Living Transplant Season 4 Ep 9

ATC Conference
[00:00:00] Living Transplant is a podcast that takes you behind the scenes of the transplant program at Toronto General Hospital with the goal to educate, inspire, and fuel your passion about transplant. I'm your host, Candice Coghlan. Thanks for joining us for Season 4. In this episode, I take you behind the scenes of the Ajmera Transplant Centre's 2nd Annual Education and Research Conference, where we heard about incredible science, clinical, and research aspects of transplantation.

I was incredibly grateful to get to sit down with Samrat Ray, Adriana, Roberta, Jer Solera, LaMi, Khain, Bonnie Chow, Laura Donahoe, Christina Lamb, and LXi

Regenron to hear about their amazing research.

First up you will hear from Samrat Ray about his research in expanding the transplant pancreas donor, using an ex vivo perfusion model.

Samrat
I'm Samra Re. I am a gastrointestinal and hepatobiliary surgeon from India, new Delhi, basically. And I joined the Toronto Organ Preservation Lab in October, [00:01:00] 2021. In Dr. Marcus Senner and Dr. Trevor Reitman's lab here.

And since then I have been given the responsibility of carrying forward the legacy of this great lab, which has done like wonders in the past by establishing the feasibility of a very important, a very noble concept and, The field of organ transplantation, which is machine perfusion. So this lab has done a significant amount of work and published some landmark papers in the past, which are widely quoted all over the world in liver and kidney transplantation.

So with that idea in mind, the idea was to like kind of move it forward to in the realm of pancreas transplantation. So that's the responsibility which was given upon me by my supervisor, Dr. Reichman. And so yeah. Since then it's been a wonderful journey working here on this expanding the the realm of machine perfusion in the field of pancreas transplantation.

Can you tell me a little bit about that perfusion? [00:02:00] Of course. So I mean, just to give a brief overview of what perfusion really is. Mm-hmm.

Because that might be the first question in anybody's mind. Yes. What exactly is machine perfusion? So in organ transplantation, as we know in North America, like there's a dearth of organs, like unfortunately the, the demand of the, the organs is way more than the supply that is existing there.

So in such a situation every organ is valuable and that's why we, we, we, we promote the idea of organ donation, which is one of the most noble act by mankind, of course. Mm-hmm. But having said that every organ has its own limitations and there is, there are various factors which limit its applicability in transplantation.

So in. In, in cases of vulnerable organs like pancreas, because pancreas transplantation is relatively a very new field in abdominal organ transplant. So pancreas is a very sensitive organ. Like it is one organ where it's super sensitive to touch, it's super sensitive to [00:03:00] handling. It is a zone where most of the surgeons don't dare to actually enter like, Many a times in, in the, in the, in the teachings of general surgery just said that whatever you do, just don't touch the pancreas.

Oh, that's what, yeah. So it's, it, it can flare up so much. So you can understand how susceptible it is to any kind of wear and tear and any kind of trauma. Mm-hmm. So in such a super sensitive organ, getting the, the most perfect organ for transplantation can be a challenge. Right. Because of which the discard rates of pancreas transplantation are very high, like the organ procurement, I mean to say like compared to the rest of the organs, the utilization rate is as low as just 9% as per the recent.

Oh, wow. Yeah. As per the recent data by the Canadian Institute of Health Information in 2019, It was found to be shockingly as low as 9%. Wow. So in, so in such a situation as surgeons, we definitely face the challenge of optimizing the use of what we have. Right? So that's where comes the role of machine perfusion.

So, [00:04:00] In, in the norm Themic machine perfusion, what we exactly do is like this, this concept has been very well established in lung, kidney, and liver transplantation. Mm-hmm. So the very idea of neuro themic perfusion is to create an environment where you are giving, where you're making an artificial lung, an artificial heart, an artificial blood, an artificial source of an environment for the organ to actually Sustain itself in is something that very closely simulates the normal physiology of the body.

Right. So, so a normal human body has a particular temperature. Mm-hmm. A particular temperature at which the organs are going to. Function, a particular kind of a pH, the right of the, of the blood and everything. So based on that, the concept of normal heric perfusion actually came where we decided that okay, there, this looks like an organ which is marginally damaged.

We are not very sure very, we are not very confident in transplanting it. Mm-hmm. By the looks of it, or by the, by the fact that it has been on ice for a very long period of time and we don't, and or it has [00:05:00] been. From a donor who is more than 60 years of age, or a donor who had some underlying cardiac disorder, or a donor who would, who was morbidly obeys.

Mm-hmm. So in those cases, those graphs are marginal graphs or the extended criteria graphs. Mm-hmm. So machine perfusion, what it does is it aims to optimize these graphs by sub, by, by giving it a supply of some nutrients. Over the period of the time in which the organ is kept on machine, so that over that period of time it starts simulating the physiology and on top of it, we are giving more and more nutrients, like making it as healthy as possible.

Right. Interesting. So going by that concept this idea was actually expanded to pancreas transplantation. That we keep the organ on machine and try to like keep it on machine for the time we think that it's producing normal pancreatic juices. The biochemistry looks fine. It, it looks like it can be salvaged in terms of the endocrine markers or the markers of the tissue injury.

So that [00:06:00] was the whole idea of expanding the concept of normal heric ex vivo perfusion in pancreas. The word ex vivo means outside the body, right? That's why it's ex vivo in vivo is inside the body. So since we are taking the organ out and we are keeping it in, in an artificial environment, simulating the human body outside of the human body.

That's why it's called ex vivo perfusion. So that's the whole concept of ex vivo perfusion. Wow. Now, My project specifically deals with the kind of graphs, which are not the usual ones. Like the, the most standard graphs that we use in organ transplantation are the graphs that we harvest from donors who have succumbed to brain death, right?

Like their heart is functioning normally, their lungs are functioning normally, but because of some Some accident or some trauma or whatever it is, they sustained a brain death. Mm-hmm. The brain is not function. Mm-hmm. They go into a stage, which is called a coma. Cerebral coma. So in those cases, the organs are functioning well, so, As a result of which the grafts are good.

Right? So those graphs are the [00:07:00] least risk graft, so easily acceptable. Mm-hmm. So what I'm trying to do is I'm trying to see if we can now expand the use of this machine perfusion in graft, which have sustained very prolonged periods of cold storage. Like for example, I get a donor call from Vancouver. And I fly there.

Mm-hmm. And I get the organ on ice. Suddenly for bad weather, the flight gets delayed, which is very common in Canada. Can happen right. In winters. And my organ is stuck with me for like almost 12 hours. So do I throw that in the bin? Mm-hmm. Or I can still transplant. Is it, is the question, because 12 hours is quite a long time.

Right. And many of the studies have actually proven that if the organism ice outside of the body for more than 12 hours, it's definitively detrimental to. The outcomes of transplantation, so keeping that in mind. We thought that why not try? Like why not test the extreme? So what we did was we used, so for our experiments, just for the starters, like we do all the experiments in PO sign models.

So [00:08:00] pigs are our patients out here. Like we are trying to, because that's the phase one of the experiment. So we are replicating everything in the PO sign models. And since pigs have a physiology very similar to humans mm-hmm. It's the closest resemblance actually you can get in the animal kingdom of all the animal models that we use.

So it can be very easily simulated into clinical practice. So in the, in the PO sign model we extract, we take the graft out from the donor and we keep it on ice for 21 hours. Wow. In the, in the storage solution, which is universally accepted, the, the University of Wisconsin Storage Solution that basically provides the nutrients to the graft while it is on ice.

So we keep it at four degrees Celsius in the refrigerator for 21 hours, and we chose this cutoff of 21 hours because this is extreme. Mm-hmm. So we know that if the graft sustains this, It can definitely sustain something less than this. Right? So we started from, like, we, we went on a top-down approach.

Mm-hmm. So for 21 hours we keep the organ and the next day we have another pig who's [00:09:00] delivered to us. That's the recipient pig. So first we take out the native pancreas of the pig and render a diabetic because if the, if the pancreas is still there and you. You basically implant another pancreas, you won't know which pancreas is actually working.

Right. So we need to render them diabetic. So we take the native pancreas out. That way the pig becomes diabetic. Hmm. So right after that, we aim to transplant the pancreas, which we have taken off from the donor pig, which was, which have been lying on the ice for the last 21 hours. So that was the control group of our experiment.

Interesting. So in, so five of the five of the pigs were transplanted like this. And remaining five were the test group. So the test group were the ones where after 21 hours of cold storage, we placed the graphs for three more hours on norm Themic machine perfusion to artificially give them the nutrients that they need and to simulate the norm hermia or the physiology outside of the body.

So after those three hours, then we transplanted the graft into the recipient pig. Now, when we [00:10:00] compared the results, there was a definitive evidence, like which we have actually shown mm-hmm. So we have definitively shown that in the test group, which was a ophthalmic xlu perfusion group, there was definitive improvement in terms of the graft function.

