HCT Podcast Ep 409: Linda DiMeglio and Emily Sims

Aaron Carroll: [00:00:00] Welcome back to the Healthcare Triage Podcast. We have two guests today to talk to us about diabetes and some of the really interesting work that they're doing. Our first guest is Emily Sims. She's an Associate Professor of Pediatrics, Associate Director of the Medical Scientist Training Program, and Assistant Director of the Wells Center for Pediatric Research at Indiana University School of Medicine.

And secondly is Linda DiMeglio. She's a Professor of Pediatrics, the Vice Chair for Type 1 Diabetes TrialNet and the Chief of Pediatric Endocrinology at Riley Hospital for Children. Both of you welcome.

Emily Sims: Hi, Aaron. Thank you so much for having us. We're super excited to be here.

Linda DiMeglio: Yeah, we are super excited to be here.

Aaron Carroll: This Healthcare Triage podcast is co-sponsored by Indiana University School of Medicine, whose mission is to advance health in the state of Indiana and beyond by promoting innovation and excellence in education, research and patient care. And the Indiana Clinical and Translational Sciences Institute, a three-way partnership among [00:01:00] Indiana University, Purdue University, and the University of Notre Dame, striving to make Indiana a healthier state by empowering research through pilot funding, research, education, and training. More information on the Indiana CTSI can be found by visiting Indiana ctsi.org.

I like to start off every episode by asking our guests, you know, how did you get here? How'd you get interested in research? How'd you get interested in diabetes? How did you get to these positions that you're in?

So why don't we start with you, Emily.

Emily Sims: Sure. I never thought that I wanted to do research. I knew I wanted to be a pediatric endocrinologist because I thought the kind of physiology of endocrinology was really cool and the medical problems I saw were really cool in med school.

And then as part of my pediatric fellowship our program does a really great job of getting people involved in research. And I actually worked with Dr. DiMeglio and Dr. Evans Molina and the Diabetes Center and had this just kind of amazing mentorship and research experience and, and thought it would be really fun to kind of keep moving.

And, and then since then I've been [00:02:00] able to get involved in a lot of. Translational clinical studies where I've gotten to kind of see how the things that

we're doing maybe are gonna impact our patients long term. And then, so it's felt really rewarding and I've kind of stayed on and continued with this career.

Aaron Carroll: What got you interested in, in diabetes or endocrinology?

Emily Sims: Yeah, I think in med school, in endocrinology, the feedback loops just made total intuitive sense. And so that was really appealing to me. I felt like I didn't kind of have to memorize everything, you know? And so I really, really liked that about it.

And then diabetes in addition. As in terms of clinical care is really fun because you get to see the patients that you take care of over, over long term. So it also feels a little bit like primary care. You get to see those kids grow up over time and, and kind of be a, a doctor they know for a long time.

So I really like that too.

Aaron Carroll: Linda, ask same question, sort of what, what got you here? What was your path like?

Linda DiMeglio: I had to write a thesis when I was in college and I actually almost wasn't pre-med in college because I hated the competitiveness of the pre-med environment there. [00:03:00] But I had to write a thesis.

I wrote it on the evolution of flight in birds, something completely separate from medicine, but that led me to be interested in research. And so I actually applied to med school, md, PhD, although I ended up not doing a PhD during medical school. But I think I kept coming back to research. And then as a resident, I got really interested in endocrinology because we used to take care of the patients with Type 1 Diabetes on the inpatient floor.

And at the time it was before you had like all these big computer spreadsheets and things and these kids would come in really sick and you'd have this written spreadsheet and you'd keep track of the fluid in and the fluid out and the insulin and all of that. And it was really. Interesting to watch the physiology and in the morning the endocrinologist would come in and be like, change that kid over to shots.

And we were, and I wanted to be that person in part, but then I even went into fellowship thinking I was gonna be a clinical endocrinologist. And then got interested in research really as a second year fellow when I decided I wasn't energized as [00:04:00] much by going to clinic as I was by some of the writing and the research and those aspects of care.

I'll say as a. Thread through all of this too. My aunt had had Type 1 Diabetes, so I was exposed to that very early, and I'm sure that also was part of what piqued my interest.

