Season 2 – Episode 4 – Dr. Pamela Ohashi
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 joining us today, dr. Pamela Ohashi, award winning senior scientist at UHN's, Princess Margaret cancer center. Doctor Ohashi's pioneering research to help prove the viability of immunotherapy as a treatment to fight cancer. Dr. Pamela Ohashi, welcome to the podcast.

DR. PAMELA OHASHI:
Hello. Pleasure to be here,

CHRISTIAN COTÉ:
Pamela. What is immunotherapy?

DR. PAMELA OHASHI:
First of all, it's something that the field is very excited about. It's really the new treatment for cancer therapy. It's really an up and coming groundbreaking new approach to treat cancer. Our immune system is normally around to keep us healthy and it fights off viruses and bacteria. And the way it works is it's composed of many kinds of cells that orchestrate a response to fight off these infections. One of the importantcell types is called a t cell, and it's a white blood cell.

And so, people talk about these t cells and their ability to actually recognize and kill certain targets, each t cell in our body. And we have millions and millions of t cells. Each one of these t cells has the ability torecognize something different, a different virus, perhaps a different pathogen that attacks our body. Now, if you take this immune system that normally keeps us healthy, really what we want to do is be able to now say, well, here is cancer. Cancer is bad, can we do something to get these t cells to attack and kill cancer? And that's really the whole concept behind immunotherapy.

CHRISTIAN COTÉ:
So, do t cells naturally seek out and fight cancer, or is thissomething you're trying to harness the immune system to do?

DR. PAMELA OHASHI:
When we look in people's tissues and their tumors, what it suggests really is that the immune system is already trying to attack the tumors. They realize it's a bad thing and there's a small battle going on as tumors develop in patients, in most patients, not all patients. Because we can also see that in some cases, the immune system doesn't seem

To be activated or triggered to naturally attack cancer. This is somethingcalled immune surveillance, where we think the immune system is really surveying our body to see if there's danger problems, tumors and so on andso forth.

So, yes, there is evidence that within our bodies, the immune system can naturally get activated and that some of these t cells can actually kill the cancers. So, then you might think what's going on in the long term. Andreally the idea, the hypothesis that the field has, is that the immune system starts to kill the cancer. And after a while it gets tired or exhausted and it stops actually running and killing the cancer. That's onepossibility.

The other possibility is we as the field, the scientists, the clinicians believethat, yes, the immune system can attack the tumors. But what happens is that the tumor, because it's very genetically unstable, it actually figures out ways to avoid the immune system and it puts up all these barriers and it blocks the immune response. And in that way, that's how larger tumors develop.

CHRISTIAN COTÉ:

Okay, so when you entered the field of research back in thelate 80s, what was known about t cells and the relationship to cancer in terms of being able to fight it off?

DR. PAMELA OHASHI:

This field has a very interesting history because for the longest time, no one actually believed that the immune system could kill tumors. And so, if we go back historically there, there were people who speculated that the immune system would have the potential to kill tumors. But actually, there was very little evidence. I guess the field was swayed by inaccurate models and incorrect findings.

There were a few experiments that were done that suggested that the immune system could not kill cancer. Part of the reason why there was confusion in the field is that it was thought that the immune system is this wonderful system that has really been designed to only attack foreign things like pathogens that are invading our body or infecting us, and that the immune system was geared specifically not to attack ourselves.

And so, this whole concept that the immune system is geared to attack pathogens and not ourselves. Really does not encompass the idea that it would attack a tumor. So, of course, the tumor is ourselves. It's part of ourbody. It's our own tissue that's just gone wrong. And so conceptually, this was a problem for a lot of the immunologists, because why on earth then would the immune system want to turn around and attack our tumor, which is kind of like our own body. And so, this was really a conceptual

Barrier for people to believe that we could, in fact, use the immune systemto attack cancer.

CHRISTIAN COTÉ:

All right pam, so around this time, late 80s. You establishyour research lab at the Princess Margaret, what did you set out to do?

DR. PAMELA OHASHI:

Here I'll step back a little bit because what i found during my post-doctoral training and so, this i actually worked in Zurich together with Rolf zinkernagel and Hans hengartner as a postdoctoral fellow.

And during that time, we did some experiments to ask the question, do t cells exist in our body that can actually recognize our tissues, or have they been eliminated and gone through this process called tolerance? So, the whole idea is, again, you don't want your t cells in your body to attackyourself. You want the t cells to attack something that's foreign, a viruses and so on. But during the early years of molecular biology in this field, we were able now to ask the question, what happens to t cells that could recognize our own tissues?

