Season 1 – Episode 8 – Dr. Valerie Wallace

Transcript

CHRISTIAN COTE

Welcome to Behind the Breakthrough the podcasts all about ground-breaking 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 Cote and our guest today on the podcast is Dr. Valerie Wallace, award-winning senior scientist and co-director of the Donald K. Johnson Eye Institute at UHN's Krembil Research Institute.

Dr. Wallace is a pioneer in research aimed at curing eye disease. She joins us in a minute. But first here's the backstory on Dr. Valerie Wallace. Growing up in Ottawa, Valerie remembers as a young girl Saturdays were spent driving around with her dad helping with errands. They'd often listen to a CBC radio program called Quirks & Quarks, to this day Valerie recalls an episode that helped spark her desire to pursue a career in medical research. A scientist was being interviewed about a study that showed the body's immune system could be used to kill cancer cells. How cool is that? She thought. Her curiosity had been triggered. In grade school. Valerie began reading biology textbooks in her spare time. Thanks to her mom, a teacher. Her goal was to better understand what we know about a subject or disease and what we don't know. Then zero in on the gaps of knowledge to try and solve the problem. For over 20 years now Valerie has applied that curiosity to pioneer stem cell based research with an eye to restoring vision in people blinded by diseases such as macular degeneration and retinitis pigmentosa.

Dr. Valerie Wallace senior scientist at UHN's Krembil Research Institute, welcome to Behind the Breakthrough.

VALERIE WALLACE

Thank you. Happy to be here.

CHRISTIAN COTE

Macular degeneration and retinitis pigmentosa, what's happening in the eye with these diseases occur.

VALERIE WALLACE

That's a very good question cause they're two very different diseases. But ultimately what happens is there's a defect in the retina and the retina is the nervous tissue that lines the back of the eyeball. It's a very thin layer of nerve cells that we need to see. If you look closer into the retina, what happens is you have a dysfunction and ultimately death of photoreceptors and photoreceptors are these highly specialized cells that capture light. So in humans most of the

cone photoreceptors are located in the central part of your vision. That's the vision you always used to see somebodies face to recognize them to see color to read and they're located in the center retina and in macular degeneration, those particular photoreceptors die off and what happens then is people lose their central vision. So people with macular degeneration might be able to see objects at the edge of their vision but they're going to have a lot of trouble reading.

In retinitis pigmentosa, typically not always but it's a condition where the other kind of photo receptor dies the rod photo receptor and those are the ones you need for peripheral vision for night vision. So people with early stage retinitis pigmentosa will have problems seeing at night, and they may not recognize they've got a vision problem for a long time because our world is very well lit. People don't really have to worry about navigating in the dark but what ultimately happens is both types of photoreceptors die in retinitis pigmentosa because it turns out the cones need the rods.

So if the rods die off for reasons we don't entirely understand the cones die off but ultimately both diseases are a degeneration of those critical light sensing photoreceptors that you need for vision. If you don't have them your eye can't detect light and then that information is not sent to your brain. And so you can't see your world.

CHRISTIAN COTE

What do we know about why these diseases occur?

VALERIE WALLACE

In the case of retinitis pigmentosa we know a lot more, over the last 30 years or so we've identified over 200 genes that cause the condition in humans and the inheritance patterns how you get it from your mom and dad can be quite varied sometimes it's only in boys it's X linked sometimes it's a recessive gene you have to inherit two bad copies one from each parent and sometimes you only need one mutant copy of the gene and some of these genes encode for proteins that are only ever expressed in photoreceptors. So some of these proteins never are made and that makes photoreceptors never work in the first place or some of these proteins are expressed everywhere

CHRISTIAN COTE

Express meaning occur or…

VALERIE WALLACE

Occur or are present in many cell types in the body and we don't understand why it's photoreceptors that are so sensitive to changes in those proteins either their levels or their function. So it's a very complicated disease. And the good news is that there are more and more preclinical studies showing that certain forms of RPE might be amenable to treatments like gene therapy. But those are still early days but very promising.

