Season 2 – Episode 6 – Dr. Sonya MacParland

Transcript

CHRISTIAN COTÉ:

Hello and 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. And joining uson the podcast today, dr. Sonya Macparland, award-winning scientist at UHN's Toronto general hospital research institute, whose pioneering workto map the liver was a world first and is now triggering a paradigm shift in liver research and therapy.

Dr. Sonya Macparland, welcome to the podcast.

DR. SONYA MACPARLAND:
Thank you. Thanks for having me.

CHRISTIAN COTÉ:
Let's frame your work first by starting with the big picture, if you don't mind, sonya, if you could just give us a sense of thescope and burden of liver disease in Canada.

DR. SONYA MACPARLAND:

So, liver disease is a very serious problem in Canada. It's estimated that one in 10 people in Canada are suffering from liver disease. So that means they either have things like hepatitis b virus, hepatitis c virus, fatty liver disease, autoimmune liver disease or liver cancer. And so the problem is, is that unlike other organs, there's no machine that's available to replace the function of the liver, which has hundreds of functions, including metabolizing food, creating clotting factors and clearing toxins from the blood. And so in these patients who develop liver disease, in some cases, the only option is liver transplantation. And that leads to a huge problem because of the fact that there are not enough organs available. So up to 25 to 30 percent of patients who need a liver transplant will not come off the waiting list due to a lack of organs.

CHRISTIAN COTÉ:

So, Sonya, when you first entered the field, how wellunderstood was the liver itself?

DR. SONYA MACPARLAND:

So, that's a great question. So, there were some very elegant and beautiful studies that had already been done on the liver, and they used the most advanced techniques that were available at that moment. So we knew from histology, which is looking at the patterns of the cells, and we also looked from different assays using biopsies from the

Liver, that there were hepatocytes that make up the liver. And they'rekind of the workhorses of the liver.

CHRISTIAN COTÉ:

Hepatocytes?

DR. SONYA MACPARLAND:
Hepatocytes.

CHRISTIAN COTÉ:
Okay.

DR. SONYA MACPARLAND:
And these cells are the workhorses of the liver. About 80 percent of the liver is made up of these hepatocytes. And so they're the ones that are pumping out these clotting factors. They're the ones that are secreting factors that break down fats, but they're also supported by cells that are not hepatocytes. And they were also describedin the liver. But the way that the liver had been described, if i can use this as an analogy, was almost like a smoothie. So what you would do when people were mapping the liver, if they take a tiny piece of the liver and they would mash it up or what we call homogenise it, and then they wouldlook at the different patterns within that tissue. So, we're looking at the rna at this point and that would tell us what messages and what functions are in those cells and what those cells are.

But if you can imagine, if you blend up a smoothie and that smoothie is mostly made up of banana and there's a little bit of blueberry in there, it'sgoing to taste like a banana smoothie. And so what we were seeing was an overwhelming signature from hepatocytes. And so, you know a lot about hepatocytes, but not so much about the support cells, like the immune cells on the endothelial cells that are a very small proportion of the cells in the liver, but are thought to have a very important function. So, you know, we want to kind of take things from that understanding of the liver, as you know, the most overwhelming signature within the liver to looking at even the small, rare populations within the liver.

CHRISTIAN COTÉ:

so, this knowledge gap of this smaller group, aside from themajority of hepatocytes, that's sort of the knowledge gap that you wanted to tackle then with your research?

DR. SONYA MACPARLAND:

Absolutely. So, we wanted to know, what are the different populations of the cells within the liver. And from there, we really wanted to look even deeper into subpopulations of these cells because you can have a population of cells within the liver that has multiple functions. And one of the neat things about the liver, it's very unique. The liver has an amazing regenerative capacity. So, it's, it's quite amazing that you can cut off you know, 75% of the liver and it will growback. And so there are cells that can support that regenerative process.But in these patients that have end stage liver disease, there are also Cells that have these regenerative abilities. But they're not able to perform their function because there are kind of dueling cells that areinflammatory.

So, they're kind of fighting against the regeneration, so you kind of need anot so much a

balance, but you really have to have your regeneration prevailing in the liver for the liver to be fully healthy.