Aaron Carroll: Even though I'm sure we've talked about it on the podcast before it's always worth a refresher. Could I, could I get you to just talk to us a bit about what exactly is diabetes, and since we're gonna be focusing on type one today, how does that differ from other types of diabetes?

Emily Sims: Diabetes, there's basically different kinds of diabetes, but the way that they're all similar is that the cells in your pancreas that make insulin, the beta cells aren't kind of making as much insulin as your body needs, and insulin is the way that you use the sugar. And your blood is fuel. And so if you don't have enough, you end up having high blood sugar levels.

And so Type 1 Diabetes is an autoimmune disease that happens when your immune system kind of attacks those beta cells in your pancreas. And over time you progressively lose more and more of those beta cells. So that [00:05:00] ultimately you just don't have enough cells to, work to make enough insulin anymore.

And we think that people who get Type 1 Diabetes kind of start with a genetic predisposition and then encounter some sort of environmental trigger that kind of tips the scales over towards immunity to those beta cells so that you have that kind of progressive loss of those beta cells over time and then eventually you just kind of don't make enough insulin.

And so the, the only treatment we have right now is to give insulin back once you've kind of reached that point. Of having a diagnosis of, of clinical Type 1 Diabetes.

Aaron Carroll: Why is the like autoimmune tax so specific to beta cells? I mean, it just seems like it's so bizarrely targeted that you know that so many people have this condition, which just goes after a certain type of cell, which is so critical.

Linda DiMeglio: I don't know that we really know the answer. I mean, certainly people, Emily may have more speculation. Some of it has to do with probably similarity between some of the proteins that are on beta cells to other things in the environment that you would wanna get rid of. For sure people with Type 1 [00:06:00] Diabetes have a predisposition to other autoimmune diseases, so it's not just beta cell specific for some individuals.

But a third will develop autoimmune thyroid disease about five to 7% celiac disease, and then other people will develop others. But Emily, you may have some other thoughts on that as well: why the beta cell?

Emily Sims: Yeah, the only other things I would add is, you know, some people think that in some cases Type 1 is triggered by some kind of viral infection, so there may be certain viruses that are more likely to be kind of trophic to your pancreas.

And then there are also some SNPs are Single Nucleotide Polymorphisms that are associated with increased risk of Type 1 Diabetes that, that we know are also expressed in the beta cells. So it could be, you know, that certain people inherit kind

of a predisposition to beta cells that get more inflamed and kind of present more autoantigens under certain conditions.

But I agree with Linda. I think it's not totally clear.

Aaron Carroll: Can you talk to us a bit about, you know, the primary ways we treat Type 1 Diabetes and how that's changed over time?

Linda DiMeglio: Fundamentally, the treatment for Type 1 Diabetes has been insulin, and we just [00:07:00] celebrated last year the hundredth anniversary of the discovery of insulin.

Insulin was certainly life changing, but not a cure. So I've been taking care of patients with Type 1 Diabetes in a clinic at Riley for 27 years now. And over that time, I've seen a lot of advances in the types of insulin we use. So we have faster acting insulins, we have more stable basal insulin.

So that kind of continuous insulin you take throughout the day, really advances in meter technology and then advances in the way we deliver the insulin such as cont as insulin pumps and insulin pumps that then work with continuous glucose monitors to regulate the blood sugars and regulate insulin delivery throughout the day.

I'll say that there's also an increasing recognition in Type 1 Diabetes of the importance of management of comorbidities. So other conditions that people have along with the diabetes. Because now that we're doing better with management of blood [00:08:00] sugars over time we're realizing that people with diabetes are not experiencing significant comp as significant complications.

Some of those microvascular complications early in life. Like when I started, we had kids with eye disease and kids with kidney disease and we don't really see that as much anymore because we can do better with the blood sugar management. And we're realizing more the importance of managing blood pressure and other aspects of overall health for people with diabetes.

Aaron Carroll: Given that you're both pediatricians, how often does this start in childhood?

