# Advancements in ADEM and Optic Neuritis Treatment with TRE-515

You can view this presentation at: youtu.be/03HAVgqSJ_M

[00:00:05] **Dr. Kenneth A. Schultz:** Great. Well, thank you everybody. It's great to be here. I actually met Sandy and the Siegel team a little bit over two years ago. We were doing research in the lab, and we're seeing very promising results on demyelinating diseases -- in fact, so much so that the FDA granted us, they reviewed our data and gave us Orphan Drug status in optic neuritis and ADEM.

[00:00:29] But our question was: Can you tell us more about the patients? As we think about this, what are their lives like, and the like? And so that invoked into a thought partnership. Then, I guess a couple months ago, they asked, "Well, could you come and tell us what you've been up to?" And it's actually pretty exciting, and I enjoy being here, getting to see the end product of the results of our research, and really learning from you guys as we go forward.

[00:00:56] First off, a little bit of a disclosure: I do spend a lot of time at Trethera, working on this project. And now, I'll go ahead and tell you what we're up to in terms of the current state. Why does an emergency room physician run a biotech and go forward with a drug to treat patients?

[00:01:15] Well, we've had some really good developments lately. First off, we dose the first patient in medical history with this drug, a dCK inhibitor, in a cancer trial. We're currently running a dose-escalation trial for patients with solid tumors.

[00:01:32] Secondly, it's been incredibly well-tolerated. This is a once-a-day pill that patients take by mouth, and so far, we've not seen any dose-limiting toxicities. We're about two dozen patients in at this point.

[00:01:47] Thirdly, we have been able to do quite a bit of research in the lab, working with mice, and we're able to be designated an orphan drug by the FDA for two of the diseases that we're looking at this weekend at the conference: ADEM and optic neuritis.

[00:02:05] Also, in the last 24 months, we've been awarded over $7,000,000 in grant monies from the NIH after scientific review, of which over half of that have been in these demyelinating disease spaces.

[00:02:18] And then, lastly, very close to home, we will be filing a pre-IND package with the FDA this year. We're about 100 pages in already to be entering an ADEM Phase I trial and able to cross-reference our existing clinical data. This is really important. We already have a clinical safety and data package already with the FDA with our solid tumors patients that we're dosing currently.

[00:02:44] Now, I like to say that who you're working with is 10 times more important than what you're working on, and we've really established a nifty team -- a superb team of scientists and physicians -- that are helping to make this go forward. Some of these have been part of this conference throughout the years.

[00:03:02] The other thing is our second team. We've been funded to date by a very tight-knit, close group of grateful patients who've been able to cheer us on with each step of the way. That's the team. Let's talk a little bit about the science.

[00:03:20] In order for cells to divide, they have to have two sets of DNA, and they can do that through one or two pathways. There's the de novo pathway, that's there on the top, and then there's the salvage pathway, that's there on the bottom.

[00:03:35] Now, the de novo pathway takes the things that we eat and then makes these DNA building blocks by scratch. That's why it's actually called de novo, right? From scratch. And then, the cell has two sets of DNA; it can divide. You may be familiar with some of the drugs that work in this pathway. Both Aubagio and Mavenclad are FDA-approved for multiple sclerosis.

[00:03:59] Now, there in the bottom of the slide, in orange, is the salvage pathway. Rather than making these DNA building blocks, called nucleotides, from scratch, they make them by exactly what the name says -- recycling or salvaging little bits of DNA that are circulating outside of the cell. They bring them in and then are able to make all four of those DNA building blocks.

[00:04:25] Our drug, TRE-515, works on dCK. This is the pathway -- the salvage pathway -- is what we are targeting, and this has never been done before. This is a first-in-pathway, first-in-class drug that we've developed with close collaboration, of course, with UCLA and other universities. The pathway is important probably for two reasons.

[00:04:49] One is that, it's upregulated in whenever cells divide abnormally and rapidly, like in autoimmune diseases. They favor the salvage pathway because it's a shortcut, right? Everything's already done; you just have one little step. It's much faster, takes less energy. The second part is dCK blocks all four of those DNA building block precursors, so it's like the rate-limiting step in the process.

[00:05:19] Well, let's go a little bit more. Where we are today was actually quite a story in the making. In fact, when I graduated medical school in the previous century -- which seems a long time ago -- we all knew dCK in terms of its identity and its function. But it was really in 2009, where scientists at UCLA started looking at dCK as a potential drug target, and they started finding a few things.

