Narrator: [00:00:30] The HD insights podcast is brought to you by the Huntington Study Group. The Huntington Study Group is a nonprofit research organization dedicated to conducting clinical research in HD, and providing critical training on HD to healthcare professionals. Funding for this podcast is made possible through the generous support of listeners like you, and sponsorship grants from organizations like Genentech, Teva Pharmaceuticals, Neurocrine Biosciences, Vaccinex and Wave Life Sciences.

Podcast Host: [00:01:00] Hello and welcome back to the HD insights podcast for another episode. I'm Kevin Gregory, director of education, communications and outreach at the Huntington Study Group. In this episode, we are privileged to sit down and chat with Dr. Joseph Higgins. Dr. Higgins is the vice president of clinical development and the Huntington's disease program lead at uniQure. uniQure is doing some exciting research in Huntington's disease. Recently, uniQure announced the start of recruitment for a very exciting new trial for an HD treatment. Dr. Higgins has a [00:01:30] really interesting background and I think you'll enjoy this interview. So sit back, relax, and take a listen.

Podcast Host: [00:02:00] All right. So, we're joined here by Dr. Joseph Higgins today. Dr. Higgins is the vice president of clinical development at uniQure for the Huntington's disease program, and I had the pleasure of meeting Dr. Higgins in Boston at the HDSA annual convention, and I found the conversation with him was really upbeat, really uplifting. Really interesting time in the Huntington's disease world in terms of treatments that are coming down the pipeline and starting to move into clinical trials. And uniQure certainly is no stranger to that right now with their treatment coming out called AMT-130.

Podcast Host: [00:02:30] So we wanted to sit down with Dr. Higgins for this episode and certainly talk to him about that, but to learn a little bit more about the person, his background, his experiences, interests in the field, in neurology. And so, Dr. Higgins, thank you for joining us today on the HD insights pod. It's a pleasure to have you on board.

Dr. Higgins: It's a pleasure to be here.

Podcast Host: [00:03:00] I want to start out with first, looking at your experience. You're board certified in pediatrics and you've worked a lot in child neurology, and now obviously you're doing work in adult neurology in Huntington's disease. Tell us a little bit about how you got into the field. What prompted you to look at a career in neurology? What started you down this path?

Dr. Higgins: [00:03:30] Yeah, that's a great question. You've given me these questions before. So I had a little time to prepare and a lot of time to reflect on how did I get interested in neurology and in the field. And I grew up in a small town in upstate New York called Fishkill. I lived next door to our family doctor who worked at West Point, and at a very early age used to hang out in his office and actually he treated me and my brothers. It's really how I got interested in medicine.

Dr. Higgins: And an interesting fact is that George Huntington actually practiced medicine in Fishkill New York, the same town that I grew up in. So I found that very interesting now that I'm here as VP of the Huntington disease program and doing one of the [00:04:00] first AAV trials in Huntington's disease. So, that's where I got interested in medicine. I graduated from NYU school of medicine, and then matched in pediatrics at Harvard medical school, Boston Children's Hospital, and wanted to do neurology in children mainly because of the developing brain.

Dr. Higgins: And I think children have the best chance of having neurological diseases cured. [00:04:30] And as I started to progress in my career, I realized that adults are actually developing too. So their brains actually develop until about the age of about 25, but it still continues all throughout their lifetime. My interest in gene therapy and in molecular biology began after I finished my residency. I did a residency in pediatrics, also adult neurology and in child neurology at Children's National Medical Center in DC, which is part of George Washington University.

[00:05:00]

Dr. Higgins: When I was there, I was introduced to a Dr. Dale McFarland who was a researcher at NIH in multiple sclerosis. And he got me interested in doing research and introduced me to Dr. Roscoe Brady, who I decided to do a three year fellowship with him in neurogenetics. Now it included both gene therapy and enzyme replacement therapy. I think I really first got really interested in neurodegenerative [00:05:30] diseases when I was with Roscoe, and when I saw the results of enzyme replacement therapy I thought, wow, this is incredible.

