Behind The Breakthrough Podcast - University Health Network

Season 3 - Dr. Catherine O'Brien

Transcript

BTB

Welcome to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host, Christian Coté, with us on the podcast today, Dr. Catherine O'Brien, a surgeon specializing in gastrointestinal cancer and an award winning research scientist at the Princess Margaret Cancer Center. In 2020, Dr. O'Brien made the world first discovery that cancer cells go into hibernation to evade chemotherapy. Her research is now focused on targeting those sleeping cells to inhibit or prevent their ability to go into that protective state during chemotherapy. Dr. Catherine O'Brien, welcome to Behind the Breakthrough.

DR. CATHERINE O'BRIEN

Thank you very much. I'm really happy to be here.

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Let's start Catherine, with big picture in your field of specialty colorectal cancer. What's the scope of this disease in Canada?

DR. CATHERINE O'BRIEN

It is actually one of the most commonly diagnosed diseases in cancers in Canada, and it's actually increasing in the younger age group and really, nobody knows why it's increasing in a younger age group. And there's different genetic subtypes of colorectal cancer, and it's something that has affected many people who have family members or friends with colorectal cancer.

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And what's typically the course of treatment for someone once they're diagnosed with colorectal cancer

DR. CATHERINE O'BRIEN

It's typically people with colon cancer undergo surgical resection and then, depending on whether or not it is spread locally or in a distant way, they receive chemotherapy. Sometimes people receive chemotherapy first and then undergo surgery. And for rectal cancer, some people require chemo radiation, followed by surgery. So there's some options. I think it's important to understand that colorectal cancer is one of the best understood cancers from a genetic perspective. However, there have not been very many new targeted therapies introduced for the treatment of colorectal cancer patients.

So this is something that's really missing in the field. The one exception being for a small subset of colorectal cancers, which are microsatellite and stable, and those cancers represent about 10 to 15 percent of all colorectal cancer patients, and they've had a great response to immunotherapy. But for the remaining 85 percent of patients, there's really been no significant novel targeted therapies introduced in the last 10 years.

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And once you get that diagnosis, Catherine, what's typically the outcome for patients?

DR. CATHERINE O'BRIEN

It really depends on the stage that you're diagnosed at, where you're seen with that early diagnosis, especially with screening, colonoscopy and the ability to diagnose these cancers earlier. You have great outcomes with 90 percent survival rates with stage one colorectal cancer, so it really emphasizes the importance of screening and colonoscopy in the context of colorectal cancer. When you're looking at a later stage of disease, such as stage four, you're looking at significantly lower long term survival percentage. However, we are actually giving people chemotherapy longer. People are responding. Some people go on to resection, so it's not necessarily a death sentence, and people do have longer term survival with later stage disease and I think there's a lot of hope on the horizon for what will happen in the next 10 years to advance colorectal cancer treatment.

BTB

I was reading in the research materials to background your work and one of your missions you describe as being quote to develop a better understanding of the molecular pathways underlying the initiation and maintenance of colorectal cancers. Could you decode that for us? What does that mean?

DR. CATHERINE O'BRIEN

Right? To actually understand what are those pathways that are key drivers that are driving the initiation and driving the start of the colorectal cancer and what are these pathways? Because if we understand what the key pathways are, the idea is that we can then develop methods to target those pathways.

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Okay, so let's dive into your discovery in 2020 that cancer cells go into hibernation to survive chemotherapy. First, is there a story to the inspiration for this trial? Like, how did you come up with the idea or how did it all come about?

DR. CATHERINE O'BRIEN

Our goal in starting this project was to treat cancer cells, colorectal cancer cells with chemotherapy, and we know that a significant percentage of patients actually respond initially to chemotherapy. However, over time, they grow resistant and the tumor start growing again. So there is this response phase in a number of patients, followed by over a long course, they start becoming resistant. We wanted to model this in the context of our experimental models, and what we did was we treated our mice models with chemotherapy and we saw this nice response and we wanted to find that one cell that was causing this recurrence, the resistant cell.

