Corbus Pharmaceuticals
Expert Symposium on the Therapeutic Potential of Targeting the Endocannabinoid System
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Ted Jenkins
Good morning, everyone. I'm Ted Jenkins, Investor Relations at Corbus Pharmaceuticals, and we're extremely pleased to have you all join us today, as we host an expert symposium discussing the therapeutic potential of targeting the endocannabinoid system. A warm welcome to all of you and to those joining us through our video webcast.

Before we begin, I'd like to remind everyone that today's remarks may contain forward-looking statements, and we encourage you to refer to our filings with the SEC and our corporate website for the latest information on our company. Additionally, the views expressed and remarks of our guest experts today are their own and not those of Corbus, and Corbus has not participated in the preparation of nor endorses their remarks.

With regard to Q&A, we ask that you hold your questions until the end of each presentation module, and we are looking forward to spending time with you this afternoon, and it is now my honor and pleasure to turn the podium over to Dr. Yuval Cohen, Chief Executive Officer of Corbus Pharmaceuticals.

Yuval Cohen
Good afternoon, everyone. Thank you, Ted, and let me just start by thanking the Corbus team, Ted and Lindsey, and the team from Jenene Thomas Communications that makes these events, which are actually very complicated to organize, seem so simple, and to our hosts, Lowenstein Sandler, our corporate councils for providing us with this space. Thanks to all for coming here on a Friday afternoon, and thank you to those who are joining us on the webcast.

My name is Yuval Cohen. I'm the CEO of Corbus Pharmaceuticals, and we're really excited about this symposium this afternoon and hope that you'll find it very interesting or as interesting as we do. My colleague, Dr. Barbara White, will introduce the speakers in a second, but before that, just a brief reminder of Corbus and what it is we're focusing on. Corbus is a clinical stage company focusing on the endocannabinoid system, and today, you'll hear much more about this system and the nexus between this system, inflammation, fibrosis, and biology of resolution. We have a number of assets that we've been focusing on since our inception in 2014.

The most advanced one, of course, is lenabasum. It's currently in four clinical programs, all of them for rare or uncommon diseases. All these are chronic inflammatory diseases. Three of them are autoimmune, and you'll hear about systemic sclerosis, our most advanced program today, of course, and one of them is genetic inflammatory disease, being cystic fibrosis.

Lenabasum is an agonist of the cannabinoid type 2 receptor, but we also have a second program, which is CRB-4001, which is an inverse agonist, focusing on the CB1 receptor, and you'll hear, again, more about what that actually means, what the difference between the

receptors are and what each one of them does and contributes to inflammation, fibrosis, and even metabolism.

Then beyond that, we have a very large library of early-stage compounds, again focusing on these G-protein coupled receptors. Some of them agonists. Some of them inverse agonists, etc. So, what we want to build at Corbus is a company that specializes with a deep understanding of this biology - all the way from the discovery of such molecules again, through our insights, going all the way to the clinical development, hopefully approval, and then beyond that, commercialization of these compounds.

So without further ado, I will introduce my colleague, Dr. Barbara White, our Chief Medical Officer. Thank you, Barbara.

Barbara White
Thank you, Yuval, and I would also like to thank all of you for coming today. It's rainy, and it's Friday. So, we appreciate your coming to this symposium that we are holding.

We had three speakers today, and I'd like to introduce our first speaker, who is Professor Charles Serhan, who is at Brigham and Women's Hospital and also at Harvard, and Charlie is going to talk to you about the importance of resolution of inflammation and the interactions between the endocannabinoid system and the resolution of inflammation. Dr. Serhan is the Chair of our Scientific Advisory Board at Corbus.

Next to Dr. Serhan is Professor Adam Friedman, who is the Interim Chair of Dermatology at George Washington, and he has longstanding interest in endocannabinoid biology and skin disease. So, he will try to bring some of the potential applicability of targeting the endocannabinoid system to your attention.

Jessica Gordon is at HSS, and Jessica sent her slides, and she showed up. She was here at noon, and about five minutes after she walked in, she got an urgent call for a family emergency, so I said goodbye, and she said to give you all her regards, but it seems much more appropriate for her to go take care of her family emergency, and so, I will fill in and do her slides. I didn't put her slides together, so it'll be a bit of winging it, but that gives us a little more opportunity with time. So, I'll do that at the end.

At this point, I would like to turn the discussion over to Professor Serhan.

Charles Serhan
Okay, good afternoon, everyone, and it's really a pleasure to be here, and you can hear that this is a New York accent, so I'm happy to be home. But we've been in Boston for about the past 33 years or so.

So, my task today is to very quickly tell you about the serendipity of how lenabasum, the drug of the day, taps into new work on the resolution mechanisms of inflammation.

And so, in our world, inflammation sits in the center. As you know, it's a protective response and can be evoked by bacterial invasion, but we also need to be concerned today with pro-inflammatory diets, new villains, "inflammaging" as people call it. All bring about a chronic state of inflammation. So, many of those diseases are listed here, as the classic chronic inflammatory diseases, and of course, many new diseases are added to the list, like asthma, which was not thought to have an important component in inflammation.

So, I want to remind you that the mechanisms that I'll talk to you about today are enabled all around the body, as illustrated by this person, and that the initial events, the recruitment of neutrophils, these are swarming neutrophils, you think of them like bees just swarming into a site to protect us, can actually lead to collateral tissue damage. And that collateral tissue damage evokes inflammation.

So, these are the different pictures of inflammation that I'm sure you're all aware of. And so, we certainly need new approaches and that's amplified by the points on this slide. This is just some of the side effects of the current anti-inflammatory agents, like steroids, eventually become immunosuppressive. Nonsteroidal anti-inflammatory drugs have a number of toxicities, selective inhibitors, anti-TNFs, whatever you like. They all have some underpinnings that are not entirely compatible with the host, the immune system.

So, I'd like you to think about for this presentation the new concept of host-directed therapies because the way I see the mechanism of action of lenabasum is into regulating the host response. So, I need to tell you a little bit about what my research laboratory in Boston has been focused on. We've been focused on endogenous controllers of the inflammatory response. What are some of those controllers? And that's where we learned that inflammation, which normally resolves on its own, evokes during this resolution phase a number of endogenous regulators. And those endogenous regulators I'll introduce you to today here: The resolvins, protectins, and maresins. And this terrain of resolution has recently become seen as a potential therapeutic area for innovation.

And I need to tell you a little bit about functional decoding metabolomics and then how lenabasum taps into the resolution mechanisms in a human challenge model, and then, I'll show you some *in vivo* human dosing with lenabasum.

So, this scientific avenue of research and our connection really comes about by serendipity, and as many of you know, you have scientific backgrounds, sometimes things are discovered quite by chance, and this is the first publication with Bob Zurier, and I want to point out that ajulemic acid here is lenabasum. This is the structure, and it was synthesized as an agonist looking to

appear like THC, which is the granddaddy of the cannabinoid field. Now, what's exciting here in this early report was that AjA stimulated the production of lipoxins, and this is with human leukocytes, and that's lenabasum stimulating lipoxin production.

So, what's a lipoxin? Well, this is the structure here of this endogenous mediator derived from arachidonic acid that is the lead in stimulating resolution of inflammation, and you can see here, and this is *in vivo* in a mouse model of peritonitis, that ajulemic acid stimulates a huge increase in the production of lipoxin A from endogenous sources. So, this was quite exciting to us.

And I now would like to tell you a little bit about how we got into the mechanisms and events and resolution. So, you're all aware the cardinal signs of inflammation. They're here: Heat, rubor, calor, tumor. These signs are all evoked by chemical mediators, and this is part of a repertoire of mediators including prostaglandins and all the chemokines and so forth that are eventually bringing about an acute inflammatory response that is evolved in nature to be protective, and that's illustrated here with bacteria being defended.

When we looked at this in the pathology textbook, we thought this looked like a decision path, how to go from acute inflammation to chronic inflammation or abscess formation or wound healing, for example, in essence unresolved. And we, as I said, focused on leukocytes because they can both be protective, but they can also lead to collateral tissue damage, and this process of resolution, the normal process of resolution, was thought to be passive, meaning what? Meaning that all the chemical mediators that helped the cells to come in to protect us were just dilute, and that would bring about the end of the acute inflammatory response.

So by studying self-limited models of inflammation, ones that would resolve on their own, as they should, we learned that this is an active process, a biochemically active process turning on the production of a whole super-family of mediators that are called the specialized pro-resolving mediators, including the lipoxins and the resolvins.

So, this is an idealized, this is from a recent JCI review we did, acute inflammatory response, and the definition is given here of resolution. This edema happens with in seconds and minutes, and then, there's a rapid neutrophilic infiltration, and it's within this time window, we see a change in the lipid mediator classes that are produced. We go from pro-inflammatory mediators, like the prostaglandins and leukotrienes, and then, this turns on the production of the specialized pro-resolvin mediators, illustrated here. Lipoxin A forms here, and then, the resolvins, protectins, and maresins.

Now, the first place we started to interrogate the inflammatory exudate was in this air pouch model. This is a place where we could capture an inflammatory exudate and basically interrogate it and learn from doing lipidomics and structural elucidation these biochemical

pathways. So, you want to think about this as the beginning signals the end or alpha signals omega. Arachidonic acid-derived products signal the utilization of omega-derived products.

