Discussing Nobel Prize winning peripheral immune tolerance research with Dr. Troy Torgerson

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Welcome to the Immune Deficiency Foundation podcast. On this special episode, Katherine Lontok, the Foundation's Director of Science and Policy Communications. Speaks with doctor Troy Torgerson, director of experimental immunology at Allen Institute for Immunology, an immune deficiency foundation medical advisory committee member about the recent Nobel Prize winning research by Mary Brunkow, Fred Ramsdell and Shimon Sakaguchi. Their research, which made groundbreaking discoveries related to peripheral immune tolerance, could lead to improvements in treatment for primary immunodeficiencies such as IPEX.
Let's get started.

Katherine Lontok: The twenty twenty five Nobel Prize in Physiology and Medicine went to three people: Doctors Shimon Sakaguchi, Mary Brunkow, and Fred Ramsdell. Can you describe what they discovered and why it's Nobel Prize worthy?

Dr. Torgerson: Yeah, so Shimon has a long history studying regulatory T cells and had studied his lab had studied these cells for a long time, even back when I was in graduate school, he had he had generated some data that suggested that there were there were regulatory T cells that sort of helped keep things that be in the immune system, but they they were very complicated experiments and they they couldn't they were difficult to reproduce. And so for a while, regulatory t cells were sort of, like, out of out of vogue. If you put Mhmm. If you put that name in a grant application, it pretty much guaranteed that you wouldn't get that grant application. Right?
Sort of as I was finishing Correct. Finishing my graduate school training. So then a few years later, the Fred and Mary were working at a biotech company here in Seattle.

Katherine Lontok: Mhmm.

Dr. Torgerson: And they were going after, you know, new drug targets, and they had got been looking at, you know, models that could help them learn about new new genetic defects that might help them steer in particular directions. And They knew about this scurfy mouse model that was a a spontaneous mutant in the non irradiated colony at Oak Ridge National Laboratories. So

Katherine Lontok: And we'll get back to that later. Could I have a question about that as well?

Dr. Torgerson: And that mouse that mouse arose spontaneously and developed this severe autoimmune phenotype. And and the mouse was was discovered in, like, nineteen fifty nine or something like that a long time ago. And and what would happen is they would be born. And then over the course of about three weeks, they would develop this severe diarrhea they would sort of undergo a wasting of their, you know, they're just a lost weight. And then, ultimately, they developed skin disease that looked sort of not exactly how they got to scurfy from scruffy, but it looks like they're they they get looking pretty scruffy when when they develop skin disease and it's it's sort of what really bad mouse eczema or kind of psoriasis might look like a little bit.
And that they were called the scurfy mice and the line was kept alive at Oak Ridge National Labs for all his years. And so they got this mouse and went and went hunting the gene that caused the defect. Using traditional cloning approaches. And they found that, and it turned out to be fox p three. And there's a sort of a long or sort of a bit of a backstory there, but the in the same tape in the same issue of the journal in which they published this new male this new gene that causes severe autoimmunity and mice they then Dr Ochs, Hans Ochs, who many of you know, and had had a paper with some collaborators here in Seattle.
And then there was a guy who had been here in Seattle a pathology resident and had gone on to to a new job in Oregon and had had some tissues that he had sort of gathered while he was a pathology resident here. And they published back to back paper saying that this was the gene that caused IPEX syndrome. And so that's the back story. The story doesn't kind of come to full sort of the impact of the story doesn't really come to full. Completion, though, until about two to three years later, when a person from [Shimon's] lab here in Seattle, showed that when you knock out when you basically remove the FOX P3 gene from a mouse, they don't develop regulatory T cells.
And that was the real sort of closing the loop of what why this was important is because it it again, it it now gave us tools to identify these potent regulatory cells that really keep the immune system in check. After it's gone through its developmental processes. And that has led to a number of discoveries, therapies that are in the market and things like that. So that's the significance. It really opened up you know, again, like I said, they were really out of vogue for a while because those experiments were hard to reproduce, but now this gave them a handle, a specific handle that they could say, we know that cells expressing this protein are probably regulatory t cells, and so they could be studied now in-depth.
And that was really the the what the award was for.