And what I did in Zurich and the findings that we had really had an impactin terms of how i think about immunotherapy. So, what we found in using mouse models is that there are t cells in a mouse's body that exist and are still there and can recognize tissues. And what this really meant to us was the field had thought, oh all these t cells that could recognize our own tissues, they were actually destroyed during the development of t cells so that the body is no longer able to recognize their own tissues. It'skind of like a default mechanism. If, if you take away all the t cells that can recognize your body, then all the ones that are left are going to be good ones to attack viruses and anything that's foreign and that will keep us healthy.

So, the field really thought, okay, that they thought it was this perfect system where all the bad t cells, the potentially harmful t cells in our body were eliminated and killed. What we showed in our experiments was,in fact, they're not eliminated. They just hang around and they're just waiting to do their job. They're waiting to see something that could be harmful, that perhaps looks like our pancreas, but they're just sitting there not, not doing anything, waiting to be activated.

CHRISTIAN COTÉ:

So, was the challenge with the fact that you showed in Zurich that these t cells are waiting around? The unknown was whetherthen okay with those t cells attack cancer, which is our body?

DR. PAMELA OHASHI:

Right, exactly. So, what we did in Zurich was we said, well, is there a way to activate these t cells to get them going because they're just sitting around waiting to do something. And we found that if we gave them a virus infection, the pancreas was designed to look like this virus. So, we come in with this virus, we activate these cells and they can go off and kill the islet cells. It was a very molecularly engineered system. It's called transgenic mice, where you can actually manipulate thegenes that are expressed within the mouse.

But the system actually allowed us to ask the question, what happens to the pancreas or islet specific t cells? And we showed they sit there in the body of the mouse. If we activate them properly, they can actually attack the islets and cause diabetes. So, this whole concept proved several things.One thing is that tissue specific t cells are present in our bodies.

And the second thing is if you activate them properly, if you stimulate them properly, then they can go off and do their job and kill a certain tissue. So that's what i did in my post-doctoral training. The next step forme was, okay, if there is tissue specific t cells in the body, that means thatthere will also be tumor specific t cells, because there's a lot of things that are shared because the tumor comes from our tissues.

CHRISTIAN COTÉ:

I see. So, this is how we relate back to cancer.

DR. PAMELA OHASHI:

Exactly. So then when i started in my lab at the Princess Margaret, the first thing i wanted to ask was my hypothesis was we have t cells in our body that can attack tissues can this actually be true for cancer. And that's one of the first models i set up here at the Princess Margaret.

And we went on to show that these t cells that initially could recognizeyour islet cells of the pancreas and cause diabetes. If i turn this into nowa tumor in the islet cells, the t cells could then attack them when we stimulated them properly. So that means in our body we have tissue specific t cells, when stimulated properly, can go off and kill the tumor cells. And that's one of the first things we showed in my lab.

CHRISTIAN COTÉ:

Wow!

DR. PAMELA OHASHI:

The second thing we showed in my lab actually was we said, well, if we give a stimulus to get these t cells going, we can get them to attack the tumors. What happens just naturally is there's this thing called immune surveillance that people speculated. So does the immune system naturally look around the body, look for danger, look for tumorsand get what we

call spontaneously activated to attack the tumor. And the answer is yes.

So that was a second paper that we published. That, yes, these so-called tissue specific cells, the ones that could recognize our tissues if you, if youchange the system a little bit and make that tissue now a tumor, those cells can be activated and can kill the tumor cells. And so, for me, this is really what drove me to believe that immunotherapy can work. I know that the t cells are there in the body. They just need to be activated.

CHRISTIAN COTÉ:

So, these research findings show that there are t cell receptors that were hanging around that will attack cancer tumors inthe body or in animal models. How was this received when these findingswere published?

DR. PAMELA OHASHI:

So, at that time, several other key papers with different models and different approaches suggested that immunotherapy would work. So, this whole idea, again, that you have or we have or the mouse has t cells in our body that can kill tumors. This was shown by other groups as well all around the same time. So, there was a feeling in the field that, yes, this is now looking very possible. There's many indications from many different models where we do believe we can trigger t cells we can activate them to kill tumors.

