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John Williams: From UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics. I'm your host, John Williams from the Division of Pediatric Infectious Diseases.

Steph Dewar: And I'm Steph Dewar, Residency Program Director and a member of the hospitalist division.

John Williams: And we are delighted to welcome our guest today, Dr. Scott Canna. Dr. Canna is a board certified Pediatric Rheumatologist. He sees children with general pediatric rheumatology diseases and inflammatory diseases in the outpatient clinic of the division of rheumatology at UPMC Children's Hospital of Pittsburgh. His research focuses on auto-inflammation in advancing both the science and clinical practice of immune dysregulation. Scott, welcome to That's Pediatrics.

Scott Canna: Thanks very much for having me.

Steph Dewar: Well, we're excited to have you here today and to hear about the types of patients that you're caring for, and the types of science that you're doing here at children's.

Scott Canna: I've been here for about two years. And the reason I bring that up is because the types of patients I see were greatly informed by where I came from. And so I was at the NIH for four years before coming here, seeing these patients with what we call auto-inflammatory diseases. And it's a little bit of a category of exclusion. So first I like to put people on the spot. So name a disease that you care for where inflammation is not one of the major most important things that is driving that disease.

Steph Dewar: Oh, that's such a great question. Let's think about that now.

John Williams: Where it's inflammation is not one of the major. Oh, I'm-

Steph Dewar: Traumatic brain injury.

Scott Canna: Oh, that's definitely way wrong. Trauma, that you release all these damage associated molecular patterns. Yeah, I think that you're throwing yourself under the bus there. So-

John Williams: I'm an infectious disease doctor, so I'm just going to give up right now and say, I think for me it's all inflammation.

Scott Canna: So I like to tell every other specialist that what they like best about their job is every day at my job. So we study inflammation. So obviously if you're infected, if you've had trauma, even if you have cancer or practically every other situation in the hospital from asthma, even to after the acute phase of epilepsy, inflammation is a major part of the problem.

So we try to go, the other part of the problem is that inflammation is really complex. And sort of the best example of that is the fact that we don't usually go after the inflammatory part of a lot of the diseases that we treat because we don't understand it very well. It's 2018 and we're still giving lots of steroids for asthma. Can we do better? Sure. But it's complex. So around the turn of the century, there was this sort of correlation of learning more about basic inflammation and having the genetic tools to figure out the underlying causes for some rare inflammatory diseases.

The first of these was called Familial Mediterranean Fever, FMF. And we figured out the gene for that. And that explained a little bit of what was causing that disease. And what was causing that disease wasn't infection, it wasn't cancer, it wasn't trauma. And it wasn't classical autoimmunity where we think of auto-antibodies and loss of tolerance to T-cells. It was actually sort of a hyper activation of our inflammatory system, our innate immune system.

And so that spawned this whole field of auto-inflammation. And so the bread and butter of the research that I've done since 2005 has been trying to connect the dots between some of these genetic diseases that we've discovered in these patients, and then why they get sick, and how they get sick. And that's been really interesting in understanding human biology in those rare patients. But it's also had a lot of just sort of spreading effects into how we understand inflammation in practically every patient that comes into the clinic.

Steph Dewar: So that is such an interesting thing that you said about steroids and asthma, as somebody who went to medical school several decades ago. I know that we know way more about inflammatory response these days. But the truth of the matter is when I give patients with asthma systemic steroids, they improve. And also when I give them a controller, which is an inhaled daily steroid, they tend to have less acute episodes. So how does what you're talking about translate to what I'm doing? Because I feel as though sometimes our body's natural response of inflammation actually makes us a little worse.

Scott Canna: Oh, absolutely. I mean, as probably one of the biggest purveyors of steroids in the hospital, rheumatologists love to use steroids. But it's a bit of a blunt instrument. And so absolutely, asthma is an inflammatory disease. And I don't think anybody would disagree with that. But what do we mean by inflammation? And can we do something better than steroids?

And certainly lots and lots of very bright people at this institution and elsewhere are trying. But it's been a tough nut to crack because inflammation's so complex. But those same patients that you're giving all those steroids to, they

get infections because the blunt instrument of steroids is immunosuppressive. They don't grow very well because steroids have all kinds of awful side effects. And so can we do better? Absolutely. And in fact, there's a lot on the hot ... I don't want to spend this whole time talking about asthma.