CHRISTIAN COTÉ:

so, tell us how you set about the process of trying to determine what are these minority cells, so to speak, in the liver thatwere not well understood?

DR. SONYA MACPARLAND:

What we wanted to do or what we did was we wanted to take the cells to a single cell level. So what we wanted to do isseparate the very small cells from the larger cells, the hepatocytes fromthe endothelial cells that line the vessels of the liver. And then we also wanted to pull the immune cells out and they're kind of sitting between cells in the little tiny blood vessels of the liver.

And so, we knew if you used a biopsy and crushed up the tissue, you wouldn't be able to see these cells very distinctly. So what we wanted to do was we wanted to introduce very gentle reagents that could go into the tissues own vasculature and then would just kind of gently tease these cells apart. And so, what that allows you to do is tease them apart to the point that they're released, but they're still healthy and viable. And so, then what we could do is use something called single cell rna sequencing. Which instead of taking the rna profile, so, the genes that are expressed in the whole tissue, we looked at the genes that are expressed inthe individual cells and what knowing that gene signature does is it tells us what the cell is and what some of its functions are.

CHRISTIAN COTÉ:

Explain to us how you were pulling this process off in terms of what were you performing your tests on or your research on?

DR. SONYA MACPARLAND:

So, that is the most exciting part of this whole project. So, you know, as a team, we kind of sat down and said, where is thisgap? So we knew actually a lot about mouse liver. We knew things about rat liver, but we didn't know very much about human liver.

And this is because it's very difficult to obtain human tissue that is ableto be perfused with those enzymes that i was talking about.

CHRISTIAN COTÉ:

So, these are the reagents that help?

DR. SONYA MACPARLAND:

That disrupt that, the junctions between the cells,but in a very gentle way. So you know, within the program, at UHN, the Transplant program at UHN, we had my surgical colleague, Dr. Ian Mcgilvray, was able to, as part of his transplant technique, was actually removing the caudate lobe to provide access for the liver transplant surgery. So he was able to take these tiny pieces of discarded human tissue,sew them off, and then we would transport them to the lab, cannulate them with any exposed vasculature that might exist, and then gently introduce these enzymes into dissociate this tissue so that we could just

very, very gently release those cells.

Because the unique thing about the liver is that not all the cells are equal in their ability to respond to things like chopping and dissociating. For example, hepatocytes because i mentioned earlier, they're very regenerative. You know, they can be replaced very quickly. So, they're finewith if there's a situation of stress with those cells dying because they know they're going to be replaced. So, they're very sensitive to any kind ofstress because as a cell, they're very quickly replaced. So, what we had to kind of work towards is making sure we didn't disrupt the hepatocytes while dissociating them enough to release them.

Because what we really want to have is a complete map, because using this technology, we can look at the, the way the cells interact with each other, not the individual populations, because, again, we're always lookingtowards how we can use this as a benchmark for disease. So eventually what we want to do is be able to compare our healthy map to our disease map to find those strange populations that pop up in disease or populations that are not present in disease that could be mediating you know this balance in the liver or cells that should be communicating to each other that just stop communicating to each other during disease.

CHRISTIAN COTÉ:

Quick sidebar here on process, because this may be instructive to others. There must have been some ethical issues you were dealing with in terms of taking a portion of a removed liver due to transplant to be able to test on a research like how did you even come upwith that idea in the first place?

DR. SONYA MACPARLAND:

Well, this is discarded tissue, and this was discardedtissue during the transplant procedure. And so, you know, for years and years and years, that tissue was just being binned. So the idea was, well, you know, can we take this tissue and can we look at this tissue and use it to understand really what a healthy liver looks like?

CHRISTIAN COTÉ:

Right. I'm wondering, was there ethical issues or rebstandards that had to be achieved or permissions gotten for that?

DR. SONYA MACPARLAND:

Certainly. So, for any human research, there has tobe ethical approvals and reb's.

CHRISTIAN COTÉ:

So, take us back to the first testing that you started to doof this human tissue of the liver. What was the process?

