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From UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics. I'm one of your co-hosts, Steph Dewar, Vice Chair of Clinical Affairs and Residency Program Director.

John Williams: And I'm your other co-host, John Williams, Division Chief of Pediatric Infectious Diseases, and I'm delighted to welcome our guest today, Dr. John Alcorn. Dr. Alcorn is an associate professor in the Department of Pediatrics in the division of Pulmonary Medicine at UPMC Children's Hospital of Pittsburgh. John is a basic scientist, and his laboratory focuses on T cell immunity, host defense, epithelial cell biology, and lung physiology. They have a primary focus that I think we'll hear about on influenza infection and host defense mechanisms of helper T cells called Th17 cells. John, welcome to That's Pediatrics.

John Alcorn: Oh, thank you for having me.

John Williams: So, I did want to first start to hear about a little bit of maybe a broad overview of your research, and specifically these Th17 cells, which probably not all of our listeners know a lot about.

John Alcorn: Sure. So, I've been working in lung immunology for about the last 20 years in my career, and this has kind of spanned both chronic and acute illness over the years. I think, for me, I started off working in the cystic fibrosis field, which is a very common problem in children, and eventually worked in asthma for several years of my training as well. The common link between these diseases is that a lot of the lung injury or the pathology that occurs is driven by T cell mediated processes.

So, the focus in the last 10 years since I've come to Children's has really been on this new subset of T cells, type 17, or Th17 cells, that were identified first in 2006 and 2007. So, this is a new player. We really just reached the textbooks. I actually was just looking through a recent The Abbas Immunology that the med students use, and there actually are Th17 cells in the book now, which is an improvement over where it had been.

But, essentially, what was missing from the textbook with the Th1s or Th2 paradigm of T cell mediated biology was the subset that mediated both host defense against extra cellular pathogens, so we're talking about things like bacteria and fungi, things that are outside the cell, and cells that may, then, mediate chronic inflammation in terms of auto-immune disorders, things like psoriasis or asthma that we were interested in.

So, that was really the starting point for me, was to try to understand the role of these new cells, these new type 17 cells. They're named ... I guess I should introduce why they're called 17 cells. They're type 17 cells because they make IL-17 as their primary cytokine. It wasn't because we couldn't count Th1, Th2, Th3. But, essentially, that's what they are. They're the third subset.

These cells, as we knew at the time about a decade ago, this cytokine, IL-17, is important in driving inflammation in many settings. It drives neutrophilic inflammation, which is common to not just infection settings, but also these auto-inflammatory disorders. What was known in asthma for quite a long time was that a large subset of severe asthmatics don't present with typical type 2 inflammation or eosinophilic inflammation, and these asthmatics generally were categorized as non-Th2, and that was kind of still where we're at right now. We don't have a good way to evaluate biomarkers in those patients if they don't have high type 2 disease.

So, what was known is that if you looked at IL-17 levels in some of those patients, that high levels of IL-17 were correlated with worse disease, worse neutrophilic inflammation, lack of steroid responsiveness. That's actually what I was initially recruited here to Children's Hospital to work on, was to develop animal models to better test the function of these type 17 immune cells and whether or not these might be playing a role in severe asthma.

John Williams: So, that's really interesting. I mean, obviously, asthma has been known for a long time, and in pediatrics it's the most common chronic disease, and something that we see all the time in the hospital, yet it sounds like what you're describing is a large chunk of these patients that had these cells that were unknown that are major contributors to the disease and that we're still trying to figure that out.

John Alcorn: Yeah, I think that's absolutely true. The large subset of non-type 2 asthmatics is fairly broad. Some of those patients will have this IL-17 signature, or this neutrophilic signature. That can be identified by looking at cytokines in their sputum or looking at biopsy samples or RNA transcriptional profiles. However, that's not all of these non-type 2 asthmatics. There's several asthmatics that have high signatures of type 1 cytokines, things like interferon gamma, that may be a holdover from viral exacerbation of asthma or something along those lines. We don't really know.

One of the problems we've had with identifying these type 17 patients is the lack of a biomarker that sufficiently would capture them. With the type 2 asthmatics in the recent years, in the last five or six years, periostin has evolved as a blood biomarker to quickly identify a high type 2 asthmatic. That, then, allows you to customize your therapy towards that asthmatic fairly quickly with anti-IL-13 or anti-IL-4 or anti-IL-5 biologics that target those type 2 cytokines. With type 17, we just don't have that.

Oddly enough, IL-17, even though it may be a driver of a lot of this disease, there isn't really a good signature of IL-17 in the blood during these processes, so you have to look for kind of the impact of IL-17 being there, cytokines or chemokines involved with neutrophilia usually is what you're looking for. But, yeah, we struggle in that area.

