1. John Williams: This podcast is for informational and educational purposes only and is not to be considered medical advice for any particular patient. Clinicians must rely on their own informed clinical judgments when making recommendations for their patients. Patients in need of medical advice should consult their personal healthcare provider.

Hi everyone. I'm John Williams, Professor of Pediatrics and Chief of the Division of Pediatric Infectious Diseases here at the Children's Hospital of Pittsburgh.

Stephanie Dewar: And I'm Stephanie Dewar, Vice Chair Of Clinical Affairs and Program Director of the Pediatric Residency Training Program and welcome to, That's Pediatrics from UPMC Children's Hospital of Pittsburgh.

John Williams: Thanks for joining us this week and we are delighted to have as our guests this week, George Gittes who's a physician and the surgeon and chief here at Children's hospital. Dr Gittes, maybe you could just tell us a little bit about yourself and what you do and then we'll talk about your research.

George Gittes: Okay, John. Yeah, so I'm a pediatric surgeon, which means I trained in general surgery and then did specialty training for focusing on children. And also during that time and prior to training, I was heavily exposed to research. So that's really helped to define me as what is generically called a surgeon scientist. So I divide my time between doing clinical surgery and basic research. And the career has evolved from that training to sort of climbing the academic ladder to the point where I was graciously offered the Chief of Surgery position here at Children's Hospital of Pittsburgh about 12, 13 years ago and it's been a great experience so far.

Stephanie Dewar: So I'm wondering if you could tell us a little bit about your recent study that was published about Type One Diabetes?

George Gittes: So that was a a fairly exciting and serendipitous result that we achieved and have since publishing it with potential applications to patients with Type One or Juvenile Diabetes. There's been quite an onslaught of inquiries from patients and families to me directly about clinical trials. But basically what it consisted of was gene therapy and gene therapy for the most part in this country involves using viruses that are carriers for genes that you, in particular, want to introduce into cells to change them and make them better in some way. And we stumbled onto it because my research is for many, many years been focused on the pancreas, which is where the insulin cells live. And we were studying at a very basic level how the pancreas develops and how the cells form and what determines which cell is which and why is the insulin cell an insulin cell.

And as part of those investigations, we really sought after various techniques that would allow us to explore in more detail at the cellular level what was happening. And along those lines, we engineered some viruses and wanted to give them to the pancreas and that way introduce special genes into the cells of the pancreas. But the problem is just giving the usual gene therapy, which is just

by an injection in the bloodstream, it was ineffective. So we had to develop a special technique that involves going into the inside of the intestine where the pancreatic juices that help digest food drain out and infusing the virus upstream back up into the pancreas. And that turned out to work really well.

The surprising result was that when we infuse the correct genes within the viruses, we were turning other hormone producing cells, insulin is an important hormone that is defective in diabetes, we turned the other hormone producing cells into insulin producing cells. And that was fairly exciting. But then the real excitement occurred when we tried this in mice that are very similar to juvenile diabetic patients. And the problem with these individuals is that their body reacts to the insulin cells and kills them. So the obvious assumption was that if we try this gene therapy to make new insulin cells in this environment where the immune system just attacks the cells and kills them, it's not going to work. It shouldn't work and those cells should be killed just like the normal original cells were killed. But the exciting thing was that they were not. And we think that what is going on, and we've done several followup studies to show that the new cells that form, their insulin cells aren't perfect. They're a little different. And that difference is enough to trick the juvenile diabetic or type one diabetic's immune system to thinking that they're not actually insulin cells and they don't pay attention to them at least for quite awhile.

And the fact that we could do a single infusion of this virus and nothing else, including no immunosuppression or anything else was fairly exciting. And nobody's ever done that without immunosuppression in these mice. So we're now moving on to try to get to the clinic.