And when we actually did the experiment, what we found was we tracked all the individual cells in the tumor. So we labeled every cell. So we knew what happened to every cell and we thought we would find the one cell that was resistant. And what we found in the experiment was all the cells came back. There wasn't one cell, it was all the cells came back. So it wasn't a question of having this one resistant clone, which we thought and we would investigate that clone. And so when we got this result, it was quite unexpected, and we didn't quite understand why all these cells actually had the ability to regrow after the chemotherapy.

And we started looking through different areas of the literature about how to explain this. And at the time, Princess Margaret has weekly seminars where they're invited guests that come to speak. And one of the guests that came to speak was Dr. Miguel Ramalho-Santos from UCSF. And now he's at the Lunenfeld Research Institute associated with Mount Sinai in Toronto. And he actually is an expert on embryology and specifically on diapause and diapause is similar to hibernation. Is this idea where actually it's not one cell, but a whole organism that goes into this quiet state, whether it's hibernation in response to cold or in the context of diapause, it's the embryo. And so this is conserved throughout the animal kingdom. Mice can do it. Deers can do it. Humans cannot. But basically in a very caustic environment, an embryo can actually stop developing.

It just halts and it just stays there until the environment improves. And when the environment improves, such as increased nutrition or better weather the embryo starts to develop normally again. And we thought this was really interesting because it means all the cells within the organism very similar to hibernation, where all the cells within the animal go into a very quiescent state. And so we took our data and matched it back to Dr. Ramalho-Santos 's data. So we started a collaboration with him and going to that talk, I didn't even know diapause existed.

From going to that talk at Princess Margaret, we went and we started this collaboration where we showed that actually our cancer cells in the state were actually more similar to mouse embryos in diapause than they were to their own parental tumor. And so they were

actually adopting the state. But when the chemotherapy was finished and the cells regrew, they were no longer in the state. So it was a transient state, very similar to embryos in diapause or animals in hibernation. So there's this state of where all organisms, all the cells have this response and it's not one particular cell within the organism, it's the whole organism.

BTB

Prior to your study. This was only believed to happen in the animal kingdom. Talk to us then or walk us through the process in the lab for the study you did?

DR. CATHERINE O'BRIEN

So we started with a patient derived colorectal cancer samples, and we're very fortunate at University Health Network to have a large bank of colorectal cancer derived specimens. And we use these specimens, we inject them into immunocompromised mice. And in the context of this experiment, what we did was we took the cells from the patient that we store and we freeze them down and we labeled each of the cells. So we labeled the kind of think about when you go to the grocery store, every item has a unique barcode. We gave every cell, we injected a unique barcode. That unique barcode then made a collection of barcodes, over two million barcodes that we injected into mice.

And then once the tumors grew, we treated them. We saw the regression. We let them regrow from the chemotherapy and then we took them back out and read all the barcodes similar to if you go to the grocery store and you pass all your items through the cash. So we read all those barcodes and we're able to see what happened to each individual cell through the course of growing and regression of the tumor. At that point, we then took those tumors and we analyzed them, so we did RNA seq. So we looked at actually what genes are they expressing and what's the expression profile. And from that, we were able to take our data and compare it to other sets of data.

So we compared it to Dr. Miguel Ramalho-Santos' diapause data. We also compared it to what's known as minimal residual disease models. So where a patient might have cancer, but it's at such a low level, you can't detect it. So our model really did get quite strong similarities to minimal residual disease models as well, in other tumors. At that point, we then started to look just because it looks like a diapause or hibernation. Does it act like that? And that's where we then looked at different pathways that were relevant, especially in the context of diapause.

And we started to test to say, is this pathway such as autophagy? Is it important in the context of our cells? And what autophagy is is when cells are under stress, they can actually eat their own or recycle their own pieces of their organelles to actually maintain their survival. So this idea of under stress a cell can actually revert into itself and recycle pieces of its own organelles to generate energy to survive during the stress. And what we found was that embryos in diapause were dependent on this, and what we looked at was were our cancer cells dependent on this, and indeed they were. And so it demonstrated that not only

did it look like diapause, but it was actually functionally similar to diapause or hibernation state where there was this dependence on this self-eating or autophagy pathway.

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The stress being introduced here, of course, was the chemotherapy.