So, i think for me, around 2001, 2002, there was sufficient evidence in the literature that this approach may work. Soon after that, Dr. Tak Mak had asked me, well, I'm establishing this new center. It's called the Campbell family institute for breast cancer research. If you came and joined us here,what would you want to do? And so, this is when i was all excited about our findings. I thought the next way forward, really for cancer therapy, i thought was immunotherapy. So, I said to Tak, okay, the first thing i would like to do is start us on a path towards cancer immunotherapy. And so that's what i did when i joined this institute. And this was, I think, 2003, 2004.

CHRISTIAN COTÉ:

So, what have you found pam is the best way to activate thet cells to become an effective therapy, to treat cancer, to fight cancer?

DR. PAMELA OHASHI:

That is a long answer. (laughing)

CHRISTIAN COTÉ:

We've got the time.

DR. PAMELA OHASHI:

So, I would still say things are ongoing. So, I will step back again a little bit and say the whole idea is what you're saying is we know that t cells can recognize and attack and kill tumor cells. And so that is the basis for immunotherapy. So, what's the best way to make theset cells? How do we get them going? How do we activate them? Where do weget them from? So, there's different therapies. One will be the vaccine approach. The other one is taking off the brakes of the immune system so

That it's just unleashed and it's just gets activated and it goes and killsthe cancer.

The other approach is really more of a designer approach where there are various strategies to engineer t cells that can kill tumors. We're involvedin many clinical trials and some of those trials were evaluating what are the best approaches, what are the best combination approaches? So, the answer to your question is that there's very, very many different ways to try to get the t cells going. And i think that's something that the field is going to be challenged with for the next 10 years or so. And that's going tobring the next breakthrough to understand how we can put those things together.

CHRISTIAN COTÉ:

In your program, is there one specific approach that youtake in terms of activating the t cells in a successful way?

DR. PAMELA OHASHI:

So, in our program and i would say specifically in my lab right now, I'm pretty much answering for the kinds of projects we do in thelab.

Different people in the lab are doing their PhDs are doing their postdocs asking questions. What are the best ways that we can really optimize the activity of the immune system? And sometimes we're exploring different ways, like blocking other molecules in the t cell, blocking that function to improve t cell activity, blocking other inhibitory cells, understandingwhere these inhibitory cells come from, how can we block them such that we can make the immune response to the tumor better?

So, there's, there's all these different barriers that are inhibiting the immune response. And there's going to be very many different ways to stopthe barriers and improve antitumor immunity.

CHRISTIAN COTÉ:

As a treatment, immunotherapy has certainly come on in the last, say, 15, 20 years. Can you give us a sense of the impact it's had on cancer treatment for patients?

DR. PAMELA OHASHI:

Yes, I think that's really part of the exciting thing in this field right now. So, I would say back in 2010, 2012, most people thoughtthe cancers that were going to be good for

immunotherapy was melanomaand maybe kidney cancer.

And so, when they first started doing clinical trials, testing these new drugs that could block inhibitory signals, the field was really thrilled tosee that lung cancer was one of the types of cancer that was responding to immunotherapy. And this was not predicted at all. So, at that moment, really, the field realized that immunotherapy had this huge potential of having impact in many, many different types of cancers, and that's reallywhat caused so much excitement and paradigm shifting, really.

So, in melanoma, approximately 30 to 40 percent of the patients will respond to this type of therapy, which is really, I think, tremendously exciting. What it says is that the body already has your t cells going and trying to attack the tumor, and you just have to block the stop signal andyou make this whole system work much better. So, it's already going you just have to push it a little bit more. And they're seeing responses in 30 to 40 percent of the patients. Other cancers, they're seeing responses at 80 to
90 percent levels.

Other ones such as head and neck. It's the cancer that doesn't respond well to many types of therapies. They're very excited because even 15 to 20percent of those patients are responding to immunotherapy. It's giving them a different avenue for treatment. So, depending on the cancer, there's different ranges of responses from the patients.

CHRISTIAN COTÉ:

Is there a downside at all to immunotherapy? I, imagine that you don't want these t cells shutting down or affecting your immunesystem, correct?

DR. PAMELA OHASHI:

Right. So that gets to the balance that i was speaking about before, this whole concept about autoimmunity. You don't want t cells in the body attacking your own tissue by unleashing the immune response. Sometimes you're getting these so-called what I've been calling tissue specific t cells, so, you get them going and as a consequence, you havean attack on your own tissue and this causes an autoimmune response. And so. There are side effects such as diarrhea and thyroiditis. So other indications that our t cells are attacking normal tissues in the body and that would be a consequence of using these types of approaches.