Katherine Lontok: For. So can you explain a regulatory t cells? How are they different from cytotoxic killer t cells. What

Dr. Torgerson: are what are t cells to that?

Katherine Lontok: Yeah. Exactly. You can help with t cells.

Dr. Torgerson: So when you get an immune response to something, you initiate that response, and it's sort of like stepping on an accelerator. You know, if you're if you're at a if you're at a stop sign and you green light goes, you step on that accelerate to accelerate to get to the next stoplight. But but the in in the case of an immune risk response. There's an initial sort of acceleration phase like that. So say, a bacteria is, you know, you get bacteria in your blood or wherever and you get this initial immune response.
And shortly after that immune response happens, we know that the immune system has a number of regulatory responses that kick in to make it so that that initial accelerator response doesn't overshoot. This is, like, again, driving down the road towards the next stop sign. You see it turns yellow. What do you do? Well, you ease off the accelerator.
You start to tap the brake a little bit. Mhmm. And then, ultimately, you stop. And that's what the regulatory cells do. And there's now really evolving out of this is identification of a number of regulatory mechanisms in many different cell types that act as these regulators and it makes it so that for instance, if you make an immune response to, say, the SARS CoV-two virus, the COVID virus that you don't, you know, during the pandemic, there were people who would sort of overshoot that response and have what we called cytokine storm, they'd get super sick, and they got they were getting super sick really because of overreaction of the immune system to that virus, either that they their immune system was too twitchy or that they that they didn't have enough regulators regulatory responses to keep that response in check.
So the ideally, what should happen is you should respond and then shortly after you you picking these regulators and that sort of slows everything down, stops it, and then you clear out during a resolution phase, you clear all of the junk that was in your tissues and all the other place, you have to clear all of that all of that immune stuff, the leftover immune cells and cytokines out of the tissues. And so so these regulatory T cells are in that, and I I joke a little bit that they, you know, regulatory T cells are sort of like the psychologists, you know, therapists of the immune system, they sort of tell these other cells like the the CD4 helper T cells and the CD8 cytotoxic T cells, they tell them, hey, you did a great job fighting off that infection last week, but, you know, it's gone now. Take it easy, cool off, go to the spleen, hang out, meet some nice cells down there. You know, so so that's sort of their role. And they play a role in maintaining just the steady state of our immune system at baseline and then helping to not let it overshoot.

Katherine Lontok: Got you. So you mentioned IPEX syndrome. What's the relationship then between ipecs and this whole story of tregs and FOX p three? We got a

Dr. Torgerson: So so a little bit. So patients with IPEC syndrome have mutations in the FOX P3 gene. And as a result, they don't make they don't generate a normal number of functional regulatory T cells. So I think of it a little bit like having an immune system with, like, eighty percent of your brake power or or brake power is gone. You know, you now got twenty percent maybe re remaining.
And so now, you know, you just you you hit the accelerator to respond to, say, an infection. And, you know, but your brakes are done working so so hot. They're very soft and you just blow right through the next the next intersection because you you couldn't stop. You know? And that's Mhmm.
That's sort of what happens in IPEX is that they've got a a lack of of these regulators that And so, again, it's an immune system with no breaks, and so they get severe early onset autoimmune disease as a result. And that's because their immune system can't even even to just non non infectious stuff, it can't keep be kept quiet. It's like always, you know, sort of going out of control, and it's going out of control, not just to sometimes pathogens, but it's going out of control to just yourself, you know,

Katherine Lontok: Mhmm. Yeah. So I've heard the Tregs sort of referred to as a peripheral immune tolerance.

Dr. Torgerson: Yeah.

Katherine Lontok: Can you explain that term a little bit?

