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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Gene Messenger: Advancing Neurological Gene Therapy

ReachMD Announcer:
Welcome to Advances in Care on ReachMD. This medical industry feature is titled “The Gene Messenger: Advancing Neurological Gene Therapy.” These podcasts are a production of NewYork-Presbyterian with doctors from Columbia & Weill Cornell Medicine.

Here are your guests, neurosurgeon Dr. Michael Kaplitt and health and science journalist, Catherine Price.

Catherine Price:
Monday, August 18, 2003, was scheduled to be the most important day of Dr. Michael Kaplitt's career. That was the day when he was planning to be in an operating room in New York City, conducting a trial for the first-ever neurological gene therapy treatment in a human patient.

Dr. Michael Kaplitt:
You can't imagine the amount of effort that had gone into not only getting this to the point that it was at, but the number of people that were planning to be there in addition to obviously the patient. We had many teams of people who had to be there, and then there were, you know, observers, there were actual, like reporters because this was gonna be a big deal if it, if it came off, because it was the first time it'd ever been done.

Catherine Price:
Dr. Kaplitt had many responsibilities when it came to preparing for this groundbreaking procedure – including safeguarding the virus which would deliver a gene into the brain of a patient with Parkinson's disease.

Dr. Michael Kaplitt:
It was made to very exacting specifications that the FDA requires. And it was sitting in a freezer in my laboratory. So, I'm trying to make sure that nothing happens to the virus.

Catherine Price:
This virus was the culmination of more than a decade of work, with the potential to make medical history. And so, you can imagine he was reluctant to leave the precious virus only days before the procedure, to go out of town for a meeting on Cape Cod. And then…

Dr. Michael Kaplitt:
While I'm there, I find out that there was a blackout on the East coast.

Catherine Price:
“The August 2003 Blackout" is considered the worst blackout in United States history to this day. The entire eastern seaboard lost power from New Jersey to Toronto. And that meant not only were there no lights, but there was no refrigeration. . .

Dr. Michael Kaplitt:
What's gonna happen if this freezer thaws out?

So, I wind up getting in touch with someone from my laboratory and I said, “Number one, put tape on the freezer with a sign: No one is to open this freezer. Okay, number two, find every piece of dry ice you can find in the hospital and bring it to the lab.”

And then of course, I needed to get back to New York so I could be around and babysit this thing myself and make sure I'm there. I couldn't take a chance of not being there with everything that had been planned.

Catherine Price:
Dr. Michael Kaplitt braved the blackout and made it to New York for the procedure. The rest of the story is medical history.

I'm Catherine Price and this is Advances in Care. Today, the Executive Vice Chair of the Department of Neurological Surgery at Weill Cornell Medicine -- Dr. Kaplitt -- tells us the story of his groundbreaking advancement in neurological gene therapy. And shares what he's working on next.

It was 1989. Dr. Kaplitt was working in the behavioral science lab of Dr. Don Faff.

Dr. Michael Kaplitt:
He had an idea that he wanted to do an experiment that would involve putting a gene into a particular area of the brain, And he said, did I have any thoughts about how one might do it?
And I was in the middle of an experiment and I said to him, “well, probably I use a virus.” And I thought, actually, this is really an interesting idea. And so I went to him and I said, “do you mind if I play with this a little bit?”

Catherine Price:
Was that something that was happening at that point with gene therapy?

Dr. Michael Kaplitt:
Not much. Gene therapy was just starting to come into our consciousness at that time.

Catherine Price:
In the late 80s gene therapy was in its infancy. But the concept was to introduce foreign DNA into existing cells, possibly to treat or cure disease. In order to do that, scientists needed to package the gene in a delivery vehicle that could carry it inside the cell -- and some researchers were using viruses.

Dr. Michael Kaplitt:
You don't wanna just put a live virus in because then people would get horrible diseases. It would spread and it would cause terrible problems. So we knew we had to disable the viruses in a way so that they would retain the ability to get into the cells, but then would not do anything else. And then once you disable the viruses, then the idea was to take out a piece of the virus that was not essential.

Especially if you were taking out pieces that were involved in the virus's ability to make more of itself to reproduce, and use that space that you created to put new genes in that would actually do something positive in the cell, then that would be gene therapy, right? That's the idea.

Catherine Price:
Right, okay so it's like a kind of benevolent Trojan horse kind of idea.

