

Behind the Breakthrough Podcast – University Health Network

Season 2 –Episode 9 –Dr. Mansoor Husain

Transcript

CHRISTIAN COTÉ:

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 Côté: joining us on the podcast today. Doctor Mansoor Husain, award winning senior scientist at UHN's Toronto General Hospital Research Institute. Dr. Husain's a pioneer in the study of heart disease and has played a pivotal role in the creation and testing of a breakthrough drug that reduces the chance of heart disease ever occurring. Dr. Mansoor Husain, welcome to the podcast.

DR. MANSOOR HUSAIN:

Thank you, Christian. I'm pleased to be here.

CHRISTIAN COTÉ:

so, as I was preparing for our interview in your bio, it says
Your research focuses on, quote, elucidating the molecular basis of heart disease, unquote.
If you don't mind, could you help us understand what that means?

DR. MANSOOR HUSAIN:

sure. Well, maybe I'll start by, you know, I'm a cardiologist, so I work here at UHN at both Toronto General and Toronto Western. And I take care of people with cardiovascular disease, which is by and large a disease that develops as we age. So, you know, we sort of call that a degenerative disease. As we get older, things start to happen with heart vessels and the heart itself. However, there are certain conditions that happen in younger adults and they can even happen in children. And then that disease stays with them. And when they become adults, we start to take care of them here at the adult hospital.

Even those diseases that occur late in life that we would call normally degenerative diseases, we believe have a strong genetic basis. In fact, a family history of heart disease is often an important risk factor for developing heart disease. And it's how your genes interact with the environment, whether you're active, whether you eat well, whether you don't smoke, and then whether you develop other risk factors like high blood pressure, high cholesterol, those are sort of environmental influences that interact with your genetic makeup. And that interaction, we believe, occurs at a cellular level.

So, in our cells, the cells that make up the lining of our blood vessels, the cells that make up the heart muscle itself. And that cellular pathology, if you will, the disease that occurs in the cells in and of itself has then a

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Molecular basis. It's that you know, our genes encode for our proteins and our proteins form the structures and the enzymes that make up all of our cell functions. So, my goal is really to study what is the normal healthy cell and what is the disease cell and that perturbation, that abnormality, we often say is at the molecular or cellular level.

So, some of my colleagues, you know, they study clinical outcomes. They study epidemiology like databases and things of that nature, whereas I have a privilege of studying cells and model systems that inform about molecular the basis of disease. A bit of a long answer, but that's why my biosays the molecular pathophysiology.

CHRISTIAN COTÉ:

it's good to have that underpinning. So I appreciate that. Thank you. Now I understand the story behind you know, this breakthrough drug discovery in terms of reducing heart disease goes back to the mid 2000s with the emergence of an experimental new diabetes drug. And you're meeting an endocrinologist who is investigating the drug. Can you take us back to that story?

DR. MANSOOR HUSAIN:

so, I wouldn't be in this field if it wasn't for one of my colleagues. So professor Dan Drucker, who used to be here at university health network, who's now across the street at the Mount Sinai Hospital in the Lunenfeld Research Center, is really a pioneer in our understanding of a class of proteins that are called the glucagon-like peptides. And these are proteins that are made by our digestive systems, by our gut, and they prepare our bodies to receive nutrients.

So, whenever you eat something, calories are ingested, and our body is designed to prepare itself to sort of metabolize those calories. And glucagon-like peptides is one family of peptides that prepare our bodies. And so, Dan had made an animal model, a mouse model, where that mouse lacked the receptor for this class of proteins. In other words, the animal did not have a glucagon-like peptide one receptor.

And there had been some inkling in the literature that maybe this receptor, for reasons that were not understood, was expressed outside of the gut, outside of the, the pancreas, which is the target organ. The pancreas produces insulin, the pancreas produces glucagon to hormones critically involved in blood sugar regulation, and so we understood. And Dan had shown that these peptides work in blood sugar regulation.

But what wasn't known is whether they did anything at all outside of the metabolic control of blood sugar, whether they worked in the cardiovascular system. And so he came to me and said, you know, we've made this animal that lacks the receptor. Therefore, it should not have any

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Function of the glucagon-like peptide. And I wonder, what would we find if we looked at the cardiovascular system? And that's really how the story began.