VALERIE WALLACE

Macular degeneration is more difficult. There are inherited forms of macular degeneration where people lose their cones and their central vision but that's extremely rare. Mostly it's a disease of aging. So not every old person will get it but typically it is older people who get it. And why do they get it? Well it's probably combination of genetics but that's very complicated. There's no one critical Gene. We know there's a link to the immune system could it be years and years of chronic inflammation at the back of the eye? That's one theory right now. And environment, so years and years maybe of smoking. Smoking is a risk factor.

CHRISTIAN COTE

Really. I did not know that.

VALERIE WALLACE

Yep might contribute to the disease. So it's kind of a perfect storm of factors genetic environmental inflammatory that converge to create this problem. So it probably is simmering there for many many years before people even realize that they're going to have a visual deficit.

CHRISTIAN COTE

What are we talking about in terms of the scale of the problem of these diseases in Canada?

VALERIE WALLACE

So right now in Canada over 4 million people are blind or visually impaired.

CHRISTIAN COTE

My goodness.

VALERIE WALLACE

And by 2030 that number is expected to double. So the leading causes of blindness right now in western developed countries are retinal in nature. So a macular degeneration is the leading cause followed by glaucoma and the next on the list will be diabetic retinopathy. And what used to be cataract but we solved that problem because we can repair cataracts surgically.

But now we're worried about these retinal diseases and I should point out that all of these diseases are associated with aging. Like I said not everybody who's old gets them but you have much higher risk, the older you are to get these diseases and yes going blind might not kill you right away but people have visual impairment have a much higher risk of mortality morbidity depression and even very specifically people who have low vision have a higher risk of hip fractures. They fall. They injure themselves more. And we already know that those kind of problems lead to a lot of morbidity amongst the elderly.

CHRISTIAN COTE

And what's on offer right now in terms of treatment?

VALERIE WALLACE

AMD treatment or macular degeneration treatment was revolutionized in the last decade or so through the use of drugs that were originally targeted for cancer therapy. So about 10 percent of patients with macular degeneration get what we call wet macular degeneration. And that's when. There's leaky blood vessels so the disease progresses to the point where the body's reaction is to make blood vessels. But they make very bad blood vessels and these blood vessels leak and leak blood into the eye which means you can't see. So there were a class of drugs developed for treating cancer patients called anti vascular agents. They basically shut down the proteins that are driving the formation of new blood vessels. Everyone thought this would be amazing in cancer but where it's been incredibly amazing is in the ophthalmology. So many patients who would have gone blind because of this complication converting from dry to wet AMD, now have this sight-restoring therapy by injection of these anti-blood vessel agents into the eye.

But right now aside from that critical advance we really don't have much to offer people with dry macular degeneration, which is 90 percent of the people with macular degeneration, except for lifestyle modifications don't smoke eat a diet that's healthy and antioxidants. And unfortunately you can't stop getting old so that ones off the table.

CHRISTIAN COTE

So with this knowledge that you've built up about the eye how did you come to the conclusion that you wanted to focus your research on applying stem cell research to the eye?

VALERIE WALLACE

We had typically studied how the eye is made. And I'm a firm believer and I think this bears out in many areas of stem cell and regenerative medicine. If you want to fix something or rebuild it you have to know how it's made. We'd spend a lot of time asking how things are made and at the time we had many tools available to us because of advances in the field to start asking questions about could we use our information to try and repair the retina. So that project about can we put cells in and repair the eye that just was a very logical extension of the way the field was moving deploying its knowledge about how things develop into trying to repair the unrepairable. And so we were asking a very simple question since photoreceptors in the eye don't regenerate mammals do not regenerate those cells other animals do by humans and mice do not. What about if we just gave them fresh cells healthy cells? Would that work? It's not a crazy question. People have been trying to get this crazy well at the time I was quite skeptical about whether it would work.

CHRISTIAN COTE

You were?

VALERIE WALLACE

Very skeptical. Yes.

CHRISTIAN COTE

But yet you decided to go down that path.

VALERIE WALLACE

I did because I thought it was a good idea to harness what we knew about development to try and look at a disease to try and treat a disease that's untreatable. But I'm a scientist so I think nothing's ever going to work sometimes. And also why did I do it if I was so skeptical?