Dr. Higgins: Gaucher disease was basically cured during that clinical trial, and it was just an amazing thing to watch from a clinical perspective. That you can inject something in a vein and actually cause shrinkage to both the liver and the spleen. That wasn't necessarily neurological, and we decided to look at Gaucher type three, and that's when I get involved in gene therapy. Gene therapy did not work during the 1990s, [00:06:00] and it was kind of put on a hold, but that's where my interest began in gene therapy.

Dr. Higgins: Also during that period of time I was part of the human genome project with Francis Collins as his lead in Bethesda. And there it became what they call a Gene Hunter, and found a lot of disease genes for diseases like Parkinson's disease, intellectual disability and ataxia. Around that time the Huntington's disease gene [00:06:30] was discovered in 1993 by James Gusella, and by a team led by Nancy Wexler, Ira Shoulson and Ann Young, down at Lake Maracaibo in Venezuela.

Dr. Higgins: And so that was a really exciting time for gene hunting, and the hope from that point onward was that if we found the gene, we'd be able to treat the disease by looking at the molecular mechanisms. And so, it was just natural that I would kind of gravitate to that field and spent a lot of time in academics making transgenic [00:07:00] animal models for human diseases, and trying to translate those animal models into therapies. Because of my expertise in gene hunting, I helped develop our next generation sequencing at Cornell.

Dr. Higgins: And because of successful publications, Quest Diagnostics contacted me and I began running their genomic program and converted their Sanger sequencing technology, which is very expensive, the next generation sequencing technology, [00:07:30] and lowered the cost of diagnostic genetic testing, which I believe will be the first step in leading to more gene therapies. Because you really can't treat genetic diseases unless you can actually identify them, and identify them in the research arena is very different than identify them in the diagnostic arena.

Dr. Higgins: [00:08:00] So that's kind of it. Then from there, uniQure and the whole gene therapy field advanced, and uniQure was treating Huntington's disease and I took a look at the company. It was recommended by someone I knew in the field and said, "Joe, you ever thinking about getting back into gene therapy." And I took a look at a uniQure and decided, okay, time is right not only from the genetic point of view and the molecular point of view, but also from neurology as a field was at a point where neuroimaging was really good. The neurosurgical techniques are more advanced and I thought it was the right time to start a clinical trial with Huntington's.

[00:08:30]

Podcast Host: Excellent. Yeah, that's quite a journey. One of the other things that I wanted to ask you about when we talked in Boston that I found particularly fascinating was, you spent a good deal of time at the National Institute for Health, NIH, and you had a particularly interesting story about how your tenure there coincided with the Gulf war. Do you want to tell the audience about that?

[00:09:00]

Dr. Higgins: Yeah. So, I joined the public health service back in 1990, and at that point in time the United States Public Health Service had never been activated in time of war, except I believe with civil war. So it was really, you were stationed at NIH, in the case of a natural disaster sometimes they activate you to participate in that. There were quite a number of people in the United States Public Health Service including [00:09:30] a lot of the neurosurgeons. And there, there was the Dr. Ed Oldfield who actually invented the technique called convection-enhanced delivery, which we actually will be using in the upcoming clinical trial.

Dr. Higgins: So I got to know Ed there, and one of his fellows was Russell Lonser who is one of the principal investigators in the trial. Actually, principal neurosurgeon in the trial. So what happened though, when Saddam Hussein invaded Kuwait, they activated only neurologists and neurosurgeons in the United States Public Health Service, [00:10:00] and I was one of them getting ready to go overseas. But the war was over in 10 days, so we never really got to go. So I was talking to Russell Lonser and I was saying to him, now that whole neurosurgical and neurological group almost went to war, but now we're going to war against Huntington's.

Podcast Host: [00:10:30] Absolutely. So, it's really interesting from your experience and your back on how many tie-ins there are to what you're doing now. So you talked about growing up in Fishkill, which is where George Huntington practiced. Did you know that at the

time, when you were spending time helping out?