You know, it's sort of like that knock on the door and you have a hallway conversation with a colleague and you begin to work in a field. And we've been working in this field ever since. It's probably approaching 20 years now. And what we were able to find is that the peptide actually does have actions outside of the pancreas and not just our own laboratory, but many laboratories around the world have now shown that the peptide has actions on the same cells I talked about earlier, endothelial cells, we believe also vascular smooth muscle cells, less certain whether it acts directly on heart muscle cells, but clearly has actions on the whole heart, we believe primarily through blood vessel cells that feed blood to the heart.

And then in parallel, this class of peptides, because of its effect on increasing insulin secretion and turning off glucagon secretion and glucagon, is the hormone our bodies make when our blood sugar is low. So, it makes our bodies produce more blood sugar. And this hormone turns off glucagon and turns on insulin secretion. And so, you could see immediately that for individuals who have diabetes, taking a hormone like this would increase their insulin and reduce their glucagon and might be beneficial for diabetes.

CHRISTIAN COTÉ:

so, before we move into your research on the drug, can you explain just the mechanism of action for patients with diabetes?

DR. MANSOOR HUSAIN:

Right. So, when we learned through Dan's work that this peptide works by increasing insulin secretion and by reducing glucagon secretion, then it became obvious that this could be a potential drug for the treatment of diabetes. And how it would work is, is that if you took this drug, which previously was only available as an injection because it is a protein and most proteins are degraded by our digestive system, and so it wouldn't survive if you took it orally. We'll come to that invention later. How it's now available as an oral agent.

But so, it was taken as an injection. And if you inject an individual with this agent, then whenever they eat anything or even when they're not eating anything, now they've activated that glucagon-like peptide receptor. And what that means is, is that for any amount of blood sugar, their body is going to produce more insulin and it's going to produce less glucagon. So, it's going to help their blood sugar levels fall. And the wonderful thing about this pathway, the glucagon-like peptide receptor pathway, is in

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Addition to these effects on the pancreas, it also has effects on the stomach.

So, it changes the motility of the stomach. And we believe that contributes to an individual feeling less hungry and it also acts on the brain and suppresses appetite in the brain. So, at higher doses, the same drug has also been used safely and effectively to treat obesity. So, it's become quite an important class of medications. But all diabetes medications now have to go through testing, which is to establish that they're safe for the cardiovascular system. And it's worth stepping back a moment and understanding why that's important. Because people with diabetes, as we talked about earlier, diabetes is one of the more powerful risk factors for the development of cardiovascular disease.

So, people with diabetes have an increased risk of developing cardiovascular disease. And therefore, if you're going to use any new drug to treat diabetes, you have to be cautious and be sure that it won't make their often advanced, underlying cardiovascular disease worse. And why this is so important is that there have been drugs that have been developed for the treatment of diabetes, that have been effective for the treatment of diabetes, but unfortunately, that has not translated into a reduction in cardiovascular disease. In some cases, my colleagues and I believe that those drugs, while they treat diabetes, actually may have made the cardiovascular disease riskier or you know, worse.

And therefore, both in North America and in Europe, the regulatory agencies, you know, those agencies that protect us, the public, have mandated that all new diabetes drugs be first tested for cardiovascular safety. And what better place to test safety than in people at highest risk of cardiovascular disease? So while the drugs that were based on glucagon-like peptide began to show in our laboratory and other laboratories potentially beneficial effects on the cardiovascular system, they initially had not yet been tested in large cardiovascular outcome trials where that proof of concept needed to be established.

And so, in the last, I would say, five years, really, we now have abundance of cardiovascular outcome trials with testing this hypothesis, testing the safety of drugs based on glucagon-like peptide one. And there are many of them now and they've all shown very consistent results that not only is the medication safe, it doesn't cause any harm in people with cardiovascular disease, but they've begun to show that it actually reduces cardiovascular events.

So, fewer cardiovascular deaths, heart attacks and strokes, which, you know, very few diabetes drugs are able to do that. And we're really

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Blessed is that in the last five years, two classes of drugs have emerged, one which i've just talked about, the glucagon-like peptides and another class, which is works by an entirely different mechanism, which i won't get into. But the whole treatment of diabetes has changed in the last five years with this knowledge.

