Dr. Mariam Hanna
Hello, I'm Dr. Miriam Hanna, and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. If you ever have trouble remembering what the common immune cell types do, we just need to have a conversation. B is for the builders, making antibodies and keeping receipts on every antigen they meet.

T is for the tacticians, leading the charge with precision and purpose. NK is for the ninjas, silent, swift, and slightly scary. And Tregs, well, oh Tregs, they're the therapists of the immune system, keeping everyone calm and collected and reminding others to just breathe before they start an inflammatory argument or before it turns into an autoimmune meltdown.

Today, we're dedicating an episode to regulatory T cells, or Tregs, the cells that keep our immune system in check. And why would we do such a thing? Simple.

Today's episode was inspired by the winners of the 2025 Nobel Prize in Medicine for their historical discoveries, as we'll learn in just a bit. It's my absolute pleasure today to introduce today's guest, Dr. Viy Kim.

She is a clinical immunologist and allergist at the University Hospital for Sick Children, and associate professor in the Department of Pediatrics at the University of Toronto. She's the program director for Pediatric Clinical Immunology and Allergy Subspecialty Residency Program at the U of T, and director of the Immunology Clinic. She also chairs the SCID Disease Specific Working Group.

This is looking at severe combined immunodeficiency in our newborn screening program here in Ontario. Dr. Kim, thank you so much for agreeing to do this podcast on such short notice, and welcome to the program!

Dr. Vy Kim
Thank you so much for having me, and it's my pleasure to be here.

Dr. Mariam Hanna
Okay, so we're going to get started with the exciting news. So Tregs is really what made the news, and so that's what we're going to delve into in quite a bit of detail today. But let's just start off with summarizing what this key discovery was that was made by our Nobel Prize winners for this year.

Dr. Vy Kim
Yes, so there were three Nobel Prize winners for this year. We have Shimon Sakaguchi, in 1995, helped to discover the regulatory T cells. And what he was doing is he was working with mouse models, and with one mouse model, he was able to identify that CD4 T cells expressing

CD25 were important or essential for maintaining self-tolerance for the immune system and preventing autoimmunity.

A number of years later, we have Mary Brunkow and Fred Ramsdell, who worked with the strain of mice that was called the Scurfy strain. And these mice were known to have lots of multi-system autoimmune disease only in the male mice, and so it was thought at that time that it was some sort of X-linked recessive inheritance. And so they looked at these mice strains and were able to identify FOXP3 from these Scurfy mice, and that was on the X chromosome, and they demonstrated that mice carrying FOXP3 is what led to that Scurfy phenotype of the multi-system autoimmune disease.

And so putting those two together, they were able to demonstrate that those CD4, CD25 positive T cells that Sakaguchi had identified actually had FOXP3 or FOXP3 was really important for the development and maturation of these T cells. And these T cells were eventually named regulatory T cells.

Dr. Mariam Hanna
And there you have it, like a whole discovery of a part of the immune system, T regulatory cells, now a part of our dictionary. So why was this recognition so important for immunologists, broadly speaking, beyond the mouse models that it was demonstrated in? What did this show us then?

Dr. Vy Kim
Yeah, it's so important because I think it opened up the whole new field of immune tolerance and the recognition of peripheral tolerance. So at the time, central tolerance was known in terms of the thymus being an important player for making sure the certain T cells that were potentially self or auto-reactive were eliminated before going into the periphery. So that's the concept of central tolerance.

But they knew at the time that central tolerance wasn't sufficient, that there were still patients who were developing autoimmune or atopic disease. And so the identification of the regulatory T cells was really central for understanding peripheral tolerance. So those T cells, these regulatory T cells, are thought to be the key players or mediators of tolerance that happens outside of the thymus.

And that has a lot of implications in terms of development of autoimmune disease, development of lymphoproliferation or inflammation, and importantly for us as clinical immunologists and allergists, development of atopy, as well as identification of inborn errors of immunity that can have defects in regulatory T cells.

Dr. Mariam Hanna
So there's already like an immediate clinical implication. And we'll get into this a little bit more as we get further into this episode. But what we're hearing is the difference between centrally and

peripherally induced T cells and really highlighting that both mechanisms exist and the difference between both these mechanisms.

So how do T regulatory cells suppress the immune response? Like how does it cause more of this suppression of this immune response? Can we get into that a little bit?

Dr. Vy Kim
Yeah. So the regulatory T cells can suppress immune responses by a variety of mechanisms. They can secrete cytokines that have immunosuppressive properties, such as IO10, TGF-beta, IO25.

They can produce enzymes that actually can lead to apoptosis of the target cells, like granzyme. They have CTLA-4 on them that can interact with CD80 or CD85 on the antigen-presenting cells, which then engulfs that CD80 or CD85 from the APCs, making those antigen-presenting cells less able to activate other effector T cells. They can also sequester, in a way, IO2.

So the CD25 that's on the regulatory T cells is able to uptake that IO2 more, and so it can prevent the surrounding cells from being able to access IO2, which is an important growth factor for the other cells. And they can also suppress autoreactive B cells as well, so making them less likely to produce IgE and even potentially class-switch to making IgG4, for example.