Dr. Higgins: No.

Podcast Host: It was just a coincidence?

Dr. Higgins: No. I just found out when you sent me the pre interview questions. I started to think about it and when I looked at Fishkill, George Huntington actually came up, and he practiced at Matteawan General Hospital, which is still in existence today.
[00:11:00] It's now part of a fiscal correctional facility, but the hospital itself is still there. So I never knew that until recently.

Podcast Host: That's fascinating. And then at the same time when you're doing your work as a gene hunter, did you actually ever have any interaction or you ever meet with any of the group that helped discover the Huntington gene back in Venezuela?

[00:11:30]
Dr. Higgins: Yeah. Interesting. Nancy Wexler, I met Nancy Wexler in the 1990s with my genetic counselor whose name was Linda Ni. And it wasn't until last year that actually I had any contact with Nancy, and met her at the [inaudible 00:11:39] foundation meeting in Boston and she recognized me, which I found pretty fascinating. We talked about Linda Ni and she remembered those days back in the 1990s when she was at NIH, and we would talking about the ethics of genetic testing at that point in time.

[00:12:00]
Podcast Host: Fascinating. Dr. Higgins, looking back at your career and your path to where you are now, is there a person or a few individuals that you look at and consider to be your mentor, your inspiration, the person that you really learn the most from, that has kind of helped shape and evolve your approach to your work?

Dr. Higgins: Yeah, I think it would have to be Dr. Roscoe Brady from NIH. He was kind of my
[00:12:30] mentor after I finished my child neurology training doing genetics. And he was the type of person that could take a disease, and then look at the biochemistry and draw the pathway on a board and say, "Oh, this is what you should be looking at, and if you do that you may be able to treat that disease." So, that's where I began to realize the power of research and knowing biochemistry and genetics, that there really was a possibility to cure some of these really rare disease where there was
[00:13:00] actually no hope for any of these patients.

Dr. Higgins: So actually Dr. Brady would be the person who really steered me in this direction.

Podcast Host: And what is the one thing in your life really that you consider your proudest accomplishment? Whether it's personal or professional or both?

[00:13:30]
Dr. Higgins: You know I would say two things. One was related to enzyme replacement therapy.

I was the fellow who actually injected some of the first patients with enzyme, and to watch those children and adults be cured of Gaucher by enzyme replacement was probably the most gratifying things I've ever seen. The other thing I would say was just clinical practice, epilepsy in particular. When a child came in and had seizures, and I was able to prescribe an anticonvulsant and then see that child after two years not need the anticonvulsant anymore.

[00:14:00]

Dr. Higgins: That was really rewarding. So I think that the general practice of child neurology is rewarding. What really drove me was the fact that there were many children out there with diseases that could not be cured. There were no treatments. And Huntington's was one of the first genetic diseases discovered and I was almost shocked that we haven't been able to cure that yet. Because you would think by this point in time that, since 1993 to present, there'd be multiple therapies

[00:14:30] available. So I think we have a long way to go with gene therapy, but I think there's an acceleration now in the field because of better understanding of the molecular mechanism.

Podcast Host: That's a great point, and that's something that I'd like to build on. So from that perspective, like you said, the gene was discovered 25 years ago and there's been

[00:15:00] treatments but no cure yet. Give me your personal perspective and how you've taken in the evolution of the HD field and the treatments that have come about, and kind of where you even see it in the next five years or 10 years going forward.

Dr. Higgins: Yeah. So, I mean, there's been a tremendous amount of progress in gene therapy. I remember when we were using retroviruses which didn't work, and then the evolution of AAV. Looking at different stereotypes and doing recombinant AAV, and

[00:15:30] looking at trans gene and replication deficient viruses. So all that took a lot of time to develop the right vectors and to understand the molecular mechanisms. And what we're doing now with microRNA is just incredible. And with Huntington's disease, we do know that it starts in the caudate and putamen.