CHRISTIAN COTÉ:

in this process, as you started to test and investigate the drug and you started to notice these benefits for the heart. What did you think?

DR. MANSOOR HUSAIN:

one always is cautious. We repeat everything multiple times to be certain. I said initially we were pleasantly surprised and we spent years making sure that the effect was real. And that's what controlled experiments are all about. So, I'll give you a couple of examples. We have the peptide and then we would take the same amino acid sequence that defines what a peptide does but scramble the sequence. So, we used a controlled peptide that has the same amino acids as the functional peptide, but they're scrambled, so it doesn't have the same sequence. And when you do that, the control peptide has no effect.

So, that's very reassuring that the act of giving a peptide any peptide doesn't do it. It's only a peptide with this very specific sequence, if you will, very specific signature. So, when you scramble the signature, that doesn't have an effect. So, that's one control experiment. And then you know, we did many other control experiments, which we not only study the whole organ, but then we study the components of the organ to find out is it working on heart muscle cells? Is it working on endothelial cells? Is it working on smooth muscle cells? So, you can really unravel, as we talked about in the beginning, at the cellular level and at the molecular level, how we believe the drug is working.

CHRISTIAN COTÉ:

so, when did you feel confident Mansoor to be able to move this drug from a purely diabetic patient treatment to preventing heart disease?

DR. MANSOOR HUSAIN:

as i said, this was happening in parallel. The drug had been developed and demonstrated in patients with type two diabetes to be effective in lowering blood sugar. And it was going through sort of the approval process and became commercially available, approved for the treatment of diabetes. But what's required is a cardiovascular outcome trial to make sure that it's safe in the highest risk people. And these trials were being done with no involvement from me or any of us here at Toronto General. But then when it came that the drug had been formulated, one of the types of this drug, there are several, as I mentioned, had been formulated now as an oral pill, then the manufacturer of that danish

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Company called novo nordisk, a multinational company, approached me and asked me if i would like to be involved in the conduct of that trial, which is called pioneer six.

And that was the first cardiovascular outcome trial with an oral version of the drug. And the drug had been tested in an injectable format already and had proven to be both safe, but also effective. And then so i was privileged to be part of myself and an endocrinology colleague in the u.k. we were the co-principal international investigators on this study in patients with cardiovascular disease for the oral agent. But, you know, i really was working on the animal models that showed that it would be beneficial in certain cardiovascular conditions. It's rare in your career that things that you've worked on at the molecule level in cell systems and animal model systems, that it always holds true all the way through to clinic.

And so, that was gratifying that even in studies that were published you know, four or five years ago, we had the first clues that this was the case. And then in our study of the oral version of the drug that was published last year, also demonstrated to be safe was a smaller study, not as long a duration study as some of the earlier studies. And therefore, it didn't have the statistical power to prove that it actually reduced cardiovascular events. There was a 17 percent reduction, but it didn't meet statistical significance because it didn't have enough events.

But in that study, the effects of the drug and the consequences on cardiovascular events mirrored what had been seen with the earlier study, with the injectable version of the drug. So recently we've published, if you put them together, the oral and the subcutaneous, you have a large data sample. And they're the conclusions are pretty clear that the drug not only very effectively treats diabetes, but also appears to reduce cardiovascular events, which is in some ways the holy grail of the treatment of diabetes is not only lower blood sugar, but reduce the complications of diabetes.

CHRISTIAN COTÉ:

what's next in terms of investigating the pill form of this drug?

DR. MANSOOR HUSAIN:

so, the pill form of the drug, because the first study that i was involved in that was published last year was a relatively small study. The company has felt the need and I'm encouraged that they are doing so, are conducting a much larger study where they'll have definitive proof that the oral drug works as well as the injectable drug. So that's the next step for the oral medication. I think the even more exciting area, which is currently under study, is that the injectable version of the drug,

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Which has been around a bit longer, is now being tested in people who don't have diabetes.

So, now this is the big transition where you're taking a drug that was developed for the treatment of diabetes but is now being tested in people at risk of cardiovascular disease. And if you have diabetes, you're actually not in the study, so it's now being tested as a drug for the reduction of cardiovascular disease, not because of its use as a diabetes drug. That's very exciting. That trial is underway. And so, both of these studies that I've mentioned, you know, it'll be a few years before we know what those results are. But that will be another big transition is if we can see whether this drug works even in people who don't have diabetes.

