Season 1 – Episode 7 – Dr. Laflamme

Transcript

CHRISTIAN COTE

This is 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 Cote joining us on the podcast today, Dr. Michael Laflamme a UHN pathologist and award-winning principal investigator at UHN's McEwen Stem Cell Institute.

Dr. Laflamme is a pioneer in the research of transplanting stem cells to repair hearts damaged by heart attack. He joins us in a minute, but first here's the backstory on Dr. Michael LaFlamme.

CHRISTIAN COTE

Growing up in a military family, Michael lived all over the United States with stops in Ohio Florida Massachusetts and Washington. According to his Mom Michael's interest in science goes back to a popular TV drama called The Six Million Dollar Man. He was hooked on the series. Although his mom says he'd get upset because the hero secret agent Steve Austin got all the credit for saving the world each episode. To Michael's way of thinking it was the scientists who created his bionic powers who should have been the heroes.

Throughout high school. Michael was a mainstay at the annual science fair. He says he loved the pursuit of learning the unknown and sharing knowledge. And during his post-doctoral training Michael had an epiphany when he saw a beating heart muscle in a petri dish, created from a stem cell. Today he's a research pioneer in the use of stem cells to regenerate heart's damaged by heart attack.

Dr. Michael Laflamme principal investigator used UHN's McEwen Stem Cell Institute. Welcome to Behind the Breakthrough.

MICHAEL LAFLAMME

Thanks, pleasure to be here.

CHRISTIAN COTE

Let's start Michael with the damage you're trying to repair, what happens to the heart when someone has a heart attack?

MICHAEL LAFLAMME

So heart attack is when you have a blockage in one of the coronary arteries that, these are the blood vessels that supply the heart and after an interruption of blood supply for as little as 15 minutes the heart muscle starts to die and because the heart is probably the least regenerative organ in the body the damaged muscle is not replaced by new muscle it's replaced by scar tissue over time. And it's that loss of force generating units lost of pump activity that can lead the patient on a course towards a disease called heart failure.

CHRISTIAN COTE

What's typically the prognosis for someone with this kind of heart damage?

MICHAEL LAFLAMME

It's gotten better over time we're much better at getting people through the acute phase of a heart attack by improvements in emergency response time and treatment immediately during the heart attack. The problem is about 25 per cent or so of the patients even with sort of optimal treatment during the heart attack will go on later to develop heart failure and a lot of people don't realize how serious that disease is. About 50 percent of people that are diagnosed with a heart attack will be dead within five years.

CHRISTIAN COTE

So what's on offer when it comes to treatment?

MICHAEL LAFLAMME

We're basically limited to treating sort of the symptoms of the disease and progression of the disease. So, a lot of times people during heart failure will start to build up and accumulate fluid in their tissues. And so, we can give them drugs that cause them to lose that fluid over time that can help them breathe.

We can also treat them with drugs that prevent the disease from progressing further. Kind of arresting the damage where it occurred. Unfortunately, the only way to replace the muscle that was lost during the initial heart attack is to give somebody an entirely new heart. So, heart transplantation as you know there's nowhere near enough donor hearts to meet demand and that's sort of the the impetus for our strategy.

CHRISTIAN COTE

So give us a sense like what's the scale we're talking about here in terms of the number of Canadians with heart damage?

MICHAEL LAFLAMME

The numbers that I've seen by say Heart and Stroke Foundation and the like are there about 700,00 heart attacks every year in Canada and that accounts for the vast majority of the 50,000 cases of heart failure that are diagnosed each year. I mean it's about a half million folks that are alive right now with a diagnosis of heart failure and that's in Canada alone. Obviously you can just scale up the numbers with population in the U.S. and other countries.

CHRISTIAN COTE

Obviously that's a good time to dive into your research. I'm thinking we need a quick biology lesson though first in terms of the makeup of the heart because it's really central to the premise of your research correct?