John Williams: So, okay, this really blows my mind. You basically, if I understand, you took a virus and squirted it into the pancreas to convince non-insulin cells to be insulin cells and then they escaped the immune system to stay there. So is there any technical reason that you couldn't do that in a human and what could happen? I have a sister-in-law with type one diabetes. I mean, is this going to turn her into Frankenstein or could this really work in a human?

George Gittes: Well, yes, the short answer is absolutely could work in humans. We've received some additional funding in support of that concept. The other kind of cool thing about this is, in order to do this infusion into that little tube in the pancreas and profuse it, you don't need to do surgery. You can go through the mouth and then go down through the intestine via the mouth and you find a little opening and put a little tube into that opening and squirt, as you say, the virus back up into the pancreas.

We have shown in the human tissues that the hormone cells that turn into the insulin cells will do the same thing in a Petri dish with the virus. We know that that part should work. What we don't know is whether the infusion in a living human or a living animal with a pancreas similar to a human will work because the mouse pancreas is a little bit different. But we do feel that if we can get this

to work in a higher animal, which we are doing now with promising early results, that we would be able to transition immediately to human trials.

Stephanie Dewar: So this is really very interesting and exciting. A question that might come to some people's mind is that you're infusing a virus into a person, is there any concern or risk that there'll be an infection with that virus that actually might make the patient worse?

George Gittes: No, these are specially engineered viruses that can't really divide and spread. And there are lots of gene therapy trials right now going on in all throughout the world using these viruses and a lot of the concerns and problems that used to exist many years ago have all been sort of figured out. The other thing that important to know is that the exposure of these patients to virus in general is much, much lower because the infusion is only directed to the pancreas. Small amounts of virus. We probably get out a little bit, but this is dwarfed by the huge amounts of virus that have to be given when a patient receives it in the bloodstream because it goes everywhere in the body.

Stephanie Dewar: So you're a pediatric surgeon and you're doing research on mouse pancreases.

George Gittes: Correct.

Stephanie Dewar: So it's an interesting, I don't quite get the connection of how that happens and how you become interested in the pancreas of mice.

George Gittes: So in many respects, 99% of the pancreas is not hormone producing. It's produces digestive juices that go into the intestine. That's why that duct is there that we put the virus into. But so when I first started my research way back when in medical school and early residency, that would be back in the 80s, I was focused on the pancreas because of the surgical relevance that it has. We as surgeons operate on the pancreas for many different conditions, not diabetes. But over the ensuing few years it became quite clear that the focus on the exocrine pancreas, the non hormone producing pancreas, it doesn't reflect as much disease processes out there when you have the biggest disease problem in the US overall, the number one biomedical cost, number one reason for kidney failure, amputations, blindness. There's something like 30 million patients in the US that have some form of diabetes. Another 60 million that are a borderline diabetic. So clearly my focus, if I'm going to be studying the pancreas needed to switch. Of course it's been a nagging annoyance in my whole career that my research focus really doesn't, it's not a surgical disease, diabetes, so it hasn't really aligned with my clinical practice and I'm very jealous of my colleagues whose research topic aligns perfectly with their clinical work because it's just much easier.

John Williams: Yeah, but they're not getting to put these like cool gene therapy viruses into mice to cure diabetes. I mean, anybody can do surgery on a mouse, but what

you're talking about is, that's pretty cool stuff. Is type one or juvenile diabetes the most common or the major pancreatic disease in children?

George Gittes: Yes. Yeah. The other ones are fairly rare. They're either a rare birth defects, occasionally that rare inflammation called chronic pancreatitis. And those probably make up 5% versus 95% diabetes.

Stephanie Dewar: So it's interesting that you say that your research doesn't specifically translate to your clinical work. So I'm assuming then that you've not ever been involved with say a pancreas transplant that might also be used for the treatment of type one diabetes.