CHRISTIAN COTÉ:

when it comes to translating this drug to be prescribed for people with obesity or heart disease. When do you see that perhaps occurring?

DR. MANSOOR HUSAIN:

the drugs already approved for the treatment of obesity. And so that translation you know, is underway. But for the treatment of heart disease, in the absence of obesity or the absence of diabetes, that will be a real leap forward. I think that we'll know from one of the trials currently underway, which, as I mentioned, is in patients who do not have diabetes, but they are people who are overweight and who have risk factors for cardiovascular disease in which you know, those individuals have a certain event rate.

We can predict that a certain percentage of them every year will have a heart attack or a stroke. And it'll be several years before we see whether that event rate can be reduced if they're treated with this class of drugs. So, I would see it's probably going to take about five years before we have the data to be able to make that next step forward in the translation to beyond diabetes and beyond obesity where they're already approved.

CHRISTIAN COTÉ:

fair enough. To get to that outcome or to be a part of you know, working towards that outcome, I mean, you call this sort of the holy grail. What's this mean to you?

DR. MANSOOR HUSAIN:

well, it's you know, it's been a privilege to be lucky enough to have that knock on the door almost 20 years ago and then for it to pan out. You know, I mean, I've been a scientist here for over 20 years, and there are several things that we've worked on in my laboratory that I'm very proud of. But it's truly rare that something is, if you will, sort of validated clinically and then becomes an important class of drug, not because of my work, but that we sort of contributed to the knowledge that led in that direction. And then again, it's rare for me as a scientist

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Who primarily works on basic molecular and cellular mechanisms to have an opportunity to be involved in clinical trials.

CHRISTIAN COTÉ:

you're listening to behind the breakthrough, the podcast, all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host, Christian Côté and we're speaking with Dr. Mansoor Husain, award-winning senior scientist at UHN's Toronto General Hospital Research Institute.

His pioneering research led to the discovery that a promising new diabetes drug also reduces mortality due to heart disease. Dr. Husain's work is funded in part by the Toronto General and Western Hospital Foundation.

You're born in Pakistan. Your parents emigrated to Calgary when you were just two years old. And then in grade six, you're on the road again a year in Libya, followed by four years in Malta. Where I understand you have your first 'aha' moment when it comes to connecting with science. Tell us the story behind that?

DR. MANSOOR HUSAIN:

Christian, you've, you've done your homework. It's a story I love to tell my students, which is it was you know, gosh must have been maybe grade 10 something in that range. And it was chemistry class. And I wasn't so fond of chemistry. I remember needing help from my mom in understanding chemistry, but we had the opportunity to make nylon.

And it's just such a powerful memory of mine from one of the few memories I have is to see those strands of nylon taking shape in the beaker when we did that chemistry experiment, knowing that you could take you know, constituent elements and essentially build, you know, molecules and build something that is of practical use, like nylon was eye-opening. And for the longest time, I want it to be a chemical engineer, to be able to sort of recreate that. If I was to think back, you know, it's that light that lit an interest in science, a sense of wonder over the natural world. And then maybe because it was about being able to you know, control that reaction to, to push it in one direction or another. That led me to sort of think, well, you know, we can we can change things. The, the natural world is wonderful, but that we could change things.

CHRISTIAN COTÉ:

you mentioned you had your sights as a result of that 'aha' moment. You had your sights set on a career in chemical engineering. What inspired you to steer towards biology and more specifically, the heart?

DR. MANSOOR HUSAIN:

so, it was another real 'aha' moment. I was, I was an undergrad and I think it was second year undergraduate at university of Calgary. And I had a wonderful professor of microbiology and it was almost like an echo of that 'aha' moment from high school where we started to talk about how did life originate.

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And we started to talk about how inorganic elements suddenly at some point had to have become both the nucleic acids that encode life, but also the proteins that enable life.

And he was a truly inspirational professor who made us think, I mean, it verged on theology, this spark of life. And it was that class, I have to say, that made me think, yeah, no, chemical engineering was cool, nylon was cool. But this life science is even more interesting. And that's what pushed me to study more microbiology and then ultimately, you know, I kind of literally applied to medical school a little bit on a lark and was very fortunate to get in. And as they say, the rest is sort of history.