So, this is an active process, and I want to illustrate here now the two main bioactions that we use to do the structural elucidation of these endogenous mediators. One is the cessation of neutrophilic infiltration. Those cells, once they come in, they need to stop, and that's illustrated here. This is a diapedesis step through the vascular endothelium, postcapillary venule for example, and on this side of the equation, it's a macrophage, efferocytosis, the picking up of apoptotic neutrophils, and carrying those dead cells and debris away to the lymphatics, and this is a critical pro-resolving response.

And so, we found later on that this also, and this is important to today's presentation, the SPMs stimulate the uptake and killing of microbes by macrophages as well as the clearance of fibrin clot. So, how do we determine this? We introduced these quantitative indices. There were no quantitative methods. These are descriptions of resolution going back 100 years or so, but we put this in cellular molecular terms quantitatively so that we could pinpoint the site of action of these mediators.

And so, the first big take-home message from this presentation is that pro-resolution is not equivalent to anti-inflammation. Why? Because pro-resolving mediators and mechanisms stimulate the clearance and killing of bacteria and the removal of apoptotic or dead cells and debris. That is something that traditional anti-inflammatories do not do.

This is just the substrate. These are essential fatty acids that are converted to each of the main families that I told you about. They're of interest to us academically because they're modulated by aspirin and by statins, but more importantly, they brought us to the concept of immunoresolvents, agents that would stimulate the resolution of inflammation, and I would class lenabasum into that group. They're endogenous mediators of the SPMs, the specialized pro-resolving mediators, and they're best known in the scientific literature, this is from *Science*, as stop signals stopping the acute inflammatory response and bringing about the return to tissue homeostasis.

Now, just to impress you, this is some of the biochemical circuitry. We have established a complete stereochemistry of each one of the molecules that are in this cascade, confirmed through organic synthesis. I want to remind you that not all endogenous metabolites have any function, but we have elucidated the functions of each family, the resolvins, protectins, and these maresins are the macrophage mediators of resolution, all having this pro-resolving function.

So, at time zero, the way we think about the acute inflammatory response now, is not that it just dwindles out, but under normal events, we have this gradient of pro-resolving molecules

that are produced, and that brings about homeostasis and the return of function, at least in laboratory animals. And we think about this as a network of resolution metabolome.

So, how potent are these? Well, these are the cardinal signs of pro-inflammatory mediators. Histamine is a log scale 10 to the minus 14 and 10 to the minus third. The pro-resolving mediators are very potent in isolated cells and in animal models. They're active in the pico-to-nanogram range, and they stimulate what we've called now as agonists of the signs of resolution.

So in animal models, there's a great potential for the use of these molecules on their own, but endogenously, they counter-regulate inflammation in a number of settings. The tissue protective, and this is a composite from many laboratories around the world, these mediators are commercially available. They also are effective in cancer models, where there's inflammation that needs to be resolved. They control infection, which was quite surprising, and relevant to today's talk, they counter-regulate pain, and they're very effective at that as well as stimulate wound healing and repair.

There are about 100 to 1,000 times more potent than traditional non-steroidals, and in terms of pain models and animal models, they're about 100 times more potent than morphine. So, the mechanism of action is illustrated here. The SPMs limit the magnitude and duration of acute inflammatory response. Here's an example of the indices. This is the neutrophilic infiltration with time out to 48 hours. If we add on board a resolvin, it goes from this interval 20 hours down to 12 hours, quite a substantial shift in the resolution time.

And they do this by, again, stimulating macrophage, efferocytosis, clearance of debris and microbes and apoptotic cells, and they counter-regulate, meaning they turn off the pro-inflammatory mediators very effectively, as listed here. And most importantly to this discussion today, the SPMs when they're evoked, are not immunosuppressive.

So, what about the human relevance? Well, in my laboratory, I focused on GPCR receptors to these endogenous mediators and have identified several, actually five, that we know of today, resolvin D1 acts at this receptor on leukocytes, RVD2, RVE1. The main point is that there are GPCRs that govern this leukocyte traffic.

And around the body, this is to illustrate the different organs that produce the SPMs. We can monitor them in tears, in bone marrow. They're produced in large amounts in human breast milk outside of the innate immune system. So, we developed a targeted metabolomics approach to monitoring these mediators that are critical for the data set that I'm going to show you.

The bottom line is that we could measure them all by tandem mass spectrometry, MSMS, and then quantitate them using deuterated internal standards, and this is a system that is useful today in thinking about personalized and precision therapeutics because we can look at the impact of the system when there's a drug onboard, and that's what we've done. We qualified that system using the National Institutes of standards, composite serum pool, and plasma pool from more than 100 individuals.

And we can mark all the pro-inflammatory mediators here, including the lipoxins which mark the beginning of the resolution phase. We could mark the E series resolvins as well as quantitate the maresins and D series resolvins as well. So, we also recently qualified this with two other groups using coded samples validating this method using a low-dose endotoxin challenge.

So, this is what we call functional decoding metabolomics. Now, are the resolvins produced on challenge in humans? So, we turned to this model, which I think is quite clever. It was introduced by Derek Gilroy, and it's a heat-killed E. coli with a suction-raised blister and it resolves on its own initiation and resolution here, given the dose of E. coli. And this is a Doppler image, just to parallel the flow that goes along with this. And you can see by this time, 0.3 days, here is its resolution.

What we can do in this blister is just like we did in the early studies with mice, as we could capture the inflammatory exudate and mark the neutrophilic infiltration, and it resolves. Then, the mononuclear cells, and we can see a repertoire of events, just as we have in experimental settings with animals.

Now, the cool thing is we can apply this metabolomics approach now to look at the pathways, and this is rather detailed. The bottom line here is this C panel. It turns out that the initial timepoints very pro-inflammatory mediators have made, and then, it's a clock for resolution that brings us back to resolvins and all the stop signals. So, we could mark all those, and we have, within this blister.

Now, if we look at the number of neutrophils and SPMs with monocytes, what's really exciting, and we were able to do this in England with medical student volunteers, is we can give them back at the amounts produced the pro-resolving mediators injected back into the site, and see expedited resolution. So, this is a full proof of concept that, once these mediators are here, they're the stop signs to move on to resolution.

So, here are some of the functions that we've identified, limiting neutrophilic infiltration, preventing collateral tissue damage, shortening the resolution interval of the time to resolve, counter-regulation of pro-inflammatory signals, and then what I personally think is the most

important, this ability to enhance microbial killing and clearance as well as the link to tissue regeneration, the next step after an acute inflammatory response.

So now I turn to the drug of the day, lenabasum, which is in this title listed here in this blister model, and the question is, does lenabasum significantly inhibit or accelerate neutrophil numbers? Here's the onset of the acute inflammatory response and its resolution, and here's the second example of an anti-inflammatory pro-resolving response. This is the study that was carried out together with Professor Gilroy and colleagues in UCL London, and here's the dosing. You can see here of lenabasum at 5 mg and 20 mg doses, the sequence of sample acquisition in the blister.

The individuals were randomized coming in. There are 23 in total to placebo or a concentration arm of lenabasum compared to steroid. The results are quite exciting. In this setting, you can see at the lowest dose of lenabasum of 5 mg – this is oral dosing now--you see a drop in the neutrophil number. You see a corresponding drop in mononuclear cells at the early phase, and I hope you can see this because it's the pro-inflammatory mediator circuit, most of the chemokines and cytokines, and you can see that they're all statistically significantly dropped within the blister fluid, and this is oral dosing now.

And when we turn to the pro-resolving circuit and initiators. We can see very clearly a reduction in the pro-inflammatory mediators, the prostaglandins, the leukotrienes, thromboxane goes down, prostaglandin D2. Principal component analysis tells us that the LCMS data is quite different from placebo to the two different doses of lenabasum, and here's very striking increase in lipoxin A_4. This is within the human blister, resolvin D1, resolvin D3, lipoxin B_4, and this was all done with coded samples coming from England.

So in conclusion, lenabasum and the way we think about its mechanism of action stimulates resolution in the human skin blister for E. coli inflammation. It's changing the trajectory and shortening the resolution interval. It does this by reducing neutrophilic infiltration, stimulating the active production of pro-resolving mediators *in vivo*, and the most exciting finding here in this human model is this increased clearance of E. coli from the site. And I don't know of any drugs today that have this repertoire of actions. It's quite interesting.

And here, we'll end on this note. I want to emphasize that this work was carried out with Derek Gilroy and his colleagues, the many medical students that gave their forearms to tap us into this endogenous biochemical circuitry that is designed to normally turn off by stimulating resolution of the acute inflammatory response. So, that's the way we think about the drug of the day, and I'm happy to take questions.

Brian Abrahams

Hi. I'm Brian Abrahams for RBC. Thanks for the presentation. Two quick questions for me. First off, it sounds like there's a pretty broad network of impact that this drug could be potentially having. I'm wondering if there may be other therapeutic areas or diseases where you think lenabasum could have opportunity based on some of this work that your lab does.

Then secondarily, you mentioned, if anything, you're seeing reduction in microbes, and there doesn't seem to be any increased risk of infection. Based on the mechanism and what you're seeing, would there be any particular on-target side effects that you might be concerned about with the drug that influences these processes? Thanks.

