Catriona Jamieson: Thank you for being at our Medicine Informing Novel Discoveries events. These are getting a momentum of their own, so we like to be mindful of what a team effort this has been. I wanted to thank Kirsten in the back here for always championing these events, which are not that easy to put together, but you can see a lot of people are getting interested. We have Michelle Ortiguerra just come in. She's our Sanford Stem Cell Institute Executive Director. I'm the director of the Sanford Stem Cell Institute for the Six Centers, the Brain Tumor Renewal Restoration Program. Most of which are actually represented here. If you're part of the Sanford Stem Cell Institute, including my lab over here, please put up your hand. You're surrounded, as you see. If you're from a philanthropic or charitable group. If you're from the industry, and then if you're a UCSD staff alumnus, yes. I think we've covered just about the whole audience. If you're a patient advocate? Yes. We're in for a real treat today. I'm Catriona James, and I go by Cat. We're thrilled to have the speaker lineup that we have today. This is the mover and shaker group. These are the improbable discoveries that actually led to really impactful clinical trials for the toughest diseases to target. These are rare diseases. I study rare diseases. I study mono proliferative neoplasms in my clinic. These affect one in 100,000 people, but this is even rarer than that. They're correctable diseases, provided you think carefully about how you're going to fix the problem. But first, as we know, there's an odyssey to having the proper diagnosis to begin with. We'll be talking about the proper approach to diagnosis and treatment for some of these inherited disorders. We live in the land of the Rady Children's Hospital, so we're thrilled to be able to work very closely with Radys, and UC San Diego Health and all the scientists around us who tend to think they want to do things for their discoveries and put them in the clinic. We'll be hearing from Stephanie Cherqui and her New England Journal paper that was just published regarding what I thought was the toughest child to ever get off the ground, and somehow, Stephanie did this with her team; Betty Cabrera was instrumental in this. But it's an example of how individuals can make a difference, individually as scientists, as administrators, but also as a family that said, we're going to step up for this. Then we'll hear from Lisa Kadyk from CIRM. It matters that we have the California Institute for Regenerative Medicine helping to navigate this difficult path, whether it's through diagnosis or therapy or both, so we can have better diagnostics, better therapeutics that match the patient as opposed to match the therapy. Lisa Kadyk will talk about that. Leo Wang is here from City of Hope. Leo is a fellow Alpha clinic director. We're thrilled that Leo is here. I first met him because he worked with Amy Wagers, and I knew her from postdoc in, but Leo has just taken on a whole zeal about developing therapies for pediatric cancers, and particularly around brain tumors. We'll hear about that. Then we're going to have a patient's story with a very strong patient advocate who's here. Daphne will tell us about her daughter's story and how that's going. Here we're doing what other people would consider improbable or impossible. Why is that? Because we have you. We have you never, ever giving up on the idea that we can find solutions to these difficult problems, even if it takes that awkward part where we don't actually know what we're doing and we figure it all out together, and that's where we combine our strengths. We're going to have Stephanie Cherqui come up and talk about her studies. Stephanie is really the pioneer of not just gene therapy for this rare disease called cystinosis, but actually the whole methodology for making this platform technology that we can use more commonly. She's a professor here in pediatrics. We work closely with her team in the Sanford Cell Stem Institute. Thank you for being here. [Applause]

Stephanie Cherqui: Thank you so much, Cat, for the introduction. Thank you for being here. I want to say a story because we say gene therapy for rare diseases, but each time it's like how many patients are there? How many patients do you treat? It's like 3,000, 5,000, 10,000, and you think, there are so many people who have cancer or like diabetes. I wanted to say, and I hope I will show you today, that walking on rare diseases, first of all, it's important because when you are a parent who has a kid who's dying from a rare disease, it's very important to have scientists to care and we work on it to find new treatments. But I want to show you more. I want to show you that walking on rare disease can also teach us so much that we will apply that to so many more diseases. That's the story I want to say. I am a professor in the pediatrics department at UCSD, and that's my disclosure that I always have to do. What is a rare disease? Usually, a rare disease affects our genes, most of them affect our