Dr. Higgins: So the neuropathology starts there, affects the medium spiny neurons. So I know in animal models that when we inject in those areas, and not only in Huntington's but

[00:16:00] with other diseases that start very specific areas of the brain, we're able to reverse the neuropathology and actually ameliorate the phenotype in these animal models. So getting it and delivering it to the right spot is critically important, and understanding the neuropathology is critically important.

Dr. Higgins: And so Huntington's disease, not only the genetics is better understood, but the neuropathology and actually the molecular neurobiology is understood. So because

[00:16:30] it's one of the older genetic disorders, there's a lot of knowledge out there that help design the micro Huntington approach. And of course there are other approaches, ASO is one of them, but it makes most sense to me to get the treatment to the place where the neuropathology starts.

Dr. Higgins: I think that makes common sense from a neuropathological point of view. So I think

that not only that, but now with better neuroimaging techniques you can target areas of the brain within 0.1 millimeters. So the delivery is another advancement in
[00:17:00] the last 30 years that has coincided with betterment in gene therapy, AAV vectors and also our understanding of those mechanisms. So the time is right for this type of thing, especially Huntington's disease because of those three different fields coming together, neuroimaging, better delivery system and understanding the molecular neurobiology.

[00:17:30]
Narrator: We'll return to the interview on the HD insights podcast in a moment. We hope that you're enjoying this episode. As a nonprofit organization, the Huntington Study Group relies on the generous support from the community and listeners like you to continue bringing you in depth content on HD, like this podcast series. If you like what you're hearing and are interested in supporting HD insights through a grant or
[00:18:00] donation, please contact us through our email address, info@hsglimited.org, or by calling toll free at 1 (800) 487-7671. We greatly appreciate your support. And now back to our episode

Podcast Host: This past June, a letter went out from uniQure to the HD community and then
[00:18:30] throughout the course of the past year plus, you've been working to get to the point with the FDA and submitting an IND and getting all that approval. And we know that you're in the process of recruiting for the first clinical trial. Tell us a little bit more about this particular treatment. We know it's a one time administered gene therapy which makes it pretty unique, but what's really the intent. What's
[00:19:00] going to happen when this treatment is administered and how it's administered.

Dr. Higgins: Okay. I just had a thought that some of these Huntington's disease specific networks such as EHDN, Huntington Study Group, ERN, CHDI. They've really been instrumental in really advancing the field, and actually organizing patients and patient groups so that it's easier to study Huntington's disease from a clinical trial
[00:19:30] perspective. So recruitment, and they enroll HD database, and they track HD studies. They've all been really good to have as far as clinical trial design and looking at what patient populations, understanding the genetics, understanding the clinical parameters and clinical endpoints.

Dr. Higgins: So, uniQure has been studying Huntington's disease now for about five or six years in animal models, particularly the Huntington's disease mouse models. The R6/2
[00:20:00] model, the Q175 mouse model, including the Q175 Delta Neo mouse model, and the Humanize 128 mouse model, which show improvement by delivering micro Huntington to silence the disease in those animal models. Probably more importantly, we used a transgenic pig model to look at the delivery system as well as silencing therapy. And then measuring mutant huntingtin, the CSF by lumbar
[00:20:30] puncture, which mimics what we'll be doing in human beings in the clinical trial.

Dr. Higgins: So by real time MRI convection-enhanced delivery, we are targeting the caudate and putamen and slowly infusing the AMT 130 into these structures over a period of about eight hours. So it is a neurosurgical procedure. The catheter is made out of

[00:21:00] ceramic and then it tapers down to the size of human hair by using silica, which is a very hardened type of a glass. And this has been done since the early 1990s with a variety of different substances but this is the best. This has been used for about 10 years in chemotherapy and other gene therapy trials.

Dr. Higgins: But what's amazing when you go into neurosurgical suite and you see the brain in three dimensions, and you see this catheter going in and then you see the infusion [00:21:30] in the structure, it's extremely accurate and you felt the structure so that it transduces the neurons within the caudate and putamen. And then something amazing happens, that after you take the catheter out, that transduction delivers the micro Huntington to the neuron.