Like we saw that 60% of the animals could actually survive for all the three days. Oh, wow. Versus 0% in the control group. So that means in which it was only cold storage, all the animals died. Like they could not stay beyond one one day. But in the ones where we did a normal heric perfusion, we could successfully keep the animals alive for three days.

And besides that, on doing a, running a battery of tests, we found that the endocrine function, which is basically the glucose tolerance of the, of the pancreas, which is basically the definitive test to say whether the pancreas is working or not, that was absolutely perfect in 80% of those cases, which in other words, There's a conclusive evidence to the fact that Norm Themic, exfil perfusion seems to kind of reanimate or salvage these [00:11:00] graft.

Mm-hmm. Which have been actually damaged by the prolonged cold storage. Wow. So that way it's a very, very promising thing, like mm-hmm. The initial results, I know like, We have a long way to go from here. Mm-hmm. Mm-hmm. It's just the initial step that we have taken, but it opens a lot of avenues for a lot of questions that that means a graft, which was definitively damaged by cold storage.

We could kind of make it alive again. It's more like a rebirth of the graft. Wow. By using the norm Themic, xlu perfusion. And if that really works, and if that's a reliable method, you can imagine, like what's how, I mean, it's going to be a

boon to the field of organ transplantation. Like significantly, all the organ utilization rates in the field of pancreas transplantation is going to go up.

Mm-hmm. So that's the whole idea of, of, of taking the realms of tmic Cleo perfusion in pancreas. Brilliant. Wow. Yeah. That is really exciting to think of. Yeah, we think of the [00:12:00] small amount of organs that are actually able to be used for transplant. And so thinking about that, how that could expand that donor pool in, you know, making those pancreas fully functional again, to be transplanted.

So would the goal be to. Always use the ex vivo machines, or is there some instances where you have the ability to transplant the, the pancreas, even if it's slightly damaged into a patient and it still work very well? So, yeah. In the clinical setting the, the category that you're talking about where it's slightly damaged and can still be transplanted are called as the donation after cardiac death donors.

Mm. So that's basically one of the marginal category of donors, which in our clinical practice at T G H, we have been transplanting. In fact recently I compiled the data of 20 years of pancreas transplantation. At Toronto General Hospital and found out that like in the last few years, [00:13:00] nearly, I mean, almost 30 to 35 of the donors out of 600, like since 2000, I, I believe were actually from the DC d donors, the donation after Cardiac their donors.

Mm-hmm. So the numbers are small. Mm-hmm. But yeah. They can be transplanted. Of course. That's where you basically see many other factors like, which is called as a donor recipient matching. Like if they are, suppose they are retrieved from a donors which have, who have succumbed to cardiac death, that itself is a risk.

Mm-hmm. So you can't afford one more risk factor in that. Right. Like if that donor is also somebody who is 70 plus. Then I don't think you're going to use that graft. Right. Because yeah, that multiplies the risk manyfold, like if it was liver transplant or kidney transplant, there significant amount of progress has been made in this field.

Mm-hmm. But in pancreas, it's still very new. Right. There are hardly any centers actually, who are doing such huge numbers of pancreas transplant in the world for that matter. Yeah. And if we talk about namic perfusion or machine [00:14:00] perfusion in the field of pancreas transplantation, Canada is definitely one of the world leaders, Toronto specifically, and it's, it's definitely making, its mark.

On the roadmap. Yeah. That's really exciting to hear. And you know, having you explain this to those of us who are not in this field thank you for doing that because it is a very fascinating thing to think about the options that are coming forward to support people who are waiting for, for donations.

So. Exactly. That's really interesting. And I'm wondering if there's anything else in your research that you think people would be interested in learning or if there's somewhere that they could read about that research that you're working on. Yeah, I mean in the, in the last like ever since I've joined this lab we have had a few, like good publications of whatever research we have done, even though we are relatively new in this field.

But as I told that like I I mentioned this to you, that we are the only center in the world who are doing you know, norm [00:15:00] Heric perfusion in PO sign survival model. Like besides us, it's France and Oxford in the UK who are doing some good amount of work. But having said that, we are still the only center who are doing survival models in pancreas transplantation.

So we have had an amazing article which was written by my, one of my predecessors out here Dr. Laura, she's from Germany, and her article was on establishing the feasibility of Norm Themic perfusion in pancreas transplantation. So that was the phase one of our study, and that was published in American Journal of Transplantation in 20 2022.

It can be very easily accessed. And we have also published a, a recent article on the use of normal themic exvivo perfusion in discarded human grafts because as a, as a parallel part of the project, we are also running this project in the graft who have like, which have been discarded. Like they, they go on retrieval operations and they get the graft.

If the thing that graft is not suitable for transplanting, then it basically is discarded. So we are, [00:16:00] we're using those graphs and trying to put them on machine just to see in an artificially as simulated environment. We keep them for four hours and we see by, with a battery of biochemical tests if it really works.

So the, we have had really good initial promising results in a series of like, around 11 or 12 cases, and we have published that in the recent edition of Transplant International by the European Society of Organ Transplantation. So these are some of the sources, which definitely the, the audience can refer to.

Mm-hmm. Besides that, like whatever I have told you about, it's in the process of definitely getting, getting published and keeping our fingers crossed. We hope to see it getting published very soon. And also apart from that, there's another very interesting part of the research that our lab is getting involved in, is we are also trying to find out the genetic signature of like the molecules or the genes which are actually implicated in causing this kind of an injury.

Okay? Because after we transplanted organ, an organ Like right after we transplant the organ and it's basically a foreign organ to a, to an to, [00:17:00] to a body, right? Mm-hmm. And it has been lying outside of the body without any blood, which is called as ischemia. Mm-hmm. For a period of time. So after we transplanted, there are a lot of like immune mediators, which are released in response to the blood flow.

So that leads to a UL kind of a reaction, which is called as an ischemia reprofusion injury. And that's the key cause of causing any kind of graft damage anywhere like. Depending on the severity. So in pancreas transplantation, I mean, no prizes to guess the ischemia hyperperfusion injury is very severe.

Mm-hmm. So we are trying to isolate some of the genes from the tissue and see like what are the genes which are actually overexpressed or under expressed, which we could potentially target as a therapy. So if we know those genes and we can target those genes as a therapy, then after transplantation or during the transplantation, if we give those drugs to the patient mm-hmm.

That might kind of theoretically suppress this kind of a reaction. And Interesting. Your post-transplant course will be much [00:18:00] less UL than expected. Right. That could, that could pave the path of a potential gene therapy. Wow. So that's definitely, I mean we could achieve some significant initial promising results in that as well

fascinating. And that is definitely music to the ears of US recipients as well, to think about that. Right? Exactly, exactly. Phenomenal. So I'm wondering timeline wise what do you think for the future of perfusion, for prop pancreas is this researched short term that you think within the next couple years this will be used on humans or is this more of a long term process that may take quite a while before it, it's being used in humans.

Realistically speaking, it'll take some time for sure. Mm-hmm. Because I mean, like I said, in lung and in liver and kidney, They are like, I mean, are at Toronto General Hospital. We are a part of the metra trial, which is basically norm Heric

perfusion in liver. Mm-hmm. So the organ trial, but then for pancreas, it's still a long way to [00:19:00] go.

Mm-hmm. But the initial promising results that we have seen. Right. That is definitely opening up a lot of avenues and it's giving courage to most of the transplant surgeons to actually consider machine profusion in pancreas transplantation. Mm-hmm. Because otherwise, so far, like I told you, the story was I either you accepted or you discarded.

Right. And the acceptance was just 9%. That's wild. But looking at the amount of diabetes, which is increasing worldwide mm-hmm. We cannot afford a 9% utilization. No. We need more than that. And pancreas is an organ, which where you can't even do a living donor transplant. Right. It has to be, it has to be from the dead donor.

It has to. So I mean so that kind of limits our. You know, pool. Mm-hmm. So having said having said all of that, we are definitely working very hard and we are sort of optimistic that we might like three years from now, I hope to talk to you again. Yeah. And then I mean, I hope to like give some more promising results to the world.

Mm-hmm. Or to our listeners. Yeah. So that, yeah. And when we think about you know, [00:20:00] medical history, three to 10 years is a very short amount of time for exactly something that big to, to make such a change in, in our Yeah. In our medical lives. Right. So, exactly. Yeah. That's phenomenal to hear. Yeah, exactly.

And going by the pace at which things are going mm-hmm. Like running, I mean, to say, Be it in at our institute or you know, like in France or in uk like we are working in close collaboration with those guys. It's, it's, it's definitely very promising and people are working very hard towards it. And these collaborative efforts are definitely going to be at the fruit in near future for sure.

