WITHER
Yeah, plain hard work. You know, you train for hours and hours a day, and in order to be successful, you have to be very focused. So I think that, yes, it does spill over to science. And one of the things that I do just to digress a bit is to interview people for our rheumatology training program. Potential applicants and a number of these people have had competitive careers. And I think when I see that, I see that people have the drive to be successful and that will likely spill over to their subsequent career directions.

BTB
You've also talked about a career defining moment while you were at the university of Alberta doing your undergrad when you spent a summer in Bethesda, Maryland, doing an elective through the national institutes of health, where you were working alongside some heavy hitters in the field of immunology, including Dr. Anthony Fauci. Talk to us about the epiphany you had that summer?

DR. JOAN WITHER
This was a number of years ago when immunology really was in its infancy, and I knew very little about immunology, but I got to go to the elective. I think I was the only Canadian and all the rest were Americans, and it basically involved rotating around different ones of the institutes, one of which tony Fauci was in. And at the time he was doing research on Wegener's granulomatosis and granulomatous disease of childhood. He wasn't working on what he's currently working on. So part of it was rotating through there. Part of it was rotating through rheumatology. So some of it was clinical because it was anchored in a medical elective. But a lot of it was immunologic and trying to understand the pathogenesis of all these conditions. And I had never really had much exposure to immunology. And here I was, having exposure like almost one on one exposure with these really giants of immunology at the time, some of which at the time were or subsequently became Nobel laureates.

BTB
Wow.

DR. JOAN WITHER
So it was a very exciting and stimulating time. And as a result, after I completed that elective, I said, you know, I'm really interested in the pathogenesis of disease. I want to do immunology. And that really was what spurred me on to want to be a rheumatologist and be a clinician scientist.

BTB
To have such an aha moment, you know, at such a young age and to be surrounded by some of the best in the field. You know, it speaks to the importance of mentorship and how it compresses our learning curve. I'm curious how you mentor. What's your approach today?

DR. JOAN WITHER
I guess I try to transmit the excitement of doing science. The excitement of asking questions and answering questions. We have regular lab meetings and they present their work. And I think that there's a tendency to try to make the data fit your hypothesis. And I'm a strong believer that you do not do that. You let the data speak for itself. And if your hypothesis is wrong, it's wrong. It's more important to be right than it is important to prove your hypothesis is just as important to disprove it as to prove it. So I try to imbue into the people that I mentor that disproving your hypothesis, as I said, it's just as important as proving your hypothesis.

BTB
You have career advice for them?

DR. JOAN WITHER
I guess my career advice is that you need to find something that you're passionate about. That life is long and you spend a large proportion of your time working. So you need to find something that you really like to do. And if you're not happy with what you're doing, then you need to change it, no matter how hard it is to operate on a principle of no regrets. So if you look at what you're doing and think that maybe 10 or 20 years down the line, you're going to regret not taking that opportunity, then no matter how hard it is to take that opportunity, you should take it.

BTB
I read where Elizabeth Blackburn, a Nobel prize winner, was asked about the virtues of successful scientists, and she said it takes resilience and persistence, as well as being opportunistic and creative. Does that resonate with you at all?

DR. JOAN WITHER
Definitely. I think resilience and persistence probably is the part that resonates the most with me. You know, when you come into science, most people who are in science have been pretty successful in their high school career, in their undergraduate career. And nothing is more humbling, I think, than being a scientist. There's lots of times that you fail

or that things don't work and you have to be resilient because you have to basically figure out, okay. So that was a problem. Or that didn't work. Now how am I going to solve that. Or okay, that hypothesis was wrong, but well then what is the right hypothesis? And then you have to figure out once you have another hypothesis, how you're going to actually test it. So I think you have to be very resilient and resourceful in terms of defining your experiments and doing them.

BTB
You're a scientist and a clinician, so you see patients, you know, the urgency for improved treatments, the need for cures. How do you reconcile that urgency with the fact that medical research takes time?