Emily Sims: It kind of was classically known as juvenile onset diabetes, right. So it, it definitely is more. Common as, as pres as presenting as a childhood illness. But it can, it can happen in adults too, and it's actually really underappreciated in adults.

I think a lot of times they get misdiagnosed as Type 2 Diabetes because people think, oh, it's an adult they have Type 2 Diabetes, right? And so a lot of times people go for a while with a misdiagnosis when they actually have Type 1 Diabetes, when they're an adult [00:09:00] that gets diagnosed with New diabetes.

Aaron Carroll: I know we're gonna focus on Type One, but what, what is Type Two? How is different?

Emily Sims: Yeah, so Type 2 Diabetes: the idea is that you kind of, I like to think of it as people kind of inherit a beta cell that's maybe like a little bit sensitive or kind of a little bit puny and you're kind of doing okay until your body encounters some, some reason that the insulin doesn't work as well in your bo in your body.

So for example, If you gain a lot of weight people usually get really resistant to insulin, so the insulin doesn't work as well in your body, and so your pancreas has to make a lot more insulin to kind of deal with that. And so in the situation where you kind of have inherited these beta cells that kind of can't really compensate that well, then they kind of poop out or don't work as well with Type 2 Diabetes.

And so you have a kind of relative insulin sufficiency relative to the amount of insulin that your body needs.

Aaron Carroll: I know you're both involved in a lot of research that has to do with diabetes. Can I get you to talk about some of the studies that you'd been involved in recently that you're most excited about?

Linda DiMeglio: So I would say that the core of a lot of what we do is [00:10:00] through a research network called Type 1 Diabetes TrialNet. And TrialNet focuses on trying to cure Type 1 Diabetes by enrolling people that are at risk of diabetes and based upon the fact that they have family members who have Type 1 Diabetes into research trials.

And sometimes in informing the prevention trials that we would do in relatives are at risk trial that also engages in trials in people that don't have relatives with diabetes. But were recently diagnosed and currently within TrialNet we are testing a variety of different approaches in people at, at risk and people recently diagnosed to try to preserve beta cell mass and therefore preserve insulin production over time.

And ultimately we would like to target the processes that lead to autoimmunity and that lead to people developing diabetes.

Aaron Carroll: Are you, so you're trying to prevent it? Is that what you're talking about? [00:11:00]

Linda DiMeglio: Yeah, the goal is to cure Type 1 Diabetes. I think when I started in diabetes research a quarter century ago now I think the hope was that we would have a single cure for Type 1 Diabetes.

And I think over time through studies such as TrialNet, we realized that Type 1 Diabetes, the load has an. Single endpoint in high blood sugars and, and insulin requirement, it's actually a disease that is multifaceted. And the reasons why people

develop diabetes probably differ between individuals who develop disease even within the same family.

And that over time as people are developing diabetes, the reasons for kind of propagating the problem and developing symptomatic disease probably change. And so it's come to a point now where people are not talking about a single cure for Type 1 Diabetes, but more like cures for diabetes. I think of it a lot as a kid of the 1970s.

I grew up during seventies when Nixon was waging his war in cancer. And the plan was we would've cured cancer by the end of the 1970s. And, and we realized that cancer was not a [00:12:00] single disease, it was multiple diseases, and we've cured some cancers and we've not done well with others. And I think it'll be similar for diabetes, where we need to really tailor therapies to individuals and to what's going on in individual more than have a, like a one size fits all.

That said we've had some successes in what we've tried with different approaches including one of the things that I, Emily is much more expert on than I am at this point because she's done a lot of the data analysis, but in the, using a drug called Teplizumab of that just got FDA approval last year for prevention of type one.

Emily Sims: I think one kind of key kind of paradigm shift that the field is thinking about is this idea of heterogeneity disease that Linda touched on. But another thing is this idea of, of applying disease modifying therapies to Type 1 Diabetes, you know, for forever. The treatment for Type 1 Diabetes has been insulin.

Right. And you know, insulin is great. Like we've had these amazing, amazing advances in the kinds of insulins we have, the technologies that we use to deliver insulin [00:13:00] and to monitor insulin, but it's kind of a bandaid to treat the kind of eventual symptoms of Type 1 Diabetes and even with all of these kind of crazy amazing advances we have, we're still kind of not achieving what we want to.