Incredible. Yeah. Is there anything else that you wanna leave our listeners with? I mean, I would just leave with the message that like, I. Keep up the idea and the spirit of organ donation, that's the best gift you can give to the mankind. Amazing. And that's the most noble act of kindness towards mankind.

So I mean, I would just encourage everybody to consider [00:21:00] organ donation because nothing can be more noble than that. That's beautiful. Thank you so much for joining me today and for sharing your incredible research that you're working on.

So thank you so much. Absolutely, absolutely. And I would encourage like. Like whosoever is listening to this. They should like definitely reach out to us if they want to. And if there are any students who are interested to actually be a part of the lab and just come in, have an experience with us, they're more than welcome.

It's, it's definitely going to be an experience of a lifetime. I can vouch for it.

Next, you will hear from Adriana Roberta about mismatches, which are located in the DQ locus and the development of chronic rejection.

Adriana
I'm Adriana Roberta. I am from Costa Rica. I did my fellowship here in the AM Jira Transplant Center during 2022, and now I'm a clinical associate in the team. I work with the long transplant team and I'm very happy to be here and join you today to explain a little bit of the research.

That I have been conducting [00:22:00] with my tutor, dr. Aa, and also with the rest of the team as well. Amazing. So can you tell us and our listeners a little bit about that research that you're doing? Yeah, of course. I can drive you through my research. So basically what we have seen in the past is that the patients that have 13 differences in the H L A, between the donor and the recipient are more prone to develop the Novo dss. And of course, this can impact their performances in terms of survival and cloud development as well.

So basically the objective of our study was to determine the impact of certain mis matches, which are located in the DQ Locos in, and the development of chronic rejection, basically. And we had hypothesized that the patients with DQ alpha mismatches or the presence of. Risk epi mismatches with basically is defined as a [00:23:00] specific mismatches in the dq.

Alpha and DQ seven have significantly reduced clot free survival compared with the patients without these mismatches. So basically we took all of our transplant population between 2014 and 2019, more than 19 years old, and with a complete CROSSMATCH data at the moment of Theran of the transplant.

And also it was very important to be the first transplant only. And we removed those that has basically no D S A testing beyond the 14 days of the transplant, and also those with DSAs at the moment or prior to the transplant. So in total or population, were 687 patients. And these patients, we divide them in four different categories.

Basically we try to think of [00:24:00] this in terms of going for from less risk to more risk, and we stratify them in green category, which is the less risk, which means no mismatches at all. The yellow category. Basically only has patients with BQ alpha mismatches. The orange category only has patients with one risk epitome mismatches.

And the red category, of course, is the highest risk. And it was composed by patients with both D qfa mismatches plus one mi one risk epi mismatch, or. Both risk epitope mismatches. Okay. Yeah. And basically for our outcomes, what we tried to see was that no is safe free survival, which means how much time after the transplant the patient is spent without developing new antibodies.

Mm-hmm. [00:25:00] Against the new lungs. Mm-hmm. And also the free survival in terms of No chronic rejection. Right, and, and we did this analysis basing use, basically using an unadjusted Kaplan measure estimate. And actually when we compared the four cohorts, they were pretty similar in terms of the diagnosis, the sex.

And also the age and the allocation status, which means the urgency to have the transplant. Mm-hmm. And also the type of transplant in terms of single or or bilateral. So actually there were no significant differences between them. But it was very interesting that we find, as we suspected, that the red population, the one that had like the more mismatches, were the ones that develop more the novo antibodies against the nuances.

So, okay. We're, we were [00:26:00] able to confirm that. But the bad thing is that we were not able to confirm that these, these de novo antibodies cause more like, cause more chronic rejection. Mm-hmm. So actually it was pretty similar, the chronic rejection between the four different cohorts. Okay, so we were, yeah, so basically this drive us to the idea that something else is happening there and we need to dig deeper to see if there is, if that's related with some infections or some.

Rejection episodes or some different medications that we are using in this patient, in these patients that cause like the four cohorts to merge. And even when we analyze like the three cohorts with mismatches versus the one that is free or mis mismatches at all. Still, we found no, no difference. So we think something [00:27:00] else is going on in there and we need to dig deeper in this group to find out what is going on.

Mm-hmm. So we can find a way to prevent that and have better results basically. Okay. Interesting. So for people who are listening who may not be as

informed about the H l a compatibility, can you explain a little bit about what that process is like for a recipient and a donor? Yeah, of course. So basically all of us, like the HLA is part of who we are is our genetics.

So we receive like on each, like a part of the HLA is based on mom. Mm-hmm. On the mom part. And the other one is based on our dads. And the combination of those two is, is who we are. Mm-hmm. So it's, mm-hmm. So when we want to have our recipient typing, we just ask to the HLA lab to analyze like, Who these patient are in terms of the hla and [00:28:00] basically we have two different kinds of HLA class one and class two, and.

And we analyze both for lung transplant, both of them are pretty important. Mm-hmm. It's not the same for other organs, for example. And one important thing is, for example, when you think about a bone marrow transplant, you try to match the patients h l A, you have to try them, like very similar. Mm-hmm. But actually in our long cohort, we, we do not match D H L A.

So, okay. Even if it's completely different from donor to the recipient, we will still do the transplant. Mm-hmm. So basically what happened is when you put the new, the new lungs of a different person, like in the recipient body, of course the recipient can see that the HLA is different and it can start an antibody response basically, right?

[00:29:00] Mm-hmm. What drive us to think this is because we have seen that the patients that develop antibody after the transplant and specifically the ones that are against the class two H l a sometimes develop more clot, like more clo chronic rejection. And they sometimes do worse than, and that's why basically drive us to all these study basically.

Mm. Okay. Interesting. And so why would you transplant someone with different h l A for a lung versus not being able to do so for bone marrow? That's basically because, you know, like for bone marrow, like you need, like you are putting like the whole bone marrow in a different patient and it will rec, like the body of the patient probably will go crazy recognizing all these new things and will cause like a dramatic rejection.

But for the lungs even the lungs are really. Misbehave compared with the other organs. [00:30:00] We have ways to immunosuppress them and like try to shut them down a little bit and try like to prevent the, the lungs to recognize like these new lungs basically with these new HLAs. Mm-hmm. But the thing is sometimes.

It happens that the body will recognize them and will start producing the antibodies, and sometimes we can do, like if they are having like a dramatic antibody rejection against the H L A, we can do certain treatments for that. That's what we call a antibody mediative rejection. And we can like do apheresis and remove the antibodies.

And we can also like provide other strategies, pharmacological strategies like I V I G and steroids and also sometimes OG globulin. But sometimes the patients develop these DSA and it's not strong enough like to provide like the full treatment and their lung function is [00:31:00] stable. But we know for sure that certain DSAs correlate.

With worse CLO survival, CLO free survival, which means mm-hmm. Like they have worse chronic rejection, pre-survival, basically. Mm-hmm. So that's in these patients that do not have like the full A M R treatment. But had these, the novel DSAs are the ones that actually, that's part of the idea of the group.

If, if we are able to find a correl relationship, maybe we can allocate organs based also on the immunological part as well. To prevent some kind of mismatches in the future. Mm-hmm. Wow, that's fascinating. And so if you were able to do that, would somebody be able to take less anti-rejection medication?

I think it's, it's hard to say that right now because mm-hmm. You have to prevent, like the lungs, as I was saying, are very misbehaved compared with the rest of the organs. So I will be [00:32:00] very afraid to give less immunosuppression to our patients, but it's something that can be explored for sure. Mm-hmm.

Interesting. Is there something about your research that is coming up or that you want people to learn more about? Or is there anything perhaps that you would wanna share that somebody could go and, and look up and read about? Well, I think the thing with, I think basically with H L A and the Novo ESAs and acute and antibody mediator rejection, still an area for all the lung transplant team that we are trying to work more on that because it's a very like not clear still, and we need to work further, like to find definition that all the transplant ar around the world agrees on, and also a treatment that we can agree on.

Mm-hmm. So what I can advise people is to stay alert because a lot more is coming about this, that everyone around the world is working very [00:33:00] hard to try to. To optimize the treatment and have a more clear strategy to

manage these cases basically. Amazing. Thank you so much, and thank you for the opportunity to share.

Javier Solera speaks next about his research in the severity of COVID 19 Omicron variant and Omicron specific immune responses in solid organ transplant patients.

Javier
My name is Javier Solera. I'm a transplant infectious disease clinical fellow. I come from Spain, from Madrid.

I was trained there in infectious disease and I decided to come here because this is a great hospital, especially in transplant, and it's a huge opportunity to be able to train two really big names in the world of infectious disease and transplant infectious disease in this hospital. Amazing. Thank you so much.

I'm wondering if you can tell our listeners a little bit about what you presented on our research day and describe to us that work that you're doing. Of course. [00:34:00] So our research is focused of the, on the impact of Covid 19 in transplant recipients because, you know, everyone knows about Covid 19.

