IL-4 and IL-13 are two pro-inflammatory cytokines that push things towards the Th2 pathway and drive a lot of inflammation in that pathway. This has been known for quite some time. But I saw a paper about a decade ago that talked about another aspect of those inflammatory cytokines, which I thought was pretty surprising. In the presence of IL-4 and IL-13, you not only get that inflammation, but you also get decreased expression of filaggrin, that important structural protein for skin barrier.

It turns out that that's not the only thing that happens in terms of skin barrier. You get decreased production of antimicrobial peptides, cathelicidins, and a host of other aspects. Probably even some of the skin fats like ceramides are also down-regulated.

So it's really interesting that at this sort of fulcrum between skin barrier issues and immune dysfunction sits IL-4 and IL-13. They're driving both of these problems. And it stands to reason, then, if you could decrease the IL-4 and IL-13, not only would you decrease some of the inflammation that's driving the itch and a lot of the disease process itself, you're also then decreasing some of the negative aspects that are happening to the skin barrier, the filaggrin deficiency, the ceramide deficiency, and maybe even some of the antibacterial capabilities of the skin. But it was a long time before we had a way to do that, and it's very specific pathway. Of course, larger immunosuppressants can do that as part of the host of things they're doing.

But with an IL-4 and 13 inhibitor, what's fascinating is with the one that's on the market already, dupilumab, it binds to one of the receptors, the IL-4 receptor alpha. And that part of the receptor which binds to IL-4, it also is part of the IL-13 receptor. So by blocking just that one half, you block IL-4 and IL-13 binding.

And what's really nice is when you have a receptor blocker, you really can get sort of everywhere and block it as opposed to trying to soak it up within the bloodstream. If you just have something that binds to the actual cytokines, you might have, theoretically, some other difficulties or some other nuances that you don't when you go right to where the receptor is. So it's fascinating that this can do both of those by just really having one target that's shared between the two of them.

What's neat, too, though, is we finally have a pipeline of IL-13 inhibitors which are coming out, and those are going to hopefully come out, if all goes well with the final trials that they're in. But the theory there is that they're going to bind to IL-13 itself. And we expect a similar result, but it may have some benefits and some negative aspects that we don't see with an IL-14-- IL-4 and IL-13 inhibitor.

There are other pathways that are being studied as well. IL-31 is considered one of the master cytokines for itch, and itch is the number one thing that drives patients crazy. At the National Eczema Association, that is the piece the patients talk about more than anything else. They don't really care directly about the inflammation. They don't often really care as much how it looks. They're really caring about the itch.

And of course, IL-4 and 13 do play a huge role in this. And we know that blocking that pathway blocks itch. But IL-31 seems to have an effect. And there are some preliminary studies that show when you give an IL-31 inhibitor, you block the itch and disease severity goes down too.

There's also an entire new category of medicines about to come out again, depending on how the trials end up. But these are the Janus kinase inhibitors, or JAK inhibitors. Now, these are already on the market. Some of them are on the market already for other indications, such as rheumatoid arthritis. But these are a little bit closer to cyclosporine and some of the traditional immunosuppressants, but more targeted than that.

So they're somewhere between the biologics and the traditional ones in that they do block these pathways as well. They also block some other pathways. And because of that, they may have some other issues in terms of monitoring and safety. But they might be extremely effective.

And there's a chance that some patients who have multiple pathways that are abnormal-- they might not respond from a very targeted biologic agent. They might say, gosh, I'm better, but that's not the whole story. They might need something just a little bit broader that can handle a couple of other aspects that maybe just one biologic alone cannot address.