MICHAEL LAFLAMME

Right. So again the job of the hardest to pump the blood that's needed to keep the body alive the heart is probably the least regenerative organ the body. So we have some arguments with folks that work in the brain.

MICHAEL LAFLAMME

I'd say the brain actually probably has more plasticity and more ability to rebound than the heart. So in most tissues we have what are called stem cells and these are cells that reside in the tissue? And their job is to replace the loss of cells that occurs over time from either sort of wear and tear or damage crown like as we're talking about here with heart attack and it was controversial for a long time whether there even is a stem cell in the heart. So there's lots of stem cells and tissues that turn over very rapidly like skin your scalp the lining of your gastrointestinal tract that kind of thing. The heart there's either not such a stem cell or if there is such a stem cell it doesn't do anything meaningful at least in the face of an insult like a heart attack. And so people had tried delivering other types of stem cells to the heart to see if they could turn into heart muscle cells replace it over time in those strategies generally haven't proven effective.

CHRISTIAN COTE

So what is your lab focused on then?

MICHAEL LAFLAMME

We're replacing the lost heart muscle cells with heart muscle cells that we generate from stem cells in the dish and we're working with a special type of stem cell called pluripotent stem cells, pluripotent is a fancy word that just means the ability to give rise to all the cell types in the body. But basically these are cells that are equivalent to cells in the early embryo that are going to give rise to bone brain cells. And for our purpose heart muscle cells and so providing the cells that can become anything with the appropriate cues that are present during development we can guide them in the dish to become really pure populations of heart muscle cells.

MICHAEL LAFLAMME

And so there's basically two different sources. So the original classic source if you will are what are called embryonic stem cells and these are the cells that are considered ethically and politically concerning by some folks. So these are cells that in the case of human embryonic stem cells are left over from in vitro

fertilization. So you can take embryos that are leftover that are actually slated to be discarded as medical waste and in some instances the couple will donate those embryos to medical research and you can isolate from those embryonic stem cells. And what a lot of people don't know is again because those cells have that ability to multiply. They're essentially a more in fact my lab works with embryonic stem cells in most of our work has been with a line of embryonic stem cells that was described in the original 1998 paper that describe the discovery of embryonic stem cells. That's one source.

A second source was described more recently in what are called this is another fancy word induced pluripotent stem cells or IPF cells. And what a scientist from Japan is Shinya Yamanaka showed is you could take any kind of cell so you could take skin cells or blood cells and grow those up and provide them factors that are normally present in the embryonic stem cells and you could reprogram these normal easily accessible cells to become the equivalent of embryonic stem cells.

My colleague Gordon Keller is one of the leaders in the world that's identified sort of the sequence of factors and the right conditions by which we can guide these cells very efficiently to become heart muscle cells and it's a process that after about 10 days you start to see the appearance of spontaneously beating cells by three to four weeks they're immature but they're further along and they sort of are are equivalent to heart muscle cells and sort of the fetal heart.

MICHAEL LAFLAMME

We've been focused on those cells as kind of the building blocks are starting material of a therapy for the heart failure that can occur after a heart attack. And so I've been working with we're approaching two decades now testing these cells out first showing that they might work in the dish developing some of the early methods to guide them to become heart muscle cells but we've really focused on is testing them in various preclinical models trying to get as close as we can to what would ultimately be the sort of patient that would receive these cells as a therapy.

CHRISTIAN COTE

So you start with a stem cell you coax it into becoming heart muscle stem cell and then you just injected into the heart?

MICHAEL LAFLAMME

That's exactly we're doing so it's conceptually just as straightforward as it sounds. So, as I said, after a heart attack you've now damaged a region of your heart and it's been replaced by non contractile scar tissue and so we can go in and inject into that scar tissue these heart muscle cells from pluripotent stem cells. We've shown that they will engraft, they'll survive, they'll live long term in the heart.

