Scientific Advancements in Gene Therapies: Opportunities for Global Regulatory Convergence
Hybrid Public Workshop
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Afternoon Transcript

Session 3: The Next Generation of Gene Therapies
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Susan Winckler:

So for our folks online, thank you for returning to our program. This next hour, I hope that you are well-fueled and you are ready because we're going to have four rapid-fire presentations describing gene therapies in development, particularly in vivo products. How those emerging technologies differ from the currently approved products, and what the general development timelines look like.

So our first speaker is Dr. David Liu. And Dr. Liu is joining us remotely so I know that he is ready to go. Dr. Liu serves as the Richard Merkin professor and director of the Merkin Institute of Transformative Technologies in Healthcare, vice chair of the faculty at the Broad Institute of MIT and Harvard, and is a Howard Hughes Medical Institute investigator. Dr. Liu, we are ready for you. We can see you. Take it away.

Dr. David Liu:

All right. Hopefully you can hear me as well.

Susan Winckler:

Yes, we can.

Dr. David Liu:

I'm trying to figure out how to control the slides. Okay. There's a little bit of a lag, but I'll get used to it.

Susan Winckler:

That's all right.

Dr. David Liu:

So I'm really happy to be at this special event. I've really enjoyed the morning so far. The organizers asked me to overview gene editing technologies that are being used in people, and to describe how they were developed and how they're being used clinically. So I'll try to do that in a relatively short period of

time. So just about any kind of DNA mutation can cause a genetic disease. If you replace the C, shown here, with a T, you get the rapid aging disease progeria. And if you replace this A with a T in the upper right, this is the cause of a painful and deadly sickle cell disease that we've already heard so much about.

If you delete three DNA letters shown in blue here, that's the most common cause of cystic fibrosis. And if you insert extra DNA letters, such as these four letters here, that's the cause of Tay-Sachs disease. And other inserted DNA letters cause other diseases like Huntington's disease. So these misspellings in our DNA collectively cause at least 8,000 or so known disorders that affect hundreds of millions of people collectively.

So driven largely by this need, scientists have recently developed gene editing technologies that can change these DNA misspellings to treat or maybe even cure genetic diseases. One of the most famous of these tools is this blue protein called CRISPR-Cas9, which naturally occurs in some bacteria. So CRISPR-Cas9 is programmed by a small piece of RNA shown in green here called the guide RNA. Once the protein finds a target DNA sequence that matches the sequence in the guide RNA, it cuts that DNA, breaking the double helix into two pieces.

Cutting DNA is a very effective way to disrupt a gene. And so these bacteria evolved CRISPR as a natural defense system to mess up the genes of infecting viruses. And disrupting genes by cutting them with CRISPR-Cas9 can also be very useful for our own applications. This approach has already been used in several clinical trials, for example, to disrupt a gene that makes too much of a protein that causes a deadly disease called amyloidosis.

And as you just heard from David Williams and others, the first FDA approved gene editing drug, Casgevy, uses CRISPR-Cas9 to disrupt a gene in order to reawaken a backup set of dormant hemoglobin genes as a treatment for sickle cell disease. And it was very moving to hear from a patient who received Casgevy in the morning session. And I think it's really a milestone achievement for medicine. That the era of human gene editing isn't just coming, as we've been saying for many years. It's already here.

Unfortunately, most genetic diseases can't be treated by disrupting a gene. Instead, for most genetic disorders, we need to precisely correct the misspelled gene into a healthy DNA sequence in order to best benefit patients. And not too long ago, this concept of how to directly fix a specific misspelling in the vast genome of a live animal or a human patient seemed like fanciful science fiction. Yet today we can do exactly that because our laboratory, building on the work of many other scientists, recently developed base editors and prime editors. These are molecular machines that precisely correct the misspellings that cause genetic diseases by actually rearranging the atoms in DNA.

The story began in 2013 when I was brainstorming projects by email with a remarkable new postdoc in the lab, Alexis Komor. And I pitched this idea. If you could directly convert one DNA letter into another at a specified position in the human genome, efficiently and without generating unwanted byproducts, I thought you could transform genome engineering, as it was called back then, and possibly human therapeutics.

So it was an exciting idea in theory, but to pull it off would going beyond the DNA cutting scissors that nature provided in CRISPR-Cas9. Instead, we needed a machine that could search for and bind a DNA sequence of our choosing just like Cas9. But instead of cutting the target gene, the machine would need to directly correct a single letter misspelling. So how can we convert one DNA letter or base into a different one? Fortunately, nature provides enzymes like this one that can convert C into a base that looks like and behaves like T through a known chemical reaction called a deamination.

But these enzymes do so indiscriminately. And so to make this conversion occur at a target C of our choosing, Alexis attached one of these enzymes to disabled CRISPR-Cas9 scissors that can still find a target sequence but can no longer cut the DNA. And we were really excited to see that in a test tube the

resulting engineered protein successfully converted a C of our choosing into a T. But while this initial base editor worked well in a test tube, when we tried it in living cells the converted base was quickly removed by the cell, undoing the edit.

And so to solve that problem, we added this small purple protein, taken from a different corner of nature, that protects the converted base. And by attaching this small purple protein to the rest of our machine, we developed a prototype base editor that, for the first time, could convert C to T or G to A at targeted sequences in the genomes of living cells. But it only worked some of the time, because if you change a C to a T you create a disagreement within the DNA double helix, a mismatch that confuses the cell. And since C only pairs with G, and T only pairs with A, the cell has to resolve this disagreement.

And if the cell resolves the disagreement by replacing the T with a C, then you end up with the original sequence. And once again, we've lost our edit. You just go back to where you started. So one morning Alexis came to me with a solution to this problem. She realized, intuitively, that if we could trick the cell into resolving the mismatch in favor of our edit, we could do this by making a small change in the machine so that it nicks the unedited DNA strand containing the G. That nick causes the cell to replace the G on the unedited strand with an A, as it remakes the nicked DNA strand. And that completes the permanent conversion of the CG-based pair to a stable TA-based pair.

So next we worked on a second class of base editor, one that could convert A into G or T into C. And this proved to be more challenging because there was no enzyme that we could borrow from nature that was known to perform the necessary chemical reaction shown on this slide. So Nicole Gaudelli, another member of the lab at the time, bravely agreed to try to evolve our own enzyme to perform the needed chemistry. And despite taking on one of the more ambitious projects in our lab at the time, Nicole succeeded in evolving this red protein shown here. And her efforts resulted in this second class of base editor that converts A to G, or T to C, at targeted bases of our choosing.

And so the two types of base editors developed by Alexis and Nicole in principle can fix many of the most common kinds of disease causing misspellings in our DNA, representing about 30% of the known total. And in the eight years since we've reported base editing, thousands of labs around the world have used base editors to make precise, single letter changes in organisms ranging from bacteria to crops to primates. Base editors have recently been used in animals to correct single letter misspellings that cause devastating genetic diseases. For example, base editors now provide a way to fix that C to T misspelling that causes progeria.

Mice with this misspelled gene, in work that Francis Collins did many years ago, suffer rapid aging and early death just like human progeria patients. So this is the untreated progeria mouse that's seven months old. These are three progeria mice, 11 months of age, that were each given a single injection of the base editor that corrects this mutation. And you can see they're doing much better. And indeed a single injection of the base editor that corrects this single letter misspelling allows the mice to live about two and a half times as long as they would live without the base editor.

And so we're currently working with many other scientists and doctors to try to advance this treatment towards a clinical trial that might offer progeria children, for the first time, a way to correct the root cause of their disease. Many other genetic diseases in animals have also been treated with a one-time dose of a base editor. For example, by base editing bone marrow to fix the misspelling that causes sickle cell disease. This is done outside of the body, as was mentioned in the morning. We could restore normal blood parameters and rescue sickle cell disease following transplantation of these edited cells into mice.

And base editors have also been used in animals to treat many other diseases including high LDL cholesterol, muscular dystrophy, ALS, phenylketonuria, iris anemia, Niemann-Pick disease, and a variety of genetic blindnesses. So base editors are molecular machines that can correct four of the most

common types of misspellings in our DNA. But that still leaves the remaining 70% of known disease-associated misspellings, which include the eight other types of single-letter swaps as well as missing letters and extra letters. And we originally thought that it would take scientists many years to develop all of the molecular machines needed to address the rest of this pie chart.

But in 2018, Andrew Anzalone, then a new postdoc in the lab, proposed a really ambitious idea that had the potential to correct almost any type of DNA misspelling in living cells. He envisioned a molecular machine that could directly rewrite DNA misspellings with a stream of corrected letters in a manner similar to the search and replace function on your computer. So if CRISPR-Cas9 is like scissors and base editors are like pencils that precisely rewrite individual letters, then Andrew was proposing to develop a type of DNA word processor.

He imagined a new machine that uses a guide RNA not only to specify where in the genome the edit should be made, but also to encode what the corrected sequence should be in a special extension added to the end of the guide RNA. The machine would then copy this corrected sequence, shown in yellow here, into a target site in the genome. And once again, to move the idea from paper to reality seemed like a very, very long road. In fact, as we broke the project down, we identified four challenges that we weren't sure would be solvable, that seemed difficult enough that the lab skeptically nicknamed them the four small miracles.

So first we had to test whether it was possible to copy the yellow sequence in the guide RNA extension into a target DNA site of our choosing. And so Andrew attached a special protein, shown in red, that naturally copies RNA sequences into new stretches of DNA to a disabled CRISPR protein, again shown in blue, that can't cut the DNA double helix, but it can nick one DNA strand at the target sequence. And so in a test tube, Andrew programmed this engineered protein with a special guide RNA that contains the extension with the corrected sequence, shown in yellow, as well as a runway shown here that precisely aligns the target DNA strand in white onto the guide RNA extension in green.

And since the target DNA primes the copying process, we called the system prime editing. And remarkably, in a test tube, all the parts of this system work together to copy the corrected sequence in yellow from the extension in the guide RNA directly onto the end of the target DNA strand. And so that was the first challenge. Second, what happens to the newly copied DNA in the living cell? The prime editor machine makes this DNA flap containing the corrected yellow sequence, but there's no guarantee that this precious flap would end up replacing the original misspelled DNA letters.

So we drew up this optimistic scheme showing how the flap might end up replacing the original DNA sequence in cells, but we really didn't know if the cells would cooperate. When Andrew performed the very first prime editing experiments in yeast cells, which are easier to work with than human cells, he was thrilled to discover that the newly copied DNA flap did in fact replace the original DNA sequence. The yellow yeast colonies shown in this petri dish are actually the very first prime edited living cells. This was an experiment where a successful replacement of the DNA sequence with the sequence in the flap would result in yellow cells. And so that was the second challenge.

So next, Andrew tried prime editing human cells. He moved the whole system into cultured human cells and observed nothing. No editing whatsoever. And at this point, I think many scientists would have been grateful to have made it this far and probably would have moved on to a safer project. But Andrew persisted and he systematically worked through a long list of potential reasons why prime editing initially failed in human cells. And ultimately he discovered that giving the red protein a Goldilocks length runway, that was not too short yet not too long, was critical. And if you got it just right, if you got the length of the runway just right, we observed a breakthrough. The very first prime editing in human cells.

And as excited as we were to observe any prime editing in human cells, the initial efficiency was terrible. For every 100 cells we treated, one cell might end up with the desired edit. And so to be useful, of course, prime editing would have to be much more efficient. Andrew tested dozens of variants of his new editing machine and he found a special combination of these five changes in the red protein supported much better editing, now often around 10% efficiency. We then applied Alexis's trick used to make base editors more efficient and found that programming the prime editor to nick the non-edited strand further improved editing, which could now exceed 30% or even 50% in human cells. These are efficiencies considered useful and potentially therapeutic for many diseases.

So the lab buzzed with excitement after Andrew completed his set of small miracles, resulting in this prime editor machine. And our lab members filed into my office for our weekly results data discussion meeting shortly after Andrew observed the first efficient prime editing in human cells. And I remember one grad student turning to me as they all walked into my office and said, "You are going to crap." Which I think is Gen Z's way of saying you're going to be really excited.

And I was really excited because prime editing enables, for the first time, true search and replace genome editing in a wide variety of living cells. You control the new sequence that gets copied into the target DNA site. So you can replace any stretch of up to dozens or hundreds of DNA letters with virtually any other stretch. So you can swap any letters, insert missing bases, or delete extra ones. Like deleting these four extra letters that causes Tay-Sachs disease. And because prime editing is so versatile, it means that it can correct the type of misspellings that collectively account for the vast majority of the known errors in our DNA that cause known genetic diseases.

We published this paper sharing prime editing with the public in late 2019. More than 500 research papers have since been published by laboratories around the world using prime editing in a wide variety of living systems, including primates, including monkeys. And just as we saw with base editing, prime editing has already been used in animals to rescue a variety of genetic diseases including retinitis pigmentosa, phenylketonuria, thirus anemia, and sickle cell disease after prime editing of the cells outside of the animal and then transplanting them back into the animal.

So to be clear, a lot of additional work lies ahead to allow Cas9 nucleases, CRISPR nucleases, base editors and prime editors, each of which offer complementary strengths, to maximally benefit patients. A variety of companies are trying to bring these technologies to patients. And while data in animals is encouraging, of course the ultimate measure of safety and efficacy of these technologies in human patients can only be validated through clinical trials.

Delivering these molecular machines into the relevant cells in the body remains a persistent challenge. Although there are now a number of promising methods, such as the ones already used to deliver COVID19 vaccines into billions of people, that have shown some degree of safety and efficacy when used to deliver gene editing agents in human patients.

And of course, as we heard already briefly, we must all, I think, work to ensure that gene editing technologies are applied in an inclusive manner to the extent possible at every year. It will start out very narrow, but hopefully will quickly become democratized as both cost and regulatory requirements and general scientific and medical and public comfort with these capabilities grows. So in an inclusive manner that thoughtfully balances potential risks and benefits, including risks from off-target editing.