Sometimes when you do experiments you learn things you didn't anticipate that you would learn that can be extremely useful. And so I figured we will learn something about the biology of photoreceptors or maybe about why these cells die in the first place or even how does the retina the damaged retina, respond to these insults? We might learn something that we could use actually to treat some of those diseases. So that's why we started doing those experiments.

CHRISTIAN COTE

So I understand a lot of vision research focuses on rod cell transplantation. But you went down the path of cone cell transplantation. What's the difference between the two, and why did you choose cone cell? Was it a coin toss?

VALERIE WALLACE

That's a really good question. Two reasons why we chose cones one no one was doing that and clinically the biggest problem for patients when losing their vision is loss of central vision that's incredibly debilitating. So in terms of what you would what I thought would help patients a lot in the clinic would be to restore or at least help them maintain their cone cell function.

The second reason was really just luck. I was working with a colleague who had developed a tool where we could purify cone photoreceptors, I should point out cone photoreceptors in the systems we work with are very rare cells and we did not have good ways to pull them out selectively to be able to enrich for them so that we could really track their fate. You can't just put one cell in a mix of hundreds of non cone cells and expect to be able to find that cell again.

Well this colleague of mine developed a tool that would allow us to isolate cones and track them again sometimes science's serendipity--right time right place and that time we had a reagent and we had a really good question to ask.

CHRISTIAN COTE

A reagent meaning a tracking device

VALERIE WALLACE

A tracking device for cone photoreceptors.

CHRISTIAN COTE

So Valerie walk us through then the process of how research unfolds in your lab.

VALERIE WALLACE

So if we're asking questions about can cone photoreceptors engraft in an animal model of blindness what I mean by that is will they go in there and restore vision. So the actual experiments take a very long time to do. They start with collecting healthy cone photoreceptors from an animal model where all the cone photoreceptors are tagged with a green fluorescent protein tag.

CHRISTIAN COTE

Is that on their own? Like they generate that or do you do that.

VALERIE WALLACE

No we had to create an animal model where we express that genes called a trans gene and we can direct it to only cones through some of the genetic tricks we have. We then go upstairs and deliver those cells right to the eye at the back of the eye in a very delicate surgery called a sub retinal injection and typically where we inject them are the models we inject them are animals that are losing their own cone photoreceptors and then we wait we wait typically several weeks and then we need to look and see in those eyes Where did ourselves go and what did they do?

And sometimes we will look at the vision in those animals we have ways to ask how do they see? Do they see any better if they were transplanted or not?

CHRISTIAN COTE

And what have you found?

VALERIE WALLACE

Well a couple of surprising things that we found were that for a long time investigators doing these experiments. Remember they're using a green fluorescent protein to track their cells. And they saw green cells inside the retinas of the animal models where they transplanted the cells. And that's actually quite remarkable because those green cells really looked like photoreceptors like healthy photoreceptors. When we started to ask a little bit more about how cones were doing this there were a lot of things that didn't add up. So the cells that we saw that were green fluorescent protein expressing weren't cones. They were rod photoreceptors.

CHRISTIAN COTE

How they get in there?

VALERIE WALLACE

That's a good question. So the animal models that we were transplanting still had rods but they didn't have cones but all the green fluorescence was in the rods. And for example we knew they were rods because they didn't look like cones. And we have other ways of assessing cones and none of that looked like they were really cones. So then we started to think well are these cells really integrating or is something happening with the GFP, the green fluorescent protein. Is it the tag is something happening with that tag?

So I remember sitting around a conference table and we thought of what are the 10 experiments that we could design to really ask?

Did those cells integrate or did they somehow donate that green fluorescent protein? So in a frenzy of experiments over the next three months we did that and we discovered that in fact no the cells were never integrating. And in fact what they were doing was donating their green fluorescent protein to the cells in the animal models.

CHRISTIAN COTE

And what was happening to the cone cells?

VALERIE WALLACE

They were just sitting there fine, happy where we delivered them to the sub retinal space but they were never connecting with the host retina. I think we would love to get cells to integrate and what we thought was actually even more interesting to understand right now is how are these cells transferring this protein because that's an awful lot of protein to transfer. Cells don't do something that they're not capable of doing just because they were transplanted. So my labs been working very intensively to try and understand how cells are doing this protein transfer.