People are still not meeting glycemic targets. And then especially I think people will appreciate, who don't have a pe a connection to people with Type 1 Diabetes. Like what a mental burden this disease is. Every day you're having to check your blood sugar, you know, before you do anything, you're having to anticipate like what that last dose of insulin that you gave is gonna.

Do, you know, hours down the road, like you can't just kind of go out for a run if you wanna go for a run, right? You've gotta think about like, what's gonna happen with your blood sugar and, and how it's gonna affect your insulin. So really like our goal is to kind of think about the underlying pathophysiology of what's happening and how we can apply new treatments to, to target that so that we can either reduce or, you know, obviate the need for insulin long term is kind of what these different therapies are offering.

Aaron Carroll: I have a number of follow up questions. So in, in no particular order, first , I'm always fascinated when people, when people used to talk about we're

gonna find a [00:14:00] cure, because in my head I always used to be like, are they talking about bringing the beta cells back to life? Because what else is there?

You know, other, how else were we going to cure diabetes? Were, was there some thinking that I'm missing?

Emily Sims: Well, I was just gonna say a, a big, kind of, another big shift in the way that our field has been thinking about Type 1 Diabetes is based on birth cohort data. Now, we know that once people kind of develop multiple autoantibodies, which are markers of eyelid autoimmunity that reflect they don't actually cause disease, but they reflect that eyelid autoimmune is there.

So now we know that once you have. More than one of those, your lifetime risk of developing Type 1 Diabetes approaches a hundred percent. The kind of rates of progression are different, but we know your risk is very, very high once you have at least two of those eyelid auto antibodies. And so now the, the field has kind of adopted this staging system of Type 1 Diabetes.

So what we used to call the onset of Type 1 Diabetes is now stage three disease. And we call stage one disease if you have [00:15:00] multiple of those eyelid auto antibodies present. And then stage two disease is when you kind of start having blood sugar changes, but you don't meet that official criteria.

And so I think a lot of people are really optimistic that, you know, by, by targeting people earlier on in the process, if you can kind of shut down that autoimmune process early on, then you don't have to go so far as to regenerating beta cells. Right? And you can protect them before they're already gone.

Linda DiMeglio: And lemme just add one other thing there because interesting because when you asked the question, I thought about the other side of diabetes. So the other side of diabetes is people with long-standing disease and the other part that's been a paradigm shift is we now know that people with long-standing diabetes continue to have beta cells and they're continuing to make new beta cells.

Or the beta cells are redifferentiating, there's a lot of kind of debate as to why those are there, but, so it is also possible in somebody with long-standing disease, if you could really stop the process, you might be able to re regain a little bit of insulin production or some insulin production, so that, that also has been a change.

Because we didn't, we didn't realize that for a long time either.

Aaron Carroll: So could you then try to, [00:16:00] you know, give them immunosuppressants and try to, to see if you could hold down the autoimmune aspects while they try to rebuild their beta cells? Or does that not work?

Linda DiMeglio: I'd be curious to hear what Emily says in the space as well.

I don't think there'll be a huge amount of beta cell mass there. So more of the focus has been on, I mean, we also do eyelet cell replacement now in some trials. We have not been part of those at IU per se, but people are doing that. But I think if you could stop the continual, like killing of those beta cells as they are differentiating those cells are differentiating in beta cells or those beta cells, you could at least probably take the edge off of some of the high and low blood sugars that are experienced with people with longstanding diabetes. So that's also just a different approach.

I don't, they, we now have data from pancreas of people who have donated their pancreases at death for and been those, those pancreas are looked at and we now find that those people still have some beta cells that are left.

So it's not it. It's not like it's all extinguished and it's all gone.

Aaron Carroll: [00:17:00] So but Emily was mentioning that, you know, now we're, we can try to pick up people in stage one and stage two, but how do we do that? I mean, unless we're sort of screening everyone all the time for those auto antibodies or you know, for even mild changes in glucose, how, how do you get people in stage one or two?

Because, you know, in the, in, in the day, everybody obviously was picked up in stage three.