CHRISTIAN COTÉ:

I imagine a big question for you is why the therapy doesn'twork on a lot of patients?

DR. PAMELA OHASHI:

Yes, of course, the field is very excited that, for example, in melanoma, 30 to 40 percent of the patients respond. But at the same time, it's a big mystery what's wrong with the other 60 percent? And we would love to be able to get those patients to respond. And the whole idea behind that is really what a lot of my lab is doing, because that bringsus back to basic science research. We need to understand why those patients aren't responding. There's a lot

of ways we can speculate how that might happen in mouse models, but it's also very advantageous to really look in clinical samples as well. And that's what many labs are doing.

CHRISTIAN COTÉ:

So where do you go next with your research?

DR. PAMELA OHASHI:

I think the major barriers going forward are twofold. One is really to understand why these patients are not responding. And sothat means understanding the inhibitory mechanisms that are in place. And there's many, many, many I would say there's at least 10 that we need to understand. And when we understand these mechanisms that are restricting the full potential of the immune response. When we understand and dissect really what's underneath that whole inhibitory pathway, we could then identify target molecules to develop new drugs and block these inhibitory mechanisms. So, I can envision in the future immunotherapy would look like let's activate the t cells, get them going, but also let's block the inhibitory pathways. And together, those approaches will really take therapy to the next level.

The second thing is really, can we understand which type of patient that will respond well to immunotherapy? And right now we don't have anything, what we would call a biomarker, a marker, a feature of these patients that we can actually track and explore and ask the question, if apatient has this biomarker or this feature, are they more suited for immunotherapy? And what does this marker look like? And although the field has tried to identify what that looks like, they really don't know right now.

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. We're speaking with Dr. Pamela Ohashi, award-winning scientist at the Princess Margaret Cancer Center and a pioneer in the research of immunotherapy, proving it is a viable treatment for cancer. Doctor Ohashi's work is supported in part bythe Princess Margaret Cancer Foundation.

Now, pam, you're Toronto born and raised and I understand one of your prime motivators to do this research is connected to your grandmother.Would you mind telling us the story behind that?

DR. PAMELA OHASHI:

I was probably about 10 years old and unfortunately, asmany people do, she was diagnosed with cancer. What was shocking to me at the time really was there was no options the way her cancer and of course, I was young at the time. So, I really don't know what kind of cancer she had. But apparently surgery was not an option. And I really thought that was just shocking to me. Like, how can people have a. Disease and there's no options for treatment,

and so that really struck me as something that we need in this world and really I was inspired to really try and figure out if there's ways to bring new therapies to cancer treatment.

CHRISTIAN COTÉ:

Do you have a sense of what it is internally that youconnect with in the world of medical research?

DR. PAMELA OHASHI:

in terms of my science career and how I move forward in this path, realizing that there were limited treatments, I thought biology,of course, was the way to go, because cancer at that time, actually they really didn't understand how cancer came about. The whole idea about oncogenes and those, I think what we would consider main concepts were not discovered at that time. So, my path led me along the biology stream.

And then I was very fortunate just to, to run into people that really gaveme the options that brought me to immunotherapy and that I would like to highlight two people. One is Dr. Jim Friesen, who gave me my first job as asummer student who made me realize recombinant dna technology was a fascinating area all the way to Tak Mak, who really, when he discovered the t cell receptor, said, you should come to my lab and learn about or let's figure out some of the immunology. And I think those were really thekey events that really got me down this path of thinking about the immune system, how we can use that to fight cancer.

CHRISTIAN COTÉ:

What's your approach today to mentorship?

DR. PAMELA OHASHI:

I think what I try to do is I look back on how my scientific path was, how I bumped into and was very fortunate in being thrown in the right direction, so to speak. And so, i try to create that same environment for a lot of my trainees. Some of the things I appreciatedas a trainee was I was given a lot of freedom to explore my ideas, to bring in new ideas, and I try to also make sure that the people in my lab have that same freedom.

And I think many of them really can show their talents and their expertiseand their ideas and their creativity really by following their own thoughts. And, you know, I don't want to hinder that, that kind of process. I think everybody's creativity is their strength. And so, I try to make sure that everybody can shine in that way. And I tell my lab, we're living history, we're making history. We are going to be defining the new therapies for cancer going forward. So, let's just have fun and, you know, work hard and move this field forward.

CHRISTIAN COTÉ:

For young people just entering their careers or thinking ofentering this field of research. What's your advice to them?