Dr. Higgins: And what it then does, the micro Huntington travels by extracellular vesicular transport, both up to the cortex and down to the other deep gray matter [00:22:00] structures, and sort of transforms a lot of the brain. We do get 75% lowering of mutant huntingtin in the striatum and 50% in the cortex with the high dose, in low dose there's 50% lowering in the striatum and 25% in the cortex.

Dr. Higgins: So we do see a lot of lowering by delivery into these structures in large animal models, including the pig model. We also did it in nonhuman primates, but nonhuman primates, I think people understand that most of these studies are done [00:22:30] in cynomolgus monkeys, which have brains the size of, they could fit in a petri dish. So they're not as big as the pig brain and definitely not as big as the human brain. So translating delivery from the monkey to humans is very difficult. It's much easier when you're looking at a pig that weighs 200 or so pounds.

Dr. Higgins: So the clinical trial is really about the delivery of this micro Huntington by using an [00:23:00] AAV5 vector. So AAV5 is an annual associated vector. It is a virus that does not replicate, so there's no infection with this virus. The virus acts as a Trojan horse when you deliver it into the brain, and it latches onto the surface of the neuron and then injects the micro Huntington into the cell, where the cell's natural machinery then processes the microRNA to turn off both mutant huntingtin as well as a small [00:23:30] toxic fragment called the mutant huntingtin exon-1 fragment.

Dr. Higgins: And that exon-1 fragment is now known to be one of the primary reasons that patients with high number of repeats have an earlier onset, because this toxic exon-1 fragment is more common when there's a larger repeat. It also is in patients with a lower number of repeats, but it seems to be at higher levels than those that have higher number of repeats. So the therapy is treating not only the full length [00:24:00] mutant huntingtin protein, but also the smaller toxic fragments. Which is something very unique about this therapy compared to other therapies.

Dr. Higgins: The clinical trial is a double blind imitation surgery controlled trial with an escalating dose. Those escalating doses, there'll be a cohort with a low dose and a cohort with a high dose. A low dose cohort is really targeted to lowering mutant [00:24:30] huntingtin by 50% in the striatum and 25% in the cortex. And that was the level where we saw a significant improvement in the Huntington disease transgenic

animal models. We also saw improvement using the higher dose.

Dr. Higgins: So both doses are showing improvement in the animal models, we just don't know which one is going to be more effective in the human, and that's why we're doing the trial. The imitation surgery is that we're not injecting anything to the brain, but because of the placebo effect seen in most movement disorders including
[00:25:00] Parkinson's disease, it was thought best because of the invasiveness of the procedure to really have a imitation surgery control arm. So there'd be no data if we did see any effect that it would be real.

Dr. Higgins: And those patients will be randomized, and there'll be a small indentation made in the skull with an incision with one stitch, so that a patient will feel that they've had something done, but they would not have had anything injected into the brain. The
[00:25:30] study core period is 18 months, and during those 18 months we'll be doing a series of tests including clinical tests, the unified hunting disease rating scale. We're doing quantitative motor function or cue motor. We'll be doing MRI imaging as well as magnetic resonance spectroscopy.

Dr. Higgins: We'll be doing CSF and blood biomarkers including neurofilament light and mutant huntingtin and the CSF. And then patient report outcome measurements. I
[00:26:00] mentioned magnetic resonance spectroscopy, which is a really important test. We did show in an animal model of Huntington's disease that when we treated with this drug AMT-130, that we had a restoration of neuronal function in the brain. And that's a pretty amazing result. Usually you don't see that.

Dr. Higgins: So what that suggests is that when we treat patients or treat mice at least at an early stage, that the neurons are sick and there's a possibility they could be
[00:26:30] rescued. So that was a really important part of our preclinical data, and we hope that by doing this in patients we may see the same thing. We went through a lot of pains to standardize this throughout all sites. And I can tell you a little bit about the sites and how many there are and what we plan on doing there, if you'd like.