We've also shown and this was one of the advances that I did sort of midway in my career is we should not only do they form new muscle within the scar tissue but that new muscle is actually capable of integrating so it can hook up electrically with the rest of the heart and contract in synchrony with the rest of the heart which would be necessary for them to form functionally meaningful new force generating units right to restore lost pump activity.

MICHAEL LAFLAMME

What happens to the scar tissue? You're literally just replacing the scar tissue with new muscle. So if you define the footprint of the scar tissue by the perimeter of it it's the exact same. It's just now within that we have islands of new muscle and we're trying to make those as big as we can. Right. So we're literally re-muscularizing the heart.

CHRISTIAN COTE

What happens once those heart muscle stem cells are transplanted? We've shown in animal models that they are there for at least as long as a year which is the longest that we've lived over time, they're looking more and more mature. So as I mentioned before one of the limitations of them is that they are relatively immature. They're more like cells in the early fetal heart.

MICHAEL LAFLAMME

But if you look at them after transplantation say three months after injection and we look at them under the microscope they're starting to look much more like heart muscle cells in the adult heart.

CHRISTIAN COTE

Let's look at some of the results and what's the survival rate of these heart muscle stem cells once they're transplanted?

MICHAEL LAFLAMME

Yeah that's one of the limitations that we still have. We know that probably 80 to 90 percent of the cells that we're delivering actually will die within the first few days. The good news is and perhaps because they're still relatively mature they still will divide a few times. So, we get to take advantage of some compound interest and the graft gets bigger over time.

CHRISTIAN COTE

So, there's 10 or 20 percent that do survive they separate and grow even further while they're alive, but you're saying so far these stem cells once injected into animal models have only lasted about a year?

MICHAEL LAFLAMME

Well that's as long as we've looked, we have no reason to believe that they wouldn't last indefinitely.

CHRISTIAN COTE

All right. Another big challenge I understand though is something called arrhythmia?

MICHAEL LAFLAMME

That's right.

CHRISTIAN COTE

What is that?

MICHAEL LAFLAMME

That's probably the biggest challenge in my mind and really probably the major focus of my laboratory right now. So, we've shown and this is something we only see in when we've transplanted the cells in large animal models animal models that have a heart rate close to humans like you or I is we do see arrhythmias and these are electrical disturbances in the heart. We see them usually appearing maybe four to five days after we implant the cells they sort of peak maybe about two weeks after delivery of the cells.

And then interestingly they go way over time such that by three to four weeks post transplantation they're completely gone. So, it's almost as if there's sort of a settling in period for the cells. Now the concern is people that have had a heart attack people that have heart failure already at elevated risk for the development of arrhythmias and the last thing we'd want to do is make that worse. And so really this as I'm seeing it is kind of job one for the laboratory right now is to identify a strategy to overcome this risk of arrhythmias.

CHRISTIAN COTE

What about results have you seen in terms of actually restoring heart function with these stem cells?

MICHAEL LAFLAMME

That's sort of ongoing work. So we've done a lot of work in small animal models and there we've shown that by the transplantation of these cells we can see quite robust improvements in the contractile function of the heart and we can measure that by using the same sort of imaging approaches that we'd use in human patients. So we can look by echocardiography or we can use a technique called MRI and you can use those to assess how much of the blood is being pumped out of the heart each time. The experiment that we're doing right now is to ask in a

large heart, a heart that's closer to a human heart. Whether we'll see similar beneficial effects on contractile function.

CHRISTIAN COTE

Where are you at do you think in terms of when is it ready for primetime in terms of moving into say a human clinical trial?

We basically have two tasks still to do. So, first we've got to overcome this arrhythmia problem and we have some preliminary data that we think we have a pretty good handle on how to overcome that worst case with treatment with certain anti rhythmic drugs seems to greatly reduce that risk. The other tasks that we need to do is to show in a heart that's closer to human heart that we can see the sort of robust movements and contractile function that we've seen in the past in these smaller animal models, rodent models we know from work from others in the field including former colleagues of mine at my previous institution that sell products similar to what we're using.