Linda DiMeglio: Firstly, we do it through studies like Type 1 Diabetes TrialNetwork. We screen relatives to people that are Type 1 Diabetes. We've screened over 200,000 relatives during the time that that network has been in place, which has been about 20 years.

We also now are engaged in efforts that are reaching out to general population screening in the United States. States and elsewhere. So through the Juvenile Diabetes Research Foundation, people can go online and order a kit and get antibody screened regardless of family history. There are also a number of places where people have enrolled birth cohorts, so people have also screened birth cohorts based upon HLA, which is part [00:18:00] of the genetic makeup that predisposes people to autoimmunity and then followed those people forward as well.

So a lot of that has been general population people. I think ultimately as we have therapies that can potentially prevent Type 1 Diabetes population. This screening for Type 1 will be something that will be incorporated maybe into part of general pediatric screening. Maybe at age like five when kids get a lead level, they would also get a antibody screen or something like that.

We're, we're a little ways away from being able to do that. But one of the first steps was being able to have some therapies in our, in our armamentarium that would allow us to change the course of the disease.

Emily Sims: We've known for a really long time that if you kind of identify people really early at these early stages of disease before they kind of meet the diagnostic criteria for stage three diabetes, that if you watch them and educate them about signs and symptoms, you can prevent diabetic ketoacidosis or DK at onset.

So that was a really important benefit, [00:19:00] but kind of, we really needed something else to kind of justify wider spread screening. And so I think that now that we have. Therapies that are potentially available to intervene in the disease process earlier on. There's been a, a lot of more support for this idea that we should be thinking more and more about this and type, you know, right now in most places, you can get screening if you're a family member through TrialNet, like Linda mentioned, but.

Most people who get Type 1 Diabetes don't have a family member. Most commonly you present, you have no family member. So really to impact the most people with these kinds of therapies, we're gonna have to start screening people in the general population.

Aaron Carroll: So I want, I'd, I'd love for you to clarify just that a little bit more.

So can you explain what diabetic ketoacidosis is and why we care about people not presenting with it?

Emily Sims: Yeah. So, you know, normally you use glucose for food, for fuel, for your body, right? And so if you don't have insulin, you can't use that glucose for fuel. And so your body kind of starts breaking down other things to get fuel because you're basically starving.

So you start breaking down your muscle and your fat [00:20:00] and you start making keto bodies, which increase the level of acid in your blood. And if that process is kind of unregulated, That acid level gets very high and you're really sick and you have to get admitted to the icu, get an insulin drip. And now luckily most kids end up, you know, not dying from it, but, but it can be life-threatening for sure.

And you know, and it's an ICU admission, so it's super expensive. And it's very, very stressful for patients and their families when they come in with a new diagnosis. So, you know, anything that we can do to kind of. Make it a smoother transition into the diagnosis of Type 1 Diabetes and, you know, slower education.

I think it's better for families long-term and and safer for our patients.

Linda DiMeglio: Like a PSA part of this Erin, that I'd like to add to the what Emily said because she did a beautiful description of dk. I'll say the other reason that so many children present in diabetic ketoacidosis is that Type 1 Diabetes is often not.

Recognized well by primary care docs, er docs even sometimes by family members who have [00:21:00] already have people with diabetes in their family. And so since

the symptoms of ketoacidosis can mimic gastroenteritis other types of in infectious diseases without the, without the fever or those kinds of symptoms there's been a lot of push to try to have people recognize that drinking more, urinating more.

And eventually abdominal pain, vomiting can be signs of diabetes and not necessarily attributable to other types of illness

Aaron Carroll: Before we get to medications to prevent diabetes, and I promise we're going to, can I get you to talk about you, you mentioned how there have been major advances in insulin and I, you know, it's just interesting that, you know, you're saying we're celebrating a hundred years of insulin and I think a lot of people think, well, that that's, we just use insulin.

But how has insulin therapy changed? What, what have been sort of the big things that have happened?

Emily Sims: Yeah, so initially, you know, they were kind of grinding up pancreas from animals to provide insulin for people. So it is super duper change. So now we have synthetic insulins that are nice [00:22:00] and safe, and then the, they, they can act on different time scales to kind of try to mimic the insulin that you make in your body a little bit better in the way that it works.