It's like something that has changed our lives, everyone's life. But in transplant, especially with the. That you need to take immunosuppressive therapy, prevent the rejection the body is in high risk for severe Covid-19. Mm-hmm. So our aim was to, we wanted to know how the transplant recipient respond, different treatments and different prevention measures, like for example, the vaccines.

Mm-hmm. And we wanted to know How clinically, how they do it with the CLO 19. How bad is the infection? How can we improve the prognosis of the patients? So we started since the beginning of the pandemic back in March of thousand and 20, it started collecting the data of every single transplant recipient that got diagnosed Covid-19.

And what we do is we analyze that data [00:35:00] and apart from that, Sometimes a new treatment appears or a new vaccine approved, and we analyze how patients respond to these different interventions. For example, recently we are analyzing how good the new be balanced vaccines mm-hmm. Are doing on our transplant patient.

And, and we are of course analyzing now that we have already three years of covid 19. We're analyzing what, how good has the transplant people done along these three years? Mm-hmm. And so what does some of that, those data pieces

look like? I know from a, from a recipient perspective myself as well COVID was definitely the scariest thing that we have faced.

For sure outside of, I would say the actual transplant ourselves. Right? Yeah. A lot of us went into our homes for a much longer time than the general population, and there's still a lot of fear out there for those of us transplant recipients. [00:36:00] So I'm wondering, thinking about the outcomes, has there been a difference between the beginning of the pandemic, how transplant recipients were doing compared to now with our vaccines?

Yeah, actually this is this is the most important question. This is, we are doing better now than before. It's good. It's working. The intervention that we are doing. And the quick answer is yes. Good. If you compare the outcomes now and the outcomes back in, in previous waves mm-hmm. Every single severity outcome, if you compare the hospitalization rate, the requirement of oxygen or the admission to the I C U or the death mm-hmm.

The numbers are decreased progressively. Great. So it's less severe than the previous one. And actually the, it's an interesting question to do because of the virus is changing and now it's less severe than before or because all the intervention that we are doing. We know for sure because we have analyzed in multiple sets of [00:37:00] population, we have analyzed the impact of vaccination.

Mm-hmm. And we know that vaccination is by far one of the most important intervention that we can do. And that's why. It was such a thing in the Covid Pandemic. We really strongly recommend the vaccination to all the transplant recipients. Mm-hmm. One of the most impactful papers published in medicine, in transplant medicine in the last few years was the study that we performed in, this is in this hospital, about the use of the third dose of the vaccine.

Mm-hmm. Cause before that study, the recommendation was to give only two doses to the transplant recipients. Right. What we, what we saw is that with two doses, it was not enough. Mm-hmm. The transplant immune response, the immune system is not strong enough Right. To respond to two doses of of the vaccine.

And however, with the third dose mm-hmm. The response was much higher. And after that we have analyzed multiple consecutive doses. Mm-hmm. [00:38:00] And we can say that we have found that. The immune response is better with the next doses, but it's not as important as received. The third dose from the second dose, like the third dose was the key.

Okay. For transfer recipients. And actually we now is, we don't consider anyone vaccinated if they are not have at least three doses. Three dose is the limit for considered a patient vaccinate. Fascinating. Our recommendation, of course, is to Boosters doses of the vaccine. Mm-hmm. We are doing now analysis of the, of the efficacy of the last Val boosters that is not not published for the moment.

So it's cannot say, but, but for the moment I can say that the boosters are very important to give immunity against the variants mm-hmm. That are designed for. So, for example, the last boosters are good for the variants that are including the booster. It is true that the new variants, mm-hmm. For example, the last [00:39:00] bval booster include the original COVID 19 mm-hmm.

And the Omicron five variant. Okay. And so this booster is quite good. Mm-hmm. Prevent infection by omicron. We know that the new variants that are called B one or Xbb, so very difficult names. Mm-hmm. But we know that these variants are quite good, avoiding the immune system. Okay? So it's difficult to prevent the infection in this cases.

However, even if the infection is not prevented, we know that the outcomes are much better. So sometimes the people say, sometimes the people that is against vaccines says, you, no, I received the vaccine, but I'm still getting infected. Mm-hmm. And one thing that is important, IM important to know, sorry, is that prevent an infection by a respiratory virus.

Covid 19, it's nearly impossible. Right? Even with the flu vaccine, you don't wanna prevention cause it's [00:40:00] so difficult. Who want to prevent the severe disease, right? Because you are giving like a weapon to your body to fight against the virus once your virus is inside, okay? Very important. Very. It is nearly impossible to create a seal, like completely prevent the infection, right?

And we can give the tools, the body, find the virus. One, you have the viruses. So this is mainly the aim of the vaccination and that's why we are so strongly recommending it and we keep seeing in our analysis that vaccines people that is vaccinated has better outcomes than those that are not vaccinated.

Amazing. The important message is like Covid-19 is better. Every, every new wave when we start collecting data mm-hmm. The rate of hospitalization was nearly 60% of the transplant recipients.

Oh wow. That had infection requires to be admitted to the hospital. Right. And now the admission rate is the [00:41:00] outcomes are better, the prognosis is better. So I can say for example, that 12% is five times lower. Oh my goodness.

But, you know, even in the, that is admitted Less than half of those require oxygen. So even the important thing, because you know the Covid 19 can be very severe if it's affect your lungs.

Because sometimes you can have diarrhea, you can have malaise, you can feel very fatigued. Mm-hmm. But if you breathe well, you don't require oxygen. It's not going to be a, a bad infection. Okay. And then the, the oxygen requirement and the ICU admission and the, and the mortality has clearly, clearly decreased the mortality.

Now in. In most of the transplant recipients is 0%. Wow. We're not seeing new cases of death by Covid in most of the transplant recipients. Of course, transplant recipients are at higher risk. L, the l the transplant, because, you know, it's, mm-hmm. For [00:42:00] transplant, the lungs are the ones that are exposed to the virus.

Right. But even in lung transplant recipients, the outcomes has clearly, clearly improved. And now it's not like not like before. And the mortality. Extremely low. Extremely low. So we're very happy. We're very happy results. Yeah. That's amazing to hear. I know, unfortunately I know most of us do know somebody who either passed away at the beginning of the pandemic or, you know, had very severe consequences to getting covid, and I'm wondering when we think about.

Starting to become a society that accepts that Covid is here and that it's not going anywhere similar to the flu as recipients, what can we do to protect ourselves continuing going forward on top of getting a mask? Like how often should we be getting boosters? Is there a schedule or, or is it very unique to each of us?

Yeah. So those are excellent questions because [00:43:00] are the important ones that is mm-hmm. You need to keep living your life. Yeah. You, you cannot live in your isolation forever. So I always tell my patients that you need to understand that you have a condition like a transplant. So your immune system is never going to be as good as a patient that is not taking the medication that you need.

It's true that Covid 19, now, the prognosis is quite good. So you need to living your life. You need to be, I mean, you need to think like, of course maybe it's not the most recommended thing to do, to go into a very crowded area without mask. Without washing your hands, because we still recommend like, use like

alcohol solution, clean your hands because it's very, very important and use mask in crowded areas.

Mm-hmm. But you can live a quite normal life. I don't think we, we need to fear like before, because before of course, it was something that, it was quite, quite [00:44:00] severe for trans. And about the vaccines. The truth is there's no an agreement between the different societies. For example, the, the American Society of Transplantation recommend to give vaccines every two to three months the transplant recipients to boosting the immune response because we know that the mRNA vaccines works very well.

But the effect decrease with the time. Right? The antibodies that your body is able to generate is with the months. It's something that is well studied, but the truth is we believe that with the content, constant mutation of the virus sometimes it doesn't make sense to give so many vaccines because at the end you have reached some level of immunity in your body.

Mm-hmm. That is going to protect you against the most severe. Part of the disease. Okay. And as I told you before, it's going to, you can give seven doses of the vaccine that is nearly impossible to prevent the infection. So the [00:45:00] infection, if it have to happen, it will happen. Mm-hmm. So actually the current Canadian Society recommendations are, give a booster vaccine every six months.

Okay. I have to tell you that I believe that these recommendations are going to change and you have to consider that new vaccines are coming. Mm-hmm. So there is a possibility that it turns into something more similar to the flu as you said. Mm-hmm. You know, for the flu for the flu vaccine, you have a different vaccine every year.

It's a different one from the previous year because the ATE every single year and you need to generate a new vaccine. Mm-hmm. So with the covid 19 probably is going to be the same. The vaccines that we are giving actually are not quite effective against the new variants because the virus is completely different from the previous one.