DR. CATHERINE O'BRIEN

Exactly, yeah. So if you make the comparison, when you think about an animal in the cold, the, the stress is the cold weather for hibernation. In the context of an embryo with diapause the stress could be the lack of nutrition or it could be the weather. In our context, the stress on the cancer cells was actually the chemotherapy. So the exogenous stress driving this response is the exogenous chemotherapy. But the response is similar whether the stress is, the cold weather, the lack of nutrition or chemotherapy. It appears from our data that the response with respect to the transcriptional profile looks very similar.

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And what was the reaction to your findings?

DR. CATHERINE O'BRIEN

I think actually very positive, and I think it's something that I'm very happy that's actually gaining a lot more attention right now. So we were not the only people to look at this in the context of diapause. We actually published at a time when two other papers came out on the exact same notion, but in the context. So one was published in Cancer Cell and that was in breast and prostate cancer, showing a very similar finding that breast and cancers and prostate cancer cells, when treated with chemotherapy or targeted agents, entered this diapause-like state. And another paper was published in Cancer Discovery, showing something similar in the context of leukemia. So I think the fact that at the same time, three papers came out in four different cancers that really led to people taking notice and being interested in the concept of this recapitulation of an embryo logically conserved survival strategy.

BTB

And this was a first I understand, Catherine, because you were testing human cancer cells, correct? That was that was also what you were humans.

DR. CATHERINE O'BRIEN

Yes, they were human cancer cells and that were injected into immunocompromised mouse models. And so that's an ongoing question is humans cannot hibernate and a human embryo cannot undergo diapause. So one remaining question is how do cancer cells actually reactivate a pathway that humans actually have lost? So it's an interesting concept that human cancer cells can behave in a manner similar to diapause or hibernation, even though

a human does not have that ability. So it's a really interesting concept of how cancer cells reactivate this, said developmental survival strategy.

BTB

I'm trying to grasp sort of this sleep state because what you showed was the sleep state allows cancer cells to avoid chemotherapy. You know, I put your chemotherapy, comes into the body, searches for the cancer cells and destroys them. How is it that the chemotherapy can't see these cancer cells?

DR. CATHERINE O'BRIEN

That's a really interesting question, and I'll take you back to microbiology for a minute because I think it's a really important point to make is that these cells are actually referred to as persister cells. They're referred to as drug tolerant persister cells. So they're a cancer cell, but that's when they're responding, when they're tolerating the chemotherapy. And this name actually comes from microbiology, where bacteria we know can tolerate high levels of antibiotics and survive. And so they're actually bacterial persisters. They do not change genetically. They do not develop mutations. They're identical to their counterparts that are sensitive to the antibiotic, but they're able to tolerate high, high levels of the antibiotic for a period of time.

And that's how things like biofilms are created so that these bacteria can tolerate the antibiotic. So what we're seeing in the context of cancer cells is that this is very similar. The cancer cells develop a method to tolerate transiently, very high levels of chemotherapy without actually dying in response to them. And so that's actually a very interesting area of ongoing research is what are the mechanisms that cancer cells use to actually develop this tolerance to chemotherapy? There's a lot of work. And in the context of bacteria and looking at how persisters develop, and I think that's one area where we can really take some of that data from the bacterial literature and try to translate to see if the cancer cells are using similar mechanisms, but it's definitely an area of interest and of ongoing research.

BTB

So this diapause, this state of hibernation, this is simply instinctual within a cancer cell?

DR. CATHERINE O'BRIEN

Well, that's what we don't know, but it seems to be that it just reactivates. So it's something that we see. It's the chemotherapy reactivates or activates rather this survival strategy. And this is something that seems to be coordinated and interesting aspect of this drug taunt persister state, it's not one or two cells that go into it. All the cells go into this state at the same time, and we know a lot in the context of bacteria that there's quorum sensing molecules. Bacteria send out quorum sensing molecules, telling all the bacteria in the population, Stay quiet, don't divide, just rest. And it's actually well-studied quorum sensing molecules that are secreted by bacteria.

This area is somewhat less studied in the context of, of cancer, but I think there's a lot of potential in the research that can be done to look at how do cells, how do cancer cells know, to react or to activate this pathway, and how do they communicate it? They all do it in a coordinated fashion. It's not one or the other. They just seem to just go into this state in a coordinated fashion. How do they coordinate that and what do they use and do they use as signals between themselves? Or is it inherent to each cell? That's something that we're very interested in looking at and trying to understand further.