DR. SONYA MACPARLAND:

Right. So, the process was quite interesting because we would take the tissue to a single cell level and then we would have to determine whether our soup of cells was the right soup, because if you dissociate the tissue too much and too harshly, you'll actually kill off allthe hepatocytes.

If you do it too gently, then you won't release cells from the tissue that needs to be included in the map and that would make an important part ofthat map. And so, when we first started disassociating the tissue, we actually would disassociate it to the point that hepatocytes would die.

So, we would have this liver that we knew when we went into the assay that this was a beautiful liver and it would come out looking like an immune organ. It was just all the rare cells. We wouldn't see a lot of thehepatocytes. And so then we knew we had to tweak those techniques to bring it down to a more gentle dissociation.

The other thing, as-

CHRISTIAN COTÉ:

I just when you say dissociation, you mean essentially teasing out these lesser known cells apart from the hepatocyte cells?

DR. SONYA MACPARLAND:

Exactly. And the thing about single cell technologies and single cell transcriptomics, it's not very forgiving. If a cell is damaged, it will have a very clear damage signature and the genes that you can detect are very low. So, you know, at the beginning, we would see a lot of dead cells. And the interesting thing that we saw was that youknow, the typical techniques to remove those dead cells would actually totally change our map. So, every time we would manipulate the cells at all, we would lose some of those cells. And then all of a sudden the map would seem skewed the wrong way because we always would have a slice of tissue that we can look at under the microscope to make sure, you know,is this all lining up.

CHRISTIAN COTÉ:

So, once you teased out the hepatocytes, what did youdiscover?

DR. SONYA MACPARLAND:

So, what we discovered was that the liver, as expected, was made up of 80 percent hepatocytes. But then we found thatthere was 20 cell populations in total within the liver.

And what we saw were we were able to take five healthy human livers and look at 8,444 cells within the liver. And we found populations along with the hepatocytes, which was expected. We found populations of endothelialcells that line the little tiny blood vessels within the liver. We found different populations of immune cells.

So, cells like t and b cells within the liver. We found small cells that makeup the bile duct called cholangiocytes. We also found populations of macrophages. So macrophages, if i can describe them as the eaters of the liver. So these are cells that have all kinds of receptors to scavenge things. So if you eat a fatty meal, if there's some bacteria coming from yourgut, they're the ones that are clearing all these bugs in the liver and they're actually able to clear them quite well themselves.

But the interesting thing that we found was that the macrophages, it waspreviously thought that there was a type of macrophage in the liver called a kupffer cell. And that was how you described liver macrophages. And what we found was that in the healthy liver, there are actually two different types of macrophages. There's, the macrophages that are your typical kind of kupffer cells, which are have properties that are very regenerative. And then there's another population that are more inflammatory within the liver. So, we kind of opened up an understanding of that there are more than one population of these eaters within the liver.

CHRISTIAN COTÉ:

So, of all these components of the non hepatocyte portionof the liver, what emerged for you in terms of what was the story there? What was there some was there things that you learned that you didn't know?

DR. SONYA MACPARLAND:

Certainly. So, the story really started to coalesce around the macrophages. And we were very excited about macrophages because within different models of liver failure and liver disease, for example, there are models in which you can promote regeneration by cutting off half the liver. It's called a hepatectomy model. In animals where you first take away all the macrophages, those livers don't grow back as quickly. So, you can tell that really suggests that macrophages have clear regenerative properties. And so, we were very interested in focusing on these as maybe in a healthy liver, you know, we may have moreof these than in a disease liver. So, we really wanted to look at the macrophages because of their clear role in liver disease.

For example, if you have a liver tumor or if you have a tumor, period, and it's surrounded by macrophages that are very immunoregulatory, that's areally bad sign you know, because they'll quiet the t cells around those

Tumors and prevent them from responding to antigens. And we know within the liver there can be tumors. It's called hepatocellular carcinoma. And we know that in livers that have liver cancer, there are quite a lot of macrophages that have these immunoregulatory properties.So, again, the end goal is to use these maps to really understand what's happening in disease and whether we can reprogram the liver diseased liver to become more like a healthy liver.