Also not just because it's interesting biology and I think it is but maybe they're trying to connect and that's a consequence of being not able to do it properly. And so what we think is happening now is in fact these cells are really trying to connect but they're not doing it the right way. And because they're not doing it the right way they're transferring to the host cells lots of things not just green florescent protein, but even proteins they make normally are being transferred and we think it's a consequence of the cells trying to mature and make a connection. So this is an example of I think we could probably harness that behavior could we redirect those cells to connect properly?

They're trying to do it which we were very surprised and now actually I think we have a way maybe to direct them to connect properly so that maybe they could restore vision but we'd have never known that if we hadn't done those kinds of experiments.

CHRISTIAN COTE

How unique is the research you're doing in your lab?

VALERIE WALLACE

There are very few labs across Canada that are doing cell transplantation to the eye and there's maybe a handful of labs around the world that are doing photoreceptors cell transplantation. But the field is very fast moving investigators are now able to make human photoreceptors in a dish quite easily. And I think it's only a matter of time before we start transplanting humans with vision loss with photoreceptors cells. So I think those kinds of clinical trials are imminent and I think us understanding these basic problems about cell transplantation will be very important for investigators to understand how cells behave even in humans.

CHRISTIAN COTE

So what's next in your lab? What what are you focused on?

VALERIE WALLACE

For cell therapy to work in the retina, what I think we really need to understand is how to get these neurons to connect? They are essentially neurons and neurons need to talk to another neuron in order to relay information. It's a big relay system. What the field hasn't solved in photo receptor transplantation is how to get photoreceptors healthy ones to reconnect. And I think what we're starting to understand are the players that help photoreceptors normally connect to the retina. And if we understand that problem we could develop tools to use that therapeutically. Maybe we could boost the connectivity part of human photoreceptors in transplants that are going into patients or select the best photoreceptors that have the capability of connecting.

And it will also inform which patients we transplant. What kind of fertile ground has to be there for a donor photoreceptors to connect? That might really influence what patients and at what stage of their disease that you will transplant. So I think by understanding these basic problems you know in the basic biology lab it will help inform the clinical studies so that actually they will be successful.

CHRISTIAN COTE

You're listening to behind the breakthrough podcast 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 Cote. We're speaking today with Dr. Valerie Wallace, award winning senior scientist and co-director of The Donald K. Johnson Eye Institute, at UHN’s Krembil Research Institute. Dr. Wallace is a pioneer in cell based research aimed at curing eye disease.

CHRISTIAN COTE

I’m curious if you ever feel pressure?

VALERIE WALLACE

I feel under tremendous pressure to get things into clinical trial to discover new targets for therapy to get grants to make discoveries. And I have to let that die down in the back of my mind and just do the best science that we can do and ask very important questions and sometimes they're not easy questions to ask or answer but I think that's where we're going to make important contributions. And people also have to remember that we are doing this because we do have in mind the people who are living with these conditions and who are desperate for treatments. But we also know that we need to do it carefully. I'll give you an example why… there have been clinics in other countries that have been transplanting people with what they call mesenchymal stem cells into the eye. And this has caused people to go blind.

CHRISTIAN COTE

Sorry what were they injecting?

VALERIE WALLACE

They are injecting stem cells what they call mesenchymal stem cells. I think isolated from the fat or other tissues in patients and re injecting those cells into the eye. And I understand why patients would want to have something done when there are no treatments but several of those people actually lost what vision they had and went blind because of those very unresearched treatments. So I think while people are very desperate for a cure I would also point out that you don't want to have those kinds of terribly unfortunate events happening and that's why I think people can appreciate why we want to do this carefully and have as much evidence that something's going to work in an experimental system before we ever test that in a human.

CHRISTIAN COTE

The scientific journey it takes time as we've been discussing it also contains roadblocks and failure. What's your approach to those challenges?