DR. JOAN WITHER
Yeah, medical research does take time. I think, you know, by seeing patients, I would say that it really motivates you to go back into the lab and to try to solve some of these problems. Because working in the lab is very open ended. There is an, it's not a nine to five job. I think it's a resolve, because you're you're motivated, you probably work way harder than, than you would if it is a nine to five job. It's very results oriented. And so you're more interested in doing whatever you have to get this result or to get this answer. And seeing patients, I think, motivates you to try to do patient related research. Research is going to have an actual impact on your patients and sometimes their research questions come out of things that you discussed with your patients in the clinic.

For example, a lot of my pre-clinical patients have fatigue, and so the question was, is fatigue a marker that you're going to progress ultimately to a sard because sometimes is sards associating with fatigue, or is it not? And so coming out of our clinic, we just did that study. We asked the question, are people who are fatigued more likely to progress to sard than people who aren't? And the answer was no, that they weren't more likely to progress. So now I can say, look, I did that study and I can tell you that you are not at increased risk of progression.

BTB
Do you ever get frustrated with the day to day of trying to advance this disease knowledge?

DR. JOAN WITHER
It is a complex process, and I do think that, you know, it's not the kind of disease where there is, the answer is real simple. Because if it was simple, I think we would have found it already. It's very complex and I think part of the problem with sard is, or we're not really sure what the chicken and what the egg is. You know, you would have said that all these immune abnormalities that we saw were what caused sard, but then we saw them in otherwise healthy people. So you can see that that clearly by itself is not enough to cause sard. So I think because they're complex and because there's an interface between the environment and genetics. I mean, they are difficult things to get a handle

on. And I think that's why it's really important, as I've found over the years, to contrast people with symptoms and those without symptoms and to try to break it down into the steps that are involved with getting sard. And the same thing applies to lupus. To not to just study flare patients against quiescent patients, but to figure out when a patient flares, what's different about their immune system, when they flare and then when they settle down. How does that look and how does that differ from the flare as I said, and try to get a handle on it from doing what's called a longitudinal study, which is actually much, much more difficult to do than one where you just compare some flaring patients and some who are inactive?

BTB
You talk with such enthusiasm about your work. I'm curious what keeps you going every day?

DR. JOAN WITHER
I think what keeps me going every day is I love my work. I think that's what keeps me going. You know, it's, it gets back to this: find something that you're really passionate about and do it as your job. Because work is an important component of your life. I'm not that unusual as far as scientists go. I think that scientists have a passion for answering questions, and the phenotype of a scientist is that you get up in the morning and you're going, okay, how am I going to do that experiment and how am I going to answer that question? And these things are constantly percolating around in your mind, and that's kind of exciting. And we are in, I think, a unique time. What we can do now to discover what's going on in terms of causing diseases and approaches to treating diseases is light years above what we could do 30 years ago when I started. So I think it's really exciting at this point, and I guess that's what keeps you going. That a, the questions are interesting and b, the research is really exciting, probably more exciting, more collaborative than it's ever been in the past. And the prospect of finally getting some answers is much more real than it was many years ago.

BTB
What should we look for next from you, Joan? What's on the horizon?

DR. JOAN WITHER
I'll continue to do work on the questions that I've outlined, but at some point I would like to translate what I'm doing to actual stuff that will improve patients lot in life and basically bring some of these biomarkers and some of these insights to the bedside so that they can have actual impact on patients. It's always been a goal, but I think it's more of an achievable goal at present, and that's probably where I'm going to focus a lot of my attention in the next few years.

BTB
Dr. Joan Wither award winning senior scientist at UHN’s Krembil research institute, thank you so much for sharing your groundbreaking research with us and continued success.

DR. JOAN WITHER
Thank you.

BTB
Dr. Withers research is made possible, in part thanks to generous donor support. If you'd like to contribute to her pioneering medical research, please go to www.uhnfoundation.ca/podcast. And for more on the podcast, go to our website. Www. Behindthebreakthrough.ca and let us know what you think. We crave feedback. That's a wrap for this edition of Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at the University Health Network in Toronto, Canada's largest research and teaching hospital. I'm your host, Christian Coté. Thanks for listening.