So Three, four doses of vaccine. Mm-hmm. The number of booster vaccine will depend with the time and with the new vaccines that are available [00:46:00] when they develop a new vaccine against the circulating variants. Mm-hmm. Recommended to receive that vaccine. But about the previous vaccines, it's, there's no a good agreement because at the end this is something that evolve so fast.

So fast, yeah. That you cannot like, Cannot know everything. Like the science is, if you want to do a studies to test, everything is going, takes longer than the covid to evolve. Mm-hmm. And that's, that's the problem that some data that you see published in the journals now are about patients that are infected with previous variants.

So you're not sure of what's, what's the correct thing to do, but. I, I, I would encourage to receive at least I would say four doses of the vaccine. It's a good number. Mm-hmm. And that's a good point because that's is going to give your body enough immunity against the severe disease. Mm-hmm. And apart from that, [00:47:00] then the recommendation of the number of booster vaccine will, will change with the time.

Mm-hmm. That's great to know. And, and especially You know, helpful to know about the hospitalizations and deaths. I think that really helps for us recipients to breathe a sigh of relief that people like you are working so hard behind the scenes to keep us safe and, and to keep us protected. So on behalf of recipients and donors, thank you so much for all of the work that you and your team do because you really did give us hope.

And you've given us the ability to come back to real life. Because, , at the beginning of the pandemic, it for sure was a thing that we weren't sure when it was gonna be or how we were going to be able to live in this new world. So the work that you guys do is just so important to our lives.

Thank you. It's a pleasure. I'm, I'm feel proud to be able to do research in a, in a hospital as good as this one. And, and it's [00:48:00] a true, a true pleasure to be here. Amazing. Is there anything that maybe I didn't ask you about that you would like to share? I don't know. I would like to, to share hope with the people.

Yeah. The viruses is still here. I, we don't know. We no one know what's going to happen with the virus. If someone tells you, oh, for sure the virus is going to be over in one year. Don't believe him because no one knows. Mm-hmm. Yeah. But the good thing is we know that the severity is every, every day is lower and lower, so, so the outcomes are better and, and it's a reason to be happy.

Next, you will hear from cougar Thassin about her systematic review and network meta analysis research in induction therapy in heart transplantation.

Lakshmi
My name is Lakshmi Coan and I did my PhD in the Department of Laboratory Medicine and Pathobiology at U F T. Mm-hmm. And over the last four years,

I've been working with dr. Alba, a cardiologist in the advanced heart [00:49:00] failure and heart transplant program at U H N. And her research interests span across the spectrum, but at one end, she's trying to better define the risk profiles of patients being diagnosed with.

Heart disease through the use of risk prediction models. And on the other end of the spectrum, we are trying to understand ways in which we may improve outcomes for patients undergoing heart transplantation. And this relates to the work I recently presented at the ET marrow Transplant Center's Research Day.

Wonderful. So can you tell our listeners a little bit about that research that you presented? Sure. Yeah. My presentation at the Mira Transplant Center's Research Day focused on a systematic review of existing scientific studies and analysis of data from these studies in trying to understand or address a controversy surrounding the benefit of a type of immunosuppressive strategy called induction therapy [00:50:00] for patients undergoing heart transplantation.

Okay, wonderful. And can you explain a little bit about that induction therapy? Sure. Yeah. So I'll, I'll start off with a bit of an introduction behind the entire research. So, heart transplantation is one of the last options in patients with advanced heart disease. Unfortunately, rejection of the transplanted heart is a commonly encountered issue.

Mm-hmm. And can occur within minutes of transplant or following years after transplantation. Mm-hmm. As our understanding of how. Our immune system works has evolved, so have the development of various immunosuppressive therapies to reduce the risk of rejection. So induction therapy happens to be one such immunosuppressive strategy.

Which is given around the time of surgery with the aim to minimize the risk of early rejection. While there are benefits to using induction therapy, there are [00:51:00] also side effects that can result including the development of infections and cancer. Okay. So because of a lack of clear benefits with the use of induction therapy due to there being a lack of adequate high quality data mm-hmm.

We were approached by a heart transplant guidelines panel that was made up of clinicians. He healthcare workers and patient partners to analyze and summarize all the available data from the existing scientific literature. Mm-hmm.

What have been some of those results that you have found? We did a systematic search of scientific databases to identify studies from the year 2000, which reported on the use of any induction therapy agent and any post-transplant outcome.

Mm-hmm. And we evaluated both randomized control trials, which provide the highest level of evidence and also [00:52:00] observational studies. Mm-hmm. Using a methodology called network meta-analysis. The outcomes that we examined were mortality or death. Mm-hmm. Rejection, infections, kidney dysfunction, cancers, and the onset of coronary disease, which is known as cardiac, allograft, vasculopathy, or Cal.

So, So apart from conducting a statistical analysis of the available data, we also evaluated the quality of evidence for each of these outcomes and presented these findings for the use of two of the most commonly used induction therapy agents known as Basil and a t g, comparing them to to the use of no induction therapy or to each other.

Okay, so in terms of a high level summary, all findings, what we saw was that because of low to very low certainty in the evidence from [00:53:00] randomized controlled trials, we were uncertain whether these two agents increased or decreased the outcomes that we assessed compared to no induction therapy or each other.

And then looking at observational studies. On the other hand, we had low certainty in the evidence with some of the comparisons for some of the outcomes, and saw that basil map may increase 30 day and one year mortality compared to no induction therapy. While a T G may decrease five year coronary disease compared to no induction therapy and that a T G may decrease 30 day one year and overall mortality compared to basil.

So we took these findings and we presented them back to our panel. Who then outlined recommendations following a discussion and suggested against the routine use of baab and a T G compared to no induction [00:54:00] therapy. Mm-hmm. But suggested that for patients in whom induction therapy may be desirable, so the, these may be higher risk patients.

Mm-hmm. The panel suggested using a t g over basil. Interesting. What do you see yourself or or your researchers doing in the future?

Oh, that's a great question. So I think what is really needed in this area is a more rigorously done randomized control trial to compare These agents. Mm-hmm.

And more importantly, to also identify subgroups of patients who may selectively benefit from the use of induction therapy. Amazing.

Is there anything that perhaps I didn't ask you about or more about the research that you would wanna share with our listeners?

I think it was just an honor and, you know, absolutely pleasure to be invited on this podcast. I'm immensely grateful to the division of [00:55:00] cardiology and in particular, Dr. Alpa and Dr. Heather Ross for the research opportunities, my co-authors, as well as expert methodologists at the McMaster University and the Transplant Center for organizing the research day. It was an absolute pleasure. Wonderful.

Bonnie Chow speaks next about her research in machine learning approaches to processing and interpreting ex vivo lung radiographs and predicting transplant outcomes.

Bonnie
My name is Bonnie. I'm a fourth year PhD student in biomedical engineering. I work with Dr. Kash, Dr. Bew, Dr. Andrew Sage on some AI applications and lung transplantation. I'm in my fourth year of PhD, so yeah. Amazing. Thank you so much for joining me today. I really appreciate it. Thank you for having me.

I'm wondering if you can tell our listeners a little bit about that research that you presented on. Yeah, so as mentioned, we work in lung transplantation and [00:56:00] specifically we're trying to take in donor lung information and try and make predictions on recipient outcome post transplant.

In our group at Toronto Lung Transplant Program, we work on a system called VU Lung Perfusion. It's basically a platform that aims to keep donor lungs alive outside of the body prior to transplantation. Mm-hmm. It is like our circulatory system in the body kind of. So we have a fluid that flows through the lungs.

The lungs kind of breed on their own, on their circuit, and we usually leave these down your lungs on the circuit for about four hours so we can make. We can take different assessments and surgeons can better make decisions on these physiological functions tests that we make on the, on the lungs.

Fascinating. Yeah. So the best thing about XV one perfusion or E V L P is that we can assess a lot of physiological functions prior to transplantation, and a lot of these [00:57:00] tests would not have been possible without this platform. So,

mm-hmm. We can measure lungs at their physiological working conditions like the body temperature and pressure can measure functional assessments like compliance.

Basically the last to see of the lungs, the pressure of the lungs, how well the lungs are exchanging gases how injured they are, by how much fluid they're accumulating. We can also measure biochemical and inflammatory signals like pH electrolytes, glucose levels, inflammatory signals like the inflammatory proteins or gene expressions.

So there's a lot of measurements we can take just by having the lungs outside of the body and kept at physiological conditions. So my research focuses on the imaging part. Mm-hmm. We take these X-ray images of the lungs outside of the body, so different from traditional chest radiographs. These x-ray images are.

Are just the lungs outside the body. So we don't see [00:58:00] obstructions from chest wall, ribs or hearts. We just see a pristine view of the lungs with vasculature, individual lobes. Yeah. So In my research, we, we want to look at whether this radiograph information of cevo donor lungs is informative in surgeons decisions to transplant or decline the lungs.