Charles Serhan
Those are difficult questions, but you give me an opportunity to speculate, which I like. So obviously, this is a new terrain to think about therapeutic modalities that taps into endogenous resolution mechanisms, and in the animal models that we've looked at in resolution, I would say that every place where we have uncontrolled inflammation today would be a potential add-on therapy or solo therapy for a pro-resolving agonist, like lenabasum.

So, I'm particularly enthusiastic about that because a lack of immune suppression, and we haven't seen this in any of our models. Stimulating resolution is about bringing about the normal closure. You want to keep in mind that we're normally bombarded every day, thousands of times a day, with microbes and small cuts, and if you think about getting a small pimple, you have to have endogenous mechanisms to turn off that pustule on site, or else every time we had an insult, we'd get a meltdown.

So, this is the first orally active drug that I know of that actually effectively taps into this system. We do know that certain statins can turn on endogenous resolvins, and so, I think that in terms of indications there are vascular indications to lower the vascular inflammation to go along with some of the anti-triglyceride drugs. I would think about pulmonary indications, where we want to clear microbes. I would think about ocular indications, where we'd want to clear excessive inflammation, conjunctivitis, but sometimes a theoretical indication doesn't translate well to a true indication because there's a lot of barriers in between.

Those barriers have already been met with lenabasum. It's manufacturable, and as far as I have examined the literature, I haven't seen any off-target sites. There may be additional sites of action. Some of the endocannabinoids are thought to interact with as many as 50 different endogenous mechanisms, but I would remind you that this is a designer drug. And the way I look at it is, Sumner Burstein when he first did the synthesis, he looked at THC and he made a synthesis of this molecule.

It's a CB2 agonist, and it taps into these systems. But it seems to selectively tap in, and I think what's reassuring is that on those forearms, I could show you some of my blister pockmarks

because I'm a subject of some of these studies myself, we would see some adverse effects there right away, and that hasn't been observed. So, I think the sky's the limit in terms of where you could add this on in terms of therapy, but I would defer to Barbara and to the other clinical groups, Adam, that are here today to tell you a little bit more about where this drug could go.

Mikhail Keyserman
Mikhail Keyserman, BTIG. Can you maybe talk a little bit about in the comparative assays for the inflammatory mediators, you had prednisone as one of the comparators, can you just talk a little bit about the benefits of having an endogenous approach to CB agonism versus a chronic steroid approach? Thank you.

Charles Serhan
Well, this is my personal opinion. I emphasized at the beginning of the presentation that we need to start thinking about host-directed responses and ways to tap into these normal mechanisms for resolution and repair. Now the steroids, of course they're synthesized based on endogenous molecules, but they bring about immune suppression, and they do this very effectively.

So, chronic treatment with a steroid is not ideal. Anti-TNFs are, of course, exciting drugs in the clinic, and they're used very effectively at the beginning of the RA diagnosis, but their long-term effect is immune suppression. And you turn around and you get whopping microbial infections, including TB, including emergence of head and neck cancer. There's a whole literature that's developed around that and the movement from one anti-TNF to another.

In thinking about pro-resolving therapies, I don't see this as an issue. As far as I've seen from the studies done with lenabasum, it has very little, if any, toxicity at all, and that is a big plus. And if you're tapping into resolution, I think you could see long-term treatment, oral dosing. I'm still quite amazed that an oral dosing of 5 mg that you can get regulation at the site of inflammation, injecting in E. coli. To me, it's the best model that this needs to go to more complex disease settings to really get the answers that you are asking for.

Trevor Allred
Trevor Allred from Oppenheimer. Two quick questions. Do we understand the source of the SPM production? Is that from Tregs? And then, a little deeper into the mechanism action that you think lenabasum could have. So, my understanding is SPMs are downstream of omega 3s. Do you have any thoughts on where that might be actually working, might be happening?

Charles Serhan
Yeah, I have a lot of thoughts on that. That's the bulk of the work in my own lab. We identify these bioactions and the mediators first, and then, we have to back up and learn that the precursors were omega 3 EPA and DHA. What cells make them? So, we focused initially on

neutrophils and on macrophages, and the N2 macrophage is the lion's share in the innate immune system, producing SPMs. But the most exciting finding that we've had, which is really not related to today's discussion, but I'd be happy to talk to you about it one-on-one, is the human vagus nerve is a big source of pro-resolving mediators and especially on electrical stimulation. That's really cool work, and I'd be happy to talk to you about that.

So, the second part of your question asked, do Tregs produce? We haven't seen Tregs producing SPMs, but Tregs are a target of SPMs, and I think I put a slide in here to show you that. This is a simple slide. I borrowed this from someone--Montero. This is the happy route of having a pro-resolving medicine, and this is the unfortunate route of some of the therapies we have today. I thought it was a nice smiley face there. You can remember that.

This is from the *New England Journal* on one of our papers. A group at NIH wrote about the production of pro-resolving mediators as local mediators regulating and clearing microbial responses, again emphasizing that this new concept of host-directed therapies, and here's what we know to answer your question about the adaptive immune response. Tregs fit right in here. This work was done with a group in Italy, Valerio Chiurchiu has been on sabbatical with us.

So, Tregs, as you know, are a major source of IL-10, and the resolvin receptors are produced there and regulate those cells, and on the other T-cell subsets, they stimulate a blockade. So, they block TNFL for production, and all the SPMs stimulate IL-10 production. They turn off IL-17, if you're an IL-17 connoisseur. But one of the more exciting areas in here has to do with B-cell biology and groups at the Rochester Rick Phipps' group discovered that the SPMs regulate Ig production.

So, that's far off I think into the future for a drug like lenabasum, but does that answer your question?

Barbara White
I think at this point we'll save the rest of the questions for the panel discussion, and at this point, we're going to turn the presentation over to Professor Friedman.

Adam Friedman
Good afternoon, everyone. That talk really is going to complement a lot of what I'm going to be talking about. More of a clinical perspective, and I kind of changed the title of my talk to really focus on the endocannabinoid system itself and really give the dermatologist's perspective, which there is a lot of overlap with what you heard in a lot of the diseases that I treat, but I'm going to take a step back first and really more focus on the system itself because it's never good to assume how much everyone knows in the room.

So, I'm going to do a deep dive into what the system is, its components, and then, we'll work our way into the skin itself, the biology the skin, and then where activating various receptors could be potentially useful for different inflammatory diseases and potentially even neoplastic diseases.

As a dermatologist, it's hard to avoid this consumer marketplace. Everyone and their mother are coming up with something containing something in this category, and the skin is a huge target for it. Certainly being the largest organ, a lot of opportunities for things to go wrong, but lots of opportunities to make money, and so, we've seen a rapid influx into the marketplace in line with the rapidly changing regulatory systems involved in phytocannabinoids, and so therefore, really you have to beg the question, what do dermatologists think about this?

Now, we did this study. We asked a bunch of dermatologists, well, what is your feeling on this space, and this was really not a surprise in that dermatologists think this is very exciting, but they know absolutely nothing about it. And there's good reason for this. We don't, unfortunately, have a lot of science in this area, forgetting the dermatology but even looking to our partners in crime in other specialties. This is somewhat of a novel space, and so while my colleagues say, yes, this is very cool, we don't know a lot about it. Is that okay to put our heads in the sand?

And the answer is no because our patients are going to ask about it, going back to that original slide. You walk outside, you're going to be slapped in the face with something related to medical cannabis or consumer cannabis. So, we need to know about what's going on and understand what's actually going on, and the only way to do this is to partner with industry and actually do the appropriate research, both bench and clinical, to understand the space.

So, I think that medical cannabinoids or ingredients that will activate or utilize or manipulate in some way the endocannabinoid system will play a big role in how I and my colleagues manage various skin diseases. So before getting into that, though, let's talk about what the endocannabinoid system is. In simplest form, there are three components. There's the goods. There's the actual endocannabinoids themselves that are meant to do their thing. There are the receptacles for these, the receptors, that receive them and then downstream will do a whole bunch of fun stuff, and then, there's the enzymes, the proteins, the machinery that will be the master regulators.

And I think that's an important place to really start in that if you have some dysfunction in any system, whether it's producing too much or not enough, or you're breaking it down too quickly, that's where a lot of pathology comes out. It's when these systems in place stop functioning the right way, that's when you run into trouble.

First off, the receptors. It's rare. There's this very clear linearity in terms of the simplicity of the system, though I will say that while we only have two cannabinoid receptors, CB1 and CB2, cannabinoids, endogenous produced synthetics, phyto-derived, plant-derived, they can target other receptors as well. But before even delving or even inducing a seizure related to that, let's focus on the cannabinoid receptors. So, CB1 is the receptor that's found predominantly in the central nervous system. CB2 is predominantly on immune cells and immune organs.

So, very clear delineation between these two. It doesn't mean they don't work together or do similar things, but there is some distinction, some delineation between these two types of receptors. So in thinking about CB1, heavily expressed in the central nervous system, brain, the spinal column, peripheral nerves, you name it. There's a lot of detail on this. This is using PET scan to actually show the expression of these receptors. The way it works in terms of how signals are transmitted is actually pretty simple.

