

**CURE Epilepsy Webinar**  
***Stem Cells and Epilepsy:***  
***A New Therapeutic Approach for Treating Drug-Resistant Epilepsy***  
**(Transcript)**

Laura Lubbers: Welcome everyone to today's webinar. I'm Laura Lubbers. I'm the Chief Scientific Officer of CURE Epilepsy, and I want to thank you for joining us today, and also thank you for your patience as we engage this WebEx webinar.

Today's webinar is entitled Stem Cells and Epilepsy: A New Therapeutic Approach for Treating Drug-Resistant Epilepsy, and it's intended for everyone, including persons with epilepsy and their caregivers. Stem cells are the cells in the body that provide the blueprint for the creation of all other specialized cells; for example, nerve, cardiac and blood cells. These cells have generated significant interest in the research community over the last decade. Stem cells can help regenerate or repair tissues in individuals that have been affected by certain disorders, and they're being assessed for the ability to reduce seizures in people with epilepsy.

This webinar is the first installment of the 2023 CURE EPILEPSY Webinar Series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE EPILEPSY website. You can also download transcripts of all of our webinars for reading. CURE EPILEPSY is proud to celebrate our 25th anniversary this year. Since our founding in 1998, we've raised millions of dollars to fund epilepsy research that supports our mission, which is to find a cure for epilepsy, by promoting and funding patient-focused research. CURE EPILEPSY provides grants that support novel research projects that advance the search for cures and more effective treatments. Today's webinar will discuss a pioneering neural cell therapy approach that can provide a novel treatment for drug-resistant focal epilepsy. Viewers will learn about the promising new clinical trial that utilizes this approach.

This webinar is being presented by Dr. Robert Beach, who is a Professor of Neurology and Director of the Epilepsy Program at SUNY Upstate Medical Center. Dr. Beach's clinical interests include epilepsy, epilepsy surgery, anti-seizure therapies including medical, surgical and experimental approaches and differential diagnosis of seizures. Dr. Beach has been instrumental in this new clinical trial, which is a first-in-human study of NRTX-1001 and entitled, Neural Cell Therapy in Drug-Resistant Unilateral Mesial Temporal Lobe Epilepsy. Dr. Beach is treating the first patient to undergo this breakthrough approach for drug-resistant epilepsy. To date, other patients have undergone this treatment, and while we'd hoped to hear from one of them during this webinar, we've made the decision to maintain anonymity as they undergo evaluation as a part of this clinical trial. Therefore, the webinar will focus on the background and approach of this clinical trial.

Before Dr. Beach begins. I'd like to encourage everyone to ask questions that we'll address during the Q&A portion of the webinar. Keep in mind you can submit your questions any time during the presentation by typing them into the

Q&A tab located on your WebEx panel and clicking send. We'll do our best to get through as many questions as we can. We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general. So, with that, I'll turn it over to Dr. Beach. Welcome, Dr. Beach.

Dr. Robert Beach: I hope everyone can hear me.

Laura Lubbers: You're a little soft.

Dr. Robert Beach: Hello, I'm Dr. Beach. I'm going to talk to you a little louder now. I wanted to give some background to try and orient people of different backgrounds into the topic we're going to talk about. I'm sure that some of this will not be clear to everybody as we go along, so please ask questions. I'll try to be a little bit redundant, so some of the information comes back in more than one format to try and help understand it.

I want to point out that this trial is due to this company called Neurona, which has created these stem cells, and some of the members of that company have been working in basic research for epilepsy and stem cell lines for many years. Stem cell lines are relatively new in the brain, and we used to, back 20+ years ago, we were trying to implant other GABAergic inputs or inhibitory inputs into parts of the brain to try and control epilepsy, because this idea has been around for a long time that if you increase inhibition, you may be able to improve seizure control. One of the experiments we did a long time ago that didn't get too far, because some concerned about possible risk was with pig cell implants from the same location as the cells that have been utilized in this are typically found, the medial ganglionic eminence or MGE.