So, we were very interested in the fact that these macrophages had these two different properties. There were these inflammatory and non inflammatory macrophages just by their rna signatures. So the genes that we could pick up from those individual cells. So we wanted to take it a stepfurther. We wanted to look using pathway analysis to see what pathways were most active in each of these populations. What we found was in the immunoregulatory macrophages, they did have pathways active in cytokine suppression and in inflammatory macrophages, they had pathways active in response to bacteria in response to different types of microbes.

CHRISTIAN COTÉ:

So, tell us Sonya, how does your map now inform future research?

DR. SONYA MACPARLAND:

Yes, the map is actually informing future researchby really providing a rich benchmark for different groups to compare either their studies of liver disease or their efforts to generate different types of cells to repopulate a liver.

For example, I'm part of a medicine by design team here at UHN. And what they're doing is they're developing different cells like hepatocytes, endothelial cells and cholangiocytes from stem cells. And what they want to do is they want to take those stem cells and use those to repopulate a liver of someone with acute liver failure. What you really need to know before you go from these cells into a patient or an animal model is how close can those cells get to something that you would find ina human liver?

It's also part of a global initiative to really understand all human organsat a single cell level. So this is part of a greater project called the human cell atlas initiative. And the mission of this initiative is to understand the building blocks of all the organs in the body across different countries, across different ages and ethnicities. For example, if you incorporate multiple different maps into a single map, you can look at the differences, for example, in sex.

And the reason that that's so important from the liver's perspective or from the perspective of someone working in liver disease is that there areliver diseases such as prima cholangitis that in fact impact men more thanwomen. As well, there's primary biliary cholangitis, and that impacts women more than men. So, one of the things that you know, this map is helping to do is help them build a greater understanding of the liver so that you know, we can understand the differences between health and disease in young people, in older people, in women and in men.

CHRISTIAN COTÉ:

It seems like a paradigm shift in terms of the study of the liver. How does this then translate to, say, at the patient level in terms ofsay a treatment?

DR. SONYA MACPARLAND:

That's a really good question. So, one of the things that you know, we're finding with single cell rna sequencing is we can take a biopsy from someone's liver and we can look at individual cells thatmake up that biopsy. And so ideally, you know, we always approach our research with a big question and then little questions.

So, the big question is, you know, how can we understand the liver so that we can reprogram the liver so that people do not need a transplant. So some of the ways you could do that is if that patient's liver shows that a particular pathway is very, very active, you could repurpose a drug that'salready existing to reprogram that liver and to change that pathway or to get that patient over the hump of that you know, severe liver injury sothat the regenerative processes start again. So, understanding individuallivers at an individual level could conceivably lead to individualized treatment for liver disease.

CHRISTIAN COTÉ:

And is it simply a case where you say you take a biopsy and you discover it's a disease liver, that you could hold it over your map of a healthy liver and right away be able to pinpoint what is wrong with thatunhealthy liver?

DR. SONYA MACPARLAND:

In theory, yes, in practice, it requires very detailed bioinformatics work to you know, remove any batch issues and to correct for any differences that might just be due to processing. And this is something that is being really spearheaded by my research colleague, Dr. Gary Bader at university of Toronto. So, they're understanding how different ways that you process the tissue, or you know, when you use different, for example, chemistries, how you can exactly impose those maps. So that's called you know, batch correction and integration. And there's all these amazing tools that have even popped up since we published that original paper that are allowing that exact thing to happen.

CHRISTIAN COTÉ:

And your paper came out in 2018, if i'm not mistaken.

DR. SONYA MACPARLAND:

Yes.

CHRISTIAN COTÉ:

Congratulations. Who do you call in a moment like thatwhen you've got a world first mapping of the liver?

DR. SONYA MACPARLAND:

Well, there was a lot of excited calls to my, my mainresearch partners. So that's dr. Mcgilvray, who's a you know, completely dedicated transplant surgeon, and dr. Gary Bader, who is a brilliant biomathematician. But, you know, it's such a big question in liver disease that it was actually interesting. You get emails after the paper kind of saying, thank you for answering this question or thank you for taking thetime to do this, because this question has been bugging me for so long. And so, you know, you call those people, the people that you know, that have been really bugged by the fact that for all this time, you know, we just didn't know the cells that make up the liver.