How does it work, you ask? I'm happy to share. So, what you are looking at here is this pre-synaptic terminal and the post-synaptic terminal, meaning if you're thinking about a telephone wire, the signals coming from here, and this is where the signal is going to perpetuate that signal. So, you cut yourself. That nerve wants to send a signal to the brain, ouch, that hurts. This whole process starts.

And so, the signal comes in. Through influx of calcium, various whether it be stimulants or inhibitory molecules, depending on what you're trying to do, go across, that in turn will increase calcium on the other side. And that's going to send that signal, but at the same time, like any good biological system, there is feedback, in this case negative feedback. If you cut yourself, you don't want that pain signal to perpetuate for the rest of your life. It needs to turn off, and that in this case is where the endocannabinoid system fits in, specifically the CB1 receptor. It's at this moment, as that increase in calcium goes up, the endocannabinoids are produced, actually rapidly from arachidonic acid, and then, they will migrate backwards to where that signal first came. And they will actually bind to their receptor there, in this case CB1 receptor, and they'll turn off that calcium influx, and they'll stop the signal. They'll cut the telephone wire. Very linear, it makes a lot of sense. That is how the regulation of nerve transduction here.

But it's a lot more complicated than that, and I don't, unfortunately, have the time to go into that because there's a lot of different things that can happen here from that binding, but simply put, as the signal comes down, there's negative feedback that goes back to turn off that signal. But I would argue in diseases where there's chronic pain and chronic itch, there's going to be this function in the system, and there's evidence to support that.

Now, CB2. I mentioned CB2 receptors, predominantly in the immune system. You see that PET scan lighting up elsewhere, the spleen on immune cells, which of course we'll not show here.

This is the delineation. The CB2 receptors are more predominantly involved in immune regulation, and I think you heard a lot about potentially how that activation will not just be, for example, inflammatory but actually enable resolution and inflammation, which are two very different things.

Now, I wish it was so linear. It'd be nice if biology were simple, but biology is messy, and while I mentioned CB1 receptors are in the central nervous system, CB2 are in the immune system, there's a lot of cross talk. And we do see both receptors in both locations and actually are endogenous cannabinoids. So, endocannabinoids, which I'll talk about in a moment, they can actually bind to both, which is why I think that was a great question before about purposeful, meaningful development to go after a particular target versus phyto or endogenous cannabinoids that can bind to both receptors, for example. That's a little messier.

And so, very often patients are like, I don't want something synthetic. Give me something natural. Natural makes mistakes. Natural's not perfect. Synthetic, why is that bad? Just because it's made in a lab doesn't mean it's bad. It's actually purposeful, meaningful to use. You take what you understand about biology, and you really isolate that and make it better, and I think that's the way to think about synthetics.

So, the story is definitely not closed. We have a lot to learn but pretty much just like how that cannabinoid was used to be a negative feedback in that signaling transduction so too are endocannabinoids used to turn off inflammation. As you're activating the inflammatory response, at the same time the body automatically says when things go right, well, too much of this is a bad thing, and so, we've got to turn it off. And that's what's actually happening here, and certainly, SPMs are a big part of that.

In the chronic inflammatory disease state, there's dysregulation of these systems. There's dysregulation in that feedback, and so, the inflammatory arm is turned on, and there are different arms to that, depending what disease you're talking about, and you can't turn it off. That is what autoinflammatory means. Diseases like hidradenitis suppurativa, even acne which I'll talk about, inflammation is turned on inappropriately, and it can't turn off. That alludes to that pustule that won't go away, or these resolving human models with that blister, you can't turn that off. That's the problem with a lot of these diseases.

So, let's go to the ligands, the goods. So, there are a bunch of them, but the two most commonly studied are an anandamide or AEA, and 2AG, and as I mentioned, these are naturally produced cannabinoids that will target both receptors. These can be rapidly mobilized in the right settings from arachidonic acid, and as I mentioned, that third arm, the regulatory part, they are degraded by endogenous enzymes.

This is a kind of a schema of how that happens. You need these. You have arachidonic acid. You make them, whichever one you're going to make, through different pathways, and then, they're supposed to be broken down. Now, we're starting to see in a lot of different disease states that this whole schema, this whole pathway, is disrupted. Actually, in lupus, it's been recently shown that FAAH is overexpressed and overactive. So, in that case, you have too little of a good thing, that you may be making endocannabinoids, but you're chomping them up way too quickly, and it's all about checks and balances, and a lot of disease physiology is you lose those checks and balances.

So, our endocannabinoid system is involved in practically everything, and between nerve transduction and regulating inflammation that really covers the gamut of life. So, no question, you want the system functioning correctly. Now, there's already a lot of things we do, and this is not specific to endocannabinoid system, but there are a lot of things that we do that already manipulate the system, and I would argue that a lot of what we already have available to us, biologics, anti-TNF drugs that were mentioned, targeted therapies, these come out of these observations that things that are somewhat generalized in terms of how they work give us a better understanding of what they're doing, and then, we can actually make more targeted therapies. But, a lot of what we do already works through the system, which is hard to avoid the system, given how much it does.

So, let's get to the skin, and the skin is a great representation of how complex the endocannabinoid system can be. The endocannabinoid system is involved in regulating literally everything: skin turnover, life and death, not to sound so dramatic, but really, it is involved in life and death. It's involved in sebum production, inflammation, pigmentation, you name it, and then given how many things it's regulating, dysregulation can result in a lot of problems. Before diving into the cutaneous ECS, we've got to talk about the skin. Anyone else here a dermatologist? Great.

So, let's get to the barebones of what the skin is, and what you're seeing here is a histopathalogical slide. This is what our skin looks like under the microscope. This is the stratum corneum, this basketweave-looking structure. This is the very top layer of our skin. This is what keeps all the disgusting things out and good things in, but it does a lot more than that. And I'll talk about that in a moment. This is our epidermis, this kind of thick-looking structure, and these little circles are the keratinocytes.

Here are your melanocytes or pigment cells, and this bubble gum-looking material, that's the dermis. That is the support structure of the skin. Your collagen, elastin. This is where your blood vessels live, your hair follicles, your sebaceous glands, sweat glands, nerves, everything. So, just to give you some sense of what these different structures are, and I'm going to talk about how the endocannabinoid system is involved at every level and expressed at every level.

So, the epidermis, the top layer, does a lot of stuff. It's self-replicating. As I mentioned, keratinocytes are the bulk of that. These are your skin cells, melanocytes being your pigment cells, but this is an organ of many faces. It's an endocrine organ. It's an immune organ. There are immune cells there that will recognize potential foreign invaders and do a whole lot of good things to protect us from those. It's also a reparative organ. So, lots going on here. So, there's a lot of functionality. There is even inherent UV protectors—there's inherent sunscreen in our skin that is mobilized in the setting of UV exposure as well. So, the skin does a lot, and there's a lot going on to really maintain that. So, to kind of give you an analogy, the ECS really is orchestrating a whole lot of things. Well, there's a lot going on in the skin. The ECS is central to a lot of that turnover. When you have such complexity, there's so many opportunities for things to go wrong, and very little things can make things go wrong. This is a very busy widget, and so, one little missing screw can certainly cause things to be problematic.

Now, even something more superficial, that stratum corneum, that basketweave dead-looking layer, it is much more than simply armor and a barrier. All the things that I mentioned that the skin does it can do just on its own. It's a raincoat. It's a barrier to ultraviolet radiation, to microbes, and its functionality in those settings is so dependent on skin hydration, acidity, a good immune function, and once again, endocannabinoid system plays a big role in maintaining that.

So, there's a lot that can influence even just skin hydration. Things we do to our skin on a daily basis, Purel, washing ourselves, scrubbing our skin multiple times, putting things on our skin, where we live even plays a big role. So right in New York City in the winter, it's cold, it's dry versus Arizona, dry heat, versus somewhere it's nice and humid like Miami. Even the environment can play a big role in skin hydration and can influence the things that regulate how our skin makes itself and protects us.

And of course, this plays a big role in skin hydration and everything I've already mentioned. So, let's talk about how the ECS is really integral to proper skin growth and really, functionality. So, both of those receptors I mentioned. CB1 and CB2 are expressed all throughout the skin. Now, they are expressed at different levels and at different levels, meaning there's different expressions at different levels of the skin. The skin is stratified in terms of how we discuss what the cells look like and what their functionality is.

You think about that epidermis I showed you. The basal layer, the bottom, that's where your resident immune cells are. That is where your machinery that makes the other keratinocytes are. That's where your melanocytes are. So, you're going to have different levels of expression of these receptors in the basal layer, for example, versus more superficially because they play different roles. Along those lines, these are not just receivers of signals. They're creators of signals.

Keratinocytes, for example, can generate endocannabinoids, and that third arm, the regulatory arm, those enzymes are also expressed in the skin. So, you can imagine if, let's say, those keratinocytes could not make endocannabinoids. Let's say that enzyme that breaks down those endocannabinoids is overactive. You can see how that could easily affect all those intricate processes that ultimately result in good skin health.

So, in thinking about the skin barrier, eczema, atopic dermatitis is a subset of eczema, --these are all chronic disabling diseases. Now, these are inflammatory diseases of the skin, but barrier dysfunction is central to that chronic inflammation. Both inflammation drives that barrier dysfunction, dysfunction of the skin, but it also could perpetuate disease.