Dr. Michael Kaplitt:
And that's exactly the term we use often. We use the term Trojan horse, so you're sneaking the gene in because the cell is taking up what it thinks is a virus, but then the virus doesn't do anything bad. It doesn't create more viruses. You're just leaving this gene behind that starts working and then it becomes part of the cell. So that you can change the way cells function, you can improve their function, you can give them new functions, or you can try to protect them from dying.

Catherine Price:
At the time, Dr. Kaptlitt's supervisor wanted to study how the introduction of certain genes into the brain might affect human behavior. But the implications were much greater than that, because if a gene could be introduced into the brain, then it might be possible to cure brain diseases which were previously thought to be incurable. That said, up until this point, no researcher had done gene therapy in the brain. Instead, researchers had only just begun early animal experiments in gene therapy for diseases in other places in the body. Doing this work in brain cells would be a very complex challenge.

Dr. Michael Kaplitt:
The types of viruses that were being used in those days to put genes into cells were mostly targeted at cells that were dividing like tumor cells, et cetera. And those would not, those would simply not work in brain cells that were not dividing. So brain cells you're born with and you live with for the rest of your life. But also, even if you can replace brain cells, they have to form the right connections, right? The brain is made up of circuits and things, so it's not simply a matter of just making a bunch of random new cells. They have to actually take on the features of the brain cells that we're missing, they have to take on the biology, they have to respond appropriately to the signals that the cells that died responded to in the past, and they have to make the connections that the cells that died were connected to in order to really restore brain function. It's not simply a matter of making new cells. So it's very complex in that regard.

Catherine Price:
In order to design gene therapy for the brain, Dr. Kaplitt first needed to choose the right virus. So far, researchers were choosing viruses which naturally infected the area they wanted to treat. For example, adenoviruses that naturally infect the lungs were selected for cystic fibrosis treatment. And retroviruses that naturally infect blood cells were being used to treat blood disorders. So, Dr. Kaplitt decided to start by selecting a virus which naturally infects brain cells. . . which led him to the Herpes virus.

Dr. Michael Kaplitt:
So, I started working with a type of virus that was based on herpes viruses, the reason they cause cold sores is because they tend to infect your neurons. They sit in the neurons that feed your face. So, when you get a cold sore on your lip or something like that, the virus is kind of sitting in the nerve. So, the virus sits there and it gets in and then it kind of sits dormant for a while and then it can reactivate itself and start to make more viruses, and that's when you have an in inflammation in response to that and you get the classic sort of cold sore and then it quiets down. So that idea that we started playing with worked beautifully in both cells in a dish, but then eventually in animals.

Catherine Price:
But despite this success, it wasn't an ideal solution. The herpes variants were complicated. The treatment only lasted for a brief period of time, and ultimately, it wasn't ideal for use in the human brain—which is what Dr. Kaplitt ultimately wanted to treat.

Dr. Michael Kaplitt:
I was really interested in trying to make some of this usable in patients. Since all we want to do in gene therapy is deliver the gene into a cell and we don't care about the rest of the biology of the virus, we don't want it to do anything more, we said, well, why are we restricting our cells only to viruses that normally cause disease in these tissues? What about other viruses that might be better, that might be safer, that might have more attractive features?

Catherine Price:
Focusing more on the, on the capacity to be a messenger- not necessarily what it's carrying, but its ability to get in.

Dr. Michael Kaplitt:
That's correct. Why are we restricting ourselves only to viruses that normally cause disease when that's not really our goal?

Catherine Price:
Dr. Kaplitt got together with some collaborators, Dr. Matthew During and Dr. Jude Samsky and broadened their virus search. Their goal was to find the perfect Trojan horse to deliver a gene to the brain.

Dr. Michael Kaplitt:
Jude was working with a virus called adeno-associated virus. So, the three of us got together and said, why don't we try to see if AAV could work in the brain? And it turned out that it did.

Catherine Price:
The team set up a series of experiments in animals which were exhibiting movement problems caused by brain cells. They selected a gene which would treat the dysfunctional cells, and they put it inside an Adeno-Associated Virus – or AAV–Trojan horse package. And their results were better than they could have possibly predicted.

Dr. Michael Kaplitt:
We actually went so far as to not only show that the virus could put a gene into the brain, but that it could actually deliver a gene that could make these animals better. And they did get better.

Catherine Price:
Do you remember the moment where you realized this was working?

Dr. Michael Kaplitt:
Well, yeah. So, we got some slides of the brain tissue to see if the gene was being produced. And I saw evidence in the cells that the gene was being produced and when I saw that that night, I went to the faculty and students club and had a lot more to drink than I probably ever have had since. So I remember it quite well.