Thought I had control. Oops, now it's going. The general idea is that in the normal brain there's a balance between excitation and inhibition, and this may be true across the brain or may be, vary in different parts of the brain. When there's a loss of inhibition or increase in excitation, you may get a more hyperexcitable area of the brain, and this may lead to seizures. This is just an oversimplification, but a good way to look at the idea to use inhibitory neurons that release GABA in the brain.

This is an older diagram that just illustrates, and I don't know if my cursor here can be seen, but there's a variety of different inhibitory neurons in the brain, and the most important ones are ones that affect cell grouping, cell function and managed output. This just shows a very simplified circuit from the hippocampus, which is one of the most well-known, well-understood areas of the brain for generating seizure foci. It's now known that some of these ideas may not be as important as others, but one thing that's been well demonstrated is that there's a loss of some types of inhibitory interneurons in parts of the brain that are responsible for modulating the output from the hippocampal circuit. These are different kinds of inhibitory interneurons that interact near the level of the cell.

These cell lines are derived from pluripotent embryonic stem cells, and they are differentiated into medial ganglionic eminence cortical GABAergic neurons, and this can be by markers of the neurons that indicate what their functions are and how differentiated they are. The differentiation takes place in culture, and then the cells are expanded, tested for purity and then saved in aliquots that can be given for a given patient. These are highly reproducible. The cells in the NRTX-1001 cells are post-mitotic. They do not divide anymore. They don't proliferate. They do not have any tumors, teratomas or ectopic tissues, and they've been demonstrated to be reproducible and standardized.

The idea that stem cell implantation may be a good approach to treating epilepsy derives from the experiments that have been done in a hippocampal model of epilepsy, which is the kainic acid or kainite epilepsy model, which is one of the most studied models for focal seizures. It's been shown in mouse models by the people who have been involved with Neurona that with cells implanted into mouse, and there's intact cell integration and survival. There's a reduction in seizures and there's relative preservation of hippocampal morphology, all of which are desirable effects for something that's going to affect your seizures.

The biggest advantage of the stem cells is somewhat similar to the advantage of surgery in that it is a focal treatment, and it avoids the effects that you see with anti-seizure medicines. You probably are aware that about 30% of people with epilepsy have seizures that cannot be fully controlled or adequately controlled with anti-seizure medications. For those people, options include surgery, both surgery that takes out tissue and surgery that damages it or modulates it by stimulation. This avoids the loss of tissue that would take place with all those ablative therapies. It's different from the modulatory therapy, but that's got some other differences which we can discuss as to relative merits versus the cell implantation.

Just to clarify what the medial ganglionic eminence is, it's a structure that comes on during embryonic development, which serves as a source for inhibitory cells to proliferate and then they migrate into the cortex. It's been shown that if you have loss or dysfunction of these neurons during development, you will develop epilepsy. This is the neurosurgeon who I work with in this study and myself. Dr. Babu has been with us for a few years now and has really helped advance the research, and he's the one that does the implantations that I will show you some examples or some information on.

Let's get to the patient. Just a summary. He's 26-year-old. He's had seizures since 19. He didn't have the usual risk factors for epilepsy like febrile seizures or trauma or something else that might trigger seizures. At the time of enrollment, he was having around 30 focal aware seizures per month, and about two focal seizures where he lost awareness per month, and he has not had generalized tonic-clonic seizures at this point. On entry his neurologic exam was essentially normal except for some nystagmus. Prior to enrollment he had extensive workup done to demonstrate that he was a candidate for possible surgery. He

had neuropsych studies, which I won't show you, that showed some mild visuospatial defects but were not terribly localizing. He had an MRI, and I'll show you the following studies. The most important one is the MRI because the right mesial temporal sclerosis is a very good marker for mesial temporal epilepsy, and it's really the main target or the most successful target for anterior temporal lobectomy, which has been the main surgery used for intractable epilepsy from temporal lobe over the years.