genes. You just need a little bit of one mutation, like one faulty base pair in your DNA, and you might not work, and you might just die, because of this faulty gene. We have most of them affect children, and also, you have a poor quality of life for many years, and eventually die as an adult. You have more than 7,000 rare diseases. Put together, there are more than 400 million people affected with rare diseases. This number alone is important because, again, the tool and technology that we are developing for rare disease, it will be true not only one disease, it will be true for so many of your disease, and that's the key that we want to understand here. What is a gene therapy? For many of these disease that affect the gene, most of the time, drug don't do much because, as I said, the gene is affecting so many parts of your body and so many heart function of yourself that it will be very hard to replace that. Gene therapy needs to act on the gene, it's to treat. The medicament is to treat the gene, to replace the faulty base pair mutation, or replace the gene. You have two ways of doing that. You can just add the gene to the body by using a viral vector. We are using the virus that exists in our system, like we use AV vector, HIV vector, things that are usually bad, we make them good. They are the ones that will bring the healthy genes to the body. Or you have ex vivo gene therapy. That's the way I'm using it for disease. In vivo gene therapy is usually good for a disease that affects only one tissue: the brain, the eye, the liver. But when you have a disease, like one gene is impacted, but all your organs are affected. Then, the ex vivo gene therapy is probably the best when they use our own bone marrow stem cells. Why? Because our bone marrow stem cells, what they will do if you have an injury, they will travel to the injury and try to fix it. It's a great vehicle to try to fix the gene that is missing. That's what we are using. In my lab, we are using the bone marrow stem cells, our own stem cells that we have in the bone marrow, and create blood cells to repair them and make them as a vehicle to bring the gene to all the organs. Again, I don't have a long time, so that's why I'm really summarizing the long story in one slide. But I started to work on cystinosis when I was a PhD student. I got from one of my committee members saying, why are you working on such a rare disease. I said, it could be very important, and I hope he would be in the room today to see what we've done and what we've learned with this disease. It's a disease that affects one child out of 200,000 births, and it's a gene that is not secreted, so it's a protein that is really inside the cells. It makes it even more difficult. The patient developed everything: kidney failure, blindness, muscle weakness, diabetes, you name it. You can imagine the poor quality of life of these children. We have a drug that they have to take every day, every six hours, even at night, around the clock, and it smells bad, and they have side effects, and they still die from the disease. There is a need for better treatment. This is what I wanted to do. Again, it was a really worst model disease to charge in therapy, and that's why I use hematopoietic stem cells. We started the idea of using these bone marrow stem cells in 2007. The mouse model I created during my PhD, we use them, and we could treat them and rescue them. I was like, wow, that's why you live, and you do research every day. That's where our first proof of concept was in 2007. Then I knew I really wanted to go to a clinical trial, and I got the first interact meeting with the FDA in 2012. Fast forward, we developed all the technology that, as Cat said, can be a platform for many diseases, and to add the gene to the stem cell and put it back into the patient. Here we have Jordan, our first patient, who was treated in 2019, more than six years ago. Jordan today is now living his life. He went back to his studies and now has a great job. He said that for the first time of his life, he spent days without thinking about cystinosis. Whereas before this was all his life. That was our success. Actually we published last month in the New England Journal of Medicine, which is the best journal of medicine in the world. Even a rare disease can be published in good journals, so that's great. But also, our success was that Novartis acquired this program, and now it is starting this same technology in kids with cystinosis. But what I want to say and want to stress the fact is that this was possible because we received money from the Cystnosis Research Foundation, because nobody at NIH would have never put a dime into these ideas at the beginning. But that created great data, and now after I got NIH. But I want to say a big thank you to CIRM because if I was able to do the whole bench to bedside as an academic researcher is because of CIRM, California Institute for Regenerative Medicine, that is giving grants to even academic researchers to be able to do this and bring it to the clinic. Now I will go faster. That was my first baby, I would say. But what we've learned

