Behind the Breakthrough Podcast - University Health Network

Season 4 - Dr. Shaf Keshavjee

Transcript

BTB

Hello and welcome to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host Christian Coté. And joining us on the podcast today Dr. Shaf Keshavjee an internationally renowned surgeon at UHN`s Sprott Department of Surgery, and award winning senior scientists at the Toronto General Hospital Research Institute. Dr. Keshavjee revolutionized lung transplant. When in the late 2000s, he invented a way to preserve and treat damaged donor lungs outside the body known as Ex Vivo. The impact of Dr. Keshavjee`s world first Toronto Ex Vivo lung perfusion machine was to double the number of lungs available for transplant. Today, research continues using his Ex Vivo intervention to treat other damaged organs including the liver, kidney, and heart, Dr. Shaf Keshavjee Welcome to Behind the breakthrough.

DR. SHAF KESHAVJEE

Thank you, Christian for having me.

BTB

Before we get into your Ex Vivo invention, let's set the scene for our audience because over the decades I understand the biggest obstacle to any transplant has been the supply of viable organs, particularly so I understand for lungs given their fragility. Talk to us about this challenge, and what that has meant over the decades for patients in need?

DR. SHAF KESHAVJEE

As organ transplantation was invented, developed to save lives of people dying of end stage organ disease, transplants of the kidney, the heart, were done in the 50s and 60s and livers in the 70s. However, the first successful human lung transplant wasn't achieved till 1983, at Toronto General Hospital, in fact. And so lung transplant was the last of the major organs to be achieved clinically, partly because of the fragility of the lung, partly because of the anatomy, the blood supply to the airway of the lung. And the fact that when someone dies, often the lungs are injured by being on a ventilator being resuscitated. And so today, only 20% of donor lungs that are available that have their organ donors card signed, are actually used. So what we set out to do is say those 80% of lungs that are not used, can we make them usable to save lives?

BTB

Okay, so let's trace the origin story of your Ex Vivo machine, which was actually I understand preceded by another one of your discoveries. Take us back to the early 1980s. You're still in med school, your first year in the lab as a resident and you're working on a master's thesis, what did you hit upon during that time?

DR. SHAF KESHAVJEE

At that time, the actual operation of lung transplantation was achieved. And that was a miracle that you could take someone's lungs out and give them new lungs, and they could survive it. But it was a very, very high risk endeavor. And the biggest problem really was preservation of the lung, once you take the lung out of the donor, and have to transport it and put it into the recipient, that period of time the organ starts to die. And so my master's thesis project was, can you preserve a lung longer, and my thesis title was the method for a safe 12 hour preservation of donor lungs for transplantation. And that was extremely radical. I mean, we used to do the lung transplants and taking the lungs out of the donor in the operating room next door to the recipient, and rushed like hell to get that lung across the hallway. Now we have 12 hours. And that was my master's thesis work. So that lung preservation solution, which we call the LPD, is now the standard of lung preservation worldwide.

DR. SHAF KESHAVJEE

Having figured out lung preservation opened the door for us to basically pick up an organ anywhere on the North American continent, bring it back to Toronto and transplant it. But we wanted to go further because the next hurdle in lung transplantation is okay, we transplant a lung into you, you survive the operation, but your body spends the rest of your life trying to reject it and destroy the organ. And we have to give you immunosuppression to prevent you rejecting which makes you more vulnerable to infections, makes you more vulnerable to cancer. So what we set out to do starting in the late 90s was can we genetically modify the lung to look more like self so that you wouldn't reject it? So that was gene therapy. So what I was using was adenovirus vectors, which is the common cold virus, you take the virus genes out and put in a human anti-rejection gene into the virus. You then put the virus into the lung, let it go into the lung cells, and it produces an anti-rejection protein called IL10.

DR. SHAF KESHAVJEE

So that is genetically modifying the organ to say to your T cells, when they come into the lung, don't protect me, it's me itself. So we showed that we could do that in the donor, we did it in rats, we did it in pig studies, we did it in human lungs, showing that you could work in the donor and upregulate, IL 10. So that at the time of transplantation, that IL10 was already up, and you wouldn't reject. But it takes about 12 hours to do that. So we don't always have that kind of time. And it's not in the most usual places, a donor could be anywhere in North America. So we said, Can we take the lungs out of the body and then do the gene therapy? And there are a lot of problems with that, because our preservation technique and the preservation of all organs really relies on cooling the organ, bringing it

down to about four degrees, so that you basically shut down the organs and you shut down the dying process.

DR. SHAF KESHAVJEE

So you preserve it at that temperature, but it can't work. It's not working. So just like all the dying processes are halted in suspension. So are the repair processes. So gene therapy can't work at four degrees. So we have to bring it back up to normal temperature, normothermia, to get gene therapy to work. That means you either do it in the donor, or you have to figure out a way to keep the lungs outside the body at normothermia. And that's where we started to develop Ex Vivo outside the body lung perfusion systems to do the gene therapy that we set out to do.

BTB

I have to say, it does sound a bit like science fiction, which I know you've also used that term over the years as well. What was the reaction from people when you started to say this is the kind of research I want to pursue?