All of his studies, including EEG, video EEG, stereotactic depth electrode study were consistent with right hippocampal onset. He had a PET scan which was not localizing. It showed bilateral hypometabolism, and he was demonstrated to have left hemispheric dominance, which for the beginning of this study is required, because there is some concern that dominant temporal lobe might be affected adversely by the presence of inhibitory cells. He was on fairly high doses of medications at the time of entry. I had actually been able to reduce these a little bit, and this one has been reduced. We switched Lorazepam to Midazolam for convenience. So, this is an EEG that shows ... Can you see my cursor?

Laura Lubbers: Yes, we can see your cursor.

Dr. Robert Beach: Okay, great. So, these things here are epileptiform discharges that are seen on the routine EEG, and they're in the anterior right temporal lobe, which is overlying the mesial temporal structures. There's also some slowing in this area compared to the other side, which is less obvious. This is the MRI, which in this plane here, and you've got to remember that on MRIs and many images, right is left and left is right. So, this is the right side of his brain, and this is the right side of his brain, whereas this is the left. You see, this is the hippocampus here on the left, which has got some structure which you don't really need to understand, but it's lost some of the volume and some of the structure here on the right side, and that can be seen to a less clear degree in these other images over here in a different plane.

This is the beginning of a seizure here. I'm not going to show the video or anything. This is a typical rhythmic activity that you may see at the beginning of a seizure. This again in the right temporal lobe, anterior portion. This is the PET scan which shows some decreased activity on both sides, which is not significantly different, so non-localizing. This is the way we demonstrate language dominance. In this case, again, this is the left side, this is the right side, and there are various tasks such as sentence completion that activate areas of the brain, both in terms of reading or seeing the sentence, and in generating a verbal output, which are almost always, well, not always, mostly localized to one side of the brain in most people.

In his case it's on the left side, which is true for 90+ percent of people, closer to 99% if you're right-handed to begin with. This is a different ... That's a duplicate. All right. This is a little, probably a little disturbing to some of you because these things here that represent electrodes are giant. They really are tiny little things,

but in order to be able to see the labels, we have them blown up to see their orientation. This is looking from the left side of the brain, and you can see in three different planes here where they go. Mostly they're directed towards the hippocampus and inferior frontal lobe on both sides. When we record from ... I'll just show it in a different way. This is from the right side. Oops, did I go through two? Well, it doesn't really matter.

When we did the recording with those electrodes in the brain, we found there are onsets from the right anterior hippocampus, and this area spread then into the right amygdala and the right posterior hippocampus, indicating that these seizures were all coming from the area of mesial temporal sclerosis and the appropriate area for somebody who might be a candidate for anterior temporal lobe surgery. He, with this information, was a good candidate for anterior temporal lobe surgery. Around the time this study was completed, we got activated for the trial that involves the stem cells, and presented this as a possibility to him, and he was very enthusiastic about participating in this.

This is the same image we saw before, but our target is going to be in the area where this atrophy sclerosis is. Dr. Babu, in the OR prepares the position of where this probe, this is actually a cannula that contains a tiny little probe that goes in, as you can see it in two dimensions here. Then there's a small burr hole placed and a tiny electro... This is again, much larger than the actual electrode that goes in the brain. Here you get a sense for the trajectory better, going right into the anterior portion of the hippocampus on the right side, and as the cells are put in with a few microliters at four different sites, drawing back from the anterior tip of the hippocampus posteriorly, a little bit of gadolinium, which is in with the cells shows up here as a marker for where the cells go. you can see here these dark lines are actually where the deposits are made.

It's a different image, so it's dark in that. This is an image taken six months later. You can see where the [inaudible 00:21:19] was placed and you see some evidence for the cells there. A little bit of brightness here. Now, one of the things that we have done or that has been done with this trial is to look at magnetic resonance spectroscopy, which can measure different metabolites including GABA and other neurotransmitters. It's been demonstrated that the cell implants have produced an increase in GABA that is sustained over time, going at least out to six months, and that's very congruent with what was found in the animal studies. So, since that implantation, he has done quite well. He hasn't had any focal aware, I'm sorry, focal unaware seizures after the first month of follow up, and they were two per month initially, and his focal aware seizures have decreased dramatically from 30.