DR. PAMELA OHASHI:

It's fun, but a lot of work. (laughing) So, i think, one thing i really like about this field is it allows you to explore and go into whatever direction your interests lie. It's a wonderful opportunity to really explore your interests and have an impact in what you believe in. The downside, of course, it's not always thatrosy. The downside is people have to realize that there are so many hurdles. There are way more hurdles than successes. I would say for every,one success, you'll have 10 hurdles or 10 barriers or 10 problems-

CHRISTIAN COTÉ:

Or failures.

DR. PAMELA OHASHI:

Yes.

CHRISTIAN COTÉ:
I'm curious what you think of the patients who decide tobecome subjects in your trials?

DR. PAMELA OHASHI:

Oh, I think they're heroes. It's really wonderful. The first patient who was part of one of our trials, I made sure I reached out to him. We texted a lot and i understood his feelings, his thoughts as whathe was going through, through a lot of these treatments. And really, they are, they're heroes.

CHRISTIAN COTÉ:

You see then the urgent need for cancer patients to get better treatments and better outcomes. And this comes up against the daily grind and the time it takes for research. How do you reconcile thispush and pull of the world you work in?

DR. PAMELA OHASHI:

The urgency is unbelievable. I get so many emails saying,oh, my mom, my brother, my sister, my uncle, they have cancer. Can you do something? And so many people reach out and really get the sense of urgency just because the way the world is, it's, it's fairly easy to email andreach out to people. And so, to me, that's an important message that i get from strangers all over the world.

But at the same time, the unfortunate thing is that science is actually quite slow. And to

make groundbreaking research in a way that is solid and meaningful and sound really takes quite some time. And so, yes, i feel that struggle, the pull and push, we work as hard as we can. We're so grateful for our granting agencies, for the foundation. Without all of that, we would not be able to move forward as fast as we can. But i think everyone is on board and always trying to move this field forward as fastas possible. Because there is that urgency.

CHRISTIAN COTÉ:

What makes you believe you can improve things?

DR. PAMELA OHASHI:

What really motivates me is if well, I maybe I'm saying I'm old, but if I see how far the field has come, it's really, truly amazing.

I think there's so much potential and having these ideas and following them through and seeing that they're successful and seeing that there ispatient impact, I think i don't need any more motivation. And I, I know perhaps not me, but as a field, there's going to be a day where we can curecancer.

CHRISTIAN COTÉ:

I read where immunotherapy was considered a part of themedical wilderness for a long time. And you've called yourself I quote unquote, "die hard." What's kept you at this for the past 25, 30 years?

DR. PAMELA OHASHI:

One of the secrets of science, i think, is make sure you are studying a good model that is telling you the truth about whatever question you're asking. And so over time, since 1991, when we published this model and our studies in Zurich. I've built upon that model, and I always do checks and balances. I say, is what we're learning from this model actuallytrue? Has it been validated by real life situations, by clinical samples, by human disease? And I do this checks and balances all along.

And I realize that the things that we are learning from our mouse models are actually coming true and being predicted and happen in real life human situations. And with this knowledge, I guess I build up inside me a picture of how I think diseases work and how I think the immune response works. When I see this picture and I see that it's really happening, I, I'm veryconfident that things will fall into place and that we're on the right path.

CHRISTIAN COTÉ:

What would your grandma think of what you've been doingfor the past 25, 30 years?

DR. PAMELA OHASHI:

(laughing) oh, wow that's a funny question. I don't havethe right words. But let me think about it.

CHRISTIAN COTÉ:

What would grandma think of what pam has done so farwith her career?

DR. PAMELA OHASHI:

Surprise, surprised, impressed, perhaps.

CHRISTIAN COTÉ:
Dr. Pamela Ohashi, award-winning scientist at UHN's, Princess Margaret Cancer Center. Thanks for sharing your discoverieswith us and continued success.

DR. PAMELA OHASHI:

Thank you very much, Christian. Pleasure to talk to youthis afternoon.

CHRISTIAN COTÉ:

Doctor Ohashi's research is made possible in part thanks togenerous donor support. If you'd like to contribute to this groundbreaking medical research, please go to www.thepmcf that's thepmcf.ca and click on the donate now button. For more on the podcast, go to our website www.behindthebreakthrough.ca and let us know whatyou think. We'd like to hear from you. That's a wrap for this edition of behind the breakthrough, the podcast all about groundbreaking medicalresearch 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.