So, I am going to be talking mostly about inflammation, but I want to highlight the role of the barrier in a lot of these diseases as well. So, this is actually from one study. This was a mouse model of atopic dermatitis. We're using exogenous compounds to actually create both barrier disruption and inflammation, and this was using synthetic cannabinoids. And similar to what you heard earlier in terms of a good comparison, it compared to a topical steroid also, and what you're seeing here are different metrics of skin integrity.

So, "TEWL" is trans epidermal water loss. It's a marker of how much water is leaving the skin, and you don't want that water leaving the skin, or you want a very little bit of water leaving the skin. And in atopic dermatitis, that ability to hold onto water, which is so integral that so much of that functionality is dysfunctional. Capacitance is another marker of skin hydration, surface acidity and even skin thickness, and it was shown that activation of the cannabinoid receptors was analogous to the impact of the anti-inflammatory activity of a topical steroid, and they looked at it through these markers of a barrier protection.

Now, as I said, atopic dermatitis is an inflammatory skin disease, but the barrier--there's this nice Venn diagram of barrier intersecting with inflammation because both are equally important in managing disease.

Itch also. So, what's the easiest way to disrupt the skin barrier? It's us. It's our nails. It's scratching, and so, this among many other skin diseases is extraordinarily itchy. And this is a unique itch, in that it feels really good to scratch. That is these patients' dirty little secret, and if you mention that to them, they're like, how did you know. That's amazing. But they scratch, and it feels good, so they keep scratching. They keep disrupting that skin barrier. They keep creating inflammation.

And so, interfering with that would be very useful, and actually, that's probably the first thing you want to turn off to stop them, the person themselves, from disrupting their skin barrier. And you can think about--well, if you have something that interferes with signal transduction, you know, nerve signaling itch, that could be very useful.

And this was one study--this is a very unfortunate animal model predominantly for students because what you do is you inject these animals with things that create itch, and then, you videotape them. And then, you have some poor student watch how many times the mouse scratches over a period of time. So, fortunately, Charlie and I never have to do that, but, students who want to go to med school or grad school--they get to sit there and watch for hours.

But, what they found was by activating specific cannabinoid receptors, you can reduce itching associated with an agent that's supposed to create itching. So, that goes to the whole point of how one agent can have so many different important impacts on the multitude of factors that go into a chronic inflammatory disease.

Anyone know what this is? Want to guess? Close, a very bad mole, a misbehaving mole. So, this is melanoma. So, this is superficial spreading melanoma. Now, how on earth does it have anything to do with what I've been talking about thus far? Well, I mentioned the epidermis--you have your melanocytes. These are the pigment producing cells. And those are important because that melanin, that pigment, is produced and then packaged and then distributed at the skin, and that's part of the skin's inherent barrier to ultraviolet radiation.

Now, interestingly enough, the production of melanin as well as the survival of those melanocytes, those pigment producing cells, is really dependent on the endocannabinoid system. So, what you're seeing in this diagram kind of split down the middle is, on this side, low levels of endocannabinoids will stimulate the production of pigment through one pathway, but higher levels activated in a different pathway through a different receptor will actually tell that melanocyte to go off and die somewhere in peace.

And so, in thinking about then things like melanoma, you know, too much of a good thing, there has been some preclinical evidence in animal models that, you know, activating the endocannabinoid system can be useful in going after this and actually many other types of cancer. So, just keep that in the back of your mind.

Alright. Let's move a little down. So, we talked--we hit on the epidermis here, this top layer of the skin. Now, let's get into the kind of deeper, more supportive and more nurturing elements of the skin, the dermis, where you have, once again, your hair follicles, your blood vessels, oil glands, everything pretty much. There's a lot going on here. And, as you can see from this diagram, there's a lot of opportunity for cannabinoids to do their jam.

So, let's first talk about the pilosebaceous unit. This is the hair follicle as well as the oil glands. So, pilosebaceous--sebaceous means oil gland, pilo referring to the hair follicle. This is important for a lot of basic functionality of the skin. Sebum coats the hair. It does contribute

somewhat to the skin barrier. There are some antimicrobial properties in sebum. And then, the hair follicle itself is important for regulating body temperature, protecting us from some external elements. But, there's a lot of things that it can certainly do.

Now, both of those receptors I mentioned are expressed at different levels of this unit. And that, once again, is why it's so important to think about what your end game is--you know, which one--or do you want to hit both or one of the other--in terms of what they'll actually do. You know, you just want to throw and maybe hit both of them--in some cases, that might be useful. But, it's all about purposeful development to go after a particular part of this unit, for example, if you're going after a certain disease states.

And so, that brings us to acne. Chronic inflammatory disease, affects anywhere from 40 million to 50 million Americans annually, probably the most common skin disease, but extraordinarily complex inflammatory and skin disease at that. Now, historically, we used to think about two types of acne. There was the noninflammatory, like whiteheads and blackheads, and then, there were the inflammatory lesions, papules and pustules. And we now know that all acne is inflammatory, that even if you see that whitehead, if you were to take a biopsy of it, you would actually see early inflammation around the pilosebaceous unit.

And the center of this are pattern recognition receptors. These are gatekeepers of inflammation. Some sit on the surface of cells like toll-like receptors. Some are in the cells like the inflammasome. And I will just refer back to Charles Serhan's lecture. He mentioned the NLRP3 inflammasome, which was shown to actually be the inflammasome for acne. And what's happening here is that these recognizers, these surveyors of signals such as bacteria, dead skin cells--in acne, they are over responsive. They are reacting to the wrong things, and they don't really know how to turn off. That's where resolution mechanisms can be very helpful.

And at the end of the day, whether you activate one or the other or both, what happens is you ultimately get the production of IL1 beta, interleukin-1 beta, which is like the master inflammatory cytokine. It does a lot of things downstream in terms of creating inflammation.

So, looking at that pilosebaceous unit, really focusing on that area of the dermis, there's a lot of opportunity here. So, we know that endocannabinoids, phytocannabinoids can have influence on the sebaceous gland when you're going to actually also have an effect on the hair follicle itself in terms of growth. We're not going to really focus on that today.

There's one nice paper looking at how the endocannabinoid system could potentially be useful in the world of acne, and that's it. It's kind of surprising, given how common and prevalent this disease is as well as given the marketplace. But, this was a nice paper published in *JCI*, which we saw many of Charles Serhan's paper published. This is one of the top tier scientific journals in the world. So, I'm not going to go too much into nitty-gritty details. But, what you're seeing

here is that sebocytes, sebaceous gland cells, annoyed with a danger signal, lipopolysaccharide, when exposed also to cannabidiol, CBD, that actually limited to the production of that interleukin-1 beta, that really master for inflammatory cytokines.

Interestingly enough, if you also gave these cells the goods to make sebum and then expose them to cannabidiol, you actually can inhibit the production of sebum. And we know that sebum, granted it's part of what we need, too much can actually facilitate the overgrowth of certain organisms in that unit that can also be pro-inflammatory. So, there are some drugs coming out. There's one, I believe, coming down pipeline or may even have just been approved, that is a sebum inhibitor. So, clearly, inhibiting sebum is going to be important for acne as well.

Now, what I have to do, given there's such limited information in the dermatology world--I have to kind of grab from my colleagues. And so, normally, you would not expect a dermatologist to be looking at cardiac journals or papers on myocardial infarction, heart attacks. But, what drew me was this: inhibition, suppression of NLP3 inflammasome mediated by CB2 receptor agonism. And so, we can draw a parallel from that that it's probably through that inhibition that we see that anti-inflammatory effects. But, I'm sure SPMs probably play a big role in this as well.

So, I think there's a lot of potential here, and this is low hanging fruit, in my opinion. A common disease state--there's a lot in the market, mostly does all the same thing. There's a unique opportunity here, I think, to provide something new with a new mechanism of action.

But, let's go into inflammation in the immune system. As I already mentioned CB1 and CB2 have been found in this system, predominantly CB2, expressed on immune cells, expressed on immune organs, and CB2 most heavily. But, CB1 is there as well. Wound healing, I think, is a nice kind of model for thinking about inflammation. And I will argue the wound market, similarly to acne, is massive because, one, wounds are very common, both acute but even more importantly chronic wounds, but two, they result from so many different things. And if you look at this multibillion dollar market, there's not a whole lot there. Most of what's there are actually antimicrobials, which--killing bacteria doesn't necessarily help a lot with wound care.

Now, I like wound healing because it's also a complete crazy high-level orchestra of cellular biology. There's so much going on here. But, central to this is one cell, and that's the macrophage. If you remove macrophages from the scene, someone will not heal, just will not happen. And it's not just about a macrophage. It's about which macrophage. And that's what's really important. And as we see wound healing progress from the inflammatory phase when you first get that injury to the colliferative phase where new collagen, elastin structures are put down, those types of macrophages changes. You need to kind of move from this M2 to an M1, this inhibitory macrophage to allow for healing. And the cannabinoid-2 receptor is central to that. And we know that a lot of chronic wounds--they just can't transition. They can't take that step. So, I think there's a unique opportunity there in wound healing as well.