At least nine base editing clinical trials have already begun, and at least three of these trials, shown here in green, have already reported clinical outcomes that indicate that the base editors were effective at correcting the mutations and offering patients benefit as a result of those corrections. The girl in the photo here is Alyssa Tapley. She was 13 years old at the time in the UK. She had T-cell leukemia and she was the first patient treated with a base edited therapeutic. In 2022 she was infused with CAR-T cells containing three base edits in a trial led by Dr. Waseem Waseem. And following treatment with these

triply base edited CAR-T cells, her T-cell leukemia went into complete remission. And as of now, more than two years after her treatment, her cancer remains undetected.

And just a few months ago, FDA cleared the first clinical trial of a prime editing therapeutic only about four and a half years after we published the first prime editing paper in late 2019. Scientists at Prime Medicine developed an ex vivo prime editing treatment for chronic granulomatous disease. This is a debilitating and lifespan shortening condition that's caused by mutations in genes encoding NADPH oxidase subunits. And so a prime editing system that corrects one of the most common mutations that causes this disease, a two base pair deletion resulted in very efficient correction of bone marrow cells from CGD patients. And those bone marrow cells then rescued the disease in mice after transplantation with no detected off-target editing.

All right, so what lies ahead in the future of gene editing technologies? Well, one exciting vista that many labs are working on is a type of molecule shown here. So this is a CRISPR associated transposase or a CAST. CASTs are naturally occurring protein assemblies that move very large pieces of DNA, tens of thousands of base pairs, very efficiently and cleanly in bacterial cells. But unfortunately, natural CASTs have not yet been reported to work in mammalian cells, at least not more than 0.1% efficient or so.

So using laboratory evolution, we recently generated highly evolved CAST variants of this protein shown here that now function efficiently in mammalian cells, allowing the introduction of healthy gene copies precisely into a location of our choosing in the human genome. And there are other approaches that researchers are taking to try to introduce healthy gene copies precisely into target sites of our choosing in human cells. Which I think may very well lead to sort of a gene therapy 2.0 renaissance. That's just one of the newer chapters in gene editing therapies.

All right. So the use of human creativity and resourcefulness to improve our condition and those of our children is arguably the defining trait of our species. And so working with the students and postdocs who built, brick by brick, some of these machines, like base editing and prime editing, that allow us to precisely correct errors in our genome, has really been a pleasure and an honor.

And has inspired me to realize that the future of this field is indeed very bright because it continues to attract students and postdocs that want to invest their scientific careers into correcting the mutations that cause disease. And that really gives me hope that one day we may finally no longer be so beholden to the misspellings in our DNA. All right, thank you and happy to answer any questions.

Susan Winckler:

Great, thank you so much Dr. Liu. We are going to go straight into our next presentation. Joining us here in person is Dr. Tony Ho, who is senior science partner at Pivotal BioVenture. I think we have everything set, ready to go and let's hear from you.

Dr. Tony Ho:

All right. Okay, great. Well thank you very much and thank you for the organizer, Reagan Woodale Foundation and Bill and Melinda Gates Foundation, to invite me to give a talk here. I was talking to Mike last night that the last time I was giving a talk at DC we were talking about Casgevy, pre-clinical data and the hope of a functional cure. And today I was thrilled to meet Jimmy for the first time, one the Casgevy treated the patient, and learn about his experience and his life-changing experience with Casgevy.

So certainly today's talk, after David Liu's talk, I would just say with all these very nice scissors, pencils and word processors, these are great. But one of the key challenge we have, as my experience at CRISPR therapeutic was, how to deliver there these nice things to the cell, to the cell of interest. And this is actually a big challenge currently and certainly also a big challenge as we try to bring, through this

functional cure, ex vivo Casgevy therapy type of benefit. From those, we estimate 5% of the patient to the rest of the world, the other 95%. So what can we do? So my talk will be basically focused on these issues.

Sickle cell, as you guys have heard, basically are a disease of adult hemoglobin. So in sickle cell disease you have point mutation and they had a tendency to polymerize and block out the blood vessels and cause a mini-stroke. And that mini-stroke will lead to very significant pain. And as we have heard from Jimmy, organ damages. And literally it's just like Jimmy was saying, picking off each organ, one organ at a time, one cell at a time.

And suddenly in thalassemia you actually have a defective hemoglobin where you, basically, lack of these oxygen-carrying hemoglobin and then the patient basically needs a transfusion every three to four weeks. And with these chronic transfusions it also damages your organ because of the iron overloads. And eventually both conditions cause a significant medical burden, not only certainly in the developed countries like US, but in the low and middle-income person. Just imagine you have a large population, millions of these people with sickle cell and beta-thalassemia. Not only the burden on your medical care, but I also want to emphasize the economic burden of these people because they're not as productive as they could be if they're healthy, like Jimmy now, where he can now climb Mount Kilimanjaro.

But with sickle cell disease, you may not be able to do full-time work. And that could be a big challenge. And certainly we have heard that this is a very common disease. 3,000 patients are babies, and 60 of sickle cell babies and 60,000 beta-thalassemia babies are born every year. And that amounts to basically 7.7 million sickle cell patients living with this disease and 1.7 million beta-thalassemia patients. And this is actually a picture I used way back in my pre-clinical days. And you can see his picture, the pain is terrible, just look at the facial expression here.

And most of the pain actually is managed at home. And I heard from Jimmy, when we were talking at lunch, and then he said he was having constant pain. And that's how he lived. He coped with this pain, lived with this pain, almost daily. And the most severe pain, of course, you go to the emergency room. There's about 230,000 emergency room visit in the US and 70,000 hospitalization per year. So this is certainly a significant cost for the medical establishment.

And this is basically an estimate of about approximately $2 billion of estimated cost in ER visits and hospitalizations. And over a lifetime of these patient in the US is about $1.7 million. And certainly this is relative to Casgevy's price of 2.2, it's about approximately the same, but you also give a lot of benefit to these patient. Not only on medical costs but their life and also their productivity and their increased lifespan. And these are basically priceless I would say.

So just a little background. And Jimmy was saying that the document he has is too complex. And so I'd like to show something that's less complex. So basically this is what happened to the patient. Basically, when you were born, after approximately one months of age basically your fetal hemoglobin gets turned off and then you rely on just on your adult hemoglobin. And, of course, in sickle cell patients, beta thalassemia patients, the adult hemoglobin is sick. They don't pump that efficiently or they fill the red blood cell with the bad hemoglobin.

And one of the challenges, and this is some of the work Boston Children has been pioneering is, can we wake up that fetal hemoglobin? And what are the ways we can do that? And certainly with the advent of CRISPR, you can see that we actually can wake up these fetal hemoglobin because we know what is the break for these hemoglobin. So normally, when you are born this gene called BCL11A acts like a break. It suppresses the fetal hemoglobin. And if you edit that low side, and basically what we do is almost like releasing the break. And once this break is released, your fetal hemoglobin now came back on. And that's really the science behind the Casgevy treatment.

And this is Victoria Gray, our first sickle cell patient that was treated in the US, at Dr. Haydar Frangoul's clinic. And she is now basically pain crisis free for almost five years. And this is what she said. "This is major for me and my family. Two years without being in the hospital? Wow. We just can't believe it. But we're so grateful. I finally get to live a normal life and be happy. It's unbelievable." So this is just like Jimmy was saying, life-changing therapy.

And we have since Victoria Gray, we have extended to many, many more patients. As you have seen on this slide. And you can see the dots in blue are these painful crises, and in green, this is what happened to them. You can see after the treatment almost everybody become pain crisis free. So this is very exciting. And we also extended this to the beta-thalassemia patients. So in these patients you almost required a transfusion, here in dots, every three to four weeks. And they basically live with transfusion ever since the age of one.

But once they got Casgevy, as you can see, they become transfusion free. And now they can go to vacation without worrying, where's my transfusion going to come from? Where am I going to go to the clinic? Am I going to get the right blood? Or like Jimmy was saying, do I get allergy antibody develop against the transfusion blood? So they don't have to worry about this.

And this is a summary of the overall efficacy. You can see that for those people, sickle cell patient treated with Casgevy, 97.4% of patient are free from hospitalization and 92.3% of people are free from the pain crisis. In beta-thalassemia patients, 94.2% of patients are transfusion independent. And of course, thanks to our collaboration with the MHRA, FDA and European Medicine Agency, we had many discussion with this and we were able to convince them to approve this transformative medicine based on just the phase one data. And bring this therapy to patients much earlier than we anticipated. However, before the first patient was treated, I was telling my team Casgevy is very challenging. It's not going to be good for everybody. The reason is that Casgevy, as we have heard, requires a very complex manufacturing process, takes approximately three months and multiple mobilization. I think Jimmy was telling me he has four blood transfusions, mobilization to get enough cells for the manufacturing. So that is certainly very challenging manufacturing process. And the other hard thing about this therapy is that require myeloablation like Dr. William was saying, the myeloablation is no picnic. These are very harsh chemotherapy and they can cause cancer, fertility risk and also patient will be immune-compromised for weeks to month. And during that time they are very susceptible to infection, they require constant care, almost intensive level care. And certainly the cost of CASGEVY is not cheap, $2.2 million and plus you have to pay for the bone marrow transplantation, which is not cheap either, approximately 100 to 150,000.

And finally, even in the US there's a fundamental limitation on how many patient we can treat. The reason is that we can only do approximately 10,000 bone marrow transplant a year and majority of that actually have to go to cancer therapy and you cannot devote that whole capacity to sickle cell and beta thalassemia. So basically the estimate is that CASGEVY can only treat approximately 5% in the US and EU, the most severe patients and we'll not be able to bring this therapy to the other 95%. So the question is for the rest of the world, the millions of patients is how can we get to the other 95%?

So here I go back to Victoria Gray again, Gray said that she still had relative who are struggling with sickle cell disease and "I hope this will be available to everyone who needs it. It's horrible knowing that something is out there that can cure your disease but you can't access it." I think that's why we are all here today.

So what is the ideal therapy? I would say the ideal therapy will be a drug in the bottle that is curative, single IV administration, that can be administered in all patient setting and with low cost of good and no need for hospitalization. And of course we had to overcome logistical costs and safety barriers. And this product if you want to address the millions of patients with this, have to be able to be shipped,

manufactured and shipped to many, many different country. And certainly you don't want that myeloablation. That is a terrible barrier for a lot of patients.

So then the question is, what is the ideal in vivo gene delivery? We know we had to go in vivo, the ex vivo way is just not scalable. So certainly an ideal in vivo gene delivery vehicle would only deliver to the cell of interest. Only biological active in the cell of interest too. And transient expression of editing machinery. This is important in that we always worry that if you have a gene editing machinery sit in the cells and sooner or later they may edit something off target wise, something that you don't like. And certainly we want these delivery vehicles to be non-immunogenic and low toxicity, and can be dosed repeatedly if needed to.

So in vivo editing is actually is here now, there are actually many trials ongoing from many companies that's target different aspect of the gene, but most of these in vivo editing using LNP has been targeting liver because that's actually where the LNP would like to go. And we have kind of overcome this NHP human barrier and found the right formulation for that. So Intellia for example, is currently conducting a phase three trial and targeting basically ATTR amyloidosis targeting the TTR gene and they are also doing hereditary angioedema targeting the KLKB1 gene. And Verve is currently conducting trial for another very large indication cardiovascular disease trying to lower your cholesterol by knocking out PCSK9. And CRISPR Therapeutics has two program in the clinic. These are all targeting cardiovascular disease including ANGPTL3 and another cardiometabolic risk factor LP(a). And hopefully trying to decrease cardiovascular disease risk for these patients.

But outside the liver has been very challenging. Most company has tried using AAV. I think later on you're going to hear a talk regarding AAV delivery. We actually have tried this at CRISPR Therapeutic for HSPC in vivo editing, it is somewhat challenging because AAV is immunogenic and all the time you need a pretty high dose of high-titer of AAV. And also the cargo size limitation. And the other thing you worry about is the persistence of the editing machinery. But certainly it is for the right tissue type, I think AAV is a nice vehicle for therapeutic editing.

So other quest of delivering in vivo gene editing using non-viral approach is a big interest in the field and we try to steer this outside liver go to the cell that you like. So one method people has been trying is something called viral-like particle. This is basically taking advantage of that certain virus like to go to certain cells and the envelope of these virus can self-assembly in vitro. So if you can sort of leverage that and package your editing machinery inside the self-assembly of a viral-like particle, then you can actually do in vivo editing. However, there is some limitation with this method because you have to make sure that this envelope go to the cell type you like.

So if you want to go to HSPC then you may have to engineer your envelope to the HSPC, and so that require additional engineering. But of course we just have just heard David Liu and this is actually some of the work from his laboratory showing that this is doable and he has using viral-like particle at the PCSK9 in the liver and also has very exciting data in separate renal injection and showing that he can deliver this using this viral-like particle.

Another approach is I think is actually using targeted LNP. This is basically you take the base LNP that is in common with all the COVID vaccine. Now you stick some targeting agents such as the antibody and let the antibody steer this LNP delivery vehicle to the cell of interest. And this approach for sickle cell and beta thalassemia actually has been published by two different labs. One is Breda et al from UPenn and they can show that using CD117 as a targeting agent they can deliver this LNP to HSPC and actually show very nice editing in using this system. And same thing as Dan Anderson also has shown similar result using CD117 approach.

And of course the ultimate goal is... I just want to go back on this slide. One of the challenges with both of these methods is that they're using a chemical conjugated LNP. So actually one of the problem is that

with chemical conjugation, you do have some toxic intermediary. So the question is how to clear that or there are other method of making target LNP without this chemical toxic intermediary. So this is kind of the current research that we're looking for.

And so basically we're in very exciting eras, we now have the basic technology and this is what I call the ultimate precision therapy. This is something we're always trying to achieve to increase your benefit and decrease your risk. And you can see that we have drug like Sinemet which deliver drug only to the brain. LYNPARZA, which only target the cell with BRCA mutations. But now we're in an era where we can actually say, hey I just want to go to this cell for example HSPC and I want to edit that and without targeting all other cells. So hopefully this will deliver the highest precision in this way. And this will be basically a molecular surgery as well.