In one case folks reported a near complete restoration of heart function. I don't know if we're going to see that but even a tiny fraction of that sort of result could make a big difference in terms of clinical outcomes.

CHRISTIAN COTE

And is there something about your work with Dr. Keller that makes this unique in terms of your lab?

MICHAEL LAFLAMME

Gordon Keller has really led the field in guiding these pluripotent stem cells not just to become heart muscle cells but the different types of heart muscle cells that you have. So if you think about the heart you have the ventricles. These are the two lower chambers of heart whose job it is to squeeze most of the blood to the either the body or the lungs. You also have other structures you have the atria those are the two smaller chambers at the top of the heart. There's a big difference between atrial and ventricular heart muscle cells. There's also

pacemaker cells. These are the cells whose job it is not to contract but to control the electrical rhythm of the heart.

Well most folks including us until very recently if we were guiding these pluripotent stem cells into heart muscle cells we were actually making a mixture a gamish of all three of these cell types. So atrial cells ventricular cells and these pacemaker cells well Gordon's lab is very nicely worked out ways to generate these ventricular heart muscle cells which are the cells that you lose during a heart attack.

And so we're really fortunate that by combining what we think of the right cell type that Gordon's lab has figured out how to make, making them at scale and then testing those out in the various preclinical models that my laboratory works with we can test the idea that these cells will give us a better safer outcome.

CHRISTIAN COTE

I understand from reading about your work that business acumen is probably a must, there's quite a learning curve I imagine for researchers and scientists to master the ins and outs of commercialization and regulatory demands. Are you taught that in university?

MICHAEL LAFLAMME

We are not or at least I was not.

CHRISTIAN COTE

So how do you navigate that?

MICHAEL LAFLAMME

The first thing I do is know what you don't know and who to ask for help. It's one of the unique things about working with these cells. There's there's always big hurdles whenever you're trying to develop a new clinical therapy right. To go through clinical trials is quite expensive. There is another challenge with this particular application which is the sheer numbers of cells that are required. So, a

typical human heart attack involves the loss of a billion heart muscle cells. So, we think that that's about the dose of number of cells you would need to meaningfully replace it. Right. So, if we're talking about doing even a small clinical trial you're talking about a need for tens of billions of cells right. You have to…

CHRISTIAN COTE

What is your threshold you think to have the equal amount going in that have been damaged?

MICHAEL LAFLAMME

We think that the approximate dose for each patient would be about a billion cells. But if you want to test it out in a dozen patients now you're talking. Ten to the 10th sort of cells and to generate those cells clinical grade, we're talking about a cell manufacturing process right. This is something we need to move from kind of the boutique scale in a petri dish in the laboratory to a true industrial process. And we recognize pretty early on to do that. We were going to have to commercialize. We were going to have to pull in industrial expertise to get there economically and practically.

CHRISTIAN COTE

Well I have to say, you must have done your business homework because you created Blue Rock the commercialization company in 2016 to do just this and it was just purchased by Bayer A.G. for a billion dollars.

MICHAEL LAFLAMME

That's right. So as vice myself..

CHRISTIAN COTE

Are you a billionaire now?

MICHAEL LAFLAMME

I'm not a billionaire far from it.

CHRISTIAN COTE

What did you think when that deal was going down?

MICHAEL LAFLAMME

That was pretty exciting. Obviously mean as we said doing this kind of work is really really resource intensive and so I'm I'm tickled pink that now the company we've helped create should have the resources to see this through. Clinical trials especially in heart failure patients are extremely expensive it's probably about the most expensive disease in which to run a clinical trial. And so it's just going to take tens of millions and perhaps ultimately hundreds of millions of dollars to get an approved therapy.