I don't have any precise numbers because this is still in process, and we're not really going to be able to assess with any confidence the effect on seizures immediately. At one year will be a detailed study of the MRIs. He also had some repeat neuropsych tests that appear improved, but again, the results are preliminary and not really appropriate to consider it as conclusively different. Overall, he feels quite well. He's had some side effects along the way. When

somebody gets the cell implants, they have to be treated fairly aggressively just like a transplant of other kinds would be treated to prevent rejection. That starts off with some fairly toxic, well, fairly strong immunosuppressants that probably cause some of the side effects.

The tremor, upset stomach, although he had some underlying factors that may have contributed to this and fatigue, which is a really common side effect with the ... As time's gone on, he's been, had the immunosuppressants reduced so that there's fewer of them and less of them. I think overall that's improved some of these side effects, but they're not completely resolved. He also had some transient constipation, which is of uncertain reason and not likely related to the study itself. All right. That's my summary, and I'd be glad to take questions after this.

Laura Lubbers: Wonderful. Thank you, Dr. Beach. We really appreciate you giving us some insights into this new approach. We do have quite a list of questions. For those of you who have not submitted your questions yet, you can go ahead and do that by putting them into the Q&A tab on your WebEx panel and clicking send. But we'll start now. I'm glad we have good time to be able to address this. So, first question. Will this approach only be useful for epilepsy located in the temporal lobe or any drug-resistant epilepsy? Where do you see this going?

Dr. Robert Beach: Well, if it is successful in this well-studied area of the brain, it will probably be useful in other focal epilepsies. As long as you can localize the seizures and target them with the cells, it has the potential to be beneficial. We're starting with the best studied and most frequently treated surgically part of the brain as a starting point because it's far and away the best understood and the most likely to provide us with realistic estimates as how it might work elsewhere.

Laura Lubbers: Okay. Along with that, so thinking into the future and align with that question, do you think it would help eventually people with Lennox-Gastaut syndrome or genetic disorders?

Dr. Robert Beach: Well, most genetic disorders are not focal. Some of them, like tuberous sclerosis for example, have multiple foci, and it might be useful in that sort of setting because it's very hard to necessarily know which is the active focus. If you're not damaging the area as you would with surgery or something, you may be able to treat more than one focus. But many of the genetic disorders are too diffuse and not well-localized enough to likely benefit from this kind of stem cell implant.

Laura Lubbers: Okay, thank you. It's helpful to try to discriminate where it be helpful and where it would not be. So, can stem cell therapy be used in a patient who has a deep brain stimulator?

Dr. Robert Beach: Well, not at this point, but it could be, theoretically. Deep brain stimulation is often used for less well-localized epilepsies, and some of those probably do not

have a focal area that could be treated. Some of them have multiple focal areas of which you've ... concurrently with the responsive neurostimulator or RNS, treat two of them, but not multiple ones. This could potentially have the ability to treat these area parts epilepsies where there are more than two foci or two foci that aren't easily addressed by the RNS.

Laura Lubbers: Okay, great. Thank you. So, more of a technical question about the stem cells. Are the cells manipulated in any way? Are they grown to increase their number or cultured in any way? Selected in any specific ways?

Dr. Robert Beach: So, yes, all of the above. They are put into culture and they're differentiated using a variety of growth factors and other things that influence distill differentiation. Then they're tested to be these inhibitory GABAergic neurons, and then they're expanded and tested for purity, and then they're frozen in small amounts to be used in a particular implantation, and that you have multiple samples of the cells that can be used over a longer period of time with the frozen cells.

Laura Lubbers: Okay. So, this isn't actually coming from the person who's having the surgery, but these are cells that were generated some time ago?