But just as an example of a disease that every of us has treated 1,000 times where our immunologic understanding of it in the lab seems to be way beyond what we're doing in the clinic in a targeted fashion. And that's where some of these genetic insights have been really helpful in not just narrowing down the pathology, but sort of pointing with a big sort of blinking finger to say this is the place where you want to intervene, that's the place where you're going to fix all of this.

John Williams: So you mentioned, Scott, and I want to hear in a second about what blinking arrows you've been seeing and following, but you really highlighted the difference between a classic autoimmune disease where the adaptive immune system, T cells, B cells, et cetera, attack tissues like Lupus or Rheumatoid Arthritis, and what you're calling innate, problems with the innate immune system. Are there a lot of diseases in that bucket? And do they collectively sort of add up to a lot of suffering in kids?

Scott Canna: Yeah, absolutely. So I think any distinction that you make in immunology is kind of arbitrary by definition because all of these systems interact. But the current best way that we parse the immune system's response is between innate and adaptive immunity. And innate immunity is sort of the more ancient version of our immune system.

And that includes things like barriers like our skin, and our gut, and some of the things that our skin and our gut make to keep those barriers intact. And then the really rapid, often really robust, but often really damaging inflammatory responses that happen really quick but not in a very adaptive way that they don't tailor themselves to one specific antigen or one specific bug.

So among the more common diseases, I would say that any disease where there's a substantial amount of inflammation where we don't think that it's an autoimmune disease, probably has a pretty big auto-inflammatory component.

Probably the most accessible one is gout, where gout is this massive inflammatory response to these weird crystals. And we now know that those crystals trigger this innate immune complex called the NLRP3 inflammasome. And because of the diseases that are associated with the NLRP3 inflammasome, that pointed to this one very specific molecule called IL1, and if you block IL1 in patients that have a mutation NLRP3, it's magical. And if you block IL1 in Gout, it's pretty magical.

It's not first line treatment because it's also pretty expensive, and you'd like to prevent gout episodes by preventing what triggers that innate immune attack.

But I would say that sort of disease burden of auto-inflammation written large is really broad. Obviously disease burden of these really rare genetic diseases is not super broad. But the things that they teach us and the mechanisms that they point out, as I said, are pretty broad.

Steph Dewar: So can you talk to us a little bit about the research that you're involved with here at Children's?

Scott Canna: Sure, I would love to. So, I love my job. I get to come into lab and we try to ask really important, interesting and hard questions every day and use the best tools that we can. Luckily we're in a place like Pittsburgh where all those tools are available to us, to answer those questions in a way that's clinically meaningful.

And so to me, that's sort of how I define translational research, is that the experiments that you do day in and day out are guided by things that are clinically meaningful. And so that's a little bit broad, but that's kind of where we bring it in. So I've been interested in auto-inflammatory diseases for a very long time. And then when I did my fellowship, I got really interested in some of diseases that weren't clearly auto inflammatory, that looked kind of like sepsis only without the infection.

So patients who were just unbelievably ill in our intensive care unit, what we might call hyper-inflammatory, often they have really high serum ferritin levels. So sometimes they get called hyperferritinemic. And what was kind of conspicuous is that we had been following what started as a few and are now dozens of genetic auto-inflammatory diseases.

And by and large, when you looked across all of these people who we knew had a genetically encoded increase in their innate immune system, they didn't get septic. They didn't get this sort of systemic inflammatory phenotype that ended up in the ICU. And so I got interested in a disease that we see in rheumatology called macrophage activation syndrome, which is just one of the names we give to this hyper-inflammation phenotype. And while I was at the NIH, we started bringing in some of these patients and doing what we do, the genetics on them.

And we found, low and behold, a genetic mutation in a gene called NLRC4, which is also a driver of this inflammasome. And it was kind of a big deal because this was the first known sort of auto-inflammatory genetic cause of something that looked like a hyper-inflammatory sepsis. So what's really great about working in the auto-inflammatory field is that everybody wants to use the work of everyone else to try and understand what makes diseases different.