Catherine Price:
Maybe you don't remember it very well.

Dr. Michael Kaplitt:
Exactly. But that was obviously quite exciting. And it lasted for a very long time, which was unexpected because the herpes viruses

really only worked for a brief period of time. The adenovirus has really only worked for a brief period of time, but AAV lasted for months, and then eventually we found out years. And so that made it very viable for a human application. And so the three of us got together, we wrote this paper. I was the first author on that paper, and that really became the foundational event for neurological gene therapy.

Catherine Price:
I mean, that must just be an amazing sense of accomplishment for yourself to know that you were, you know, integral to the beginning of this field.

Dr. Michael Kaplitt:
It is. I mean, it's, you know, it's funny that when you do something that's that important, it gets to the point where nobody even remembers it because it's become so ubiquitous. You know you've done something when people stop citing the paper from, you know, 30 years ago because it's so ubiquitous that no one even remembers where it started from. But of course, yes, that, that was a big deal.

Catherine Price:
At the time Dr. Kaplitt and his peers published this paper in the mid-90s, theirs was the only strain of AAV being used for gene therapy. Today, there are dozens. In fact, the use of AAV to deliver gene therapy is now ubiquitous. Entire fields of medicine like Optogenetics and gene-editing with CRISPR are based on the foundational premise of this very study.

The next step was to figure out how to administer gene therapy in a human patient. For a few years during his residency, Dr. Kaplitt had been researching Parkinsons -- which seemed like the perfect disease to target. He called his colleague, Dr. Matt During.

Dr. Michael Kaplitt:
I said to him, maybe we can try that virus in Parkinson's actually, because unlike more global brain disorders, Parkinson's is really caused by very specific sets of brain cells that are dying. So there are certain spots in the brain that are abnormally active and perhaps if we put this gene in there, we could make that better. We could make the circuits function better.

Catherine Price:
At that point in time, the newest and most cutting-edge treatment for Parkinsons was something called Deep Brain Stimulation --- where electrodes are attached to the spots in the brain which were over-firing and causing tremors. This treatment was (and still is) very effective and a good option for patients with Parkinsons -- but it has downsides.

Dr. Michael Kaplitt:
Deep brain stimulation is a great technique. We still do it to this day. But it still does involve putting a device in the human body. There's a wire in the brain that's attached to a wire under the skin that goes to a battery that goes in the chest, and then that battery has to be optimized; the programming is very complicated in terms of how we adjust the settings, so patients have to come back several times to get the settings adjusted. Also, you have to live in proximity to a center like ours to be able to go back and forth, right? If you have to come back several times over months to get the device optimized and reprogrammed, that can be challenging, which limits access to certain patients. So, our view was that we could potentially resolve a lot of these issues with this particular gene therapy approach.

Catherine Price:
Gene therapy had never been attempted in the human brain – only in animals. And now, Dr. Kaplitt and his colleagues wanted to use the AAV virus to deliver a gene into a human brain with Parkinson's. It was 2000, only one year after the FDA had enacted a sweeping moratorium on all gene therapy trials due to the tragic death of a patient in a gene therapy trial in Philadelphia. So the research, while exciting, was coming together at a complicated time.

Dr. Michael Kaplitt:
The idea of putting any type of modified virus into the brain of an adult patient who's not dying of some lethal disorder was very daunting, right? But if we can show gene therapy could work in this situation, be safe and effective, it would have the greater good. It was an attractive opportunity to help people

Catherine Price:
After a careful audit, the FDA concluded that the patient's death in the 1999 trial was a complicated anomaly, and they determined gene therapy research was safe enough to continue.

Dr. Michael Kaplitt:
Fundamentally, gene therapy was found by the FDA to not have any unusual risks to justify continuing to deny it to patients, so they eventually opened it back up. So that led to what became the first human trial of AAV or any gene therapy in the adult human brain for any disorder.

Catherine Price:

55-Year-old Nathan Klein was a New Yorker, the father of 15-year-old twins, and a former TV producer. His tremors had gotten so bad that he was no longer able to work. Certain parts of Nathan's brain had become overactive due to low dopamine caused by his Parkinson's.

Dr. Michael Kaplitt:
He had tremors that were a real problem for him. And this area of the brain, as well as the areas that it connects with, were firing abnormally causing all of these problems and we knew that if you could quiet them down, that you could make things better. But we don't want them to completely shut down because you need those areas at times.

Catherine Price:
Nathan had been on medication to increase his dopamine but he wasn't doing well on it. He needed another solution.