Dr. Robert Beach: Yes. I don't know exactly when they were generated, but they were generated from stem cells that have been obtained from, not from an embryo or not from a fetus, I should say. I don't know exactly where they're obtained from. Theoretically, you might be able to generate stem cells from the individual, which would have immense advantages in terms of not needing the immune suppression. That is one of the more complicated parts of this kind of approach, and I think that that's potentially doable. It may be that cord stem cells may be more versatile and require less immune suppression. These are things that I don't have a lot of information on, but are potential.

Laura Lubbers: Okay. It's certainly forward-looking, and actually this relates to another question I think we have part of the answer too, but you could clarify. So, this person has a daughter with epilepsy, but an SCN1A mutation. They have stem cells saved from birth via the cord stem cell banking, and they've saved it from both of their children. Do you think this type of stem cell can come in handy for treating epilepsy?

Dr. Robert Beach: That's a very good question. I think there probably is a potential for those stem cells for this person, but I don't think it's going to be necessarily this kind of stem cells delivered focally, and it may not be primarily GABAergic neurons. It may be something that might introduce a different or correction of a different deficit that would be seen in SCN1A. But at this point, I really don't know exactly how that would work.

- Laura Lubbers: Okay. Yeah, lots of research to be done on this topic for sure. So, if somebody has had a surgery already in the hippocampus, is it possible that these stem cells could be helpful in any way for them?
- Dr. Robert Beach: I mean, a lot of times when surgery is unsuccessful, there's either some residual areas that are hyperactive that may have been difficult to take out or may be difficult to take out, and I think that this kind of approach might be able to address those residual or unremoved foci better than a second surgery. But this is far in the future, I think.
- Laura Lubbers: Okay. Okay. How long does it take to see improvement, for example, a reduction in seizures after cell implantation?
- Dr. Robert Beach: Well, we don't know. We were pretty surprised that this person did as well as he did in terms of seizures. So, the hypothesis that we are operating under is that the benefit of the cells would come mostly after they integrated with the other cells, and form new connections and new networks, which would take time. The plan was to assess this over a year, basically, be looking at six months, but expecting to find some realistic estimate over a year. This is, being the first patient, I think it's premature to say that this is going to be a characteristic of everybody getting these cells, but it's very encouraging.
- Laura Lubbers: Okay. Yeah, absolutely. Absolutely. So, if somebody has a VNS, we've talked about the deep brain stimulator, but if somebody has a VNS and can't have an MRI, is it still possible to be assessed for this?
- Dr. Robert Beach: Well, a person with a VNS, as long as they don't have it slipped way down below their chest or in the lower part of their chest, can have an MRI. There's a, you require certain things in the MRI to be able to get, in the scanner, be able to get an MRI in somebody who has a VNS. There's an absolute area of exclusion where if it exists, you can't do it. But for the most part, they are coils that are used that go around the head and localize the flow of the changes of magnetic fields that keep it from interfering and keep it from damage the VNS. The VNS has to be turned off during the MRI. One obvious reason is if somebody has their magnet on and they go through the MRI, they're going to be exposed to rapidly fluctuating magnetic fields, which will trigger it on and off multiple times, which would be intolerable very quickly. But most people with a VNS can get an MRI.
- Laura Lubbers: Okay.
- Dr. Robert Beach: If they have a focal abnormality that is likely to be the source of their seizures, or a couple maybe in the future, they may be candidates, but for now we're looking at one focus.



Laura Lubbers: Okay. Yeah, I think it's important information, because I've heard too confusion around whether or not people with VNS could have an MRI. So, thank you for talking to-

Dr. Robert Beach: Well, not every scanner has the right coil, and not every place has the ability to turn on and off the MRI at the time of the scan, but many places like us, like our center do.

Laura Lubbers: Okay. So, that's an important question for patients to ask their doctors. Yeah. What's limiting this? So, thank you again. So, back to the GABAergic interneurons, will they only work in the hippocampus or could they work in other areas?