George Gittes: That's correct. Those procedures are done by the transplant surgeons and what they do is they remove the entire pancreas. First of all, they don't do pancreas transplants really for diabetes so much anymore. They do islet transplants, but even those are fraught with problems. One fascinating thing that most people don't realize is the immunosuppression that you have to give for a transplant, which is sort of transplant immunology and it's called allorejection is not effective in treating autoimmune disease. They are different pathways, so in order to fight the immune rejection of islet transplantation in a patient that is type one diabetic and received islet transplant, you need to fight both of those immune systems. The alloreactivity and the autoimmune. It's quite a bear. And the idea that we can potentially do this procedure where A, you're not giving any transplant, it's their own cells that are turning into insulin cells and B, these seem to somehow go under the radar of the autoimmune system is a potentially exciting. Although I must say in surgically the procedure that we worked out in mice and are now doing a nonhuman primates, that was all feasible because of my experience in surgery. Working out those techniques and how to do it and especially now in the nonhuman primates could not have been done by a non surgeon.

Stephanie Dewar: So really the good news, just to go back to what you were saying about the immune suppression, is that you're able to potentially offer a therapy without potentially making the patient sicker with the treatment to avoid rejection of the transplanted Beta cells basically.

George Gittes: That's right. That's right. And again, the procedure's noninvasive through the mouth and could potentially just obviate their need for exogenous insulin for insulin injections.

John Williams: Well, speaking as a non-surgeon, you definitely don't want somebody like me trying to do these techniques in a mouse or in a nonhuman primate, let alone a human. So, Dr. Gittes, where, with this procedure, although it sounds like from the paper which we should note was published in Stem Cell in January of this year, 2018.

George Gittes: That's correct.

John Williams: It sounds like it was really geared towards type one or juvenile diabetes. Would it also work for type two or adult onset diabetes?

George Gittes: Absolutely. The problem in type two diabetes is still a Beta cell or insulin producing cell failure. It's a little different because they tend to have a different constellation of problems. They don't attack their own insulin cells, but their insulin cells sort of burnout and fatigue because they've been trying to overcome a resistance of the body to insulin's actions. And that burnout can be greatly improved or helped or cured, potentially, by recruiting new insulin cells and these would again come from these other hormone producing cells.

The other thing that's really interesting about this is that the specific cells that are turning into insulin cells make another hormone called glucagon. And glucagon is supposed to be the counterregulatory or anti-insulin hormone and they're supposed to be in balance. But when you run out of insulin, you have this unopposed glucagon which drives your blood sugars higher and higher and higher. So the fact that we're actually turning these glucagon cells like making the bad acting hormone, turning them into insulin cells and therefore decreasing the bad one and increasing the good one is kind of a nice double whammy.

John Williams: You're turning bad guys into good guys.

George Gittes: Right.

John Williams: I like it.

Stephanie Dewar: So Dr Gittes, I'm just curious what we can expect moving forward. My first question is do you have collaborators in other locations? Are there other people helping you with this research? And what timeframe are we looking at here to move forward when we could potentially think about curing diabetes?

George Gittes: So my collaborators, much of it is related to the gene therapy because I'm not knowledgeable about that and I've been educated that the nonhuman primate work, although it's not an autoimmune juvenile model, it is a proof of principle that it's translatable. And when I met with them, they felt that that was really what was needed was success in a nonhuman primate model and that's all and then move straight to human trials. In terms of the other collaborators, the immunologists have been very important and there's John Piginelli at Children's and to some others who are expert in diabetes immunology has been very helpful. So I think your question about where, when, what's the time frame and where are we going? You're asking the same question all these families and patients are asking me. And we've been at this with a nonhuman primates for three years. And there's been a lot of stumbling blocks, a lot of hurdles, and we had no success for the first two years. And we figured out that there was a technical problem with the way that we were doing the infusion that we've fixed. And now we are seeing a reaction of the cells of the glucagon cells to

potentially turn into insulin cells. They haven't done it yet and the animals are having some unstable physiology because of things that we weren't anticipating.