Dr. Michael Kaplitt:
The analogy that I often use is like the engine in a, in a car, right? So, if you lose the key to the ignition, your car won't work, right? That's like losing the dopamine in your brain.

Catherine Price:
Right…

Dr. Michael Kaplitt:
But if you can go beyond where the key is needed and hotwire the car, like when people steal cars, I don't know how to do that, 'cause I've never had to steal a car…

Catherine Price:
Uhhuh sure!

Dr. Michael Kaplitt:
Right. But if you know how to do that right, you're bypassing the key, the rest of the engine can function just fine. You can drive it away, right? So that's the idea here, is that it might be a better option to bypass the whole dopamine problem.

Catherine Price:
In order to "hotwire" Nathan's brain, Dr. Kaplitt and his colleagues wanted to introduce a new gene that would quiet down the neurons which were over-firing.

Dr. Michael Kaplitt:
So when you have like an eyedropper where you make one drop, it was actually slightly less than that volume of fluid that was being injected that contained 10 billion of these little modified viral packages containing this gene called GAD, or glutamic acid decarboxylase, that was designed to go into a region of the brain that we normally do brain stimulation so we knew how to get there but instead of delivering this electrode, we were delivering these gene packages.

Catherine Price:
And, and what was the, what was the gene supposed to do? Like why did you think that this would be useful in Parkinson's?

Dr. Michael Kaplitt:
So the gene was going to make a chemical called GABA. This was a neurotransmitter that was going to quiet down nerve cells, stop them from excessively firing. So the idea behind this was that it would deliver this GABA neurotransmitter both locally to the target area we were going into in the brain, as well as through its connections to all the other regions it connected with to try to quiet down the entire circuit when it became hyperactive. And then based on the studies we had done leading up to this in animal models, et cetera, we felt that this should not only hopefully work, but that it actually could regulate itself. Meaning when the brain needed more of this, it would make more. When the brain needed less, it would make less. So there was a, what we refer to as an auto regulatory function, meaning the brain would do as much or as little of this as it needed, we hoped, so that it wouldn't just be on all the time, but it would actually be responding to the need. So that was the idea behind it.

Catherine Price:
The FDA approved Nathan's surgery as the first ever human trial for neurological gene therapy. It was scheduled for August 18, 2003. The GAD gene was packaged inside its AAV Trojan horse according to FDA specifications and stored inside a super cold laboratory freezer. And then, one historical northeast blackout later, Dr. Kaplitt was in the OR, ready to attempt to infuse his precious virus into Nathan . . . who, by the way, would be awake the whole time.

Dr. Michael Kaplitt:

When it came time to actually put the thing in the brain, we put in this little microscopic tube that's made of kind of a form of glass that was attached to a syringe and that was attached to a little pump that would pump the fluid in at a very particular rate of flow, right? I think it took a little under two hours to, for the viral infusion to happen because we wanna do it at a fairly slow rate. So that was probably the worst of the whole thing, because that's like standing there watching paint dry. If, you know any other surgeons, surgeons temperamentally don't like standing around doing nothing for two hours.

Catherine Price:
I've gotten that sense.

Dr. Michael Kaplitt:
It's just, it's the way we are, right? I mean, we're trained to act.

Catherine Price:
Dr. Kaplitt later said in a press release that throughout the 90-minute procedure, Nathan Klein was calm, telling jokes that were quote, “not repeatable.” The operation was successful, and history was made.

Dr. Michael Kaplitt:
And it became a big deal. It was front page news everywhere after we were done with it because of the implications. So for, you know, maybe 24, 48 hours, I was probably the most well-known neurosurgeon in America. And that, like any of these things lasted about 24, 48 hours. And then the hard work begins.

Catherine Price:
The procedure was a phase I trial, meant to determine the safety of neurological gene therapy—not the efficacy. But Nathan's tremors did improve, as did symptoms of stiffness and freezing. But as part of the study design, the FDA had only allowed Dr. Kaplitt to treat one side of Nathan’s brain, so he continued to have symptoms from the untreated portion of his brain. Later on, Dr. Kaplitt would treat the other side of Nathan’s brain with deep brain stimulation, but it required so little electricity that Dr. Kaplitt suspects the gene therapy was still benefiting Nathan all those years later. With safety having been adequately established, the next step was to evaluate the treatment for efficacy. And sure enough, in the phase II trial, the patients who received treatment got significantly better as compared to the sham group.

Dr. Michael Kaplitt:
And that was the first, and still the only time that a gene therapy in the brain actually showed real improvement, you know, based on what the sort of pre-planned endpoints were.