Dr. Robert Beach: Well, these are neurons that come from an area of the brain that spreads out throughout the cortex. The cells are formed in the median ganglia eminence, and then they migrate to various parts of the cortex. The reason it's being tested in the hippocampus is because it's a well-studied model, and we know that there's GABAergic cell loss. They should potentially work in many other areas if there is a loss of GABAergic input and they can be replaced, which if there's a loss of GABAergic cell loss, and it's an area that can be, well almost in the area can be accessed using stereotactic implantation. So, probably, as long as there's a focal area that can be identified as a seizure source, and there's a good reason to think there's GABAergic cell loss, it does have potential again, in the future.

Laura Lubbers: Okay. So, how long do you think it will take to get a good readout from this clinical trial and know what next steps will be? We're getting a lot of questions about the future of this and where it could be used, but clearly we've got to complete this trial first. Talk about this trial and how long it might go?

Dr. Robert Beach: The way the trial's set up now is the first two patients had to be separated by I think, three months. So, second patient was implanted about three months ago, who I don't know much about their seizure effects or side effects. But I note, they've had no major side effects, and the cells were implanted a very similar way as to what I demonstrated with our patient in approximately on, well, actually as of now, there's been several things that the Data Safety Monitoring Board has allowed us to do that's going to facilitate getting patients in faster. One of them is to open it up for additional studies in this preliminary group of patients who are really getting a low dose, and there'll be five people in that initial cohort that should probably be all implanted within the next six months, I would hope. Approximately a year after those five people go through, we should have some idea as to whether this effect on epilepsy is real, and whether there are side effects that we haven't yet seen that are going to be an issue.

We also may have an idea, because they've opened it up now, so we can do non-dominant hemisphere patients, I'm sorry, dominant hemisphere patients as well as the non-dominant hemisphere patients. We may get an idea as to whether the most important benefit for this, it may be realized, and that is if

you're treating the dominant hemisphere temporal lobe epilepsy, in somebody who has relatively normal verbal memory and function, you're going to get a decrement on surgery, because you're going to be taking out areas important for that. But it is very possible, and it's been shown with the less you take out, the more likely you are to have less effect on memory and language function. It's very likely that with this kind of approach that you'll have even less effect, or we hope that there's even less effect on the language and verbal memory, and that we might have some information on that within the next year. I'm not really sure.

It might take longer than that, but it's going to take larger numbers to really get a good sense for how likely various things are. I think we're definitely seeing some very promising results, but it's very early to know.

Laura Lubbers: Okay. Okay. So, we've got a question about eligibility, and you've been talking about unilateral mesial temporal lobe epilepsy in the non-dominant side, and you just shared that there's been a loosening of restrictions to also now allow the dominant side. It sounds like that might be because of the lack of concern around changes in some function.

Dr. Robert Beach: Well, it's because there doesn't appear to be any major risk showing up from what we've done so far. It's the dominant hemisphere of patients who this is most likely to be the most attractive approach for, because of that potential for sparing language function or even getting improvement potentially. So, as long as somebody has unilateral at this point, unilateral left or right mesial temporal sclerosis and seizures coming from that area, and no progressive degenerative diseases, and various other minor or unusual restriction criteria, they would be a candidate for this. But it's basically, think of it as somebody who might be a candidate for epilepsy surgery on one temporal lobe, may be a candidate for this. There's some details beyond that, but that's a good starting point.

Laura Lubbers: Okay. Is there an age restriction or an age range for eligibility?

Dr. Robert Beach: There is. I think it's 18 to 65 at this point, but I'm not actually sure.

Laura Lubbers: Okay. Are there any discussions about trying this in children? I know that's a difficult question, I'm sure.

Dr. Robert Beach: Yeah. I think there will be plans to do that, because temporal lobe epilepsy is fairly common in children. But I think that there are some differences in, I would guess that's going to take a while before we have a good handle on anything that's going to actually try that. If it's very successful, maybe a no-brainer to go forward with children, but it's a little unclear at this point.

Laura Lubbers: Okay. Thank you. Yeah, I know there are a lot of families out there who are looking for new treatments. It's an obvious question. So. You've talked about some of the conditions to go through this, and that includes being on

immunosuppressants. Do immunosuppressants have any effect on seizures themselves?