about it is like, how come bone marrow stem cells that do blood cells can rescue a disease like cystinosis with all the organs degenerating, the protein not secreted. What we discover is actually the stem cells become some immune cells in the body, and they create these tunneling nanotubes with the transfer of a lysosome with the protein. That was the new discovery of how we could engineer hematopoietic stem cells in vitro, and it could be this great reservoir of a protein of every cells and bring the protein everywhere. Based on this, we were like, so if I can do that on cystinosis, then I could do that on many of your disorders. This is what we are doing now. We are now working on Danon disease because it's the same family of disease, which is called lysosomal disease with a transmembrane protein. We are doing that in conversation with Dr. Adler, and the kid required a heart transplant. Hopefully, we will be able to avoid that one day. We are working on Sanfilippo Syndrome C, which is a neurodegenerative disorder. This is Rafael, a postdoc in my lab, who's leading this project. But I wanted to go further, and I wanted to apply that on other diseases because these tunneling nanotube can transfer lysosomes, but also mitochondria. I went to another disease, which is Friedreich's ataxia, and it's also a terrible disease where the kids just have like an imbalance at the beginning, that little by little, they lose the locomotibility and end up in a wheelchair for five, 10 years, and they eventually die from a heart defect. We did the same principle, and used the hematopoietic stem cells, CRISPR-Cas9, to fix the gene. Now we could rescue completely the locomotive function of mice. It was really like they were healthy mice. Based on that, again, we went to the FDA. Again, it was first funded by the advocacy group, FARA, and NIH. Again, we got CIRM funding to be able to bring that to the clinic. Now we are doing the studies required by the FDA, and hopefully we will be in a clinical trial next year. The last disease I want to talk about is with everything we learned, and we were able to riscue a neurodegenerative disorder like Friedreich's ataxia. We were like, if we can do that, why not go into Alzheimer's? Because the hematopoietic stem cells may be are powerful enough to help diseases like Alzheimer's, which is much more prevalent. Then we try. Again, in my lab, it's a go, no go. We treat the mice, and we look at how they behave, and it has to be obvious. It was really obvious. Again, it's a lot of things, but the memory function was completely restored in this mice after one treatment. Now we are trying to bring this project again to a clinical translation and bring it to the clinic and treat Alzheimer's. I hope I will do that one day because I really want to bring the message out there that treating rare diseases is important. It's important for the family, it's important for the patients, for the kids. But also, we learned so much that we can treat much more diseases down the line. I would just finish by, donation is also very important because that's how you can stop this crazy idea that nobody would bet on, because they want to have concrete reserves, and you cannot create these reserves if you don't have funding. That's why we created a gene therapy initiative with philanthropy money from Nancy and Jeff Stack, here at UCSD. We are providing a seed grant to all the researchers at UCSD who have a great idea with gene therapy on rare diseases to be able to treat them, and we are supporting that by educating, accelerating, and by partnering. On that, I hope I was on time, and I want to thank you for your attention. [Applause]

Catriona Jamieson: Fantastic. That was amazing, I remember, Stephanie, when you first presented that work on stem cells can traffic to the brain because they're looking for sites of injury, it was heretical. People said, no, hematopoietic blood forming stem cells cannot get to the brain. Then the whole nanotube idea was also mind blowing. It's been a very exciting journey to watch that. We're here, thanks in large part to T. Denny Sanford, as well. I wanted to mention the power of individuals to really make a difference. He's really invested in all of us working together. Lisa Kadyk has come all the way from CIRM. Thank you for being here. She's a champion for rare diseases, and I wanted to underscore this point that Stephanie made. If you look at cancer, 30% of all cancers are rare. If you look at how cancer was revolutionized in terms of treatment, the first molecularly targeted therapy was for one of the rarest forms of cancer, chronic myeloid leukemia, 1,400,000 people diagnosed annually. I always thought rare diseases are important, but clearly that's how we make inroads by establishing platform technologies as Stephanie has done and by having champions like you here. Thank you, Lisa, for being here, and guiding the way so we can use these as platforms to tackle really

tough diseases that just weren't fixable before. Thank you for being here.