[00:05:47] One was: if you inactivate dCK, there's these immune cells, T cells and B cells, that they seem to be impacted. And so, the next thing they found is: well, if you do it while they're dividing, it creates replication stress. So, that could potentially treat diseases of abnormal cell division.

[00:06:10] And very interestingly, when they knocked out dCK genetically -- when mice were born with no DCK, no gene -- they live normal, healthy lives. That puts you on the trail of drug development. In 2014, they started thinking, “Well, what about T cell cancers? Could we look at something like that in the mice and the like?”

[00:06:32] And then, things really started to develop. They took over 1,000 different compounds and screened them. They found that TRE-515 seemed to be the optimal structure. We have developed some biomarkers that are very important -- we'll talk about those a little bit more -- both the PET probe and the liquid biomarker that we can measure with both patients (we're doing it now) and also with mice.

[00:06:58] And then, we formed a company -- actually, I wasn't there. I came a little later -- and we also did the neuro pilot study. And it was really at the end of 2021 that things got interesting. We got the Orphan Drug designation for optic neuritis and ADEM, and we did a first-in-human dosing, dosing a patient with the solid tumors.

[00:07:23] And this is really our story: we think the salvage pathway plays a real major role in that rapid, abnormal cell division, which you can find in autoimmune disorders as well as cancers. So, let's see what that looks like. This is a mouse model of demyelinating disease. Actually, Kyle talked about it yesterday in his presentation, but this is like a MOG challenge that induces demyelination in the mice. And you can see -- if I can be as successful here -- there we go.

[00:07:56] These mice, they're having seizures, right? They can barely move, they're very skinny. The one on the bottom left has one working paw. He's able to pull himself barely across the cage. Here is the same study: mice on our drug. Wow. Healthy, doing what mice do -- climbing up the cages, all these sorts of things.

[00:08:23] If you want, you can take a picture of the QR code and show this at football games or cocktail parties, whatever you like. But this is the data that we took to the FDA, and then we went ahead and then replicated the data, two independent labs, plus again at UCLA. So, how we got to that is, I think, really important, and we played the role of a private detective. It was a mystery to solve. And the first thing you have to do is ask yourself, “Well, where are we going to see high levels of dCK?

[00:08:58] I mentioned we have this PET probe where we can measure, on a cellular basis, where DCK is. You see there on the slide -- this is a MOG mouse model of a normal mouse and then one that's been induced with demyelinating disease. And with a PET probe, the brighter colors mean higher activity. And so, you can see that when mice go into the states of MS, optic neuritis, and ADEM, there's a whole, whole bunch of activity.

[00:09:29] So, that put us on the trail, and our PET probe it's very specific. It's almost like having fingerprints. But if you're going to be a good detective, the next question, of course, is: “Well, okay, if dCK is there, can we block it?” And the answer is an emphatic, “Yes.” So, this is a mouse with demyelinating disease. It's a PET scan, and you're looking at a cross-section of the belly of the mouse.

[00:09:59] And the red spot is the spleen, where immune cells go to grow and develop when you have an autoimmune disease. And you see the red there without drug on board. Unfortunately, your own army, your immune cells, are getting activated and going out and attacking your neurons. Once we give the drug, as you see it on the right, the red's gone away. The dCK activity has decreased.

[00:10:26] And we did the same thing -- I mentioned we are treating tumors. We did the same thing with mice with tumors. This is a tumor cells that have been implanted in the shoulder of a mouse. You see that there's no drug on board. The dCK is activated because the cancer cells are using the salvage pathway to short circuit and grow quickly and divide. And then, of course, you put the drug on board, and there's a 100% knockout.

[00:10:55] And so, it's good that you can find the dCK. Now you can knock it out. And then, as we talked before, as you saw the video, we then had efficacy. So, the next question, of course, is: Safety, right? If you have those elements in place in drug development, the next thing is: Well, is it tolerable?

[00:11:13] So, non-clinical first: Looking at our neurology platforms, we were able, with our drug, we decreased those activated immune cells that are attacking the body, but had no measurable effects on any of the other cell populations. Now, I would add, in another mouse study, we administered the COVID vaccine while the mice were on our drug, and they mounted a normal immune response to the vaccine. So, potentially, this is a vaccine-friendly drug that we're developing. But what about the patients, right?

[00:11:48] So, this is from our solid tumors trial. We're seeing the exact same thing. No changes in the normal cell populations. And then, as you see there, whether we've given 40 milligrams or 480 milligrams, looking at the various cell populations, white blood cells fight infection, red blood cells carry oxygen, platelets are blood cells that help you with clotting and the like.