VALERIE WALLACE

So as I say to the trainees in my lab is it a failed experiment or is it a negative experiment. Failed Experiment means something technically went wrong. You won't know your answer at all. OK you got to figure that out. A negative experiment is interesting it tells you something. So you build on that don't panic. What does that actually mean? And sometimes you might be at a loss for where to go next. That's OK because you might have to think a little bit longer about your problem. But usually people come up with the next question they need to ask and I would also say if everything works that's too easy. We're used to having a lot of fails but negative answers are OK and they help guide you with how to do or what to do next.

CHRISTIAN COTE

You and I have talked in the past and I love an analogy that you used about a scientist is an explorer. Talk to us about that.

VALERIE WALLACE

The scientists are going into the unknown. We're discovering things that nobody has seen before. You have to have a lot of passion and curiosity and it has to be something fundamental to your makeup because you will fail a lot and you have to enjoy those moments where you see something amazing and they do come. Because if you don't ask very hard questions you won't get amazing answers. So I think yeah it's a long journey but it's an exciting journey. And some of the best things that I've seen in my career when students in my lab make a discovery they usually fall over them they stumble on these discoveries and to see a young person so excited that they discovered something that nobody else has and they're the first to do it. It's a great icing on the cake in my career and I think it's an incredible career to have to be an explorer.

CHRISTIAN COTE

I'm curious though, do you ever have doubts? Do you ever go, am I making a difference?

VALERIE WALLACE

I don't doubt that we're going to make a difference. What I don't always know is what that will look like and I think any scientist who tells you that they know how this is going to pan out is probably wrong. What I can say is that over a cumulative 30 years I've made discoveries that have impacted things that have even gone into the clinic.

But you also have to remember and be humble about it that these solutions to these problems involve people working on a big puzzle and most people are contributing a few pieces to that puzzle. They're important pieces. They probably give fundamental knowledge for the next person to find the next piece of the puzzle and I think that's incredibly satisfying.

So I don't go into the lab thinking I'm going to find the blue juice that is going to cure this problem but I do go into the labs thinking we are going to understand this problem better so that either we will find a cure or somebody else will. And so I don't have doubt about that because of the scientific method and because of our rampant curiosity.

CHRISTIAN COTE

Is there ever a sense of isolation in this work for you?

VALERIE WALLACE

A lot of people think that science is done in a very quiet set off siloed environment and nothing could be further from the truth. The lab is an incredibly dynamic crazy place with a bunch of young people who are very very curious about whatever question they're asking in the lab and

they work together. It's very very collaborative. You know something I don't know if you're going to help me and back and forth or I don't understand this result. And then that leads to a conversation that may take an hour. So I don't find it isolating.

And also you need to talk to your colleagues who might be anywhere in the world either at meetings or you email them? And again I find that a very collegial interactive process. So no I wouldn't say science is a guy in the basement lab tucked away who doesn't talk to anyone. In my experience research is incredibly dynamic environment to work in.

CHRISTIAN COTE

Prior to going on the air, you mentioned some key moments in your education where teachers gave you a boost. When you reflect back, what role has mentorship played in your career trajectory?

VALERIE WALLACE

I think mentorship has been huge. Right from high school having teachers that believed in your cause actually I almost failed grade 9 science and wanted to drop science…

CHRISTIAN COTE

Should we edit that out?

VALERIE WALLACE

No, a lot of people come to this through very strange roots but I had some amazing science teachers in high school that just seemed to be able to convey the information in a way that I got it and thought it was really interesting and they were males and females.

I had some really wonderful mentors in undergraduate training who encouraged me to go into research instead of medical school and then I had really wonderful mentors who had a lot of faith in me and provided me with a lot of opportunities to do what I do today and that would be when I did my PhD with Dr. Tak Mak University of Toronto? And when I trained with Martin Raff at UCL and then a number of people in senior leadership throughout my career as an independent investigator who made it possible for a young person to succeed in science and those people were instrumental in building institutes getting them funded providing the resources and the encouragement and the infrastructure for young scientists to succeed. So mentorship has been critical.

CHRISTIAN COTE

And what's your approach today as a leader to mentorship?