DR. SHAF KESHAVJEE

Well, I mean, it is surreal. I mean, it's science fiction. And it's surreal. And even to this day, when you see human lungs breathing on their own on the table outside the body, you do a second take. I think the reaction was first disbelief. That's not possible. You can't do that, then the other part of it was good scientific curiosity. Wow. That's amazing. Could you imagine if you could do that, what does that open the door for? And I think that's the most exciting thing about Ex Vivo organ perfusion. I mean, the fact that we've achieved it has allowed us to use more lungs, we can, if we're not sure about a lung, we can test it on our system. And that's fully doubled the number of lung transplants we do at Toronto General Hospital, and we are the largest lung transplant program in the world as a result of that. But that's not the big deal. The real big deal is the fact that we can actually do all kinds of things in terms of precision medicine for the organ, just like we do precision medicine for patients today, we have so many opportunities to treat these organs, with drugs, with gene therapy with cell therapy, all kinds of ways that we can make that organ better.

BTB

So let's go through the research phase. You mentioned starting in the late 90s. You sort of solved the first problem in terms of typically you preserve lungs on ice by keeping them outside of the body. Second issue I understand you had to overcome was the circulatory system that keeps the lung basically viable. You couldn't use artificially pumped blood because that can cause inflammation and injury. So what did you turn to as a substitute for the circulatory system and the lungs while it's outside the body?

DR. SHAF KESHAVJEE

So the concept of perfusing and keeping organs alive outside the body is not new. In fact, DaVinci tried it and DaVinci has elaborate drawings of hearts and kidneys outside the body being perfused. Charles Lindbergh in the 30s and Alexis Carrel, a vascular surgeon, worked together to try and develop Ex Vivo organ perfusion actually for Lindbergh's sister who needed a transplant. And ever since everybody has dreamed of doing it. And even when I set out to do gene therapy, it seemed like the way to do it, but Ex Vivo work in perfusion was not achievable. So we went to prove the concept of gene therapy first and then realize that you know what, we've got to cross that bridge. If we're ever going to make this practical, and bring it to the bedside, we have to develop a perfusion system. Now. I think the one error made in history looking back, is that everybody was looking for a universal system, your body in your body, all your organs are perfused by one profuse, your blood by one organ, a pump. So let's just do the same thing, put blood and a pump together and hook it up to the organ. It doesn't work. Right. And so the advantage we had is we said okay, I'm not gonna worry about the heart and the liver and the kidneys. I just want to know, what does it take to keep a lung alive and not damage it all the systems make it worse, you watch lungs deteriorate in support systems.

DR. SHAF KESHAVJEE

So what does it take to maintain it and just the lungs? So we said, okay, let's put everything we've learned about protection of the lungs together in the system, what's the protective way to ventilate it to let it breathe? What's a protective way to perfuse it? Well, we can control all of this, we can decrease the amount of flow per minute through the lung, we can decrease how many the volume of ventilation in the lung, we can manipulate the oxygen, the carbon dioxide, we can manipulate everything. And the other thing is, while the organ is Ex Vivo, outside the body, it's vulnerable, it's damaged. So you need to support it, and not add additional injury, the circuits and systems, we benefited from that, like 50 years of development of support systems for human beings. Extracorporeal Membrane oxygenators means we have better oxygenators, better tubing, better things that don't cause as much inflammation, but they still damage blood cells. And so I said, Look, you know, we have an oxygenator, we have a pump, we have a way to deliver oxygen, we have a way to remove carbon dioxide. We don't need the red cells. So let's do without the red cells. And that was a huge step. And when you say, What did people think when we did it that they thought was crazy. They said that would never be possible. We've tried that it won't work, it'll never be possible.

DR. SHAF KESHAVJEE

So we systematically worked it out in little app, and Marcelo Cypel was my fellow at the time and, and we did it and showed that you know what, you can keep a lung alive outside the body for a day, without blood. If you manipulate the system and create what we call a homeostatic system, it just keeps the lung in equilibration. Not trying to test it, not trying to push it, not trying to make it do things. Just keep it alive and not damage it, and then go from there. So that was a big eureka moment, we can take a normal lung on our current system, put it outside the body at 37 degrees, normally a lung dies in 20 minutes, we can keep it for a full 12 hours and showed no deterioration. And we've recently published last month in The Lancet, actually a paper where we are now keeping lungs for three days, using a

combination of Ex Vivo lung perfusion at 37 degrees and 10 degree preservation, which preserves the mitochondria, which are little organelles that have the energy inside yourself.

DR. SHAF KESHAVJEE

So three days, I mean, could you imagine taking a lung on a Friday afternoon and saying, Okay, we're going to transplant it on Monday morning at 8 am. And it's going to be a better lung on Monday, then it was on Friday, not compromising anything, making it better. We're on the threshold of that.

BTB

So Shaf we'll post a video of the Ex Vivo machine in action along with the podcast. But maybe if you don't mind, could you describe for the audience what this machine looks like.