Steph Dewar: So, it's interesting, as somebody who went to medical school perhaps in the 80s when we knew way less about immunology, I'm curious, are these those patients, those patients with asthma, who were chronically on systemic steroids or what have you? We just didn't have what it took to keep them well.

John Alcorn: Right, at least in our hands, when we look at samples from the Severe Asthma Research Program that have been collected here at the University of Pittsburgh, a lot of those asthmatics, the asthmatics with the high neutrophilia, low type 2 signature in terms of their sputum, just by looking at what cells are there. Those asthmatics tend to be the highest users of systemic steroids, not to the level of where we could significantly say that that's the case, but it seems to be the trend, that perhaps the worst responders are in this class.

But, like I said, it might very well be that we can't always detect these patients, anyway, because we don't have a good marker to find them, and even when we look at the sputum type cytokine profiles, you find a lot of severe asthmatics in a bucket where they don't really have type 2 or type 17 markers. So, it's hard to sort those out as well.

Steph Dewar: I'm just wondering what the availability of those alternative therapies are that you mentioned.

John Alcorn: Yeah, so, there has been a single clinical trial with an anti-IL-17 receptor antibody in asthma that was performed by Amgen about 5 years ago. Part of the problems with that trial ... So, the trial was not successful. The study didn't find a benefit. However, it was targeted to mild and moderate asthmatics more than severe, largely because we were still trying to figure out these endotypes or these different subsets of asthmatics.

So, I'm not entirely sure the book is closed on IL-17 in disease. What we do know is, from other types of diseases, autoimmune disorders, the drugs against anti-IL-17, anti-IL-23, another cytokine involved in the pathway, are to market already for things like psoriasis and rheumatoid arthritis and other diseases in that area. Yeah.

John Williams: So, John, you started in asthma, and you've worked in that for a long time, and that's how you got into these Th17 cells, but since your lab is near ours, and, in fact, your lab has been very helpful to people in my lab, I'm aware that now you study influenza and bacterial infection. How did you make that transition?

John Alcorn: Yeah, how did I make the jump? So, the first 10 years of my career was very much chronic illness, and what really struck me and has kind of held me my entire career, why I work in the lung, is this idea that the lung has a surface area the size of a tennis court, and we breathe probably 25 thousand breaths a day of air in and out, and this idea of barrier immunity which is now kind of called mucosal immunity, has always intrigued me.

For me, chronic disease always holds a place of interest, but the idea that your child could be well one day, and in 48 end up in the ICU, really has invoked a passion in me. When I came here to Children's, that was my goal, was to start to study some more acute models. In fairness, there was always a little bit of luck in where you end up in this career, and honestly I started working in influenza in late 2008. We started working in our own models of secondary infections, with bacterial infections or complications in pneumonia about a month before the pandemic in 2009.

So, there was certainly a little bit of right place, right time, involved in working on flu. But flu's always fascinated me, because there really isn't anything that we have in the toolbox to treat these patients other than supportive care. We have antivirals that only work very early during infection, and often the horse is already out of the barn by the time you would come to the ED. So, there seemed to be a large unmet need, and that's how I got into the field initially, and where we've been really for the last 10 years, built the lab around.

John Williams: Yeah, it's really true. Although, I'll note that the CDC recommendations are that any hospitalized patient with influenza should get treated, the evidence for benefit beyond the first 72 hours is not very good. So, what are the things that you're learning using your laboratory and animal models?

John Alcorn: Right, so, I think with flu, and this is not unlike some other viral illnesses, that a lot of the pathology is host-mediated, meaning that people don't generally die of a viral infection or the viremia caused by flu. You don't end up with flu systemically. Generally it's restricted to the lung, and cell death caused by the virus is generally restricted to areas of the lung.

What generally happens is something called cytokine storm, it's been kind of a buzz term for this, where the host immune response becomes aberrant or over-activated. That over-activation, then, leads the increased fluid accumulation, increased cellular accumulation, and eventually more tissue damage, and that's what leads to the need for supportive care.

I think what we've found quite a bit is that there are ways to modulate that immune response, and this is kind of the hot area in a lot of diseases right now, is this kind of biologic immunomodulation therapy. There might be ways where we can tune back some of that inflammation and not really compromise the clearance of the virus. You need cells like CD8 T cells, for example, to kill a virus, but you may not need inflammatory macrophages that are there to clean up a mess and tend to create a mess as they're there in the lung tissue.

So, a lot of the work that we've done and others in the field have focused on ways to manipulate that pathway. First off, trying to understand what's driving the injury, and then, secondly, trying to understand what parts of the immune response to the virus are actually detrimental versus beneficial.