VALERIE WALLACE

It's very important to be encouraging to talk to young people about what their career aspirations are and to tailor their research projects so that they make sense for those career aspirations. To be a role model in terms of scientific integrity to not be afraid when things don't work to show people how to use that as an opportunity. And then more generally in my leadership of the eye institute. I'm a builder and just like senior people made it possible for me to succeed. I think it's a very important role that I have is to make sure that investigators at the Eye Institute are the best that they can be and that we can recruit the best people to have a very fertile research area in vision because I think that is what is going to give us the information and the discoveries that we need to change the outcome for people with retinal diseases.

CHRISTIAN COTE

I read a story as part of my prep for speaking with you today where you said when you first emerged as a principal investigator in your own research lab in the late 90s there weren't many women principal investigators. Talk to us about that experience.

VALERIE WALLACE

When I started my lab in 1998 I believe there were only two women investigators in the entire Institute.

CHRISTIAN COTE

And where was that?

VALERIE WALLACE

That was in Ottawa. You know at the time there weren't very many women who continued past PhD into postdoctoral studies and then to be PI's. So I think it was a reflection on just the gradual drop off in female participation at the later and later stages of research careers.

CHRISTIAN COTE

That's just a given?

VALERIE WALLACE

No that's really changing. There's more and more women involved in research and I've seen that change over time is more and more women in leadership including myself. So that has changed what I can say though is that I still worked in an incredibly supportive environment, maybe many of my colleagues were men but they were very enlightened men and it really didn't matter that I was a woman. I just seize those opportunities. But I know it has changed and it's changing for the better. There are more and more women represented through the ranks through a research careers now.

CHRISTIAN COTE

What has changed that reversed or has tried started to maybe perhaps halt that trend that you're talking about? The drop off I mean.

VALERIE WALLACE

Why do women drop out? Maybe they find something better to do. No one ever thinks about that possibility but also that I think there's more female role models. So I think the more young women who see senior women having a research career and having a life is an encouraging thing. I think there's more and more women generally going to university. So right away you're going to increase the odds of people going on to graduate work and then beyond and staying in academia. I think the perception that science is boring or unexciting I think that's changed tremendously because I think there's just been more news about research about genetics about stem cells is far more reported now. So people hear about these things and they're exciting. So I think that encourages young people boys and girls to pursue careers in STEM in science technology engineering medicine.

CHRISTIAN COTE

So what would be your advice that to a young aspiring scientists perhaps maybe still in high school who doesn't quite know where to go?

VALERIE WALLACE

If you're inherently curious and this is something you have to do and would really enjoy doing then go and talk to professors who run labs go and talk to the students in their labs find out what an active research environment looks like. Many undergraduates are turned off maybe by the lab work they may do as an undergraduate it's very prescriptive and it's when they get into a basic science lab that their perspective is completely altered.

I remember as an undergraduate thinking that the chemistry graduate students were heroes. They worked all the time and they looked exhausted but it was obvious that they loved what they were doing. Talk to them talk to the grad students who you know T.A. your labs. Ask them what they do, ask them to go on a tour. Spend time as a summer student in a lab and doesn't really even matter what topic you'd be amazed at what research really looks like in you know the type of stuff we do what it really looks like in an active basic science lab. And it's very exciting. So don't be shy. Go talk to those people because usually they love to tell you what they're doing.

CHRISTIAN COTE

And anybody out there listening who is curious you can actually go online to the UHN YouTube site and see Dr. Valerie Wallace’s lab in action. What keeps you going every day?

VALERIE WALLACE

I like to think about problems. I really love to sink my teeth into a juicy problem. I find that exciting. I like talking to the people in my lab about their results. I love going to the microscope. So those are the kinds of things that really make my day.

CHRISTIAN COTE

Dr. Valerie Wallace senior scientist at UHN's Krembil Research Institute. Thanks for speaking with us. And continued success.

VALERIE WALLACE

Thanks very much.

CHRISTIAN COTE

For more on the podcast go to our Web site www.behindthebreakthrough.ca and let us know what you think. We love feedback. That's a wrap for this episode of Behind the Breakthrough the podcast all about groundbreaking medical research and the people behind it at University Health Network in Toronto. Canada's largest teaching and research hospital. I'm your host Christian Coté, thanks for listening.