Dr. Torgerson: Yeah. So we to to so we sort of we ask the immune system to do this kind of really insanely impossible thing, which is it's given the mandate that it has to be able to respond to absolutely any infection that could ever be imagined. Right? You want it to be Mhmm. You want it to be, you know, widely diverse, diverse enough that it can respond to anything.
But we say, oh, by the way, that you have to do that. But you can't respond to me. Right? You can't respond to self. And it's sort of kind of a counterintuitive.
You think, wait a minute. We want it to respond to everything, but now it can't respond to no. Wait. It doesn't make sense. So So the way that that works is that there's this very intricate ways that the immune system as it's developing goes through the sort of sort of the thinning to get rid of those cells that respond to us.
And that's called central tolerance for the t cells. Most of that happens in the thymus before they before they get out. And any cells that are strongly auto reactive will be told to die in the thymus, so they don't escape in risk auto reactivity.

Katherine Lontok: Right.

Dr. Torgerson: And so for the B cells that happens in the bone marrow and then later in the spleen, But with the t cells, they get selected to select out the good ones that we want that respond to bad things, but to get rid of the bad ones that are responding to strongly to us. But even with all of that happening, there will be some auto reactive cells or cells with an auto reactive tendency that sneak out of the thymus. They don't get they don't get clipped off in the thymus, and so they go out into the periphery. And you know, there's a couple of places where even in health, our immune system is constantly being poked and agitated. And that's where we tend to see the the first problems arise in people who have regulatory t cell problem.
So in ipecs, and those two areas are the gut, which is, of course, filled with bacteria. And so constantly exposed to these bacterial products that are activating the immune system, and the skin where again, constantly bathe in external bacteria, you know, that are on the skin that want to, you know, they're they're it's it's important for development of our immune system, but it's also if that if if you don't have a way to calm down those just normal immune responses at the skin and gut. Then what happens is the immune system, again, no breaks, sort of takes off. And that's what happens in the absence of regulatory t cells. And that's that's what is what we consider peripheral immune tolerance.
So the central immune tolerance takes care of, you know, the really bad actors. The peripheral immune tolerance just keeps everybody that made it out of the thymus in check. Gotcha. K?

Katherine Lontok: And and so that's using that analogy. You know, you you could imagine that if Tregs were sort of equally important everywhere in terms of the exposure of the immune system to these constant insults that you would actually see in IPEX just so much autoimmunity all over the place. But that's really interesting because that explanation sort of clarifies why it's the gut and the and the skin and the particular autoimmunities that you see. With eye packs. That's really interesting.
Yeah.

Dr. Torgerson: And and eye packs patients can get autoimmunity kind of all over the places that are there are some organs that are preferential, but gut and skin are by far and away the most common manifestations of eye packs initially. The other place that they that regulatory t cells play a really important role is in the lymph node where the t cells and the b cells are talking to one another to get those b cells fully activated and going there are regulatory T cells that live in the lymph node that help to regulate that process as well. And so in IPEX patients, for instance, they develop a lot of auto antibodies, we assume it's because that the absence of functional regulatory cells within the lymph nodes themselves, which are, you know, I think that the lymph nodes is sort of the singles bar of the immune system. That's where t cells and t cells go to kind of get together, you know,

and and do their job. And so but if you're not regulating that process, then that can also get out of control and lead to the development of autoimmunity.

Katherine Lontok: Okay. Very interesting.

Dr. Torgerson: Antibody production. Yeah.

Katherine Lontok: Yeah. Yeah. So I'm gonna switch gears a little bit and head back to the mouse, the mouse line. And you mentioned that it came out of Oak Ridge Laboratories, which is where the Manhattan project was located. So in researching the history of all of this, it was really interesting to see that sort of weird random path, I guess. Can you can you talk a little bit about how this connection with the Manhattan project how that happened? And and your thoughts about how research can lead to, you know, unrelated, unexpected developments?