Lisa Kadyk: Thank you, and thanks to the organizers for inviting me to represent CIRM at this event. I'm happy to be here. I'm just going to give you a little bit of overview about CIRM. I know many of you are familiar but may not all know the whole history. I'm not going to go through the whole history, but I'll give you our origin story, and some of our accomplishments, and then in the theme of today's meeting, I'm going to talk a little bit more about CIRMs role in funding gene therapy approaches to rare disease, and I think at the end, I want to end on a positive note of some of the more recent changes that I think are going to help accelerate rare disease therapy development and make it not only faster but less expensive, I hope. A little bit about CIRM. We were created by a ballot proposition here in the State of California back in 2004 that designated $33 billion in funding to be spent on stem cell research and development of stem cell-based therapies. This is at a time when the federal government was putting a moratorium on new funding for embryonic stem cell-based research, and this was California's response to that. Then 16 years later in 2020, the first three billion dollars was pretty much spent, and California voters again supported CIRM with another $5.5 Billion of funding with Proposition 14 had a couple of differences with Proposition 71. First of all, it had an yearmark of $1.5 Billion specifically for research, and development for diseases of the Central Nervous system, and brain. I should say, a lot of rare diseases fall into that category. The other change was that CIRM could now fund gene therapy research in addition to stem cell-based research. That gets us to where we are today. Our mission is a mouthful, but it's trying to capture, many of our mantras, and important goals, which is to accelerate world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California, and world. How do we address getting to that mission or accomplishing that mission? CIRM funds several different aspects of the ecosystem for supporting therapy development from bench to bedside, and first and foremost would be just the research and development discovery pipeline, which is shown on the top here, going from foundational we have program announcements funding foundational research, therapeutic candidate identification, pre-clinical research, which is often used to be called the valley of death because other agencies don't fund that very often. Then the whole gamut of clinical research from first in human trials all the way to pivotal trials, and BLA filing with the FDA. That's our core funding programs, but to support those funding, we also have infrastructure programs such as Shared Resource Labs, GMP Manufacturing Facility Network. Importantly, the Alpha Stem Cell Clinic Network, which we have two of the program directors here, doctor Jamison, and doctor Wang. Also, we've now started funding what we call Community Care Centers of Excellence, and these are meant to partner with the Alpha Clinics, which are, I should say, the clinics that really specialize in delivery of these advanced therapies, cell and gene therapies. The Community Care Centers of Excellence are located in other parts of the state that are really not that close to the Alpha Clinics. The idea is to help democratize delivery of these advanced therapies beyond those centers of excellence that exist today. Then last but certainly not least, CIRM funds education, and workforce development, everything starting at high school, all the way through graduate school, and clinical fellows. We are intending then to be able to sustain the workforce, and the scientists of the future to carry on this work beyond what we're doing today. This is just the numbers slide to give you an idea of our impact of the 8.5 billion combined between Proposition 71, and 14, we've spent a little over 4.6 billion funded over 1,400 projects, over 115 clinical trials. More than 4,300 participants have been in those clinical trials. CIRM funded projects have also been able to raise $25 billion or more than that of industry support between acquisitions, and co- funding, and so forth. It really has been a good return on the initial investment. But so, beyond these numbers here, what is the impact on patients? That's what we really care about. Now, I want to talk a little bit more in depth about CIRM Funding of Gene Therapies for Rare Diseases. We've funded 160 awards for gene therapy approaches to rare disease, including both, as doctor Turkey mentioned, the in vivo therapies, and then the ex vivo gene modified cell therapies that are then transferred back to patients. I want to just tell you an illustrative story about this little boy here Ronnie. Ronnie was born in 2017 in the Sacramento area with a devastating, usually fatal immune deficiency, excellent (SCID), Severe Combined Immune Deficiency. Basically, he didn't have an