Mm-hmm. And previously we've already worked with a radiologist to go through about 200 images from our, from our E V L P subset. Basically looking at these ex radiographs and seeing. Like trying to see what he can actually visibly. See from these images and correlating these findings with poor recipient outcomes.

But the caveat of that is we would have to always work with a radiologist. Mm-hmm. Which is a bit of a limitation because most E V L P or most lung transplant centers don't currently work with the radiologist. Ok. So we [00:59:00] wanted to build a algorithm that can kind of act as a virtual radiologist in the room.

The algorithm. Ideally it would read the images and output as much information by the images as possible for the surgeons. Yeah, that's really cool. Yeah. Yeah. So based, usually we take two images at different time points. Mm-hmm. Over the course of four hours. And what we, what we did was we concatenated the two images into basically one, I guess.

Larger image for, to, to make one classification. Mm-hmm. Yeah. So each case would have two images and we, we would make one single classification based on the two images together and our classification There are three classes.

Basically, we're trying to see the lungs would be declined by the surgeon if the lungs would be transplanted, but with a longer extubation time from the recipients or if the lungs would [01:00:00] be transplanted with a shorter extubation time for the recipients.

And I guess in simpler terms, we can see these three classes as decline lungs, transplant lungs with worse outcomes, and transplant lungs with better outcomes. So yeah, those three case classes are the ones we're trying to classify for. And in total we have 650 cases thousand 300 images. Wow.

And we were able to get a pretty good classification accuracy. Mm-hmm. We were able to get like a 76% accuracy when we classified for these three classes. And if we simply classified for a transplant or decline decision at the end of E V L P, then we would get a 90% accuracy. Mm-hmm. So it is working pretty well and we found no significant differences between.

This approach, this computer vision approach versus the radiologist manually labeling approach predicting outcome. [01:01:00] Wow. So that is pretty encouraging. Mm-hmm. And As I mentioned earlier, we also take these other functional assessments like the physiological, biochemical and in inflammatory signal.

Mm-hmm. During E V L P. And we previously worked on a study classifying the same outcomes using these we call them tabular data. So these are data kind of in a table structure. Mm-hmm. pH level 5.8, something like that. So we took all those I guess numerical data to perform the same classification, and that returned a accuracy of 72%.

And when we found that, when we added these images to as input to the The tapping our data modeling, we were able to increase the accuracy by 6%, which is very, very significant statistically. Mm-hmm. People who are, are listening, I mean, we, we've heard a lot about ai doing a lot more in the medical field.[01:02:00]

Um mm-hmm. Thinking about being able to use resources like this to classify things, do you think this could have broader reach in things that could, , support physicians in being able to diagnose. Certain things or use it for medical imaging, maybe for those types of.

Yeah. So in terms of images, it can definitely be applied to other forms of diagnostics. So I C U or Ward or even just incoming patients, they in some countries they don't have as many physicians or radiologists. Mm-hmm. So this

can really help. Facilitated the workflow so the algorithm can flag the images that seem to have a problem that would then prioritize these images for the radiologist to look at.

Mm-hmm. In terms of other medical data, like those tabular data, like our physiological assessments that we usually take, like blood tests and icu mm-hmm. Or [01:03:00] ward. Those people have also made really cool models. Kind of monitoring these I C U or ward patients and flagging the ones that could potentially deteriorate in the next 24, 48 hours, et cetera.

So it can really help physicians focus on the patients in need. Mm-hmm. Yeah. Yeah, a lot of really applications for sure. Mm-hmm. And then thinking about the ex vivo perfusion with lungs Has that been used on patients already or is this still in the, the processing and testing area?

Yeah, so we got our F D A and Health Canada approval in, I believe, 2012 and 2013. So this is this is a, I guess, clinical application that's been actively used regularly. We get about. Two cases per week. Generally only the dollar lungs that are marginally [01:04:00] acceptable are put on E V L P because it does incur extra costs on the healthcare system.

Mm-hmm. So if the dollar lungs are obviously healthy they get directly transplanted. If they're obviously injured, then they get declined. Only the ones that the surgeons aren't so sure about. Go on E V L P. Mm-hmm. Yeah. And E V L P is a good platform to help the lungs repair themselves because when the organ is at a physiological condition, the tissues are able to self repair.

And furthermore, we can administer antibiotics and other potential treatments like cellular treatments, gene engineering to like repair these lungs before they're transplanted. It's so cool. Yeah. So thinking about your research, is there anything perhaps outside of what we've talked about today that you think people would be interested in or something that maybe I didn't ask you about?

I guess there's always a lot of discussions on. Implementations and [01:05:00] ethics. Mm-hmm. Biases. Biases. When it comes to AI and medicine, it is a very important topic. Technically a lot of these problems are not easy to solve, but a lot of us are trying It's deep warning still remains as a black box in most applications.

Mm-hmm. There are interpretation methods. They are not everything, they are limited. Mm-hmm. But it's a very important area of research and medicine, especially when you want to know exactly how, like we can trust the models

and how. Much like we can apply it like across different centers. Mm-hmm. So that's like a important but difficult part of research.

Because deep learning, one reason why it's so powerful is that it can take in so much data at once and process it internally and there's just not really a effective way. As of now to kind of [01:06:00] open the black box and see what it's actually doing to these data. Mm-hmm. So it's hard. We're not there yet, but mm-hmm.

I think having AI applications in medicine will really help push this aspect of research cause it's probably more important in medicine or healthcare than many other fields. For sure. Interesting. And it's amazing to know that people like you and your team are working really hard and, and advancing this.

It's, it's super cool to get to listen to you and to hear about what your team is doing. And so thank you so much for giving us the opportunity to kind of get a look inside and behind the curtains of your research. Yeah. Thank you so much. That was a fun interview. It was fun to talk my about my own research as well.

Next, you will hear from Laura Donahoe and her innovations in improving the quality of lung transplantation through a technical skills simulation program for surgical lung transplant fellows.

Laura
My name is Laura Donahoe. I'm one of the thoracic surgeons and lung transplant surgeons in the [01:07:00] Mira Transplant Center. I'm also the fellowship director for the Lung Transplant Surgical Program and I'm the program director for the thoracic surgery Residency program.

Amazing. And can you tell our listeners a little bit about that research that you presented? Yeah, so my research interest is in education of surgical trainees. So the traditional model of learning how to do surgery is that we practice on patients. It's really an apprenticeship model. So you start as a junior resident start by watching you learn the steps of the procedure, and then it's a gradual increase over time in terms of how much responsibility you get during the surgery.

How much you get to do. It's always overseen by the staff surgeon. But really it is, it is a graded responsibility and graded increase in the the difficulties of the

tasks you're asked to be doing. Mm-hmm. In lung transplantation and in any, any type of transplantation. So it's the same for liver and kidneys.

Hearts. It, it is a subspecialty of an already established [01:08:00] surgical specialty. So for instance, we train as, as thoracic surgeons. That means I've done five years of general surgery. I then do two years of thoracic surgery and then I did an extra year to learn how to do lung transplants. Wow. Part of which was lung transplants.

And this is the same across surgical specialties. It's, it's extra training in addition to your training that you do to become a, a certain type of specialty surgeon. So these are very, very highly trained people that we're teaching how to become surgeons in transplantation. And we know that these that these trainees, these fellows a lot of them have been practicing as staff surgeons in their own countries.

And they come in you know, from all over the world to train in the transplant center. And so what they need to learn here is very different than what say a junior resident would need to learn when doing a surgery. Right. So for our senior trainees they need to learn things like how, how you sow the lung in.

You know, they don't need to learn the basic anatomy of the chest. They already know that they've done all that [01:09:00] training. They've, you know, established their competency in that. But my, my educational research focus is on teaching these very senior trainees how to learn how to do transplant surgeries and trying to teach them outside of the operating room.

Okay, so over the course of the past number of years, there's been a lot of research on simulation and mm-hmm. What's simulation in medical education. And it's used in a lot of other different areas such as you know, in the aviation industry they do a lot of simulation, so, Basically it's practicing a task outside of the situation where you would usually do it.

In order to learn in an environment that's low stress has no consequences. And so you can learn a lot of the information that you need to know when you're put in that situation. In real life, right? So in surgery there's a lot of simulation research that's been done, learning how to teach people surgical skills outside of the operating room.

But what I've, I, I did a master's in health sciences education a few years ago and learned that really a lot of the focus on simulation is in junior learners. [01:10:00] So again, back to those junior residents who need to know just the

steps of the procedure, and I realized that for our very senior learners, that's not really what they, they need to learn.

And simulation to teach them the steps of something isn't probably going to be the, the most important way or most important thing for them to learn. Right. So my research has been focusing on creating simulation models or things to practice on that would then be very similar to what it's like in the operating room, so they can learn the specific skills that we need them to know to do a lung transplant.