But finally I would like to just end about the challenges of the in vivo editing, certainly internal scientific development. We want the vehicle to be low immunogenicity, low toxicity, sufficient editing of the target cell. You heard David talk about he go from the 5% now to 50% and he think that is therapeutically relevant now. So that is always challenging. Other thing we want to look for is make sure there's no off-target editing and if it's there on-target and they're also the on-target, off-target cell editing. So you edit the cell but in the wrong cell type. So are there way we can mitigate the potential risk or making sure the risk is tolerable. And finally with these in vivo editing, you also want consider whether or not you will cause germline editing as these may pass on to generations.

In terms of regulatory, certainly we have heard talk today benefit risk evaluation for the one time in vivo gene editing. The framework for early approval like CASGEVY has done the phase one approval by several regulatory agency. The need for long-term follow up. Global regulatory approval, I think that's a big challenge here. From a drug development point of view, we always talk about incentive. It's not practical for if you ask us to submit for 300 country and that the man power require is just tremendous. How do we overcome this and simplify so there is incentive for the company to go after this.

And certainly access problem. And this is going to be especially critical for developing drug in this area. Certainly we know in the developed country we're going to charge much higher price than say patient with low and middle income country. But with in vivo, one time dose editing potentially is that patient from US could fly to these low and middle country and basically get this therapy at a fractional price and this will become a disincentive for the company to actually make these therapy available in those country. So what kind of mechanism we need to put in to prevent these medical tourism?

So I think one of the things I was listening, sitting here and listening to the panel discussion. One of the thing I was thinking is that, well from the company point of view we always say, well what's the incentive and what is easy to do? You have to lower the barrier for the company and then collaborate and build the framework so we can actually deliver this. And so if we... ultimate goal is like what Mike want to do is to treat what, not only the 10 million sickle cell patient but also what, 40 more million HIV? Then we had to develop a manufacturing infrastructure, pair infrastructure and incentive infrastructure to make that possible. It's not going to be an easy feat, but I hope if everybody come together, start discussing now and by time we get the next in vivo therapy approved, we have a system ready to go. So thank you very much.

Susan Winckler:

Fabulous. Thank you. So that's halfway through our new technologies and really appreciate your discussion there on the LNPs and some of the other components. We'll turn now to Dr. Tisdale in addition to your title in being the senior investigator and chief of the Cellular and Molecular Therapeutics branch at NHLBI. You also I think get the award for the lowest carbon footprint for getting here today because I'm pretty sure you rode your bicycle.

Dr. John Tisdale:

Yes, yes.

Susan Winckler:

All right.

Dr. John Tisdale:

So thank you Susan and thank you Mike for the opportunity. In fact, I do for those of you in the room live just beyond the National Cathedral there, which you can see is uphill. So not only did I ride my bicycle here, I got to ride it downhill. I got to ride uphill going back. But anyway, so I'm going to try to pick things up a little bit. I know we're a little behind time and much has been said of what I already wanted to say. So I'll just hit some highlights, you know about sickle cell disease. The one point I want to make here is that it's a single gene disorder in an organ that we can take out and give back. So why it's taken us so long to get to where we are now, even I'm not sure, but it has in fact been a complicated journey. I thought it was going to be something simple 30 years ago when I started working on it, but there were a lot of barriers to getting where we are now.

But right now, I mean the science is just incredible. Things are moving so fast. You come back next week and David Lu has invented three more things. So here we are with lots of tools. And so on the left we can do this, we can take bone marrow, we can add a gene, we can edit a gene, we can give it back in Jimmy's testament to the fact that that works and works really well. But what we are now focused on doing is this in vivo gene editing or gene addition that you just heard Tony introduce. And the benefit there is that's something you can do on a walk-in basis, hopefully one time only at a low cost.

And then it would be more accessible here in the US. We talk about places other than the US as if it's different here in the US. I'd say it's pretty similar here actually, most patients can't access these new therapies even here in the US. But we now have lentiviral based gene transfer that's working. These are two papers that we published describing our efforts along the way, groups A and B on the left and group C on the right where we made a lot of process and manufacturing improvements that helped us to get over the finish line and to wind up with a graph that looks just like the one Tony and David earlier showed for CASGEVY, just resolution for most patients of the pain that's bringing them back and forth to the hospital.

And one thing I can mention is that we also do allogeneic transplants. So we know how this looks when you give somebody else's bone marrow and completely replace the patient's bone marrow with the new one. And we still have some patients who have chronic pain required pain medications because of the ravages of the disease that are permanent, for example, to their skeletal system.

So I want to give a shout-out to Francis. Francis is part of the reason why we're all gathered here today. Francis and I for the last 25 years have actually played in a rock band together and we invite ourselves to events and usually embarrass ourselves. But we've gotten better over the years and have had some invitations. And at this one invited concert, we were giving in a bar in Bethesda. We were having a bite of pizza beforehand and everything was working in the lab and group C was working in the clinic and I told Francis, "We really need a moonshot for sickle cell disease. We're there, we have current ones working, we have new ones with great promise, we need to really ratchet up the efforts."

And he seemed interested, but then I didn't hear from him about it again until a few weeks later when I got an email from people in building one asking me to come and pitch this to Francis and all the people in building one. Which of course I gladly did, put together a proposal, a presentation, what have you. And that launched the Cure Sickle Cell Initiative, which is now run through NHLBI by Gary Gibbons and

led to some meetings with Francis and I and Bill Gates where we tried to convince him to expand the effort to include sickle cell disease. And as you know, that was ultimately successful. And the hook was really that if we can make this work for sickle cell, we can also make it work for HIV. So these are some comments that Francis made when he was presenting at the ASGCT meeting just after finishing his term as NIH director.

So you've heard about the barriers here. This is kind of an oversimplification, but we have to get in, escape the immune system, get through endothelial cells, home to the bone marrow, get specifically to the hematopoietic stem cell and then get inside. So that's a pretty difficult task to ask of one system. So one thing that we focused on is CD117. You've heard about it in prior talks. It's expressed on hematopoietic stem and progenitor cells. So that gives us kind of a zip code to go after when we send something in to try to change a bone marrow stem cell. We know it works because in collaboration with Magenta Therapeutics, we made an antibody drug conjugate. So we stuck a drug onto a CD117 antibody, gave it to animals and completely ablated their bone marrow. So this is an antibody ablating the bone marrow, not a chemotherapy.

And you can see a comparison in the right two panels, the antibody drug conjugate with fully ablated Busulfan dosing. We knocked the bone marrow cells out equivalently with this antibody. And the benefit to this was that not only do we get good gene transfer and graftment the same we get with Busulfan. These animals remained fertile, we put them in group housing. And four of the six in the first breeding season had successful pregnancies. So this was a big step forward. But still that's ex vivo, we're giving a drug. At least it tells us that the antibody gets to the bone marrow and can carry a drug and deplete the bone marrow. Maybe that same antibody could get us in with an editing reagent as you've heard.

So we've used this scFV from the CD117 antibody to try and get specific. So we have a cell line that's about 80% CD117 positive and we use it at low titer to screen to see if we can get selectivity from this antibody. And we do this at low MOI, so 0.5 that means there's one copy of the virus vector for every two cells. So we should get about 50%. It's not perfect number, but here you can see when using this selection strategy with CD117, we screened a whole bunch of scFVs from a library for binding and then made them into vectors and then tested them on cell lines. And in red you see CD11 positive cells and in blue you see CD117 negative cells and compared to the 79D, which was the published scFV, we can get really good selection with our vectors that have on them an antibody targeting C kit. So we're hopeful that that will get us into the bone marrow compartment if we try this in vivo.

But we're first trying to focus on getting a really good antibody or even getting a really good peptide. And we further optimized this delivery system now. We're mostly using VSVG where we just add to it the sequence for the scFV and we have to mutate the binding domain because VSVG binds to everything. So we can make it specific. But we're not even really sure that it gets expressed well enough to find its way. So we're also working on a tube protein envelope, which the measles envelope can allow us to do. That way we just mutate the binding domain and stick the targeting domain right on that. And then we add both and we can control what we've added better. So there's ways to make this better that we're working on.

And we know that CD117 works. Tony just showed you these data from Breda so we know we can get now with this antibody, even the one that works the least well for us into bone marrow cells. So just want to drive that point home again.

We've also switched to making peptides so that we can make lipid nanoparticles. And so I'm really supposed to be talking about lentiviral vectors, but lipid nanoparticles can also be directed as you just saw. And so, one of the ways we're screening for peptide is to again, do a phage display, look for peptides, find the ones that bind well, and then use those to go in and chase the stem cell. And so this is much easier to conjugate to a lipid nanoparticle. That's the reason for switching to a peptide. So we

generate this random peptide library, we screen it over CD117 negative cells to get rid of non-specific binding. Then we screen it on CD117 positive cells, get the cells that stick and get the cells that go inside by lysing the cell because ultimately we want to find the peptide that binds and gets internalized. So if we break the cells at the end of this, we find sequences that have bound.

We get a bunch of peptides through this screen. We literally screened billions and this is what we've come up with so far. Some in different plasma concentrations because we know we need to be in that... That's my alarm for another meeting.

And then we can check those. Again, this time with targeted vectors. We've also conjugated them to lipid nanoparticles because again, they're easier to get in to a lipid nanoparticle. And here again, you can see red performing really well with these targeted peptides linked to a viral vector.

Lentiviral vectors have been used in animal models now to try and approach disease. So this is a tyrosinemia type one pig model. So this is a big model like a human. And you can see that in the treated group in green you have a resolution of the tyrosine, AST, ALP, ammonia, bilirubin, and lowering of the alpha-fetoprotein suggestive of a cure of this animal model of disease.

We've seen the same type of lentiviral approach being used in vivo in a mouse model of Duchenne muscular dystrophy where you can see over 26 weeks restoration of the pull force. We've seen in vivo lentiviral delivery for the treatment of hemophilia A, where they used a five vector system to get this all in. Intra or subretinal injection of lentiviral vector into the eye of mice with an age-related macular degeneration. Again, in vivo lentiviral vector therapy working in this mouse model. And finally in vivo car T cell generation in a non-human primate. And in the bottom right you can see these CAR T cells are eliminating B cells for around two months in two or three of the four treated animals shown here.

So how many cells do we have to reach? This is a big issue for all of us to consider. We need to make a vector that gets in, that can go to all the cells that we want to reach. And so I thought back, actually Mike asked me this question, I thought back to a experiment that we did many years ago, actually decades ago when we were doing oncoretroviral vector gene transfer in the non-human primate. Had just gotten to a point where we could get 5, 10% that allowed us to track cells clonally. We developed a method to amplify where these vectors landed, identify them based on the sequence next to where the vector landed and then plot them over time. And this was a really inefficient system. We have a lot better ways to do it now, but we could estimate the total amount of the population of cells by using this capture recapture method.

And around about 50 clones were making blood at any given time in these monkeys and that was about 5% of hematopoiesis. So we did a sort of back of the napkin calculation based on the starting number of cells that we'd infused, how much that represented and estimated that about five cells per 10 to the seventh mononuclear cells in the bone marrow are a stem cell. So it's a pretty rare cell. That's a good thing. And if we figure that we have about three or four liters of bone marrow, that's about a hundred thousand hematopoietic stem cells in a human at any time making blood. And that agrees with what ChatGPT says. If you ask how many hematopoietic stem cells are in the body, it just spits it right out.

But it also agrees with what we see in our clinical trial. So this is integration site analysis, looking at unique integration sites in groups A and C versus vector copy number. So you can see there's a correlation, higher vector copy number, higher number of integration sites. Higher hemoglobin T87Q on the right, which is the vector encoded hemoglobin, higher unique integration sites. And interestingly, the median is somewhere between 20 and 30,000 unique integration sites. So again, around that ballpark of hematopoietic stem cells that we need to try to reach.

So I'll stop there with just one caveat. This is my group at a recent gathering, but when thinking about targets like CD117, there's a rub. And that is that reticular sites also express CD117, and they can be a

sink for where you're trying to go. And there's probably about 500 billion reticular sites in a human. So we also have to be careful to think about what other cells might soak up the zip code that we use to get in. So I'll stop there and we can keep moving.

Susan Winckler:

All right, thank you so much Dr. Tisdale. Which takes us 75% of our way through the emerging technology. It's just fascinating. And then I am reminded that next time I'm going to book for every presenter of scientific information a meeting that they have to be at. But no, this is fascinating. He does have to be at that meeting. But so fascinating as we learn about what's on the horizon. So to close us out and you have your time because what we are going to do is we're going to roll through the break. You all are adults, you can get up and take a break if you need it. We're going to roll right into our next session after we hear from Dr. Hildegard Büning who is professor of infection biology of the gene transfer and deputy director of the Institute of Experimental Hematology at Hanover Medical School in Germany. So you did not ride your bike.

Dr. Hildegard Büning:

No.

Susan Winckler:

We appreciate you coming here and take us from, we've done lipid nanoparticles and had just done the lentiviral vectors. Would you help us with AAV and ADV?

Dr. Hildegard Büning:

I'll try at least.

Susan Winckler:

All right.

Dr. Hildegard Büning:

So I mean it's really a great pleasure to be here. Thanks again for the invitation. And what I would like to do with you today is really look into vector system, which have been used in vivo already, what we have learned there and what we need to do and what has already done.

So let me start with my house pad, which is the adeno-associated viral vector system. And so it's based on a virus, the adeno-associated virus. And if you look what it is, it's looking like that. Oh, come on. So we have a non-enveloped protein capsid of only 25 nanometer in diameter. And this little thing delivers a DNA of approximately 4.7 kb. Wow.