BTB

This finding, it sounds like, is chemotherapy being rendered, you know, useless?

DR. CATHERINE O'BRIEN

No, I think that there's more to be learned about this, but we know for a fact that, for example, in colorectal cancer, if you keep somebody on chemotherapy for a long time, they may have a response initially, but over time they're going to lose that response, and that's a given. And so I think the important thing to think about is that are there strategies that we can use while chemotherapy while people are responding to chemotherapy to target this diapause or hibernation state? So is there a therapeutic opportunity?

We know for a fact based on our work, as well as the work of other groups, that this hibernation state is not benign. When these cells are quiet, they're actually generating mutations, and over time, one of these mutations will take off and be genetically irreversibly resistant. So this is a time when cancer cells are in the state that they're actually trying different mutations and that different mutations are being generated and over time, eventually one of them will take off and will be irreversibly resistant. And we did this in the context of our own work, and we looked at it and we know that when we barcoded the cells, if we kept the chemotherapy on for seven months in a mouse, which is actually quite a long time in the context of a mouse's lifespan, after five to seven months, we actually generated irreversibly genetically resistant clones.

So what I think is really interesting for the field and why the interest is there is because there's this opportunity when cancers are responding to chemotherapy that their identity is different and they're in this hibernation state. And are there ways that we can actually introduce novel therapies or different therapeutic strategies to target cells when they're responding, as opposed to continuing chemotherapy and waiting until they become resistant. And I think it's an important point to make because even if you do a targeted therapy, our colleagues and who published in cancer cells show that targeted therapies also can cause cancer cells, at least breast and prostate cancer cells to enter this diapause like state. So it's not something that's just a unique phenomenon to chemotherapy. So we feel that it's a really important aspect to look at when these cells are responding, when they're hibernating. How do we target them?

BTB

You mentioned this or indicate that this is now a new path of work. Is there a way to inhibit these hibernating cancer cells? Where are you on that road?

DR. CATHERINE O'BRIEN

Yeah, we're definitely looking at autophagy inhibitors as well as antiepileptic inhibitors. So BH3 mimetics and we're looking at combined inhibition in the context of our preclinical models. And we're also looking at another aspect. As I mentioned previously, a colorectal cancer is very well studied with respect to the genetic subtypes. And so the other aspect that we're looking at is, do all the genetic subtypes enter this state equally or are some more prone to entering this state are some less prone to entering this state? And what are the genetic mutations that actually might drive the ability of cancer cells to enter the hibernation state? And that's something we're also very interested in because we want to understand the mechanisms and we want to understand the underlying strategies that cells use and what are the mutations that may drive this ability.

BTB

And I suppose also the timing of when to introduce these inhibitors is another issue?

DR. CATHERINE O'BRIEN

Absolutely. And that's something we're definitely looking at in the context of autophagy inhibitors and the BH3 mimetics. When do we have to introduce these and at what time point with respect to when the cells enter this state? And how long are they in this state? Do we have to introduce it earlier versus later? And that's something that we're looking at. And I think one of the exciting aspects for us is that autophagy inhibitors, as well as the BH3 mimetics or the NTA apoptotic inhibitors are both drugs that have been in clinical trial in the context of solid tumor, but really haven't shown a great effect.

And so what we have seen in the context of our models, if we treat with these inhibitors when cells are not in the hibernation state, we don't see an effect. The cells have to be in a hibernation state to see the effect. And so that's something that's interesting for us because these are drugs that have been trialled but not trialled in the context of the hibernation state. And so that's what we're really trying to model in the context of our work is how does it work that these cells, when they're actually in this hibernation state, are sensitive to these inhibitors when they're not in the hibernation state, it doesn't matter. They're not sensitive at all. And it might speak to why these trials actually did not work out in the context of solid tumors past trials.

BTB

So the precision of timing is going to be critical here. Do you have any results that you can share at this point or too early?