Wow. That's fascinating. So these are the people who are coming through who have, you know, lots and lots of experience but are now looking to be highly specialized in that surgical realm. So what do those simulations look like for, for these people? Yes, that's exactly right. So very highly trained.

So what we've been working on is creating models for each of the steps of doing a lung transplant. So it's a pretty simple concept to do a lung [01:11:00] transplant. You take the lung out and put the new one in, and you have to divide the artery. The veins and the bronchus are the airway and then hook each of those structures back up.

So we've been working on coming up with an artery model that's very similar to what an artery would feel like in the operating room, but using other materials such as silicone. We're looking at different, you know, different recipes basically of coming up with materials that might mimic what it's like in the operating room.

We've created a bronchus. So that the airway anastomosis, her hookup is very similar to what it's like in the operating room. And we're working on the veins. And the steps are very similar even though it's different structures, but it's a similar concept for most of the types of transplant. So, but the harsh, you know, it's similar vessels, they have to also sew the pulmonary artery to hook the heart back up.

Mm-hmm. They have to sew, you know, the, the inferior and superior vena cava. Which are a little bit different texture, but the same idea of sewing them together to put the heart back in. So there's very similar across all organ groups in terms of [01:12:00] what these fellows need to know. Wow, that's really cool.

And so this has, has begun, these simulations have begun already. Yes. It's a work in progress. I'm working with the surgeon out of Boston and then an

amazing PhD student, Kate Calovich. So we've been working on developing these models. We, we've created a box, we call it the Marshall three after Dr.

Blair Marshall, who's a surgeon in Boston. It was her original design and then we've been just slowly working on it over the course of the last couple of years. To improve it. And then in the meantime we have rolled it out to our fellows. So still working on developing a formal simulation curriculum.

But our fellows each get a box and they get some arteries, and they get some bronchi that they can practice with. And the other important part of this is that it's very difficult to plan anything when you're dealing with surgical transplant fellows because the life is so unpredictable, right?

So oftentimes I've planned a, a course or a, a session one afternoon, and then, you know, five of my six fellows are off on a, on a donor or doing a transplant. So the, [01:13:00] the way we've done it they can take them home practice on their own time and so they're already in use. That's fas fascinating. And so what have you found the people who have been using these already what has the feedback been from them?

Our early feedback is, has been very good. We actually also had it last year at our thoracic surgery bootcamp, which is a three and a half day course that we run for all the first year thoracic surgery residents in the country. We had our simulation boxes and models there and we got really good feedback.

You know, the ultimate goal would be to show that. Practicing outside of the operating room actually improves the, the surgical skills inside the operating room and then improves patient outcomes. Mm-hmm. And that's sort of the, the overarching ultimate goal of simulation. But at this point we're sort of near the beginning and just know that our fellows have really appreciated we've gotten a lot of good feedback and are going to continue with it.

Amazing. And do you think this also builds confidence as well in, in them? For [01:14:00] sure. So in order to, to sew anything, you use what's called a needle driver. So it's an instrument that actually holds the needle, but there's different models of them. And we use one specifically in lung transplant surgery that's very different than many of them have ever used before, and it's a bit fitting.

So having the ability for them to practice that outside of the operating room just to learn how the instrument works, I think is very beneficial and, and I think helps. That's fascinating. And do you see this growing in other areas as well? Could that potentially work for other transplants?

Yes, absolutely. I would love to expand this to other organ groups. You know, we can definitely create something that looks like, can, feels like a bile duct. Mm-hmm. So that leverage liver transplant fellows can learn how to, you know, or practice how to sew in bile ducts outside of the operating room.

So I think there's a lot of potential. One of the other interviewees that I spoke with was about how sensitive the, the pancreas is as well. And just thinking about that, how interesting that may support people even in that [01:15:00] realm of learning how to use different materials and things.

I didn't know that the pancreas was that sensitive until I interviewed him as well. Yeah, we like to, I mean, I've no longer do general surgery, but I trained as a general surgeon and that's the, you wanna stay away from the pancreas. That's so, I really admire pancreatic transplant surgeon. Yeah. Oh, that's so interesting.

Yeah. And, and, you know I'm a kidney transplant recipient and so thinking about you know, all of these new initiatives that are going into improving care for patients and, you know, the passion that, that the team at U H N has to just make things better and smoother for those learning. It's, it's really fascinating to hear.

Is there anything that perhaps I didn't ask you about or that you think would be interesting for our listeners to hear?

Oh, good question. I think it's important just to know that a lot of education does happen in, in other ways as well, but I think it would be really exciting if we could create a way to to really teach everybody [01:16:00] everything they need to know outside of the operating room.

That's, that's another kind of lofty goal. But and I know from a patient perspective, like when you hear that it's a teaching hospital and you have people learning you know, it is, it is Part of part of surgery and part of our model. But I just think that there's ways that we can improve it so that it makes it better learning environment for the trainees and then, you know, overall safer for the patient, which is the ultimate that really matters.

Amazing. Well, thank you so much for joining me today and for sharing your amazing research and I would love to see what's inside of that box. That would be really cool. Love that. I'll definitely show you. Thank you so much for having me.

Christina Lam talks to us next about the fibrinogen like protein 2 molecule and how it influences the development of thymic regulatory T cells.

Christina
My name is Christina. I am currently a PhD candidate at the University of Toronto. I am part of the Institute of Medical Science Department, and my lab is located in the Lab Thoracic Surgery Research Center.

[01:17:00] Amazing. I'm wondering if you can tell our listeners a little bit about what research you're doing. Sure. So, Transplant immunologist by training. I try to understand the immune system and how that contributes to the process of organ rejection in transplanted patients.

So my recent project focuses specifically on a compound called fibrinogen like protein two or FGL two. It's such a bad name. Like it. Okay. It doesn't roll off the tongue. So if I'm explaining it to a non-line person, I always , just call the actor.

That's good enough. I like that. Yeah. Yeah. So this molecule is a very interesting, it has been found to have a regulatory function in our immune system, specifically in a subset of cells called regulatory T-cells. Test, the name suggests the, these B cells are able to regulate the immune system.

So normally, you know, it's a healthy human D cell. Like they play important role in preventing things like autoimmune [01:18:00] diseases and also in control, controlling the. Immune system so that you don't just to prevent excessive damage on the host. So these cells are obviously really great interest in the field of transplantation because the main problem that is playing and sort of hindering the field from advancing forward is the chronic rejection.

With the rise of regenerative medicines and cell transplant therapy, a lot of people specifically immunologists like me, I really interested in understanding how regulatory T cells can be used and how.

So that we can able to improve long-term tolerance in patients. So go back to the F factor. So this protein has been, this molecule has been shown to be used by regular T-cell to regulate the immune response. But it was, so my, it was very interesting when I did my experiment, we found that no, it's not just being, the protein doesn't just regulate immune response the way that we previously thought it can actually [01:19:00] control.

The development of regulatory T cells as well, and it was the most striking observation we saw was that depending on where the protein was coming from, it actually had opposing effect on regulatory T-cell functions. Which, which we thought was a very interesting because for a long time, this molecule, we just thought to like really augment regulatory T-cell capacity to suppress the immune response.

We found that in my, at least in my, in my data, it can actually add, it can also downregulate the regulatory T-cell as well. So it's sort of just like a built-in mechanism. So as for the south, you also like control themselves. Which is really interesting. So I'm mean the ultimate goal like this, like it just, you know, trying to understand the biology of these cells so that we can move closer to today where we can harness their using clinical in clinical practice.

That's fascinating. I mean, I think for any of us transplant recipients, when we hear the word tolerance, we get really excited. Because when we think about transplant, [01:20:00] definitely our immunosuppressants are, are the biggest bane of our existence. Right. Keep us alive. Yeah. Yeah, they keep us alive, but they also have their own their own side effects too, right?

Mm-hmm. That's fascinating. Research and so thinking about the future what are your ultimate goals for this research i, I'm obviously there are a lot of cells in the immune system and I'm obviously very biased to, to our regulatory T-cells. So I would like to just, by understand, by furthering our understanding on how this factors is actually modulate regulatory T-cell function.

I'm hoping that we can somehow use the information that we found to. Improve the regular g T-cell, maybe make them into like super regulatory T-cells and then really will augment izing capacity and, give them to patients. Mm-hmm. That's amazing. Is there anything perhaps that I didn't ask you about [01:21:00] or that you didn't speak about that you think our listeners would be interested in knowing?

Well, maybe this is not the right crowd cause they probably already know this, but I always ask, tell people that to opt like it is in Canada is an opt-in system. Mm-hmm. For organ transplantation. So you can sign up DB in organ donation. I think it's like a check mark. Yes. And that will significantly help our organ donor poor.

Absolutely. Absolutely, yes. Be a donor.ca. Register your consent. Talk to your family. Absolutely. That's the best advice we can leave people with. Mm-hmm.