CHRISTIAN COTE

You're listening to behind the breakthrough a podcast about groundbreaking medical research and the people behind it at the University Health Network in Toronto, Canada's largest teaching and research hospital. I'm your host Christian Coté We're speaking today with Dr. Michael Laflamme award winning principal investigator at you a chance stem cell institute and a pioneer in the research of using stem cells to repair broken hearts. So, Michael we mentioned in your back story that you are an American. You've lived all over the country, you're part of a military family and as your career later unfolded, you were well established as a pathologist and researcher at a medical centre in Seattle, yet you've said your decision to come to Toronto in 2015 was a no brainer. Why is that?

MICHAEL LAFLAMME

I had been in Seattle first as a resident and then later as faculty for I believe it was 16 or 17 years before I moved and things were going reasonably well there. So I think we were successful. We're getting traction so I I was not shopping around for other opportunities but we had collaborated with Gordon Keller and other scientists here. From a distance in Toronto so I certainly knew about the reputation of the place and we'll come back to that in a second. But when they approached me for this opportunity I did not have to think about it too long. And

that's because Toronto is one of the meccas of stem cell research in fact I'm surprised by people that have lived in Toronto their whole life that don't know that history. So stem cells were actually discovered right across the street from where we're sitting here in Toronto and it's sort of a unique ecosystem if you will.

CHRISTIAN COTE

You're talking about Till & McCulloch as correct back in the early 60s.

MICHAEL LAFLAMME

That's correct. Who discovered the stem cells in bone marrow that replaced the circulating blood cells type? So one of the adult stem cells that we were talking about before and of course Gordon Keller is here who had always been one of my heroes in the field and somebody we had collaborated as I said before we moved? And as I say this is kind of a unique place in terms of not just the community of scientists here but it's also a very blessed place and support for stem cell research and regenerative medicine. Martin McEwen institutes so the McEwen's have been very generous in supporting that work.

There's also been excellent support from government as well so there's something called the Ontario Institute of Regenerative Medicine that's provincial support that was really helpful after I moved here and moving our experiments forward. There's other funding mechanisms through the University of Toronto. And so this is just a unique place. There's really no other place like it on the entire planet and I'm surprised by how people again that have lived here their whole life don't really realize that.

CHRISTIAN COTE

I think you've discovered one of our small little Canadian flaws of how we under promise and over deliver and sometimes don't sing our own praises enough.

MICHAEL LAFLAMME

That's probably that's that's certainly true I'd say.

CHRISTIAN COTE
We're too polite given the stakes that we talked about earlier about the number of Canadians who suffer heart attacks each year.

CHRISTIAN COTE

What kind of pressure do you feel when it comes to translating your research into a safe and effective treatment for patients?

MICHAEL LAFLAMME

It's certainly a balance. There is an urgent need for new therapies in heart failure as we've discussed. At the same time the last thing we want to do is do harm and so we've taken what I hope is sort of a patient methodical approach. So, I did my first transplantation in a rat model in I believe it was 2003 and we've gradually worked our way to a point in time now where I think it's realistic to in fact we expect to be able to get into human clinical trials in something like a three to four year time horizon. And we're not talking about what I'm expecting to be in our grandchildren's therapy. But it's taken a long time to get here and we still as we described have work to do.

CHRISTIAN COTE

So, that'll be close to 20 years from your first foray into this field to perhaps getting to a human clinical trial?

MICHAEL LAFLAMME

Embarrassed to say but I think that's true.

CHRISTIAN COTE

Well I don't know if it's is it embarrassment because you know better than anybody science is rigorous it takes time. I'm wondering though, how do you reconcile that urgency to come up with a breakthrough with the time, the rigour that science takes?

MICHAEL LAFLAMME
It's certainly what drives us and why you know the folks in my lab work as hard as they do you'll find everybody in on the weekends is because there is such an urgent need.

CHRISTIAN COTE

Something that struck me when we chatted prior to the show is your attitude towards failure.