And one of the problems is the first thing that's happening, before they were for these bad cells turned into good cells, is they stop making the bad hormone. But the problem is there is a dependence develops where their blood glucose stays high, but when you take away that source of making it high, it drops way, way too low. They have sort of lost the ability to kind of regulate it properly. So that's what we're dealing with now. But I think that's a good problem to have because it means we're getting close.

Stephanie Dewar: So I'm just curious. That's an interesting to recognize, how long does that problem persist and would that mean that a person after this type of a therapy as we move forward, would need to be in a hospital and have that monitored for a period of time before we can let them return to their regular life?

George Gittes: That's right. Probably would be, I don't think it would be more than a few days, but I think it would be something we would have to monitor fairly closely and we didn't anticipate that. So we weren't set up properly with these nonhuman primates to deal with that in an effective way. So that's why we've lost some time there. But I think once this is working, the numbers I'm guessing are around, if we can do about eight to 10 of these where it works, I think we've got a green light.

John Williams: Well it's also a great example of how, even though humans are not mice and we're not nonhuman primates, you really, there are things that you can learn in these animals settings. My kids have taken part in research trials in vaccine trials, but I wouldn't sign my kid up to be the first living creature to get a therapy that hadn't been tested in some other kinds of animal so you can learn these things.

George Gittes: Yes. And a nonhuman primate work is very expensive and very slow moving because there's a lot of regulation, a lot of costs. So it's a little frustrating. But we're slugging through it and we're getting there.

Stephanie Dewar: This sounds to me like you stumbled onto something that you weren't looking for in search for something else.

George Gittes: That's right.

Stephanie Dewar: So you don't have any personal or professional mission to solve diabetes, but you found this way to change the pancreas.

George Gittes: Yeah, I mean that's, the generic term for it is serendipity. And this clearly was serendipity. But you have to be prepared. I mean serendipity, another person who might've had a similar result and not realized. So is if you're prepared and you kind of have a, and that's why I think a physician scientists, in my case

surgeon scientists, bring such value to research because we have the backdrop of knowing more details about diseases and how some unexpected or finding rather than being dismissed as, oh, it didn't work the way we thought it would, actually has a whole different meaning that we know of because of our clinical background.

John Williams: You know, I'm reminded Dr Gittes, Louis Pasteur famously said, "Chance favors the prepared mind." So I think that's a question I wanted to ask you. Your mind is prepared for this as a clinical practicing surgeon who takes care of patients when you make this research discovery. But I wanted to ask how you sort of balance those two things that, as you said, are very different. Being a practicing surgeon, operating on children versus doing basic research in the lab. How do you balance those and what do you get from each of those?

George Gittes: So it's an extremely difficult balance and the balance gets more and more difficult as science progresses and med and clinical medicine progress. So in the days of Louis Pasteur, it wasn't that hard because things weren't that different, I would say even 40 years ago in surgery and maybe to the same in non surgical specialties, the models that we use were whole animals and physiology and whatnot. A lot of it was very similar. Now we're talking about single cell RNA sequencing and complex DNA analysis. This has very little application to clinical medicine, certainly for a surgeon. But I need to maintain my surgical skills. So the divergence of the complexity of these two areas is more and more challenge every year. It just takes a lot of energy, a lot of time to read and keep your skills up. And it's a huge challenge.

John Williams: Are they fulfilling to you in different ways? Do you get different things out of these two aspects of your professional life?

George Gittes: Yeah, I'm like a kid in a candy store. It's absolutely fulfilling to have this breadth of exposure and working with all assortments of types of people, hardcore, basic scientists. And then on the clinical side, of course, all the nurses that are caretakers, other doctors that don't have this variety in life. So yeah, it's quite a treat.

Stephanie Dewar: Well, we're so happy to have had you join us today, Dr Gittes. This is very exciting news and information and I'm anticipating your future success.

George Gittes: Sure.

John Williams: Yeah. Thanks, Dr Gittes, for joining us and thank all of you for listening. We'll talk to you next time.