DR. SHAF KESHAVJEE

So basically, it's a ventilator, which is a breathing machine that you run in the ICU standard state of the art ventilator now I say standard because a ventilator is a very sophisticated machine. It can measure the pressures in the lung and the pattern of delivery of gas, the breathing rate, all kinds of things. So state of the art ICU ventilator, a state of the art centrifugal pump, so a centrifugal pump is the heart. It pumps the fluid around, but it works by centrifugal force, meaning it isn't a roller pump. If it meets resistance, it backs off and so on. It's a state-of-the-art artificial heart. So we got a centrifugal pump, and we got a ventilator, then we have an oxygenator. We have a membrane, which is the surface area of a football field where the fluid goes across and the gas is swept across the other side of the membrane. Oxygen is taken out of the system. And carbon dioxide is added to the system. And the lung by breathing on the ventilator adds the oxygen which comes through the ventilator and removes the carbon dioxide so you can measure the function of the lung on the system.

DR. SHAF KESHAVJEE

Now you can imagine this was another breakthrough of the homeostasis is the fact that if you just have a lung breathing on a system, it clears all the carbon dioxide, adds oxygen, the system becomes alkalotic, and the lung gets damaged. But now we're adding carbon dioxide just like your body would. And you're and you're adding oxygen like the way your lung would and it keeps the system in balance. And then we have a patient monitor that measures the pressures and the volumes and the oxygenation and so on. And so I mean those are the key concepts of it. It's a small room of equipment that goes together. Now we have put that all into one combined device that we're launching out of UHN as Trypharox a company that makes these devices for clinical use.

DR. SHAF KESHAVJEE

So what we've worked at is really to simplify it. Because what we did was when we brought this from the lab, to the clinic, that was one of the translations, which is one of the fantastic things about University Health Network, that we have the pathway to bring discoveries like this from the bench, to the bedside, and to do it safely to do it through the appropriate clinical trials, and so on. So we did that.

And we've shown the world that we can do this, but other surgeons around the world have not had the same degree of success that we've had here. And we realized it's partly because it's still complicated. Okay, there's still many, many steps to it. And so we work to refine that. And we work to build that into a device to make it simpler to perform Ex Vivo lung perfusion, we now have a school through the Medstar Institute, that trains organ perfusion specialists to do this for the surgical team.

DR. SHAF KESHAVJEE

So at the very beginning, when we started the EVLP, at Toronto General, Marcelo and myself would do the EVLP and create and give a perfect lung to the surgeon to implant and we did all the EVLPs. And we slowly realized that there's surgeons, when you have a big operation to do, you don't really want to have the ability to look after and treat a lung on the EVLP. So we trained organ perfusion specialists, and they do this for us. They send us reports every hour, and sometimes they'll wake you up and say, Okay, this lung's been going four hours, it's really good, are you gonna go and transplant and you go look at the data and transplant it. So I think that's where the field will go. We've also developed in partnership with United Therapeutics, Lung Bioengineering, which is a company that provides Ex Vivo lung perfusion as a service to transplant centers. So thirty transplant centers in the US and Canada use lung bioengineering as their EVLP Service. So a lung is taken at the donor center, flown to Lung Bioengineering, they do the EVLP, the organ perfusion specialist there are trained by us at TGH. And when the lung is ready to go, it's flown back to the transplant center where it's implanted. So it's already increasing the rate of transplantation in the US significantly.

BTB

So over the course of your research into the 2000s. When do you have, when did you and your team have a sense of you know, you had the results that made you believe you could move this into human clinical trial?

DR. SHAF KESHAVJEE

The development of Ex Vivo lung perfusion moved quite rapidly. And I think it was because of the huge unmet need. I mean, patients are dying, needing a lung transplant, and most lungs are not being used. So you know, everybody knows that. The government agencies know that, the funding agencies know that and so on. And honestly, it was the Latner family, one of our gracious donors, at University Health Network that donated millions of dollars to start this project. And they asked me, well, what would you - Albert Latner asked me, what's your dream? What would you like to do? And I said, I would like to develop a system to keep lungs outside the body so we can repair them and transplant them. And he said, Okay, well go to it and gave us several million dollars. And that launched the EVLP program.

DR. SHAF KESHAVJEE

And we started out with can we just perfuse the lung and we could go 90 minutes, it was just a disaster. It wasn't working wasn't working, but fine tuning, adding things, making it a closed system, adding the right kind of pump, taking the cells out, a bunch of things, we optimized it. And aha, we got a system

that we could perfuse the lungs. So that was in 2006, okay. In 2007, we buy a year of work, which is extremely fast. When you think of the 100 years that went before and Ex Vivo organ perfusion. We got a system that could keep the lung for 12 hours okay, and we were ready to move it clinically.

DR. SHAF KESHAVJEE

So we did the Phase One human trial in 2008. So it was really very, very quick. But then we got it from basically achieving the success in 2006. First in-human in 2008 approval by Health Canada in 2010 or 12. So it really moved very quickly to doing that. You could say we were lucky but I think the fact that what you were doing was taking a lung that had risk as a leading lung transplant program. You would take lungs that were not entirely perfect, but you know, you could get through with good critical care, good management, you'd do it. Now you'd take that kind of lung, you put it on the EVLP. And you know, it's a good lung before you even start the operation. That was, what I would say was the really positive impetus that actually made it safer. And for me, as a lung transplant surgeon, I'd grown through those years of having to push the limits by taking a lung that wasn't perfect and get the patient through because the alternative, they were going to die in a month, so you take more risk. Now it's taken the risk out of lung transplant a lot, not completely, of course, but a lot like this dress on you as a surgeon is hugely less, because you know, the lungs gonna be okay, before you start your operation. I had never had that privilege.