Dr. Torgerson: Yeah. I so I I actually don't know fully I mean, what I do know is that they had a number of you know, they were looking at the effects of radiation on mice as part of the Manhattan project. I I'm it's a little bit dubious to me that they that this mutant arose out of the non irradiated colony because you wonder really how much of Oak Ridge was really non expansion or some degree of irradiation. Was that correct? Or was it just the was it just the less radiation

Katherine Lontok: the right

Dr. Torgerson: part of the gut quality. You know, I think, you know, that the thing about radiation is that radiation causes double stranded breaks in the DNA. And when that gets repaired, oftentimes there are mutations created at the sites. And it's just random, you know, where it happens to break. And that's, you know, that's why these things happen there.
Some people, you know, some scientists have used radiation or chemotherapy type drugs to to actually create mutations purposefully in a mouse colony for instance to see of those mutations that arise how many of them affecting the immune system. So there are a number of programs that have been done to do that. I think what's amazing, again, you know, you think about this mouse arising spontaneously, supposedly in at at Oak Ridge National Labs in, I think, nineteen fifty nine, that's when the original paper came out somewhere in there. And it really wasn't until two thousand one. So forty years later, that really that that that that mouse now becomes the key to understanding a huge, you know, a big section of immunology.
And it's often the way that science works is that, you know, we there are discoveries made oftentimes kind of kind of by chance. They study those as far as they have technology to study them, but can't figure it all out at that time point. Mhmm. And you know, curious

scientists digging back through the historical literature find this interesting model and say, well, wait a minute. That's that's really curious.
Why is that happening? I wanna figure out why that's happening. They then bring it in and they re study that. But now with a new set of tools that allow you to study that mouse more deeply and and and more mechanistically and that leads to these new discoveries that really change how things happen. It's there there are many, many examples of this where a discovery, you know, sometimes many decades before ends up being the you know, with it with a well described result ends up being the key piece to allow now with new tools the ability to make really key discoveries.
And it's just sometimes the way that science is done and it's you know, just to make a plug for for science and and the the importance of doing this, I think, you know, it it sort of does show the danger of not you know, sometimes we think, well, why are they studying fruit flies? Or why are they, you know, where are they studying, you know, mice or heaven's sakes? Or, you know, something else. But sometimes that's that was the critical breakthrough that led to them that being able to study that in more detail in the future. So I'm not I'm not so quick to discount some of that really kind of basic work that's done sometimes even in models that seem like they wouldn't be relevant.
And the importance of keeping that, you know, keeping that running because what it what will happen if we don't do that is that it will slow the pace of discoveries in the future. We may not see it in the next twenty, thirty years, but we will see it. It's going to come back to revisit us. In probably not so good ways in the future.

Katherine Lontok: So can you talk about – so we've talked about IPEX a bit. Are there other PIs that are affected where where the Tregs are affected either they don't work or there aren't enough of them?

Dr. Torgerson: There are a number of them. So I think about like CTLA-four haploinsufficiency, which is usually presents in patients who have antibody deficiency a lot of times, but they also get a fair bit of autoimmunity and immune dysregulation. And regulatory CTLA-four is a molecule that is expressed highly on regulatory T cells, and it's one of the tools that regular the CTLA-four is one of the tools that regulatory T cells use to turn down the immune response to it's CTLA-four – those regular – that sort of regulatory response that follows the activation. CTLA-four is another one of the regulators that is in that group. That is expressed highly on regulatory T cells, it's expressed on some other highly activated cells to begin to put the brakes on an immune response and slow it down. And so CTLA-four half one's efficiency for example is one of those. The stat one, stat three gain of function disorders, those have regulatory T cell issues. There are, I mean, can rattle them off, but there there are a number of PIs that have defects. Maybe the maybe it doesn't

cause a complete loss of regulatory T cells, but it causes a decrease in their function or a decrease in their number that allows the immune system to just outpace the regulators.