[00:12:13] We've not seen any significant changes within the cell populations, which is very promising because, you can imagine, many of the drugs that work in the diseases we're talking about today are immunosuppressive, right? And infection is one of the things that, as patients, can be quite fearful.

[00:12:32] Let's take it though another step on safety. So, this is a demyelinating disease mouse model that we used where we decided to break things apart a little bit. Let's look on the left part of the slide, which is those activated, abnormally activated, dividing immune cells. And then, let's look at the good cells, if you will, the normal resting naive cells.

[00:12:57] And what you see is that our drug is more of a scalpel than a hammer for taking out the bad acting on the left -- anywhere from two-thirds to four-fifths -- while the normal cell populations have remained stable throughout the treatment period of the mice. And I think that's very important because we can take out the cells that cause the diseases of ADEM or optic neuritis but have no effect on those healthy cells that are there, that our body uses to fight diseases.

[00:13:31] Now, I told you we have some patients. I'd like to introduce you to one of the bravest people in the world. This is Stephanie. So, Stephanie was the first patient to ever be dosed with a dCK inhibitor. She is 50 years old. She had a very rare tumor in her abdomen. In her own words, she described it as, “the size of small watermelons.” She had gone through every chemotherapy, cell therapy -- some investigational -- and was out of options.

[00:14:06] And so, Stephanie elected to be the first patient dosed with a first-in-class drug, and she had a remarkable run, I have to say. She ended up getting her weight back, her hair grew, and she even took a trip of a lifetime with her two daughters for three weeks. In her own words, “There are even days that I forget that I have cancer,” which is really promising. And I think Ben said yesterday that the first 50 patients are more valuable to us, as researchers, than perhaps we are to them.

[00:14:41] I would argue the first patient dosed with a drug that has no clinical history, in many ways, it's an act of medical altruism, and we're in her debt that she paved the way for the two dozen patients that have since followed her. What are we seeing in those patient populations? So, safety-wise: no dose-limiting toxicities; it's very well tolerated. As we measure the amount of drug in the blood, it has a nice once-a-day profile, a good half-life. It's a once-daily pill.

[00:15:17] About one in four patients have had antitumor activity. So, that means it's on target; it's taking out the salvage pathway. And the biomarkers have been rather impressive. We've been able to see that on a liquid biomarker basis as well as on the PET probes with the patients. And so, we have the cumulative evidence of the safety and the pharmacologic side of things all in place now for about two dozen patients, and we continue to dose-escalate at this time.

[00:15:49] So, what does that mean for the future? What does the future hold? This is always the fun part of conferences like this. So, we have a few things going for us. Like I said before, we are submitting our pre-IND package to the FDA for ADEM clinical entry. We're looking at the critical ADEM patients -- very much like Ashley, who we met in person yesterday and then just saw on the video -- pediatrics and adults that require intensive care.

[00:16:19] And the thing we have going for us quite well is: we have a cross-linked IND. We have an open trial and open package with the FDA. They've already checked our manufacturing. They've looked at quite a few things in the application. Based on the FDA's feedback from the pre-IND, you then switch into an IND submission, which would then allow us to proceed into clinical trials for these patients. We will need to raise more capital for those clinical operations, but this would be U.S.-based Phase I trial that we would then be activating.

[00:16:55] And then lastly, in 2026 and beyond, we can see ourselves expanding our neuroimmune clinical trial offerings, getting into optic neuritis and other diseases, and as well as petitioning the FDA for a Phase II registrational. So, Phase II registrationals allow approval of a drug on a Phase II package as opposed to having to go through Phase III and beyond.

[00:17:20] So, that's our high-level timeline. And then, I would just say thank you for hearing our story. It's been one, as we say, decades in the making. And it takes a whole lot of effort, as you see. Hopefully, that timeline shows the people, the institutions, and all the things that go into place.

[00:17:41] If you want to see more of the science, we did make the cover manuscript of Immunology. You can scan the QR code and get as much science as you like -- it's about 45 pages. We just want to again thank Siegel for being our thought partners all along the way. So, thank you. Any questions? Yes. Oh, Sandy. Okay.

[00:18:13] **Sandy Siegel:** First I'm going to say, any kind of science that involves ADEM, I'm going to be eternally grateful for, because it has been a population that has been unbelievably understudied. So, thank you so much for that work.

[00:18:35] **Dr. Kenneth A. Schultz:** So understudied -- if you look at clinicaltrials.gov, there's not a trial.

[00:18:39] **Sandy Siegel:** I'm aware.

[00:18:42] **Dr. Kenneth A. Schultz:** Okay.