Certainly, our understanding of the cells that make up the liver will grow as we incorporate more patients into the map, and we can expand to you know, look at pediatric liver. We look at male versus female liver. Butreally, it's a very great starting point. So it is very exciting. I certainly called up my my PhD mentor because we would sit in meetings and you know, we would use the blood as a surrogate for what was happening in the liver. And so any time you present at a conference, the last question would always be what's happening in the liver? And the question from thephd defense committee was always what's happening in the liver. So, you know, it's a question that's been bugging a lot of people in liver for a longtime.

CHRISTIAN COTÉ:

Well, congratulations. I understand also you've made thisdiscovery open access. What does that mean? Like how does that impact research and why did you do that?

DR. SONYA MACPARLAND:

We believe very strongly in publishing things, open access, so that people have access to all the materials, have access to all the code and all the methods, no matter where they are. And without them even having to contact us. Often, they'll fire us off an email. But we really want to share this as widely as possible so that if researchers don't have the ability to access healthy tissue because they're not in a citywhere there's a transplant center, but they're in a city where they're biopsying patients for a very rare liver disease that's very geographically centered, they can use this as their guide.

And so, it's very important for us to understand science is only going topush forward the field if it's being shared and it's being used. And we're

Part of the Chan Zuckerberg initiative were funded by the Chan Zuckerberg initiative. And one of the big things that this initiative really pushes as well, and we totally agree with that and very much believe in it,is, is sharing science as openly as possible. So we even share methods and protocols and data pre-publication.

CHRISTIAN COTÉ:

I'm curious, how do you know you have captured or isolatedevery single cell in the liver? How did you know like you could stop counting?

DR. SONYA MACPARLAND:

So, we don't. The very simple answer is we don't. Andso, when we have a scientific question and when we answered it in 2018, that's to the best of our knowledge in 2018. But we're always going to be building on this. For example, you know, we're building out our map 2.0.
There'll be more patients, they'll be stratified by age and sex. We'll usemore techniques to look at these different tissues to really pull out other subpopulations.

But one thing we thought about as a team is at what point should we sharethis data. And when we found that all five livers were clustering on top of each other and there was some very clear scientific messages from that, we said, you know what, we'll share this now and then we'll just keepbuilding. And at some point, the data could be replaced by other data or you know, we could even add additional populations. But we're fine with that because we've moved the field forward.

CHRISTIAN COTÉ:

I'm curious what makes the liver so difficult to understandthat we didn't have this information?

DR. SONYA MACPARLAND:

The liver is a very difficult organ to look at, first of all, because when you take tissue out of a liver as opposed to taking tissue out of a spleen or taking cells out of the blood, the tissue in the liver is very sensitive to any kind of stress. It's because of the fact that the liver regenerates and has this huge regenerative capacity. And so because it has this great regenerative capacity, if there is a liver injury, those cells, know, actually we can die. We know we're going to be replaced.So, they're very sensitive to any stress cues from within the tissue.

So, normally if you took an organ to a single cell level, you would mince that tissue. But what you really have to do with the liver is you have to introduce enzymes and very gently tease that liver apart. The other thingis it's very difficult to obtain healthy liver tissue. You have to be part of atransplant center. You have to have a fully engaged transplant team. And by saying engage, it's not just kind of lip service engaged, these transplant surgeons would have to actually add time to their transplant in order to

Get that tissue to you. And they would have to really be thinking hard about that, because if the communication is not there and that tissue sitson a back bench for eight hours, that tissue also is very sensitive to dyingwithout any manipulation.

So, there needs to be kind of a perfect storm of having this technology, having a way to take the tissue apart and having this amazing team that's really so fully engaged in research that at 11:00 at night when that liveris coming in, they'll fire off a text and get the whole thing moving while they're already planning their 12 hour surgery. So, it's a very unique team and a very unique ability that you don't really find in a lot of places.