BTB

Let's just mark this moment, because we should, as it was a world first December 5th, 2008 was the first human transplant of damaged lungs treated by your Ex Vivo machine, convincing that first patient to give this a try - what was that like?

DR. SHAF KESHAVJEE

You know, our patients at Toronto General have been a really important part of our leadership in this field. Okay. So I mean, if you think about it, Joe Cooper had to go to Tom Hall and say, Would you consent for a lung transplant, knowing that it's been tried 44 times around the world, and no one had survived?

BTB

You're talking about the first successful transplant in '83.

DR. SHAF KESHAVJEE

Yeah, in 1983, Tom Hall went into the Toronto General operating room knowing that no one had come out of an OR and survived a lung transplant. And he lived for many years after. And then with low potassium Dextra. And we did the same thing. We went to our patients and said, look, this is what we've been doing in the lab. And here's the difference of the lung preserved with LPD versus the standard technique and how much better it is, would you consent to being part of the trial and

everybody went one and two, with the Ex Vivo lung, the same thing? So we showed them what it does and how we can evaluate lungs? And we said, look, if the lungs the standard usual, we'll go to a transplant, if the lung has any issues where we're not sure, we'll evaluate it, but we will only transplant it if it meets the criteria. And all the patients said yes. And right now the patients are all asking when can I get a gene modified lung, because they know the big hurdle in lung transplantation now is chronic rejection, that the lungs are not going to last forever. And the mantra in our lab is make an organ that will last forever make an organ that will outlive the recipient, you put it in.

BTB

What was the outcome of that first surgery Shaf?

DR. SHAF KESHAVJEE

The patient's done very well. And many, many more patients have done well, their Ex Vivo lung perfused patients using the Toronto technique are doing equally well or better than standard lungs. And we've published that multiple times, because we've actually done 850 clinical cases now.

BTB

And I have to ask, that was, you know, a world first success back in 2008? How did you react?

DR. SHAF KESHAVJEE

As anything, you know, you're nervous at first when you bring this forward, but it is part of the courage you're required, like, why are we doing research, right? We're doing it to improve healthcare. So when you bring that, of course, you're nervous, but we made sure that everything was done absolutely carefully, we brought the system into the OR we worked with our nurses to optimize how to do EVLP in a human OR what instruments, what kits, how should the kits be built, and we set up for success? And so again, you know, like I said, the fortuitous thing about EVLP is like once you do it you know, the lungs, good. So then it was just okay, good surgeons do your thing. And the patients did very well. And it was off to the races after that.

BTB

How did the healthcare world react to your breakthrough?

DR. SHAF KESHAVJEE

I think at first people said, well, you know, there's no blood in the system, and therefore the airway circulation may not be so good. And the anastomosis may fall apart. Well, it didn't. In fact, the airway complications are even less because it's better preserved. You know, and I guess just waiting to see the results. But having said that, I mean, our first 20 cases was a lead article in the New England Journal of Medicine. So it's gotten a lot of recognition. Recognition as a world class invention,

transformative event in organ transplantation. The Oxford team gave us a lot of credit because soon after we achieved it in lung, Peter Friend is the professor there, achieved Ex Vivo liver perfusion, and then others have gone on to do heart and so on. So I think it opened the door to this new activity, and as you know, paved the way for the other organs and people have recognized us for that. What I'm most excited about is really engineering organs. You know, I think when we can truly do the first in human transplant of a gene modified organ, that would be really EVLP coming to fruition.

BTB

I want to get into that. But we should also make a mention that you continue to innovate in terms of how to treat damaged lungs outside the body. And a recent innovation of yours was you were able to take lungs damaged by hepatitis C and successfully treat them, talk to us about that.

DR. SHAF KESHAVJEE

So we set out to say, can we actually sterilize organs? Can we clear all the viruses so that you transplant an organ that won't transmit a virus with the transplant and started with hepatitis C, and they've gone on to EBV, and now some CMV protocols. So I think that's very exciting. Now, with the hepatitis C, we were able to clear the virus in two out of nine transplants. So it's not completely sorted out yet. But if you think about it, taking a Hep C, organ, and transplanting it, and in two of the patients, they never converted, never needed pills for hepatitis C, that tells you it's possible, we just have to figure out how to do it 100% of the time. Now, Hepatitis C is a backup, there are pills for hepatitis C, but Hepatitis B is not so much.

DR. SHAF KESHAVJEE

And other viruses are more of a challenge. And when you think of the Xeno viruses, that if we were to transplant animal organs, the idea that we could clear all viruses is exciting. So we're using a combination of drugs and energy techniques a special UVC light that kills viruses, it's the same UVC type of light that's used to sterilize blood for transfusion, and platelets, and plasma and so on. But because you can take the organ out of the body, now you can use these energy sources that you can't radiate people with, but you can treat the organ. So it's really thinking out of the box, if you will, and saying, Well, if you have an opportunity to do something, can you actually use those technologies to your advantage.