We do have some very low-level evidence. This was--not a study. This was self-reported patients. So, these were families with children who have a rare genetic disorder called epidermolysis bullosa simplex, where they're not making an adhesion protein that keeps the epidermis bound down into the dermis. So, these patients will get blistering on stress bearing areas. And these three families just decided to take it upon themselves to use CBD oils, whatever that means. We know there's not a lot of quality assurance there. And they all reported there was some benefit there. So, that's really where we are with the evidence. We need more information to really make any judgment calls here.

Alright. Psoriasis--very common disease, affects about two and a half to three percent of the U.S. population. That's about roughly the population of New York. We know this is a disease of inflammation. And interestingly enough, if you look at the indications for physicians writing letters of recommendation--can't prescribe medical cannabis--but for writing letters of recommendation for someone to go to dispensary, psoriasis is actually indication in two states even though there's absolutely no evidence in the setting of psoriasis to support that.

If you go online and Google "cannabis psoriasis," you're going to get a whole lot of these, but not a lot of information. Most of these cite basic science papers, cell-line papers. So, what are they citing, and what are they thinking about? So, as I mentioned, this is a disease of inflammation, and the story of that inflammation has changed. Historically, we thought this was a disease of too much TH1. So, we thought that naive T-cells were being stimulated to kind of go down this pathway, specifically IL-12 was to the cytokines, kind of pushing towards that pathway. And these cells would then produce TNF-alpha. You've heard that. This is a very important proinflammatory cytokine.

And so, all those drugs were targeting TNF-alpha because that had to be the problem. That's where you saw a lot of the original biologics. Now, serendipitously Janssen came out with ustekinumab, which they were going after this P40 subunit of IL-12, and they didn't know it was shared by IL-23. And that's where the whole market of interleukin-17 blockade or IL-23 blockades really came from, that serendipitous discovery. And so, now we know that it's really this pathway that's very important. Now, I'm harping on this because, as I said before, I have to kind of borrow data outside the dermatology world to kind of make sense of where the endocannabinoid fits in for psoriasis.

So, you heard about neutrophils. These are the kamikaze pilots of the immune system. These come in very early on in inflammation. They generate a ton of free radicals, killing everything and themselves in the process. A pustule--you heard about these little blisters filled with pus. That pus are dead neutrophils. That's not infection. Those are dead cells. And what happens is it's from stimulation of these pathways, those neutrophils will come out of the blood vessels and enter the skin, in this case.

And so, you heard about how SPMs can prevent that entry into, in this case, the skin from the vasculature, which is called diapedesis. And in this study, similarly, they showed that activation of the CB2 receptor prevented that and I would argue probably have something to do with those SPMs.

I mentioned interleukin-17. That's like the target molecule nowadays. But, Charles Serhan and I were talking about this before and Barbara as well that, yeah IL-17 is hot right now but, who knows what the next target will be? It keeps funneling down. But, right now, that pathway, that TF-17 pathway is what we're looking at. And so, I grabbed this from, once again, a paper outside of dermatology, looking at how do phytocannabinoids have that anti-inflammatory effect, and it's through reduction of interleukin-17 secretion in this proinflammatory model. So, clearly, something's going on when you activate the endocannabinoid system that you were inhibiting secretion of this very important cytokine in psoriasis.

Potential for autoimmune disease--clearly that is the topic for today. And I'm not going to steal Barbara's thunder. But, I will say I think there's tremendous potential. But, I also want to comment--as of right now, we've got really nothing. The majority of drugs we use to treat all of these horrible disabling diseases are all off label. We're using them because we know how they work. We know they're anti-inflammatory, the different mechanisms. But, nothing's actually indicated for these. Lupus--yes, there are. But, dermatomyositis, scleroderma--we've got nothing. We're pulling out all the stops using our understanding of how these other drugs work. So, I will not go further than that. I will let Barbara kind of talk about that area.

But, I'm going to finish up by kind of going back to the beginning in terms of the climate we're living in. So, with those regulatory changes, we see this influx of all these different products in the market. The FDA's like, "I don't know what's going on here. Oh, yes, I do. We've got to do something." And so, just the other week, we saw this release of additional 14 letters being sent to different companies who are putting cannabidiol in oral products, in systemic products because we have a CBD-derived drug that is FDA approved for two different seizure disorders. And therefore, it's now a drug. So, there is a rapidly changing market. We're going to see a lot going on.

But, at the end of the day, what we need is industry to actually do the science. And so, that's what we're seeing with Corbus. We are seeing the right science being done, the right pathways being followed to, one, get a drug approved, but also, to better understand this really rich and complex network, but also to understand how it impacts our patients. Thank you so much for your attention. I'm happy to take any questions. Okay, thanks.

Barbara White

I'm going to do an abbreviated version of Dr. Gordon's presentation so that we can get to a panel discussion before too much longer. So, I think what--I'm going to hit a few high points and then a bit of data. I think the first point she wanted to make was about the underlying path of physiology of the disease. Scleroderma, this rare, life threatening, systemic autoimmune disease with high morbidity and mortality, has three major components: chronic inflammation--that sort of migrates into autoimmunity, fibrosis--which is really characteristic, skin, internal organ leads to a lot of dysfunction, as well as vascular damage. And the vascular damage is really proliferative, you can almost think of it as the fibrosis of the vessels.

And I think she would have--the next thing I want to show you are really just to bring home what this disease is. People have inflammation early on, and you will see swelling—they're actually swollen. That may be the first thing they notice. And then, after a while, it gets very hard, and they cannot even move their hands, their digits. And then, it gets atrophic, and the skin actually becomes more normal like, but there just really isn't normal skin structure underneath, and they can get a lot of contractions.

Here's another example of--it may be a little hard for you to tell. But, this person's skin is swollen, and if you actually touched it, you could leave your fingerprints if you pressed hard enough throughout that person's skin. And this is a picture of a gentleman--it's usually more women than men--but, a gentleman with some very characteristic signs. You see some darkening of his skin and some lightening of his skin. Those are effects on the melanocytes that you just heard about, the actual loss of some and activation of others. You see swelling in his hands. You see joints contracted because of inflammation in the synovium. You see that this man can't actually open his mouth to eat easily because of scarring of the skin in his face. He can't open his eyes. He looks like he has this staring look. He's lost all the tissue in his face. But, the skin is very tight.

I once had a lady who was really into plastic surgery, and she said, "I wish I'd known I was going to get scleroderma. I could have saved so much money," because they really have this tight look to their face. No wrinkles. And these are the hands of an African American. They often have worse disease. You can just see how dysfunctional that is, ulcers on the fingers, loss of finger pulp, and amputations.

And as she would have pointed out too, the major cause of death is now interstitial lung disease. It used to be renal crisis, renal involvement with vascular disease. It's becoming less of a problem. But, problems from pulmonary artery, hypertension, and pulmonary fibrosis are increasing.

And she just shows you here how this lung disease can progress in these patients. It starts out with a little bit--they would call this ground glass. It's kind of fluffiness there. It progresses. This is the beginning of some scarring. These little poles are beginning to structural--loss of normal

structure and then, you just see here whole lung constriction of the lungs. That lung is all scarred down.

And so, she wanted to point out to you that the current treatments are not as effective as she would like them to be. As you've heard, it's mostly off label use of immunosuppressants of choice. In the U.S., it's mostly mycophenolate, methotrexate, and some steroids thrown in.

So, then, she would have moved to another discussion of the endocannabinoid system. You heard the major role of the cannabinoid receptor-2 in inflammation and modulating inflammation and resolution of inflammation. There are even knockout mice that have the loss of CB2. And if you use--these mice are normal unless they're stressed. And if you stress them with a chemical, in this case, hypochlorite, which generates oxygen radicals, you actually get really pronounced inflammation in their lungs and in their skin, compared to the normal degree you would get in a wild type mice when stressed with the same agents as generates oxygen radicals.

And this is some background data from John Varga, a mouse model of skin fibrosis induced by bleomycin. So, it's an inflammatory model--they get inflammation and then they get fibrosis. Normal skin looks maybe not quite like human skin, but normal skin in a rodent and a mouse against bleomycin and after a while, you get a lot of thickness. This is exactly what happens in patients with scleroderma.

That thickness is actually just too much extracellular matrix. Extracellular matrix is nothing more than a concrete of your skin. If you think of a brick wall, you have bricks. That's the cells. But, you have the concrete between the bricks. That's the extracellular matrix. Scleroderma is too much of the concrete. It's too much of that matrix in the skin. So, it just gets thick and hard. And that's what you see in this model. That's just too much extracellular matrix. And animals when treated with a fairly low dose of this CB2 agonist, lenabasum, have normalization of that skin thickening.

And I think then she had planned to go onto some of the results of this study. I'm going to skip a lot of it and just show you the most recent open label data because I think you've seen the other stuff before. This study was an initial 16 weeks, double blind, randomized, placebo-controlled study. Folks were off drug for about 20 weeks. Meanwhile, we got an open label started, which we weren't initially planning to do. And then, the study is continuing. So, close your eyes while I flip the slides --you'll get vertigo or seizures here. She had a lot of stuff in there. Oh, okay.