Okay. But what makes it challenging is, and good for us is that Mama nature has put us a lot of serotype and variants around which differs in the receptor it is using for cell entry, which helps us in gene therapy then because we can just pick another serotype. And what is nice is that we know where these different serotypes differ and this helps us in engineering. So make these two notes to your memory.

But when we use now a vector delivery tool, you don't want to use a virus. So how do we go from a virus to a vector? So you see we have here the capsid, we have the DNI, which naturally is transported in this vector system. And if we now would like to use a vector, we are depleting all viral genes, which are here, rep and cap by our transgene expression cassette of choice, just leaving a little signal, which is called the packaging signals there that the cell knows what to package where.

And with this basic concept, we have ended up with a lot of approved AV gene therapies approved by FDA and by eMAR. And you see in green those which are really used intravenously by the others are locally used, but all are done in vivo with this first generation vectors, just using the caps that mama nature has developed and put in your gene of interest instead of the viral genome.

What we have learned here with these first-generation vectors is of course mama nature is not perfect leaving some jobs for us. And one issue is, for example, which we call low efficacy. So AAV vectors, if you put them intravenously, like to go to the liver. And when you look here at the vector doses, which we require per kilogram body weight to really have a therapy. And when you just look into the red marked box, which shows you the number of cells we have in the body, then you see what I mean by low efficacy? Yeah? Okay.

And it even gets worse. We would like to convince our AAV vector not to go to its target organ, which is the liver, but help us reaching the multineurons in the brain or even go to the different muscles in our body. To convince the vector to go there to the less preferred organ, we have to inquire the dose, get higher doses. These are the numbers for example, which I used to go to the multineurons [inaudible 01:08:57] Sorgensma.

And I mean there's nothing behind you really believe me, that this guest does not go unnoticed to our immune system. So these are the challenges. What can we do? So this nice capsid, which I showed you, is the one which makes the interaction with the cell, the binding and also helps the DNI being then delivered to the cell nucleus where the transgene expression occurs. So what about engineering this capsid in the lab to make it better? And so what we look at here, and a lot of labs all over the world are doing this, is look at the cap gene and modify this by rational design. What is nice for us is that we know that the main areas which are really binding to the cells are those which you see here in the picture in red. So what about changing exactly these areas by mutating them, blinding them and putting back little peptides, which really helps them to direct this capsid to your receptor of choice. You can also do this not on a genetic basis, but you first produce your particle. And then, by chemical modification, put an antibody on top of this. Yeah. Also, with the purpose of redirecting the tropism to a new receptor.

However, we have to admit that we humans are not that smart as nature, right? And so, the easiest way is to look what nature is commonly doing, and this is evolution. So, what we do therefore is, it shows up, is that we generate libraries of AAV capsids. So, 10 to six or more, where you change each of the components either by pointing, point mutation, swapping around some sequences of the capsids, or just at these red areas of the capsid, put in small peptides of random sequence.

Then, you throw all this into your animal and then pick up those AAVs who, under your conditions, found the target cells, entered and put the DNA there, where you would like to have it. So, more sophisticated thing because it's really that you can select the best performer, not only for binding, but also for doing all the challenges which a virus faces intracellularly in the best way with these processes. And by this you really come up with vectors, which doing much better. So, second generation.

So, you see, these are, for example, examples of primary human keratinocytes, where you would like to convince an AAV2 to transduce it by GFP. So, when it is successful, you see green cells. You see, we start, natural AAV serotype is not really working. But having these techniques, it's all green. And these are only some examples. If you type this in literature into PubMed, you see a lot of these examples. And what you end up with is really vectors, where you have a higher efficacy, so you can lower the dose which you put into your patient. And this will also lower the production cost.

What about specificity? If we have the right... Come on, move. If you really know the right parking lot, then you can generate a particle which is absolutely specific, precisely targeting your cell types. This is an example here. Again, we start from something which is unspecifically, which is from a natural AAV. You see the AAV, where we try to get into the tumor cell, but it's not enlightening. But you see, when

you do this modification on the capsid, all the AAVs really go into the tumor cells, with a wonderful collaboration with Christian Buchholz.

A lot of examples are around that really you can improve and redirect the tropism, which, again, will generate in the lowering of the dose, which you have to do to the patient because you're not ending up in the liver. But you just end up there where you would like to be. It also will lower the production cost and, of course, it will increase your safety of the whole procedure, because you are not having expression of target organs.

And you can now imagine that if you do all this engineering of the capsid, it looks different than what is around in Mama Nature. And so, you can believe that patients which have antibodies due to pre-exposure to the AAVs in childhood, may have also, due to these changes in the capsid, now the option to be treated, because these capsids look different. And the antibodies are not binding to this capsid anymore. So, you have maybe a capsid which allows you to include your patient despite the presence of neutralizing antibodies. And maybe this is also an option to do repeated administration.

All this engineering can also be done to really hook onto the question of, how can we avoid or modulate the novel immune responses? Because what you can do is, you use this capsid, put an information on top, saying to the immune system, "Hello, don't look at me." And as you see, it works. You get a lower innate immune response. You see that you have less T-cells, and so on and so forth, which is a safety contribution.

And now, the second culprit here, or the second wild component which you can engineer, is your genome. What can we do here? We have a single-stranded vector genome. We can convert it into something which, as soon as the cell has to work on it, is a double strand. We call this a self-complementary. You can look into the promoter, which is a switch. You can do the cell type selective. You can look which level would be the best one. You can really have a switch on and off. You can optimize the codon sequence, so that it's better served. And you can also deplete their sequences, which your immune system would recognize. You can increase the stability of your mRNA. All this is done. A lot of people work on this. And you can then put both together to really have your next-generation AAV tools.

And all what I showed you here, the principles of targeting you can do for lentis, you can also in principle do for non-viral particles. But this has been also done for adenoviral vectors. And I'm grateful here for slides which I received from André Lieber. So, a adenovirus is a little bit larger than AAVs, so we are in the ballpark of 90 nanometer. But it's a nonenveloped capsid. We have a lot of serotypes around, which like to park in different parking lots, which is good for us in gene therapy. But we can also deliver a lot more of coding sequences, which is very good in gene therapy.

And as I said, also here, the strategies of engineering, changing the tropism, has been developed. And this is the slide, as I said, which I received from André, where he showed that you can change these recognition sites, which are here, the fiber knobs, really in a way that they can now interact with cell surface molecules, which you find on hematopoietic stem and progenitor cells.

And so, what you can do now, and the vision here, would be that you mobilize your stem cells into the periphery, that you then inject your modified adenoviral vectors. That then, the cells are transduced and then home back into your bone marrow. And indeed, he and other groups really showed how well this works. Oh, this was a bit too much.

So, coming now to our topic. So, I'm really believing that we need to go in vivo, and I heard this a lot today. And this is because we have this wonderful results in the ex vivo gene therapies, but we know that we have to really bring it to improve accessibility. We need to move for in vivo. And this slide, you

have seen some harm already in other talks, and it's indeed the issue that there are a lot of challenges when you just look into ex vivo gene therapy.

We heard about the specialized centers. We heard about the time to treatment, which is really difficult if you have to look into ex vivo approaches. We spoke about cost. We really spoke about that. That is not an off-the-shelf medication. But then, also, look at the cells. You get them out of a body, put them in an artificial environment, so they are not the same. You impact viability, the pluripotency, the engraftment efficacy. You also put them under genotoxic stress if you go for lentiviral vectors, or gamma retroviral vectors or whatever, something which integrates. You have them also stressed just because you modify them ex vivo. And then, of course, we heard about the patients.

So, if we now really just look at what in vivo could help us with is, of course, we don't need specialized centers, then we hope that we can really lower the treatment cost because we have highly potent vectors with lower doses. And you are just applying the vectors, not having the ex vivo manipulation on top. The time to treatment should be quite short because you can store them. It's an off-the-shelf product because it's the vector which you deliver. And we should even be able to go without the conditioning.

What about the plural cells? It's not an ex vivo culture, what you do. And at the moment, I showed you one example from André Lieber, where you have the mobilization into the periphery. And the cells which are then modified, go back. But you can envision that you can do this even without mobilization.

What about gene integration, genomic integration? Yes, you need to do this, and adenos and AAVs are not integrating with regard to having an integrase. But with the help of gene editing, you can have a precise landing platform. And this all because it's in vivo, should have a lower stress for the cell.

And then, of course, there are drawbacks, which, for example, you put in a viral vector, for example. Now, this is an antigenic load. You have really the issue of pre-existing immunity and the risk of off-target. But therefore, maybe we are already ahead, because I showed you what engineering can do really to lower the dose, to really lower the antigenic load to have a precise targeting, and so on and so forth. Thank you very much.

Session 4: Regulators' Perspective

Sol Ruiz, PhD, Spanish Medicines Agency (AEMPS)
Peter Marks, MD, PhD, Center for Biologics Evaluation and Research, FDA
Eric Karikari-Boateng, MS, Food and Drugs Authority (Ghana)

Susan Winckler:

Thank you. Dr. Büning, you took us through all that it is that we needed to know in the... You are at zero time, but that's all right. What we wanted to think about in our next generation of gene therapies. So, with that, I'm going to turn us next to our panel that will talk from the regulatory perspective. And I need Dr. Marks to come forward and join me on the stage, and then all of these other chairs will get filled after we finish our regulator conversation. So, Dr. Marks, if you would join me, that would be great.

And then, we have two regulators, who are going to join us virtually. And Dr. Ruiz, welcome. So, joining us from her role as head of biologics, Biotechnology and Advanced Therapies for the Spanish Medicines Agency. We have a new face joining us. Dr. Ruiz, thank you for joining us. If you would do a quick AV check, say hello, and then we'll know we can hear you.

Dr. Sol Ruiz:

Yeah. Hi. Hello. Good afternoon. I hope you can hear me well.

Susan Winckler:

We can hear you well. Dr. Marks and I are looking right at you.

Dr. Sol Ruiz:

That's great. Thanks.

Susan Winckler:

And I think you appear right behind us. So, you actually have the strongest presence in the room, which is fabulous. And then, Dr. Karikari-Boateng, who we heard from earlier as the director of the Center for Laboratory Services and Research at the Food and Drug Authority in Ghana, is also with us. So, Dr. Boateng, would you double check that we have your sound again?

Dr. Eric Karikari-Boateng:

Yes, I can clearly hear you. You have me.

Susan Winckler:

Excellent. And we can hear you.

Dr. Eric Karikari-Boateng:

Hi, Peter.

Susan Winckler:

So, let's turn from that fascinating science and the science that's on the horizon to what, of course, I have to say is even more fascinating, which is the regulatory structure. Only a lawyer would say that, but that's okay. I want to open and turn to you, Dr. Marks.

We do have to think about the framing. There's great promise here. But I guess to say that typically regulators are risk-averse serves us really well. Give us the regulator perspective. How, as a regulator, do you look at these products? And just what needs to go into the framing as you're leading your staff to evaluate these promising developments?

Dr. Peter Marks:

Right. So, I think when we talk about these gene therapies, be they directly administered genome editors or other gene therapy products, I think we have to categorize these into very small populations and larger populations. And the risk benefit considerations are going to be somewhat different. Because you can imagine that very small population, very bad disease that has a potential gene therapy. One, knowing that it is a very small population and knowing that you can take the time to have informed benefit-risk considerations and conversations with parents of children, it's a different situation than if we have a directly administered gene therapy that we are going to give to a large number of people. And I would say, the sickle cell indication in Africa is a large indication. It's a rare disease, but that's a large indication.

Now, I'm going to get non-loyally, because I don't care for a few minutes about what the Orphan Drug Act says. I care about what a large population is, and that is a large population. And to be honest, even

though it technically qualifies as a rare disease in the United States, or an orphan disease, 75 to 100,000 people in the United States, if that were the overall population, which isn't really where we're thinking that gene therapy would be used in the United States anyway. But what I'm trying to say is, it's larger populations have different risk considerations. And they have to. Because if we unleash a gene therapy on a large number of people and it turns out to have even a one or 2% chance of something very serious, adverse happening, we could set the whole field back pretty significantly.

Now, you might say, "Well, but couldn't that happen in a small population?" It could, but in the smaller populations, we've already seen setbacks like this. And because of the benefit-risk considerations, the number of people involved, it seems to be more accepted. So, I think as we're thinking as regulators, we do need to think that, and I think this is important for product developers to understand, when we're talking about these very small populations, we may be talking in a different manner than we are as we start to get to larger populations. And I know what the next question is. So, is it 100? Is it 1,000? Is it 10,000? Where does it convert over? Somewhere in there. As you go from 100 to 1,000, to 10,000, you're starting to move to products that are being used in enough people that us regulators, we, I think, start to get nervous if we don't have good manufacturing practices, good clinical data. Safety needs to be batted down.

It doesn't have to be perfect, but we need to have the kind of data that will make us feel more comfortable in this kind of a setting.

Susan Winckler:

Which, I think, is consistent. Earlier today, Dr. Miller had a phrase where they said, "A regulatory structure that was safe but simple might be helpful." And I think you're saying safe and potentially simple, but that we have to recognize the safety dynamic also changes when there's broad use. Is that a way to think about it?

Dr. Peter Marks:

That's correct. So, maybe the best way to do this is to go right back to our benefit-risk framework, which is benefit, risk and uncertainty. So, as a population gets larger, our tolerance for uncertainty gets smaller, right?

Susan Winckler:

Yep.

Dr. Peter Marks:

If you have a very small population, the uncertainty that you can tolerate there is probably greater because it's a small number of individuals. And a mistake in your calculation affects a small number of individuals. As you get to larger numbers of individuals, that uncertainty that you can accept in not knowing what could go wrong, you need to reduce that somewhat. I think that's a fair way of saying that. The other thing that affects that uncertainty is the nature of how severe the outcome is, right?

Susan Winckler:

Right.

Dr. Peter Marks:

If the outcome is certain death at age three, it's a different calculation. Even if it's in a large number of individuals, then it would be if it's possible, disease at age 60.