So that's really nice. And then a thing that's been huge in the past. Maybe five, five to 10 years has been delivery systems. So there are insulin pumps now that kind of constantly administer really small amounts of short acting insulin over time that really allow for a lot more flexibility in your lifestyle and when you eat and the amount of insulin that you're delivering.

Then an standard kind of subcutaneous injectable insulins. And now over the past few years there have been a few models of those pumps that have come out that talk to glucose sensors. So those are sensors that you wear that are kind of continuously measuring the, the sugar in your kind of subcutaneous tissue, which mirrors what it is in your in your blood, and it kind of communicates with the pump and they talk to each other.

The pump kind of sees what the blood sugar is doing and it adjusts the insulin in the background so that if your blood [00:23:00] sugar is dropping, dropping, dropping, the pump can kind of pull back on the amount of insulin that it's giving you.

Or if it notices that, geez, this person is really climbing in their blood sugar, it can increase the insulin and allow for kind of tighter control of your blood sugar. So they're not perfect yet. They kind of can't really. Cover what you eat unless you give them pretty accurate information still.

And it's, it's still, they're still not perfect, but they really, they're very nice. I think, and, and it's been a big improvement for a lot of people's quality of life,

Aaron Carroll: Given that the body, you know, pancreas doesn't know what you eat normally, and it just has to sort of, I guess, detect glucose levels and respond accordingly, it feels like.

At some point we could get, I won't, I mean I maybe won't call it artificial pancreas, but it sounds like we could get to the point where the, if the sensor is, is, is sensitive enough that it could, you know, talk to the, the pump in a way that would almost deliver normal glucose levels all the time. Or normal, you know, insulin levels are, is that, is that what people are shooting for and if so, like are we like getting near [00:24:00] there?

Linda DiMeglio: We have those devices that do exactly what you said the. Problem, so to speak, is that people live lives and it's the matter of giving the algorithm or giving the computer within the system all the information that's needed. So the pump can know what your blood sugar is and it can know what your insulin delivery is, and it can match those.

And actually, overnight, these systems do amazingly well when people are asleep and there's nothing else going on. But once you go to eat or exercise or get sick or anything else especially if you change your activity pattern in some way. The pumps are not that smart. They're also not that smart for women to account for things like increased insulin resistance during menstrual cycles or things like that as well.

And so there's been a lot of ways of looking at trying to optimize around that. But right now it still requires that these systems still require the user to. Talk to it on occasion and say, well, I'm eating, and then figure out about how much eating, how much they're eating, and how much that'll affect the system.

I'm gonna [00:25:00] exercise, I'm gonna be in the car all day and I, I'm not gonna be as active as normal. But they're getting better and I think they, some of the systems are actually getting much more simple, which is important because otherwise we're asking people with diabetes to do an incredible amount of thinking about the diabetes.

The, estimate is that the average person with diabetes makes over 500 more decisions a day than somebody without diabetes. So that's, that's a lot of burden on a day by day basis, and that's part of why we're passionate about doing research to try to reduce that burden for people living with the disease.

Aaron Carroll: Well, let's talk about some of that research and, and you brought up more than once, Teplizumab, so could, could one of you talk about what that is? What the studies that you were conducting, how were they done and, and what did we learn?

Emily Sims: Yeah, I can talk about it. So that Teplizumab is it's a monoclonal antibody to CD three, which is a molecule on the surface of T-cells.

And so the idea with this drug is that you give it, you deplete a person's T-cells temporarily, and then they come back. And so the hope [00:26:00] is, you know, the kind of bad T-cells go away and then, T-cells that aren't autoreactive to your beta cells are the ones that recover. And so there have been multiple studies using this drug after people got Type 1 Diabetes and it showed an improvement to kind of preserve their loss of their own insulin secretion over time compared to placebo.

But the kind of. Really exciting study that's gotten everybody in our field, you know, super, super pumped in the past few years was this prevention study that actually the Type 1 Diabetes trial not implemented. But what they did was they, they treated individuals who are at risk for disease.