BTB

And in terms of moving forward, talk to us and about your research, you mentioned just a few minutes ago about developing ways to repair organs so that you can eliminate rejection.

DR. SHAF KESHAVJEE

I started out, as we mentioned, using the common cold virus and taking its genes out and using the virus to get into the lungs. And that gives you a very rapid upregulation of the gene, you're interested in

the anti-rejection gene. What's been more exciting was the development of CRISPR gene editing. Okay. So if you think about what I was doing with gene therapies is you take a gene, and you use a virus to plunk a gene into the nucleus, and it makes your protein from that gene product, right. And the problem with that is some of the insertions of the genes are random. So they could end up anywhere in your genome. And sometimes they could be next to something that isn't so good, like a cancer producing gene, and input turned it on. But the chances of that are minuscule, minuscule, minuscule compared to the chances of dying because you didn't get an organ transplant.

DR. SHAF KESHAVJEE

So it's still an acceptable way to move forward to say, make an organ that won't be rejected, significantly improve the chance of success of transplantation, with a very, very, very small risk of a cancer. Okay, now comes CRISPR gene editing. And that's really like a word processor for your genome. So the development of CRISPR technology, to me, is the most significant discovery in genomics, since the identification of DNA itself. It's huge, and what it's gonna do for medicine. So I said, Well, now you can edit the genome, can you actually do this for organs, so people have done it in cells. And the people that discover it and work on it are doing it in cells. They're doing it in bacteria, all the time, and so on, but not in full organs.

DR. SHAF KESHAVJEE

And again, this is what most people said, is not going to be possible. It's hard to do. And you know, you can't really do it. Well guess what EVLP creates the ability to do CRISPR gene editing of our own organ. And that's what we're doing now. We've achieved it in cells, we've achieved it in rats, and we're doing it in whole lungs now on EVLP. So now, you've got the idea that you can do the gene modification without the risk of what we call off target effects. So that's what I'm working on now. I mean, it's huge. It's very exciting, because it has all of the promise of gene therapy with less of the risk and more precision medicine.

DR. SHAF KESHAVJEE

The other thing about CRISPR editing is you can make it permanent. So some of the genes, we were inserting your body says this gene doesn't belong here, let's fix this little defect that’s shown up in my DNA, or it lands in the wrong place, as you know, and then it might get edited out again, that's our normal protection. So now you can actually word process, you put it in nip and tuck, it's all neat it's in the genome forever.

BTB

I want to briefly touch on the business side of medical research, because that has certainly emerged for you as something you've had to learn on the fly. It's not taught in med school. Talk to us about the business side of things.

DR. SHAF KESHAVJEE

Yeah, no, I mean, I think it's something that I'm very interested in my new position as chief of innovation for UHN. Innovation is bringing your discovery to the bedside. So I mean, it's what I've been all about. And I think what we need to do more of. You know, the other thing is, I started out the idea of commercializing and things like that was viewed as dirty and non-academic in the academic circles. And I have, you know, grown up and ascended through the academic process in the usual way with grants and professorships and whatever. But the point of it is, you cannot bring an invention or discovery to the bedside without commercializing, it has to go through regulatory, it has to be approved, it has to be manufactured, someone has to buy it, a hospital has to buy it before you can put it in a patient. So that process needs to be put in place. You know and many of the young doctors now need the advice, okay, you've got this great idea. You can save lives, you can improve health. But how do you get from your great idea, to something that we can safely use in patients that people will buy.

DR. SHAF KESHAVJEE

So I think that that is important. And there are processes I declare all of you know, the company, I've spun out three companies out of UHN. UHN is a participant in that it, this feeds back into sustainability of our research program. So I think it's really important to do more of that. And what I'm going to be looking for now is investment to be able to help others in UHN to do that, and in fact, our new frontiers research grant, we just got a $24 million grant from the Canadian Institutes of Health Research, for Ex Vivo organ perfusion to advance lung Ex Vivo lung to do the CRISPR and things that I talked about, but also to develop Ex Vivo perfusion for kidney, heart, and liver and pancreas, which we're doing with the whole transplant team in the Ajmera Transplant Center at UHN.

BTB

You're listening to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it and Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host Christian Coté, and today we're speaking with Dr. Shaf Keshavjee, award winning surgeon at UHN's Sprott Department of Surgery and senior scientist at the Toronto General Hospital Research Institute, Dr. Keshavjee's research discovery of the Toronto Ex Vivo lung perfusion machine doubled the number of lungs now viable for transplants in the world. Shaf you were born and raised in Nairobi, Kenya, your dad was a businessman, your mom worked at an airline and they had built their dream home. When you're just 12 years old, though, they decide to uproot you and your sister and move halfway around the world to Canada. What do you remember of the circumstances that led to this decision?

DR. SHAF KESHAVJEE

You know, we had a pretty good life in Kenya. But it was clear even at that stage that things were changing. And the biggest change actually was education, and the opportunities for education. And I think my parents saw that, that the quality of education in Kenya was deteriorating. And they wanted to

keep the family together, rather than sending the kids away. So they decided to uproot and move. So as a kid, I mean, it was exciting. I mean, we did the safaris and everywhere. Very good memories of that. And then moving to Canada was great. I mean, it was an exciting place to come and different and in general was exciting. As I grew up later, I realized that my parents had taken a significant step back in lifestyle and sacrifice for that.