And so because I'd been studying inflammasome problems for so long, we were able to compare these new patients with this NLRC4 problem with other patients that we knew had inflammasome problems, but had a totally different phenotype, at least to people who look only at inflammation. And what really

stood out was this other molecule called interleukin 18, or IL 18. And so that has become one of the cornerstones of what our lab works on now, is trying to understand what's unique about IL 18, and why does it seem to predispose people to this really horrible phenotype called Macrophage Activation Syndrome.

John Williams: So some patients, all of these are patients who have mutations in these innate immune responses. But it sounds like what you're saying is only a subset develop this severe systemic overwhelming inflammation, and that's mainly driven by IL 18?

Scott Canna: Yeah. So we think that IL 18 is one of the mechanisms, because of genetic work that was done long before I got into science. We know another mechanism actually has to do with killer cell function. So part of our immune system includes these killer cells. We have natural killer cells and we have cytotoxic T cells. And they're called killers because they kill through this granule mediated process.

And so if you have a genetic problem in killing, you get a very similar phenotype. And so we're trying to, actually, it's one of the projects we're working very closely on right now, is figure out how do you get to the same horrible systemic inflammatory phenotype from these two very different mechanisms of killing problems or excess IL 18? Is it all one thing that converges somewhere upstream of that disease? Or do they get there from totally different mechanisms?

And the relevance here is that IL 18 and killer cell function are things that are variable in the population in general. And so just because we use these genetic diseases as kind of what I'll call inflammatory archetypes, they define a very pure and very sort of clean mechanism of disease. But that tells you what kinds of mechanisms you should be looking in patients where you don't have a genetic cause. And that's where we've tried to build in a lot of biomarker discovery, to say, "What are the biomarkers of our inflammatory archetypes? And then how do they function, those biomarkers? What do they look like in our patients who we don't have any genetic reason to think that they have a disease?"

Steph Dewar: So what I think I hear you saying is pursuing this line of inquiry could potentially allow us to better understand what child is more at risk for this type of response, and potentially intervene and prevent that?

Scott Canna: Absolutely. And I mean we've been doing this since the beginning of things. So when we first found some of these auto-inflammatory diseases, and we saw this dramatic response of blocking IL 1 in those inflammatory diseases, we said, "Well, we have a whole bunch of other patients. We don't know what their genetic problems are, but because of their clinical description, or because of these biomarkers, they look similar to these genetic patients. Let's try blocking IL 1 in them."

And bam, it's been revolutionary. And so now we're blocking IL 1 in all kinds of diseases that we wouldn't necessarily have ever gotten to if we hadn't studied these rare genetic diseases so closely. And so we're doing the same thing now with IL 18 in sort of a later generation.

Steph Dewar: Are there unintended consequences? It seems as though this is a body's response. Are you modulating it or shutting it down?

Scott Canna: So of course I have a response to this.

John Williams: An inflammatory response?

Scott Canna: Well, depending on who you ask, all of my responses are inflammatory. So, I think that there are, again, not to get too out in space here, but this is what I try to tell the residents to get them excited. We're biologists, basically functional biologists. There are three main drivers of evolution in my mind. One is sort of food, you got to eat. One is reproduction, say no more. And then one is host defense.

And host defense comes from defending yourself from predatory animals like sabretooth cats. You got to be able to run, and you've got to be able to see your environment. But you also need to defend yourself against bugs and pathogens. And so no self-respecting, multicellular organism only has one way of fighting off a bug. But when things go wrong, either genetically or in our clinic, it's usually not everything gone wrong.

It's usually one or maybe just a couple things. And so I think that helps explain why we seem to get away with blocking specific things. And the side effects we see from blocking what we thought were just these linchpin cytokines or mediators, we get away with it. And this is why you turn on your TV and you see all these commercials for TNF blockers. Psoriasis is practically a solved problem now because there's all these different targeted therapies.

Now, do these therapies have side effects? Of course. Are those side effects as bad as steroids? No. We're using them in place of steroids because they're much more well tolerated, they're less immunosuppressive, and they have fewer off target effects. Now of course we're still learning about all of them. And they're coming, the pipeline is just dropping new drugs constantly.