CHRISTIAN COTÉ:

so, Sonya, in preparation for speaking with you, i came across a question you ask in response to a question about the purpose of your research. You said, quote, “how can we get the liver back to a normalstate,” unquote? How, how close are you to answering that question?

DR. SONYA MACPARLAND:

Yeah, that's a great question. It is a question that really guides my research, and it's part of that big question that we ask. So, the simple answer is it's a good step in that direction. So, in order for usto understand how we could reprogram, we need to know the gold standard, where do we want to end up? And so, you know, it's one of those steps in that 10 year process to understand. Here's our gold standard. Here's our expanded gold standard. Here's what we're seeing in disease.

And then using some of these brilliant drug discovery pathways or techniques that, for example, Gary Bader has developed, we can then findout which pathways we can use and how we can repurpose drugs to then reprogram that liver. But all this information is building towards understanding how these diseases look different than healthy. And how can we either remove a population that seems to be mediating disease or how can we shift that population to become more regenerative?

CHRISTIAN COTÉ:

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. Today, we're speaking withdr. Sonya Macparland, whose pioneering research led to mapping the liver,a world first discovery that has triggered a paradigm shift in liver research and therapy. Dr. Macparland's work is supported in part by the Toronto general and western hospital foundation.

So, Sonya, you're born and raised in st. John's, newfoundland. Your dad wasa chef, your mom a social worker. And I understand they nurtured your interest in science and medicine from an early age. Like take us back to iunderstand it's age six and a coloring book of encyclopedias.

DR. SONYA MACPARLAND:

Yes. So my brothers and sister and i, we had this encyclopedia set and they were color pictures. We couldn't even read them at that point. So our parents would read them to us. And it was aboutvalues, but it was featuring all these different scientists. And the one that really struck me was Marie curie, and it was the value of learning. And so it just really struck me that in her discovery of radioactivity, she lived a life of curiosity and constant learning. And it seemed like that kind of a life would be very exciting and very fulfilling.

CHRISTIAN COTÉ:

But you're in elementary school, like you can remember,connecting to that feeling of curiosity when you were, what, age six?

DR. SONYA MACPARLAND:

Absolutely. I broke a lot of toys, taking them apartand trying to do things with them.

CHRISTIAN COTÉ:

So, let's jump forward your recruitment to UHN. Whatattracted you to come here?

DR. SONYA MACPARLAND:

i was attracted to the scientific climate at UHN. It isso unique and the way that the UHN and the transplant program values basic science and clinical collaborations was absolutely amazing. The energy, the amount of interest in really great and functional collaborations was, was amazing to me. You can't really quantify the excitement that exists when there are people that are just able to sit down and talk about science for hours.

And this was something that really drew me to UHN. Also you know, it's a fantastic transplant program with unparalleled access to tissue and really within the institute themselves, they have a fantastic genomics core where, you know, if there is something that's going to come throughthe pipeline, it's going to be first adopted at the Princess Margaret genomics center. So, it just such an exciting possibility to work alongside these just extremely dedicated and brilliant scientists and clinicians.

CHRISTIAN COTÉ:

You are a pure researcher, correct? You work in the lab allday. What, what keeps patients top of mind for you?

DR. SONYA MACPARLAND:

Within the setup of UHN actually the hospital and the research institute are very intertwined. So, you will literally be sitting down in the Starbucks at Toronto general, and you'll be having a research discussion with your collaborators, with your students. And patients will come up and thank the surgeon for you know, how well theyfeel. And you know, they're beaming. They speak specifically about how

Their quality of life has improved. I guess on the other side, you can see the patients when they're not having a great day and they're coming to ask for advice for their loved ones or for themselves. And then every day you kind of see what your goal is and how important it is to be doing this research.

CHRISTIAN COTÉ:

And yet the rigor of science demands time. How do you reconcile this urgency to come up with cures and better treatments forpatients with the time it takes for science?

DR. SONYA MACPARLAND:

That is a tough one. So, you know, we really have todo is set long-term goals. And obviously the long-term goal is to reduce those people that die on the waiting list. But then understanding scientifically, you have to make these steps and you know, make these discoveries that are going to lead you to that appropriate goal. So you have to set short-term goals and long-term goals and understand that you can keep your eye on the prize, understanding that everybody would like to have the ability to you know, reach those goals much faster.