BTB

As an adult now, when you reflect on their decision to leave their homeland, leave everything behind, start over. How does that experience shape you today?

DR. SHAF KESHAVJEE

It's incredible. Because you sort of realized, like, what would I have been? What would I have done? What opportunities would I have had? If they had not moved right? My mom still reflects on that saying, Wow, what a great idea we had to move. I mean, it's those things in life, you never know. I mean, you might think like, well, you know, you had a pretty good life, and why did you move, you know, and risk it all and so on. And, and I think that that's some of the spirit of people who look for a better life, who look for opportunities, and who seize opportunities. I worked hard in school, I was excited about what I did and got good advice.

BTB

I'm curious if, you know, as you grew and matured and realized the sacrifice they made, did that put pressure on you to succeed?

DR. SHAF KESHAVJEE

Not really. It's interesting because I never really felt pressure and I even said that to my mum, like people say like, did your parents like push it in? They weren't in medicine. They just wanted me to get a good education. But my mum said she never had to tell me to study, I was a good student. I did my stuff. The natural curiosity of how things work and wanting to learn about biology was there. I don't know where that came from. But I didn't feel the pressure to succeed but I did become increasingly grateful or appreciative of what they did?

BTB

In preparing for our conversation today, I read that you always knew you wanted to be a surgeon. I'm curious if you can take us back to say that moment in your youth, was there an ah-ha moment for you? Like, do you recall what you had seen or read that inspired you to be a surgeon?

DR. SHAF KESHAVJEE

I really have thought hard about that. And I'm just not sure where it came from. Because I think that the image of a doctor was a surgeon for me, right from the beginning. And I don't know where. The one Inkling I had, but it was even before I decided to be a doctor even, I did one of those aptitude tests in high school. And you know, you answer all these, like, a million questions, and then they tell you what you're most likely to be good at. And it said, cartographer, and surgeon, and at the time, I said, like, that's BS, like, like, what kind of garbage is that? I'm not gonna draw maps, you know, but it's interesting, because in retrospect, I, you know, realize that cartographers are very precise people, they get the details there, they're good with their hands, their, with their vision, their ability, their spatial orientation, and surgeon, and those two actually do go together.

DR. SHAF KESHAVJEE

It is who I am, you know. So I think that that was a very interesting thing. So I decided I was going to be a doctor and surgeon was in my mind. The other thing that I thought was that I was going to find the cure for cancer. Like I said, that's what I'm going to set out to do. But the fascinating part of it is, I had read some articles that talked about how cancer was a failure of the immune system. And it is, and the cure for cancer will be taming the immune system. As you're seeing it play out. It's quite fascinating that I learned a lot about the immune system, was fascinated with it and went the other direction of taming the immune system in another way to accept a foreign organ. Cancer is when your host accepts a foreign cell that it shouldn't, that it should reject and kill. It's fascinating how things play out as you try and think but I don't know when why is a surgeon but I do know that in medical school, I found so many interesting things neurology, GI, cardiology, I did the electives in all of them and they said, not for me. No, it's just not me, so.

BTB

It always came back to surgery.

DR. SHAF KESHAVJEE

Yeah.

BTB

Let's talk about mentorship. Because you clearly got a once in a lifetime opportunity in terms of mentorship when you were in med school at the University of Toronto, and across the street at Toronto General are some of the giants of lung transplantation, Joel Cooper, Alec Patterson and Griff Pearson. All of them were part of the world's first successful lung transplant, which you mentioned back at Toronto General in 83. What was the impact on you being a part of that group?

DR. SHAF KESHAVJEE

I've often said it was just luck of happening to be at the University of Toronto and which again, I had some direction in but being at the University of Toronto, I do think it's luck. I mean, I just basically walked into these guys who were the giants in the field, and who were doing many world firsts. And they were the thoracic surgeons at Toronto General Hospital. The other thing was, they were very nice people. They were good. You know, they took you under their wing. And if they saw, you're a good student, and you were committed, they were committed to you. And I think again, that's a two-way street, and mentorship. People like Alec and Joel have been mentors to this day, even though they left Toronto, have been mentors at a distance have advised me on my career and various things. And they have celebrated my successes in taking what they started way beyond where they ever dreamed, which is a huge, huge honor for me when they say that, but you know, it was an opportunity and I continued to work on it.

BTB

How do you in turn mentor today?

DR. SHAF KESHAVJEE

I try and do the same, you know, in terms of being decent to people and particularly proud of DOTS, the doctors of thoracic surgery or division, where we've almost tripled in size of the division with when Joel and Alec and Griff were there. But we also are friends, an incredibly talented group of surgeons, all of them are in the top 5% in the world. And they're all in TGH, you know, but they see value in this team and being together as opposed to being a lone wolf chief of some group, right. That's a very talented group. And I think that, you know, I've been able to impart some of that on the whole Sprott Department of Surgery. With that attitude of developing excellence of working together, of building together, of doing the world first. So I think that that's important. I think the other part of mentoring obviously, is recognizing the students with the commitment and the talent and bringing them along, whether you're training medical students and inspiring them to the future, which I really like to do, I also have a program of bringing high school students into the lab and into the OR.