Dr. Robert Beach: Not that I know of. I mean, they have side effects that can be somewhat systemic, but I'm not aware that any of them are actually anti-convulsant. Now, there are drugs that reduce proliferation that are in some ways related to the immune suppressants that can affect development of some of the epilepsies that require things like tuberous sclerosis, where you get growth of cell populations as tubers or as giant cell astrocytomas, where they suppress that. But that's not truly an immune suppressant. I'd have to look to see what data there is. I'm not aware of any, but there might be some data on that.

Laura Lubbers: Yeah. Epilepsies are so complex, and that's an interesting example of tuberous sclerosis, where immunosuppressants are being used but for a different purpose. Thank you. Here's somebody who is asking about autoimmune epilepsy and its impact on the hippocampus, which has ... the autoimmune epilepsy appears to have shrunk or changed the hippocampus. So, is somebody like this a candidate?

Dr. Robert Beach: So, autoimmune epilepsy should first be treated to reduce the impact of the molecule causing the autoimmune response and the autoimmune response itself. If that is unsuccessful, and there's residual long-term epilepsy, then they may be a candidate for this, but autoimmune epilepsy is usually a monophasic course where if you can remove the inciting antigen, which might be in some cases related to a tumor or an abnormal cell growth, or if you can suppress the response adequately, you can get control of those seizures in most people. And, if they are treated quickly enough and aggressively enough, they're likely to get enough of a benefit. So, long-term epilepsy is not likely to occur, but for some people it does, and I think those people, if it's in the hippocampus, would be candidates. I don't think they'd be candidates for this study because that's probably a restriction, but because autoimmune is not really a clearly defined stimulus that ends at a given time, but I think that they would be candidates for this kind of approach.

Laura Lubbers: Okay. Okay. Great. Thank you. Thank you. So why do the cells have to be injected into the brain? Why couldn't they be injected into the bloodstream?

Dr. Robert Beach: So, there are immune therapies to which are largely for blood cells where there can be replacement or treatment directly into the blood, and there may be epilepsies which are widespread and without a focus that might benefit from some blood cell treatments in the future. But for the effect of the GABAergic cells to be beneficial without causing widespread suppression of activity, you want to be able to put them where the abnormality is, where the hyperexcitability is, and that requires injecting them into the brain. There might be some genetic cases where that would be different, but not at this point.

Laura Lubbers: Okay. Okay. Are there any outwardly visible components of implanting stem cells in long term?

Dr. Robert Beach: Outwardly visible? Well, I guess if you palpated their skull, you might find a small little burr hole in the back where the burr hole is made. If the person is on long-term immunosuppressants, there might be some side effects that could last over a longer period of time, and of course, being on immunosuppressants does increase the risk for infections, but that's not really a marker. That's just a risk, I'd say.

Laura Lubbers: Right. That's That's very, very thorough answers. I think that's really helpful. So, you've talked about long-term immunosuppressants. It's likely that people would have to be on immunosuppressants for their lifetime or do we know?

Dr. Robert Beach: Probably on some level for lifetime. The aggressive approach initially is much more, all of, I think he was at one point on three strong immunosuppressants, and is now on a single low dose of Tacrolimus, which is one of the more common immunosuppress use for tissue transplants, which is probably not causing significant side effects at this point. Does have the increased risk of possible infection though.

Laura Lubbers: Okay. Okay. Do you see this being used for any other kinds of neurological disorders?

Dr. Robert Beach: Yes. I don't think the, there's probably ones where I think GABAergic cells may be beneficial, but I do think that stem cell of particular kinds will be useful in some other diseases, perhaps even in something like Parkinson's disease where we now do stimulation, there might be potential to use certain kinds of cell implants to benefit there, but that's something that I really don't know for sure, and it's in the future for sure.

Laura Lubbers: Absolutely. Yeah. I think if there's some promising signals out of this trial there could, it would certainly increase interest in trying it for other things as well.