Katherine Lontok: Gotcha. Okay. So as much as we would all love the Nobel committee to honor our particular fields and our little niche things that we like to to study, they generally give it to transformational work. Right? So, obviously, this work in on regulatory T cells goes beyond the field of PI.
Can you talk a little bit about how those discoveries have impacted other fields?

Dr. Torgerson: Yes, for sure. So we know, so we've learned a lot about the role of regulatory T cells in cancer for instance. And while they're great in the setting of an infection, they're not so great in the setting of cancer because the cancer cancer is a very tricky beast. There are a set of very tricky beasts. What they'll do is they will trick the regulatory T cells to come into the cancer and hang out in that microenvironment so that they're, again, they're they're sitting in there and so the rest of the immune cells want to come in and attack that cancer, but oh hey, there's regulatory T cells there and they're telling me I should cool off and not be so activated.
And so it's one way that it's one way that the cancer tricks the immune system and creates sort of an immune shield for itself from the activator parts of the immune system is that it sort of recruits regulatory T cells to its side so that they can now say, no, everything's Nothing to see over here. Don't worry about it. You know, we we you know, it's it's okay. Don't worry about it. And so it's played a big role in cancer biology because the whole, you know, I think after learning about regulatory t cells, we learned about all these checkpoint molecules that are other way other other types of breaks that helps, you know, regulatory breaks that slow the immune system down, but they all to to make it all work to they all kind of have to be present and working together.

Katherine Lontok: Mhmm.

Dr. Torgerson: So after the, you know, after Tregs were identified, then these additional regulatory molecules were identified, some of them expressed by Tregs, and that laid the groundwork really for the the development of these checkpoint inhibitors that basically now you purposely in cancer, for instance, you take away the breaks of one of these particular one of these particular breaking molecules. You take them away by neutralizing them with a drug, with an a drug that is an antibody, and it basically unleashes the t cells to go crazy and attack the cancer. And so it's had a huge impact there. For some cancers, it's changed outcomes substantially. So that has later on, people have been working on trying to understand how can you dial the activity of a regulatory T cell up or down.
Because of course Mhmm. In the setting about immune disease, in general, you wanna dial that activity up, just tone the immune system down. In the setting of cancer, you wanna dial

that activity down. To rev up the immune system or allow the immune system to go a little crazy. And so those are certainly in autoimmunity in cancer more broadly.
Those have it's had huge impacts in those fields. The other thing that I think is exciting now and we'll have to see really how this all plays out, but there are adaptive cell therapy. So t cells. So these are these are t cells that have been engineered to do particular things, but they've they're now engineering CAR regulatory t cells. So the idea is that you could give those to someone for instance, with a terrible autoimmune disease, and you could now those that x, it's like applying, you know, much more powerful breaks to the system in an effort to try and slow down the immune response.
So It's just a handful, but it really has open you know, obviously, one discovery didn't drive all of that, but one discovery sort of led to the next discovery and the next one that drove big part of that. And the next one that drove a big part, you know, something else, so it really has been foundational for a lot of that work to take place.

Katherine Lontok: So you mentioned these CAR T regulatory cells. How close are we to any of those actually being available to patients?

Dr. Torgerson: So some of them are already starting into early phase safety trials. So So phase one is Phase one safety trials. Yeah. And just to make sure that they don't do bad things, you know, when we put them in in in numbers that are possibly beyond what we have normally. So they're getting pretty close and it's all dependent on whether or not they have the intended effect as to whether or not they make it into further clinical trials and onto actual therapeutics for disease.

Katherine Lontok: Okay. Is there any particular autoimmune condition that you think might have this sort of therapeutic before others?