DR. SHAF KESHAVJEE

So that they can see the future of medicine in in front of their eyes. And or whether it's training, fully trained surgeons trained already somewhere else that come here for thoracic surgical or lung transplant, fellowship training, where you training, I mean, these are surgeons that have trained for 10 years. And they come for an additional year of finishing, but it's a joy to work with such talent. And then they go and set up programs and thoracic surgery and lung transplantation in their home countries. All over the world. We have hundreds of people across the globe, flying the Toronto General flag.

BTB

I read where an important trait of a scientist or a medical researcher is to be able to tolerate uncertainty. Does that resonate with you?

DR. SHAF KESHAVJEE

Yeah, there's two types of uncertainty. I mean, the uncertainty of a scientist has a certain luxury to it, because you know, it's uncertain you do it, if it works out great. If it doesn't work out, well, you go back to the drawing board. There's uncertainty as a clinician, which is a different kind, as a surgeon, you have to deal with uncertainty, you have to make decisions without all the information. And if it doesn't work out, it's not all okay. So it's a different kind of uncertainty when you come back and you know when you ask, Well, what was it like when you did the first EVLP? Well, we've done everything to say that it probably would be okay. But you don't know until you do it. Right. And so that's an uncertainty, that does take a bit more courage. And I think, you know, it's something that modern medicine doesn't tolerate uncertainty as well. They don't tolerate failure. So you have to work in that kind of a system. How are you going to do world firsts like not everything you do is going to succeed?

DR. SHAF KESHAVJEE

Like, there will be failures? I think you need to minimize the risk of failure, you need to minimize the number of failures. Some people say it's important to fail, I don't think so. I think it's important not to fail, I think you should prevent failure. But I think it's important to pick yourself up and continue to move forward and find out why and make sure it doesn't happen. But I think a lot of failure can be mitigated, prevented.

BTB

You see patients every day, you know, their need for improved treatments. How do you reconcile that urgency of their need with the fact that science takes time?

DR. SHAF KESHAVJEE

That's hard? I think that it's been partly the idea of changing your target in your horizon. Right? When I started, the urgency was, get the patient out of the OR alive. Okay, now, 98% of them get out alive, they're fine. They go home, and guess what, in 10 years, they start rejecting the lung, and then it fails, and they die of lung failure again. So now it's changing the horizon to can you actually prevent that failure? And that's what we're doing. But it's hard to reconcile because I'm looking at patients that say, look, I want an IL 10 Gene modified lung transplant now, can you do it? You know, I'm not ready yet. But they're dying. And that's hard, because the science isn't there for them yet. But they're also the ones supporting us. They're philanthropists. They know that what they're investing in, that maybe it'll help them but maybe at least it'll help others in the future. And they're signing up for the clinical trials.

DR. SHAF KESHAVJEE

You know, I mean, there's a bunch of patients that want the first gene modified lung, there's risk in that, but they know that this is the science behind it. And I think it's important, you can explain that to the lay public, that this is what we're doing, just like I told you, we're like good word processor editing and so on. And here are the risks and it's never been done before and so on, but they get it.

BTB

I read a quote from you once where you talked about, you know, the burden of patients you couldn't help. How do you move through that weight?

DR. SHAF KESHAVJEE

There's various levels of intensity of medicine and surgery. Some areas are less intense, and this happens to be an area that is very intense and you can't help everybody. I work in cancer and I work in transplant. I mean, they're very high stakes, big problems. And what keeps you going is the ones that you can help. I met a lady the other day who had a lung transplant 32 years ago, okay, she should have been dead in six months, 32 years ago, she worked all her life, she became a grandmother had grandkids, you know, lived a life that keeps you going now, only about 30% of lung transplant patients will live a life that long. So two thirds aren't making it. Right. So we're failing, if you will. But those successes keep you going.

DR. SHAF KESHAVJEE

You know, I often have patients who are referred, who are told their cancer’s inoperable and so on. That's a lot of risk upfront to try and operate on a patient like that. But on the other hand, when you see them 10 years later in your clinic, and they're free of cancer, cured, you know that you're taking the risk that time 10 years ago was worth it. And you don't win them all. But we're getting better and better at it.

BTB

I know over the years, you've likely had the chance to move elsewhere, to be lured elsewhere. What has kept you in Toronto at UHN?

DR. SHAF KESHAVJEE

No, I've had significant major offers to leave Toronto General and UHN. And I've looked at some of them. And I do think that UHN is a unique place that I don't think I could have achieved as much in the research and translation elsewhere. A lot of people think it's just one person that does it and want to hire me and just say, just recreate Toronto General here. And I say, well, I need four other thoracic surgeons and 10 scientists, and they say, well, we don't we can't really do that. Or they can work at the VA or something like that. I say, no, no, they have to work together, you know. So I think a lot of places don't get it. I mean, there's a lot of fantastic institutions that do have a lot of resources and so on. But

many of those institutions send their people to us to see, how is it you guys at Toronto General, are doing this, like all these world firsts? And you bring them in and so on?