immune system, and was really at risk of death. I mean, there are potential that he could have been cured with an allogenic stem cell transplant, but that doesn't, I think you don't always have a donor and that has comorbidities. But Ronnie was lucky in some ways first, that he got that diagnosis early on with newborn screening. Second, CIRM was funding a clinical trial at UC San Francisco at that time to address excellent SCID with a gene therapy approach. Ronnie was enrolled in that trial. His blood stem cells were taken. The normal copy of the gene was inserted into the genome of the blood stem cells, and then the cells were transplanted back into his body, where they regenerated the hematopoietic system and including a normal healthy immune system. In this picture, he's out on the beach. He can go out into the world just like any other kid. He has a normal healthy system. He was cured. In fact, more than 50 children have been cured of similar fatal diseases in CIRM funded trials. Clearly, these therapies are really transformational, the difference between life and death here, and they really work. Where's the rub? Part of the problem is that getting funding, first of all developing these therapies takes a long time and it costs a lot of money, and there aren't that many patients that receive the therapies. Investors don't always want to invest in these because they don't see a return on investment. This is an area that the rare disease field has struggled with, for some time. But I think I want to end on a positive note here because I think there is momentum because of changes in technology, and regulatory innovations that is going to make gene therapy for rare diseases be much more accelerated and at lower cost. I'm going to end with this last slide. As you can tell, I like pictures of incredibly cute little babies. You may have heard of Baby KJ. He was in the news last year just about a year ago, and I just want to give a disclaimer. CIRM did not fund his treatment, but he was born in Pennsylvania with an incredibly devastating metabolic disorder caused by single gene mutation gene that's normally expressed in the liver. When his diagnosis was obtained, his doctor there, doctor Rebecca Ahrens Nicklas, and one of her colleagues, Kiran Musunuru decided that they could work with a team of experts from across the country, I won't name them all. To develop a personalized therapy for him. They knew exactly what the mutation was, and they set a record by treating him at age seven months. He went from diagnosis to treatment in seven months. This normally would take five years maybe at minimum. It was amazing. I know it wasn't easy. It was not cheap. But why is this important? Well, part of the reason is because the type of therapy is it's a CRISPR base editor therapy, and it's delivered into the body, so that makes it less expensive than ex vivo therapy, and it's with a lipid nanoparticle. Basically, you can just change one tiny aspect of that therapy, which is the guide RNA and treat a different disease. It's a potential platform. You were mentioning platforms also. The team at shop has proposed to the FDA that they be able to then treat patients with a lot of other related. They could have different mutations in the same gene or they could have mutations in different genes in the same metabolic pathway, for example, and then all be tested in one single clinical trial instead of each one being done tested in a separate trial. You can imagine how much time and money that would save. The FDA in February came out with a guidance document outlining their view of what would be required, it's called the Plausible Mechanism Pathway to implement such a platform. I'm a little bit over time here, so I just want to say that CIRM has also jumped on this bandwagon, and we here later this month where we're going to be posting a program announcement to fund exactly this type of a platform trial. It's called the Rapid Program, and we're asking for applicants to propose treating multiple different diseases with leveraging the same pre-clinical data, and then in a single clinical trial. I think we have a lot of optimism for the future because of these new innovations. With that, I would like to thank you for your attention.

Catriona Jamieson: Ending on a very positive note. Science became more nimble, and so did clinicians and funders. Thank you so much for telling us about that Rapid Program. I think what we're learning today is with advances in technology, we can do so much more for a combination of diseases, and what I've been surprised by is how nimble, the FDA has become. Proudly because our patients go there, and our advocates for better therapy, right, Andrew? Yes. We'll hear more about how to do this even more effectively. We've got the Alpha Clinic director from City of Hope, Leo Wang, we've known each other for quite a while. Leo is not just an amazing, brilliant innovator, but actually somebody who brings us all together. I say, that's a huge problem. It'll never work and Leo goes, no I think we

just need to talk to them. We'll all get together. He's a peacemaker, and makes everything look easy even when it's hard, like Stephanie. Thank you, Leo, for being here.