You said you do not expect anything to work the first time or the second time, so obviously to be a research scientist requires resilience. How did you develop that quality?

MICHAEL LAFLAMME

I don't know if that reflects pessimism or realism but that's sort of the advice I give to new students in a laboratory is you know do the experiment. Don't expect it to work the first time learn what you did wrong go back and do it again and I think you you have to be persistent. I mean the idea of turning a scarred heart back into a functionally electrically integrated new muscle that's difficult right. If it was easy the heart would be doing it on its own or somebody else would have done it decades ago.

CHRISTIAN COTE

You've mentioned in other interviews that I read the importance of mentors along the way in your career path. What is it they gave you or that benefited you from them?

MICHAEL LAFLAMME

I've been fortunate I've had many excellent mentors at every level during my training and even today there's people that I still go to for advice. The ones that have that I have admired the most that I tried to emulate as best I can have two properties. I mean one is they're absolutely scientifically fearless right. So, they're willing to to learn a new technique to travel to a new place to do whatever is

necessary to answer the questions at hand. Some of them can be quite dogged and willing to spend 20 years of their life dealing with a challenging problem like the one we're talking about here. The other thing is you've got to be creative. You've got to ask the right questions and you've got to develop new approaches in some instances to answer those questions.

CHRISTIAN COTE

And what's your advice to young aspiring medical research scientists these days?

MICHAEL LAFLAMME

I encourage folks to think outside the box as you said you got to be creative you've got to be persistent. I encourage people to focus on disease. Everything we're trying to do is to try and improve the lives of patients at the end. The other thing that I find is very helpful it may not be intuitive is to get people to put their thoughts to their plan to writing very early on. It forces one to crystallize one's thoughts to actually articulate and sketch out a plan step one step two step three and so within the first six weeks of joining lab everyone is expected to do that.

That doesn't mean that the plan always fleshes out the way we're expecting but it's important to start with one.

CHRISTIAN COTE

I'm curious if you ever have doubts in what you're doing every day?

MICHAEL LAFLAMME

Oh of course that's the scientific method right. So, we need to be questioning everything we do. And so, as just as I said I tell every student expect things not the work the first time. We also need to teach them to question their assumptions. Right. The whole idea of the scientific method is you should be able to do an experiment. So, we're on a Wednesday today I should be able to do it in another place on a Thursday and get the same result. And I think where people go astray in science is assuming that they've got it right that they know how the universe works.

CHRISTIAN COTE

What keeps you at this every day?

MICHAEL LAFLAMME

It really goes back to my clinical work as a pathologist.
So again I don't see patients but I see tissues that come from patients and so I see for example all of the hearts that come out of patients that have undergone a heart transplant. And so you see these scarred damaged up hearts and you know it's the ultimate motivation. I mean we're seeing I guess the worse outcomes there are people that actually had to go on to get a heart transplant. I'm hopeful that we have a strategy to give them an alternative.

CHRISTIAN COTE

So what should we look for next from your lab?

MICHAEL LAFLAMME

We're working hard on this arrhythmia problem and what we've got as I said some strategies that we're really really bullish on we think if we can overcome that hurdle a lot of the other challenges that look so daunting just a few years ago we feel like we've got a much better handle on we can make billions and tens of billions of these cells reasonably economically now reasonably efficiently. We talked about their strategy out there I can't take any credit for this other folks have develop these really elegant strategies to deal with the immune system with these universal donor cells.

They're clever ways to deliver these cells to injured hearts you can do it either open chest by directly injecting the cells or they're non-invasive or minimally invasive ways and we're starting to some work in that area but we really feel like if we can overcome this arrhythmia problem we've leaped the last hurdle to really get into the clinic.

CHRISTIAN COTE

Dr. Michael LaFlame award-winning principal investigator at UHN's McEwen Stem Cell Institute thanks for speaking with us and continued success.

MICHAEL LAFLAMME

Thank you.

CHRISTIAN COTE

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