CHRISTIAN COTÉ:

I'm curious about your thoughts on what it takes in this profession to succeed. Like I read where Elizabeth Blackburn, who's a Nobel Prize winner, was asked about the virtues of successful scientists and she says resilience, persistence, as well as being opportunistic and creative. Does that resonate with you?

DR. MANSOOR HUSAIN:

Very much so. I did not fully appreciate how much creativity is required. To me as you're taught, and I think very important to distill. Almost everybody from high school should come away with an appreciation of the controlled experiment. Right. To prove a cause and effect, you've got to have controls and to understand what is the basis of a controlled experiment and how do we analyze the data. And that's in many ways very reductionist, right? You break things down, you do one experiment, then another, then another.

And on the surface, it seems like that's not very creative, that, that is you go through the steps and it's a bit formulaic or a recipe like. But then when you start to hit on the limits of your knowledge, when you when you aren't certain, well, what's my next experiment or what should I do to prove something? Then that is really about creativity. Sometimes it's you have to create a new tool. Or you have to create, where a tool didn't exist, you want to measure something, but you can't measure it yet, so you have to be creative and I'm going to develop a tool that lets me measure this. And then you run into where you now you've created your tools, you've made all your measurements, but now you run up against. But how does this affect the big picture?

And again, you have to be creative. Am I going to study this in a cell or in an animal model? But ultimately, as a physician, my interest is in helping people. But how do you do experiments in people? So you have to then

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Imagine, well, what is the blood sample that I'm going to measure or what is the imaging modality, the imaging tool that I can use to be able to measure inside patients with disease and then over time. So, there's a tremendous amount of creativity. But because results take years and years and years, all that patience and resilience and perseverance that you mentioned are also critical factors right. I joke with my students that that's, that's why they put the re in research. If it was simple, they'd just call it search. But it's research because you have to do it over and over and over again.

CHRISTIAN COTÉ:

which leads us to something that happens often in research, which is you face an obstacle or a dead end or a failure. How do you manage these tests of your resilience? Because we're not really taught how to deal with failure.

DR. MANSOOR HUSAIN:

yeah, that is something you know, i again did not fully appreciate. I think when you're younger, you see failure as something to be avoided. Right? You see failure as i don't want to fail. One of the hardest lessons to learn, but even harder to teach is that only through failure do you get better. It's only when you fail at something that you practice so that you get better at it and it's so obvious, but as it's going on, you're frustrated by failure.

But once you grasp that having failed at something, well, now I'm going to design it better, do it better, and then I'm going to succeed. So, failure is the i would say the master teacher. And therefore, once you learn that, i think you inherently then gain resilience because you know that I'm going to fail, and failure is okay. In fact, some would argue it's good. I still don't like to say failure is good, but, but i acknowledge that by failing you become better.

CHRISTIAN COTÉ:

have you ever had doubts or fears along the way in your career journey?

DR. MANSOOR HUSAIN:

Absolutely. Yeah. Again, speaking more from the, the privilege that I have of being both a physician and a scientist, I sometimes do wonder whether my time would be better spent simply not simply I don't mean to underemphasize it, but in that incredible privilege of caring for my patients. In other words, more time in clinic versus more time in the lab. More time in the lab means more time with my students. And I would be not fully honest if i didn't say that i struggle with that to this day. Where will I make the greatest contribution?

And I oscillate between thinking, well, I'm a pretty good scientist. I should spend more time in the lab where I get tremendous satisfaction and feel

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That I do some good if I spend more time in the clinic. But one thing I will say is that being in clinic makes me, I believe, a better scientist. And being in the lab, I believe, makes me a better doctor. So that's the, the message I try to instill in both my graduate students who may not do medicine, but also in my medical trainees who may not do science is we're obliged, I think, to have an appreciation for both because the frontiers of medicine are science-based.

CHRISTIAN COTÉ:

what do you think of patients who decide to become subjects in your research trials?

DR. MANSOOR HUSAIN:

so appreciative of them, so honored to work with them. They have to have all the information for them to make that informed decision to consent to be part of the trial. But you know, without their participation, medicine would not move forward in science of medicine, would not move forward. It is absolutely the foundation of everything that we do. And I'm a big believer that in one way, shape or form, every patient that UHN treats contributes to growing knowledge. Right. Even if it's just that they may after their blood test is done for medical purposes, a portion of their blood might be used for research study, for example.