Podcast Host: Yeah, yeah, absolutely. Because I was going to ask you what's the nature of the
[00:27:00] patient population. Are you looking for people, pre manifest, early HD, the total size of this initial phase one trial that you're doing? Absolutely.

Dr. Higgins: Yeah. So there's a total of 26 patients in the trial in total, and divided between cohort one and two. There's a randomization scheme because of the imitation surgery. We plan on having three surgical sites and these neurosurgeons. I mentioned before a friend of mine, we were colleagues at NIH, he's going to be doing the study at Ohio state university. We also have a neurosurgeon at University
[00:27:30] of California, San Francisco, Dr. Paul Larson, and also at Johns Hopkins, Dr. Stan Anderson.

Dr. Higgins: These neurosurgeons are highly specialized in real time MRI convection-enhanced delivery. Stan Anderson is going to scrub in with both Paul and Russ in the initial
[00:28:00] surgeries because he has not done AAV delivery with these other two

neurosurgeons have done AAV delivery. We also have a neurosurgical planning committee. So, because of the improved neuroimaging technique, it's now possible to actually do a virtual operation before the patient is touched in the cloud.

Dr. Higgins: [00:28:30] So, Dr. Jan Vesper who's at Dusseldorf university in Germany, he has been inserting deep brain electrodes in the brains of patients with Huntington's disease. And he's going to also be part of that team to look at the pre-surgical trajectories and pre-surgical planning on these patients, because he's most familiar with the Huntington disease neuroanatomy. So there'll be making decisions weeks before they actually go into the operating room by getting consensus and standardizing the procedure.

Dr. Higgins: [00:29:00] So then there'll also be other sites referring patients in. These hunting disease centers of excellence which would... So far Virginia Commonwealth university is one participant and we plan on having others join that. Those nonsurgical sites refer patients into those three surgical sites. We have a total of 26 patients. The first cohort will have six treated and four imitation surgery patients, and the next cohort would have 10 treated and six untreated or imitation surgery patients.

[00:29:30]
Dr. Higgins: The total core study period's 18 months, followed by a total of five years of longterm follow up. If we do see an effect, we will approach the FDA and ask them if we should do a open label extension trial.

Podcast Host: [00:30:00] Excellent. Dr. Higgins, what from your perspective has been the biggest challenge in getting to this point? Has it been just strictly the amount of time necessary to get it to a clinical trial phase? Have there been roadblocks or things that you didn't anticipate? If you had to summarize your biggest challenge in this, what would it be?

Dr. Higgins: [00:30:30] I think when I first joined uniQure we got the IND approved within eight months. So that wasn't really a big challenge. I don't think the regulatory pathway was a big challenge. UniQure had done a great job in looking at all the different animal models and the preclinical work was pristine. It was just incredible how much work and thought went into the procedure, and animals went into the GLP tox studies, went into the preclinical work looking and silencing. So that was absolutely state of the art, and more so than I've ever seen in any other clinical trial as far as preclinical work.

Dr. Higgins: [00:31:00] We got the IND approved in January. And I think realistically is that, when you're dealing with multiple institutions with a gene therapy trial, I think just the administrative part, the paperwork is something that I don't think people have a big appreciation for. When it comes down to contracts between different institutions and IRBs, and then you have other committees that have to look at the safety. It does take longer than you would expect. And I would say that was the biggest obstacle.

Dr. Higgins: Also last year, the recombinant DNA committee at NIH disbanded. So now the IRBs

have that added responsibility, and it could have been a little bit slower, is because now they're looking at it more closely because they didn't have the government
[00:31:30] agency as oversight.

Podcast Host: You've had the chance now to interact with obviously patients and helping advise uniQure, you've been to HDSA. What's your perspective or takeaway on the reaction from the HD community about this upcoming trial?