Susan Winckler:

Okay. That's very helpful and, I think, tees up to something, a theme we heard earlier, which had to do with collaboration. And so, it strikes me that this is an area where regulators would want to collaborate to keep pace with what's emerging, and to help with some of that uncertainty dynamic.

So, Dr. Ruiz, I want to turn to you. You've been involved with some of the collaborative regulatory efforts in the European Union that are applied in emerging areas like this. Would you describe some of those efforts to us?

Dr. Sol Ruiz:

Yep. Sure. And well, first of all, thank you so much for inviting me to participate. Sorry that I could not be there face to face. So, regarding this collaborative regulatory efforts, I would say there are different modalities. So, for instance, we could have face-to-face training courses and workshops. And we have done that already for biosimilar training, these biological biosimilar products in many countries in Central and South America, and also in several countries in Africa.

Also, another possibility is online training, organized by the European Medicines Agency. And after these workshops, all the video and presentations are available in a report on the EMA website. And for instance, we had in 2018 an EMA-FDA workshop to support the quality development of early-access approaches, such as for gene therapy products through the PRIME scheme, PRIority MEdicines for breakthrough at the EMA. But we had also another one on RNA-based medicines.

Also, there is a project under preparation that involves the African Medicines Agency. The EMA has received a grant of 10 million euros from the European Commission to support regulatory system systems at national level and regional level in Africa. And in particular, for setting the African Medicines Agency in collaboration with African, European, and international actors. So, I think this is a very good initiative. And information, if you're interested, the information about this project is available also on the EMA website. And the Spanish Medicines Agency has already presented a proposal to collaborate on this training.

And also, I think another very good opportunity for regulatory harmonization is participation in regulatory discussions at the different groups or committees at the EMA. And that is being done for different products. For instance, during the COVID-19 pandemic, there were frequent interactions between FDA, EMA, Health Canada, PMDA in Japan, and other regulatory agencies, to try to harmonize their requirements. This was done also during the Ebola outbreak in West Africa around 2014. So, there were frequent discussions to try to get as quick as possible through scientific advice for vaccines and treatments.

And also, for instance, a recent example a few years ago for a dengue vaccine, where regulators from other parts of the world where the vaccine could be used participated at the discussions at the CHMP, at the EMA. And you can hear the different points of view, these benefit-risk assessment, as Peter Marks mentioned. So, all these possibilities are in place, and I would say they are all good to try to harmonize. Thank you. Thanks.

Susan Winckler:

Yeah. Thank you, Dr. Ruiz. And so, I think that helps just in the recognition that there needs to be significant oversight. We want these products to work. We've heard about the great promise, but then

also making sure that they do what they're supposed to, and nothing they don't, to have the regulators collaborate on that.

Dr. Peter Marks:

Yeah. I think there's no room for fake gene therapies. And actually, no, I don't laugh about that because I worked in the pharma industry. And at that time, in the early 2000s, we knew that about 30% of the medicines that went into Africa were either fake or subpotent, and this will not be... So, we do, I think as regulators, need to come together to make sure that confidence in these is really there, especially because of all the support. This isn't just like giving someone a pill. There's all the supportive care that will go around these products. So, these products, they better be what they say they are.

Susan Winckler:

In fact, Dr. Inamdar had mentioned that earlier today, about making sure that it was legitimate product in legitimate trials. So, very helpful.

Dr. Karikari-Boateng, I want to make sure that we hear your voice today. What would you add as we continue this conversation? And you've heard a bit about how gene therapy is changing, and the new technology may be even closer than we thought. What would be helpful to you as a regulator, as a key regulator in Ghana? What would help you keep pace with these technology developments and help you as you think about this responsibility?

Dr. Eric Karikari-Boateng:

Thank you, Susan. And I think Peter and Sol, they've said much about that. And so, what will help us keep in touch or abreast with modern development is by collaboration. As she said, we collaborate a lot with the EMA and also through others. But the USFDA, also they help a lot. So, one, the collaboration is there. And then, sharing of information, so that we can also rely on the decisions that are taken by EMA and then the USFDA. Possibly, Health Canada and PDMA.

And also, building the capacity of, or building expertise of regulators on the continent. That, we've started with the EMA. We've started this exchange program thing. But one thing I can tell about this, in this day and age, I am not sure. It's not likely we would [inaudible 01:34:31] happen 10 to 15 years ago. At least, if it goes through the central VIRC system, we would be able to differentiate or distinguish good application from bad applications. Over, Susan. That's what I can add.

Susan Winckler:

Yes, thank you so much. And that's, I think, helpful in saying that, the collaboration and the ability to have the conversation and to learn from what others have done. Dr. Ruiz, what would you underscore as activities that help regulators in this space?

Dr. Sol Ruiz:

So, from our experience, I would say that early and frequent interactions with developers of gene therapy, medicinal products, either industry or academia, hospitals, is very, very helpful. Because you start this interaction, you know what the project is. And in the European Union, this can be done nationally. So, you can go to a particular country in the EU and interact with them. For instance, in Spain, we have the Innovation Office, and this is a point of entrance. And you can have as frequent meetings as you need at no cost. So, we follow the development from the quality development, nonclinical studies, and the clinical development.

Also, at the EMA, through the Innovation Task Force, it's an early interaction, and they can guide you through the different steps. Also, I think it's very important to have good experts outside the agency, for instance, from university or hospitals. Because these are novel therapies that having the support or the expertise, as we have heard in previous presentations, is very good. And also, interaction with other regulators on specific topics. And we have, for instance, on vaccines, but also gene therapy, meetings, frequent meetings with EMA, FDA, and other agencies. So, also this interaction is very helpful to move forward. Thank you. Thanks.

Susan Winckler:

Yes. Well, and that makes a lot of sense in saying that having the conversations with regulated industries, so you know what, in fact, is being developed and what they're learning and components. And then, really helpful to have the organization of the agency to facilitate that innovation.

I think Dr. Marks, you've done some work at CBER to try and make sure that you're a bit more, I was going to say nimble. I'm not sure that that's the right word, but that you're better structured to interact with industry, or to facilitate the technology.

Dr. Peter Marks:

Yeah. We have divided up the Office of Therapeutic Products. We had various reorgs, but in the latest invention of the way the office looks, we've divided up to a gene therapy chemistry, manufacturing, control group that is able to speak the language early on in development. And then, we have a clinical group that handles that portion as well. As a pharm-tox group, you might say, "Well, aren't they all related?" Yes, they are all related. But in some cases, it's just very helpful to have all the expertise in chemistry, manufacturing, controls concentrated, so that those issues can be dealt with.

And I think we're trying to also just going to also provide nimble regulatory advice is encouraging people. I think the comment that keeps getting said over and over again is, having people come in early and often, so that they don't make mistakes. And that was what was behind the START Regulatory Pilot that's been going on with the Center for Drugs and Center for Biologics, with this concept of taking a couple of programs, giving them... Essentially, it's like feeding ad lib. It's regulatory advice ad lib as people needed it. It's like having a bunch of sandwiches out that people can take anytime they want. Except here, you don't gain weight. You just hopefully gain knowledge about how to do things better.

And it's actually based on what we did during Operation Warp Speed during the pandemic, where giving sponsors ongoing regulatory advice without making them go through the machinations of sending in a formal meeting request, scheduling something, having a meeting 60 days later after sending in a package. It really sped stuff up there. So, the idea is, could it speed things up here and make us more nimble in getting over some of the challenges? Particularly because we've already heard, you could hear from the complexity some of... I was listening to Dr. Liu's lecture, some of the scientific lectures. There's a lot of complexity here.

And the ability to be able to be nimble and deal with those issues, address them, I think is really helpful. So, hopefully, this different approach will be well-tailored to quickly moving science.

Susan Winckler:

So, I'm now internalizing your snack bar analogy, that it's the advice is available to access more easily than-

Dr. Peter Marks:

That's right. That's right.

Susan Winckler:

... requiring to order it off the menu.

Dr. Peter Marks:

That's right. That's right.

Susan Winckler:

Okay. Okay. We certainly saw great benefit.

Dr. Peter Marks:

No, it's a pilot project.

Susan Winckler:

Right.

Dr. Peter Marks:

It's a pilot project right now. We're going to measure it. And the idea would be, if it turns out that that really works well, we'll have to staff up to be able to do it. Because just like there's a cost to sandwiches, there's a cost to developing-

Susan Winckler:

Indeed, to available regulatory advice on demand.

Dr. Peter Marks:

Right. Exactly.

Susan Winckler:

Yes, yes, yes.

Dr. Peter Marks:

Sorry for the analogy.

Susan Winckler:

No, it works. I can see and hear that it works for folks. And then, I would think that also gives you an opportunity to have that exchange that Dr. Ruiz mentioned is so important between the regulator and industry. It provides perhaps more an easier environment for that?

Dr. Peter Marks:

Well, it's actually quite satisfying. Because for the reviewers, it's really nice for them to have the immediate feedback of, "Oh, we thought you were going to acquire X for toxicology." You're requiring half of that. That speeds us up by... It's the real time interaction is, I think, mutually beneficial. It's

reinforcing. It makes it more fun to work on these programs, to see them move ahead. Again, we'll have to see-

Susan Winckler:

Right.

Dr. Peter Marks:

It will have to be measured, and we'll have to see that it makes a difference. But the initial feedback that we're getting from this, from the sponsors, is quite positive. Again, will that translate into products getting across the finish line more effectively and more rapidly? We'll be measuring that.

Susan Winckler:

Very helpful. Well, I wanted to hold for our last question, to make sure that we have enough time to have full answers here. Because I think each of you as regulators has a great window into this. And so, specifically, what I'd like Dr. Ruiz, Dr. Marks, and Dr. Boateng to think about is, think about the future. And particularly, what does success look like in gene therapy interventions in five years? And what does success look like in 10 years from the regulator perspective? And because I've got Dr. Ruiz right in front of me, you get to pick up and answer that question first. From a regulator perspective, what does that success look like?

Dr. Sol Ruiz:

Yeah. No, thank you. And I think it's very difficult to define five years or 10 years. Maybe a little bit more like long term or short term.

Susan Winckler:

You can redefine the question Dr. Ruiz.

Dr. Sol Ruiz:

Sure.

Susan Winckler:

Feel free.

Dr. Sol Ruiz:

Yeah. Thank you. Thanks. No, I think it depends on how do we define success? If we define success as something that can make an impact, obviously, treatment for patients would be the goal. But considering that the current experience that we have with the gene therapy medicine products already approved, this probably is a long-term goal. And there are many factors to consider. Not only the availability of a particular gene therapy product, but also the cost of these products, as we have heard, the facilities and medical care in a particular country, if it's possible to monitor a patient for outcomes or serious side effects. So, all these things need to be considered, not only the availability of a particular product.

And also from our experience, we have seen that promoting clinical research is very important, because it's a way for patients to have access. And in our experience, for instance, in Spain, that you know clinical

research, it is very important. We have seen that that is a way for patients to get access to new therapies and very novel therapies.

Also, if we define success as a cure for the disease, ideally for life, well, or for long term, we have examples in which there's still uncertainty. For instance, the gene therapy for hemophilia. The products that are already available, they seem to work for a few years, but we don't know if that is going to be for life, or if it's only for five, 10 years. But we'll have to see. But this seems like also something that will take time. And obviously, there are advances in genome editing, also as heard from different presentations. That obviously, there are many, many methodologies being tried. So maybe, I don't know, there's a change that allows for this goal to be a little bit shorter. Then obviously, in a short term timeframe, maybe improvement in manufacturing methods that allow a larger scale production that could help and could facilitate the access of these products for more patients.

Or maybe if there's development in the point of care manufacturing technologies using automated closed systems that we know are also under development, that could also facilitate wider access to these therapies. Hopefully, all those areas move forward and we can see better outcomes. Thank you. Excellent.

Susan Winckler:

Yes. Well really helpful in the recognizing there are a lot of places where we need to see improvement, but also that in five and 10 years we'll have a better understanding of the durability of these interventions. Which I guess is just a good reminder that we are learning as we have more and more individuals who have received them.

Dr. Marks, what does success look like from your perspective? You can do five years, you can do 10 years, you can change it like Sol did.

Dr. Peter Marks:

I'm not going to talk about... Maybe I'll talk about, it won't be all-inclusive, but at least I think five years from now, success would look like starting to have much more regulatory convergence globally so we actually are able to have relatively rare disease gene therapies that don't just make it to a United States population or a European Union population, but one application could potentially satisfy global regulators. Whether it's every last one, I can't say.

It would be nice to have a system whereby we at least come to convergence enough that there's that type of harmonization of what we want, so that more developers are encouraged to go into the area. Right now, the idea that you have to slug it out between different regulators with different requirements globally, if you're starting out with small populations, it just leads to all the different countries being disadvantaged except for the country that has it licensed.

Hopefully that will come about, because once you have that kind of convergence, then you can also start to speak about regulatory reliance so that you take some of the burden off of any given regulator and do regional approvals or even a reference type of approval, such as what we do for vaccines with pre-qualification with WHO. Then 10 years from now... Now I'll switch to the scientific end. I think that within 10 years we'll hopefully start to see the transition from AAV-based gene therapies to these CRISPR-delivered gene therapies.

Although they may not be wildly proliferating by that time, I suspect that it will be transformational because the cost should drop very significantly. AAV cell-based process, it's like fine French cooking, you've got to have everything right. To be honest, if everything goes the way it should, and with all due respect to those who are working on CRISPR genome editing, the manufacturing could be more like a

McDonald's approach where, for a consistent product you got to have everything right, but the cost could go significantly down because it could be a fair amount of synthetic biology, artificial intelligence doing off-target checking, and moving from one disease to another by just shifting guides rather than entire products altogether.

I think that's the five and 10 years, and there's obviously a lot of other stuff that could go with that. It may be wishful thinking for 10 years to get there for CRISPR, but I think we're not making the progress that we'd like to see with AAV and thinking about that transition is a good thing.