DR. CATHERINE O'BRIEN

So we actually have ongoing studies, both in mice and petri dishes in the lab, and we know that if we actually allow these cells to enter into the states, we start the chemotherapy off. We give two to three cycles when the cells are regressing, we start with an anti apoptotic as well as an autophagy inhibitor. And that's what we've been trialling and it's looking very promising. But we definitely have to try more samples in more a larger number of mice to see if this actually repeats. So that's something that we're definitely very excited about and interested in.

And then in the context of looking at targeting them, the other side of that is how do we induce the state? So we know that some cancers, for example, rectal cancers treated with chemo radiation often go into the state and you see that there's tumor regression. Many lung cancers have tumor regression with primary therapy, but our interest is how do we actually induce the state in other tumors? How do we actually find the pathways that actually induce a hibernation state or a diapause like state? And so that's another aspect. So one is how to target it. The other is how do you actually induce the state?

Because if you can induce it, theoretically, you can target it. And so that's something that we're very interested in understanding more about how to induce the state. And we definitely are interested in looking at this in the context of both different genetic subtypes of colorectal cancer, but also in broader different types of cancers. Because it might be that this is all conserved and it's the same pathway, but it might be different. And so that's something that remains to be answered. Are there different pathways and strategies to become a drug tolerant persister and what are those pathways?

BTB

And I suppose another question would be at what point when they face these stressors? Do they go into this state of diapause, do we do we know that?

DR. CATHERINE O'BRIEN

We are doing that now and what we're doing is a time course? So we take the cancer cells and we treat them and we actually take different time points based on the treatment. And we go approximately once a week for about eight weeks and then we actually take all those samples and analyze them at the level of what genes they're expressing. And one other thing that we did not do initially in the paper is do single cells. So one is to look at what genes are expressed by the bulk, all the cancer cells together. And that's what we've done so far.

What we've started to do is to look at it on a single cell. So at each time point, you actually do the what genes are these cells expressing, but look at it on a single cell basis. And the reason to do that is to say we know that all the cells do it. But do they all have the same gene profile or are they different? It might be that one of these cells is actually directing the others. It's secreting them messages it's telling them. But it might be that they, as I mentioned before, it might be that they all have this inherent capacity and it's there's no difference. And so we're really interested to know how much heterogeneity there is

between these cells in the DTP state. Do they all look very similar or are there different subsets? And if there's different subsets, are some of these subsets driving the state?

And are the other cells responding sort those one cell subset? Are they sending out the messages similar to bacteria and quorum sensing molecules? Are they sending out the message to say, enter this state or is it autonomous and does every cell do it on their own? So these are a lot of questions that we're very interested in. But as I mentioned, it really does take a time course and we're doing that now, sort of taking cells at each week at weekly intervals and then doing the analysis both bulk and single cell.

BTB

Does this cross cut all cancers, the potential to go into this diapause state?

DR. CATHERINE O'BRIEN

We don't know now. What we know is that it appears to be in leukemia and AML. It also appears to be in breast and prostate and colorectal. We know, however, though, that the diapause like state is one aspect. But drug tolerant persister cells have been known for approximately the past 10 years, and we know that if we look at drug tolerant persister cells, they've been identified in lung cancer, in pancreatic cancer, in ovarian cancer. So they've been identified in many cancers for drug tolerant persister cells.

However, in the context of diapause, we don't know what we don't know is are all drug tolerant persister cells entering this hibernation state or is drug tolerant persisters an umbrella and there's many different pathways within it. And that's what we don't know. We know what we've done and what we've done is a lot of the data is actually publicly available. So the people who've published in lung and in ovarian and also in glioblastoma, that data is available. And so we've taken our data and matched it back and the signatures are very similar.

So that would suggest that we're all looking at a very similar entity, and this all reflects back on hibernation. The only thing being is that the people that published on DTP's before never looked back to hibernation or diapause, but were essentially all looking at a similar phenomenon. That would be my opinion on it, I think, to actually definitively state that it's going to take more research because drug tolerant persisters have only been around 10 years and there's not a plethora of papers on it. So I think this is really in its infancy and there's a lot of interest in it and I think a lot of interest, in part because it represents also a novel therapeutic opportunity that when these cells are in this state, it might be a different therapies and another opportunity to target the cells.