Leo D. Wang: Thank you so much for having me. It's a real honor to be here. Tonight is great, I've never been to one of these before, but I love this theme of making the impossible possible. You've already heard about several instances of really just doing impossible things, curing children with these lethal single gene disorders, Cystinosis, SCID, also going from end of one bespoke therapies to platform trials and platform approvals. These are things that would have been impossible. Three years ago, five years ago, for sure. I think it just highlights what we can do in this space, whether it's for other disorders that don't have cures yet or larger indications. I'm a pediatric brain tumor doctor, When I first came to City of Hope, I had the opportunity to meet a mom, and in my office, she gave me this card. This was a card that she used to hand out because her child had a lethal brain tumor, known as (DIPG) Diffuse Intrinsic Pontine Glioma. This is a terrible and invariably lethal disease that steals kids' ability to move, and also to regulate their emotions. Her daughter, Katie, would have these incredible outbursts in places like Target and Walmart, and all the other parents would judge the mom, how could you let your child do this? She had these business cards made out, and made up, and she would hand them to parents or onlookers that she thought were being judgmental. I have this in my office as a reminder of what we're doing, why we're doing this. I never got to meet Katie because DIPG is a terrible disorder, terrible disease with a median survival from diagnosis to death of about 11 months. If you saw in the card, it was 7-9 months at the time that Katie was diagnosed, and now it's 11 months. It is a rare disease. It's a rare disease. About 150 to maybe 400 patients a year diagnosed in the United States. It's a rare disease of the central nervous system. It's a disease for which, really, the cure rates have not gone up in the past 50-60 years. It's I think currently an impossible disease, but there's a lot of optimism that we can make it possible. One of the things that I work on is chimeric antceptor T cells. Those of you who are alumni of the mine symposiums have listened to Dan Kaufman talk about this, and these are really just reengineered immune cells that can target and kill cancer cells. This is just a time-lapse photograph that I got from my colleague and friend, Christine Brown, who really pioneered this work at City of Hope. What you're seeing here are brain tumor cells. Those are the fried egg types of cells. Then around them, you're seeing really small. These are the reengineered immune system cells. When you reteach these immune cells to kill cancer cells, you can see that they do a phenomenal job of just killing them. CT cells have really revolutionized the way that we think about and treat leukemia and formal blood cancers. There's a lot of enthusiasm that they can also change the way that we think about solid tumors. As I said, fundamentally, this is reprogramming the immune system by inserting this chimeric anti-receptor that reprograms the T cells, in this case, to kill cancer cells. Then you take the cells, as Stephanie, as Dr. Turkey, was explaining about ex vivo gene therapies. What you do is you take the cells out of the body, and then you expand them, and you introduce this chimeric antceptor using a lentiviral vector, and then you expand them and put them back into the body. When I moved to City of Hope, almost ten years ago, Christine and others at the institution had been working on chimeric anti-receptor therapy for leukemia and lymphoma. They'd started doing brain tumors, and they wanted to know if I would be interested in taking on this impossible task of bringing this to children with brain tumors. I instantly said yes. We had this idea that we could use these therapies to treat children with these devastating brain tumors. Initially, when we went to apply for funding, people were like, That's impossible; that's crazy. One of the things about these tumors is that they're in the brainstem often, which is the place it's a connection between the brain and the rest of the body. These tumors, if you cause them to swell, that swelling can be lethal. There had been in the field some pretty difficult experiences with immune therapies with some pretty bad toxicity. Initially, when we went to propose, there's a lot of conventional funding agencies said, No, no way, that's impossible. We're not going to do it. Fortunately, we were able to go to really forward-looking donors who said, this is something we'd be interested in funding. Also, critically, we had the partnership of patients, the patient families who said, Look, we want the right to try this. There's nothing else available to us, and we recognize that there's a risk. But we are willing to do this with our eyes open. When we combined the patient