Steph Dewar: So, I'm curious, John, you put a lot of energy and effort into the lung and what happens there, and I love the analogy about the surface area, because it is pretty impressive barrier to the outside world. Where did you come into this? How does this happen? Where does someone like you end up doing what you're doing?

John Alcorn: Right. I think that a lot of us start off where many students even today do. They're in their undergraduate program, and they're trying to decide, do they want to do research or do they want to go to medical school? Or, do they want to do both, those special few MD, PhD folks that really think they can do that.

For me, it was early on and much more about fit, what fit my style, my learning style. My approach to work and science fit better with the research aspect of things. I actually did a master's degree first before I went to a PhD program to kind of find that out. I went and did the job for a while to see if I liked it as opposed to just default, "I'm going to go to medical school," like so many students think, right?

For me, what evoked the passion was the highs, for me, were valuable enough. I have this talk all the time with trainees about how, in basic science, there are an incredible amount of lows. You're trying to discover something that has never been shown before, and the odds are that your hypothesis is either wrong, or it's correct, but you don't have the right tools or ability to really prove it.

The day-to-day of that job really requires a lot of beating your head against the wall. You have to be the kind of person that is rewarded much greater by the successes than the more numerous failures. For me, that's always been the case. That one piece of data, when it happens, you get as high as you can get, and that's what kind of keeps you moving forward. Going into this job, you expect that it's going to be difficult, right? We're trying to unravel things that have never been known, right? So, I think that's kind of the healthy approach for it.

Why the lung for me? That's always been an area interest in terms of function. I've always kind of been interested in terms of large-scale organ systems. I think for me early on it was kind of the lung or the heart, cardiovascular system, were probably going to be my home. For me, I had a really good mentor when I actually did enter the PhD program at Duke University with Jo Rae Wright, who later went on to be the president of the American Thoracic Society. She was just an excellent mentor in terms of kindling that interest and getting people excited about research. At the time, I was one of six graduate students in her laboratory, so she was very dedicated to training young scientists. That's something I try to do now.

Steph Dewar: So, it sounds like you're not a native of Pittsburgh. What brought you to this facility?

John Alcorn: Well, kind of. So, I actually grew up about two hours from here up in the middle of Pennsylvania, kind of rural Pennsylvania. But, yeah, I've been up and down the east coast from North Carolina, and we were in Vermont for my post-doctoral training. For me, this has always kind of been a home city even though I grew up in a rural area, and my family also, my wife has family nearby as well, too.

So, there were geographical interests, for sure, but really what got me excited about coming here was the division chief at the time in Pulmonary medicine was Jay Kolls. Jay was at the forefront of the field for IL-17 and Th17 biology, and these cells had just come out in the last six months of my post-doc, so this was hot, exciting science to do.

Steph Dewar: And you had mentioned that you were involved with cystic fibrosis research previously, and that translates reasonably well?

John Alcorn: Sure. Yeah, so, CF research, what I was doing 20 years ago, was kind of what everyone was doing at the time, studying pseudomonas and understanding interactions with the host. What's actually very applicable now, is that I'm actually part of the executive committee of the CF Center here at Children's, so it's something that I'm still involved in, is that the pathogens I work on, flu, for example, is a very important exacerbating pathogen in CF, the bacteria we study most.

So, we're very interested in things like viral bacterial secondary interactions, because a lot of infections aren't just one pathogen, especially in children. So, the bugs we work on are MRSA or staphylococcus, and MRSA is generally a colonizing bacteria in CF. It actually is the earlier life colonizing bacteria in most CF patients that eventually tends to kind of wane and be replaced by pseudomonas.

So, a lot of the pathogens we work on in the acute setting are relevant in terms of the chronic disease and CF, and we constantly are trying to bridge the knowledge that we gain from acute models in animals with something that we really can't model in animals well, which is chronic infection. The mice are very, very good at killing human pathogens, as it turns out.

John Williams: Well, you've really hit on a couple of key things here, John. It's just a beautiful description of the joy of discovery, even though that doesn't come all that often in science, when it does come, and serendipity. Pasteur said, "Chance favors the prepared mind." So, I think there's often an element of chance there. I think the points you made about flu are really important. Obviously the best way to prevent severe flu is for people to get a flu shot, but the flu shot's not always a great match every year, and that pandemic in 2009-2010, that was the fourth

one in that century. We'll probably, within 100 years, we'll have more, surely, in our lifetime.

So, do you think your research is moving towards ways to modulate the host, or do you think if we had better virus tools that could help? There's kind of different ways that you could take that.