Dr. Mariam Hanna
And again, this is interesting because immediately you can see targets for different conditions that we can target now, knowing what T regulatory cells do, and when we suppress that immune response, what potential impact that would have. Let's flip it to the context of allergy. How do T regulatory cells influence more that type 2 inflammation in IgE production and mast cells, so things that we're more familiar with talking about in the allergy side of the clinic?

Dr. Vy Kim
Yeah, so mast cells produce IL4 amongst one of their cytokines, and that can actually inhibit some regulatory T cells. So there is some thought that, again, in certain individuals who may be more prone to developing allergic diseases, maybe there's something in the way that those mast cells, with their IO4 production, inhibit some of the regulatory T cells, which can lead to, again, some more increase in autoimmunity or atopy. On the other side, we do see, again, that when Tregs don't work, we have some inborn errors of immunity, and they have given us some really great examples of allergic or autoimmune diseases deriving from that.

So again, the thought is that our T cells should be able to differentiate self from form, and one of the primary roles of the immune system is to prevent infection, but it also needs to make sure it doesn't react against itself. And those regulatory T cells, as you mentioned, like our therapists, or some people have called them peacekeepers, or security guards, sometimes I refer to them as policemen, they monitor the immune system in terms of making sure that cells aren't overreacting. And when they are overreacting, those regulatory T cells can put out some kind of

immune suppressive signals to say, calm down, let's keep the peace, let's not create any more havoc.

But also, if some of those cells are reacting against self, which again, sometimes they escape the central tolerance from the thymus and have that auto-reactive ability, or sometimes again, when those cells are encountering new antigens in the environment, which is what those kind of peripherally or induced Tregs are thought to monitor, they should be able to, again, not react against everything or not react against things that aren't a threat.

So, when those regulatory T cells aren't working well, then some of those T cells that have that potential to misbehave, continue to misbehave, it's kids who are partying when the parents are out, and so the parent needs to come back and just make sure everything is in check, then that can cause lots of autoimmunity. So again, one example that in part came out of the work that Brunkow and Remsdell had done with discovering FOXP3, is that the human counterpart for FOXP3 was identified in a condition that's called IPEX, an immune dysregulation polyendocrinopathy enteropathy X-linked syndrome, where these patients had very early onset polyendocrinopathies like thyroid disease, early onset diabetes, as well as multiple food allergies and eczema, and so it was identified that regulatory T cells can be very important in prevention of these types of complications. So going back to the allergic implications as well with regulatory T cells, we do know that the regulatory T cells, again, can control suppressive abilities on the different innate or adaptive immune systems, and it's not, again, sure 100% why in many allergic conditions people develop allergies in the first place, but maybe there is some sort of either reduced function or number of regulatory T cells. So they've seen in a number of studies that, for example, people who outgrow their milk allergy were more likely to have a higher proportion of regulatory T cells that were specific to milk, and having more regulatory T cells specific to milk increases the likelihood that you were going to outgrow your milk allergy, and they've also seen this in some of the immunotherapy studies as well, that having an elevation or an increase in your allergen-specific regulatory T cell is a good marker of a success of the immunotherapy or a good marker that the immunotherapy is working.

Dr. Mariam Hanna
This is fantastic because, you know, oftentimes in clinic they're like, what is the cause of allergies? And I often have joked and said the Nobel Prize will be won by somebody that really figures that out. And lo and behold, this year, this Treg situation and shedding light on one of many factors responsible for it, and the flip side that its presence may be a good indicator of response to therapy or restoration of a proper immune response or tolerance, really.

Do we have other examples outside of food immunotherapy? As you've nicely already mentioned, a food immunotherapy example, for example, with older therapies that we do for subcutaneous immunotherapy or venom immunotherapy, perhaps?

Dr. Vy Kim
Yeah, they've seen that in subcutaneous immunotherapy and SLIT as well with regards to the increase in regulatory T cells, the increase in IgG4 that's been seen over time, and it's thought

that, again, the Tregs help with suppressing the B-cell IgE production and switching or class switching to the IgG4 production as well.

Dr. Mariam Hanna
And can we routinely measure this in clinical practice? If we want to know if our patients are responding or not, how far away are we from this?

Dr. Vy Kim
Oh, I don't think we can do this on a clinical basis. Not at this point, and I'm not sure it's going to be readily available within the next year, per se. We have abilities to measure total regulatory T cell proportion, but in terms of measuring antigen-specific regulatory T cells, that's not currently available on a clinical basis as far as I know.

Dr. Mariam Hanna
I didn't even know that you could measure total T regulatory cells. Is this like a functional assay?

Dr. Vy Kim
There are a number of flow cytometry labs that can perform Treg enumeration and percentage, just like doing T-cell, B-cell, NK-cell enumeration.

It's looking for markers of the regulatory T cells, such as the FOXP3, the CD25, CD4 expressions.