advocates and the donors, we were able to get enough money to start the trial. We were able to show that it was safe in two patients, and with that, we went to SERM, and SERM said, Okay, we will fully fund your trial. That was what allowed us to do this trial. We owe a tremendous debt of gratitude to all of those people in getting this therapy to come to fruition. What we've shown now we've completed the first two courts of the trial, and we've shown that it is safe. It is well tolerated, and it works. This is just some MRIs of a couple of patients. The top one is the one I want to focus on, who has this diffuse midline glioma. You can see that this is a 14-year-old kid who came to us with this brainstem glioma, or sorry, mid-NG glioma. This white mass is this tumor. After four cycles of therapy, it really just shrank. It melted away. This is accompanied by tremendous clinical improvement. When he came to us, he was very somnolent, which is not uncommon. He was sleeping about 22 hours a day. But by the time he left the hospital, he was sitting up in bed. He was joking with all the nurses, and he was able to go home. He had missed his prom because he'd been in the hospital. It was an eighth-grade prom or whatever, and he was able to have that at his house, which was hugely gratifying for all of us, including his family. His mom said to me, You gave me my son back, which was an amazing gift to them and unhosted to all of us as well. This over here is just a waterfall plot showing that about 50% of the patients on the trial have some response. The tumors shrink, and that's great. That's often accompanied by clinical response. This on the bottom is what's called a spider plot. This just gives you a sense of how durable responses are. The problem is that their responses are not particularly durable. Usually by about 8-12 weeks, the tumors have started growing again. This is the next stage of impossible. This is the next thing that we need to tackle. But on the strength of those findings, we were able to expand our trial to two other sites around the country, in Michigan and in CHLA, Children's Hospital in Los Angeles. This was also actually something that people thought was going to be impossible because it's very complex to make these cells and to ship them across the country, but we were able to do it. What's the next thing? How do we get from 20? I should have mentioned that the median survival from diagnosis of the patients on our trial who had DIPG and DMG is 20.5 months, which, if you remember, I told you that normally it's 11 months. That was great and is also very much in keeping with other major trials in the field. But 20.5 months isn't cure. How do we get the next level of impossible? This is where we go back to the lab. What we found in our trial is that actually children on these trials are developing immune responses to the chimeric anti-receptors, the CAR itself. Remember I told you that this is an engineered protein. It doesn't exist in nature. What we're actually functionally doing is immunizing our patients against this new cell that we're introducing. The goal of which is to kill their tumor, and they're now mounting an immune response against the thing that we're putting in to try to help them, which is infuriating. Not just us; two other groups at Stanford and MGH have also seen this. Initially, what we saw was that if you look in the cerebrospinal fluid, the CSF of these patients as we're delivering these cells, some of them have very, very high levels of CT cells in their CSF, and others don't. It turns out that what we're seeing is anti-antibodies in both the peripheral blood serum and in the cerebrospinal fluid. In addition, sorry, I'm just going to skip through this quickly because we're running out of time, we identify T cell responses. We actually have found specific expanded cytotoxic T cells in the CSF of these patients over the course of therapy, and they end up actually recognizing the CAR construct. We need to figure out now how to mitigate that specific adaptive cellular and human immune response against the CAR so that these CARs can stick around and do what they're intended to do. That's the next level of impossible, but we have some pretty good ideas about how to do that. That's something that I'd be very happy to talk to people about in the social hour. This is a very, very brief synopsis of a tremendous amount of work. This is just a very small portion of a very large clinical team, but a lot of this work started with Christine Brown, and we have collaborators at Michigan, CHLA, and a whole group of people who've done this, as well as our patients. That is just a track back to where the cells come from, just to demonstrate that those are what are called CDA-effective memory cells. Those are the ones that are killing things. This is the acknowledgment side for all of the people who've been doing this work, including our patients, their families, and their care teams. It really has been a tremendous amount of coordination and logistics to get this done. But I think that that's sort of the

sweet spot of where this field is and what this field requires in order to get impact to patients, and we really look forward to moving it forward in the next iteration. These are some of our scientific collaborators, CHLA, TGN in Phoenix, and my lab as well. Then, of course, our patients, collaborators, colleagues, supporters, and we couldn't have done it without any of them. Thank you very much for your time. [Applause]