I do want to talk about safety. So, I think that the finding is we've had a number of patients on this drug now, maybe in their third year. So, first, we've had good persistence, about 81 percent of patients are still in active completion of two years. And what we've seen most commonly are

common things in people - upper respiratory tract infections. Common things in people on immunosuppressants - urinary tract infections. Common things in scleroderma – anemia, skin ulcers, cough, dizziness - which is probably an expected class effects pretty infrequent here in the open label, a little more than ten percent of patients have it.

So, this is the summary, as I said, that nearly all patients will have an adverse event. These are sick people on immunosuppressants, and they're followed for more than two years. So, I'm actually surprised there's one of them who hasn't reported something yet. But, there haven't been any serious or severe adverse events or study discontinuation from this open label related to lenabasum to date. We've had two patients--we had two patients drop out with tendonitis and scleroderma renal crisis, things that would be understandably related to the disease. And the serious AEs were expected things, in large part, again, not thought to be related to the drug.

And you've seen this American College of Rheumatology CRISS score. We've talked about it before. And simply, what I show you, if you weren't at the American College of Rheumatology is the extension of the CRISS data in the open label, out now to a couple of years. And I think the important part is the response is durable. It's not really changed much. So, I think that's actually fabulous news if you want to treat a chronic disease and have patients continue to maintain some benefits. So, that is very reassuring. Now, there will be wobble from visit to visit and what they report. And maybe this will be better this visit and that will be better at the next visit. But, in general, they're overall pretty stable.

And here's the change from baseline, again, in the mRSS, which is the skin thickening. The doctor pinches the skin--it's not a very high-tech measurement--the doctor pinches the skin and assesses how thick it is, how much of that concrete or extracellular matrix is in the skin beyond what you would suggest. And you see that there is an improvement. And, again, that persists. Wobbles a bit, but it persists.

And here are improvements--it shows improvements in patient reported outcomes, how much the skin bothers the patients. It's a symptom. These are some pretty substantial improvements here. And, again, they're persistent. And itch--I know that Adam Friedman talked to you about itch and the importance in many diseases, and itch is a terrible component of scleroderma.

The lung function was relatively stable during about the first nine months of the open label extension. It certainly declined a bit more. It's hard to say what would be normal to be expected in this group of patients. Most of these patients are on MMF, mycophenolate. So, if you were going to look at that, it might be a couple percent over that year. So, I don't think it's unexpected, and it maybe isn't quite as bad as I might have expected. So, I'm okay with those data. We'll see what it would look like with a placebo control group in the Phase 3.

And function--this is just a measurement of function. Again, stable and improved. And the docs and the patients think the patients are still doing better than baseline. So, I think the summary that she had was--and most importantly, because we've heard about this--and Charles Serhan talked about it at length--the importance of having a chronic therapy for chronic bad diseases in which the safety profile is tolerable. And the fact that we've got so many patients still in this study in their third year and in the dermatomyositis open label, we're at 90 percent at the end of two years. That really speaks well to how they can tolerate this and what it's worth to them to come back and keep these regular visits. So, to date, it's been safe and well tolerated, and we have durable efficacy in this study.

And I think with that, I'm not going to take questions. But, I'm going to invite Charles Serhan and Adam Friedman back up to the front, and we'll entertain questions from the rest of you. Are there any questions? Any questions from the group?

I actually told them I was going to ask them each one to get you kind of warmed up because this is all about a potential therapeutic usefulness of targeting the endocannabinoid system. And I know they each gave you a whole plethora of potentials, which is great. But, I wanted to ask them each what their favorite was, what their favorite would be to target because these are experts. Charles Serhan is the world's expert on resolution. Where he sees real value, where you would go, Charles Serhan, what you will tell me to do when you're sitting on the scientific advisory board, where you would go with potential drugs, whether it's another CB2 agonist or CB1 inverse agonist. What would you be thinking? And then, Adam Friedman, from you.

Charles Serhan
Well, my personal favorite would be to target that M2 macrophage because I like this capability of clearing debris. It's the way nature's evolved. It extends all the way over to cancer models. And we found most recently that if you could stimulate clearance of debris and inflammation around tumors in animal models, that you could lower the burden of tumor to that mouse. It's a mouse model. And you can lower the amount of tumor therapy. So, I think that's pretty dramatic in terms of the mechanism of turning on something.

And I don't--I'd have to say that Big Pharma has not taken advantage of knowledge of agonists in the system. And they have focused--really the concept that we're seeing introduced by Hippocrates - go chew some bark of the tree if you are pregnant and have some pain. And that, of course, turned out to be salicylate, and you all know the story between salicylate and aspirin. But, almost all the non-steroidals that were developed and synthesized in the 1950s and 60s--I don't know if you mentioned over the counter drugs. But, things that you would take for a headache. They all block. So, the next generation of drugs--they blocked the innate immune system. They inhibit enzymes.

So then, the next biologics come along. And the same line of thinking, "Oh, we've got to block this. We have to block that. We have to block IL-17. We have to block IL1-beta." And all I can tell you is, from my perspective, you don't want to block TNF-alpha. We have to take a different view. It's such a critical mediator in the innate immune response that when we do block it 100 percent, we've become immune suppressed. We open up the system to TB, everything across the board.

So, I'd really like to see agonists developed and agonists that target the macrophage, like CB2 is a player. And I think the--I began by talking about serendipity. It was really a serendipitous finding to take ajulemic acid, which is lenabasum today, that was some years ago, more than ten years ago, with a very bright medical student, a Harvard, MIT student, today is a cardiologist, and do that experiment with Bob Zurier that taught us that the mechanism of action of this drug is stimulating endogenous resolution mechanisms. So, I'd like to see as many of those mechanisms extended as possible.

Barbara White
Thank you, Charles Serhan. Adam Friedman?

Adam Friedman
I was happy I was going second. It gave me more time to think. But, that was beautifully said. So, that's hard to follow. So, I think the concept of not blocking but more modulating and more bringing back to biology and how biology is supposed to be, I think, is something we're striving to. I mean, even thinking about the term small molecule inhibitors, IL-17 blockers--I think there's a huge opportunity, not to say these drugs I don't use on a daily basis. They are game changers. But, I think, as you follow how biology functions and you develop based on that, I think you're going to get better outcomes.

In terms of picking one disease, that's really hard. I think--I can put on a couple of different hats. So me personally, what disease, I think, has great need in my practice for which we have some but not a lot would be a disease called hidradenitis suppurativa. This is an autoinflammatory disease where patients get what in essence look like abscesses, boils, in their underarms and their breasts and their groin. It's deforming because of this chronic inflammation you actually don't heal. So, talking about wound healing, they don't heal properly. So, as this boil ruptures, instead of healing with a scar, they actually form these sinus tracts and these weird scars that don't come together correctly, and that actually perpetuates the disease. And it is extremely painful. We talk about itch. Extremely painful. We have one FDA approved drug, which is adalimumab, Humira, which has been around for a while. But, there's huge opportunity there. And I'd throw everything and the kitchen sink at these patients. And even with that, I can't get them under control, and they are miserable. So, that's me, personally.

I think certainly, from a business side, I mentioned acne. Acne would be a clear target, no question, will continue to affect more and more people. It too, like hidradenitis, is deforming. It's not the acne that worries me. It's the scarring that comes afterwards. And so, a drug that can both reduce inflammation, get you back to baseline, but also modulate healing would be extremely impactful and then, of course, from a business side, be very lucrative. So, I have to go with both of those.

Barbara White
We have a question.

Operator
Thank you. We do have a question from Liisa Bayko with JMP Securities. Please proceed.

Liisa Bayko
Hi. Thanks for taking the question. I appreciate it. I was curious if you'd be looking at the data in scleroderma or dermatomycosis to really kind of--as a read through or any information to how lenabasum may benefit some of these other dermatological indications you're thinking of. And, I guess, for the Company, what comes to mind?

Barbara White
Liisa, this is Barbara. I think we lost the last part of the question. Would you at least repeat the last phrase or so? It didn't come through clearly.

Liisa Bayko
Yeah. The last phrase was really around--what was I going to--now, I forgot my train of thought. Never mind. It'll come to me.

Barbara White
But, I think the first part, if I understand, and I'll direct it I think, probably, Adam Friedman, to you first is--is there any read through from potential efficacy of a CB2 agonist such as lenabasum in chronic autoimmune diseases - scleroderma, dermatomyositis that effect the skin to other skin diseases?

Adam Friedman
So, I think the most obvious translation would be to do--I mentioned before--the atopic dermatitis. So, I don't want to kind of minimalize how the immune system works. But, you have TH1 or you think of your innate immune response, which is your immediate frontline to offenders outside trying to get in and cause harm and then you have your adapted immune response which takes time to manifest. And that's where you have your proteins, your immunoglobulins.

Autoimmune diseases fall under TH2. And so, I think that a lot of the factors that we've seen from a preclinical studies, from the early clinical work, what's actually being modulated, I think, would actually translate very well to atopic dermatitis, which actually affects roughly between 20 million to 30 million Americans, including kids. So, I think there's certainly potential there. I think we are seeing some parallel clinical programs going after indication. But, that seems to be the most obvious.

But, I think it's not a one trick pony. I think activation of this system isn't necessarily specific for one type of inflammation. It's a feedback mechanism. So, I think it will down regulate over expression of other arms too, like we saw--some of the data you saw with interleukin 17, T17 pathway, or even TH1. I think it will affect all these. But, from that data specifically, atopic derm would make a lot of sense.