CHRISTIAN COTÉ:

I'm curious, though, do you ever feel pressure?

DR. SONYA MACPARLAND:
I feel a lot of pressure, but it's really good pressure.I feel it, you know, as i mentioned, from seeing the patients, from seeing their families, from seeing right in front of me how severe liver disease can be and also from knowing the fact that there are a lot of patients that will not come off the transplant waiting list, that that's a good pressure. I also feel pressure being part of such a dynamic team where everyone is just really thoughtfully engaged in research and looking at that goal from different perspectives. So you feel like you need to really pull your weight. And then the third type of pressure, of course, is that i have all these brilliant and wonderful students that are trusting me with their graduate program and that i need to make sure that I'm really there for those students and really guiding them in the same way that I've been guided. So, lots of pressure, but good pressure.

CHRISTIAN COTÉ:

What makes you think you can improve things?

DR. SONYA MACPARLAND:
I am an absolute optimist. And the other thing is, I just think that, you know, when you're surrounded by such brilliant people who really are constantly immersed in the literature and really understand the scope of disease and that they're all sitting in the same room. And so, everyone's discussing everything very openly and you know, no one's kind of protecting their research niche. And that is probably the best possibility or the best environment in which you're going to find something innovative or you're going to find something unique, or you're going to really make the best use of your time, your skills, your energy. So,

I think that's extremely exciting and positive. And I think if there is a wayto improve things for patients with liver disease, it's by just assembling the absolute best team. And i think that that's what we've done.

CHRISTIAN COTÉ:

We find it instructive to ask all our scientists how they deal with failure. What's your roadmap when you encounter dead ends orchallenges in your research?

DR. SONYA MACPARLAND:

So, I encounter dead ends all the time. I think the most important thing is to and I tell this to my lab as well is to understand all the rationale for taking each step along the way and then being able to trace your steps back to where you kind of diverted from your scientific question or where you kind of have to refine things. So, you know, I think in science you have to take risks. If you have a good rationale,you do have to take risks and understand that experiments can fail. As long as it's a well thought out and well rationalized experiment or decision, then I think that failure is just part of the process. I think it's important to share failures. I think it's important to be like, very clear about the fact that nobody succeeds without failures, but I think it's part of the process.

CHRISTIAN COTÉ:

I know you credit great mentorship as part of the foundation for your success. How do you now approach being a mentoryourself?

DR. SONYA MACPARLAND:

yeah so, I take that very seriously. Like you said, you know, I do credit mentorship for really getting me to where i am. And i think that part of my responsibility, having received such great mentorship, is i need to pay it forward. And so, the way I like to mentor my students is by understanding as much as possible about their goals, about where they've come from, where they want to go, and how i can stay out oftheir way and push them along.

CHRISTIAN COTÉ:

Is there any kind of secret sauce to how you inspirepossibility within your lab team?

DR. SONYA MACPARLAND:

I tell them that everything's on the table, absolutely everything. If they want to go across the street and train in someone else's lab, I'll make that happen. If they want to try a new technique, then we sit down and we workshop it as a team. So, you know, asopenly as possible, we discuss what their roadmap is, why they want to askthat question. And then we also as a team, take responsibility for if that experiment fails. And again, what i try and tell the students as I've been told before, it's not about whether the experiment worked or didn't

Work. It's about whether we can learn from the experiment or we canlearn from the failure.

CHRISTIAN COTÉ:

What's your career journey advice then to young scientists,those thinking of entering the field or early career?

DR. SONYA MACPARLAND:

my career advice to those people are one of the things that is most fulfilling about being a scientist and having this career is that you're allowed to mentor students. And even if a scientist isvery busy, they will take time and they really get a lot out of providing advice and providing mentorship or listening because they've been in your shoes.