So they met stage two criteria. So they had multiple eyelid auto antibodies and they were starting to have blood sugar changes, but they kind of didn't meet those diabetes criteria yet. And they treated them with a two week course of this drug and then followed them over time. And compared to placebo they had about a 32 and a half month delay in the onset of diabetes.

Yeah. So, you know, pretty significant, almost three years. You know, you think about like a kid who's about to get diabetes and, and need to take insulin and, [00:27:00] and not having to take insulin for three years. I mean, I think that's, For a one time course of drug, a pretty, you know, significant improvement in quality of life and disease burden.

So everyone was really excited. And so what's the next step? Yeah, I think it's just the beginning, even though it was a super exciting result. So actually there was the, the company that's marketing this drug was able to get FDA approval in November. So this was the first ever F d A approved disease modifying therapy for Type 1 Diabetes.

Delay. So, so that was huge. Big landmark step. But then kind of there are many, many more questions coming up. So one thing Linda mentioned was this kind of heterogene and disease. So, you know, is it, are there other mechanisms we can target? So there are lots of other types of drugs we're testing.

You know, could it be that, A combination that targeting multiple mechanisms of disease would be more effective than just one drug. Could it be that we need to do multiple courses of treatment instead of this kind of just one time course? And then we also don't know kind of when, when the best timing for treatment is either.

So I think there are still a lot of remaining questions to test and lots of [00:28:00] work for us to do.

Linda DiMeglio: We're just finishing another trial too, using the same drug in a new onset population. And that one did involve retreating people while either at six or 12 months. So initially the plan was to retreat everybody.

After six months. But then because of the Covid pandemic and the the re the fact that this drug can cause some immune suppression, we actually ended up extending and allowing people to at, at times we retreat at 12 months. So it'll actually be interesting to look at what happens in that trial, and those data should start to report out likely in the fall of this year.

Aaron Carroll: What are some other areas of research that you're excited about?

Emily Sims: Yeah, so my lab actually kind of covers the gamut from kind of very, very basic to translational to clinical research, but our kind of lab mantra is that the beta cell is also really important in Type 1 Diabetes. So, you know, everybody thinks about the immune system, which makes sense because it's an autoimmune disease, but you know, the, the beta cell itself maybe isn't an innocent bystander.

Maybe there are ways that it's also kind of contributing. So for example, [00:29:00] like in Type 2 Diabetes, if you kind of inherit a. A, a beta cell with like a predisposition to being a little bit sensitive under autoimmune attack, it might die sooner or, you know, not work as well sooner. And so we've really been interested in developing biomarkers of beta cell stress and function to kind of help predict Type 1 Diabetes and the way that different immunotherapies are working.

But also developing new drugs that target beta cell stress. And so actually Linda and I are heading a trial now. That kind of started as a, a preclinical study at iu. It's like a very bench to bedside story, so it's really cool. I think in, in Ragu mi mirror's lab actually where they were kind of studying the impact of this drug to target beta cell stress and preclinical models of Type 1 Diabetes.

And Linda did a safety study. Showing that it was kind of safe and well tolerated in people around the time of type one onset. And we kind of had an early signal in this kind of very small safety study that it seemed like it helped improve their C peptide compared [00:30:00] to placebo. And, and c peptide is a marker of your endogenous insulin secretion.

So now we're kind of expanding that to full like six center study that IU is leading. And I think it has a really great acronym, which is tadoo. That might be the thing I'm the most excited about with the trial. We have a really cute study logo too. But and it's it's an oral drug that's kind of been studied in, in other indications.

It's, it's pretty safe, but it it's been used for cancer prevention including down to like toddlers to prevent neuroblastoma recurrence. And so the safety profile is pretty well known and it's kind of neat because it has a kind of different mechanism of action than. Than some other drugs. So I think it'll be really fun to see kind of how it plays out and, and again, I think it just is reflective of the great stuff that IU does, you know, kind of working from bench to bedside, like translational to clinical and, and the stuff that we're doing in our diabetes center.

Aaron Carroll: So how do you get people to enroll in these studies?