BTB

In the meantime, does this concern you at all, Catherine, in terms of the effectiveness of chemotherapy? Because, you know, we used to say after a certain number of years after

chemotherapy, if you're still cancer free, you're cancer free. Does that throw that into question?

DR. CATHERINE O'BRIEN

I guess I have more questions than answers for you, so I guess that's a reality of science and research. So it's a great question. And why this is a great question is because we know that some cancers can show up 20 years later. Whereas other cancers rarely do colorectal cancer, it's very rare to see a recurrence 20 years out. If you get two, three or four years, you can be fairly confident. Never say never, but you can be fairly confident that you're cured. You're more at risk of having a new colorectal cancer develop. However, for breast and melanoma, it's not uncommon to have a recurrence. You can have a recurrence 20 years later. And so one of the questions for us is that are these things the same?

And so keep in mind that drug tolerant persisters enter the state based on being treated with a chemotherapy or a targeted agent. Whereas when you see a breast cancer that happens 20 years later and the idea that these cells have been sitting around in a dormant state, or in a quiescent state and become reactivated. I think that this is a really exciting area to take a look at these cells. And can you match them back? And are they undergoing a different type of hibernation or diapause? And is this similar or are they completely different entities? But I think it's important to point out that these cells that we're looking at enter the state in response to a stressor. They enter it in response to a chemotherapy.

In the context of breast and melanoma, where you can recur 20 years later. We don't know if it's the same mechanisms that they're using, but I think it's a very exciting area to look at and a very exciting aspect of cancer research. And so far, as can you match back this long term recurrence with a diapause or a hibernation like state? I think that's a pretty exciting area to look at. And then to also look at the connection between this drug tolerant persister state and these long term recurrences that are 20 years out. What's the connection there? Are they similar to these entities? Do they look similar transcriptional or are there gene profiles similar? Or are these two different, completely different entities? It's a really interesting biological question in this area.

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You're listening to behind the breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host, Christian Coté, and today we're in conversation with Dr. Catherine O'Brien, an award winning scientist at the Princess Margaret Cancer Center. Dr. O'Brien's pioneering research is made possible, in part thanks to generous donor support. So if you'd like to contribute to Dr. O'Brien's research, please go to www.thepmcf that's pmcf.ca and click on the Donate Now button.

Catherine, you were born and raised in Montreal and in Grade 10, you had an AHA career moment on high school career day. What happened?

DR. CATHERINE O'BRIEN

I you could pick whatever you wanted to do, so you could just have. It was pretty much unlimited, and I chose to spend the day with a female surgeon at the time. Yeah, it was a great experience, and I just thought it was just such a fun way to spend a day. I couldn't imagine how much fun it would be as a career.

BTB

What's your sense now reflecting on that moment or that day that you felt a connection to what was going on in the O.R.?

DR. CATHERINE O'BRIEN

I still think today that it's actually quite a privilege to be a part of a person's life when they're going through oftentimes life changing experiences. Their diagnosis and basically shepherding them through the process of diagnosis and treatment and recovery and watching these people. And I think that day, I just I was really affected by the fact of how important it is to be a part of a person's life when they're actually undergoing surgery and to see the outcome. I just thought it was a really incredible career if I could have the opportunity to do it.

BTB

And so later, around the time you were into your surgical training, I understand you had some personal experiences that have had a direct impact on your career trajectory. Do you mind telling me what happened?

DR. CATHERINE O'BRIEN

So during my residency, which was five years, my father died of kidney cancer within the first six months of my residency, he was diagnosed a week before I started residency and died within six months. And then three years into my residency my aunt, was diagnosed with metastatic colorectal cancer and died within a year and a half of her diagnosis. A very difficult death and very stressful and unfortunate. And I think I really didn't know what subspecialty I wanted, and I think it really did sway me. And with respect to the direction of not only looking at the patients that we were treating, but also looking at the personal aspect. And I think the the combination really did push me towards a career in oncology and surgical oncology. And then the research aspect.

BTB

Oh, we're sorry for your loss. Having that impact on you and as a clinician, it probably brings to the fore all the more the fact that you know, the stakes involved in the need to make things better for patients. How do you balance that urgency with the fact that science takes time?