DR. SHAF KESHAVJEE

And then there's some that sort of look at Oh, well, in Canada, you can do anything you want? Well, no, you can't. There are important regulatory steps, and so on. And we're not a backwards place, we're actually very forward thinking. But we do do it carefully. And we do have the same protections of patients or more sometimes. So we figured out a way to do it. I think the combination of being in a great institution, this institution wants to be great. It wants to do world first and enables you to do it, you know, in the 90s, when we had a huge exodus of thoracic surgeons, was when I came on the scene. And there was great wind in the sails to rebuild thoracic surgery, because they wanted to be back on top again. And I think that's what's kept me here, an institution that wants to be on top that wants to lead. And honestly, I don't think there's a better country in the world than Canada to live in.

BTB

There's a leadership author, Simon Sinek, who I love to quote, he says people don't buy what you do. They buy why you do it. Why do you do what you do Shaf?

DR. SHAF KESHAVJEE

It comes down to what we talked about - the patient, right? When I look at what I do today, and what we do at UHN, like this was not possible, 20 years ago, 30 years ago, when I was a resident. Like it was just not even dreamed of these people would all die, you know, and the expectation of health is risen. But we've raised it, you know, we've shown that people don't need to die, we can improve quality of life, we can do it. So it's exciting. One is it's interesting and exciting. I'm lucky that I find that that way. There's not a day where I don't feel like boy, I have a really cool job. And then the fact that you can do it helping people and you can change how care is delivered. And the other thing is influencing how it's done all over the world. People take note of what we're doing and they do it this way. That's a huge honor and a responsibility.

DR. SHAF KESHAVJEE

But obviously, it's also your harshest critics, right? Like, I mean, they wouldn't do it if they thought your what you're doing was stupid, right? They sort of look and say, aha, that's a good idea. I think you know, and what they're doing and TGH is the way to do it and to be successful. There's a lot of satisfaction in doing that.

BTB

I'm curious if you've thought at all about your legacy?

DR. SHAF KESHAVJEE

It's hard to talk about one's own legacy, but I do think that what I have been able to do or have continued to strive to do is take the best out of everything I see and keep pulling it together. Okay, and hopefully teaching a way to do that. I mean, a lot of people look particularly at our thoracic division. Okay, surgeons are headstrong, type A personalities, these are very talented surgeons, how do you all stay together? You know, there's nine of you like and I said nine top 5% people, like how do you actually work as a collegial group and not backstab each other, not compete with each other, not split up building that culture, of the teamwork of everybody having a role and an opportunity to lead an opportunity to shine, I think are important things.

DR. SHAF KESHAVJEE

And I think also, I think the other legacy, I think, for UHN as a whole, is the idea of thinking big, and thinking world first thinking we can do it. Why are we number four, we could be number one, I think that we need to think more that way. And inside UHN there's often used to be a practice of robbing from Peter to pay Paul. So if one program was growing, the other had to shrink. And I said no grow them both, okay, like, that's the radical thing that I would say would be my legacy, for UHN. Is don't sort of threaten one to grow the other, grow both. And when I'm saying, grow, all our surgical programs are grow, grow all of UHN. If we go to 50,000 cases, I'm not saying somebody else has to stop doing something, it's let's get the money, let's get the revenues, let's get the commitments and contracts to do more to deliver more excellent care to more patients.

BTB

We talked earlier about your parents sacrifice, moving from Kenya to Canada, moving all the way to start over and give you a new opportunity in life, what do they think of your achievements?

DR. SHAF KESHAVJEE

My dad's not alive anymore, but I think he would be proud. You talked about mentorship, and probably the most important mentorship was his. And you know, what he said was, whatever you do, do it well, and make sure you enjoy it. So that was important. My mom is alive and well. And it's quite funny because she sees the work is important than any mother and probably more so I don't know. But it's very interesting, because, you know, I was thinking about running for CEO of UHN a few times ago, and there are two people that I asked for advice. You talk about mentors, I called Joel Cooper and I said, they're all saying I should be the next CEO and this and that, you know, it is it's a great job to be the CEO of the largest institution in the country, and so on. And he said, like, you know, people will flatter you by telling you that you should be CEO. And of course, you could be a good CEO, this is but you have far better things to do and different talents that no one else has. You should not waste your talent being CEO, which is kind of interesting, right? But again, let's I said mentoring at a distance.

DR. SHAF KESHAVJEE

Because I mean, I feel that way too. Like I couldn't be the CEO. I know I work hard to do it, but isn't what I should be doing. But then I said to my mom, I said, you know, they're asking me to be CEO of UHN you know, this and that. And she said, like, what would happen to all your other work? That's so much more important.

BTB

Good advice. Dr. Shaf Keshavjee, award winning surgeon at UHN's Sprott Department of Surgery and senior scientist at the Toronto General Hospital Research Institute. Thanks so much for sharing your groundbreaking research with us and continued success.

DR. SHAF KESHAVJEE

Thanks, Christian.

BTB

For more on Dr. Keshavjee's work and our podcast, go to the UHN website or www.behindthebreakthrough.ca. And let us know what you think we'd love your 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