And so, one thing I've told grad students postdocs is if there's someone that you want to talk to and you think their perspective is important, you know, fire them off an email, ask them to have a coffee with you. No one is ever going to say no to a coffee and they will enjoy it. You know, as a PhD student, I would not approach someone because I was like, they're very important. They're very busy. And what I try and tell my students is no one is too busy or important to have a coffee with a student. They'll enjoy it. They like to share it. They, they remember what it's like to make mistakes. And they do want to prevent other people from doing it. So, I tell students,you know, reach out to anyone and anybody because it's part of their passion is mentoring students and kind of guiding them along the way.

CHRISTIAN COTÉ:

There's an author, Simon sinek, who says people don't buy what you do, they buy why you do it. So why do you do what you do, Sonya?

DR. SONYA MACPARLAND:

The simple answer is because someone will let me. I think that being able to do science and I've said this lots of times, being able to do science and being able to discover on a daily basis and to learn together on a daily basis is a gift. It's a wonderful gift and it's a very fulfilling lifestyle and a very exciting lifestyle. And the fact that I'm ableto do this and work with these brilliant students and work with these brilliant scientists and see these wonderful patients is just so fulfilling. And so, and I'll keep doing it until the time we have to stop. (laughing)

CHRISTIAN COTÉ:

Well hopefully no one does. Given your track record, i remember in our preinterview when we were talking about those coloringbook encyclopedias and you said part of what attracted you to the world of science was the possibility to make a discovery that no one else had ever done. You've done that. What does that mean to you?

DR. SONYA MACPARLAND:

It feels like it's just the first step along the way andthat, you know, plenty of people will continue to make discoveries. But it feels nice that this data, this process, this information will help move the Field forward and will help kind of push not only our discoveries, but other discoveries. So it does feel like we're really contributing, which isthe goal of every scientist is to be able to contribute, to be able to help people along with their questions as

well. And so it's pretty cool.

CHRISTIAN COTÉ:

It is. What's next for you?

DR. SONYA MACPARLAND:
So, there's a lot, there's a lot of questions, obviously, that that need to be answered. As i mentioned earlier, you know,we really want to understand the liver more deeply. So, we want to understand what makes a healthy child's liver healthy? What does, an adult liver from a man look like compared to a woman? And because really, you know, once we start asking questions about disease, it becomes very complicated if we don't have a very rich map, that we can kind of pull out the differences between patients. Because liver disease impacts children differently than it impacts adults. You know, little kid's livers are not just mini adult livers, you know. So, what we want to understand isreally as much as we can about the liver and use that to guide different therapies.

We also obviously want to really get into liver disease and understand how the cell populations that appear in liver disease, how they can be manipulated. And some of that actually involves going back to the drawing board and find different ways to tease out tissue from disease, liver. For example, if you have something called cirrhosis, it is scarring of the liver. And within those cirrhotic tissues, those little scars, it's very hard to pull cells out. So, we're finding ways to pull those cells out whenthey're they're not as easy to tease apart. We're also trying to find out whether the placement of those cells within the liver is important.

So, you know, say, for example, a cell is found in the healthy liver and disease liver, but it's in the wrong place in the disease liver. And we know that even though the liver is made up of lots of repeating units, there is quite a bit of division of labor within the liver. And so, we can look kind ofat where these cells are found within the liver. We obviously really wantto understand, you know, diseases like liver cancer, primary sclerosing cholangitis. These are diseases that are very severe and that, you know, really there's not a lot known about how these diseases develop and how they can be treated. And so, we're doing exactly what you described earlier, you know, imposing disease maps on healthy maps and understanding. You know, maybe we can manipulate these different populations of cells to change a disease liver into a healthy liver.

CHRISTIAN COTÉ:

Well, dr. Sonya Macparland, thank you for sharing yourdiscovery and breakthrough with us and continued success.

DR. SONYA MACPARLAND:
Thank you for having me.

CHRISTIAN COTÉ:
Dr. Macparland's research is made possible, in part thanks to generous donor support. If you'd like to contribute to this groundbreaking medical research. Please go to www.tgwhf that's tgwhf.ca/podcast. For more in the podcast, go to our website www. Behindthebreakthrough.ca and let us know what you think. We'd love to hear from you. 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.