And that's how we'll learn more and be able to treat not only them like some sometimes people are of the belief that this is going to benefit future patients, it's not going to benefit me. Well, nothing could be further from the truth. You know, the pace of medical science and discovery is accelerating at such a such a speed that what we couldn't treat a few years ago we can treat now. And so, my encouragement to prospective patients in clinical trials is this may actually help you, not just future generations. It's a good, selfish thing to do.

CHRISTIAN COTÉ:

there's a saying I read, where every living thing has its antithesis, and if you apply that to disease such as heart disease, which is a living thing, does it follow for you that there's absolutely a cure, a treatment?

DR. MANSOOR HUSAIN:

yeah, I use the word cure very, very sparingly. I think control and management is far more often how we approach disease. And a cure is sort of like there's an infectious disease and you've beaten that infection, right, it's over, until you get another infection. Yes, I believe that we're on the verge of curing certain diseases by wiping them out, like wiping out an infection. But remember, I started by saying cardiovascular disease is a degenerative disease.

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As you get older, you grey some hair and you lose some more, and your skin isn't as elastic as it was and you're not as flexible and mobile as you were. And that is the gradual onset of the effects of time and aging on the human body. The same holds true for the cardiovascular system. Your blood vessels aren't as elastic as they were. They're stiffer and your heart is having to work harder to pump blood through stiffer blood vessels. And your heart is having to work harder when it's 60 than when it was 40.

And therefore, it's more a matter of time. So, what we look at is, do you what are the risk factors that we can control, not cure, but control? And then when there is signs that the heart is struggling, what are the medications that we can use to ease the struggle of the heart? So, most cardiovascular diseases control, not cure.

CHRISTIAN COTÉ:

your career, your approach I think it was around 25 years now, in terms of research, what keeps you going?

DR. MANSOOR HUSAIN:

I see my patients get better. That is extremely gratifying. I see them feel unwell and then feel better. And that keeps me going in clinic and in the lab. Yes, you've got to have resilience and perseverance and you've got to accept failure, but you've got to have some wins along the way. And that that's what keeps you going. And sometimes the win can be a single experiment that you may never publish, but you made it work and then that keeps you going.

CHRISTIAN COTÉ:

What should we look for next from you?

DR. MANSOOR HUSAIN:

Well, it's a good question. I have these days the privilege of leading the Ted Rogers Centre for Heart Research, which is a unique centre because it's a partnership between UHN and sick kids and the University of Toronto. And it's about trying to tackle a specific cardiovascular disease that's called heart failure. So I spend a lot of time now working with a tremendous group of colleagues that are part of the center where we're imagining the future of how we will better treat heart failure, which is you know, a growing public health problem, growing societal health burden. So, a lot more of my own laboratory work is gearing towards heart failure because of this role that I'm playing.

I've sort of got to walk the talk. And so, I'm shifting and it fits quite well because diabetes not only increases cardiovascular disease, but has this specific, very profound effect on heart failure, that's not completely understood. And one of the challenging types of heart failure, all types of heart failure are difficult to treat, but one of the more challenging types of heart failure is the type that people who have obesity,

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Overweight, diabetes are more likely to get. And so, i'm spending a lot of time working on that.

CHRISTIAN COTÉ:

so, Dr. Mansoor Husain, award-winning senior scientist at UHN's Toronto General Hospital research institute, thanks for sharing your groundbreaking research with us and continued success.

DR. MANSOOR HUSAIN:

Thank you.

CHRISTIAN COTÉ:

Dr. Husain's research is made possible in part thanks to generous donor support. If you'd like to contribute to this groundbreaking medical research, please go to [www.tgwhf](http://www.tgwhf.ca), that's www.tgwhf.ca/podcast.

For more on the podcast, go to our web site, www.behindthebreakthrough.ca and let us know what you think. We love feedback. That's a wrap for this edition of behind the breakthrough, the podcast all about groundbreaking medical research and the people behind it at the university health network in Toronto, Canada's largest research and teaching hospital. I'm your host, Christian Coté. Thanks for listening.