Dr. Torgerson: I think that, you know, certainly probably lupus rheumatoid arthritis when you think of sort of big players The other one that I do wonder a little bit about is that there are there are new there's relatively new findings about autoantibodies causing ulcerative colitis, which is a type of inflammatory bowel disease. And it's – the data is quite convincing, and the mechanism has been looked at and is very plausible that these autoantibodies are causing the ulcerative colitis inflammation. And again, remember that I mentioned that the regulatory T cells play a role in the development of auto antibodies. And so it may be that those could play a role in that. You know, again, you think about where the regulatory T cells, the types of clinical problems you have early after regulatory T cells are gone.
You know, it's gotten skin. So I think about like diseases with strong gut and skin manifestations would be obvious places to try those.

Katherine Lontok: Mhmm.

Dr. Torgerson: So Okay. You know those cells. Anyway.

Katherine Lontok: Yeah. So what do you think are some of the biggest questions that still remain in terms of how this peripheral immune tolerance works? Or just immune tolerance in general?

Dr. Torgerson: So I think I mean, I think there's several. I think even though we've been studying once we got a handle for these regulatory T cells in FOX P3, they've been extensively studied and we still don't fully understand the program that gets turned on in the Thymus as they're developing to flip them over to becoming to deciding to spend their lives as a regulatory T cell as opposed to CD4 or CD8 effector T cell. So that remains a good question. If we could crack that nut, you know, and it would really help with our ability to be able to understand how to engineer these cells to give them as a therapeutic more readily. You know?

And it may be Right. There would be small molecules that would push more of your t cells that you could that you could take, that would push more of your t cells to become regulatory or a few maybe fewer of them, you know, based on development in the thymus. So that's one big question. I think, you know, we we understand a lot of tools that regulatory t cells use to suppress the immune responses or regulate it, but we don't understand the full set of tools. That regulatory T cells use to tone down the immune system.

We understand a fair number of them, but we don't thoroughly understand really all of the ways that a regulatory T cell can regulate. And I think that's another big question related to regulatory T cells. I think the other big question that I see in terms of immune tolerance is that there's a question as to whether if you've broken immune tolerance and you've started to make auto antibodies Mhmm. Are there any drugs who can truly that can truly reset the palate of your immune system Mhmm. To really say, you know, that in other words, can you can you actually fully restore immune tolerance or not?

Or is it a matter of, you know, that you get close, but not quite there and it's a matter of balance, you know, trying to keep that in balance. I think there's some new therapies that are showing a lot of promise in really severe autoimmune diseases where they're taking CAR T cells have been used to treat B cell or B cell cancers Mhmm. And using those and maybe those will kind of reset the system But, you know, it's not clear that they'll fully reset the system. And I think that's one really big question is, you know, is tolerance once it's broken, is it sort of elusive to see if we can actually regain tolerance really in a person or is it that you'll always be sort of out of balance and it's a matter of trying to, you know, steer things back in balance. And then I I I would say the last one would be, you know, how do we turn up and turn down the function of regulatory t cells?

Because if you if we had a way to do that very, very precisely with with therapies, boy, I'll tell you, it would give us a chance. You Where you could dial in, you know, I wanna turn it down fifty or I want to turn it up fifty percent, it would really allow you to treat cancers better. It would allow you to treat autoimmune disease better. You know, it so I think that for me, those are the four it's kind of four holy grails of this whole tolerance business that we still there there are complex problems that we still need a lot of lot of work on.

Katherine Lontok: Yes. I know. I often get the sense that people think, oh, you know, we understand the immune system all done.

Dr. Torgerson: Yeah. Oh, boy.

Katherine Lontok: Yeah. Definitely not the case. Definitely not the case. Alright. Any closing comments that you wanted to make?
Any points that I didn't touch on?

Dr. Torgerson: No. I don't think so. I think, you know, this is it's an interesting story. And and I I think some people were surprised when the Nobel Prize was awarded for it, but when you really look at the again, the Nobel Prize tends to be awarded for things that have a long term impact, and that's where you really see that's where you see the impact of this. So it's it's pretty it's pretty cool.
And the and and and the regulatory t cells are pretty cool cells.