Susan Winckler:

Yeah, so great advancements in access in the technology itself as well as the convergence. Dr. Kakari-Boateng, I feel like we should give you the opportunity to have the last word among our regulators to tell us what success looks like for you and other regulators in that five or 10 year timeframe.

Dr. Eric Karikari-Boateng:

Thank you, Susan. I think within the next five years we see it as possible, when we see about five to 10 clinical trials authorized and ongoing in the continent. Especially with respect in the area of sickle cell and then other hemoglobinic factors. We'll see that as a very big success because we carry the highest burden of that disease. Then in the long term we expect to see more studies move to the other areas like HIV and then oncology. Then later, I mean the technology become so available, prices might drop. Those who have these delegations will have access to this medicine. That's the long term. That's 10 years [inaudible 01:50:45]. That's how I foresee things.

Susan Winckler:

That's pretty crystal clear, that you're saying you want to see clinical trials in Ghana and other places in Africa within the five years.

I think, Dr. Nyarko, you're going to help make sure we do that. Then to see some of these deployed beyond sickle cell and to bring therapies to reality, did I hear you?

Dr. Eric Karikari-Boateng:

Yeah, that's right. That's right. The reason why the clinical trials are so important, yes, we keep on pushing rely on. Yes, you can rely on quality, you can rely on non-clinical, but for clinical sometimes due to polycogenesis, especially with this type of treatments where genetics play a very big... It will always be very good to have [inaudible 01:51:34] your own population. For us, the clinical trials is very, very important.

Susan Winckler:

Daniel, that's worth underscoring. I think it ties into a piece that both Doctors Marks and Ruiz have talked about that there are some things where you can rely on the decisions of others and learn from that. Then there are things that we need to learn from clinical trials in the populations where we would want to see the product perform. It seems like if we could get collaboration at a minimum on the learning and keeping pace and then collaboration and convergence on some of the core areas that allows...

Eric, I think that would allow you to focus your resources on those clinical and risk benefit questions.

Dr. Eric Karikari-Boateng:

Exactly, exactly. There will be no need to reinvent the wheel [inaudible 01:52:29]. That would be very useful way of savings case resource.

Susan Winckler:

Yes. Excellent. All right, well that is our regulator perspective for this afternoon. Let's thank our speakers please. Thank you.

Dr. Sol Ruiz:

Thank you.

Session 5: How do we prepare for the next generation of gene therapy, as industry, regulators, and a health care system?

Hildegard Büning, PhD, Hannover Medical School
Cecelia Calhoun, MD, MPHS, MBA, Yale University School of Medicine
Jeremy Farrar, MD, PhD, World Health Organization
Julie Makani, MD, PhD, Muhimbili University of Health And Allied Sciences (Tanzania), Tanzania High Commission to the UK
Peter Marks, MD, PhD, Center for Biologics Evaluation and Research, FDA
Kwasi Nyarko, PhD, WHO Regional Office for Africa (WHO-AFRO)
Jimi Olaghere, Gene Therapy Recipient

Susan Winckler:

Dr. Ruiz, Dr. Karikari-Boateng, thank you so much for joining us. We are going to roll right into our last panel, which has more than a few folks coming up to fill these chairs that are right here that I'm going to let everybody settle into.

Dr. Marks, I'm going to have you stay on stage and we will welcome to the stage Dr. Buning, if you would come back up, Dr. Calhoun, Dr. Makani, Dr. Nyarko. We're just going to elevate you today, Dr. Olaghere, because frankly we need to learn from you and so glad to have you here. Then also, Dr. Farrar to our virtual presence. I think I'm only missing Dr. Makani, and we will welcome her to the stage when she has a chance to join us.

Boy, have we heard a lot from the stage setting conversation about the current state of gene therapies to grounding and thinking about those therapies then in India and Ghana and more broadly on the continent of Africa, to that immersion into the next generation of gene therapies and what might happen. We have a lot to do. We did also hear about purple chickens, safe but simple collaborating, and being transformative.

I want this final panel is going to help us kind of think through and pull all of this together and we have two new faces and as you know, new faces get to go early, get to go first so that we for sure have those new voices. Actually, Dr. Calhoun, I'm going to turn to you first. Let me introduce you in that Dr. Cecilia Calhoun is Assistant Professor of Medicine and pediatrics at Yale University School of Medicine and Medical Director of the Adult Sickle Cell Program at Smilow Cancer Hospital.

What we haven't talked much about today is the healthcare delivery system that would be expected to deliver this next generation of gene therapy. Would you share some thoughts? How should we be thinking about that? I was struck by the observation that the current therapies are for about the 5%. You live this every day. Help ground us in that healthcare professional thinking.

Dr. Cecelia Calhoun:

I first have to say what a tremendous pleasure it is to be in this group. We have learned so much about the science, we've learned so much about practical application and then obviously Jimmy sharing his story was just absolutely phenomenal. Thankful to be here with this amazing group.

I do think Dr. Williams opened the door a little bit in alluding to implementation of gene therapy in the United States for persons with sickle cell disease with which we already have so many challenges. One of the things that really resonated today, and you mentioned it again, was this purple chicken that Dr. Nyarko mentioned. While that's quite a vivid image, one thing that I really, really was struck by is the point is that innovation exists in those places. I believe that innovation is bi-directional.

As we're having these conversations about what we are going to partner with our colleagues on, what is important to know is that we here in the states are going to learn so much about how to properly deliver gene therapy to persons with sickle cell disease here in the US. I think that this knowledge that we're coming together and these questions we're asking will answer a lot this question about how we do it well here, how do we build capacity here, how do we identify the best patients? How do we support them along their trajectory, which Jimmy alluded to, not just before or during, but after? There's so many opportunities here and I think that we in the US will answer these questions as we partner with our international colleagues to think through these things.

Susan Winckler:

That's really helpful framing. I think we tend to think about one geography versus another, but really it's this community learning and that we in fact will all benefit from the advancements of the therapy and learning how to better deploy them. That's great. Thank you, Dr. Calhoun.

Our second new voice is joining us on our virtual stage and that is Dr. Jeremy Farrar, who's Chief Scientist at the World Health Organization. Dr. Farrar, tell us a bit about what you've been thinking and thank you for joining us today, but I want to give you an opportunity to open with few remarks.

Dr. Jeremy Farrar:

Yeah, thanks so much. Can I just check you can hear me? It's coming from a long way away.

Susan Winckler:

Yes, we can hear you and we can see you.

Dr. Jeremy Farrar:

Oh my goodness, sorry about that. Firstly, thanks very much to being asked to join you. I've been able to listen to a little bit earlier on in the conversations as well. I'm just sorry I can't join you in person. It's effective. One is, we are in what I regard as a golden scientific age. I think when you're in those moments in history, you sometimes don't appreciate it. As a result of 20, 30, 40 years of investment in science, we are starting to see the impact of that starting to be possible to change people's lives. That's to be applauded and it's wonderful. Many in this room will have been on that journey with everybody else.

The challenge we've got is that we can either use that science to ensure it reaches everybody who needs it, and in other words, decrease inequality around the world. Or if we do nothing, my worry is that actually science indirectly will be contributing to greater inequality and we store some of that through COVID. A phrase that I used often in the first few months of 2020 was, "Science was our exit from the

pandemic." I think with the coming of vaccines and therapeutics, early diagnostics, better clinical care, public health awareness, we achieved that, but we did not achieve it equitably. We increased inequity.

There were those, the countries and I was living in the UK at the time who had immediate access to vaccines, therapeutics, and there were those countries in the world that were left behind. When we now come on to talk about future advances in science, gene therapies for sickle cell, cell therapies for cancer, indeed gene therapies for cancer, as well as immune disease, diabetes and infectious diseases, of course, then I think our challenge is how can we ensure that we use the science for the maximum number of people and we use science to decrease inequality around the world.

I think if we do nothing and we just expect it to trickle in any direction, it won't happen. Those would be my opening remarks, a scientific golden age and how can we use science to decrease global inequality?

Susan Winckler:

Thank you, Dr. Farrar. It's a really helpful reminder that trickle won't be enough and that we want to expand this technology and do it equitably.

I want to turn then to Dr. Makani. You gave us such wonderful framing remarks this morning making sure that we would coordinate our efforts and think through the potential for expanding the technology. Now you've heard a lot of other people speak in between. What do you want to bring us back to?

Dr. Julie Makani:

Thank you. This works?

Susan Winckler:

It does.

Dr. Julie Makani:

Yes. Thank you. I just wanted to say three things. One is partnership, partnership, partnership in that the whole concept of global convergence, whether you're regulators, whether you are patients, and it's really, for us, it makes a big difference to say we may not have anybody who's received gene therapy, but hey, we'll get on a call and we'll speak to Jimmy and he will share with you his experience and how it works.

This is more effective to have Jimmy talking to another patient than to have John Tisdale talking to myself because the conversation needs to be between peers, patients to patients or physicians to physicians. With regards to that, in terms of partnerships, one of the other things that we are doing is saying we may not have the capacity in a particular area in Africa, but what we can do is we can set up MBT groups, multidisciplinary meetings, where we have discussions where we can talk about a case, we can talk about a patient and we can learn from each other and learn how to provide care in a setting where instead of having a patient fly from Tanzania to India, we can have the patient remain in Tanzania.

This is something that is actually happening, remain in Tanzania. We have meetings on a daily basis where we say, how's the patient doing? Can you do this test? Can you do that test? I think that's another way of really encouraging partnerships. From a policy perspective, I think we've heard a lot about how we don't need to do that. The second thing I wanted to say is really about the business case, the investment case.

I think there was a discussion earlier in terms of how do we incentivize businesses to invest in clinical trials in gene cell therapy in Africa. I think in this instance it's really, and I think Guaco, you spoke about

this where you talked about the numbers. When we are talking about the number of patients just with sickle cell disease in Africa, we're talking about close to 5 million individuals.

I'm not an economist, but when you look at the economies of scale, it just makes a lot of sense to invest. I think the second thing, and this is something that we learned, I work in a public institution, work closely with government, and we have to convince our presidents, our heads of state to invest in this. It's possible. In the past five years in Tanzania, we have gone from a situation where there was no bone marrow transplant services, which is vital for XV-virgin therapy.

And now, we have two hospitals who are providing bone marrow transplant services, which means that we can now talk about participating in XV-virgin therapy trials. Now it's easier for us and the people that we work in to talk to their governments and convince the governments to invest. You can guess what happens once a government invests in the infrastructure, the private sector will come and it becomes easier, relatively easy to do that.

One of the things, again, it's really approaching it not with the thinking that finances are finite, it's really recognizing that there are enough resources for us to do this if we work together. I think the final point is really about the patient. I can't express how much I appreciate Jimmy talking about this. We have in Tanzania three patients that I can think of, we speak on a daily basis, who have come back from receiving bone marrow transplant.

Nasra Ramadhani, they ask a very simple question. They say, "We've received bone marrow transplant, we're struggling. Can we go to John, to Germany, to wherever, France with Marina Covetan and get gene therapy there?" In that instance, it becomes really difficult for us as patient, as providers or as scientists to say, "Well, you are not ready for it," because the patients are asking for this. If we do not provide it to them, they will find a way of getting this.

And so, how do we have that conversation? How do we listen to that, talking to the patients, understanding that for them this is something that they want and we should step back from the arrogance that we have as scientists, as physicians, as regulators step back and say, "What do the patients want and how can we provide this to them?" Because if we don't, they will seek it out in a way that is not effective.

I guess the final thing, again with patients, it's really time. With all the conversations in, I think it was in 2019 in Ethiopia, this is when the initiative from the Gates Foundation and the NIH was announced with regards to the investment in gene therapy for sickle cell and HIV in Africa. Since then, I shudder when I think about the number of patients who have already died. We cannot afford to think about. We have these arguments with Mike frequently, what we think in vivo gene therapy, "No, we'd be thinking about 10 to 15 years time."

I'm thinking, no, we should get this five years time. If we were able to get a solution for COVID-19 within less than a year or less than two years, surely we can get together, address this from a time equity perspective and get in vivo gene therapy for sickle cell disease in a shorter period of time. Thank you.

Susan Winckler:

You've set out quite the vision and the challenge for us, but also reminding us why everyone who spoke today is doing this work. Thank you for that. I'm then reminded though there are some very important steps that have to be taken before we can see the promise of the technology that's been talked about materialize as potential healthcare treatments.

Dr. Buning, to you, as you think about that path to taking the fascinating research that you shared and bringing it to reality, what are some components that you want to underscore there?

Dr. Hildegard Büning:

I think when we now look at science and I think the session which we had looking into the different tools ahead, we see that science really has I think learned from the results we saw in the past and doing the next step and is really advancing. I think what is now required is that we as scientists sit together with the patient, that we sit together with the regulators and also with industry and look how we now get these things streamlined with a clear item, a clear topic and really forget about, "Oh, let's go this system or that system now." Sit together on the table what we have achieved so far and really have something like a task force with a clear aim. The experts are there and we just have really to get them together on a table.

Susan Winckler:

Which you remind us about such an important dynamic of research and needing to continue to learn and share and learn in a multidisciplinary way, perhaps applying some of your partnerships model as you pointed out. Let's then talk about that, come back to the voice about deploying clinical research in Africa.

Dr. Nyarko, what do you see as essential points of awareness in the continued development and evaluation of gene therapies in Africa?

Dr. Kwasi Nyarko:

Yes, the benefit, or at least the good thing is that it's starting. For Africa, at least it's green shoots. It is just about to begin and therefore because of that, we can do it right. Because of that, from the regulatory point of view, we can start with harmonization. From the training, we can do this together. Now we talk a lot about capacity building. Capacity building is not only throwing money at us. Capacity building involves exchange, even sharing information, working outside of emergencies.