So that's a challenge for everyone. And one of the reasons that I think that a working knowledge of immunology is certainly fundamental for my specialty, but I think actually unfortunately a working knowledge of immunology is going to become really an essential piece of every part of medical training because every doctor uses steroids right now, and every doctor knows they probably could do better.

And so what are they going to do better with? Well, it depends on the disease. And that means you've got to know that the IL 4 and IL 13 signaling pathway converges on the same receptor, and there's a drug for that now. And it works great in atopic disease. So I think we get away with it because these drugs are targeted, and because the immune system does things redundantly, otherwise we wouldn't have evolved.

John Williams: So we're all pediatricians, we take care of human patients, of children. But with your research you have worked both with doing human research and in animal models. So could you talk a little bit about what you learned from each of those and why you use both?

Scott Canna: Absolutely. So obviously, as I said before, every experiment we do, we try to make it clinically relevant. But there's just so many really important questions that can't be asked in people, for obvious logistical or ethical reasons. And so if you want to know if blocking pathway X is effective in this patient population, that is a very large undertaking in people.

You have to put together a big enough cohort, you have to get regulatory approval, you have to have the safety information about the drug. That's to do one experiment that may or may not work. And so we use model systems, not only animals, but cell lines, as the best systems that we can that are the least invasive. And of course we do everything under the supervision of our code and as humanely as possible.

But if you want to answer some of these questions so that you can move on, these model systems give you a way of not just doing that experiment, but also looking at why and how things are happening. Because maybe you thought drug X was going to work great and it didn't. And now you can interrogate that system and you can look at what cells were there? I thought it was going to be this big TREG expansion, but now there's all these TH 17 cells, or we have tools to interrogate this.

And the other part is that I've made a lot about talking and studying humans with genetic mutations. And I maintain that that is incredibly valuable. But especially in model systems and especially in mice, there are genetic tools far beyond what you could ever find in people, and in a much more controlled way so you can actually learn something. And so taking advantage of some of those genetic tools is a huge sort of leap forward.

And then finally, there's just so much complexity to these inflammatory and immunologic systems that trying to boil everything down to a Petri dish, you're just missing too many variables. So it's really important, at least for the work we do, to be able to study a whole organism. Because a lot of our outcomes in our studies are kind of clinical outcomes. We have a CBC machine in my lab. We do blood counts in our animals all the time. Find out, did we improve their anemia? Or did we, things like that.

Steph Dewar: This has been fascinating, as somebody who remembers a bit about immunology from oh, so long ago. It is amazing how much we continue to learn. And obviously there's still a lot for us to learn out there. I really appreciate you explaining a lot of this to us. It gave me a little bit of tense remembrances back to medical school. But this has been illuminating.

Scott Canna: So you're going to open up your immunology text tonight.

Steph Dewar: I might.

John Williams: Well, and it's really fascinating because I think it's one of the areas of clinical medicine that we practice, like you, Steph. I remember when basically all we had was steroids. And then we started using IVIG as the steroid of the 90's. Right? It was called that, steroid of the 90's, because it was good for every inflammatory disease except for those that it wasn't. And so it's really been remarkable to see in our career, these much more specific targeted tools and treatments become available through this really sort of basic work.

Scott Canna: And I mean, if you're paying attention, basically the most recent Nobel Prize was for cancer immunotherapy. And that's basically awarding the cancer doctors for discovering that the immune system was there and was probably pretty good for treating cancer, which people like to malice and have been trumpeting for decades. And it turns out, yeah, this is a really big deal.

So I think as we alluded to at the very beginning, inflammation is important in every disease process. And so whether you like it or not, if you're treating patients, you're manipulating their immune system. And because we have all these tools, you're going to have patients in your clinic, whether you're treating them or not, that are on drugs you've never heard of, and using mechanisms that you're going to have to go back to your text. So it's what I call a living knowledge. You have to have just sort of this living appreciation, and this includes me. I mean, I Google image search pathways 10 times a day because I forgot how SRC signals, or what is six phosphorylate again?

Steph Dewar: So thanks so much for joining us. I really appreciate you taking the time to chat with us today.

Scott Canna: Thanks for having me.

John Williams: Scott, it's been a pleasure to have you. Thanks to everyone for listening, and we'll speak to you next time on That's Pediatrics.