Catriona Jamieson: In the next couple of minutes, we'll hear from Daphne, a patient advocate. She is coming here to talk about the journey about how to get the proper diagnosis, get on a fundamentally important, impactful therapy that was quite bespoke and developed for her daughter. We will move on. [Applause]

Daphne Graskewicz-Prado: Hi, everybody. Thank you so much for having me this evening. I'm here to talk about my 4-year-old daughter, Harlow, who was diagnosed with adrenoleukodystrophy in July of 2023. I'm thrilled to say she just became the first female to be treated for euphori ukodstrophy in the world on October 15th. [Applause] Harlow was born. Everything was very typical. She went home, no NICU stay. At 15 months, we started to notice that her balance was off. She wasn't able to take independent steps. She fooled our pediatrician repeatedly because we went in and she was cruising around. It was effervescent and very bright, and pointing to the animals on the wall and saying their names. But once we did not see the progression in walking, eventually, I had to fight to get an MRI and get a referral to neuro. Through that odyssey, the doctor seeing her, how she was able to move, how she was able to engage. They actually said, Daphne, do you think you might have some postpartum anxiety? Because I just had my third child. No, I know what this looks like. I have an older child. I've been around children all my life. Once we received the referral, there was about a seven-month wait. We went, and we got the MRI. That showed less than normal white matter. At that point, we received a referral for neurology, and I went on LinkedIn, and I wasn't willing to wait the seven months. Not while I watched my child struggle. I messaged every pediatric neurologist within a six-hour drive of Southern Illinois at the time. I was able to get in the next day with a neurologist at my alma mater, Vanderbilt. She looked at the MRI, and she said, I'm going to request a leukodystrophy panel. From looking on TikTok, from looking at all the social media apps, I had seen kids with leukodystrophy, and I just begged God, please, whatever this is, don't let it be leukodystrophy because I knew she was going to die. I knew what the path was. We received the call on July 28th of 2023 that she was diagnosed with euphoria hypomyelating leukoystrophy, six. There she is one in 37 million. She's one of 300 kids in the world with euphori leukodystrophy. She is one of six with her particular variant. When we received that diagnosis, our doctor said, I'm Googling this in real time. This is the first time I've ever heard of this disease. He referred us to Chop, and then he said, Well, there's one more thing I'm going to mention. There was this nonprofit foundation that came to Vanderbilt three months ago called in Lauren. They may be able to help. I'm not sure. But that's a route that I would pursue. Six weeks later, I showed up here in San Diego at a Global Genes event that I knew Lauren was going to be at with a picture of my daughter, and I begged them to help me. They agreed. They agreed. They told me I had to find a doctor. Then, yet again, I go out to LinkedIn, I go out to social media. I had over 600,000 eyes that saw my plea for somebody to please help me save my child. Olivia Kim McManus, here at Rady, was the only one who said yes. We packed up, and we moved out to California with my three kids, and Harlow received her first dose on October 15th. Since we received the dose in the first two months post-dosing, she's completely potty trained. That was not the case before. A few weeks ago, she was standing up watching TV. She wasn't able to stand before. It's still for a short period of times, but it's life-changing. She is walking with elbow crutches now, and I'm getting ready to show you a video of her riding her bike for the first time. What the people in this room do, it matters. It matters so much to families like mine. When the doctor told me that my daughter was going to die, I had the audacity, or maybe it was denial, I don't know, but I said, No, my child. Without the help of people in this room, I know what her fate would have been. At this point, we are praying that with this ASO, it will stop the progression of the disease, and then I have to figure out next steps because when she woke up right there after receiving her first dose, the first

thing she said to me was, Mama, can I walk yet? Darn it, I'm going to find a way. I'm going to find a way, and if it has to be stem cells, whatever we have to do, I will find a way. Thank you. Thank you for all that you do. Rare disease research matters. I know personally. Let me show you Harlow riding her bike for the first time. Go, baby, go, baby. Go. Go, baby, go, baby, go. Push, push, push. Can you go fast? I don't think you can go fast. I don't think you can go fast. I don't think you can go fast. Thank you. [Applause]