Dr. Mariam Hanna
Okay. And as we have learned through the development of biologics and their rapid evolution and application in the allergy space, can you foresee emerging therapeutics happening for T regulatory cells now that we understand their critical role in both tolerance, atopy, and autoimmunity?

Dr. Vy Kim
Yeah, I think there is a lot of potential for regulatory T cells. Again, regulatory T cells play an important role in many conditions, such as autoimmunity, allergy, but also from a transplant perspective, graft-versus-host disease, from a malignancy perspective in terms of tumors that are evading the immune system, they do tend to see Tregs affecting or being predictors of response to treatment as well. So there is a lot of potential that is being worked on in terms of ways to try to increase regulatory T cells, whether or not in vivo with, for example, low-dose IO2 or in vitro with creating certain antigen-specific regulatory T cells as well, or potentially checking some of these checkpoint inhibitors and manipulating some of these checkpoints along the way too.

So I think there is a lot of potential. At this point, though, I'm not sure anything is clinically available yet, but I think, again, we're just hitting kind of the tip of the iceberg with the potential for harnessing the power of regulatory T cells in controlling certain aspects of the immune system or suppressing certain aspects that we don't want to be around.

Dr. Mariam Hanna
Perfect. And how might this kind of Nobel Prize recognition speed that along? Well, clearly, we're now talking about T regulatory cells in many different fields in medicine, and there is public awareness on the importance of these cells, but how else might you feel like this will feed into research for this cell?

Dr. Vy Kim
I think it creates a lot of excitement and buzz. Not like there wasn't any excitement around Tregs before, but I think, again, as you mentioned, the awareness is helpful in terms of driving the need for this, getting more people excited about immune tolerance and regulatory T cells, and getting more people curious about it and asking those questions and getting involved in the research projects to be able to drive some of these therapies or, again, further our understanding of why people develop allergic conditions and identification of what is it that drives a Treg dysfunction leading to certain allergic conditions.

Dr. Mariam Hanna
And it's interesting talking about it purely from an immune side, when in clinical practice, we often end up being like, well, you know, we got to start with the milk earlier or let's do it in baked format or let's give it this way. But from an immunologist's perspective, you're discussing all about, well, why were their T regulatory cells like gone haywire to begin with? And is this something that we can deal with with their immune system?

So I always find it fascinating when we discuss it from clinical allergy side versus immunology. We're both talking about the same disease in the same condition, but the targets are very different. What are key unanswered questions for you before this becomes ready for prime time?

Where will we have to take these discussions?

Dr. Vy Kim
We still have a long way to go before the Treg therapy can be routinely integrated into clinical practice. So Tregs generally are about 10% of CD4 T cells, and they have immunosuppressive function. We don't know what happens if you have too many Tregs.

So again, if we're looking at therapies that expand your regulatory T cell repertoire, does it have then anti-tumor or anti-infection effects as well? So would we see more infections because you're potentially suppressing the immune system more than it should be? Or could you then have some more malignancy escaping because of again, that effect?

Hard to know, again, because again, the immune system generally likes to be a well-balanced machine. So it's kind of like Goldilocks. Too much is no good, too little is no good, and it's finding that balance.

So whenever we're giving a therapy that overexpresses or potentially reduces it too much, we can see again some potentially unexpected or expected negative side effects as well. So I think it is balancing that. The other aspect as well is that these T cells, again, need to recognize antigen in the context of MHC.

You would need to make sure that if you're going to manipulate the T cells, the T regulatory T cells, that you have a way to do it personally for each person. And so that can have its own kind of issues as well. But they are doing things like that for CAR T cells, for example.

So it's not completely out of possibility. But as with any new therapies, it's always important to look at the safety and efficacy profiles.

Dr. Mariam Hanna
An exciting world for the future, and stay tuned for a different episode on CAR T cells because they get their own episode all by themselves. All right, time to wrap up for today and ask today's immunologist, Dr. Vy Kim, for her top three key messages to impart to patients and physicians on today's topic, T regulatory cells. Dr. Kim, over to you.

Dr. Vy Kim
Okay, so my big three takeaways are one, regulatory T cells, think of them like the peacekeeper, but they are critical for immune tolerance and have a key role in prevention of autoimmune and allergic disease. Number two, we know that dysfunction of regulatory T cells are implicated in allergic and autoimmune disease. And number three, we know that there are human inborn areas of immunity that involve regulatory T cell defects like IPEX CD25 deficiency, CTLA4 haploinsufficiency, where autoimmunity such as the autoimmune endocrinopathies, cytopenias, enteropathies, as well as atopy and food allergy can be the predominant clinical features too.

So as practicing allergist immunologist, don't forget that, again, if they have a lot of atopy as well as autoimmunity, you could consider that too.

Dr. Mariam Hanna
Perfect. Thank you, Dr. Kim, for joining us on today's episode of The Allergist. Thank you so much for having me.

Leave a review and a five-star rating. It helps others find the show. And remember, if Goldilocks had met an immunotherapist, she would have found things just right.

Thanks for listening. Sincerely, The Allergist.