We do get a lot of help during emergencies, but what happens between the emergencies? It's all these that I think help in creating the awareness, but it's not only awareness in the scientific community or within the regulators. It's gradually this seeping through the community as well. Interestingly, if you pull many people on the streets on gene therapy here, people know about it. It's difficult for there to be misinformation. Misinformation is everywhere. We're dealing with that as well. Even with the COVID and with vaccines, we have an increasing number of children that are choosing not to be vaccinated.

Part of it is misinformation. I think the earlier and sooner that we are integrated and we integrate whole of society where possible, that would really help in increasing the awareness so that we are able to advance together. There's a lot of good things happening. And also, being able to tell the good stories, like what we're hearing from Jimmy here. It's all good. There is a lot of progress. Just lunchtime, I was talking what I learned in undergrad, and I may be dating myself, but the stuff we learned was just the basics.

Now most of what was presented today 30 years ago was not in the textbooks, and 30 years ago is not that far away. I think given the basis of what we have, building on it is going to go faster than what happened in the last 30 years. When we are looking at what's going to happen, we should hope that yes, within five years a lot can happen because the background, a lot has been done. From a regulatory point of view, as an example, if we look at what's happening on the African continent for harmonization, it's incredible.

But the countries have been working together for the last 18 years. I remember when I started with the AVREV meetings, the technical officers, and now I would say that 18 years ago, most of the folks that came as the technical officers are now the DGs that have been working in the last 18 years. With that

and with that kind of work, you begin to see the convergence. You begin to see people working together because they've known each other, they've built together. I think we can continue that. Thank you.

Susan Winckler:

I want to underscore two parts that I don't think we've talked a lot about but is important in doing the clinical research in Africa, is that I think it can help with the exposure and addressing misinformation because people who look and live like me were involved in the research to learn about the interventions. Also, so not only the innovation, then there was a second one, but it's just gone from my head that I wanted to underscore. We're just going to curb that until I come back later.

I am struck about the importance of learning locally and being able to respond and develop that insight. I know what it is, it's that things are moving so quickly in order to have that acceptance, we want to learn locally and build from that. All right, so Dr. Marks, you know that at the foundation we think a lot about the role of the regulator and how to support regulators who are protecting and promoting the public health.

We just had that rich conversation on collaboration and global regulatory convergence. What do you want to underscore there or perhaps add to remind us to make sure that we're headed in the right direction in all of this conversation?

Dr. Peter Marks:

I think what you're hearing here is there's obviously a balance here. There's a drive here to get products that patients need to them in a very timely manner, but also to make sure we have the evidence base as regulators that makes us feel confident that when they get there, they're going to bring the benefit that we say that they're going to deliver. That doesn't mean they're going to be perfect because I'm sure that as we move forward in the gene therapy world, we're going to have occasional issues, which we will have to go back and correct.

We can't live in a world where perfection is the enemy of good. Which is very easy to live that way as a regulator. There was never a product that was safe enough to approve. On the other hand, we do need to make sure that we work together to come to an understanding of what we expect from these products. I do think that especially, and this goes to the fresh area, gene therapy, fresh area for in this area, especially with genome editing for all of us as regulators, it's probably a good time to learn together, work together, and reduce the amount of rework that we have done repeatedly over time.

I hate to keep going back to COVID, but look, in retrospect, thinking back four or five years ago, it was a little ridiculous that we had 100 regulatory authorities across the globe trying to look at a regulatory file on a COVID vaccine, when you got to think that in the middle of a really serious pandemic, there should have been some better source of reliance. Now, there ultimately was. There was a certain... It happened in a very inorganic way.

Whereas, we probably should have had something in place sooner. I think we could do better here to come together to make it so that those who are familiar with these products can help educate those who are less familiar. Then we come to a place that makes it easier to have them bring benefit to the groups may benefit the most. I do think it goes back to something I said all the way at the beginning from over there, I practically can see it from here, which is that it will be an incredible shame if gene therapy becomes something that's a niche product for high-income countries and doesn't bring its benefit to all of those across the globe where it could really make a huge difference in public health.

In a way, it's a little bit this concept of fixing something at its source as opposed to many medicines which need to be produced on an ongoing basis and taken lifelong. It's so attractive that I think we have to find a way to work together to get there.

Susan Winckler:

Even just, I'm reflecting on the mice that Dr. Liu showed and the difference in their performance and ability to move. What a powerful intervention and opportunity.

Let me turn, Dr. Olaghere, because you have that perspective of the most important constituency in healthcare, the patient. Your reflection earlier today about the current technology was very helpful. I want to challenge you to think about, we've been then talking about what gene therapy might look like in five to 10 years. What would you highlight for patients and what should researchers, regulators, and healthcare professionals keep in mind about that patient perspective as we look to the new technology?

Jimi Olaghere:

I'm bullish on in vivo like the next researcher, but I want us to not lose sight of the fact that the only thing that we have now is ex vivo. I think we can walk and chew gum at the same time. While we continue to innovate with in vivo, we should also innovate with ex vivo. One of the things I've learned because I've become so fascinated with gene therapy, is that manufacturing costs a lot. 30% of manufacturing comes from plasmids alone.

If we learn to decrease the cost of plasmids, that could potentially decrease the cost of gene therapy, ex vivo gene therapies in general. Also, there's something called point of care manufacturing, which could be very, very beneficial in places like Africa where you don't have to ship cells across the globe. I haven't seen it spun up here, but I heard it's been talked about. That could potentially help drive the cost down as well.

Think about it in vivo, it's still, as much as, I hate to say this, it's a tall order, and looking at the data we have from Vertex, I think last month they published that only 20 patients have been commercially approved to have the treatment. Now, depending on where you fall on the medical spectrum, you could think that's a good number. And me from my side, that's very, very little knowing what sickle cell is.

That picture of Hertzner's ear that you had on the screen with his famous art, that's going on right now in emergency rooms across the globe. We have a true bonafide therapy that in my opinion, and I'm going to get a lot of crap for this, it's a cure. And only 20 people have access to it so far, and they haven't even been dosed yet. They're still six to eight months out to being dosed. While we work on in vivo, I think we have to not forget that ex vivo is here and we can innovate that as well and make these incremental changes that can drive down the cost, that could potentially take it to Africa as well.

Susan Winckler:

That's really, I think, Jimi, so important to remind us that innovation needs to occur in all of these places. And I'm struck by your observation earlier about the post-intervention care, that while I think from a research perspective and maybe even a bit from a regulatory perspective, does it do what it's supposed to? And then there's kind of the great... You have sickle cell anymore, at least the pain from it, and have a cure as you noted, but you do have a very different lifestyle that you've not ever known. And what are the supports that are important for that? So could you give us a window a bit into that transformation and what that meant and how we might think about the healthcare support that's necessary when you have an intervention that's literally transformative?

Jimi Olaghere:

Absolutely, yeah. For me, my wife had given me this one directive, don't die. And that was my goal, not to die. And when I was fortunate enough to escape the clutches of the disease, I found myself not equipped to really handle life because for most of my life, I was bedridden. When I wasn't in ICUs or emergency rooms, I was at home in bed. And then to have the good fortune of being healed or being functionally cured by it, you realize that you're not quite equipped to handle life, particularly as a... I had my transplant at 35, I came out of it 36.

You realize that, first of all for me, in my particular situation, I had built up all these coping mechanisms to live with sickle cell disease. And all of a sudden, overnight, those mechanisms were rendered useless so I had to almost retrain myself not to be paranoid. I tell people paranoia kept me alive and there's no need to be paranoid when you don't need it anymore. So you go through, for lack of a better word, an identity crisis because your identity is so enmeshed with the disease because it completely encapsulates everything that you are. And when that's gone, and it'll be in different levels for each individual patient how enmeshed you are with that disease, you're kind of lost. And like I was saying, we really need to make sure that there's a holistic approach to attacking that issue once you come out of the transplant, life post-transplant.

Susan Winckler:

Mm-hmm. So helpful. Thank you. What an important framing when you have an intervention that can literally change someone's life. You have changed someone's life and that is a difference in how they interact with the world.

So obviously, I could just continue this conversation for forever because you all are sharing such great insights, but there are two concepts that we haven't addressed very well so far. One is paying for these technologies so that more patients can benefit. And separately, looking at what type of long-term monitoring or continuing assessment we need. As we said, we're continuing to learn about that.

So I want to turn it to the panel. Who wants to talk about procurement? And I hope that we didn't lose Dr. Farrar because I'm going to look at him for the first answer on this one. But how should we be thinking about procurement? Will existing systems for deploying treatments in low and middle income countries be adaptable for these technologies? Dr. Farrar, do you want to take a run at that? And then I will say to anyone else on the panel, I welcome your thoughts here as well.

Dr. Jeremy Farrar:

Can you hear me with the video off? Apologies for this.

Susan Winckler:

We can hear you, yes. Yes.

Dr. Jeremy Farrar:

Okay. The bandwidth, I'm afraid, at my end is not good enough to share the video, but a fascinating conversation that I've been able to hear most of. I'm going to make the point around the procurement because I do think it's important, but it's also about the regulatory environment. And then just make another point, if you let me do.

This technology is coming and it's happening very dynamically and it's going to speed up, as was said just a few minutes ago. We shouldn't be reacting to that in one, three, five years time when it starts to be possible to roll it out. We, I believe, can anticipate that that is going to be true. And instead of reacting to that dynamic progress, I think thinking through now, actually, what would it take in procurement, in

logistics supply, in clinical care, in post-care as we just heard about, the regulatory harmonization will be critical. And put in place the package, which may be a five year, 10 year vision of how it is, but then we're not reacting, and therefore delaying when things become available.

I mean, others would be better positioned than me to talk about the procurement lines that currently go on. I think they would have to be adapted for the type of procurement and logistics and cold chains and everything else that goes with it, but also that critical clinical care pre and post intervention, as we just heard, including emotional and mental care. I think it's a whole package rather than thinking it's a building we built, we'll turn on a machine and it'll happen. And whether that's in Midwest America or it's in Europe, it's in Sub-Saharan Africa or Southeast Asia, Latin America, anticipating what is coming and thinking what should we have in place in order to do that, I think, is critical.

And then if you'll allow me just while this bandwidth is working, the other thing is making the case that with this sort of technology, yes, it's focused on sickle at the moment, but the technology, the clinical care, the post-care, the logistics, the supply chain issues will lift all boats, and the clinical care from all other conditions will be improved by doing this. We've seen that in every intervention that's come along. When an intervention comes, you improve the outcomes of that intervention, but you lift the whole nursing, medical, post-operative, post medical care in all conditions. And so in fact, you raise all boats of healthcare wherever you are, in America, Europe, north of Africa, Sub-Saharan Africa, East, Southeast Asia. So anticipating and then making the case that, actually, this will have a broader impact than just the individuals that happen to benefit from the sickle cell gene therapy over.

Susan Winckler:

Great. Thanks so much, Dr. Farrar. Anyone else want to talk a bit about procurement? I love the idea that we need to build the systems. All right, I've got Dr. Nyarko and Makani. Dr. Nyarko and then Makani.

Dr. Kwasi Nyarko:

Yeah. I think with procurement, as with many things that we're starting to do on the African continent, we should look at it from a continental point of view because if you do that, it enlarges the options and it allows maybe bringing cost down and so on and so forth. So I think we need to look at stuff more on a global scale. For example, I know that there is... We're looking at research. We were coming up with vaccine research, where we should do, what we should do in vaccine research. And most countries have national research strategies, but this is Africa. It's fairly little, I'm sure, in terms of what we can do.

It would be better to have a continental research strategy as opposed to 55 national research strategies. Similarly, when it comes to this procurement of gene therapies, I think we need to start looking at this. Get all those who are involved, the economists and so on and so forth, to look at different models and really start working now to a future where you can bring cost down or find ways to really get it and for it to be accessible. Sure, if you have five millionaires who can do, it's probably not as profitable as having a million, thousand years or whatever. Who can do that? Thank you.

Susan Winckler:

We can do the math on the other side. Yes, very helpful. Dr. Makani.

Dr. Julie Makani:

Thank you. For me, whilst we're talking about this from a regulatory perspective or from a provider perspective, what's actually happening is patients are just going, getting the transplants, and coming back. And what we are having to do now, what we were planning on doing five years from now, which is

we need to provide post-transplant care now. We need to provide that care now. And we can't afford to say, well, the policy is not in place, the regulatory aspect is not in place because we've got a patient in the ward in Zambia or in Nigeria who needs care. So what has happened now in terms of the whole procurement aspect thing is that... And when you look at it, the patients are raising money themselves. They're going and they're paying for it a lot more. By going to India, it costs $100,000 to get a transplant. If we can do it, and we've done this in Tanzania, we can do the transplant in Tanzania for $30,000 to $50,000. It's a lot of money, but it's much cheaper than if they go out.

And we talked about, I think it was David Williams, and John talked about repatriation and then relocation or relocation and repatriation when patients go back. And this is something that we have to think about because we will not be able to do that. And what we're doing, and this is the point that you're making, is that as a continent coming together and saying, rather than go off the continent to get the transplant, go to country one, two, three where you can have the transplants. And there are enough regional bodies, regional collaborations to be able to do that.

I think the other thing is, really, the perspective of partnership. I cannot emphasize this enough, in that if we... As countries in Africa, as patients, as providers, as regulators, if we partner together and we say, this is what we're going to do, it'll really bring the cost down. We've learned this from HIV. We've learned it from COVID. We've learned it from genetic research. When we started with genotyping or sequencing, it was really expensive. But with time and with the right kind of policies but with the right kind of advocacy, we can get the price down. And so for me, it's really looking at it in that perspective and saying that it is going to come down because it's not realistic, the price. It's not realistic for it to remain at that level.

Susan Winckler:

Mm-hmm. Yeah.

Dr. Hildegard Büning:

And then we have seen this in history, that we start with a very high price. And then when it comes more and more common, it goes down. This in conjunction with science, which is ongoing, and trying, for example, to get high efficacy and so on and so forth, better manufacturing whatsoever. So this goes hand in hand. And I think it's something like we have to set the stage while we're on fly in all the different regions we have spoken about today.