Emily Sims: Yeah, I think it really helps that we have a really active clinical diabetes program. So, you know this trial [00:31:00] is targeting people who were recently diagnosed not people who are antibody positive. Those are. Those people are hard to identify, as you mentioned.

You know, it's, you gotta go through the screen lots and lots of people to, to find people. So we're starting with people who are recently diagnosed and so we have tons and tons of kids coming through Riley, you know, with new diagnoses of Type 1 Diabetes. And so when people are interested in research we talk to them, you know, kind of explain risk and benefits and.

See if they wanna participate and we've had a lot of luck that way.

Aaron Carroll: Are there any other studies that you're excited about that we should, we should chat about before we go?

Linda DiMeglio: So I'd say that another study that I'm excited about that we just finished and was just published was another Test of two ways to potentially improve beta cell function and preserve c peptide production after diagnosis.

The study was a really interesting study designed to me because it involved two studies in one, so it was a nested study. The first study was testing a question as to whether or not [00:32:00] I'm really, really. Tight blood sugar control shortly after diagnosis would help the beta cells kind of stay in a recovery phase, do better over time, and whether it could improve insulin production by those beta cells a year out.

And sadly, even though across six centers, we used those devices we spoke about earlier, which were these closed loop systems where the insulin is delivered based upon the c the continuous glucose monitor, and we were available to study patients. 24 hours a day, seven days a week. We were able to get the time and range, which is a time in blood sugars between 70 and 180, which is what's considered optimal to be about 80% across the study.

We did not see a difference in C peptide. Within in within that study was a slightly smaller study because we were using the drug rabil, which is a blood pressure medicine and repurposing an existing drug. And the drug only came in a tablet size. That could be not, could, could not be used in the very [00:33:00] youngest children.

But it, so there was a a nested study in there looking at the effect of rol and. Rap is also a beta cell agent. It had been tested previously in adults. It reduces beta cell stress and in this small adult study it was found to potentially preserve C peptides. So the Juvenile Diabetes Research Foundation that funded the study was very, very interested in trying Verapamil in a larger trial.

And in that study we were successful with the Verapamil and at a year. Out from we treated capable for Appel for six months, and about at a year out, they were still

making 30% more insulin than the group that did not get appol. And that's really interesting because Appel one is super, super cheap.

So anybody can take it. Our safety profile with the Appel looked good. But also it, it speaks to this idea that the beta cell really does matter and it's a drug that could readily be used in combination. So we didn't cure. Diabetes with [00:34:00] ail, but we made an impact. And I think part of the future is thinking about doing things in combination.

So in that trial we did, you know, we did tight glucose management along with ail. In the future you could, you know, potentially use Combinations of therapies that may just like, again, going back to that analogy around cancer, where you you don't treat cancers in general with a single drug and then you just watch people, you treat them, you look for a biomarker, you retreat, you look for the next biomarker.

There's this is the disease evolves. You're changing your strategies. And I think that's ultimately where we need to get. And I think some of these studies are starting to pave the way for that.

Emily Sims: Yeah, for Verapamil, really interesting. I think like we don't totally understand. I think exactly how it's working.

The preclinical data kind of pointed to it, working through the beta cell and preventing beta cell death, but. There are also some signals in that smaller study Linda mentioned that maybe it's affecting immune cells too. So I use in charge of the mechanistic studies for the, [00:35:00] the clever trial that she mentioned.

So I think it'll be really neat to, to kind of work on that and understand how, what's going on there better. Because it was a total surprise, I think to everyone that that trial was a positive study. The first one. Yeah.

Aaron Carroll: Well, I mean, it's, it's heartening to hear how many different things are going on and you know, how much improvement.

It continues to happen and I, I hope as, as you get more results and you keep doing this work, you'll come back and talk to us and tell us all about it.

Emily Sims: Yes. It's been so much fun. We appreciate the invitation

Aaron Carroll: Once again this Healthcare Triage podcast was co-sponsored by Indiana University School of Medicine, whose mission is to advance health in the state of Indiana and beyond by promoting innovation and excellence in education, research and patient care, and the Indiana Clinical and Translational Sciences Institute.

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