Barbara White
Charles Serhan, did you have any comments?

Liisa Bayko
Then, I guess I would ask Barbara and Yuval--what are your priorities beyond scleroderma and dermatomyositis in terms of any other dermatological indications you're thinking about? Thanks.

Barbara White
Liisa, this is Barbara. I'll address that in just a minute. You couldn't see but, Charles Serhan had a comment he wanted to make to your first question. So, I'm going to go back to Charles Serhan first.

Charles Serhan
I'll try to be very quick. So, I think it's--I can't underestimate the--we're talking about here. That we have an agent, a drug, if you will, that's tapping into this endogenous resolution mechanism. In some of the more recent work that's going in my group in Boston is--we've been looking at communication molecules that stimulate into tissue regeneration. Now, why is that important? Because you heard about IPF in the lung. You heard about excessive scarring in kidney. And this is really a big problem in many--in aging populations, in this disease and others.

And what we found in very primitive systems--and you have to extrapolate on this—is that resolution stimulates tissue regeneration. And there are three additional pathways that I didn't talk about today that resolution signals proper tissue regeneration. So, those are the mechanisms that are very likely failed in these diseases. So, the question would be--can we use lenabasum or "son of lenabasum" to—or "daughter" --that can tap into tissue regeneration programs through resolution, prevent organ scarring. I mean, that would really be exciting.

And you'll know that the nonsteroidal anti-inflammatory drugs enhance organ scarring. This is a big problem. So, that would be my wish list for the holiday season.

Barbara White
And Liisa, I think your next question was directed to Yuval or me. So, I'll take it because he's sitting down. But, I'll ask him if he wants to say anything. And that would be--what else are we thinking of? Right now, we have our plates full. We have got Phase 3 data coming out in the scleroderma study this coming summer, midsummer. We have data coming out in the Phase 2b CF study, probably right on top of that. We are hunkering down to finish enrollment in the dermatomyositis Phase 3 study. It's going well. But, I imagine it will finish somewhere about the same time, at least in terms of enrollment.

So, we have a very, very busy next six months. And we want to deliver those things. We think that that's really our first priority. We're certainly thinking about other opportunities, and there are many. And we have not yet made a decision. But, we are thinking about where we'll go explore. And as soon as we make up our minds, we'll let you know. But, it is under consideration.

Liisa Bayko
Thank you.

Barbara White
Any other questions?

Owen Drinkwater
Hey, Owen Drinkwater at RBC. Just two quick ones for the doctors from me. First, we didn't directly touch on this today, but thinking about the CRISS composite endpoint in scleroderma, I'm wondering if there are any of the components in particular that you look for as treating physicians that correlate best with real clinical benefit or if you're really thinking about it from a totally--as a composite score.

And then, secondly, we spent a lot of time, particularly Dr. Friedman, about skin inflammation. And I'm wondering if you can comment on any differences between skin and muscle inflammation and how that might affect how a drug targeting the endocannabinoid system would work in a disease like dermatomyositis. Thank you.

Adam Friedman
So, this the first question--actually, I'll take the second question. Well, I will make a comment about--so, realize, when you're trying to get a drug approved, you need validated research tools that, if anyone got their hands on that tool doing a study, that they would get similar data to someone across the world. And that's--the whole idea of a Phase 3 is you have several hundred

people, different locations, different times of years. And you're repeating that, and you're hoping to see that your range in terms of those percent of patients meeting primary outcomes are pretty much maybe one or two percent apart. That's really what you want to see.

So, you're right. A lot of these tools we use we don't use in the clinic. I think the value of those tools is only there, from a clinician's perspective, as you're disseminating information you explain what they really mean. The opposite is also true that just because someone doesn't meet the primary outcome doesn't mean they don't get benefit.

And so, you get whatever percent of patients hit that kind of mark on whatever tool you're using, chances are a big chunk of people who are actually doing really well but, to the FDA's perspective, aren't a clinical success. So, I think you have to take those types of scores with a grain of salt. I think--what's not even--what isn't even fit into that is also patient reported outcomes. So, if I see a patient, I'm like, "Yeah, you're doing okay," and they're like, "I feel great. I feel the best I've ever felt in my entire life. Thank you." That almost is more important than that.

So, I think there are a lot of other metrics that don't necessarily fall into those validated tools. But, you need those tools in order to get to that point where you can actually have that conversation. And then, I'll let Barbara jump into answer the rest of that.

In terms of muscle inflammation, it's hard to say. That's a little outside my scope. You can certainly jump in if you'd like to talk about it. But, with dermatomyositis, for example, we have patients with skin only dermatomyositis. And we call it dermatomyositis sine myositis, and it's almost a different type of disease. So, I think there are some differences in terms of how a drug would possibly work on one or other. And then, you have polymyositis where you just have muscle inflammation. You may not have skin disease. But, from the muscle inflammation I'm not really sure how distinct those differences are and how it relates to endocannabinoid system. And I will pass it on.

Charles Serhan
Before you get to the disease, I'll just make a point about muscle. So, it turns out that if you talk to people in the exercise physiology world, they think about muscle now as in a state of inflammation resolution. That's its homeostasis. And there are studies in humans that were done in New Zealand recently where they did strenuous exercise and shown that they have this temporal change in initiators, the pro-inflammatory mediators, and then, turning on of pro-resolving mediators.

And in 60 individuals, they showed that if they take a nonsteroidal anti-inflammatory drug, they uncouple that. And it has a lot of consequences, if you think that through. The study was published. The first author is Mark Werth, and it's the *American Journal of Physiology.*

Barbara White
Two quick comments because you addressed them, first - muscle does express CB2. Activated muscle expressed CB2. So, there's reason to believe the receptors are on there. And there's data in the literature, not in scleroderma, but activating CB2 actually has beneficial effects that would be consistent with resolution, normalization of activity.

In terms of the ACR CRISS score, which is a primary outcome in the Phase 3 scleroderma study, indeed it in a composite. It will come out as a number, and it's the likelihood that the patient has improved from baseline. And you're right. That's difficult to interpret. But, it's very useful for regulatory purposes. But, it has the components, and I think that the value will be to look at the individual components, make sure that they all improve in a directionally correct manner to see how much the components improve and, again, take a look at the patient reported ones. There are two cases--there's a patient reported global: "How am I doing? I'm doing great," or, "No, I'm doing better," as well as function, a very well validated patient reported function. And I think those will help with the interpretation beyond the number.

Mikahail Keyserman
Just a question for the two physicians. Can you just maybe comment a little bit about the patient journey in terms of diagnosis? So, one of the presentations made reference to sort of initially for scleroderma, seeing some inflammation in the digits and extremities. But, given that it's a multiorgan driven disorder, renal, pulmonology--how do you sort of--how is that journey of diagnosis sort of happening? How can we accelerate that for different practices?

Adam Friedman
So, I think it's tough and if you just look at autoimmune diseases overall, I think some of these patients will get to me first. Others will get to pulmonology. Some will get to nephrology. Some will get to rheumatology. It's highly variable. With scleroderma, early on, patients often don't really understand what's going on. You heard before that these patients actually ended up looking younger because of that tightening, they actually lose wrinkling. But then, what can happen with the involvement of the face, your ability to open your mouth to smile. That's actually one of the things we do when we walk in the room. If we're suspicious, we say, "Give me a big smile. Show me your teeth," and they can't.

They may not come our way. I definitely do have scleroderma patients in my practice. I find they often don't start with me. They get to me. However, there's a form of, what's called localized scleroderma called morphea which is--it's pretty much, in essence, scleroderma that just affects the skin. Those patients are coming to me. They tend not to have other organ involvement but, we still have to make sure they don't. We have to work them up.

Lupus and dermatomyositis--I think those patients definitely make my way because they're presenting sign can be rash and then I'd see that rash and say, "Can you raise your hands above your head," or, "Can you get out of that chair?" And that's where the kind of muscle involvement can certainly be woken up. But, in those cases, being that these are multi-system diseases, I'm definitely phoning a friend. I'm getting those other specialists involved and actually given that skin's so accessible, a skin biopsy can actually be very helpful in terms of saying, "This is an autoimmune disease," because you actually can't distinguish between classic acute lupus and dermatomyositis under the microscope. But, at least it's suggestive.

So, sometimes we're the starting place, and sometimes we're just being thrown into the mix. For scleroderma, a lot of wound care discussions are needed. There are a lot of topical therapies that can be an adjunct to what they're doing systemically that maybe a non-dermatologist doesn't know. But, it is a very different journey for almost every patient. But, I think what you're probably getting at is all these patients coming into my office and there's an opportunity for me as a dermatologist to be their first point of care and prescribe something systemic. And the answer is yes. So, dermatologists are very comfortable and familiar with using systemic agents. We use all the biologics. We use all the classic immunosuppressants. And so, yes, if I had a drug that was indicated for this and my suspicion was high, I'd be starting them on that.

Barbara White
Other questions? If not, I wanted to thank everyone on the webcast--and Liisa, thank you for your question. Thank you, all for listening, a special thanks for everyone in the audience who have come and sat and participated and listened. We're very grateful to you. And we'll see you again soon, I hope.