Dr. Peter Marks:

I just want to bring up something. I think it's absolutely correct. We have to essentially continue to fly the plane while everything else is going on. But I think sometimes we underestimate the amount of work we need to do in bringing the manufacturing technologies forward that can support these products because I think we have had these tremendous leaps in science. I mean, when you look at what David Liu has done in the past four years, it's breathtaking, right? Four or five years, it's breathtaking. But the technology to make a product at an affordable price has not come forward that way.

And in many ways, it reminds me of the technology that ultimately helped us to land on the moon was the same technology that's in your iPhone, except somebody had the brilliance of realizing, look... And in some ways, this is a little bit of an example of what we have to think about for gene therapy, which is when... I think the Steve Jobs brilliance was, look, I want it in a box that's this big, that can fit in your pocket, and it can't cost that much that your average person couldn't afford it with a little stretch. And setting that, and then he bent reality a little bit to get there. But I think we may... To be provocative, we may need to set a target product profile here, which includes not just what we're expecting out of these

products from the medical perspective, but what we need to expect out of them from an economic perspective and from a clinical benefit perspective versus cost perspective.

Susan Winckler:

Yeah, I think that idea of thinking more holistically and making sure that we address that early on will be helpful. I want to turn to the long-term monitoring. That was another piece that we didn't quite touch on yet. And actually, Dr. Calhoun, I want to turn to you first because I'm struck. Gene therapy, as we have more applied, more patients like Jimi are the patients in your clinic versus facing something different. What do you think about that future of long-term monitoring of the interventions, the durability, the safety? Does that become part of your clinical practice and maybe a welcome part?

Dr. Cecelia Calhoun:

Well, I really think it just depends. I think part of the reason we have such trepidation in calling it a cure is because we don't have long-term data yet.

Susan Winckler:

Correct.

Dr. Cecelia Calhoun:

And it's hard for me as a hematologist who, for many of my patients, have seen them since they were children, are helping to take care of them as adults, to just let them go off to the transplanter and never see them again. But we really have to think about how we support patients. And so when Dr. Ho was talking earlier, he talked a lot about healthcare costs in the US, but then mentioned that there is this non-quantifiable quality of life change that I think Jimi really continues to lift up.

When we think about systems-level interventions, we're thinking about cost avoidance. How much money are we going to save? Oh, how do we proportion that against $2.2 million? But when we have one-on-one interactions with the people that we care for, with the people who we've had a handful of interventions to offer them for decades and decades and decades, then it becomes a lot more meaningful. And so long-term, I really think we need to actually ask patients, where do you want to be seen? You have a relationship with your hematologist, do you want that to continue? As we think about different toxicities that emerge, where's the safest place for them to be cared for? And then how do we partner? I think, again, across the board, collaboration is a theme. Dr. Makani mentioned that, right now, irrespective of where people went and got transplant, they're coming back home and we have to collaborate and work together to think about how we continue to keep them healthy and we keep them safe.

Susan Winckler:

That's really helpful and I think raises that question not only about what monitoring should be done, but then where it should be. So Dr. Buning, Dr. Marks, do you want to say anything about the kind of long-term monitoring and how we should be thinking about that structure?

Dr. Peter Marks:

Yeah, I think trying. We're still struggling. I mean, there are various entities that are trying to do monitoring of patients who have had transplants. It's easier in some ways for transplanted patients in the United States because there's the National Marrow Donor Program that has helped follow people,

IBMTR. But as we see more and more people treated with gene therapies, the follow-up is more and more essentially segmented. And so some of the learning that we could have if there was a more centralized way of monitoring and ensuring privacy could be very helpful. I think also it's going to be more of an issue as we see people across the globe, how do we monitor in many areas? But I don't think it's impossible because we did pharmacovigilance for the COVID vaccines in Africa, and I think we can do something similar. So I think it's just putting in place the systems and understanding what really is critical to collect here. So it's just a matter of doing so with good forethought.

Susan Winckler:

Yeah, yeah. Dr. Buning, anything you want to add there?

Dr. Hildegard Büning:

Yeah, I totally agree. I think we're still at the stage where we, through monitoring, will learn a lot. So we don't have to really tick every box, but it really will show us how long we have therapeutic effects, long-term outcome and so on, and also when we come back to the point of post-treatment. So what is this meaning for the patient and so on? We have no data about that. This is above the medical parameters to measure. And this is all things, I think, which we still need to monitor because we're still here having the learning curve.

Susan Winckler:

Mm-hmm. Yeah, that learning curve is striking. I think we all accelerated our learning curve with the sessions today, and yet there's so much more that we'll continue to learn.

All right. Okay, panelists, are we ready? Because I'm about to turn to each of you. You're going to get up to two minutes, although the timer won't go off, but I will let you know. But I want to turn to each of you to either underscore something that you heard or that you said today that you want attendees to remember, or to share something that hasn't yet been said but is important for the continued work in this space. So if we've got the ground rules, does that make sense?

All right, let me give you the rolling order. Dr. Nyarko, you're first, then Dr. Makani, and then Dr. Olaghere. So that's our initial rolling order. So Kwasi, may I turn to you for the underscore? Something you heard or said or... Actually, if you don't mention purple chickens, we're all going to be really disappointed. But something that has not yet been said that you want to share.

Dr. Kwasi Nyarko:

I've heard so many things. I think folks should remember everything. That being said, the point that Dr. Calhoun just made about learning being bidirectional kind of just hit me just now. Because a lot of the times when we're talking about capacity building and stuff, it seems like it's presented in a one-directional way, and I recognize that it is bidirectional and that is really true. And just to make this segue, I think if we could learn how to trick hawks, looking at the purple chicken thing, that may become handy somehow. So at least I answered that part.

The next is, really, the speed at which things are happening, which makes it imperative for us to actually continue moving forward because we can't afford to sort of wait until the perfect condition is there. And gene therapies offer a great opportunity, particularly for communities that need this and that must have it. And so just as what Dr. Marks was saying about maybe coming up with parameter on what we want as a target and working towards that from a financial point of view, from a scientific point of view, and getting more hands on it in terms of innovation may be helpful. And so I'm encouraged by all the accumulation of information and what is there, and we will continue. For the regulatory harmonization

part, there are initiatives that's supporting this. It's ultimately going to be based on the regulators like Eric and Cole, but we will support them. And I know that for all those here, if we reach out, we will get the help that is needed so that we're able to advance, so that the patients that need this will feel supported. And we need to continue with also the information. Thank you.

Susan Winckler:

Brilliant. And I know there's renewed interest in making sure that we'll be deploying the gene therapies in the clinical trial sites you told us about in the infrastructure. So let's do Dr. Makani, Dr. Olaghere, and then Dr. Calhoun. Dr. Makani.

Dr. Julie Makani:

Thank you. So the things that I want to emphasize, the first is that we should not have an approach that is dichotomized. It isn't an issue of either this or that. We can do now and learn as we're doing it. We can't afford. Because patients are dying, patients are suffering, we can't afford to say, we need to do things in a sequential manner. We need to do things and then learn as we do it and go forward. The second aspect is that we just have to partner. It just seems very obvious, but we have to partner in. And by partnering, it means learning and being aware of what is happening. There are two gene therapy trials that are happening, one in hemophilia in South Africa and another. And if we do not know that this is happening, we miss the chance of learning from what is already happening and we assume this is not happening.

So let's learn from each other. Let's partner. Let's learn and see what is happening with CAR T-cell therapy in India, and let's just partner and partner and partner at different levels and in different ways. And then finally is that we've got to engage our policymakers. And this is something that as scientists, as healthcare providers, we tend to hesitate and think about what's the best way of engaging policymakers. If we do not engage them, we will not be able to make those huge investments, those huge decisions that can be made by policymakers or by the public sector in that manner. And by having the public sector involved and engaged, it will increase the chances of getting the private sector engaged and invested in as well. And then just my final point is just emphasizing, let's just think about the patient, the patient, the patient. Thank you.

Susan Winckler:

Mm-hmm. So we've got the partnership in the patients. Excellent.

Dr. Julie Makani:

And the doing.

Susan Winckler:

And the doing, yes. Getting it done. Dr. Olaghere, Dr. Calhoun, Dr. Buning.

Jimi Olaghere:

I'll continue Dr. Makani's echo points on the patients. I think I do love that title, but I'll stick with the patient perspective. Yeah, I think I really want to paint a picture of how tough it is to live with sickle cell disease. Many times, patients are constantly living in hospitals. There were times I had to dress up to go to the hospital so they believed I was in pain. There are times I had a crisis throughout the whole triage period and no one saw me because sickle cell disease predominantly affects people of color. And at the

time, I was living in Newark, New Jersey. So no one took the pain so seriously that the pain had actually subsided like five hours after. And I'm sitting in the lobby thinking, should I still go in? My pain's basically gone now. That's how bad the disease is.

So the good news is that there's so many options. Even as fascinated I am with gene therapy, there's even options that are not gene therapy that could be perfect for someone else who doesn't need gene therapy. I was talking to Dr. Ho at lunchtime. I was pitching him a radical idea about, what about small molecules that can bind to BCL11A? We need to find more options and give patients just more time, another day to fight. And really just want to encourage anyone living with a disease that it's really a day-by-day battle to survive.

Most of the times when we hear patients dying of sickle cell disease, it's either from some organ failure, but patients give up, too, and the medical term is whatever made them perish. But you can continue to fight with sickle cell disease. So I just really want to encourage that. I think it's completely unfair to have to debate whether life is worth living because you have an inherited condition that you had no control whatsoever of. So just wanted to really highlight that patient voice and continue to encourage you guys to do the work to... I would love for this to be the last generation of sickle cell as we know it and access to gene therapy for the ones that want it and any other type. I mean, this is fantastic, what's going on. I call it a red carpet moment and people have told me, no, this is not a flash in the pan. This is here to stay. So I'm encouraged. And yeah, thank you.

Susan Winckler:

I love the capturing that as the last generation to experience it. Doctors Calhoun, Buning, Marks.

Dr. Cecelia Calhoun:

So I just want to lift up. Jimi said that he was sitting in an emergency department in the US for five hours in pain and nobody saw him. And so the point that I want to lift up is one that Dr. Farrar mentioned, which is that of equity. And so he gave us some strategies with which he had to employ or deploy to navigate healthcare inequities in our developed country. And so when we think about... And I'm so inspired by my scientific colleagues who are asking these really ambitious questions and answering them, and I'm so inspired by my colleagues here who are thinking about innovative ways in which we implement gene therapy. But more than anything, I agree with Dr. Farrar's sentiment of being intentional about doing it equitably, that it's an active decision that we have to make as a community to make sure that as we make these advancements, as we're building this plane, as we fly it, that we're doing this in a way that is impacting the patients who it needs to impact so that Jimi's vision of this being the last generation can be true.

Susan Winckler:

So important to remind us of that broader underscoring the equitable component and we must do better. Yeah. Dr. Buning, Dr. Marks, and then Dr. Farrar, you're going to get the last word. Dr. Buning.

Dr. Hildegard Büning:

Yeah, thanks. We first maybe have to step back for a minute because when we go for the gene therapy definition, then we always, at least we teach our students that gene therapy is the only curative way to treat a genetic disease. And I mean, this is something which we found as a definition and we have to see that it indeed has become true. We really can tick this box, and this has been achieved in a team effort. And this team effort, multiple disciplines really closely work together, and this also implements the patients. Without the patients, this would never have been achieved.

And at the moment, the current situation is we have to ensure that what has been developed is becoming accessible to everybody. This is our duty to do. And then the next team play, which we have to do is then to move it forward to the next stage. And this is, in my belief, it would be in vivo gene therapy just to really overcome some of the hurdles I was trying to list in my talk. But really, also in that regard, it's again a team effort, partnership. Without this, it'll never, ever work.

Susan Winckler:

Brilliant. Thank you. Dr. Marks.

Dr. Peter Marks:

Yeah, so I'll try to be brief. I think we need to manage the access to gene therapy that we have right now as best as we can and make it as equitably available as we can. At the same time, I think we can peer ahead, as some of what was presented today, at really the tremendous progress that's possible. I think if we want to do the right thing as regulators, we have to develop the frameworks that we're going to need to make these products much more accessible in the five to 10 years in the future as the scientific progress occurs. And so we'll be ready to have broader usage of them at that time. So I think there's dealing with the now and also preparing for the future, which will take a lot of work.

Susan Winckler:

Mm-hmm. So we're going to partner to do that equitably and be ready. Dr. Farrar.

Dr. Jeremy Farrar:

Can you hear me?

Susan Winckler:

Yes, we can.

Dr. Jeremy Farrar:

Two points. One is anticipate. As Peter was just saying, I think we can predict where we're likely to go and get it perfect, but let's anticipate rather than reacting-

Susan Winckler:

Hey, Dr. Farrar?

Dr. Jeremy Farrar:

... to events. And secondly, we're in the boring bits, but I include in that, don't forget the TPP, the product profiles that we're wanting. Don't forget the logistics and the supply chains. Don't forget the regulatory environment, the manufacturing, the progress and engineering and manufacturing, which will drive down price and the policy. And then finally and critically, communication and trust. Those all need to be done. It's not just about individuals, individual clinicians, individual nurses and patients and their families. It's about putting that all together. And often, the boring bits, the regulation, the policy, the logistics, the supply chains, the manufacturing and the engineering get left out and forgotten, and they're often the things that therefore delay being able to roll things out.

Susan Winckler:

Very helpful. I think it's always important to call out at the end that we don't forget the boring bits and those pieces that get us to the promising technology. So with that, let's thank this brilliant panel for sharing and helping us pull everything together.

And that brings us to the end of our day. Thank you so much to those of you who invested time in coming here to our truly outstanding speakers all day long to help us learn more in this space. The recording, the slide deck, and the transcript will be posted to our website late this week or early next. And let's look forward to collaborating, to partner to make it a reality that it is the last generation of individuals who experienced sickle cell disease. All right, thank you all.