John Alcorn: Yeah. Yeah, so influenza is a really smart little virus. It doesn't have a whole lot of genes in it to shuffle around, but it's really good at changing them. A lot of thought, at least, if we believe the classical thought from the CDC, that this virus has been around for potentially hundreds to thousands of years. We know for sure at least the last 150 years that we've had flu around. I think that we're kind of taking a two-fold approach. My previous research, and what we mainly are focused on, is certainly host modulation. So, once the kid is sick, how do we fix the problem?

But I think something we've done in the last year or two, we've gotten very involved in vaccine efficacy trials through the CDC. This is happening in collaboration with the folks over in Family Medicine that run these studies in both children and in the elderly. What my laboratory actually does is we collect all of the blood samples that come from these patients before vaccination and then after vaccination at different time points.

Oddly enough, what's really missing in the vaccination study literature are studies focused on T cells. Most of the time when we look at vaccines, whether they work or not, what is measured is antibody response. But, as it turns out, antibody response is a poor predictor of protection, particularly in elderly patients. Nobody really understands fully why. It might be the quality of antibody is a problem, or something along those lines. So, there's a niche there available for kind of cell-mediated immunity studies in terms of that.

So, one of the things we've been trying to really push is, can we leverage the ability of our hospital to collect these samples and to ... ability to generate data to drive these universal flu vaccine progress that's happening in the field? I think there's a lot of focus at the NAH in terms of dollars being put into the universal flu vaccine. There's a lot in the literature in terms of a suggestion that there are conserved epitopes in the virus that we might be able to use. We might come up with a better flu vaccine, initially, probably, something you would still get every year, but it might be broader specificity.

We still don't fully understand why people who are vaccinated don't get protection, really, though. That's one of the problems always in vaccine research, is how do you determine efficacy? We can't just come back and challenge the person with the virus and see if they got sick or not, right? So, oddly enough, when you look at children, about 50% of kids get vaccinated, and efficacy is about 50%. So, what in the world in half of those kids is causing this loss of efficacy? It really isn't known. There's really not a good immunologic

reason why it shouldn't work. Kids have lots of naïve T cells, and lots of cells that could be primed, or B cells to make antibody.

So, I think that there's a current focus in this area, and I think prevention, like anything else, if we could ever quite hit it, it would be the optimal goal.

Steph Dewar: So, that's interesting. Do you see a similar efficacy in the older folks? You said 50% of children are vaccinated and 50% protected, I think, is what you said, 50% of those.

John Alcorn: Yeah, I think it's actually a little bit lower in terms of efficacy in the elderly. There's a lot of confounders in terms of studying elderly vaccine responses. One of those is pre-existing immunity. I think this is a major issue. A lifetime of flu exposure, and also a lifetime of vaccination, really can change your ability of your immune system to respond to a new vaccine. There's this concept of original antigenic sin in humans that actually is being tested quite largely now with birth cohort type studies, but the idea being that, when you were born, the first flu virus that you are exposed to, you will bias your immune response towards that strain of virus.

So, people that were born before World War II had seen H1N1 exclusively, so when this pandemic virus came around in 2009, there actually was less severity in older patients than in younger patients. Whereas, somebody born in the 70s like I was, it was more exposed to H3N2, so we probably have a push in our immune system to be more protected against H3 and less against H1, which also fits with what happened in the pandemic. People in their 40s, a lot of people suffered, previously healthy people.

John Williams: Well, and another thing just on that point you just made, John, is that we're not very good at measuring protection against very severe disease. Those numbers are protection against getting the flu, but if you kind of turn that on its head and look at the children who die each year in this country of flu, of which there are several hundred each year, almost all of them were unvaccinated and were previously healthy. So, I think although protection against getting sick from the flu, the vaccine is not great against that, although it's better than nothing, it's probably pretty good at protecting against very severe disease.

John Alcorn: Yeah, absolutely. I would agree with that, too. And that's another thing where we don't have an endpoint. How do you measure that protection versus severity versus mild? The other confounder, too, really, with flu vaccination or flu severity is the fact that genetic studies haven't really shown much promise. People have been looking for a longtime for susceptibility genes in flu like you might in other diseases, and very few have been identified, and those that have been identified often don't reproduce in other cohorts. So, while genetics likely do play a role, it's likely multifactorial or more complex than our ability to detect.

Steph Dewar: So, it sounds like what we're left with is to continue to recommend universal immunization against influenza.

John Alcorn: Mm-hmm (affirmative).

Steph Dewar: Well, John, thank you so much for joining us today. I've learned a lot more about T cells and immunity and the work that you're doing, and I appreciate knowing that you're here on this team.

John Alcorn: Thanks for having me.

John Williams: And thanks again for joining us, John. Thanks to all of our listeners. You can find other episodes of That's Pediatrics on iTunes, Google Play Music, and YouTube. Be sure to subscribe to keep up with new content. Leave a review and tell us what other topics you'd like our experts to cover. Thanks for listening.