You're doing amazing work and thank you. Continue with that F factor. Thank you so much.

Last up, we hear from lexi Regendron about the Toronto management of initially unrespectable liver metastasis for colorectal cancer in a living donor liver transplant program.

Luckshi
My name's Lexi. I'm a fourth year general surgery resident at the University of Toronto. And I'm very interested in transplant and live [01:22:00] transplant oncology. Amazing. So can you tell us a little bit about that research that you presented at our education day?

Yeah, absolutely. So the research really focuses on living donor liver transplant as one potential option for colorectal liver metastases in a setting where it's unresectable. And so really it is kind of broadens what tools we have for that patient population. Amazing. And so for that research what you're doing right now is Actually transplanting a portion of a liver to somebody who has cancer and then removing their liver.

Yeah, absolutely. So it's currently in a trial setting. So around 2016 the University Health Network, they adopted the living donor liver transplant trial, specifically for patients that have unresectable disease and really patients who have been. Seen and screened and throughout the process or maintained on chemotherapy for at [01:23:00] least six months and up until transplant and have to demonstrate that their disease is stable.

Mm-hmm. And there's a lot of factors that do come into play in making sure that they're still candidates. But then the patients that do end up being candidates for our trial and do end up getting transplant we've shown that they have really good outcomes in the end. Amazing. And we had Dr.

Sapa Soin and Natalie on our podcast last season. And they talked about their journey together, which was absolutely remarkable. If people wanna listen to that episode it's called James Bond and Cancer Muggles which was really great to have them both on. So how many, approximately how many people have been through this process so far in your research?

Yeah, so in total about 106 patients have been referred and this is kind of taken around the time of late February. Mm-hmm. And of those people only eight patients actually made it to transplant so far. So it is a pre intensive screening process and the median time [01:24:00] to transplant from the initial.

Consultation is about 15.4 months, so it's quite a long period of time. There's a lot that's involved and it's a very select patient population that do end up going through and getting transplant. For those people who did go through this process what makes them eligible to be part of this trial?

Yeah, so we have a strict inclusion exclusion criteria, and some of that really involves patients who Do not have a b a f B 600 primary. They have stable disease meaning stable imaging findings and stable c e A levels which is a tumor marker. And so they have to be have to demonstrate disease stability.

They have to be on chemotherapy, as I said, for about at least six months or so. And up until the point of transplant they also can't have that. Any extra hepatic disease and. It's also making sure that clinically so patients that have other concurrent cancer or have had previous transplant do get [01:25:00] excluded.

And the other key thing is they do have to have a, a living donor. Mm. So all of those factors do come in. And we do see patients, so they receive regular oncologic screening. Or surveillance while they're along or on the trial. So every three months or so patients will get CT scans as well as CEA levels.

And if at any point either they have disease progression they have development of extra P disease, or they, if they become resectable at any point they are no longer eligible for transplant. Wow. So it is a very strict process, a really tight group of people who would be eligible for that. From that group of people who have been transplanted, what have the outcomes been for them so far?

Yeah, so overall the overall survival has been really great. So only one of the eight patients has died and the time from transplant to death was about 39 months, so it's quite an extended period of time. Mm-hmm. We did have two [01:26:00] recurrences in the patient population and of those recurrences, they were extra atic disease.

One of them was a, an earlier recurrence after transplant at about three months to the lung, and that might have just been a missed. Metastases at the time. But when we compare them to patients who've had liver resection within our population who were excluded from transplant and instead were downgraded from their disease burden with the chemotherapy and then went on to have liver resection, the resected patients actually.

Almost all of them. So well over 75% of them did develop recurrence. And within three years versus the transplant population, the recurrence-free survival

was dramatically better. Wow. We know that there is a shortage of organs for the need right now. And that gap is filled by, by our living donors.

Is that the reason why you only accept living liver donors? Why somebody couldn't have a deceased donor for this, or Why you would [01:27:00] have that as a requirement. Yeah, absolutely. Especially in Canada. In North America in general deceased donors, we have such limited supply.

And given the shortage, it's very difficult to extend the criteria to include this population, but specifically also through U H N. We're not able to use that deceased donor just. From kind of the politics and the, the protocols that are established. Mm-hmm. So living donor does give you an option.

And the other things too is with living donor, it also gives you an elective operation. You have more control over the timing of chemotherapy. Mm-hmm. And so you're able to kind of control when we stop the chemotherapy and give them some time prior to the. Surgery. So you do have a little bit of leeway that way.

And we've also shown that living donor leads to better, if not at least comparable if not better outcomes compared to deceased donor liver transplant for other conditions. Mm-hmm. Such as H C C. And so I think it's a very [01:28:00] great option. And I mean, you know, we never use the other c word when we're talking about cancer cure.

Right. Because it's a very difficult thing to think about. But when we think about recurrence of cancer and remission from the two people that I've spoke to who have been part of this trial, they have been in remission since they had their liver transplant. And for them often they will use that word here, that they've felt that living donor transplant has so far cured their cancer from coming back.

What does that do, emotionally to somebody to know that this is a new opportunity and, have you seen that with your patients, that this is a new hope, I guess, for a treatment? Yeah, absolutely. I mean, I think the, the goal is towards cure. It's, so the idea really is to, that hopefully the disease is just in the liver, that there's no extra packed disease, that's the patient population that we're offering this for.

Mm-hmm. And so the idea is you're [01:29:00] removing essentially the disease, the entire liver. Mm-hmm. And you're replacing with a new liver that shouldn't have any disease. So in pa, in patients where there is no missed extra

hepatic disease hopefully that. We are aiming towards a cure and I, I think there is a lot of hope for both patients and ourselves as providers.

Mm-hmm. I mean, I'm still in training for me, it's obviously I'm not the one that's kind of directly responsible for like those patients, but at the same time, I'm, I've been involved in their care and it's really, really great to be able to see those patients kind of in follow up and see how well they, they've done and not seeing them come back with any recurrence many years out.

So it's, I think it does provide hope for both ends. And I do think that our goal at the end of the day is towards cure. And I think transplant is a great option, especially in this disease. And patient population. Amazing. And one of the questions that I get often being a recipient myself too, you know, we, we focus heavily on our [01:30:00] immunosuppressants.

So if somebody is receiving a transplant for, for their cancer, are they also on immunosuppressants the rest of their life similar to the rest of us transplant recipients? Yeah, absolutely. So they, they do continue on with almost the usual transplant immunosuppression protocol. Mm-hmm. Of course with any cancer, you do have to be also careful with immunosuppression in the sense that you could also be at risk for recurrence of cancer to, but it is still kind of a balance between making sure that there's no rejection, but also making sure that you're not reducing the immune system to a point where recurrence is higher.

Possibility, an amazing balance that you guys are able to, to figure out. I know in the past I've called it my, my Miracle Cocktail that I take every day. Kudos to the teams and the pharmacists who figure all of that out cuz it's far beyond me.

But I'm wondering if there's anything else that maybe I didn't ask you about that you think our listeners would be interested in knowing [01:31:00] more. I think just in general, kind of the, as a, a summary, I would say that living donor liver transplant is a great option, but in a very select patient population.

As we've seen kind of in our study, we've screened and really followed Large proportion of patients and only a very select number of those patients do go on to have liver transplant. Mm-hmm. And so I think we do have to be very mindful in terms of selecting patients that are going to benefit because you do have to balance out the risks and benefits to both the donor and the recipient.

Mm-hmm. But I also think that in, at the end of the day, this is going towards, Basically cure. And it's also providing a new kind of tool and hope, I think for a

patient population where otherwise they would've received just systemic chemotherapy and the survival rates would've been very poor. Wow.

That's very, very promising and definitely hopeful for all of us to hear about. I'm wondering if there is anywhere that if people were interested in [01:32:00] learning more about the research or the, the project that they could go and read about. Yeah, so it should be listed on the U H N website.

So I think that's always a good toolkit. And then I think the, the end game, of course is to make sure that more healthcare providers are also aware that this is an option. I think being able to disseminate our research at meetings through our paper, I think trying to get the word out that this is a possibility.

And I do. Think more and more places are considering transplant. There's a, there definitely is a bit of a, a shift, but also a little bit of a debate around the role and potential benefit of transplant. So I do think that in the next few years this is gonna be, continue to be a very hot topic, and I do think that it's gonna be a bit more, hopefully, widely expected.

Amazing. Well, thank you so much for joining me today and for sharing your research. It's definitely hopeful and inspiring to know what you guys are doing, so thank you so much. Thank you so much for having me.

We hope you [01:33:00] enjoyed this episode of the living transplant podcast. If you did, please leave us a review and share with your friends. Don't forget to subscribe to living transplant wherever you are listening today. If you have any ideas for podcast episodes, you can reach out to us at livingorgandonationatuhn.

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