So thinking about the pathophysiology of atopic dermatitis, we've had different perspectives over time as we emphasized different aspects of our disease understanding and also discovery. But there's a little bit more unification of it over time. And that very much relates to some of our newer systemic medicines, specifically biologic agents that are TH2 skewed in terms of their impact on the disease.

So what do I mean by sort of a change in perspective? Well, for a while, we were really recognizing some of the intrinsic problems with barrier dysfunction in atopic dermatitis. This is erratic skin-- the ability in clinical studies for someone to do transepidermal water loss studies on a baby and predict the development of atopic dermatitis because that might be associated with skin that both has a tendency to be drier and maybe potentially sensitize.

So we have barrier dysfunction. And then with this open skin and presentations of antigens potentially, that skin gets sensitized, which goes along with probably other aspects of the immune system that makes someone have more of a tendency to develop inflammation in the skin, which manifests as atopic dermatitis.

So we know that if we minimize barrier dysfunction with moisturizers, we may improve skin barrier, and in some cases, even treat low levels of inflammation. But we also know that anti-inflammatory agents, whether they're topical or now systemic, can improve the inflammation in the skin, but also a barrier dysfunction.

So our insight into this is very much affected by the studies that have been done, specifically on IL-4 blockade. We know that the TH2 cytokine profile was important to atopic dermatitis. At least, we thought it was. And then it was proven that it was, in that when you used dupilumab, a specific TH2 blocker via IL-4 and IL-13 cytokines, that we influenced atopic dermatitis.

So just visualize that if I have someone who's got very inflamed skin and they had the cubital fossa on their face and neck, for instance, and I give them a systemic agent that blocks IL-4 and IL-13, and I look a few months later and if they're in that clear, almost clear group, they're clear or almost clear. And it's worked essentially through the bloodstream in terms of impacting on the influence of IL-4 and IL-13 cytokine.

By blocking that down through the systemic aspects of the disease, we also block the clinical manifestations in the skin. Now we know that also improves skin area or function. It actually regularizes the microbiome, so we have less staph aureus and more of other bacterial agents or other microbes on the skin that are more normally there.

So there's an improvement of different aspects of the pathogenesis by giving a systemic cytokine blocker. So this is fascinating is that we've learned this, as I said, a sort of unification of barrier dysfunction to some of the genetic elements that contribute to that and inflammation, showing that effective anti-inflammatory therapy improves both the inflammation in the skin, as well as the barrier dysfunction, and of course, some of the symptoms as compared to signs. Because you can have markedly decreased itch with systemic dupilumab use as well.