[00:18:43] **Sandy Siegel:** So, my questions are really coming from an anthropologist because I don't exist on the molecular level.

[00:18:51] **Dr. Kenneth A. Schultz:** Sure.

[00:18:53] **Sandy Siegel:** My first question is: How would you anticipate the timing on when a person who's having that inflammatory attack and then is diagnosed with ADEM -- what would be the timing when you would introduce this medication? And my second question is: How would you design a clinical trial for those people with the other -- I don't even know at this stage of the game whether we have standard of care for treatment of ADEM acutely. Do we, Ben?

[00:19:29] **Dr. Kenneth A. Schultz:** We do. It's not approved products, but there is standard of care that's accepted in the treatment of ADEM.

  

[00:19:34] **Sandy Siegel:** Yeah. So, how would you anticipate how this strategy would work with the other widely acceptable treatments for ADEM? How would you design that clinical trial?

[00:19:51] **Dr. Kenneth A. Schultz:** Sure. So, the first question is: When would this drug be used? And then the second question is: How would it be used with existing standard of care? So, for when it would be used: this is the drug that you try to get in as soon as you can because it has a very quick -- what's called a Tmax -- so the rapid absorption of the drug in the stomach is usually within about an hour or so, and we start getting some peaks that then continue.

[00:20:21] So, from a treatment perspective, this is when the ADEM patient is diagnosed, especially the critical care patient that's been diagnosed as critical care dependent, on the ventilator, all these sorts of things.

[00:20:35] Now, we do have a bit of a debate going on right now between our two potential clinical sites, Harvard and Stanford, over how long can you go before you start the drug. But I believe where we're going to be landing, Sandy, is: if the patient's in the hospital and in critical care, they get the drug no matter if it's been unrecognized for a day or longer than that.

[00:20:59] How would this work in a clinical trial? So, part of our submission process to the FDA for pre-IND is actually having a clinical trial synopsis. So, this clinical trial will give quite a bit of latitude to the principal investigators to be able to use standard of care.

[00:21:16] Right now, standard of care is: steroids are number one. Then it bifurcates a little bit, right? Is it IVIG or is it PLEX? And then rituximab is usually bringing up the third line, fourth line. So, what we would be doing is, on top of that, typically, in these critical care -- these more severe cases of ADEM, many things are used and all things would be permitted with our drug on top. Does that help, Sandy?

[00:21:47] **Sandy Siegel:** It does but the interesting piece of that would be: How would you be able to isolate the impact of this strategy from the other strategies that are being used?

[00:22:02] **Dr. Kenneth A. Schultz:** Historical. Yeah, chart reviews. Yeah, historical. Because there's standards of care for ADEM, what you would look at is the historical recovery rates of these ADEM patients at the various treating sites compared to those who received our therapy.

[00:22:19] When you're Phase I, you're not placebo-controlled or anything like that; it's open label. And you would look to see on two measures: One, mortality; but the second, morbidity -- so long-term cognitive or motor dysfunctions in this patient population. There are some scoring systems that allow for that. Even in the pediatric side, we found a few that we'll be asking the FDA's opinion on.

[00:22:50] **Audience Member:** Yes. Pardon my ignorance, but is the dCK pathway found in other diseases and could this be extrapolated to other diseases? And the second question: you mentioned for pediatric ADEM, are you all looking at getting this approved through the Pediatric Priority Review Voucher process and getting approved earlier?

[00:23:10] **Dr. Kenneth A. Schultz:** Sure. So, for starters, any disease that has abnormal cell division and proliferation typically utilizes the dCK pathway -- the salvage pathway. So, we do have potential in Crohn's. We actually had a patient with Crohn's disease go through the PET probe, and it lit up just like you saw the mice with MS.

[00:23:32] We also have strong potential in lupus -- is something else we're seeing. Interestingly, I'm treating

  

a patient with a solid tumor right now who also has myasthenia gravis and a couple of other neuro things going on. So, we have to wonder what might be happening on multiple levels there with this drug.

[00:23:50] For the Priority Review Voucher, for the pediatric side, that is granted after the approval. So, right now, what this would be is, we would involve the Orphan Disease Division of the FDA plus the Neuro Division, and we would try for fast track first, and then it goes into breakthrough. And then, on approval, you would get the Pediatric Priority Review Voucher.

[00:24:13] That's an incentive that the FDA gives to develop drugs for children since, typically, not many people do. So, it's one of those things that they try. But our trial will be open for children and adults -- our Phase I ADEM trial. Great. All right. Well, thank you everybody, very much.