DR. CATHERINE O'BRIEN

It's very difficult. And I think for somebody like me who does the clinical aspect and the research, I think there's quite a dichotomy. Everything in surgery is very much about deadlines and fast pace and moving and getting the treatment started. And in the context of research, everything moves very slowly. And I think it's just the reality, and I feel that sometimes it's frustrating, but I think everybody feels the same way. And I think if you look at some aspects, there's been incredible advancements like in the context of immunotherapy and for the subset of colon cancers that are microsatellite and stable. It's revolutionary.

And so I think everybody who does research kind of hopes for that pushing to see and we're all hoping to push and try and see something that really changes the outcomes for patients. And I think it's a great place to work for that with respect to you have clinicians, clinician scientists and you have scientists and you see everybody working together to try and push things forward. And I think that's a really exciting aspect to the sense of community and this sense of collaboration that you have at the Princess Margaret and UHN in general.

BTB

Let's turn to mentorship. One of your Ph.D. supervisors was Dr. John Dick, who is a legend in the world of cancer stem cell research. Talk to us about this influence and say the guidance in your career trajectory.

DR. CATHERINE O'BRIEN

Well, I mean, it's hard to explain the influence of Dr. John Dick. I mean, he is a pioneer. He is brilliant. He's a great mentor. He's just a great senior colleague, too. It's incredible to watch him and it's incredible to see a man that I mean, he has so many ideas and he's so generous, both with his time and his ideas. And he took me into his lab as a surgical oncology fellow, and nobody else was doing colorectal cancer in the lab. And really, he encouraged and fostered in me this love of science, and he's very passionate about the science and still very much actively involved and thinking of ideas. And I think to watch him work is actually quite impressive, and I'm still impressed today. And I think that without working with Dr. John Dick, I wouldn't be here if I had chosen a different lab. There is no doubt in my mind that I would not be here. I would not have a lab and things would not have worked out.

So I think that's important actually for younger people to realize, like, really think about what you're going to do and think about who you're going to work with and don't necessarily take the path that is expected, but choose who you want to work with. When I finished surgical oncology, a lot of people thought I was crazy to start a Ph.D., and so I just didn't tell people I just didn't mention it. The people in the lab knew other people really didn't know, and I think that worked out well.

BTB

That's kind of like that challenge to what you want to pursue when you face those obstacles. How do you overcome them?

DR. CATHERINE O'BRIEN

I think it depends on the obstacle in many ways. But for me, I have to just take the time and it's what I try to advise that younger colleagues is just to take the time to listen and an older colleague, not a surgical colleague, once mentioned, like, we become so busy and there's not a lot of time to think and to sit down. So I think one of the most important things is to just sit and think and give yourself the time. You can be so busy that you're running around, running around. By the time you get home, you're just too tired, you want to eat and you want to sleep. And I think you need some time to just sit down and think about what you want to do and think about what means the most to you and what are you most passionate about? And how do you incorporate those aspects into your career?

Because if you don't have those aspects over time, you're going to get bored, you're going to get frustrated. So you have to really think my opinion early on, you have to spend the time to have quiet time to think and to say, What am I passionate about? What do I want to make sure that I'm doing every day for the next 30 years or that I have involved in my life for the next 30 years? So I think for me, that's really important because lots of people will tell you what and you have to take all that in. But at the end of the day, you have to sit down, you have to have your quiet time and you have to actually think about what you're passionate about and what you want out of your life.

BTB

What happens when you experience failure in the lab? How do you approach or navigate failure because we're not taught how to deal with it?

DR. CATHERINE O'BRIEN

I think over time I initially it would be very hard no matter initially. It was very hard when things didn't work out. And I think as you get older with everything, you realize that, you know, some things aren't going to work out, some things do work out. And sometimes when things don't work out, they lead to better things. And that was what happened with this paper, right? We thought for sure we would find that one special barcode. And I'll tell you, when we didn't find that one special barcode, we kind of sat on the data six months and we said, Oh, maybe that's wrong because we were supposed to see one special barcode and we just there was no selection.

And so then what we did was we were kind of depressed for five months. And in that time we said, Well, we're going to start another experiment and we're going to see because the next one, we definitely did something wrong on the last experiment because it didn't work out. So we started a whole other experiment with another sample doing this again, and these experiments take six months right. So it's a long time, and at the end we found that it

was the same thing. So I just to point out that what you think sometimes is a step back. I used to get very upset and very worried.