Dr. Higgins: I would think this was almost a year ago, that we had a patient advocacy group
[00:32:00] come here to uniQure, and we went over the protocol with them. We asked them for advice, which is really important to ask patients for advice on a clinical trial. That's a really really good insight and I think when I left that meeting, to see the enthusiasm and just the bravery of these patients, because most of the patients that came, they had Huntington's but they represented families that had between two and 10 people in their family with the disease. So they were advocates not only
[00:32:30] for themselves but their entire family and the whole community. And I found that to be very touching.

Dr. Higgins: I mean, as a physician I've seen patients with Huntington's in isolation. They were accompanied by maybe one family member, but I've never seen that many patients together in one group working together. And I would say when I gave the talk to the advocacy group, I used the analogy of being astronauts. Myself remembering the first man walking on the moon thought like these people have to be really
[00:33:00] brave to get this gene therapy done. It is the first in human study, using AAV in Huntington's disease.

Dr. Higgins: But it's actually one of the first gene therapy trials using micro Huntington and actually using this technique of convection-enhanced delivery with direct delivery to the brain. So the tremendous amount of bravery and courage really touched me, which is something that you don't see in a regular clinic, but in the research community you really do see that this whole community is a very brave and resilient group.

[00:33:30]
Podcast Host: It really is. It's amazing to see and it's amazing to interact with these strong and brave patients. Dr. Higgins, I want to shift gears just a little bit but kind of dovetailing off the discussion of the AMT 130 and the trial. Like you said, this is going to be a first for this particular community. So, I'm curious as I'm sure a lot of
[00:34:00] listen listeners are, assuming everything goes great, you have approval for the treatment. How do you see clinical Huntington's disease practices evolving in the years or the period after a successful trial of this kind?

Dr. Higgins: Yeah. You had mentioned before it's been a quarter of a century since the discovery of the gene, right? And then George Huntington described the disease
[00:34:30] more than a century ago. So that's a long time. You would hope from the animal data that we have in this trial, and also looking at the other therapies available and their animal data, that this type of therapy, whether it'd be ASL or gene therapy,

would have an impact upon the clinical aspects of the disease. And that's the main reason to do a clinical trial, is really to look at the clinical effects.

[00:35:00]

Dr. Higgins: Not so much the biochemical or biomarker effects which is very encouraging in lowering mutant huntingtin, the CSF is great. But it's really to have that clinical effect to reverse the chorea, to improve their life, to stop the progression disease or even better to just halt the progression of the disease. Is that a realistic goal? Well, everyone would hope for that but I think when you really sit down and think about it, it's probably going to be multi-modality treatments.

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Dr. Higgins: The one thing that's good about gene therapy is that, you do it once and then you're done. Right? It will last for a very very long time, and we know there's expression in other genetic diseases for at least up to five to eight years. So we know this is a longterm therapy. Is that going to be enough is the big question. Is it a combination therapy where you may have a little bit of chorea and you may need to have some symptomatic treatment for that?

[00:36:00]

Dr. Higgins: You may need another therapy to stop the cortical involvement, another therapy to stop the motor progression. That would be a more realistic view. But of course we all hope that with this therapy that we would have a significant impact on the progression. And also just looking at other things going on with Huntington's epigenetic factors, there's a lot going on there. And are you getting in all the cellular compartments. You're getting into [inaudible 00:36:28] therapy, the

[00:36:30] cytoplasm and nucleus. Is there any mitochondrial issues?

Dr. Higgins: We really don't know that much about that. So, even though Huntington's a monogenic disease with a CAG trinucleotide repeat, things are usually more complex than what they first appear. So I think in the future you're going to see a lot of great research going on, understanding the molecular pathophysiology of Huntington's, and there'll be multiple shots on goal to help cure the disease.

[00:37:00]

Podcast Host: I'd also like to ask you from your experience, because you've been on the front lines in neurology when it comes to quality of care and in terms of the HD population. What are your thoughts over the years where there've been hits or where they've been misses with quality of care that the community, the industry, the field, should really be focused on going forward?