Dr. Robert Beach: I actually think that, I think it was not in this country, there have been some trials of using dopaminergic cell implants but not stem cells. I think that may be, at least to my knowledge, not stem cells, I would expect that may be done, but because you can create a whole bunch of different kinds of stem cells by these differentiating factors. So, if there's a trial ongoing with that, I don't know, but there could be for a few other conditions where that might be a particular cell type might be beneficial.

Laura Lubbers: Okay. Okay. Thank you. So, you've talked about, you mentioned these people who are being enrolled are on a low dose. So, is the anticipated that the next steps in the clinical trial will try different levels of stem cell infusion or different numbers of stem cell infusions?

Dr. Robert Beach: Yeah, the plan was to try a higher dose with the second cohort, which would be after these five people have gotten adequate results, which would be roughly a

year from now or maybe slightly more. I'm not sure if the results are particularly impressive with the low dose. That may be modified.

Laura Lubbers: Okay. I know we are getting close to time, and I just want to summarize. There've been a lot of questions about whether or not this would be useful for generalized genetic epilepsies, and generalized epilepsies in general. I think you've addressed it, but again, questions keep coming in about that, and it sounds like it's still uncertain, but can you clarify?

Dr. Robert Beach: Well, I think most of the generalized epilepsies don't have a focus where we could inject GABAergic neurons and expect to get a benefit. There may be particular subtypes of GABAergic cells that might be useful in some of the generalized epilepsies, but that's very theoretical, because you'd have to be able to figure out which subtype and where to inject it. Theoretically, with some of the generalized epilepsies, it might be in the internuclear or reticular thalamic nuclei, which is part of the relay for some of the so-called spike wave epilepsy, which are often called primary generalized. But I think that's highly theoretical at this point.

Laura Lubbers: Okay. Okay. So, there's lots to be done, lots of work to go into.

Dr. Robert Beach: Lots of potential to be done. Always. Yes.

Laura Lubbers: Always. Always indeed. So, we've been asked whether or not this, this presentation would be made public, and yes, I want to reassure people that we are recording it and it will be made available through the Cure Epilepsy website. Just please give us a couple of days to get that uploaded, and the slides will also be available at that time. Dr. Beach, is there a way for people to learn more about this trial or when there will be more information available?

Dr. Robert Beach: I think that probably the company will share information in the future as it gets more definitive. I can ask if the company has any information yet. I think, being is how this is a trial and they're trying to develop a product, I'm not sure that there's any much more information that they're going to make available yet.

Laura Lubbers: Okay. I know that it is listed on [clinicaltrials.gov](http://clinicaltrials.gov), so everybody is welcome to go there and see how the trial is, the information that's shared in that format. Again, the name of the trial is listed on one of the first slides on Dr. Beach's slide deck, so you can go there as well. Also, you can always contact us at Cure Epilepsy for more information. So, we only have one minute left, so I want to conclude this webinar about stem cells and epilepsy. Although we still have more questions, we will see if we can sort through them and perhaps get answers, make those available on the website as well. We want to thank you, Dr. Beach, for this really interesting presentation. It generated a ton of questions.

It's a really exciting trial. We want to thank you for your participation in that, and also we want to thank the patients and families who have taken on this step to learn more and to help others that may have an epilepsy like this. It takes a lot of courage to do this, so we want to thank them for that as well. I'd also like to extend a great thank you to our amazing audience, once again, coming up with great questions. If you have additional questions about this topic or wish to learn about more of Cure Epilepsy's research programs or webinars, you can visit our website or email us at [research@cureepilepsy.org](mailto:research@cureepilepsy.org).

Please be sure to register for our next webinar on February 23rd. That will be presented in recognition of Rare Disease Day later in that month. The webinar will feature information on the foundation called n-Lorem Foundation. n-Lorem is focused on creating individual treatments for patients in the US with nano rare diseases caused by genetic mutations that affect less than 30 people in the world. Registration details will be announced shortly, so I want to thank you all again, and be well.