Catherine Price:
Dr. Kaplitt’s groundbreaking discovery launched avenues of research in neurological gene therapy that are still ongoing. So far, gene therapy trials for Parkinson’s have focused on helping the brain fix damage that has already been done to brain cells. But now, Dr. Kaplitt and his colleagues are wondering if they can intervene earlier...

Dr. Michael Kaplitt:
There are multiple ways to try to do this, right? So one way is to take patients who are already symptomatic and try to make their brain work better, right? Another way is to try to prevent the disease from progressing in the first place, but you have to be able to identify those patients.

Catherine Price:
Most Parkinson's patients aren't identifiable until they begin exhibiting symptoms, so Dr. Kaplitt and his colleagues are focusing on a form of Parkinson’s that’s slightly more predictable—namely, an inherited form of Parkinson’s caused by a mutation in the GBA gene. Some research estimates between 5 and 15% of ALL Parkinson’s is caused by this mutation. This means that for patients who have the mutation, treatment can be delivered before they ever develop a symptom.

Dr. Michael Kaplitt:
So we've been doing trials of gene therapy here at Cornell, trying to deliver genes that could stop the degeneration, the dying of cells.

Another way that we're working on in our laboratory right now is a very radical and controversial concept of could you actually let the brain itself regenerate itself, right? Are there cells already in your body, in your brain that could be converted to new brain cells? Our brain is composed, not just of neurons, which are kind of the circuitry of the brain, but there are also a lot of other cell types that aren't neurons that are in those areas that help neurons function better, that protect them, that affect the immune system of the brain. There's lots of different cell types, so can you convert some of these other cells into neurons in the brain itself? There's some evidence that you can, we have some evidence in the laboratory that you can, it's a very early concept, but, you know, that is another way to potentially

approach this.

Catherine Price:
But Dr. Kaplitt's search for innovation doesn't stop here. He is pioneering the use of focused ultrasound to treat essential tremors and movement disorders; he has contributed to the development of gene therapy for Alzheimers; he's researching implanting patients with stem cells derived from their own bodies to improve brain function; and he is working on gene therapy for magnetic pain management - which would give patients with chronic pain the ability to instantaneously stop pain with the wave of a magnet. So perhaps it's unsurprising that when I asked him what he was the most proud of, this was his response:

Dr. Michael Kaplitt:
I mean, that's tough because, you know, with an almost 23-year career, it's hard to pick just one thing. I mean, obviously, the early work, particularly, that idea that AAV could work in the brain and that original paper, you know, I'm extremely proud of because it really has changed the face of how we do neuroscience research around the world, and so that is obviously a major contribution. It's hard to point to one thing because when you have such a multifaceted career in an institution like this that allows you to do these things... one of the things I've always loved about being in this place, is that there is a real sense of not only of community among the physicians and the scientists–which there is, a very unusual sense of collegiality and community–but there also is a level of support and recognition of the importance of these types of advances at the highest levels of leadership that I don't think is true in a lot of places. Because let's face it, if you're supposed to be a surgeon, they want you operating all the time. That's what you're supposed to do. And a lot of people feel that scientists should do science and surgeons should do surgery, and you know, you're wasting your time if you're not in the operating room, if you're a surgeon. But this institution really recognizes that there is a very important place for people who are at the interface between science and medicine, and that we can play an important role in doing the kinds of things that we've talked about here.

When I was a medical student and a resident, it was Cornell Medical School and the New York Hospital. And then when I was at the sort of tail end of my residency, the hospitals merged between, Presbyterian Hospital and New York Hospital to become this huge NewYork-Presbyterian hospital.

And nobody knew whether that was gonna be successful or not.

The idea that you could bring two ivy League medical schools together and be a successful entity was very much in question at the time including amongst, you know, many of us who are here. But the success of that endeavor, I think for those of us, and I'm just a small part of it, but for those of us who've been part of it throughout, is also an enormous source of pride, having helped be a part of building this thing with my colleagues and of course with the broader institutional leadership. So it really, there's a lot to point to and I could go on obviously, but there's a lot.

Catherine Price:
Well, that seems like a wonderful place to end, so I just wanted to thank you so much for making the time to speak with me today. I really enjoyed our conversation.

Dr. Michael Kaplitt:
Oh, it's absolutely my pleasure. Thanks for having me.

Catherine Price:
I'm Catherine Price; Advances in Care is a production of NewYork-Presbyterian hospital. As a reminder, the views shared on this podcast solely reflect the expertise and experience of our guests.

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