[00:37:30]

Dr. Higgins: Yeah. Genetic diseases in general, including Huntington's, is that it's usually a multidisciplinary approach. So, from input from an expert physician that's a Huntington expert, rehab specialists, nurses, psychologists, genetic counselors, you got social workers, psychiatrist. So, the coordination of that care is daunting. And I guess there's no really good model. And from my experience, the only time I've

[00:38:00] ever seen it work was at Boston Children's. Where a patient would come to the clinic, and older specialists would go to that one room.

Dr. Higgins: So instead of the patient going to all these different specialists, all the specialists would come to them. And I think that that made a lot of sense to me, and I've never seen it done in any other place except for Boston Children's. And then I learned later on that was because of insurance reimbursement. That you need to have separate visits on separate days for the doctors to get paid, which to me was mind boggling.

[00:38:30]
Dr. Higgins: But I think when you look at spinal muscular atrophy, right, that's a disease in childhood where there's been tremendous amount of advancement in therapies, both ASL and now gene therapy. The gene therapy that was this clinical trial run by AveXis, some amazing results there with those children who were all dead at the age of two, are now running around and riding bicycles. And so, that's the hope
[00:39:00] that gene therapy could bring to diseases like Huntington's disease, is that you would alleviate the need for a lot of these specialists and doctors.

Dr. Higgins: But I think for the time being, the gaps in quality of care currently is really that multidisciplinary care, which is lacking not only in Huntington's, but I think in a lot of other diseases.

Podcast Host:
[00:39:30] Absolutely. Dr. Higgins, before we go, I just want to ask you one other question and you touched on it, various experiences working with children. But is there one particular moment or one particular event that really has been the inspiration for you? The one example that you always cite when people ask you, what do you remember most about working in this field?

[00:40:00]
Dr. Higgins: Yeah. I would have to say when I injected this little girl with enzyme and she had a very... and I still have a slide of her at home, an abdomen that protruded out. I'd say at least her abdominal girth was at least 40 to 50 inches. And she was only six and she was anemic and pale and with thin legs. And when I saw her back a month later, and I saw that her cheeks are rosier, and that her abdominal girth had
[00:40:30] decreased, and then when I get the MRI back, that showed that her liver and spleen were shrinking.

Dr. Higgins: That was one of the most amazing moments in my career. Besides that, seeing many many patients over the years where seizures were cured. When you cure somebody or you take a patient from a state of severe disease and you can normalize their life, to me that's the best feeling in the world.

[00:41:00]
Podcast Host: That's amazing. That's a great story and I appreciate you sharing it, and I appreciate your time speaking with us today. I'm sure our listeners will come away with a lot of great insights both on Huntington's disease, the work that uniQure is doing with

[00:41:30] the AMT 130. But most of all I hope people get to know the Dr. Higgins that I've had a chance to speak with a couple of times now, and just really come away with the same impression that you're one of the positive examples in this field. And again, I thank you for joining us on this episode.

Dr. Higgins: Yeah, thank you Kevin for your time. I appreciate it.

Podcast Host: [00:42:00] Once again that was our interview with Dr. Joseph Higgins from uniQure. We hope you enjoyed this podcast and ask that you please continue to support us by downloading future episodes. You can subscribe. We ask that you please rate and review, provide your feedback, or suggestions for future topics that we'd like to try and bring you. Our hope is with this podcast, to bring you more in depth insight into the people behind the research taking place in Huntington's disease. And again, look for our future episodes coming soon. Thank you again for joining us. I'm Kevin Gregory with the Huntington Study Group. Thank you again.

[00:42:30]

Narrator: [00:43:00] We hope you enjoyed this edition of the HD insights podcast. Remember to subscribe to this podcast to make sure you automatically get the latest episodes to your device. Please rate and review this podcast with your feedback so we can continue providing the best possible content. If you are interested in providing financial support for the work needed to produce this content, you can do so by becoming an ongoing sponsor, or through a tax deductible donation. To do so, please email us at info@hsglimited.org, that's info@hsglimited.org, or by calling our toll free number at 1 (800) 487-7671. Thank you for joining us on the HD insights podcast from the Huntington Study Group.