And now I think, well, maybe this is telling me something else. Maybe this is telling me I have to do something different. Now, I'm more laid back and I just go with these setbacks and I get a little bit frustrated and then kind of sit down and you think, okay, so that didn't work out. Where do you go from here? What's this telling us? And maybe it's more exciting. And that was the case with this data. It was actually more exciting than what we had thought, and what I thought was a setback was nothing was actually fantastic. Finding hope for the first six seven months this data sat and we didn't do anything with it because we thought it was a setback. We thought we made a mistake, we thought it was wrong.

And so it just goes to show you sometimes you think something's a step back and it's not. And sometimes you think you just did this incredible thing and and it actually turns out to be not so incredible. So I think it's keeping an open mind is the most important thing for me and not letting anything get you too down and not letting anything get you too up, either. So not thinking that you know everything, because when you know everything, that's when you make a mistake and when you've made a mistake like we thought we did. Sometimes it's not. Sometimes it's actually more exciting. So I guess I try to just take a very even keel approach to things and try to not let setbacks get me too down. Or if I do let them get me down, I let them get me down for a week and then I get up and I start fighting again. But it's definitely the getting up, that's the important part for certain.

BTB

You mentioned earlier your connection when you went to a talk at Princess Margaret that you connected with this other researcher and it led you to the discovery of diapause. Does serendipity or randomness play a role in medical research?

DR. CATHERINE O'BRIEN

I think it absolutely plays a role 100 percent, and I think the key is actually keeping your ears and your eyes open and just always thinking about how things could be connected, even though it doesn't seem like it's connected to your work, how could it be connected to your work? And I think that's one of the keys. Somebody else gave me great advice, and that was to go to scientific meetings that are not in your field. Once a year, pick a scientific meeting that's not in your field, nowhere near your field and go to it. And I think that's really great advice. Because, you know, serendipity is great, but if you just turn off and you're not listening and you're not paying attention because it's not your field, for example, if I hadn't been paying attention and said, Well, embryology is not my field, this is not what I do, then you wouldn't appreciate it.

So I think that's something I do tell people in my lab is just, you have to be observant. And I think that's a key part of looking at a science is you have to be observant, you have to have an open mind and you have to see how things that might seemingly not be connected to your work, they might be they might actually be connected. And it's something that's really

important to keep in the back of your mind, not just to look within your field, but to look beyond your field and look at how things might actually influence your work.

BTB

Why do you do what you do?

DR. CATHERINE O'BRIEN

Because it makes me happy. I'd say for the most part, that's why it's that if I wasn't happy, I wouldn't do it. I think that it's something that I like the clinical aspect of it, and I like the research and I like the mix of both. I really like the immediate gratification of surgery, but I also like the long term investment of the research. And I think the combination for me keeps me actually very excited about my work and it keeps me motivated and I enjoy coming to work. There's no doubt.

BTB

What's next for you, Catherine, what should we be watching for?

DR. CATHERINE O'BRIEN

That's a great question. I really want to focus on how to propel forward, whether it's me that propels it or somebody else. The idea of treating cancers when they're in this response phase and whether it's me that does it or somebody else. I think there's such a great therapeutic opportunity where we can treat people when they have a low disease burden, they're responding to chemotherapy. And I think it's an uncharted territory right now in the context of cancer. And I think the increase in and I think this research is increasing exponentially. This interest in this state and whether it's our group or another group that finds means to actually target the state. And I think it's going to be a very rich area of research, and that's really where I want to focus all of my attention on understanding the state, understanding how to target it, understanding how complex it is, how heterogeneous it is or how homogeneous it is we don't know right now. And so understanding that understanding is it different, how different between different cancers, is it different in the context of different therapies? But I think understanding how to target it and how to actually target cancer cells in this state is where I want to focus my energy.

BTB

Dr. Catherine O'Brien, award winning scientist at the Princess Margaret Cancer Center. Thanks for sharing your pioneering research with us and continued success.

DR. CATHERINE O'BRIEN

Thank you so much for having me. It has been such a pleasure, and I really thank you for having such a great experience with this.

BTB

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